

RESEARCH FINDINGS

BASIC NEUROSCIENCES RESEARCH

Function of Human $\alpha 3\beta 4\alpha 5$ Nicotinic Acetylcholine Receptors is Reduced by the

$\alpha 5$ (Asp398Asn) Variant

Genome-wide studies have strongly associated a non-synonymous polymorphism (rs16969968), which changes the 398th amino acid in the nAChR $\alpha 5$ subunit from aspartic acid to asparagine (Asp398Asn), with greater risk for increased nicotine consumption. The authors have used a pentameric concatamer approach to express defined and consistent populations of $\alpha 3\beta 4\alpha 5$ nAChR in *Xenopus* oocytes. $\alpha 5$ (Asn398; risk) variant incorporation reduces ACh-evoked function compared to inclusion of the common $\alpha 5$ (Asp398) variant, without altering agonist or antagonist potencies. Unlinked $\alpha 3$, $\beta 4$ and $\alpha 5$ subunits assemble to form a uniform nAChR population with pharmacological properties matching those of concatameric $\alpha 3\beta 4^*$ nAChRs. $\alpha 5$ subunit incorporation reduces $\alpha 3\beta 4^*$ nAChR function following coinjection with unlinked $\alpha 3$ and $\beta 4$ subunits, but increases that of $\alpha 3\beta 4\alpha 5$ vs. $\alpha 3\beta 4$ -only concatamers. $\alpha 5$ subunit incorporation into $\alpha 3\beta 4^*$ nAChR also alters the relative efficacies of competitive agonists and changes the potency of the non-competitive antagonist mecamylamine. Additional observations indicated that, in the absence of $\alpha 5$ subunits, free $\alpha 3$ and $\beta 4$ subunits form at least two further subtypes. The pharmacological profiles of these free subunit $\alpha 3\beta 4$ -only subtypes are dissimilar, both to each other, and to those of $\alpha 3\beta 4\alpha 5$ nAChR. The $\alpha 5$ variant-induced change in $\alpha 3\beta 4\alpha 5$ nAChR function may underlie some of the phenotypic changes associated with this polymorphism. George AA, Lucero LM, Damaj MI, Lukas RJ, Chen X, Whiteaker P. J. Biological Chemistry 2012 Jun 4 [Epub ahead of print].

Use of SPME-HS-GC-MS for the Analysis of Herbal Products Containing Synthetic

Cannabinoids

The increasing prevalence and use of herbal mixtures containing synthetic cannabinoids presents a growing public health concern and legal challenge for society. In contrast to the plant-derived cannabinoids in medical marijuana and other cannabinoid-based therapeutics, the commonly encountered synthetic cannabinoids in these mendaciously labeled products constitute a structurally diverse set of compounds of relatively unknown pharmacology and toxicology. Indeed, the use of these substances has been associated with an alarming number of hospitalizations and emergency room visits. Moreover, there are already several hundred known cannabinoid agonist compounds that could potentially be used for illicit purposes, posing an additional challenge for public health professionals and law enforcement efforts, which often require the detection and identification of the active ingredients for effective treatment or prosecution. A solid-phase microextraction headspace gas chromatography-mass spectrometry method is shown here to allow for rapid and reliable detection and structural identification of many of the synthetic cannabinoid compounds that are currently or could potentially be used in herbal smoking mixtures. This approach provides accelerated analysis and results that distinguish between structural analogs within several classes of cannabinoid compounds, including positional isomers. The analytical results confirm the continued manufacture and distribution of herbal materials with synthetic cannabinoids and provide insight into the manipulation of these products to avoid legal constraints and prosecution. Cox AO, Daw RC, Mason MD, Grabenauer M, Pande PG, Davis KH, Wiley JL, Stout PR, Thomas BF, Huffman JW. J Anal Toxicol. 2012 Jun; 36(5): 293-302.

Quantum Rods As Nanocarriers Of Gene Therapy Both antisense oligonucleotides (ASODN) and small interfering RNA (siRNA) have enormous potential to selectively silence specific cancer-related genes and could therefore be developed to be important therapeutic anti-cancer drugs. The use of nanotechnology may allow for significant advancement of the therapeutic potential of ASODN and siRNA, due to improved pharmacokinetics, bio-distribution and tissue specific targeted therapy. In this mini-review, the authors have discussed the advantages of using a nanocarrier such as a multimodal quantum rod (QR) complexed with siRNA for gene delivery. Comparisons are made between ASODN and siRNA therapeutic efficacies in the context of cancer and the enormous application potential of nanotechnology in oncotherapy is discussed. The authors have shown that a QR-interleukin-8 (IL-8) siRNA nanoplex can effectively silence IL-8 gene expression in the PC-3 prostate cancer cells with no significant toxicity. Thus, nanocarriers such as QRs can help translate the potent effects of ASODN/siRNA into a clinically viable anti-cancer therapy. Drug delivery for cancer therapy, with the aid of nanotechnology is one of the major translational aspects of nanomedicine, and efficient delivery of chemotherapy drugs and gene therapy drugs or their co-delivery continue to be a major focus of nanomedicine research. PMID: 22643056 [PubMed - in process] Aalinkel R, Nair B, Reynolds JL, Sykes DE, Law WC, Mahajan SD, Prasad PN, Schwartz SA. Quantum rods as nanocarriers of gene therapy. *Drug Deliv.* 2012 May;19(4): 220-231.

Allosteric Modulator ORG27569 Induces CB1 Cannabinoid Receptor High Affinity Agonist Binding State, Receptor Internalization, and Gi Protein-Independent ERK1/2 Kinase Activation The cannabinoid receptor 1 (CB1), a member of the class A G protein-coupled receptor family, is expressed in brain tissue where agonist stimulation primarily activates the pertussis toxin-sensitive inhibitory G protein (G(i)). Ligands such as CP55940 ((1R,3R,4R)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol) and $\Delta(9)$ -tetrahydrocannabinol are orthosteric agonists for the receptor, bind the conventional binding pocket, and trigger G(i)-mediated effects including inhibition of adenylate cyclase. ORG27569 (5-chloro-3-ethyl-1H-indole-2-carboxylic acid [2-(4-piperidin-1-yl-phenyl) ethyl]amide) has been identified as an allosteric modulator that displays positive cooperativity for CP55940 binding to CB1 yet acts as an antagonist of G protein coupling. To examine this apparent conundrum, the authors used the wild-type CB1 and two mutants, T210A and T210I (D'Antona AM, Ahn KH, Kendall DA. (2006) *Biochemistry* 45, 5606-5617), which collectively cover a spectrum of receptor states from inactive to partially active to more fully constitutively active. Using these receptors, the authors demonstrated that ORG27569 induces a CB1 receptor state that is characterized by enhanced agonist affinity and decreased inverse agonist affinity consistent with an active conformation. Also consistent with this conformation, the impact of ORG27569 binding was most dramatic on the inactive T210A receptor and less pronounced on the already active T210I receptor. Although ORG27569 antagonized CP55940-induced guanosine 5'-3-O-(thio)triphosphate binding, which is indicative of G protein coupling inhibition in a concentration-dependent manner, the ORG27569-induced conformational change of the CB1 receptor led to cellular internalization and downstream activation of ERK signaling, providing the first case of allosteric ligand-biased signaling via CB1. ORG27569-induced ERK phosphorylation persisted even after pertussis toxin treatment to abrogate G(i) and occurs in HEK293 and neuronal cells. Ahn KH, Mahmoud MM, Kendall DA. Allosteric modulator ORG27569 induces CB1 cannabinoid receptor high affinity agonist binding state, receptor internalization, and Gi protein-independent ERK1/2 kinase activation. *J Biol Chem.* 2012 Apr 6; 287(15): 12070-12082. Epub 2012 Feb 16.

Lipid Rafts and Functional Caveolae Regulate HIV-Induced Amyloid Beta Accumulation In Brain Endothelial Cells Amyloid beta (A β) levels are increased in HIV-1 infected brains due to not yet fully understood mechanisms. In the present study, the authors investigate the role of lipid rafts, functional caveolae, and caveolae-associated signaling in HIV-1-induced A β accumulation in HBMEC. Both silencing of caveolin-1 (cav-1) and disruption of lipid rafts by pretreatment with beta-methyl-cyclodextrin (MCD) protected against A β accumulation in HBMEC. Exposure to HIV-1 and A β activated caveolae-associated Ras and p38. While inhibition of Ras by farnesylthio-salicylic acid (FTS) effectively protected against HIV-1-induced accumulation of A β , blocking of p38 did not have such an effect. The authors also evaluated the role of caveolae in HIV-1-induced upregulation of the receptor for advanced glycation end products (RAGE), which regulates A β transfer from the blood stream into the central nervous system. HIV-1-induced RAGE expression was prevented by infecting HBMEC with cav-1 specific shRNA lentiviral particles or by pretreatment of cells with FTS. Overall, the present results indicate that A β accumulation in HBMEC is lipid raft and caveolae dependent and involves the caveolae-associated Ras signaling. András IE, Eum SY, Toborek M. Lipid rafts and functional caveolae regulate HIV-induced amyloid beta accumulation in brain endothelial cells. *Biochem Biophys Res Commun.* 2012 May 4; 421(2): 177-183. Epub 2012 Apr 3.

Rapid and Reliable Quantitation Of Amino Acids and Myo-Inositol In Mouse Brain By High Performance Liquid Chromatography and Tandem Mass Spectrometry Amino acids and myo-inositol have long been proposed as putative biomarkers for neurodegenerative diseases. Accurate measures and stability have precluded their selective use. To this end, a sensitive liquid chromatography tandem mass spectrometry (LC-MS/MS) method based on multiple reaction monitoring was developed to simultaneously quantify glutamine, glutamate, γ -aminobutyric acid (GABA), aspartic acid, N-acetyl aspartic acid, taurine, choline, creatine, phosphocholine and myo-inositol in mouse brain by methanol extractions. Chromatography was performed using a hydrophilic interaction chromatography silica column within in a total run time of 15 min. The validated method is selective, sensitive, accurate, and precise. The method has a limit of quantification ranging from 2.5 to 20 ng/ml for a range of analytes and a dynamic range from 2.5-20 to 500-4000 ng/ml. This LC-MS/MS method was validated for biomarker discovery in models of human neurological disorders. Bathena SP, Huang J, Epstein AA, Gendelman HE, Boska MD, Alnouti Y. Rapid and reliable quantitation of amino acids and myo-inositol in mouse brain by high performance liquid chromatography and tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2012 Apr 15; 893-894: 15-20. Epub 2012 Feb 28.

The Cystine-Glutamate Transporter Enhancer N-Acetyl-L-Cysteine Attenuates Cocaine-Induced Changes In Striatal Dopamine But Not Self-Administration In Squirrel Monkeys Extrasynaptic glutamate has been shown to regulate dopamine function in the mesocorticolimbic pathway, which plays an important role in the behavioral pharmacology of psychostimulants. Basal levels of glutamate are primarily regulated by the cystine-glutamate transporter and provide glutamatergic tone on extrasynaptic glutamate receptors. The present study examined the effects of a cystine-glutamate transporter enhancer on the neurochemical and behavioral effects of cocaine and amphetamine in nonhuman primates. It was hypothesized that augmenting extrasynaptic glutamate release with N-acetyl-L-cysteine (NAC), a cystine prodrug, would attenuate cocaine- or amphetamine-induced increases in extracellular dopamine and their corresponding behavioral-stimulant and reinforcing effects. In vivo microdialysis was used to evaluate cocaine-induced changes in extracellular dopamine (DA) in the caudate nucleus (n=3). NAC significantly attenuated cocaine-induced increases in dopamine but had inconsistent effects on amphetamine-induced

increases in dopamine (n=4). Separate groups of subjects were either trained on a fixed-interval schedule of stimulus termination (n=6) or on a second-order schedule of self-administration (n=5) to characterize the behavioral-stimulant and reinforcing effects of psychostimulants, respectively. Systemic administration of NAC did not alter the behavioral-stimulant effects of either cocaine or amphetamine. Furthermore, cocaine self-administration and reinstatement of previously extinguished cocaine self-administration were not altered by pretreatment with NAC. Hence, drug interactions on caudate neurochemistry in vivo were not reflected in behavioral measures in squirrel monkeys. The present results in nonhuman primates do not support the use of NAC as a pharmacotherapy for cocaine abuse, although rodent and clinical studies suggest otherwise. Bauzo RM, Kimmel HL, Howell LL. The cystine-glutamate transporter enhancer N-acetyl-L-cysteine attenuates cocaine-induced changes in striatal dopamine but not self-administration in squirrel monkeys. *Pharmacol Biochem Behav.* 2012 Apr; 101(2): 288-296. Epub 2011 Dec 31.

Smoking Behavior and Exposure To Tobacco Toxicants During 6 Months Of Smoking Progressively Reduced Nicotine Content Cigarettes

Recent federal legislation gives the U.S. Food and Drug Administration authority to regulate the nicotine content of cigarettes. A nationwide strategy for progressive reduction of the nicotine content of cigarettes is a potential way to reduce the addictiveness of cigarettes, to prevent new smokers from becoming addicted, and to facilitate quitting in established smokers. The authors conducted a trial of progressive nicotine content tapering over 6 months to determine the effects on smoking behaviors and biomarkers of tobacco smoke exposure and cardiovascular effects. One hundred and thirty-five healthy smokers were randomly assigned to one of two groups. A research group smoked their usual brand of cigarettes followed by five types of research cigarettes with progressively lower nicotine content, each smoked for one month. A control group smoked their own brand of cigarettes for the same period of time. Nicotine intake, as indicated by plasma cotinine concentration, declined progressively as the nicotine content of cigarettes was reduced. Cigarette consumption and markers of exposure to carbon monoxide and polycyclic aromatic hydrocarbons, as well as cardiovascular biomarkers remained stable, whereas urinary 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) excretion decreased. No significant changes in biomarkers of exposure or cardiovascular effects were observed in controls. These data support the proposition that the intake of nicotine from cigarettes of smokers can be substantially lowered without increasing exposure to other tobacco smoke toxins. These findings support the feasibility and safety of gradual reduction of the nicotine content in cigarettes. Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev.* 2012 May; 21(5): 761-769. Epub 2012 Feb 21.

Nicotinic Acetylcholine Receptors In Rat Forebrain That Bind ¹⁸F-Nifene: Relating PET Imaging, Autoradiography, and Behavior

Nicotinic acetylcholine receptors (nAChRs) in the brain are important for cognitive function; however, their specific role in relevant brain regions remains unclear. In this study, the authors used the novel compound ¹⁸F-nifene to examine the distribution of nAChRs in the rat forebrain, and for individual animals related the results to behavioral performance on an auditory-cognitive task. They first show negligible binding of ¹⁸F-nifene in mice lacking the $\beta 2$ nAChR subunit, consistent with previous findings that ¹⁸F-nifene binds to $\alpha 4\beta 2^*$ nAChRs. They then examined the distribution of ¹⁸F-nifene in rat using three methods: in vivo PET, ex vivo PET and autoradiography. Generally, ¹⁸F-nifene labeled forebrain regions known to contain nAChRs, and the three methods produced similar relative binding among

regions. Importantly, ^{18}F -nifene also labeled some white matter (myelinated axon) tracts, most prominently in the temporal subcortical region that contains the auditory thalamocortical pathway. Finally, the authors related ^{18}F -nifene binding in several forebrain regions to each animal's performance on an auditory-cued, active avoidance task. The strongest correlations with performance after 14 days training were found for ^{18}F -nifene binding in the temporal subcortical white matter, subiculum, and medial frontal cortex (correlation coefficients, $r > 0.8$); there was no correlation with binding in the auditory thalamus or auditory cortex. These findings suggest that individual performance is linked to nicotinic functions in specific brain regions, and further support a role for nAChRs in sensory-cognitive function. Bieszczad KM, Kant R, Constantinescu CC, Pandey SK, Kawai HD, Metharate R, Weinberger NM, Mukherjee J. Nicotinic acetylcholine receptors in rat forebrain that bind ^{18}F -nifene: relating PET imaging, autoradiography, and behavior. *Synapse*. 2012 May; 66(5): 418-434. doi: 10.1002/syn.21530. Epub 2012 Feb 15.

Agonist-Selective Effects Of Opioid Receptor Ligands On Cytosolic Calcium Concentration In Rat Striatal Neurons

Buprenorphine is an opioid receptor ligand whose mechanism of action is incompletely understood. Using $\text{Ca}(2+)$ imaging, the authors assessed the effects of buprenorphine, β -endorphin, and morphine on cytosolic $\text{Ca}(2+)$ concentration $[\text{Ca}(2+)](i)$, in rat striatal neurons. Buprenorphine (0.01-1 μM) increased $[\text{Ca}(2+)](i)$ in a dose-dependent manner in a subpopulation of rat striatal neurons. The effect of buprenorphine was largely reduced by naloxone, a non-selective opioid receptor antagonist, but not by μ , κ , δ or NOP-selective antagonists. β -Endorphin (0.1 μM) increased $[\text{Ca}(2+)](i)$ with a lower amplitude and slower time course than buprenorphine. Similar to buprenorphine, the effect of β -endorphin was markedly decreased by naloxone, but not by opioid-selective antagonists. Morphine (0.1-10 μM), did not affect $[\text{Ca}(2+)](i)$ in striatal neurons. These results suggest that buprenorphine and β -endorphin act on a distinct type/subtype of plasmalemmal opioid receptors or activate intracellular opioid-like receptor(s) in rat striatal neurons. Brailoiu GC, Deliu E, Hooper R, Dun NJ, Undieh AS, Adler MW, Benamar K, Brailoiu E. Agonist-selective effects of opioid receptor ligands on cytosolic calcium concentration in rat striatal neurons. *Drug Alcohol Depend*. 2012 Jun 1; 123(1-3): 277-281. Epub 2011 Dec 21.

Presynaptic Imaging Of Projection Fibers By In Vivo Injection Of Dextran-Conjugated Calcium Indicators

Dextran-conjugated calcium indicators are stably retained within neurons. As a result, they are well suited to measuring presynaptic calcium at physiological temperatures. In addition, dextran indicators can be used to label neurons and their presynaptic boutons in vivo. This has allowed measurements of calcium in the presynaptic boutons of projection fibers that cannot be stably loaded with other types of indicators. This protocol describes a technique for in vivo loading of the climbing fiber projection to the cerebellum with dextran-conjugated indicators for subsequent presynaptic calcium imaging in brain slices. This technique is applicable to studies of projection fibers in many species from which brain slices can be prepared. The dextran indicator is injected into the inferior olive using a stereotaxic device. After a period of 1-3 d, cerebellar slices are prepared and presynaptic calcium transients are measured at physiological temperature in labeled climbing fibers. The protocol also discusses important considerations for using dextran-conjugated indicators to measure presynaptic calcium. Brenowitz SD, Regehr WG. Presynaptic imaging of projection fibers by in vivo injection of dextran-conjugated calcium indicators. *Cold Spring Harb Protoc*. 2012 Apr 1; 2012(4): 465-471. doi: 10.1101/pdb.prot068551.

Behavioral Effects and Central Nervous System Levels Of The Broadly Available κ -Agonist Hallucinogen Salvinorin A Are Affected By P-Glycoprotein Modulation In Vivo Active blood-brain barrier mechanisms, such as the major efflux transporter P-glycoprotein (mdr1), modulate the in vivo/central nervous system (CNS) effects of many pharmacological agents, whether they are used for nonmedical reasons or in pharmacotherapy. The powerful, widely available hallucinogen salvinorin A (from the plant *Salvia divinorum*) is a high-efficacy, selective κ -opioid agonist and displays fast-onset behavioral effects (e.g., within 1 min of administration) and relatively short duration of action. In vitro studies suggest that salvinorin A may be a P-glycoprotein substrate; thus, the functional status of P-glycoprotein may influence the behavioral effects of salvinorin A or its residence in CNS after parenteral administration. The authors therefore studied whether a competing P-glycoprotein substrate (the clinically available agent loperamide; 0.032-0.32 mg/kg) or a selective P-glycoprotein blocker, tariquidar (0.32-3.2 mg/kg) could enhance unconditioned behavioral effects (ptosis and facial relaxation, known to be caused by κ -agonists in nonhuman primates) of salvinorin A, as well as its entry and residence in the CNS, as measured by cerebrospinal fluid sampling. Pretreatment with either loperamide or tariquidar dose-dependently enhanced salvinorin A-induced ptosis, but not facial relaxation. In a control study, loperamide and tariquidar were inactive when given as a pretreatment to ((+)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidiny)-1-oxaspiro[4.5]dec-8-yl]-benzeneac etamide (U69,593), a κ -agonist known to be a very poor P-glycoprotein substrate. Furthermore, pretreatment with tariquidar (3.2 mg/kg) also enhanced peak levels of salvinorin A in cerebrospinal fluid after intravenous administration. These are the first studies in vivo showing the sensitivity of salvinorin A effects to modulation by the P-glycoprotein transporter, a major functional component of the blood-brain barrier. Butelman ER, Caspers M, Lovell KM, Kreek MJ, Prisinzano TE. Behavioral effects and central nervous system levels of the broadly available κ -agonist hallucinogen salvinorin A are affected by P-glycoprotein modulation in vivo. *J Pharmacol Exp Ther.* 2012 Jun; 341(3): 802-808. Epub 2012 Mar 20.

Highly Selective Inhibitors of Monoacylglycerol Lipase Bearing a Reactive Group that Is Bioisosteric with Endocannabinoid Substrates The endocannabinoids 2-arachidonoyl glycerol (2-AG) and N-arachidonoyl ethanolamine (anandamide) are principally degraded by monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH), respectively. The recent discovery of O-aryl carbamates such as JZL184 as selective MAGL inhibitors has enabled functional investigation of 2-AG signaling pathways in vivo. Nonetheless, JZL184 and other reported MAGL inhibitors still display low-level cross-reactivity with FAAH and peripheral carboxylesterases, which can complicate their use in certain biological studies. Here, the authors report a distinct class of O-hexafluoroisopropyl (HFIP) carbamates that inhibits MAGL in vitro and in vivo with excellent potency and greatly improved selectivity, including showing no detectable cross-reactivity with FAAH. These findings designate HFIP carbamates as a versatile chemotype for inhibiting MAGL and should encourage the pursuit of other serine hydrolase inhibitors that bear reactive groups resembling the structures of natural substrates. Chang JW, Niphakis MJ, Lum KM, Coggnetta AB 3rd, Wang C, Matthews ML, Niessen S, Buczynski MW, Parsons LH, Cravatt BF. Highly selective inhibitors of monoacylglycerol lipase bearing a reactive group that is bioisosteric with endocannabinoid substrates. *Chem Biol.* 2012 May 25;19(5): 579-588. Epub 2012 Apr 26.

Controlling Murine and Rat Chronic Pain Through A3 Adenosine Receptor Activation Clinical management of chronic neuropathic pain is limited by marginal effectiveness and unacceptable side effects of current drugs. The authors demonstrate A(3) adenosine receptor (A(3)AR) agonism as a new target-based therapeutic strategy. The development of mechanoallodynia in a well-characterized mouse model of neuropathic pain following chronic

constriction injury of the sciatic nerve was rapidly and dose-dependently reversed by the A(3)AR agonists: IB-MECA, its 2-chlorinated analog (Cl-IB-MECA), and the structurally distinct MRS1898. These effects were naloxone insensitive and thus are not opioid receptor mediated. IB-MECA was ≥ 1.6 -fold more efficacious than morphine and >5 -fold more potent. In addition, IB-MECA was equally efficacious as gabapentin (Neurontin) or amitriptyline, but respectively >350 - and >75 -fold more potent. Besides its potent standalone ability to reverse established mechanoallodynia, IB-MECA significantly increased the antiallodynic effects of all 3 analgesics. Moreover, neuropathic pain development in rats caused by widely used chemotherapeutics in the taxane (paclitaxel), platinum-complex (oxaliplatin), and proteasome-inhibitor (bortezomib) classes was blocked by IB-MECA without antagonizing their antitumor effect. A(3)AR agonist effects were blocked with A(3)AR antagonist MRS1523, but not with A(1)AR (DPCPX) or A(2A)AR (SCH-442416) antagonists. Our findings provide the scientific rationale and pharmacological basis for therapeutic development of A(3)AR agonists for chronic pain. Chen Z, Janes K, Chen C, Doyle T, Bryant L, Tosh DK, Jacobson KA, Salvemini D. Controlling murine and rat chronic pain through A3 adenosine receptor activation. *FASEB J.* 2012 May; 26(5): 1855-1865. Epub 2012 Feb 17.

Pharmacologic Characterization Of A Nicotine-Discriminative Stimulus In Rhesus Monkeys

This study examined mechanisms by which nicotine (1.78 mg/kg base s.c.) produces discriminative stimulus effects in rhesus monkeys. In addition to nicotine, various test compounds were studied including other nicotinic acetylcholine receptor agonists (varenicline and cytisine), antagonists [mecamylamine and the $\alpha 4\beta 2$ receptor-selective antagonist dihydro- β -erythroidine (DH β E)], a nicotinic acetylcholine receptor antagonist/indirect-acting catecholamine agonist (bupropion), and non-nicotinics (cocaine and midazolam). Nicotine, varenicline, and cytisine dose-dependently increased drug-lever responding; the ED(50) values were 0.47, 0.53, and 39 mg/kg, respectively. Bupropion and cocaine produced 100% nicotine-lever responding in a subset of monkeys, whereas mecamylamine, DH β E, and midazolam produced predominantly vehicle-lever responding. The training dose of nicotine resulted in 1128 ng/ml cotinine in saliva. Mecamylamine antagonized the discriminative stimulus effects of nicotine and varenicline, whereas DH β E was much less effective. Nicotine and varenicline had synergistic discriminative stimulus effects. In monkeys responding predominantly on the vehicle lever after a test compound (bupropion, cocaine, and midazolam), that test compound blocked the nicotine-discriminative stimulus, perhaps reflecting a perceptual-masking phenomenon. These results show that nicotine, varenicline, and cytisine produce discriminative stimulus effects through mecamylamine-sensitive receptors (i.e., nicotinic acetylcholine) in primates, whereas the involvement of DH β E-sensitive receptors (i.e., $\alpha 4\beta 2$) is unclear. The current nicotine-discrimination assay did not detect a difference in agonist efficacy between nicotine, varenicline, and cytisine, but did show evidence of involvement of dopamine. The control that nicotine has over choice behavior can be disrupted by non-nicotinic compounds, suggesting that non-nicotinics could be exploited to decrease the control that tobacco has over behavior. Cunningham CS, Javors MA, McMahon LR. Pharmacologic characterization of a nicotine-discriminative stimulus in rhesus monkeys. *J Pharmacol Exp Ther.* 2012 Jun; 341(3): 840-849. Epub 2012 Mar 21.

Concomitant Lethal Mutagenesis Of Human Immunodeficiency Virus Type 1 RNA virus population dynamics are complex, and sophisticated approaches are needed in many cases for therapeutic intervention. One such approach, termed lethal mutagenesis, is directed at targeting the virus population structure for extinction or error catastrophe. Previous studies have demonstrated the concept of this approach with human immunodeficiency virus type 1 (HIV-1) by use of chemical mutagens [i.e., 5-azacytidine (5-AZC)] as well as by host factors with mutagenic

properties (i.e., APOBEC3G). In this study, these two unrelated mutagenic agents were used concomitantly to investigate the interplay of these distinct mutagenic mechanisms. Specifically, an HIV-1 was produced from APOBEC3G (A3G)-expressing cells and used to infect permissive target cells treated with 5-AZC. Reduced viral infectivity and increased viral mutagenesis were observed with both the viral mutagen (i.e., G-to-C mutations) and the host restriction factor (i.e., G-to-A mutations); however, when combined, they had complex interactions. Intriguingly, nucleotide sequence analysis revealed that concomitant HIV-1 exposure to both 5-AZC and A3G resulted in an increase in G-to-A viral mutagenesis at the expense of G-to-C mutagenesis. A3G catalytic activity was required for the diminution in G-to-C mutagenesis. Taken together, these findings provide the first demonstration for potentiation of the mutagenic effect of a cytosine analog by A3G expression, resulting in concomitant HIV-1 lethal mutagenesis. Dapp MJ, Holtz CM, Mansky LM. Concomitant lethal mutagenesis of human immunodeficiency virus type 1. *J Mol Biol.* 2012 Jun 8;419(3-4):158-70. Epub 2012 Mar 15.

Targeting the Overproduction Of Peroxynitrite For The Prevention and Reversal Of Paclitaxel-Induced Neuropathic Pain

Chemotherapy-induced peripheral neuropathy (CIPN) accompanied by chronic neuropathic pain is a major dose-limiting side effect of a large number of antitumoral agents including paclitaxel (Taxol). Thus, CIPN is one of most common causes of dose reduction and discontinuation of what is otherwise a life-saving therapy. Neuropathological changes in spinal cord are linked to CIPN, but the causative mediators and mechanisms remain poorly understood. The authors report that formation of peroxynitrite (PN) in response to activation of nitric oxide synthases and NADPH oxidase in spinal cord contributes to neuropathological changes through two mechanisms. The first involves modulation of neuroexcitatory and proinflammatory (TNF- α and IL-1 β) and anti-inflammatory (IL-10 and IL-4) cytokines in favor of the former. The second involves post-translational nitration and modification of glia-derived proteins known to be involved in glutamatergic neurotransmission (astrocyte-restricted glutamate transporters and glutamine synthetase). Targeting PN with PN decomposition catalysts (PNDCs) not only blocked the development of paclitaxel-induced neuropathic pain without interfering with antitumor effects, but also reversed it once established. Herein, the authors describe our mechanistic study on the role(s) of PN and the prevention of neuropathic pain in rats using known PNDCs (FeTMPyP(5+) and MnTE-2-PyP(5+)). They also demonstrate the prevention of CIPN with their two new orally active PNDCs, SRI6 and SRI110. The improved chemical design of SRI6 and SRI110 also affords selectivity for PN over other reactive oxygen species (such as superoxide). These findings identify PN as a critical determinant of CIPN, while providing the rationale toward development of superoxide-sparing and "PN-targeted" therapeutics. Doyle T, Chen Z, Muscoli C, Bryant L, Esposito E, Cuzzocrea S, Dagostino C, Ryerse J, Rausaria S, Kamadulski A, Neumann WL, Salvemini D. Targeting the overproduction of peroxynitrite for the prevention and reversal of paclitaxel-induced neuropathic pain. *J Neurosci.* 2012 May 2; 32(18): 6149-6160.

Effects Of Neonatal Methamphetamine and Thioperamide Exposure On Spatial Memory Retention and Circadian Activity Later In Life

Methamphetamine (MA) use increases the likelihood of engaging in risky sexual behavior and most MA-using women are of child-bearing age. Therefore, cognitive effects following MA exposure to the developing brain are concerning. Exposure of mice to MA during hippocampal development causes cognitive impairments in adulthood. These effects are more severe in female than male mice and mimicked by the H(3) receptor antagonist thioperamide (THIO). In this study, the authors assessed whether neonatal exposure to MA or THIO also affects cognition in adolescence. As these effects might be associated with alterations in circadian activity, they also assessed circadian activity in a subgroup of

neonatally exposed mice. Sex-dependent treatment effects were seen in the water maze. While THIO-, but not MA-treated female mice showed hippocampus-dependent spatial memory retention in the first probe trial, MA-, but not THIO-treated female mice showed spatial memory retention in the probe trial following reversal training. In contrast, MA- and THIO-treated male mice showed spatial memory retention in both probe trials. When sensorimotor gating was assessed, MA-treated male mice showed greater pre-pulse inhibition than MA-treated female mice. Regardless of sex, THIO-treated mice gained on average more weight each day and showed an enhanced startle response. In addition, MA increased the length of the circadian period, with an intermediate effect following THIO treatment were observed. No treatment effects in exploratory behavior, measures of anxiety, or contextual or cued fear conditioning. Thus, the water maze is particularly sensitive to detect sex-dependent effects of neonatal MA and THIO exposure on spatial memory retention in adolescence. Eastwood E, Allen CN, Raber J. Effects of neonatal methamphetamine and thioperamide exposure on spatial memory retention and circadian activity later in life. *Behav Brain Res.* 2012 Apr 21; 230(1): 229-236. Epub 2012 Feb 11.

Inhibition Of GSK3 Attenuates Amphetamine-Induced Hyperactivity and Sensitization In The Mouse

Glycogen synthase kinase 3 (GSK3) is implicated in mediating dopamine-dependent behaviors. Previous studies have demonstrated the ability of amphetamine, which increases extracellular dopamine levels and influences behavior, to regulate the activity of GSK3. This study used valproic acid and the selective GSK3 inhibitor, SB 216763, to examine the role of GSK3 in amphetamine-induced hyperactivity and the development of sensitized stereotypic behavior. Pretreatment with valproic acid (50-300 mg/kg, i.p.) or SB 216763 (2.5-5 mg/kg, i.p.) prior to amphetamine (2 mg/kg, i.p.) significantly reduced amphetamine induced ambulation and stereotypy. To assess the development of sensitization to the stereotypic effects of amphetamine, mice were pretreated daily with valproic acid (300 mg/kg) or SB 216763 (5 mg/kg) prior to amphetamine (2 mg/kg) for 5 days. Upon amphetamine challenge (1 mg/kg) 7 days later, mice pretreated with valproate or SB 216763 showed a significant attenuation of amphetamine-induced sensitization of stereotypy. To determine whether regulation of GSK3 activity was associated with attenuation of acute amphetamine-induced hyperactivity by valproic acid, valproate (300 mg/kg) or vehicle was injected prior to amphetamine (2 mg/kg) or saline and brain tissue obtained. Analysis of the levels of phospho-GSK3 α and β by immunoblot indicated that valproate increased phosphorylation of ser²¹-GSK3 α in the frontal cortex, as well as ser⁹-GSK3 β in the frontal cortex and caudate putamen of amphetamine-injected mice. These data support a role for GSK3 in acute amphetamine-induced hyperactivity and the development of sensitization to amphetamine-induced stereotypy. Enman NM, Unterwald EM. Inhibition of GSK3 attenuates amphetamine-induced hyperactivity and sensitization in the mouse. *Behav Brain Res.* 2012 May 16; 231(1): 217-225.

A Reliable Protocol For The Manual Segmentation Of The Human Amygdala and Its Subregions Using Ultra-High Resolution MRI

The measurement of the volume of the human amygdala in vivo has received increasing attention over the past decade, but existing methods face several challenges. First, due to the amorphous appearance of the amygdala and the difficulties in interpreting its boundaries, it is common for protocols to omit sizable sections of the rostral and dorsal regions of the amygdala comprising parts of the basolateral complex (BL) and central nucleus (Ce), respectively. Second, segmentation of the amygdaloid complex into separate subdivisions is challenging due to the resolution of routinely acquired images and the lack of standard protocols. Recent advances in technology have made ultra-high resolution MR images available, and in this study the authors provide a detailed segmentation protocol for manually tracing the whole amygdala that incorporates a greater portion of the rostral and dorsal sections with

techniques illustrated in detail to maximize reproducibility. In addition, they propose a geometrically-based protocol for segmenting the amygdala into four component subregions of interest (sROI), which correspond largely to amygdala subnuclear divisions: the BL sROI, centromedial (CM) sROI, basomedial (BM) sROI, and the amygdaloid cortical (ACo) sROI. The authors performed an intra- and inter-rater reliability study of our methods in 10 adults (5 young adults and 5 older adults). The results indicate that both protocols can be implemented with a high degree of reliability (the majority of intra-rater and inter-rater correlations were > 0.81). This protocol should aid further research into the alterations in amygdala anatomy, connectivity, and function that accompany normal aging and pathology associated with neuropsychiatric disorders. Entis JJ, Doerga P, Barrett LF, Dickerson BC. A reliable protocol for the manual segmentation of the human amygdala and its subregions using ultra-high resolution MRI. *Neuroimage*. 2012 Apr 2; 60(2): 1226-1235. Epub 2012 Jan 5.

Sumatriptan Inhibits TRPV1 Channels In Trigeminal Neurons To understand a possible role for transient potential receptor vanilloid 1 (TRPV1) ion channels in sumatriptan relief of pain mediated by trigeminal nociceptors. TRPV1 channels are expressed in small nociceptive sensory neurons. In dorsal root ganglia, TRPV1-containing nociceptors mediate certain types of inflammatory pain. Neurogenic inflammation of cerebral dura and blood vessels in the trigeminal nociceptive system is thought to be important in migraine pain, but the ion channels important in transducing migraine pain are not known. Sumatriptan is an agent effective in treatment of migraine and cluster headache. The authors hypothesized that sumatriptan might modulate activity of TRPV1 channels found in the trigeminal nociceptive system. They used immunohistochemistry to detect the presence of TRPV1 channel protein, whole-cell recording in acutely dissociated trigeminal ganglia (TG) to detect functionality of TRPV1 channels, and whole-cell recording in trigeminal nucleus caudalis (TNC) to detect effects on release of neurotransmitters from trigeminal neurons onto second order sensory neurons. Effects specifically on TG neurons that project to cerebral dura were assessed by labeling dural nociceptors with DiI. Immunohistochemistry demonstrated that TRPV1 channels are present in cerebral dura, in trigeminal ganglion, and in the TNC. Capsaicin, a TRPV1 agonist, produced depolarization and repetitive action potential firing in current clamp recordings, and large inward currents in voltage clamp recordings from acutely dissociated TG neurons, demonstrating that TRPV1 channels are functional in trigeminal neurons. Capsaicin increased spontaneous excitatory postsynaptic currents in neurons of layer II in TNC slices, showing that these channels have a physiological effect on central synaptic transmission. Sumatriptan (10 μM), a selective antimigraine drug, inhibited TRPV1-mediated inward currents in TG and capsaicin-elicited spontaneous excitatory postsynaptic currents in TNC slices. The same effects of capsaicin and sumatriptan were found in acutely dissociated DiI-labeled TG neurons innervating cerebral dura. These results build on previous work indicating that TRPV1 channels in trigeminal nociceptors play a role in craniofacial pain. These findings that TRPV1 is inhibited by the specific antimigraine drug sumatriptan, and that TRPV1 channels are functional in neurons projecting to cerebral dura suggests a specific role for these channels in migraine or cluster headache. Evans MS, Cheng X, Jeffrey JA, Disney KE, Premkumar LS. Headache. Sumatriptan inhibits TRPV1 channels in trigeminal neurons. 2012 May; 52(5): 773-784. doi: 10.1111/j.1526-4610.2011.02053.x. Epub 2012 Jan 30.

Intracranial Self-Stimulation Of The Paraventricular Nucleus Of The Hypothalamus: Increased Facilitation By Morphine Compared To Cocaine Neuropathic pain attenuates opioid facilitation of rewarding electrical stimulation of limbic dopaminergic pathways originating from the ventral tegmental area. Whether neuropathic pain alters opioid effects of other brain-reward

systems is unknown. Control and spinal nerve-ligated (SNL) rats had electrodes implanted into the paraventricular nucleus (PVN) of the hypothalamus or medial forebrain bundle. Control and SNL rats were trained to lever-press for intracranial self-stimulation (ICSS), and modulation by morphine or cocaine was assessed. Control and SNL rats lever-pressed for stimulation of the PVN and medial forebrain bundle. Morphine produced greater reductions in the frequency at which rats emitted 50% of maximal responding for PVN ICSS (maximal effect 24.67 ± 4.60 [mean \pm SEM] and 24.11 ± 5.96 in SNL [n = 6] and control [n = 8] rats, respectively, compared with medial forebrain bundle ICSS (12.38 ± 6.77 [n = 8] and 12.69 ± 1.55 [n = 7]). In contrast, cocaine was less efficacious in potentiating PVN ICSS (maximal effect 11.76 ± 2.86 and 12.38 ± 4.01 in SNL [n = 12] and control [n = 8] rats, respectively) compared with medial forebrain bundle ICSS (30.58 ± 3.40 [n = 9] and 27.55 ± 4.51 [n = 7]). PVN ICSS is facilitated to a greater extent by morphine than cocaine, and the effects of each drug on this behavior are unaltered after spinal nerve ligation. These effects contrast those observed with direct stimulation of limbic dopamine pathways, suggesting that the PVN may have a greater role in the reinforcing effects of opioids than classic limbic regions, particularly in the presence of chronic pain. Ewan EE, Martin TJ. Intracranial self-stimulation of the paraventricular nucleus of the hypothalamus: increased facilitation by morphine compared to cocaine. *Anesthesiology*. 2012 May; 116(5): 1116-1123.

Cocaine Self-Administration Produces Pharmacodynamic Tolerance: Differential Effects On The Potency Of Dopamine Transporter Blockers, Releasers, and Methylphenidate

The dopamine transporter (DAT) is the primary site of action for psychostimulant drugs such as cocaine, methylphenidate, and amphetamine. The authors' previous work demonstrated a reduced ability of cocaine to inhibit the DAT following high-dose cocaine self-administration (SA), corresponding to a reduced ability of cocaine to increase extracellular dopamine. However, this effect had only been demonstrated for cocaine. Thus, the current investigations sought to understand the extent to which cocaine SA (1.5 mg/kg/inf \times 40 inf/day \times 5 days) altered the ability of different dopamine uptake blockers and releasers to inhibit dopamine uptake, measured using fast-scan cyclic voltammetry in rat brain slices. The authors demonstrated that, similar to cocaine, the DAT blockers nomifensine and bupropion were less effective at inhibiting dopamine uptake following cocaine SA. The potencies of amphetamine-like dopamine releasers such as 3,4-methylenedioxymethamphetamine, methamphetamine, amphetamine, and phentermine, as well as a non-amphetamine releaser, 4-benzylpiperidine, were all unaffected. Finally, methylphenidate, which blocks dopamine uptake like cocaine while being structurally similar to amphetamine, shared characteristics of both, resembling an uptake blocker at low concentrations and a releaser at high concentrations. Combined, these experiments demonstrate that after high-dose cocaine SA, there is cross-tolerance of the DAT to other uptake blockers, but not releasers. The reduced ability of psychostimulants to inhibit dopamine uptake following cocaine SA appears to be contingent upon their functional interaction with the DAT as a pure blocker or releaser rather than their structural similarity to cocaine. Further, methylphenidate's interaction with the DAT is unique and concentration-dependent. Ferris MJ, Calipari ES, Mateo Y, Melchior JR, Roberts DC, Jones SR. Cocaine self-administration produces pharmacodynamic tolerance: differential effects on the potency of dopamine transporter blockers, releasers, and methylphenidate. *Neuropsychopharmacology*. 2012 Jun; 37(7): 1708-1716. doi: 10.1038/npp.2012.17. Epub 2012 Mar 7.

Ventral Pallidum Mediates Amygdala-Evoked Deficits In Prepulse Inhibition Prepulse inhibition (PPI) is an operational measure of sensorimotor gating. It is defined as a reduction in magnitude of a startle response when a startling stimulus is preceded by a weaker "prepulse." PPI has been found to be altered in patients with schizophrenia, autism spectrum disorders, and other

neuropsychiatric illnesses. As such, the neural substrates regulating PPI are of particular interest. Previous studies using lesions, selective blockade of N-methyl-d-aspartate (NMDA) receptors, and pharmacological disinhibition have demonstrated that impairment of the function of the basolateral and lateral nuclei of the amygdala (BLA) disrupts PPI. However, transient gamma aminobutyric acid-mediated (GABA-mediated) inactivation of BLA has not been evaluated for effects on PPI. Furthermore, the downstream projection targets that mediate BLA-evoked disruptions of PPI have not been elucidated. Thus, in the present study, the authors evaluated the effect on PPI of bilateral and unilateral inactivation of BLA, by microinfusion of the GABA-A receptor agonist, muscimol. They found that either bilateral or unilateral inactivation impaired PPI. Because unilateral inactivation was sufficient to impair PPI, they hypothesized that this was due to an indirect activation of a downstream target of BLA, the ventral pallidum (VP). Because VP inhibition normalizes PPI deficits evoked from nucleus accumbens (Kodsi & Swerdlow, 1994), they next tested the degree to which VP inhibition would normalize PPI deficits evoked from BLA. The authors unilaterally inactivated BLA with concurrent inactivation of VP and found that VP inactivation blocked BLA-evoked deficits in PPI. The authors suggest that BLA inactivation disrupts PPI through disinhibition of VP. Forcelli PA, West EA, Murnen AT, Malkova L. Ventral pallidum mediates amygdala-evoked deficits in prepulse inhibition. *Behav Neurosci*. 2012 Apr; 126(2): 290-300. Epub 2012 Jan 16.

Human Cathepsin V Protease Participates In Production Of Enkephalin and NPY

Neuropeptide Neurotransmitters Proteases are required for processing precursors into active neuropeptides that function as neurotransmitters for cell-cell communication. This study demonstrates the novel function of human cathepsin V protease for producing the neuropeptides enkephalin and neuropeptide Y (NPY). Cathepsin V is a human-specific cysteine protease gene. Findings here show that expression of cathepsin V in neuroendocrine PC12 cells and human neuronal SK-N-MC cells results in production of (Met)enkephalin from proenkephalin. Gene silencing of cathepsin V by siRNA in human SK-N-MC cells results in reduction of (Met)enkephalin by more than 80%, illustrating the prominent role of cathepsin V for neuropeptide production. In vitro processing of proenkephalin by cathepsin V occurs at dibasic residue sites to generate enkephalin-containing peptides and an ~24-kDa intermediate present in human brain. Cathepsin V is present in human brain cortex and hippocampus where enkephalin and NPY are produced and is present in purified human neuropeptide secretory vesicles. Colocalization of cathepsin V with enkephalin and NPY in secretory vesicles of human neuroblastoma cells was illustrated by confocal microscopy. Furthermore, expression of cathepsin V with proNPY results in NPY production. These findings indicate the unique function of human cathepsin V for producing enkephalin and NPY neuropeptides required for neurotransmission in health and neurological diseases. Funkelstein L, Lu WD, Koch B, Mosier C, Toneff T, Taupenot L, O'Connor DT, Reinheckel T, Peters C, Hook V. Human cathepsin V protease participates in production of enkephalin and NPY neuropeptide neurotransmitters. *J Biol Chem*. 2012 May 4; 287(19): 15232-15241. Epub 2012 Mar 5.

Synaptic Underpinnings Of Altered Hippocampal Function In Glutaminase-Deficient Mice

During Maturation Glutaminase-deficient mice (GLS1 hets), with reduced glutamate recycling, have a focal reduction in hippocampal activity, mainly in CA1, and manifest behavioral and neurochemical phenotypes suggestive of schizophrenia resilience. To address the basis for the hippocampal hypoactivity, the authors examined synaptic plastic mechanisms and glutamate receptor expression. Although baseline synaptic strength was unaffected in Schaffer collateral inputs to CA1, they found that long-term potentiation was attenuated. In wild-type (WT) mice,

GLS1 gene expression was highest in the hippocampus and cortex, where it was reduced by about 50% in GLS1 hets. In other brain regions with lower WT GLS1 gene expression, there were no genotypic reductions. In adult GLS1 hets, NMDA receptor NR1 subunit gene expression was reduced, but not AMPA receptor GluR1 subunit gene expression. In contrast, juvenile GLS1 hets showed no reductions in NR1 gene expression. In concert with this, adult GLS1 hets showed a deficit in hippocampal-dependent contextual fear conditioning, whereas juvenile GLS1 hets did not. These alterations in glutamatergic synaptic function may partly explain the hippocampal hypoactivity seen in the GLS1 hets. The maturity-onset reduction in NR1 gene expression and in contextual learning supports the premise that glutaminase inhibition in adulthood should prove therapeutic in schizophrenia. Gaisler-Salomon I, Wang Y, Chuhma N, Zhang H, Golumbic YN, Mihali A, Arancio O, Sibille E, Rayport S. Synaptic underpinnings of altered hippocampal function in glutaminase-deficient mice during maturation. *Hippocampus*. 2012 May; 22(5): 1027-1039. doi: 10.1002/hipo.22014. Epub 2012 Mar 19.

Can Humanized Mice Reflect The Complex Pathobiology Of HIV-Associated Neurocognitive Disorders?

There is a rebirth of humanized mouse models in reflecting human immunodeficiency virus (HIV) pathobiology. This has allowed new investigations of viral diversity, immunity and developmental therapeutics. In the past, HIV infection and disease were, in part, mirrored in immune deficient mice reconstituted with human hematopoietic stem cells. What remained from early studies reflected the ability to mirror central nervous system (CNS) disease. As the wide spread use of combination antiretroviral therapies has changed the severity, but not prevalence, of HIV-associated neurocognitive disorders (HAND), mimicking such virus-induced CNS morbidities in humanized animals is essential for HIV/AIDS research activities. To this end, the authors now review the evidence for how and under what circumstances humanized mice may be utilized for studies of HIV-1 neuropathogenesis. Gorantla S, Gendelman HE, Poluektova LY. Can humanized mice reflect the complex pathobiology of HIV-associated neurocognitive disorders? *J Neuroimmune Pharmacol*. 2012 Jun; 7(2): 352-362. Epub 2012 Jan 7.

The Duration Of Nicotine Withdrawal-Associated Deficits In Contextual Fear Conditioning Parallels Changes In Hippocampal High Affinity Nicotinic Acetylcholine Receptor

Upregulation A predominant symptom of nicotine withdrawal is cognitive deficits, yet understanding of the neural basis for these deficits is limited. Withdrawal from chronic nicotine disrupts contextual learning in mice and this deficit is mediated by direct effects of nicotine in the hippocampus. Chronic nicotine treatment upregulates nicotinic acetylcholine receptors (nAChR); however, it is unknown whether upregulation is related to the observed withdrawal-induced cognitive deficits. If a relationship between altered learning and nAChR levels exists, changes in nAChR levels after cessation of nicotine treatment should match the duration of learning deficits. To test this hypothesis, mice were chronically administered 6.3mg/kg/day (freebase) nicotine for 12 days and trained in contextual fear conditioning on day 11 or between 1 to 16 days after withdrawal of treatment. Changes in [(125)I]-epibatidine binding at cytosine-sensitive and cytosine-resistant nAChRs and chronic nicotine-related changes in $\alpha 4$, $\alpha 7$, and $\beta 2$ nAChR subunit mRNA expression were assessed. Chronic nicotine had no behavioral effect but withdrawal produced deficits in contextual fear conditioning that lasted 4 days. Nicotine withdrawal did not disrupt cued fear conditioning. Chronic nicotine upregulated hippocampal cytosine-sensitive nAChR binding; upregulation continued after cessation of nicotine administration and the duration of upregulation during withdrawal paralleled the duration of behavioral changes. Changes in binding in cortex and cerebellum did not match behavioral changes. No changes in $\alpha 4$, $\alpha 7$, and $\beta 2$ subunit mRNA expression were seen with chronic nicotine. Thus, nicotine withdrawal-related deficits in contextual

learning are time-limited changes that are associated with temporal changes in upregulation of high-affinity nAChR binding. Gould TJ, Portugal GS, André JM, Tadman MP, Marks MJ, Kenney JW, Yildirim E, Adoff M. The duration of nicotine withdrawal-associated deficits in contextual fear conditioning parallels changes in hippocampal high affinity nicotinic acetylcholine receptor upregulation. *Neuropharmacology*. 2012 Apr; 62(5-6): 2118-2125. Epub 2012 Jan 21.

Low Concentrations Of Nicotine Differentially Desensitize Nicotinic Acetylcholine Receptors That Include $\alpha 5$ Or $\alpha 6$ Subunits and That Mediate Synaptosomal Neurotransmitter Release

Desensitization is a complex property of nicotinic acetylcholine receptors (nAChR). Several subtypes of nAChR have high sensitivity to nicotine and mediate effects of nicotine at concentrations found in blood of tobacco smokers. Desensitization of some of these receptor subtypes has been studied in model systems, however, other subtypes have been difficult to express heterologously in native forms. In addition, model systems may not have the same accessory molecules and post-translational modifications found in native populations. The authors have used wild-type and subunit null mutant mice to study desensitization properties of the high sensitivity $\alpha 4\beta 2$ -nAChRs including those that have $\alpha 5$ subunits at both GABAergic and dopaminergic nerve terminals. In addition, they have studied the desensitization of one subtype of $\alpha 6\beta 2$ -nAChRs at dopaminergic terminals using $\alpha 4$ subunit null mutant mice. Exposure to low nicotine concentrations, leads to rapid, but partial desensitization of activity mediated by these receptors. $\alpha 4\beta 2$ -nAChRs including $\alpha 5$ subunits show faster rates of recovery from desensitization than $\alpha 4\beta 2$ -nAChRs without $\alpha 5$. Inclusion of the $\alpha 5$ subunit significantly shifts the concentration response for desensitization to higher values, indicating that receptors with $\alpha 5$ subunits are less desensitized by a 10-min exposure to low concentrations of nicotine. Receptors with $\alpha 6$ subunits appear to desensitize to a lesser degree than those with $\alpha 4$ subunits, indicating that $\alpha 6\beta 2$ -nAChRs are somewhat resistant to desensitization by nicotine. These results highlight the importance of studying various receptor subtypes in native systems and how they may differentially respond to nicotine and to nicotinic drugs. Grady SR, Wageman CR, Patzlaff NE, Marks MJ. Low concentrations of nicotine differentially desensitize nicotinic acetylcholine receptors that include $\alpha 5$ or $\alpha 6$ subunits and that mediate synaptosomal neurotransmitter release. *Neuropharmacology*. 2012 Apr; 62(5-6): 1935-1943. Epub 2012 Jan 2.

Structure Of The Δ -Opioid Receptor Bound To Naltrindole The opioid receptor family comprises three members, the μ -, δ - and κ -opioid receptors, which respond to classical opioid alkaloids such as morphine and heroin as well as to endogenous peptide ligands like endorphins. They belong to the G-protein-coupled receptor (GPCR) superfamily, and are excellent therapeutic targets for pain control. The δ -opioid receptor (δ -OR) has a role in analgesia, as well as in other neurological functions that remain poorly understood. The structures of the μ -OR and κ -OR have recently been solved. Here the authors report the crystal structure of the mouse δ -OR, bound to the subtype-selective antagonist naltrindole. Together with the structures of the μ -OR and κ -OR, the δ -OR structure provides insights into conserved elements of opioid ligand recognition while also revealing structural features associated with ligand-subtype selectivity. The binding pocket of opioid receptors can be divided into two distinct regions. Whereas the lower part of this pocket is highly conserved among opioid receptors, the upper part contains divergent residues that confer subtype selectivity. This provides a structural explanation and validation for the 'message-address' model of opioid receptor pharmacology, in which distinct 'message' (efficacy) and 'address' (selectivity) determinants are contained within a single ligand. Comparison of the address region of the δ -OR with other GPCRs reveals that this structural organization may be a more general phenomenon, extending to other GPCR families as well. Granier S, Manglik A, Kruse AC, Kobilka

TS, Thian FS, Weis WI, Kobilka BK. Structure of the δ -opioid receptor bound to naltrindole. *Nature*. 2012 May 16; 485(7398): 400-404. doi: 10.1038/nature11111.

Spinal 12-Lipoxygenase-Derived Hepoxilin A3 Contributes To Inflammatory Hyperalgesia Via Activation Of TRPV1 And TRPA1 Receptors

Peripheral inflammation initiates changes in spinal nociceptive processing leading to hyperalgesia. Previously, the authors demonstrated that among 102 lipid species detected by LC-MS/MS analysis in rat spinal cord, the most notable increases that occur after intraplantar carrageenan are metabolites of 12-lipoxygenases (12-LOX), particularly hepoxilins (HXA(3) and HXB(3)). Thus, they examined involvement of spinal LOX enzymes in inflammatory hyperalgesia. In the current work, they found that intrathecal (IT) delivery of the LOX inhibitor nordihydroguaiaretic acid prevented the carrageenan-evoked increase in spinal HXB(3) at doses that attenuated the associated hyperalgesia. Furthermore, IT delivery of inhibitors targeting 12-LOX (CDC, Baicalein), but not 5-LOX (Zileuton) dose-dependently attenuated tactile allodynia. Similarly, IT delivery of 12-LOX metabolites of arachidonic acid 12(S)-HpETE, 12(S)-HETE, HXA(3), or HXB(3) evoked profound, persistent tactile allodynia, but 12(S)-HpETE and HXA(3) produced relatively modest, transient heat hyperalgesia. The pronociceptive effect of HXA(3) correlated with enhanced release of Substance P from primary sensory afferents. Importantly, HXA(3) triggered sustained mobilization of calcium in cells stably overexpressing TRPV1 or TRPA1 receptors and in acutely dissociated rodent sensory neurons. Constitutive deletion or antagonists of TRPV1 (AMG9810) or TRPA1 (HC030031) attenuated this action. Furthermore, pretreatment with antihyperalgesic doses of AMG9810 or HC030031 reduced spinal HXA(3)-evoked allodynia. These data indicate that spinal HXA(3) is increased by peripheral inflammation and promotes initiation of facilitated nociceptive processing through direct activation of TRPV1 and TRPA1 at central terminals. Gregus AM, Doolen S, Dumlao DS, Buczynski MW, Takasusuki T, Fitzsimmons BL, Hua XY, Taylor BK, Dennis EA, Yaksh TL. Spinal 12-lipoxygenase-derived hepoxilin A3 contributes to inflammatory hyperalgesia via activation of TRPV1 and TRPA1 receptors. *Proc Natl Acad Sci U S A*. 2012 Apr 24; 109(17): 6721-6726. Epub 2012 Apr 9.

Dysregulation Of D₂-Mediated Dopamine Transmission In Monkeys After Chronic Escalating Methamphetamine Exposure

Compulsive drug-seeking and drug-taking are important substance-abuse behaviors that have been linked to alterations in dopaminergic neurotransmission and to impaired inhibitory control. Evidence supports the notions that abnormal D₂ receptor-mediated dopamine transmission and inhibitory control may be heritable risk factors for addictions, and that they also reflect drug-induced neuroadaptations. To provide a mechanistic explanation for the drug-induced emergence of inhibitory-control deficits, this study examined how a chronic, escalating-dose regimen of methamphetamine administration affected dopaminergic neurochemistry and cognition in monkeys. Dopamine D₂-like receptor and dopamine transporter (DAT) availability and reversal-learning performance were measured before and after exposure to methamphetamine (or saline), and brain dopamine levels were assayed at the conclusion of the study. Exposure to methamphetamine reduced dopamine D₂-like receptor and DAT availability and produced transient, selective impairments in the reversal of a stimulus-outcome association. Furthermore, individual differences in the change in D₂-like receptor availability in the striatum were related to the change in response to positive feedback. These data provide evidence that chronic, escalating-dose methamphetamine administration alters the dopamine system in a manner similar to that observed in methamphetamine-dependent humans. They also implicate alterations in positive-feedback sensitivity associated with D₂-like receptor dysfunction as the mechanism by which inhibitory control deficits emerge in stimulant-dependent individuals. Finally, a significant degree of

neurochemical and behavioral variation in response to methamphetamine was detected, indicating that individual differences affect the degree to which drugs of abuse alter these processes. Identification of these factors ultimately may assist in the development of individualized treatments for substance dependence. Groman SM, Lee B, Seu E, James AS, Feiler K, Mandelkern MA, London ED, Jentsch JD. Dysregulation of D₂-mediated dopamine transmission in monkeys after chronic escalating methamphetamine exposure. *J Neurosci*. 2012 Apr 25; 32(17): 5843-5852.

Cognitive Control and The Dopamine D₂-Like Receptor: A Dimensional Understanding Of Addiction

The phenotypic complexity of psychiatric conditions is revealed by the dimensional nature of these disorders, which consist of multiple behavioral, affective, and cognitive dysfunctions that can result in substantial psychosocial impairment. The high degree of heterogeneity in symptomatology and comorbidity suggests that simple categorical diagnoses of "affected" or "unaffected" may fail to capture the true characteristics of the disorder in a manner relevant to individualized treatment. A particular dimension of interest is cognitive control ability because impairments in the capacity to control thoughts, feelings, and actions are key to several psychiatric disorders. Here, the authors describe evidence suggesting that cognitive control over behavior is a crucial dimension of function relevant to addictions. Moreover, dopamine (DA) D(2)-receptor transmission is increasingly being identified as a point of convergence for these behavioral and cognitive processes. Consequently, they argue that measures of cognitive control and D(2) DA receptor function may be particularly informative markers of individual function and treatment response in addictions. Groman SM, Jentsch JD. Cognitive control and the dopamine D₂-like receptor: a dimensional understanding of addiction. *Depress Anxiety*. 2012 Apr; 29(4): 295-306. doi: 10.1002/da.20897. Epub 2011 Dec 6.

Differences In The Locomotor-Activating Effects Of Indirect Serotonin Agonists In Habituated and Non-Habituated Rats

The indirect serotonin (5-HT) agonist 3,4-methylenedioxymethamphetamine (MDMA) produces a distinct behavioral profile in rats consisting of locomotor hyperactivity, thigmotaxis, and decreased exploration. The indirect 5-HT agonist α -ethyltryptamine (AET) produces a similar behavioral profile. Using the Behavioral Pattern Monitor (BPM), the present investigation examined whether the effects of MDMA and AET are dependent on the novelty of the testing environment. These experiments were conducted in Sprague-Dawley rats housed on a reversed light cycle and tested during the dark phase of the light/dark cycle. The authors found that racemic MDMA (RS-MDMA; 3 mg/kg, SC) increased locomotor activity in rats tested in novel BPM chambers, but had no effect on locomotor activity in rats habituated to the BPM chambers immediately prior to testing. Likewise, AET (5 mg/kg, SC) increased locomotor activity in non-habituated animals but not in animals habituated to the test chambers. These results were unexpected because previous reports indicate that MDMA has robust locomotor-activating effects in habituated animals. To further examine the influence of habituation on MDMA-induced locomotor activity, the authors conducted parametric studies with S-(+)-MDMA (the more active enantiomer) in habituated and non-habituated rats housed on a standard or reversed light cycle. Light cycle was included as a variable due to reported differences in sensitivity to serotonergic ligands during the dark and light phases. In confirmation of the authors' initial studies, rats tested during the dark phase and habituated to the BPM did not show an S-(+)-MDMA (3 mg/kg, SC)-induced increase in locomotor activity, whereas non-habituated rats did. By contrast, in rats tested during the light phase, S-(+)-MDMA increased locomotor activity in both non-habituated and habituated rats, although the response in habituated animals was attenuated. The finding that habituation and light cycle interact to influence MDMA- and AET-induced hyperactivity demonstrates that there are previously unrecognized complexities associated with the behavioral

effects of these drugs. Halberstadt AL, Buell MR, Price DL, Geyer MA. Differences in the locomotor-activating effects of indirect serotonin agonists in habituated and non-habituated rats. *Pharmacol Biochem Behav.* 2012 Jul; 102(1): 88-94. Epub 2012 Mar 31.

Subunit-Selective Allosteric Inhibition Of Glycine Binding To NMDA Receptors NMDA receptors are ligand-gated ion channels that mediate excitatory neurotransmission in the brain and are involved in numerous neuropathological conditions. NMDA receptors are activated upon simultaneous binding of coagonists glycine and glutamate to the GluN1 and GluN2 subunits, respectively. Subunit-selective modulation of NMDA receptor function by ligand binding to modulatory sites distinct from the agonist binding sites could allow pharmacological intervention with therapeutically beneficial mechanisms. Here, the authors show the mechanism of action for 3-chloro-4-fluoro-N-[(4-[(2-(phenylcarbonyl)hydrazino)carbonyl]phenyl)methyl]-benzenesulfonamide (TCN-201), a new GluN1/GluN2A-selective NMDA receptor antagonist whose inhibition can be surmounted by glycine. Electrophysiological recordings from chimeric and mutant rat NMDA receptors suggest that TCN-201 binds to a novel allosteric site located at the dimer interface between the GluN1 and GluN2 agonist binding domains. Furthermore, the authors demonstrate that occupancy of this site by TCN-201 inhibits NMDA receptor function by reducing glycine potency. TCN-201 is therefore a negative allosteric modulator of glycine binding. Hansen KB, Ogden KK, Traynelis SF. Subunit-selective allosteric inhibition of glycine binding to NMDA receptors. *J Neurosci.* 2012 May 2; 32(18): 6197-6208.

Intense Exercise Increases Circulating Endocannabinoid and BDNF Levels In Humans--Possible Implications For Reward and Depression The endocannabinoid system is known to have positive effects on depression partly through its actions on neurotrophins, such as Brain-Derived Neurotrophic Factor (BDNF). As BDNF is also considered the major candidate molecule for exercise-induced brain plasticity, the authors hypothesized that the endocannabinoid system represents a crucial signaling system mediating the beneficial antidepressant effects of exercise. Here they investigated, in 11 healthy trained male cyclists, the effects of an intense exercise (60 min at 55% followed by 30 min at 75% W(max)) on plasma levels of endocannabinoids (anandamide, AEA and 2-arachidonoylglycerol, 2-AG) and their possible link with serum BDNF. AEA levels increased during exercise and the 15 min recovery ($P < 0.001$), whereas 2-AG concentrations remained stable. BDNF levels increased significantly during exercise and then decreased during the 15 min of recovery ($P < 0.01$). Noteworthy, AEA and BDNF concentrations were positively correlated at the end of exercise and after the 15 min recovery ($r > 0.66$, $P < 0.05$), suggesting that AEA increment during exercise might be one of the factors involved in exercise-induced increase in peripheral BDNF levels and that AEA high levels during recovery might delay the return of BDNF to basal levels. AEA production during exercise might be triggered by cortisol since the authors found positive correlations between these two compounds and because corticosteroids are known to stimulate endocannabinoid biosynthesis. These findings provide evidence in humans that acute exercise represents a physiological stressor able to increase peripheral levels of AEA and that BDNF might be a mechanism by which AEA influences the neuroplastic and antidepressant effects of exercise. Heyman E, Gamelin FX, Goekint M, Piscitelli F, Roelands B, Leclair E, Di Marzo V, Meeusen R. Intense exercise increases circulating endocannabinoid and BDNF levels in humans--possible implications for reward and depression. *Psychoneuroendocrinology.* 2012 Jun; 37(6): 844-851. Epub 2011 Oct 24.

Nicotinic Neuromodulation In Auditory Cortex Requires MAPK Activation In Thalamocortical and Intracortical Circuits

Activation of nicotinic acetylcholine receptors (nAChRs) by systemic nicotine enhances sensory-cognitive function and sensory-evoked cortical responses. Although nAChRs mediate fast neurotransmission at many synapses in the nervous system, nicotinic regulation of cortical processing is neuromodulatory. To explore potential mechanisms of nicotinic neuromodulation, the authors examined whether intracellular signal transduction involving mitogen-activated protein kinase (MAPK) contributes to regulation of tone-evoked responses in primary auditory cortex (A1) in the mouse. Systemic nicotine enhanced characteristic frequency (CF) tone-evoked current-source density (CSD) profiles in A1, including the shortest-latency (presumed thalamocortical) current sink in layer 4 and longer-latency (presumed intracortical) sinks in layers 2-4, by increasing response amplitudes and decreasing response latencies. Microinjection of the MAPK kinase (MEK) inhibitor U0126 into the thalamus, targeting the auditory thalamocortical pathway, blocked the effect of nicotine on the initial (thalamocortical) CSD component but did not block enhancement of longer-latency (intracortical) responses. Conversely, microinjection of U0126 into supragranular layers of A1 blocked nicotine's effect on intracortical, but not thalamocortical, CSD components. Simultaneously with enhancement of CF-evoked responses, responses to spectrally distant (nonCF) stimuli were reduced, implying nicotinic "sharpening" of frequency receptive fields, an effect also blocked by MEK inhibition. Consistent with these physiological results, acoustic stimulation with nicotine produced immunolabel for activated MAPK in A1, primarily in layer 2/3 cell bodies. Immunolabel was blocked by intracortical microinjection of the nAChR antagonist dihydro- β -erythroidine, but not methyllycaconitine, implicating $\alpha 4\beta 2^*$, but not $\alpha 7$, nAChRs. Thus activation of MAPK in functionally distinct forebrain circuits--thalamocortical, local intracortical, and long-range intracortical--underlies nicotinic neuromodulation of A1. Intskirveli I, Metherate R. Nicotinic neuromodulation in auditory cortex requires MAPK activation in thalamocortical and intracortical circuits. *J Neurophysiol.* 2012 May; 107(10): 2782-2793. Epub 2012 Feb 22.

A Convergent Functional Architecture Of The Insula Emerges Across Imaging Modalities

Empirical evidence increasingly supports the hypothesis that patterns of intrinsic functional connectivity (iFC) are sculpted by a history of evoked coactivation within distinct neuronal networks. This, together with evidence of strong correspondence among the networks defined by iFC and those delineated using a variety of other neuroimaging techniques, suggests a fundamental brain architecture detectable across multiple functional and structural imaging modalities. Here, the authors leverage this insight to examine the functional organization of the human insula. They parcellated the insula on the basis of three distinct neuroimaging modalities - task-evoked coactivation, intrinsic (i.e., task-independent) functional connectivity, and gray matter structural covariance. Clustering of these three different covariance-based measures revealed a convergent elemental organization of the insula that likely reflects a fundamental brain architecture governing both brain structure and function at multiple spatial scales. While not constrained to be hierarchical, the authors' parcellation revealed a pseudo-hierarchical, multiscale organization that was consistent with previous clustering and meta-analytic studies of the insula. Finally, meta-analytic examination of the cognitive and behavioral domains associated with each of the insular clusters obtained elucidated the broad functional dissociations likely underlying the topography observed. To facilitate future investigations of insula function across healthy and pathological states, the insular parcels have been made freely available for download via http://fcon_1000.projects.nitrc.org, along with the analytic scripts used to perform the parcellations. Kelly C, Toro R, Di Martino A, Cox CL, Bellec P, Castellanos FX, Milham MP. A convergent functional architecture of the insula emerges across imaging modalities. *Neuroimage.* 2012 Jul 16; 61(4): 1129-1142. Epub 2012 Mar 13.

Simultaneous Measurement Of Extracellular Dopamine and Dopamine Transporter Occupancy By Cocaine Analogs In Squirrel Monkeys

Several classes of drugs bind to the dopamine transporter (DAT) with high affinity, but some are weaker positive reinforcers than cocaine, suggesting that affinity for and occupancy of the DAT is not the only determinant of a drug's reinforcing effectiveness. Other factors such as the rate of onset have been positively and strongly correlated with the reinforcing effects of DAT inhibitors in nonhuman primates. In the current studies, the authors examined the effects of acute systemic administration of cocaine and three cocaine analogs (RTI-150, RTI-177, and RTI-366) on binding to DAT in squirrel monkey brain using positron emission tomography (PET) neuroimaging. During the PET scan, the authors also measured drug effects on dopamine (DA) levels in the caudate using in vivo microdialysis. In general, their results suggest a lack of concordance between drug occupancy at DAT and changes in DA levels. These studies also indicate that acute cocaine administration decreases the availability of plasma membrane DAT for binding, even after cocaine is no longer blocking DA uptake as evidenced by a return to basal DA levels. Kimmel HL, Nye JA, Voll R, Mun J, Stehouwer J, Goodman MM, Votaw JR, Carroll FI, Howell LL. Simultaneous measurement of extracellular dopamine and dopamine transporter occupancy by cocaine analogs in squirrel monkeys. *Synapse*. 2012 Jun; 66(6): 501-508. doi: 10.1002/syn.21536. Epub 2012 Mar 16.

Cocaine Decreases Expression Of Neurogranin Via Alterations In Thyroid Receptor/Retinoid X Receptor Signaling

Mounting evidence suggests a potential link between cocaine abuse, disruptions in hypothalamic-pituitary-thyroid axis signaling, and neuroplasticity, but molecular mechanisms remain unknown. Neurogranin (Ng) is a gene containing a thyroid hormone-responsive element within its first intron that is involved in synaptic plasticity. Transcriptional activation requires heterodimerization of thyroid hormone receptor (TR) and retinoid X receptor (RXR) bound by their respective ligands, tri-iodothyronine and 9-cis-retinoic acid (9-cis-RA), and subsequent binding of this complex to the thyroid hormone-responsive element of the Ng gene. In this study, the effects of chronic cocaine abuse on Ng expression in euthyroid and hypothyroid mice were assessed. In cocaine-treated mice, decreased Ng expression was observed in the absence of changes in levels of thyroid hormones or other hypothalamic-pituitary-thyroid signaling factors. Therefore, the authors hypothesized that cocaine decreases Ng expression via alterations in 9-cis-RA availability and TR/RXR signaling. In support of this hypothesis, RXR- γ was significantly decreased in brains of cocaine-treated mice while CYP26A1, the main enzyme responsible for neuronal RA degradation, was significantly increased. Results from this study provide the first evidence for a direct effect of cocaine abuse on TR/RXR signaling, RA metabolism, and transcriptional regulation of Ng, a gene essential for adult neuroplasticity. Kovalevich J, Corley G, Yen W, Kim J, Rawls SM, Langford D. Cocaine decreases expression of neurogranin via alterations in thyroid receptor/retinoid X receptor signaling. *J Neurochem*. 2012 Apr; 121(2): 302-313. doi: 10.1111/j.1471-4159.2012.07678.x. Epub 2012 Mar 13.

Noninvasive Detection Of Neural Progenitor Cells In Living Brains By MRI

The presence of pericytes in brain regions undergoing repair is evident of the recruitment of bone marrow-derived multipotent regenerative cells to the neurovascular unit during angiogenesis. At present, post mortem sampling is the only way to identify them. Therefore, such cell typing is inadequate for preserving neural progenitor cells for any meaningful stem cell therapy. The authors aimed to target cerebral pericytes in vivo using dual gene transcript-targeted MRI (GT-tMRI) in male C57black6 mice after a 60-min bilateral carotid artery occlusion (BCAO). They attached superparamagnetic iron oxide nanoparticles (SPIONs) to phosphorothioate-modified micro-DNA that targets actin or nestin mRNA. Because BCAO compromises the blood-brain barrier (BBB) and induces expression

of α -smooth muscle (α SM)-actin and nestin antigens by pericytes in new vessels, the authors delivered pericyte-specific magnetic resonance contrast agents (SPION-actin or SPION-nestin at 4 mg Fe/kg) by i.p. injection to C57black6 mice that had experienced BCAA. They demonstrated that the surge in cerebral iron content by inductively coupled plasma-mass spectrometry matched the increase in the frequency of relaxivity. They also found that SPION-nestin was colocalized in α SM-actin- and nestin-expressing pericytes in BCAA-treated C57black6 or transgenic mice [B6.Cg-Tg(CAG-mRFP1) 1F1Hadj/J, expressing red fluorescent protein by actin promoter]. They identified pericytes in the repair patch in living brains after BCAA with a voxel size of 0.03 mm³. The presence of electron-dense nanoparticles in vascular pericytes in the region of BBB injury led us to draw the conclusion that GT-tMRI can noninvasively reveal neural progenitor cells during vascularization. Liu CH, Ren JQ, You Z, Yang J, Liu CM, Uppal R, Liu PK. Noninvasive detection of neural progenitor cells in living brains by MRI. *FASEB J.* 2012 Apr; 26(4): 1652-1662. Epub 2011 Dec 23.

Semisynthetic Neoclerodanes As Kappa Opioid Receptor Probes Modification of the furan ring of salvinin A (1), the main active component of *Salvia divinorum*, has resulted in novel neoclerodane diterpenes with opioid receptor affinity and activity. Conversion of the furan ring to an aldehyde at the C-12 position (5) has allowed for the synthesis of analogues with new carbon-carbon bonds at that position. Previous methods for forming these bonds, such as Grignard and Stille conditions, have met with limited success. The authors report a palladium catalyzed Liebeskind-Srogl cross-coupling reaction of a thioester and a boronic acid that occurs at neutral pH and ambient temperature to produce ketone analogs at C-12. To the best of the authors' knowledge, this is the first reported usage of the Liebeskind-Srogl reaction to diversify a natural product scaffold. They also describe a one-step protocol for the conversion of 1 to 12-epi-1 (3) through microwave irradiation. Previously, this synthetically challenging process has required multiple steps. Additionally, the authors report in this study that alkene 9 and aromatic analogues 12, 19, 23, 25, and 26 were discovered to retain affinity and selectivity at kappa opioid receptors (KOP). Finally, the authors report that the furan-2-yl analog of 1 (31) has similar affinity to 1. Collectively, these findings suggest that different aromatic groups appended directly to the decalin core may be well tolerated by KOP receptors, and may generate further ligands with affinity and activity at KOP receptors. Lovell KM, Vasiljevik T, Araya JJ, Lozama A, Prevatt-Smith KM, Day VW, Dersch CM, Rothman RB, Butelman ER, Kreek MJ, Prisinzano TE. Semisynthetic neoclerodanes as kappa opioid receptor probes. *Bioorg Med Chem.* 2012 May 1; 20(9): 3100-3110. Epub 2012 Mar 1.

SHAPE-Directed Discovery Of Potent shRNA Inhibitors Of HIV-1 The RNA interference (RNAi) pathway can be exploited using short hairpin RNAs (shRNAs) to durably inactivate pathogenic genes. Prediction of optimal target sites is notoriously inaccurate and current approaches applied to HIV-1 show weak correlations with virus inhibition. In contrast, using a high-content model for disrupting pre-existing intramolecular structure in the HIV-1 RNA, as achievable using high-resolution SHAPE (selective 2'-hydroxyl acylation analyzed by primer extension) chemical probing information, the authors discovered strong correlations between inhibition of HIV-1 production in a quantitative cell-based assay and very simple thermodynamic features in the target RNA. Strongest inhibition occurs at RNA target sites that both have an accessible "seed region" and, unexpectedly, are structurally accessible in a newly identified downstream flanking sequence. The authors then used these simple rules to create a new set of shRNAs and achieved inhibition of HIV-1 production of 90% or greater for up to 82% of designed shRNAs. These shRNAs inhibit HIV-1 replication in therapy-relevant T cells and show no or low cytotoxicity. The remarkable success of this straightforward SHAPE-based approach emphasizes that RNAi is governed, in

significant part, by very simple, predictable rules reflecting the underlying RNA structure and illustrates principles likely to prove broadly useful in understanding transcriptome-scale biological recognition and therapeutics involving RNA. Low JT, Knoepfel SA, Watts JM, ter Brake O, Berkhout B, Weeks KM. SHAPE-directed discovery of potent shRNA inhibitors of HIV-1. *Mol Ther.* 2012 Apr; 20(4): 820-828. doi: 10.1038/mt.2011.299. Epub 2012 Feb 7.

Simultaneous Oxytocin and Arg-Vasopressin Measurements In Microdialysates Using Capillary Liquid Chromatography-Mass Spectrometry

Oxytocin (OXT) and arg-vasopressin (AVP) are nonapeptides with many important functions both peripherally and centrally. Intracerebral microdialysis has helped characterize their importance in regulating complex social and emotional processes. Radioimmunoassay is the most commonly used analytical method for OXT and AVP measurements in microdialysates. These measurements have several well-known issues including single peptide per assay limit, possible cross-reactivity between structurally related peptides, and laborious sample preparation with radioactive materials. Here the authors demonstrate the use of capillary LC-MS(3) for measuring OXT and AVP simultaneously in dialysates at a 10min sampling frequency. Microdialysate samples required no preparation and instrumentation was commercially available. Microdialysis probes made with polyacrylonitrile membranes were suitable for high level recovery of the peptides in vitro and in vivo. Responses were linear from 1 to 100pM. Matrix effect was assessed by standard addition experiments and by comparing signal intensities of OXT and AVP standards made in aCSF or dialysate. It was determined that the online washing step used on this setup was adequate for removing contaminants which interfere with electrospray ionization efficiency. In vivo, both peptides were stimulated by high K(+) (75mM) aCSF perfusion in the paraventricular nucleus (PVN). Also, a systemic injection of high Na(+) (2M) caused a rapid and transient increase in PVN OXT while AVP increased only after 1.5h. These findings suggest that capillary LC-MS(3) is a straightforward method for monitoring OXT and AVP simultaneously from complex samples such as dialysates. Mabrouk OS, Kennedy RT. Simultaneous oxytocin and arg-vasopressin measurements in microdialysates using capillary liquid chromatography-mass spectrometry. *J Neurosci Methods.* 2012 Jun 16; 209(1):127-133. [Epub ahead of print].

Protein Interacting With C Kinase 1 (PICK1) Reduces Reinsertion Rates Of Interaction Partners Sorted To Rab11-Dependent Slow Recycling Pathway

The scaffolding protein PICK1 (protein interacting with C kinase 1) contains an N-terminal PSD-95/Discs large/ZO-1 (PDZ) domain and a central lipid-binding Bin/amphiphysin/Rvs (BAR) domain. PICK1 is thought to regulate trafficking of its PDZ binding partners but different and even opposing functions have been suggested. Here, the authors apply ELISA-based assays and confocal microscopy in HEK293 cells with inducible PICK1 expression to assess in an isolated system the ability of PICK1 to regulate trafficking of natural and engineered PDZ binding partners. The dopamine transporter (DAT), which primarily sorts to degradation upon internalization, did not form perinuclear clusters with PICK1, and PICK1 did not affect DAT internalization/recycling. However, transfer of the PICK1-binding DAT C terminus to the $\beta(2)$ -adrenergic receptor, which sorts to recycling upon internalization, led to formation of PICK1 co-clusters in Rab11-positive compartments. Furthermore, PICK1 inhibited Rab11-mediated recycling of the receptor in a BAR and PDZ domain-dependent manner. In contrast, transfer of the DAT C terminus to the δ -opioid receptor, which sorts to degradation, did not result in PICK1 co-clusters or any change in internalization/recycling. Further support for a role of PICK1 determined by its PDZ cargo was obtained for the PICK1 interaction partner prolactin-releasing peptide receptor (GPR10). GPR10 co-localized with Rab11 and clustered with PICK1 upon constitutive internalization but co-localized with the late endosomal marker Rab7 and did not cluster with PICK1 upon agonist-induced internalization.

These data suggest a selective role of PICK1 in clustering and reducing the recycling rates of PDZ domain binding partners sorted to the Rab11-dependent recycling pathway. Madsen KL, Thorsen TS, Rahbek-Clemmensen T, Eriksen J, Gether U. Protein interacting with C kinase 1 (PICK1) reduces reinsertion rates of interaction partners sorted to Rab11-dependent slow recycling pathway. *J Biol Chem.* 2012 Apr 6; 287(15): 12293-12308. Epub 2012 Feb 2.

Differences In The Characteristics Of Tolerance To μ -Opioid Receptor Agonists In The Colon From Wild Type And β -Arrestin2 Knockout Mice

Drawbacks to opioid use include development of analgesic tolerance and persistent constipation. The authors previously reported that tolerance to morphine develops upon repeated exposure in the isolated ileum but not the isolated colon. The cellular mechanisms of antinociceptive tolerance vary among μ -opioid receptor agonists. In this study, the authors assess β -arrestin2 deletion on the development of tolerance to different opioids in ileum and colon circular muscle. Tolerance was determined by assessing the ability of repeated in-vitro opioid exposure to induce contraction of the circular muscle from C57BL/6 wild type (WT) and β -arrestin2 knockout (KO) mice. Repeated exposure every 30 min with in-between washes resulted in tolerance to all agonists in the ileum of both WT and KO mice. However, in the colon of WT mice, comparison of the contractions between the 4th exposure and 1st response was similar to DAMGO ($100 \pm 10\%$; N=5) but reduced to fentanyl ($62 \pm 13\%$; N=8) and etorphine ($38 \pm 4\%$; N=7) indicative of tolerance to fentanyl and etorphine but not DAMGO. In contrast, all agonists produced tolerance in the colon of KO: DAMGO response at the 4th exposure decreased to $52 \pm 10\%$ (N=5), fentanyl to $20 \pm 5\%$ (N=6) and etorphine $33 \pm 7\%$ (N=6). Differences in tolerance among opioid agonists in the colon suggest ligand bias. The deletion of β -arrestin2 in colon appears to be necessary for tolerance to DAMGO but not fentanyl or etorphine. β -arrestin2 potentially represents an important target for treating opioid-induced bowel dysfunction and warrants further exploration of its ligand bias. Maguma HT, Dewey WL, Akbarali HI. Differences in the characteristics of tolerance to μ -opioid receptor agonists in the colon from wild type and β -arrestin2 knockout mice. *Eur J Pharmacol.* 2012 Jun 15; 685(1-3): 133-140. Epub 2012 Apr 11.

Crystal Structure Of The μ -Opioid Receptor Bound To A Morphinan Antagonist Opium is one of the world's oldest drugs, and its derivatives morphine and codeine are among the most used clinical drugs to relieve severe pain. These prototypical opioids produce analgesia as well as many undesirable side effects (sedation, apnoea and dependence) by binding to and activating the G-protein-coupled μ -opioid receptor (μ -OR) in the central nervous system. Here the authors describe the 2.8 Å crystal structure of the mouse μ -OR in complex with an irreversible morphinan antagonist. Compared to the buried binding pocket observed in most G-protein-coupled receptors published so far, the morphinan ligand binds deeply within a large solvent-exposed pocket. Of particular interest, the μ -OR crystallizes as a two-fold symmetrical dimer through a four-helix bundle motif formed by transmembrane segments 5 and 6. These high-resolution insights into opioid receptor structure will enable the application of structure-based approaches to develop better drugs for the management of pain and addiction. Manglik A, Kruse AC, Kobilka TS, Thian FS, Mathiesen JM, Sunahara RK, Pardo L, Weis WI, Kobilka BK, Granier S. Crystal structure of the μ -opioid receptor bound to a morphinan antagonist. *Nature.* 2012 Mar 21; 485(7398): 321-326. doi: 10.1038/nature10954.

Effects Of Serotonin 2C Receptor Agonists On The Behavioral and Neurochemical Effects Of Cocaine In Squirrel Monkeys

Accumulating evidence indicates that the serotonin system modulates the behavioral and neurochemical effects of cocaine, but the receptor subtypes mediating these effects remain unknown. Recent studies have demonstrated that pharmacological activation of the serotonin 2C receptor (5-HT(2C)R) attenuates the behavioral and neurochemical effects of

cocaine in rodents, but such compounds have not been systematically evaluated in nonhuman primates. The present experiments sought to determine the impact of pretreatment with the preferential 5-HT(2C)R agonist m-chlorophenylpiperazine (mCPP) and the selective 5-HT(2C)R agonist Ro 60-0175 [$(\alpha$ -S)-6-chloro-5-fluoro- α -methyl-1H-indole-1-ethanamine fumarate] on the behavioral and neurochemical effects of cocaine in squirrel monkeys. In subjects trained to lever-press according to a 300-s fixed-interval schedule of stimulus termination, pretreatment with either 5-HT(2C)R agonist dose-dependently and insurmountably attenuated the behavioral stimulant effects of cocaine. In subjects trained to self-administer cocaine, both compounds dose-dependently and insurmountably attenuated cocaine-induced reinstatement of previously extinguished responding in an antagonist-reversible manner, and the selective agonist Ro 60-0175 also attenuated the reinforcing effects of cocaine during ongoing cocaine self-administration. It is noteworthy that the selective agonist Ro 60-0175 exhibited behavioral specificity because it did not significantly alter nondrug-maintained responding. Finally, in vivo microdialysis studies revealed that pretreatment with Ro 60-0175 caused a reduction of cocaine-induced dopamine increases within the nucleus accumbens, but not the caudate nucleus. These results suggest that 5-HT(2C)R agonists functionally antagonize the behavioral effects of cocaine in nonhuman primates, possibly via a selective modulation of cocaine-induced dopamine increases within the mesolimbic dopamine system and may therefore represent a novel class of pharmacotherapeutics for the treatment of cocaine abuse. Manovich DF, Kimmel HL, Howell LL. Effects of serotonin 2C receptor agonists on the behavioral and neurochemical effects of cocaine in squirrel monkeys. *J Pharmacol Exp Ther.* 2012 May; 341(2): 424-434. Epub 2012 Feb 10.

Rimonabant Abolishes Sensitivity To Workload Changes In A Progressive Ratio Procedure

Despite its propensity to increase motivation for food consumption, marijuana use in humans has been associated with "amotivational syndrome." This "amotivational syndrome" can be characterized by a reduction in response persistence in tasks requiring sustained, but not maximal, effort. To examine this hypothesis, dose-effect functions for THC (0.03-10 mg/kg) and rimonabant (0.1-10 mg/kg) were first determined under a time-constrained PR 5 schedule. During the second phase of the study, doses of THC and rimonabant that did not affect the responses/total reinforced responses were chosen for further evaluation in a series of PR schedules with step sizes of PR 3, PR 5, PR 10, and PR exponential. THC and rimonabant produced decreases in responses per reinforcer, and response rate when behavior was maintained on a PR 5. Rimonabant also decreased session length. During the PR step size manipulation phase, rimonabant decreased responses/total reinforced responses, response rate, and session length, whereas THC only decreased response rate. These results are consistent with previous literature demonstrating that rimonabant decreases motivation for food both in cases where it is earned, as well as under free-feeding conditions, whereas the effects of cannabinoid agonists such as THC on responding for food exhibit greater dependence upon motivational and non-motivational factors, including workload and duration of the task. Marusich JA, Wiley JL. Rimonabant abolishes sensitivity to workload changes in a progressive ratio procedure. *Pharmacol Biochem Behav.* 2012 Jun; 101(4): 575-580. Epub 2012 Mar 9.

Leishmania Induces Survival, Proliferation and Elevated Cellular dNTP Levels In Human Monocytes Promoting Acceleration Of HIV Co-Infection

Leishmaniasis is a parasitic disease that is widely prevalent in many tropical and sub-tropical regions of the world. Infection with *Leishmania* has been recognized to induce a striking acceleration of Human Immunodeficiency Virus Type 1 (HIV-1) infection in coinfecting individuals through as yet incompletely understood mechanisms. Cells of the monocyte/macrophage lineage are the predominant cell types coinfecting

by both pathogens. Monocytes and macrophages contain extremely low levels of deoxynucleoside triphosphates (dNTPs) due to their lack of cell cycling and S phase, where dNTP biosynthesis is specifically activated. Lentiviruses, such as HIV-1, are unique among retroviruses in their ability to replicate in these non-dividing cells due, at least in part, to their highly efficient reverse transcriptase (RT). Nonetheless, viral replication progresses more efficiently in the setting of higher intracellular dNTP concentrations related to enhanced enzyme kinetics of the viral RT. In the present study, in vitro infection of CD14⁺ peripheral blood-derived human monocytes with *Leishmania major* was found to induce differentiation, marked elevation of cellular p53R2 ribonucleotide reductase subunit and R2 subunit expression. The R2 subunit is restricted to the S phase of the cell cycle. The authors' dNTP assay demonstrated significant elevation of intracellular monocyte-derived macrophages (MDMs) dNTP concentrations in *Leishmania*-infected cell populations as compared to control cells. Infection of *Leishmania*-maturated MDMs with a pseudotyped GFP expressing HIV-1 resulted in increased numbers of GFP⁺ cells in the *Leishmania*-maturated MDMs as compared to control cells. Interestingly, a sub-population of *Leishmania*-maturated MDMs was found to have re-entered the cell cycle, as demonstrated by BrdU labeling. In conclusion, *Leishmania* infection of primary human monocytes promotes the induction of an S phase environment and elevated dNTP levels with notable elevation of HIV-1 expression in the setting of coinfection. Mock DJ, Hollenbaugh JA, Daddacha W, Overstreet MG, Lazarski CA, Fowell DJ, Kim B. *Leishmania* induces survival, proliferation and elevated cellular dNTP levels in human monocytes promoting acceleration of HIV co-infection. PLoS Pathog. 2012 Apr; 8(4): e1002635. Epub 2012 Apr 5.

The Activation Of The Cannabinoid Receptor Type 2 Reduces Neutrophilic Protease-Mediated Vulnerability In Atherosclerotic Plaques

The activation of cannabinoid receptor type 2 (CB(2))-mediated pathways might represent a promising anti-atherosclerotic treatment. Here, the authors investigated the expression of the endocannabinoid system in human carotid plaques and the impact of CB(2) pharmacological activation on markers of plaque vulnerability in vivo and in vitro. The study was conducted using all available residual human carotid tissues (upstream and downstream the blood flow) from a cohort of patients symptomatic (n = 13) or asymptomatic (n = 27) for ischaemic stroke. Intraplaque levels of 2-arachidonoylglycerol, anandamide N-arachidonoylethanolamine, N-palmitoylethanolamine, N-oleoylethanolamine, and their degrading enzymes (fatty acid amide hydrolase and monoacylglycerol lipase) were not different in human plaque portions. In the majority of human samples, CB(1) (both mRNA and protein levels) was undetectable. In downstream symptomatic plaques, CB(2) protein expression was reduced when compared with asymptomatic patients. In these portions, CB(2) levels were inversely correlated (r = -0.4008, P = 0.0170) with matrix metalloprotease (MMP)-9 content and positively (r = 0.3997, P = 0.0174) with collagen. In mouse plaques, CB(2) co-localized with neutrophils and MMP-9. Treatment with the selective CB(2) agonist JWH-133 was associated with the reduction in MMP-9 content in aortic root and carotid plaques. In vitro, pre-incubation with JWH-133 reduced tumour necrosis factor (TNF)- α -mediated release of MMP-9. This effect was associated with the reduction in TNF- α -induced ERK1/2 phosphorylation in human neutrophils. Cannabinoid receptor type 2 receptor is down-regulated in unstable human carotid plaques. Since CB(2) activation prevents neutrophil release of MMP-9 in vivo and in vitro, this treatment strategy might selectively reduce carotid vulnerability in humans. Montecucco F, Di Marzo V, da Silva RF, Vuilleumier N, Capettini L, Lenglet S, Pagano S, Piscitelli F, Quintao S, Bertolotto M, Pelli G, Galan K, Pilet L, Kuzmanovic K, Burger F, Pane B, Spinella G, Braunersreuther V, Gayet-Ageron A, Pende A, Viviani GL, Palombo D, Dallegri F, Roux-Lombard P, Santos RA, Stergiopoulos N, Steffens S,

Mach F. The activation of the cannabinoid receptor type 2 reduces neutrophilic protease-mediated vulnerability in atherosclerotic plaques. *Eur Heart J.* 2012 Apr; 33(7): 846-856. Epub 2011 Nov 22.

A Single Injection Of A Novel Kappa Opioid Receptor Agonist Salvinorin A Attenuates The Expression Of Cocaine-Induced Behavioral Sensitization In Rats

Kappa opioid receptor (KOPr) activation antagonizes many cocaine-related behaviors but adverse side-effects such as sedation, dysphoria, and depression limit their therapeutic use. Recently, salvinorin A (Sal A), a naturally occurring KOPr agonist, has been shown to attenuate cocaine-induced drug seeking in a model of relapse in rats. The present study evaluated the effects of acute Sal A exposure on cocaine-induced hyperactivity and cocaine sensitization in rats. Acute treatment with a dose of Sal A that decreased drug seeking in a previous study (0.3 mg/kg) significantly attenuated the expression of cocaine sensitization. This dose of Sal A failed to affect spontaneous locomotion or to produce a conditioned taste aversion to a novel-tasting saccharin solution. However, Sal A decreased climbing and swimming time and increased time spent immobile in the forced swim test. These findings indicate that Sal A, just like traditional KOPr agonists, attenuates cocaine-induced behavioral sensitization but does not produce the adverse effect of conditioned aversion, suggesting improved potential compliance. However, prodepressive effects were also produced and these effects may limit the therapeutic potential. Morani AS, Schenk S, Prisinzano TE, Kivell BM. A single injection of a novel kappa opioid receptor agonist salvinorin A attenuates the expression of cocaine-induced behavioral sensitization in rats. *Behav Pharmacol.* 2012 Apr; 23(2): 162-170.

Investigations On The 4-Quinolone-3-Carboxylic Acid Motif Part 5: Modulation Of The Physicochemical Profile Of A Set Of Potent And Selective Cannabinoid-2 Receptor Ligands Through A Bioisosteric Approach

Three heterocyclic systems were selected as potential bioisosteres of the amide linker for a series of 1,6-disubstituted-4-quinolone-3-carboxamides, which are potent and selective CB2 ligands that exhibit poor water solubility, with the aim of improving their physicochemical profile and also of clarifying properties of importance for amide bond mimicry. Among the newly synthesized compounds, a 1,2,3-triazole derivative (1-(adamantan-1-yl)-4-[6-(furan-2-yl)-1,4-dihydro-4-oxo-1-pentylquinolin-3-yl]-1H-1,2,3-triazole) emerged as the most promising in terms of both physicochemical and pharmacodynamic properties. When assayed in vitro, this derivative exhibited inverse agonist activity, whereas, in the formalin test in mice, it produced analgesic effects antagonized by a well-established inverse agonist. Metabolic studies allowed the identification of a side chain hydroxylated derivative as its only metabolite, which, in its racemic form, still showed appreciable CB2 selectivity, but was 150-fold less potent than the parent compound. Mugnaini C, Nocerino S, Pedani V, Pasquini S, Tafi A, De Chiaro M, Bellucci L, Valoti M, Guida F, Luongo L, Dragoni S, Ligresti A, Rosenberg A, Bolognini D, Cascio MG, Pertwee RG, Moaddel R, Maione S, Di Marzo V, Corelli F. Investigations on the 4-quinolone-3-carboxylic acid motif part 5: modulation of the physicochemical profile of a set of potent and selective cannabinoid-2 receptor ligands through a bioisosteric approach. *ChemMedChem.* 2012 May; 7(5): 920-934. doi: 10.1002/cmdc.201100573. Epub 2012 Mar 2.

In Vitro Blood-Brain Barrier Models: Current And Perspective Technologies

Even in the 21st century, studies aimed at characterizing the pathological paradigms associated with the development and progression of central nervous system diseases are primarily performed in laboratory animals. However, limited translational significance, high cost, and labor to develop the appropriate model (e.g., transgenic or inbred strains) have favored parallel in vitro approaches. In vitro models are of particular interest for cerebrovascular studies of the blood-brain barrier (BBB), which plays a critical role in maintaining the brain homeostasis and neuronal functions. Because the

BBB dynamically responds to many events associated with rheological and systemic impairments (e.g., hypoperfusion), including the exposure of potentially harmful xenobiotics, the development of more sophisticated artificial systems capable of replicating the vascular properties of the brain microcapillaries are becoming a major focus in basic, translational, and pharmaceutical research. In vitro BBB models are valuable and easy to use supporting tools that can precede and complement animal and human studies. In this article, the authors provide a detailed review and analysis of currently available in vitro BBB models ranging from static culture systems to the most advanced flow-based and three-dimensional coculture apparatus. They also discuss recent and perspective developments in this ever expanding research field. Naik P, Cucullo L. In vitro blood-brain barrier models: current and perspective technologies. *J Pharm Sci.* 2012 Apr; 101(4): 1337-1354. doi: 10.1002/jps.23022. Epub 2011 Dec 27.

The Role Of Mu Opioid Receptors In Psychomotor Stimulation and Conditioned Place Preference Induced By Morphine-6-Glucuronide

Previous studies have shown that morphine-6-glucuronide (M6G), a metabolite of morphine, induces reward and psychomotor stimulation but the role of the mu opioid receptor in these actions of the drug is not fully characterized. Thus, using mice lacking exon-2 of the mu opioid receptor and their wild-type littermates/controls, the authors determined the role of this receptor in psychomotor stimulation, sensitization, and conditioned place preference (CPP) induced by M6G. For comparison, they also assessed the role of the mu opioid receptor in the rewarding action of morphine. For the measurement of locomotor activity and sensitization, mice were habituated to motor activity chambers for 1h, then injected with M6G (10mg/kg) and locomotor activity was recorded for an additional 1h. The same treatment was given for five days and mice were tested for sensitization a week later. For the CPP experiments, mice were tested for baseline place preference on day 1, then received single or repeated alternate-day saline/drug or drug/saline conditioning and tested for CPP the following day. Mice were also tested for CPP under a drugged state. M6G induced psychomotor stimulation, a response that was enhanced upon repeated administration of the drug, showing that locomotor sensitization developed to the motor stimulatory action of M6G. However, M6G induced a weaker CPP response compared to morphine. None of these actions of M6G was detected in mice lacking the mu opioid receptor. Together, the current results suggest that M6G induces psychomotor stimulation and a weaker rewarding action via the mu opioid receptor. Nguyen AT, Marquez P, Hamid A, Lutfy K. The role of mu opioid receptors in psychomotor stimulation and conditioned place preference induced by morphine-6-glucuronide. *Eur J Pharmacol.* 2012 May 5; 682(1-3): 86-91. Epub 2012 Feb 21.

β -Arrestin2 Regulates Cannabinoid CB1 Receptor Signaling And Adaptation In A Central Nervous System Region-Dependent Manner

Cannabinoid CB(1) receptors (CB(1)Rs) mediate the effects of Δ^9 -tetrahydrocannabinol (THC), the psychoactive component in marijuana. Repeated THC administration produces tolerance and dependence, which limit therapeutic development. Moreover, THC produces motor and psychoactive side effects. β -arrestin2 mediates receptor desensitization, internalization, and signaling, but its role in these CB(1)R effects and receptor regulation is unclear. CB(1)R signaling and behaviors (antinociception, hypothermia, catalepsy) were assessed in β -arrestin2-knockout (β arr2-KO) and wild-type mice after THC administration. Cannabinoid-stimulated [(35)S]GTP γ S and [(3)H]ligand autoradiography were assessed by statistical parametric mapping and region-of-interest analysis. β -arrestin2 deletion increased CB(1)R-mediated G-protein activity in subregions of the cortex but did not affect CB(1)R binding, in vehicle-treated mice. β arr2-KO mice exhibited enhanced acute THC-mediated antinociception and hypothermia, with no difference in catalepsy. After repeated THC

administration, β arr2-KO mice showed reduced CB(1)R desensitization and/or downregulation in cerebellum, caudal periaqueductal gray, and spinal cord and attenuated tolerance to THC-mediated antinociception. In contrast, greater desensitization was found in hypothalamus, cortex, globus pallidus, and substantia nigra of β arr2-KO compared with wild-type mice. Enhanced tolerance to THC-induced catalepsy was observed in β arr2-KO mice. β -arrestin2 regulation of CB(1)R signaling following acute and repeated THC administration was region-specific, and results suggest that multiple, overlapping mechanisms regulate CB(1)Rs. The observations that β arr2-KO mice display enhanced antinociceptive responses to acute THC and decreased tolerance to the antinociceptive effects of the drug, yet enhanced tolerance to catalepsy, suggest that development of cannabinoid drugs that minimize CB(1)R interactions with β -arrestin2 might produce improved cannabinoid analgesics with reduced motor suppression. Nguyen PT, Schmid CL, Raehal KM, Selley DE, Bohn LM, Sim-Selley LJ. β -arrestin2 regulates cannabinoid CB1 receptor signaling and adaptation in a central nervous system region-dependent manner. *Biol Psychiatry*. 2012 Apr 15; 71(8): 714-724. Epub 2012 Jan 20.

Effects Of Palmitoylation Of Cys(415) In Helix 8 Of The CB(1) Cannabinoid Receptor On Membrane Localization and Signalling

The CB(1) cannabinoid receptor is regulated by its association with membrane microdomains such as lipid rafts. Here, the authors investigated the role of palmitoylation of the CB(1) receptor by analysing the functional consequences of site-specific mutation of Cys(415), the likely site of palmitoylation at the end of helix 8, in terms of membrane association, raft targeting and signalling. The palmitoylation state of CB(1) receptors in rat forebrain was assessed by depalmitoylation/repalmitoylation experiments. Cys(415) was replaced with alanine by site-directed mutagenesis. Green fluorescence protein chimeras of both wild-type and mutant receptors were transiently expressed and functionally characterized in SH-SY5Y cells and HEK-293 cells by means of confocal microscopy, cytofluorimetry and competitive binding assays. Confocal fluorescence recovery after photobleaching was used to assess receptor membrane dynamics, whereas signalling activity was assessed by [(35)S]GTP γ S, cAMP and co-immunoprecipitation assays. Endogenous CB(1) receptors in rat brain were palmitoylated. Mutation of Cys(415) prevented the palmitoylation of the receptor in transfected cells and reduced its recruitment to plasma membrane and lipid rafts; it also increased protein diffusional mobility. The same mutation markedly reduced the functional coupling of CB(1) receptors with G-proteins and adenylyl cyclase, whereas depalmitoylation abolished receptor association with a specific subset of G-proteins. CB(1) receptors were post-translationally modified by palmitoylation. Mutation of Cys(415) provides a receptor that is functionally impaired in terms of membrane targeting and signalling. Oddi S, Dainese E, Sandiford S, Fezza F, Lanuti M, Chiurchiù V, Totaro A, Catanzaro G, Barcaroli D, De Laurenzi V, Centonze D, Mukhopadhyay S, Selent J, Howlett AC, Maccarrone M. Effects of palmitoylation of Cys(415) in helix 8 of the CB(1) cannabinoid receptor on membrane localization and signalling. *Br J Pharmacol*. 2012 Apr; 165(8): 2635-2651. doi: 10.1111/j.1476-5381.2011.01658.x.

Effects Of The Histamine H₁ Receptor Antagonist and Benztropine Analog Diphenylpyraline On Dopamine Uptake, Locomotion and Reward

Diphenylpyraline hydrochloride (DPP) is an internationally available antihistamine that produces therapeutic antiallergic effects by binding to histamine H₁ receptors. The complete neuropharmacological and behavioral profile of DPP, however, remains uncharacterized. Here the authors describe studies that suggest DPP may fit the profile of a potential agonist replacement medication for cocaine addiction. Aside from producing the desired histamine reducing effects, many antihistamines can also elicit psychomotor activation and reward, both of which are associated with increased dopamine concentrations in the nucleus

accumbens (NAc). The primary aim of this study was to investigate the potential ability of DPP to inhibit the dopamine transporter, thereby leading to elevated dopamine concentrations in the NAc in a manner similar to cocaine and other psychostimulants. The psychomotor activating and rewarding effects of DPP were also investigated. For comparative purposes cocaine, a known dopamine transporter inhibitor, psychostimulant and drug of abuse, was used as a positive control. As predicted, both cocaine (15 mg/kg) and an equimolar dose of DPP (14 mg/kg) significantly inhibited dopamine uptake in the NAc in vivo and produced locomotor activation, although the time-course of pharmacological effects of the two drugs was different. In comparison to cocaine, DPP showed a prolonged effect on dopamine uptake and locomotion. Furthermore, cocaine, but not DPP, produced significant conditioned place preference, a measure of drug reward. The finding that DPP functions as a potent dopamine uptake inhibitor without producing significant rewarding effects suggests that DPP merits further study as a potential candidate as an agonist pharmacotherapy for cocaine addiction. Oleson EB, Ferris MJ, España RA, Harp J, Jones SR. Effects of the histamine H₁ receptor antagonist and benzotropine analog diphenylpyraline on dopamine uptake, locomotion and reward. *Eur J Pharmacol*. 2012 May 15; 683(1-3): 161-165. Epub 2012 Mar 15.

Seminal Plasma Accelerates Semen-Derived Enhancer Of Viral Infection (SEVI) Fibril Formation By The Prostatic Acid Phosphatase (PAP248-286) Peptide

Amyloid fibrils contained in semen, known as SEVI, or semen-derived enhancer of viral infection, have been shown to increase the infectivity of HIV dramatically. However, previous work with these fibrils has suggested that extensive time and nonphysiologic levels of agitation are necessary to induce amyloid formation from the precursor peptide (a proteolytic cleavage product of prostatic acid phosphatase, PAP(248-286)). Here, the authors show that fibril formation by PAP(248-286) is accelerated dramatically in the presence of seminal plasma (SP) and that agitation is not required for fibrillization in this setting. Analysis of the effects of specific SP components on fibril formation by PAP(248-286) revealed that this effect is primarily due to the anionic buffer components of SP (notably inorganic phosphate and sodium bicarbonate). Divalent cations present in SP had little effect on the kinetics of fibril formation, but physiologic levels of Zn(2+) strongly protected SEVI fibrils from degradation by seminal proteases. Taken together, these data suggest that in the in vivo environment, PAP(248-286) is likely to form fibrils efficiently, thus providing an explanation for the presence of SEVI in human semen. Olsen JS, DiMaio JT, Doran TM, Brown C, Nilsson BL, Dewhurst S. Seminal plasma accelerates semen-derived enhancer of viral infection (SEVI) fibril formation by the prostatic acid phosphatase (PAP248-286) peptide. *J Biol Chem*. 2012 Apr 6; 287(15): 11842-11849. Epub 2012 Feb 21.

α -Ketoheterocycle-Based Inhibitors of Fatty Acid Amide Hydrolase (FAAH) A summary of the initial discovery and characterization of the enzyme fatty acid amide hydrolase (FAAH), and the subsequent advancement of an important class of competitive, reversible, potent and selective inhibitors is presented. Initially explored using substrate-inspired inhibitors bearing electrophilic carbonyls, the examination of α -ketoheterocycle-based inhibitors of FAAH with the benefit of a unique activity-based protein-profiling (ABPP)-based proteome-wide selectivity assay, a powerful in vivo biomarker-based in vivo screen, and subsequent retrospective X-ray co-crystal structures with the enzyme, is summarized. These efforts defined the impact of the central activating heterocycle and its key substituents, provided key simplifications in the C2 acyl side chain and clear interpretations for the unique role and subsequent optimization of the central activating heterocycle, and established the basis for the recent further conformational constraints in the C2 acyl side chain, providing potent, long-acting, orally-active FAAH inhibitors. Otrubova K, Boger DL. α -

Ketoheterocycle-based inhibitors of fatty acid amide hydrolase (FAAH). ACS Chem Neurosci. 2012 May 16; 3(5): 340-348. Epub 2011 Dec 20.

Genome-Wide Association For Fear Conditioning In An Advanced Intercross Mouse Line

Fear conditioning (FC) may provide a useful model for some components of post-traumatic stress disorder (PTSD). The authors used a C57BL/6J × DBA/2J F(2) intercross (n = 620) and a C57BL/6J × DBA/2J F(8) advanced intercross line (n = 567) to fine-map quantitative trait loci (QTL) associated with FC. They conducted an integrated genome-wide association analysis in QTLRel and identified five highly significant QTL affecting freezing to context as well as four highly significant QTL associated with freezing to cue. The average percent decrease in QTL width between the F(2) and the integrated analysis was 59.2%. Next, they exploited bioinformatic sequence and expression data to identify candidate genes based on the existence of non-synonymous coding polymorphisms and/or expression QTLs. They identified numerous candidate genes that have been previously implicated in either fear learning in animal models (Bcl2, Btg2, Dbi, Gabr1b, Lypd1, Pam and Rgs14) or PTSD in humans (Gabra2, Oprm1 and Trkb); other identified genes may represent novel findings. The integration of F(2) and AIL data maintains the advantages of studying FC in model organisms while significantly improving resolution over previous approaches. Parker CC, Sokoloff G, Cheng R, Palmer AA. Genome-wide association for fear conditioning in an advanced intercross mouse line. Behav Genet. 2012 May; 42(3): 437-448. Epub 2012 Jan 12.

Electroencephalographic Recovery, Hypnotic Emergence, and The Effects Of Metabolite After Continuous Infusions Of A Rapidly Metabolized Etomidate Analog In Rats

Methoxycarbonyl etomidate is an ultrarapidly metabolized etomidate analog. It is metabolized to methoxycarbonyl etomidate carboxylic acid (MOC-ECA), which has a hypnotic potency that is 350-fold less than that of methoxycarbonyl etomidate. The authors explored the relationships between methoxycarbonyl etomidate infusion duration, recovery time, metabolite concentrations in blood and cerebrospinal fluid (CSF), and methoxycarbonyl etomidate metabolism in brain tissue and CSF to test the hypothesis that rapid metabolism of methoxycarbonyl etomidate may lead to sufficient accumulation of MOC-ECA in the brain to produce a pharmacologic effect. A closed-loop system with burst suppression ratio feedback was used to administer methoxy-carbonyl etomidate infusions of varying durations to rats. After infusion, recovery of the electroencephalogram and righting reflexes were assessed. MOC-ECA concentrations were measured in blood and CSF during and after methoxycarbonyl etomidate infusion, and the in vitro half-life of methoxycarbonyl etomidate was determined in rat brain tissue and CSF. Upon termination of continuous methoxycarbonyl etomidate infusions, the burst suppression ratio recovered in a biexponential manner with fast and slow components having time constants that differed by more than 100-fold and amplitudes that varied inversely with infusion duration. MOC-ECA concentrations reached hypnotic concentrations in the CSF with prolonged methoxycarbonyl etomidate infusion and then decreased during a period of several hours after infusion termination. The metabolic half-life of methoxycarbonyl etomidate in brain tissue and CSF was 11 and 20 min, respectively. In rats, methoxycarbonyl etomidate metabolism is sufficiently fast to produce pharmacologically active MOC-ECA concentrations in the brain with prolonged methoxycarbonyl etomidate infusion. Pejo E, Ge R, Banacos N, Cotten JF, Husain SS, Raines DE. Electroencephalographic recovery, hypnotic emergence, and the effects of metabolite after continuous infusions of a rapidly metabolized etomidate analog in rats. Anesthesiology. 2012 May; 116(5): 1057-1065.

Mephedrone ("Bath Salt") Pharmacology: Insights From Invertebrates Psychoactive bath salts (also called meph, drone, meow meow, m-CAT, bounce, bubbles, mad cow, etc.) contain a substance called mephedrone (4-methylcathinone) that may share psychostimulant properties with amphetamine and cocaine. However, there are only limited studies of the neuropharmacological profile of mephedrone. The present study used an established invertebrate (planarian) assay to test the hypothesis that acute and repeated mephedrone exposure produces psychostimulant-like behavioral effects. Acute mephedrone administration (50-1000 μ M) produced stereotyped movements that were attenuated by a dopamine receptor antagonist (SCH 23390) (0.3 μ M). Spontaneous discontinuation of mephedrone exposure (1, 10 μ M) (60 min) resulted in an abstinence-induced withdrawal response (i.e. reduced motility). In place conditioning experiments, planarians in which mephedrone (100, 500 μ M) was paired with the non-preferred environment during conditioning displayed a shift in preference upon subsequent testing. These results suggest that mephedrone produces three behavioral effects associated with psychostimulant drugs, namely dopamine-sensitive stereotyped movements, abstinence-induced withdrawal, and environmental place conditioning. Ramoz L, Lodi S, Bhatt P, Reitz AB, Tallarida C, Tallarida RJ, Raffa RB, Rawls SM. Mephedrone ("bath salt") pharmacology: insights from invertebrates. *Neuroscience*. 2012 Apr 19; 208:79-84. Epub 2012 Jan 20.

Epitope-Tagged Dopamine Transporter Knock-In Mice Reveal Rapid Endocytic Trafficking and Filopodia Targeting Of The Transporter In Dopaminergic Axons The plasma membrane dopamine (DA) transporter (DAT) is essential for reuptake of extracellular DA. DAT function in heterologous cells is regulated by subcellular targeting, endocytosis, and intracellular trafficking, but the mechanisms regulating neuronal DAT remain poorly understood. Hence, the authors generated a knock-in mouse expressing a hemagglutinin (HA)-epitope-tagged DAT to study endogenous transporter trafficking. Introduction of the HA tag into the second extracellular loop of mouse DAT did not perturb its expression level, distribution pattern, or substrate uptake kinetics. Live-cell fluorescence microscopy imaging using fluorescently labeled HA-specific antibody and a quantitative HA-antibody endocytosis assay demonstrated that in axons HA-DAT was primarily located in the plasma membrane and internalized mostly in growth cones and varicosities, where synaptic vesicle markers were also concentrated. Formation of varicosities was frequently preceded or accompanied by highly dynamic filopodia-like membrane protrusions. Remarkably, HA-DAT often concentrated at the tips of these filopodia. This pool of HA-DATs exhibited low lateral membrane mobility. Thus, DAT-containing filopodia may be involved in synaptogenesis in developing DA neurons. Treatment of neurons with amphetamine increased mobility of filopodial HA-DAT and accelerated HA-DAT endocytosis in axons, suggesting that chronic amphetamine may interfere with DA synapse development. Interestingly, phorbol esters did not accelerate endocytosis of axonal DAT. Rao A, Richards TL, Simmons D, Zahniser NR, Sorkin A. Epitope-tagged dopamine transporter knock-in mice reveal rapid endocytic trafficking and filopodia targeting of the transporter in dopaminergic axons. *FASEB J*. 2012 May; 26(5): 1921-1933. Epub 2012 Jan 20.

Auditory Steady State Response In The Schizophrenia, First-Degree Relatives, and Schizotypal Personality Disorder The power and phase synchronization of the auditory steady state response (ASSR) at 40 Hz stimulation is usually reduced in schizophrenia (SZ). The sensitivity of the 40 Hz ASSR to schizophrenia spectrum phenotypes, such as schizotypal personality disorder (SPD), or to familial risk has been less well characterized. The authors compared the ASSR of patients with SZ, persons with schizotypal personality disorder, first degree relatives of patients with SZ, and healthy control participants. ASSRs were obtained to 20, 30, 40 and 50 Hz click trains,

and assessed using measures of power (mean trial power or MTP) and phase consistency (phase locking factor or PLF). The MTP to 40 Hz stimulation was reduced in relatives, and there was a trend for MTP reduction in SZ. The 40 Hz ASSR was not reduced in SPD participants. PLF did not differ among groups. These data suggest the 40 Hz ASSR is sensitive to familial risk factors associated with schizophrenia. Rass O, Forsyth JK, Krishnan GP, Hetrick WP, Klaunig MJ, Breier A, O'Donnell BF, Brenner CA. Auditory steady state response in the schizophrenia, first-degree relatives, and schizotypal personality disorder. *Schizophr Res.* 2012 Apr; 136(1-3): 143-149. Epub 2012 Jan 28.

Cerebral Blood Flow Imaged With Ultrahigh-Resolution Optical Coherence Angiography and Doppler Tomography

Speckle contrast based optical coherence angiography (OCA) and optical coherence Doppler tomography (ODT) have been applied to image cerebral blood flow previously. However, the contrast mechanisms of these two methods are not fully studied. Here, the authors present both flow phantom and in vivo animal experiments using ultrahigh-resolution OCA (μ OCA) and ODT (μ ODT) to investigate the flow sensitivity differences between these two methods. Results show that the high sensitivity of μ OCA for visualizing minute vasculature (e.g., slow capillary beds) is due to the enhancement by random Brownian motion of scatterers (e.g., red and white blood cells) within the vessels; whereas, μ ODT permits detection of directional flow below the Brownian motion regime (e.g., laser-induced microischemia) and is, therefore, more suitable for brain functional imaging. Ren H, Du C, Pan Y. Cerebral blood flow imaged with ultrahigh-resolution optical coherence angiography and Doppler tomography. *Opt Lett.* 2012 Apr 15; 37(8): 1388-1390. doi: 10.1364/OL.37.001388.

Nanoparticle Based Galectin-1 Gene Silencing, Implications in Methamphetamine Regulation of HIV-1 Infection in Monocyte Derived Macrophages

Galectin-1, an adhesion molecule, is expressed in macrophages and implicated in human immunodeficiency virus (HIV-1) viral adsorption. In this study, the authors investigated the effects of methamphetamine on galectin-1 production in human monocyte derived macrophages (MDM) and the role of galectin-1 in methamphetamine potentiation of HIV-1 infection. Herein they show that levels of galectin-1 gene and protein expression are significantly increased by methamphetamine. Furthermore, concomitant incubation of MDM with galectin-1 and methamphetamine facilitates HIV-1 infection compared to galectin-1 alone or methamphetamine alone. They utilized a nanotechnology approach that uses gold nanorod (GNR)-galectin-1 siRNA complexes (nanoplexes) to inhibit gene expression for galectin-1. Nanoplexes significantly silenced gene expression for galectin-1 and reversed the effects of methamphetamine on galectin-1 gene expression. Moreover, the effects of methamphetamine on HIV-1 infection were attenuated in the presence of the nanoplex in MDM. Reynolds JL, Law WC, Mahajan SD, Aalinkeel R, Nair B, Sykes DE, Yong KT, Hui R, Prasad PN, Schwartz SA. Nanoparticle based galectin-1 gene silencing, implications in methamphetamine regulation of HIV-1 infection in monocyte derived macrophages. *J Neuroimmune Pharmacol.* 2012 Jun 12. [Epub ahead of print].

Morphine and Galectin-1 Modulate HIV-1 Infection Of Human Monocyte-Derived Macrophages

Morphine is a widely abused, addictive drug that modulates immune function. Macrophages are a primary reservoir of HIV-1; therefore, they play a role in the development of this disease, as well as impact the overall course of disease progression. Galectin-1 is a member of a family of β -galactoside-binding lectins that are soluble adhesion molecules and that mediate direct cell-pathogen interactions during HIV-1 viral adhesion. Because the drug abuse epidemic and the HIV-1 epidemic are closely interrelated, the authors propose that increased expression of galectin-1

induced by morphine may modulate HIV-1 infection of human monocyte-derived macrophages (MDMs). In this article, they show that galectin-1 gene and protein expression are potentiated by incubation with morphine. Confirming previous studies, morphine alone or galectin-1 alone enhance HIV-1 infection of MDMs. Concomitant incubation with exogenous galectin-1 and morphine potentiated HIV-1 infection of MDMs. They used a nanotechnology approach that uses gold nanorod-galectin-1 small interfering RNA complexes (nanoplexes) to inhibit gene expression for galectin-1. They found that nanoplexes silenced gene expression for galectin-1, and they reversed the effects of morphine on galectin-1 expression. Furthermore, the effects of morphine on HIV-1 infection were reduced in the presence of the nanoplex. Reynolds JL, Law WC, Mahajan SD, Aalinkeel R, Nair B, Sykes DE, Mammen MJ, Yong KT, Hui R, Prasad PN, Schwartz SA. Morphine and galectin-1 modulate HIV-1 infection of human monocyte-derived macrophages. *J Immunol.* 2012 Apr 15; 188(8): 3757-3765. Epub 2012 Mar 19.

Effects of Sazetidine-A, A Selective $\alpha 4\beta 2^*$ Nicotinic Receptor Desensitizing Agent, On Body Temperature Regulation In Mice and Rats Nicotine-induced hypothermia is well established, but the nicotinic receptor actions underlying this effect are not clear. Nicotine causes activation and desensitization at a variety of nicotinic receptor subtypes. Sazetidine-A [6-(5(((S)-azetidine-2-yl)methoxy)pyridine-3-yl)hex-5-yn-1-ol] is a novel compound that potently and selectively desensitizes $\alpha 4\beta 2^*$ nicotinic receptors. The main goal of this study was to investigate the effects of sazetidine-A, on core body temperature (T_c) in mice and rats. Sazetidine-A effects on T_c and the interactions of sazetidine-A with nicotine and selective nicotinic antagonists were investigated to determine the receptor actions underlying nicotine-induced hypothermia. Adult male mice were injected with different dose of nicotine (0.2, 0.4 and 0.8 mg/kg), sazetidine-A (0.3, 1, and 3mg/kg), a mixture of nicotine (0.4 or 0.8 mg/kg) and sazetidine-A (0.3 or 0.6 mg/kg) or saline and T_c was monitored telemetrically. In another set of experiments, the interaction between sazetidine-A and dihydro- β -erythroidine (DH β E), an $\alpha 4\beta 2^*$ nicotinic receptors antagonist, and methyllycaconitine (MLA), an $\alpha 7$ antagonist, was investigated. T_c of mice was monitored following DH β E (1, 3 and 6 mg/kg), a combination of DH β E (3mg/kg) and sazetidine-A (0.6 mg/kg), MLA (1.5, 3 or 6 mg/kg) or combination of MLA (6 mg/kg) and sazetidine (0.6 mg/kg) or saline. The acute effect of sazetidine-A (1, 3, and 6 mg/kg) on rats T_c was also studied. Acute sazetidine-A caused a pronounced and long-lasting hypothermia in mice; T_c decreased to about 28°C at 100 min and recovered within 230 min. The hypothermic effect of sazetidine in rats was much less in magnitude (about 3°C) and shorter in duration compared with that in mice. Nicotine co-administration with low doses of sazetidine potentiated the magnitude and duration of hypothermia in mice. The $\alpha 4\beta 2^*$ nicotinic receptors antagonist DH β E significantly prolonged sazetidine-A-induced hypothermia but did not increase its depth. The $\alpha 7$ antagonist MLA caused a modest degree of hypothermia with relatively short duration in mice. MLA failed to counteract the sazetidine-A-induced hypothermia. Overall, these results show that pharmacological modulation of $\alpha 4\beta 2^*$ nicotinic receptors elicits changes in body temperature that may involve desensitization of these receptors. Rezvani AH, Timofeeva O, Sexton HG, DeCuir D, Xiao Y, Gordon CJ, Kellar KJ, Levin ED. Effects of sazetidine-A, a selective $\alpha 4\beta 2^*$ nicotinic receptor desensitizing agent, on body temperature regulation in mice and rats. *Eur J Pharmacol.* 2012 May 5; 682(1-3): 110-117. Epub 2012 Feb 24.

Opioid-Induced Hypernociception Is Associated With Hyperexcitability and Altered Tetrodotoxin-Resistant Na^+ Channel Function Of Dorsal Root Ganglia Opiates are potent analgesics for moderate to severe pain. Paradoxically, patients under chronic opiates have reported hypernociception, the mechanisms of which are unknown. Using standard patch-clamp technique, the authors examined the excitability, biophysical properties of tetrodotoxin-resistant (TTX-R)

Na(+) and transient receptor potential vanilloid 1 (TRPV1) channels of dorsal root ganglia neurons (DRG) (L5-S1) from mice pelleted with morphine (75 mg) or placebo (7 days).

Hypernociception was confirmed by acetic acid-writhing test following 7-day morphine. Chronic morphine enhanced the neuronal excitability, since the rheobase for action potential (AP) firing was significantly ($P < 0.01$) lower (38 ± 7 vs. 100 ± 15 pA) while the number of APs at $2\times$ rheobase was higher (4.4 ± 0.8 vs. 2 ± 0.5) than placebo ($n = 13-20$). The potential of half-maximum activation ($V(1/2)$) of TTX-R Na(+) currents was shifted to more hyperpolarized potential in the chronic morphine group (-37 ± 1 mV) vs. placebo (-28 ± 1 mV) without altering the $V(1/2)$ of inactivation (-41 ± 1 vs. -33 ± 1 mV) ($n = 8-11$). Recovery rate from inactivation of TTX-R Na(+) channels or the mRNA level of any Na(+) channel subtypes did not change after chronic morphine. Also, chronic morphine significantly ($P < 0.05$) enhanced the magnitude of TRPV1 currents (-64 ± 11 pA/pF) vs. placebo (-18 ± 6 pA/pF). The increased excitability of sensory neurons by chronic morphine may be due to the shift in the voltage threshold of activation of TTX-R Na(+) currents. Enhanced TRPV1 currents may have a complementary effect, with TTX-R Na(+) currents on opiate-induced hyperexcitability of sensory neurons causing hypernociception. In conclusion, chronic morphine-induced hypernociception is associated with hyperexcitability and functional remodeling of TTX-R Na(+) and TRPV1 channels of sensory neurons. Ross GR, Gade AR, Dewey WL, Akbarali HI. Opioid-induced hypernociception is associated with hyperexcitability and altered tetrodotoxin-resistant Na⁺ channel function of dorsal root ganglia. *Am J Physiol Cell Physiol.* 2012 Apr; 302(8): C1152-1161. Epub 2011 Dec 21.

A Novel Tetrode Microdrive For Simultaneous Multi-Neuron Recording From Different Regions Of Primate Brain

A unique custom-made tetrode microdrive for recording from large numbers of neurons in several areas of primate brain is described as a means for assessing simultaneous neural activity in cortical and subcortical structures in nonhuman primates (NHPs) performing behavioral tasks. The microdrive device utilizes tetrode technology with up to six ultra-thin microprobe guide tubes (0.1mm) that can be independently positioned, each containing reduced diameter tetrode and/or hexatrode microwires (0.02 mm) for recording and isolating single neuron activity. The microdrive device is mounted within the standard NHP cranial well and allows traversal of brain depths up to 40.0 mm. The advantages of this technology are demonstrated via simultaneously recorded large populations of neurons with tetrode type probes during task performance from a) primary motor cortex and deep brain structures (caudate-putamen and hippocampus) and b) multiple layers within the prefrontal cortex. The means to characterize interactions of well-isolated ensembles of neurons recorded simultaneously from different regions, as shown with this device, has not been previously available for application in primate brain. The device has extensive application to primate models for the detection and study of inoperative or maladaptive neural circuits related to human neurological disorders. Santos L, Opris I, Fuqua J, Hampson RE, Deadwyler SA. A novel tetrode microdrive for simultaneous multi-neuron recording from different regions of primate brain. *J Neurosci Methods.* 2012 Apr 15; 205(2): 368-374. Epub 2012 Feb 2.

Statistical Parametric Mapping Reveals Regional Alterations In Cannabinoid CB1 Receptor Distribution and G-Protein Activation In The 3D Reconstructed Epileptic Rat Brain

The endocannabinoid system is known to modulate seizure activity in several in vivo and in vitro models, and CB(1) -receptor activation is anticonvulsant in the rat pilocarpine model of acquired epilepsy (AE). In these epileptic rats, a unique redistribution of the CB(1) receptor occurs within the hippocampus; however, an anatomically inclusive analysis of the effect of status epilepticus (SE)-induced AE on CB(1) receptors has not been thoroughly evaluated. Therefore, statistical parametric

mapping (SPM), a whole-brain unbiased approach, was used to study the long-term effect of pilocarpine-induced SE on CB(1) -receptor binding and G-protein activation in rats with AE. Serial coronal sections from control and epileptic rats were cut at equal intervals throughout the neuraxis and processed for [(3) H]WIN55,212-2 (WIN) autoradiography, WIN-stimulated [(35) S]GTP γ S autoradiography, and CB(1) -receptor immunohistochemistry (IHC). The autoradiographic techniques were evaluated with both region of interest (ROI) and SPM analyses. In rats with AE, regionally specific increases in CB(1) -receptor binding and activity were detected in cortex, discrete thalamic nuclei, and other regions including caudate-putamen and septum, and confirmed by IHC. However, CB(1) receptors were unaltered in several brain regions, including substantia nigra and cerebellum, and did not exhibit regional decreases in rats with AE. This study provides the first comprehensive evaluation of the regional distribution of changes in CB(1) -receptor expression, binding, and G-protein activation in the rat pilocarpine model of AE. These regions may ultimately serve as targets for cannabinomimetic compounds or manipulation of the endocannabinoid system in epileptic brain. Sayers KW, Nguyen PT, Blair RE, Sim-Selley LJ, DeLorenzo RJ. Statistical parametric mapping reveals regional alterations in cannabinoid CB1 receptor distribution and G-protein activation in the 3D reconstructed epileptic rat brain. *Epilepsia*. 2012 May; 53(5): 897-907. doi: 10.1111/j.1528-1167.2012.03460.x. Epub 2012 Apr 17.

A Genetic Animal Model Of Differential Sensitivity To Methamphetamine Reinforcement

Sensitivity to reinforcement from methamphetamine (MA) likely influences risk for MA addiction, and genetic differences are one source of individual variation. Generation of two sets of selectively bred mouse lines for high and low MA drinking has shown that genetic factors influence MA intake, and pronounced differences in sensitivity to rewarding and aversive effects of MA play a significant role. Further validation of these lines as a unique genetic model relevant to MA addiction was obtained using operant methods to study MA reinforcement. High and low MA drinking line mice were used to test the hypotheses that: 1) oral and intracerebroventricular (ICV) MA serve as behavioral reinforcers, and 2) MA exhibits greater reinforcing efficacy in high than low MA drinking mice. Operant responses resulted in access to an MA or non-MA drinking tube or intracranial delivery of MA. Behavioral activation consequent to orally consumed MA was determined. MA available for consumption maintained higher levels of reinforced instrumental responding in high than low MA drinking line mice, and MA intake in the oral operant procedure was greater in high than low MA drinking line mice. Behavioral activation was associated with amount of MA consumed during operant sessions. High line mice delivered more MA via ICV infusion than did low line mice across a range of doses. Thus, genetic risk factors play a critical role in the reinforcing efficacy of MA and the oral self-administration procedure is suitable for delineating genetic contributions to MA reinforcement. Shabani S, Dobbs LK, Ford MM, Mark GP, Finn DA, Phillips TJ. A genetic animal model of differential sensitivity to methamphetamine reinforcement. *Neuropharmacology*. 2012 Jun; 62(7): 2169-2177. Epub 2012 Jan 20.

Ligand-Dependent Conformations and Dynamics Of The Serotonin 5-HT(2A) Receptor Determine Its Activation and Membrane-Driven Oligomerization Properties

From computational simulations of a serotonin 2A receptor (5-HT(2A)R) model complexed with pharmacologically and structurally diverse ligands the authors identify different conformational states and dynamics adopted by the receptor bound to the full agonist 5-HT, the partial agonist LSD, and the inverse agonist Ketanserin. The results from the unbiased all-atom molecular dynamics (MD) simulations show that the three ligands affect differently the known GPCR activation elements including the toggle switch at W6.48, the changes in the ionic lock between E6.30 and R3.50 of the DRY motif in TM3, and the dynamics of the NPxxY motif in TM7. The computational

results uncover a sequence of steps connecting these experimentally-identified elements of GPCR activation. The differences among the properties of the receptor molecule interacting with the ligands correlate with their distinct pharmacological properties. Combining these results with quantitative analysis of membrane deformation obtained with our new method (Mondal et al, Biophysical Journal 2011), the authors show that distinct conformational rearrangements produced by the three ligands also elicit different responses in the surrounding membrane. The differential reorganization of the receptor environment is reflected in (i)-the involvement of cholesterol in the activation of the 5-HT(2A)R, and (ii)-different extents and patterns of membrane deformations. These findings are discussed in the context of their likely functional consequences and a predicted mechanism of ligand-specific GPCR oligomerization. Shan J, Khelashvili G, Mondal S, Mehler EL, Weinstein H. Ligand-dependent conformations and dynamics of the serotonin 5-HT(2A) receptor determine its activation and membrane-driven oligomerization properties. PLoS Comput Biol. 2012 Apr; 8(4): e1002473. Epub 2012 Apr 19.

Pharmacological Chaperoning Of Nicotinic Acetylcholine Receptors Reduces The Endoplasmic Reticulum Stress Response

The authors report the first observation that endoplasmic reticulum (ER) stress and the unfolded protein response (UPR) can decrease when a central nervous system drug acts as an intracellular pharmacological chaperone for its classic receptor. Transient expression of $\alpha 4\beta 2$ nicotinic receptors (nAChRs) in Neuro-2a cells induced the nuclear translocation of activating transcription factor 6 (ATF6), which is part of the UPR. Cells were exposed for 48 h to the full agonist nicotine, the partial agonist cytisine, or the competitive antagonist dihydro- β -erythroidine; the authors also tested mutant nAChRs that readily exit the ER. Each of these four manipulations increased Sec24D-enhanced green fluorescent protein fluorescence of condensed ER exit sites and attenuated translocation of ATF6-enhanced green fluorescent protein to the nucleus. However, they found no correlation among the manipulations regarding other tested parameters [i.e., changes in nAChR stoichiometry ($\alpha 4(2)\beta 2(3)$ versus $\alpha 4(3)\beta 2(2)$), changes in ER and trans-Golgi structures, or the degree of nAChR up-regulation at the plasma membrane]. The four manipulations activated 0 to 0.4% of nAChRs, which shows that activation of the nAChR channel did not underlie the reduced ER stress. Nicotine also attenuated endogenously expressed ATF6 translocation and phosphorylation of eukaryotic initiation factor 2 α in mouse cortical neurons transfected with $\alpha 4\beta 2$ nAChRs. The authors conclude that, when nicotine accelerates ER export of $\alpha 4\beta 2$ nAChRs, this suppresses ER stress and the UPR. Suppression of a sustained UPR may explain the apparent neuroprotective effect that causes the inverse correlation between a person's history of tobacco use and susceptibility to developing Parkinson's disease. This suggests a novel mechanism for neuroprotection by nicotine. Srinivasan R, Richards CI, Xiao C, Rhee D, Pantoja R, Dougherty DA, Miwa JM, Lester HA. Pharmacological chaperoning of nicotinic acetylcholine receptors reduces the endoplasmic reticulum stress response. Mol Pharmacol. 2012 Jun; 81(6): 759-769. Epub 2012 Feb 29.

Reproducibility Of The Nicotine Metabolite Ratio In Cigarette Smokers

The nicotine metabolite ratio (NMR or 3-hydroxycotinine/cotinine) has been used to phenotype CYP2A6-mediated nicotine metabolism. The authors' objectives were to analyze (i) the stability of NMR in plasma, saliva, and blood in various storage conditions, (ii) the relationship between NMRs derived from blood, plasma, saliva, and urine, and (iii) the reproducibility of plasma NMR in ad libitum cigarette smokers. They analyzed data from four clinical studies. In studies 1 and 2, they assessed NMR stability in saliva and plasma samples at room temperature ($\sim 22^{\circ}\text{C}$) over 14 days and in blood at 4°C for up to 72 hours. In studies 2 and 3, they used Bland-Altman analysis to assess agreement between blood, plasma, saliva, and urine NMRs. In study 4, plasma NMR was measured

on six occasions over 44 weeks in 43 ad libitum smokers. Reliability coefficients for stability tests of NMR in plasma and saliva at room temperature were 0.97 and 0.98, respectively, and 0.92 for blood at 4°C. Blood NMR agreed consistently with saliva and plasma NMRs but showed more variability in relation to urine NMR. The reliability coefficient for repeated plasma NMR measurements in smokers was 0.85. The NMR is stable in blood, plasma, and saliva at the conditions tested. Blood, plasma, and saliva NMRs are similar whereas urine NMR is a good proxy for these NMR measures. Plasma NMR was reproducible over time in smokers. One measurement may reliably estimate a smoker's NMR for use as an estimate of the rate of nicotine metabolism. St Helen G, Novalen M, Heitjan DF, Dempsey D, Jacob P 3rd, Aziziyeh A, Wing VC, George TP, Tyndale RF, Benowitz NL. Reproducibility of the nicotine metabolite ratio in cigarette smokers. *Cancer Epidemiol Biomarkers Prev.* 2012 Jul; 21(7): 1105-1114. Epub 2012 May 2.

Morphine History Sensitizes Postsynaptic GABA Receptors On Dorsal Raphe Serotonin Neurons In A Stress-Induced Relapse Model In Rats

The serotonin (5-hydroxytryptamine, 5-HT) system plays an important role in stress-related psychiatric disorders and substance abuse. Previous work has shown that the dorsal raphe nucleus (DR)-5-HT system is inhibited by swim stress via stimulation of GABA synaptic activity by the stress neurohormone corticotropin-releasing factor (CRF). Additionally, the DR 5-HT system is regulated by opioids. The present study tests the hypothesis that the DR 5-HT system regulates stress-induced opioid relapse. In the first experiment, electrophysiological recordings of GABA synaptic activity in 5-HT DR neurons were conducted in brain slices from Sprague-Dawley rats that were exposed to swim stress-induced reinstatement of previously extinguished morphine conditioned place preference (CPP). Behavioral data indicate that swim stress triggers reinstatement of morphine CPP. Electrophysiology data indicate that 5-HT neurons in the morphine-conditioned group exposed to stress had increased amplitude of inhibitory postsynaptic currents (IPSCs), which would indicate greater postsynaptic GABA receptor density and/or sensitivity, compared to saline controls exposed to stress. In the second experiment, rats were exposed to either morphine or saline CPP and extinction, and then 5-HT DR neurons from both groups were examined for sensitivity to CRF in vitro. CRF induced a greater inward current in 5-HT neurons from morphine-conditioned subjects compared to saline-conditioned subjects. These data indicate that morphine history sensitizes 5-HT DR neurons to the GABAergic inhibitory effects of stress as well as to some of the effects of CRF. These mechanisms may sensitize subjects with a morphine history to the dysphoric effects of stressors and ultimately confer an enhanced vulnerability to stress-induced opioid relapse. Staub DR, Lunden JW, Cathel AM, Dolben EL, Kirby LG. Morphine history sensitizes postsynaptic GABA receptors on dorsal raphe serotonin neurons in a stress-induced relapse model in rats. *Psychoneuroendocrinology.* 2012 Jun; 37(6): 859-870. Epub 2011 Nov 1.

Deconstructing 14-Phenylpropyloxymetopon: Minimal Requirements For Binding To Mu Opioid Receptors

A series of phenylpropyloxyethylamines and cinnamyloxyethylamines were synthesized as deconstructed analogs of 14-phenylpropyloxymetopon and analyzed for opioid receptor binding affinity. Using the Conformationally Sampled Pharmacophore modeling approach, the authors discovered a series of compounds lacking a tyrosine mimetic, historically considered essential for μ opioid binding. Based on the binding studies, the authors have identified the optimal analogs to be N-methyl-N-phenylpropyl-2-(3-phenylpropoxy)ethanamine, with 1520nM, and 2-(cinnamyloxy)-N-methyl-N-phenylethanamine with 1680nM affinity for the μ opioid receptor. These partial opioid structure analogs will serve as the novel lead compounds for future optimization studies. Stavitskaya L, Shim J, Healy JR, Matsumoto RR, Mackerell AD Jr,

Coop A. Deconstructing 14-phenylpropyloxymetopon: Minimal requirements for binding to mu opioid receptors. *Bioorg Med Chem.* 2012 Jul 15; 20(14): 4556-4563. Epub 2012 May 11.

Structural Intermediates In A Model Of The Substrate Translocation Path Of The Bacterial Glutamate Transporter Homologue GltPh

Excitatory amino acid transporters (EAATs) are membrane proteins responsible for reuptake of glutamate from the synaptic cleft to terminate neurotransmission and help prevent neurotoxically high, extracellular glutamate concentrations. Important structural information about these proteins emerged from crystal structures of GltPh, a bacterial homologue of EAATs, in conformations facing outward and inward. These remarkably different conformations are considered to be end points of the substrate translocation path (STP), suggesting that the transport mechanism involves major conformational rearrangements that remain uncharted. To investigate possible steps in the structural transitions of the STP between the two end-point conformations, the authors applied a combination of computational modeling methods (motion planning, molecular dynamics simulations, and mixed elastic network models). They found that the conformational changes in the transition involve mainly the repositioning the "transport domain" and the "trimerization domain" identified previously in the crystal structures. The two domains move in opposite directions along the membrane normal, and the transport domain also tilts by $\sim 17^\circ$ with respect to this axis. Moreover, the TM3-4 loop undergoes a flexible, "restraining bar"-like conformational change with respect to the transport domain. As a consequence of these conformational rearrangements along the transition path we calculated a significant decrease of nearly 20% in the area of the transport-to-trimerization domain interface (TTDI). Water penetrates parts of the TTDI in the modeled intermediates but very much less in the end-point conformations. The authors show that these characteristics of the modeled intermediate states agree with experimental results from residue-accessibility studies in individual monomers and identify specific residues that can be used to test the proposed STP. Moreover, MD simulations of complete GltPh trimers constructed from initially identical monomer intermediates suggest that asymmetry can appear in the trimer, consonant with available experimental data showing independent transport kinetics by individual monomers in the trimers. Stolzenberg S, Khelashvili G, Weinstein H. Structural intermediates in a model of the substrate translocation path of the bacterial glutamate transporter homologue GltPh. *J Phys Chem B.* 2012 May 10; 116(18): 5372-5383. Epub 2012 May 2.

Structure Of The Nociceptin/Orphanin FQ Receptor In Complex With A Peptide Mimetic

Members of the opioid receptor family of G-protein-coupled receptors (GPCRs) are found throughout the peripheral and central nervous system, where they have key roles in nociception and analgesia. Unlike the 'classical' opioid receptors, δ , κ and μ (δ -OR, κ -OR and μ -OR), which were delineated by pharmacological criteria in the 1970s and 1980s, the nociceptin/orphanin FQ (N/OFQ) peptide receptor (NOP, also known as ORL-1) was discovered relatively recently by molecular cloning and characterization of an orphan GPCR. Although it shares high sequence similarity with classical opioid GPCR subtypes ($\sim 60\%$), NOP has a markedly distinct pharmacology, featuring activation by the endogenous peptide N/OFQ, and unique selectivity for exogenous ligands. Here the authors report the crystal structure of human NOP, solved in complex with the peptide mimetic antagonist compound-24 (C-24) (ref. 4), revealing atomic details of ligand-receptor recognition and selectivity. Compound-24 mimics the first four amino-terminal residues of the NOP-selective peptide antagonist UFP-101, a close derivative of N/OFQ, and provides important clues to the binding of these peptides. The X-ray structure also shows substantial conformational differences in the pocket regions between NOP and the classical opioid receptors κ (ref. 5) and μ (ref. 6), and these are probably due to a small number of residues that vary between these receptors. The NOP-compound-24 structure explains the divergent selectivity profile of NOP and provides a new structural template for the design of NOP

ligands. PMID: PMC3356928 [Available on 2012/11/16] PMID: 22596163 [PubMed - in process] Thompson AA, Liu W, Chun E, Katritch V, Wu H, Vardy E, Huang XP, Trapella C, Guerrini R, Calo G, Roth BL, Cherezov V, Stevens RC. Structure of the nociceptin/orphanin FQ receptor in complex with a peptide mimetic. *Nature*. 2012 May 16; 485(7398): 395-399. doi: 10.1038/nature11085.

Tachykinin NK₁ Receptor Antagonist Co-Administration Attenuates Opioid Withdrawal-Mediated Spinal Microglia and Astrocyte Activation Prolonged morphine treatment increases pain sensitivity in many patients. Enhanced spinal Substance P release is one of the adaptive changes associated with sustained opioid exposure. In addition to pain transmitting second order neurons, spinal microglia and astrocytes also express functionally active Tachykinin NK₁ (Substance P) receptors. In the present work the authors investigated the role of glial Tachykinin NK₁ receptors in morphine withdrawal-mediated spinal microglia and astrocyte activation. Their data indicate that intrathecal co-administration (6 days, twice daily) of a selective Tachykinin NK₁ receptor antagonist (N-acetyl-L-tryptophan 3,5-bis(trifluoromethyl)benzylester (L-732,138; 20 µg/injection)) attenuates spinal microglia and astrocyte marker and pro-inflammatory mediator immunoreactivity as well as hyperalgesia in withdrawn rats. Furthermore, covalent linkage of the opioid agonist with a Tachykinin NK₁ antagonist pharmacophore yielded a bivalent compound that did not augment spinal microglia or astrocyte marker or pro-inflammatory mediator immunoreactivity and did not cause paradoxical pain sensitization upon drug withdrawal. Thus, bivalent opioid/Tachykinin NK₁ receptor antagonists may provide a novel paradigm for long-term pain management. Tumati S, Largent-Milnes TM, Keresztes AI, Yamamoto T, Vanderah TW, Roeske WR, Hruby VJ, Varga EV. Tachykinin NK₁ receptor antagonist co-administration attenuates opioid withdrawal-mediated spinal microglia and astrocyte activation. *Eur J Pharmacol*. 2012 Jun 5; 684(1-3): 64-70.

Waterpipe Tobacco Products: Nicotine Labelling Versus Nicotine Delivery Waterpipe tobacco package labelling typically indicates "0.0% tar" and "0.05% or 0.5% nicotine". The objective of this study was to determine the extent to which nicotine labeling is related to nicotine delivery. 110 waterpipe smokers engaged in a 45-minute waterpipe smoking session. Puff topography and plasma nicotine were measured. Three waterpipe tobacco brands were used: Nakhla (0.5% nicotine), Starbuzz (0.05% nicotine), and Al Fakher (0.05% nicotine). Data were analyzed by one-way ANOVA. Topography did not differ across brands. Peak plasma nicotine varied significantly across brands. Al Fakher had the highest nicotine delivery (11.4 ng/ml) followed by Nakhla (9.8 ng/ml) and Starbuzz (5.8 ng/ml). Nicotine labelling on waterpipe tobacco products does not reflect delivery; smoking a brand with a "0.05% nicotine" label led to greater plasma nicotine levels than smoking a brand with a "0.5% nicotine" label. Waterpipe tobacco products should be labelled in a manner that does not mislead consumers. Vansickel AR, Shihadeh A, Eissenberg T. Waterpipe tobacco products: nicotine labelling versus nicotine delivery. *Tob Control*. 2012 May; 21(3): 377-379. Epub 2011 Jun 2.

Morphine Activates Neuroinflammation In A Manner Parallel To Endotoxin Opioids create a neuroinflammatory response within the CNS, compromising opioid-induced analgesia and contributing to various unwanted actions. How this occurs is unknown but has been assumed to be via classic opioid receptors. Herein, the authors provide direct evidence that morphine creates neuroinflammation via the activation of an innate immune receptor and not via classic opioid receptors. They demonstrate that morphine binds to an accessory protein of Toll-like receptor 4 (TLR4), myeloid differentiation protein 2 (MD-2), thereby inducing TLR4 oligomerization and

triggering proinflammation. Small-molecule inhibitors, RNA interference, and genetic knockout validate the TLR4/MD-2 complex as a feasible target for beneficially modifying morphine actions. Disrupting TLR4/MD-2 protein-protein association potentiated morphine analgesia in vivo and abolished morphine-induced proinflammation in vitro, the latter demonstrating that morphine-induced proinflammation only depends on TLR4, despite the presence of opioid receptors. These results provide an exciting, nonconventional avenue to improving the clinical efficacy of opioids. Wang X, Loram LC, Ramos K, de Jesus AJ, Thomas J, Cheng K, Reddy A, Somogyi AA, Hutchinson MR, Watkins LR, Yin H. Morphine activates neuroinflammation in a manner parallel to endotoxin. *Proc Natl Acad Sci U S A*. 2012 Apr 17; 109(16): 6325-6330. Epub 2012 Apr 2.

Translating The Brain Transcriptome In NeuroAIDS: From Non-Human Primates To Humans

In the post-human genome project era, high throughput techniques to detect and computational algorithms to analyze differentially expressed genes have proven to be powerful tools for studying pathogenesis of neuroAIDS. Concurrently, discovery of non-coding RNAs and their role in development and disease has underscored the importance of examining the entire transcriptome instead of protein coding genes alone. Herein, the authors review the documented changes in brain RNA expression profiles in the non-human primate model of neuroAIDS (SIV infected monkeys) and compare the findings to those resulting from studies in post-mortem human samples of neuroAIDS. Differential expression of mRNAs involved in inflammation and immune response are a common finding in both monkey and human samples - even in HIV infected people on combination antiretroviral therapy, a shared set of genes is upregulated in the brains of both infected monkeys and humans: B2M, IFI44, IFIT3, MX1, STAT1. Additionally, alterations in ion channel encoding genes have been observed in the human studies. Brain miRNA profiling has also been performed, and up-regulation of two miRNAs originating from the same transcript, miR-142-3p and miR-142-5p, is common to human and monkey neuroAIDS studies. With increases in knowledge about the genome and advances in technology, unraveling alterations in the transcriptome in the SIV/monkey model will continue to enrich our knowledge about the effects of HIV on the brain. Winkler JM, Chaudhuri AD, Fox HS. Translating the brain transcriptome in neuroAIDS: from non-human primates to humans. *J Neuroimmune Pharmacol*. 2012 Jun; 7(2): 372-379. Epub 2012 Feb 28.

Synaptic NMDA Receptors Mediate Hypoxic Excitotoxic Death Excessive NMDA receptor activation and excitotoxicity underlies pathology in many neuropsychiatric and neurological disorders, including hypoxia/ischemia. Thus, the development of effective therapeutics for these disorders demands a complete understanding of NMDA receptor (NMDAR) activation during excitotoxic insults. The extrasynaptic NMDAR hypothesis posits that synaptic NMDARs are neurotrophic/neuroprotective and extrasynaptic NMDARs are neurotoxic. The extrasynaptic hypothesis is built in part on observed selectivity for extrasynaptic receptors of a neuroprotective use-dependent NMDAR channel blocker, memantine. In rat hippocampal neurons, the authors found that a neuroprotective concentration of memantine shows little selectivity for extrasynaptic NMDARs when all receptors are tonically activated by exogenous glutamate. This led us to test the extrasynaptic NMDAR hypothesis using metabolic challenge, where the source of excitotoxic glutamate buildup may be largely synaptic. Three independent approaches suggest strongly that synaptic receptors participate prominently in hypoxic excitotoxicity. First, block of glutamate transporters with a nonsubstrate antagonist exacerbated rather than prevented damage, consistent with a primarily synaptic source of glutamate. Second, selective, preblock of synaptic NMDARs with a slowly reversible, use-dependent antagonist protected nearly fully against prolonged hypoxic insult. Third, glutamate pyruvate transaminase, which degrades ambient but not synaptic glutamate,

did not protect against hypoxia but protected against exogenous glutamate damage. Together, these results suggest that synaptic NMDARs can mediate excitotoxicity, particularly when the glutamate source is synaptic and when synaptic receptor contributions are rigorously defined. Moreover, the results suggest that in some situations therapeutically targeting extrasynaptic receptors may be inappropriate. Wroge CM, Hogins J, Eisenman L, Mennerick S. Synaptic NMDA receptors mediate hypoxic excitotoxic death. *J Neurosci.* 2012 May 9; 32(19): 6732-6742.

Structure Of The Human K-Opioid Receptor In Complex With JD_{Tic} Opioid receptors mediate the actions of endogenous and exogenous opioids on many physiological processes, including the regulation of pain, respiratory drive, mood, and--in the case of κ -opioid receptor (κ -OR)--dysphoria and psychotomimesis. Here the authors report the crystal structure of the human κ -OR in complex with the selective antagonist JD_{Tic}, arranged in parallel dimers, at 2.9 Å resolution. The structure reveals important features of the ligand-binding pocket that contribute to the high affinity and subtype selectivity of JD_{Tic} for the human κ -OR. Modelling of other important κ -OR-selective ligands, including the morphinan-derived antagonists norbinaltorphimine and 5'-guanidinonaltrindole, and the diterpene agonist salvinorin A analogue RB-64, reveals both common and distinct features for binding these diverse chemotypes. Analysis of site-directed mutagenesis and ligand structure-activity relationships confirms the interactions observed in the crystal structure, thereby providing a molecular explanation for κ -OR subtype selectivity, and essential insights for the design of compounds with new pharmacological properties targeting the human κ -OR. Wu H, Wacker D, Mileni M, Katritch V, Han GW, Vardy E, Liu W, Thompson AA, Huang XP, Carroll FI, Mascarella SW, Westkaemper RB, Mosier PD, Roth BL, Cherezov V, Stevens RC. Structure of the human κ -opioid receptor in complex with JD_{Tic}. *Nature.* 2012 Mar 21; 485(7398): 327-332. doi: 10.1038/nature10939.

Rodent Models Of HAND And Drug Abuse: Exogenous Administration Of Viral Protein(S) and Cocaine Humans and chimpanzees are the natural hosts for HIV. Non-human primate models of SIV/SHIV infection in rhesus, cynomolgus and pigtail macaques have been used extensively as excellent model systems for pathogenesis and vaccine studies. However, owing to the variability of disease progression in infected macaques, a phenomenon identical to humans, coupled with their prohibitive costs, there exists a critical need for the development of small-animal models in which to study the untoward effects of HIV-1 infection. Owing to the fact that rodents are not the natural permissive hosts for lentiviral infection, development of small animal models for studying virus infection has used strategies that circumvent the steps of viral entry and infection. Such strategies involve overexpression of toxic viral proteins, SCID mice engrafted with the human PBLs or macrophages, and EcoHIV chimeric virus wherein the gp120 of HIV-1 was replaced with the gp80 of the ecotropic murine leukemia virus. An additional strategy that is often used by investigators to study the toxic effect of viral proteins involves direct stereotactic injection of the viral protein(s) into specific brain regions. The present report is a compilation of the applications of direct administration of Tat into the striatum to mimic the effects of the viral neurotoxin in the CNS. Added advantage of this model is that it is also amenable to repeated intraperitoneal cocaine injections, thereby allowing the study of the additive/synergistic effects of both the viral protein and cocaine. Such a model system recapitulates aspects of HAND in the context of drug abuse. Yao H, Buch S. Rodent models of HAND and drug abuse: exogenous administration of viral protein(s) and cocaine. *J Neuroimmune Pharmacol.* 2012 Jun; 7(2): 341-351. Epub 2012 Mar 24.

6 β -N-Heterocyclic Substituted Naltrexamine Derivative NAP As A Potential Lead To Develop Peripheral Mu Opioid Receptor Selective Antagonists

A 6 β -N-heterocyclic substituted naltrexamine derivative, NAP, was proposed as a peripheral mu opioid receptor (MOR) selective antagonist based on the in vitro and in vivo pharmacological and pharmacokinetic studies. To further validate this notion, several functional assays were carried out to fully characterize this compound. In the charcoal gavage and intestinal motility assay in morphine-pelleted mice, when administered 0.3mg/kg or higher doses up to 3mg/kg subcutaneously, NAP significantly increased the intestinal motility compared to the saline treatment. The comparative opioid withdrawal precipitation study and the lower locomotor assay demonstrated that NAP showed only marginal intrinsic effect in the central nervous system either given subcutaneously or intravenously: no jumps were witnessed for the tested animals even given up to a dose of 50mg/kg, while similar noticeable wet-dog shakes only occurred at the dose 50 times of those for naloxone or naltrexone, and significant reduction of the hyper-locomotion only happened at the dose as high as 32mg/kg. Collectively, these results suggested that NAP may serve as a novel lead to develop peripheral MOR selective antagonist which might possess therapeutic potential for opioid-induced bowel dysfunction (OBD), such as opioid-induced constipation (OIC). Yuan Y, Stevens DL, Braithwaite A, Scoggins KL, Bilsky EJ, Akbarali HI, Dewey WL, Zhang Y. 6 β -N-Heterocyclic substituted naltrexamine derivative NAP as a potential lead to develop peripheral mu opioid receptor selective antagonists. *Bioorg Med Chem Lett*. 2012 Jul 15; 22(14): 4731-4734. Epub 2012 May 26.

Design and Synthesis Of A Bivalent Ligand To Explore The Putative Heterodimerization Of The Mu Opioid Receptor and The Chemokine Receptor CCR5

The bivalent ligand approach has been utilized not only to study the underlying mechanism of G protein-coupled receptors dimerization and/or oligomerization, but also to enhance ligand affinity and/or selectivity for potential treatment of a variety of diseases by targeting this process. Substance abuse and addiction have made both the prevention and the treatment of human immunodeficiency virus (HIV) infection more difficult to tackle. Morphine, a mu opioid receptor (MOR) agonist, can accelerate HIV infection through up-regulating the expression of the chemokine receptor CCR5, a well-known co-receptor for HIV invasion to the host cells and this has been extensively studied. Meanwhile, two research groups have described the putative MOR-CCR5 heterodimers in their independent studies. The purpose of this paper is to report the design and synthesis of a bivalent ligand to explore the biological and pharmacological process of the putative MOR-CCR5 dimerization phenomenon. The developed bivalent ligand thus contains two distinct pharmacophores linked through a spacer; ideally one of which will interact with the MOR and the other with the CCR5. Naltrexone and Maraviroc were selected as the pharmacophores to generate such a bivalent probe. The overall reaction route to prepare this bivalent ligand was convergent and efficient, and involved sixteen steps with moderate to good yields. The preliminary biological characterization showed that the bivalent compound 1 retained the pharmacological characteristics of both pharmacophores towards the MOR and the CCR5 respectively with relatively lower binding affinity, which tentatively validated our original molecular design. Yuan Y, Arnatt CK, Li G, Haney KM, Ding D, Jacob JC, Selley DE, Zhang Y. Design and synthesis of a bivalent ligand to explore the putative heterodimerization of the mu opioid receptor and the chemokine receptor CCR5. *Org Biomol Chem*. 2012 Apr 7; 10(13): 2633-2646. Epub 2012 Feb 22.

Cholesterol Level Influences Opioid Signaling In Cell Models and Analgesia In Mice and Humans

Cholesterol regulates the signaling of μ -opioid receptor in cell models, but it has not been demonstrated in mice or humans. Whether cholesterol regulates the signaling by mechanisms other than supporting the entirety of lipid raft microdomains is still unknown. By modulating cholesterol-

enriched lipid raft microdomains and/or total cellular cholesterol contents in human embryonic kidney cells stably expressing μ -opioid receptor, the authors concluded that cholesterol stabilized opioid signaling both by supporting the lipid raft's entirety and by facilitating G protein coupling. Similar phenomena were observed in the primary rat hippocampal neurons. In addition, reducing the brain cholesterol level with simvastatin impaired the analgesic effect of opioids in mice, whereas the opioid analgesic effect was enhanced in mice fed a high-cholesterol diet. Furthermore, when the records of patients were analyzed, an inverse correlation between cholesterol levels and fentanyl doses used for anesthesia was identified, which suggested the mechanisms above could also be applicable to humans. These results identified the interaction between opioids and cholesterol, which should be considered in clinics as a probable route for drug-drug interaction. These studies also suggested that a low cholesterol level could lead to clinical issues, such as the observed impairment in opioid functions. Zheng H, Zou H, Liu X, Chu J, Zhou Y, Loh HH, Law PY. Cholesterol level influences opioid signaling in cell models and analgesia in mice and humans. *J Lipid Res.* 2012 Jun; 53(6): 1153-1162. Epub 2012 Feb 29.

Endocannabinoids At The Synapse A Decade After The Dies Mirabilis (29 March 2001):

What We Still Do Not Know Endogenous cannabinoids (endocannabinoids, eCBs) are ubiquitous regulators of synaptic transmission in the brain, mediating numerous forms of short- and long-term plasticity, and having strong influences on synapse formation and neurogenesis. Their roles as retrograde messengers that suppress both excitatory and inhibitory transmission are well-established. Yet, despite intensive investigation, many basic aspects of the eCB system are not understood. This brief review highlights recent advances, problems that remain unresolved, and avenues for future exploration. While 2-arachidonoylglycerol (2-AG) is probably the major eCB for intercellular CB1R-dependent signalling, anandamide (AEA) has come to the forefront in several novel contexts, both as a dual endovanilloid/endocannabinoid that regulates synaptic transmission acutely and as the source of a steady eCB tone in hippocampus. Complexities in the cellular processing of 2-AG are receiving renewed attention, as they are increasingly recognized as major determinants of how 2-AG affects cells. Long-standing fundamental issues such as the synthesis pathway for AEA and the molecular mechanism(s) underlying cellular uptake and release of eCBs remain problematical. Alger BE. Endocannabinoids at the synapse a decade after the dies mirabilis (29 March 2001): what we still do not know. *J Physiol.* 2012 May 1; 590(Pt 10):2203-12. Epub 2012 Jan 30.

Dual Control of Dopamine Synthesis and Release by Presynaptic and Postsynaptic Dopamine

D2 Receptors Dysfunctions of dopaminergic homeostasis leading to either low or high dopamine (DA) levels are causally linked to Parkinson's disease, schizophrenia, and addiction. Major sites of DA synthesis are the mesencephalic neurons originating in the substantia nigra and ventral tegmental area; these structures send major projections to the dorsal striatum (DSt) and nucleus accumbens (NAcc), respectively. DA finely tunes its own synthesis and release by activating DA D2 receptors (D2R). To date, this critical D2R-dependent function was thought to be solely due to activation of D2Rs on dopaminergic neurons (D2 autoreceptors); instead, using site-specific D2R knock-out mice, we uncover that D2 heteroreceptors located on non-DAergic medium spiny neurons participate in the control of DA levels. This D2 heteroreceptor-mediated mechanism is more efficient in the DSt than in NAcc, indicating that D2R signaling differentially regulates mesolimbic- versus nigrostriatal-mediated functions. This study reveals previously unappreciated control of DA signaling, shedding new light on region-specific regulation of DA-mediated effects. Anzalone A, Lizardi-Ortiz JE, Ramos M, De Mei C, Hopf FW, Iaccarino C, Halbout B, Jacobsen J, Kinoshita C, Welter M, Caron MG, Bonci A, Sulzer D, Borrelli E. Dual control of dopamine

synthesis and release by presynaptic and postsynaptic dopamine D2 receptors. *J Neurosci.* 2012 Jun 27; 32(26): 9023-9034.

Complex Autonomous Firing Patterns Of Striatal Low-Threshold Spike Interneurons During sensorimotor learning, tonically active neurons (TANs) in the striatum acquire bursts and pauses in their firing based on the salience of the stimulus. Striatal cholinergic interneurons display tonic intrinsic firing, even in the absence of synaptic input, that resembles TAN activity seen in vivo. But whether there are other striatal neurons among the group identified as TANs is unknown. The authors used transgenic mice expressing green fluorescent protein under control of neuronal nitric oxide synthase or neuropeptide-Y promoters to aid in identifying low-threshold spike (LTS) interneurons in brain slices. They found that these neurons exhibit autonomous firing consisting of spontaneous transitions between regular, irregular, and burst firing, similar to cholinergic interneurons. As in cholinergic interneurons, these firing patterns arise from interactions between multiple intrinsic oscillatory mechanisms, but the mechanisms responsible differ. Both neurons maintain tonic firing because of persistent sodium currents, but the mechanisms of the subthreshold oscillations responsible for irregular firing are different. In LTS interneurons they rely on depolarization-activated non-inactivating calcium currents whereas those in cholinergic interneurons arise from a hyperpolarization-activated potassium conductance. Sustained membrane hyperpolarizations induce a bursting pattern in LTS interneurons, probably by recruiting a low-threshold, inactivating calcium conductance and by moving the membrane potential out of the activation range of the oscillatory mechanisms responsible for single spiking, in contrast to the bursting driven by non-inactivating currents in cholinergic interneurons. The complex intrinsic firing patterns of LTS interneurons may subservise differential release of classic and peptide neurotransmitters as well as nitric oxide. Beatty JA, Sullivan MA, Morikawa H, Wilson CJ. Complex autonomous firing patterns of striatal low-threshold spike interneurons. *J Neurophysiol.* 2012 May 9. [Epub ahead of print]

A Protein Cross-Linking Assay For Measuring Cell Surface Expression Of Glutamate Receptor Subunits In The Rodent Brain After In Vivo Treatments Trafficking of neurotransmitter receptors between intracellular and cell surface compartments is important for regulating neurotransmission. The authors developed a method for determining if an in vivo treatment has altered receptor distribution in a particular region of rodent brain. After the treatment, brain slices are rapidly prepared from the region of interest. Then, cell surface-expressed proteins are covalently cross-linked using the membrane-impermeable, bifunctional cross-linker bis(sulfosuccinimidyl)suberate (BS(3)). This increases the apparent molecular weight of surface receptors, while intracellular receptors are not modified. Thus, surface and intracellular receptor pools can be separated and quantified using SDS-PAGE and immunoblotting. This method is particularly useful for analyzing AMPA receptor subunits, offering advantages in accuracy, efficiency, and cost compared to biotinylation. A disadvantage is that some antibodies no longer recognize their target protein after cross-linking. The authors have used this method to quantify changes in receptor distribution after acute and chronic exposure to psychomotor stimulants. Boudreau AC, Milovanovic M, Conrad KL, Nelson C, Ferrario CR, Wolf ME. A protein cross-linking assay for measuring cell surface expression of glutamate receptor subunits in the rodent brain after in vivo treatments. 6. *Curr Protoc Neurosci.* 2012 Apr; Chapter 5: Unit 5.30.1-19.

Delayed Calcium Dysregulation In Neurons Requires Both The NMDA Receptor and The Reverse Na⁺/Ca²⁺ Exchanger

Glutamate-induced delayed calcium dysregulation (DCD) is a causal factor leading to neuronal death. The mechanism of DCD is not clear but Ca²⁺ influx via N-methyl-d-aspartate receptors (NMDAR) and/or the reverse plasmalemmal Na⁺/Ca²⁺ exchanger (NCXrev) could be involved in DCD. However, the extent to which NMDAR and NCX(rev) contribute to glutamate-induced DCD is uncertain. Here, the authors show that both NMDAR and NCX(rev) are critical for DCD in neurons exposed to excitotoxic glutamate. In rat cultured hippocampal neurons, 25 μM glutamate produced DCD accompanied by sustained increase in cytosolic Na⁺ ([Na⁺]_c) and plasma membrane depolarization. MK801 and memantine, noncompetitive NMDAR inhibitors, added shortly after glutamate, completely prevented DCD whereas AP-5, a competitive NMDAR inhibitor, failed to protect against DCD. None of the tested inhibitors lowered elevated [Na⁺]_c or restored plasma membrane potential. In the experiments with NCX reversal by gramicidin, MK801 and memantine robustly inhibited NCXrev while AP-5 was much less efficacious. In electrophysiological patch-clamp experiments MK801 and memantine inhibited NCXrev-mediated ion currents whereas AP-5 failed. Thus, MK801 and memantine, in addition to NMDAR, inhibited NCXrev. Inhibition of NCXrev either with KB-R7943, or by collapsing Na⁺ gradient across the plasma membrane, or by inhibiting Na⁺/H⁺ exchanger with 5-(N-ethyl-N-isopropyl) amiloride (EIPA) and thus preventing the increase in [Na⁺]_c failed to preclude DCD. However, NCXrev inhibition combined with NMDAR blockade by AP-5 completely prevented DCD. Overall, these data suggest that both NMDAR and NCXrev are essential for DCD in glutamate-exposed neurons and inhibition of individual mechanism is not sufficient to prevent calcium dysregulation. Brittain MK, Brustovetsky T, Sheets PL, Brittain JM, Khanna R, Cummins TR, Brustovetsky N. Delayed calcium dysregulation in neurons requires both the NMDA receptor and the reverse Na⁺/Ca²⁺ exchanger. *Neurobiol Dis.* 2012 Apr; 46(1): 109-117. Epub 2012 Jan 10.

Tobacco Addiction and The Dysregulation Of Brain Stress Systems

Tobacco is a highly addictive drug and is one of the most widely abused drugs in the world. The first part of this review explores the role of stressors and stress-associated psychiatric disorders in the initiation of smoking, the maintenance of smoking, and relapse after a period of abstinence. The reviewed studies indicate that stressors facilitate the initiation of smoking, decrease the motivation to quit, and increase the risk for relapse. Furthermore, people with depression or an anxiety disorder are more likely to smoke than people without these disorders. The second part of this review describes animal studies that investigated the role of brain stress systems in nicotine addiction. These studies indicate that corticotropin-releasing factor, Neuropeptide Y, the hypocretins, and norepinephrine play a pivotal role in nicotine addiction. In conclusion, the reviewed studies indicate that smoking briefly decreases subjective stress levels but also leads to a further dysregulation of brain stress systems. Drugs that decrease the activity of brain stress systems may diminish nicotine withdrawal and improve smoking cessation rates. Bruijnzeel AW. Tobacco addiction and the dysregulation of brain stress systems. *Neurosci Biobehav Rev.* 2012 May; 36(5): 1418-1441. Epub 2012 Mar 3.

Differential Dopamine Release Dynamics In The Nucleus Accumbens Core and Shell Track Distinct Aspects Of Goal-Directed Behavior For Sucrose

Mesolimbic dopamine projections to the nucleus accumbens (NAc) have been implicated in goal-directed behaviors for natural rewards and in learning processes involving cue-reward associations. The NAc has been traditionally subdivided into two anatomically distinct sub-regions with different functional properties: the shell and the core. The aim of the present study was to characterize rapid dopamine transmission across the two NAc sub-regions during cue-signaled operant behavior for a natural (sucrose) reward in

rats. Using fast-scan cyclic voltammetry (FSCV) the authors observed differences in the magnitude and dynamics of dopamine release events between the shell and core. Specifically, although cue-evoked dopamine release was observed in both sub-regions, it was larger and longer lasting in the shell compared with the core. Further, secondary dopamine release events were observed following the lever press response for sucrose in the NAc shell, but not the core. These findings demonstrate that the NAc displays regional specificity in dopamine transmission patterns during cued operant behavior for natural reward. Cacciapaglia F, Saddoris MP, Wightman RM, Carelli RM. Differential dopamine release dynamics in the nucleus accumbens core and shell track distinct aspects of goal-directed behavior for sucrose. *Neuropharmacology*. 2012 Apr; 62(5-6): 2050-2056. Epub 2012 Jan 12.

Selective Bilateral Lesion To Caudate Nucleus Modulates The Acute and Chronic

Methylphenidate Effects The psychostimulant methylphenidate (MPD) is currently the most prescribed drug therapy for attention deficit hyperactivity disorder (ADHD) and is used by students as a cognitive enhancer. The caudate nucleus (CN) is a structure within the motive circuit where MPD exerts its effects. It is known to contain high levels of dopaminergic cells and directly influence motor activity. The objective of this study was to understand the role of CN in response to acute and chronic administration of MPD. Specific and non-specific bilateral ablations were created in the CN using electrolytic lesion and 6-Hydroxydopamine (6-OHDA). Four groups of rats were used: control (n=4), sham (n=4), CN electrolytic lesion group (n=8) and CN 6-OHDA injected group (n=8). On experimental day one (ED 1) all rats received a saline injection and baseline locomotive activity was recorded. On ED 2 and ED 3 CN sham, electrolytic lesion and/or 6-OHDA injected groups were made followed by four to five days recovery (ED 3-7), followed by six daily 2.5 mg/kg MPD injections (ED 9-14), three days of washout (ED 15-17) and an MPD re-challenge of drug proceeding the washout days (ED 18). Locomotor activity was obtained at ED 1, 8, 9, and 18 using an open field assay. The results show that the CN electrolytic lesion group responded to the acute and chronic MPD administration similar to the control and sham group, while the CN 6-OHDA injected group prevented the acute and the chronic effects of MPD administration. One possible interpretation why nonspecific electrolytic lesioning of the CN failed to prevent acute and chronic effects of MPD administration is due to destruction of both the direct and the indirect CN pathways which act as an inhibitory/excitatory balance, electrolyticelectrolytic. The selective dopaminergic lesioning prevented the effects of MPD administration suggesting that dopaminergic pathways in CN play a significant role in the effects of MPD. Claussen CM, Chong SL, Dafny N. Selective bilateral lesion to caudate nucleus modulates the acute and chronic methylphenidate effects. *Pharmacol Biochem Behav*. 2012 Apr; 101(2): 208-216. Epub 2012 Jan 11.

Deployment Of The Human Immunodeficiency Virus Type 1 Protein Arsenal: Combating The Host To Enhance Viral Transcription and Providing Targets For Therapeutic

Development Despite the success of highly active antiretroviral therapy in combating human immunodeficiency virus type 1 (HIV-1) infection, the virus still persists in viral reservoirs, often in a state of transcriptional silence. This review focuses on the HIV-1 protein and regulatory machinery and how expanding knowledge of the function of individual HIV-1-coded proteins has provided valuable insights into understanding HIV transcriptional regulation in selected susceptible cell types. Historically, Tat has been the most studied primary transactivator protein, but emerging knowledge of HIV-1 transcriptional regulation in cells of the monocyte-macrophage lineage has more recently established that a number of the HIV-1 accessory proteins like Vpr may directly or indirectly regulate the transcriptional process. The viral proteins Nef and matrix play important roles in modulating the cellular activation pathways to facilitate viral replication. These

observations highlight the cross talk between the HIV-1 transcriptional machinery and cellular activation pathways. The review also discusses the proposed transcriptional regulation mechanisms that intersect with the pathways regulated by microRNAs and how development of the knowledge of chromatin biology has enhanced our understanding of key protein-protein and protein-DNA interactions that form the HIV-1 transcriptome. Finally, the authors discuss the potential pharmacological approaches to target viral persistence and enhance effective transcription to purge the virus in cellular reservoirs, especially within the central nervous system, and the novel therapeutics that are currently in various stages of development to achieve a much superior prognosis for the HIV-1-infected population. Dahiya S, Nonnemacher MR, Wigdahl B. Deployment of the human immunodeficiency virus type 1 protein arsenal: combating the host to enhance viral transcription and providing targets for therapeutic development. *J Gen Virol*. 2012 Jun; 93(Pt 6): 1151-1172. Epub 2012 Mar 14.

Rac1 Is Essential In Cocaine-Induced Structural Plasticity Of Nucleus Accumbens Neurons

Repeated cocaine administration increases the dendritic arborization of nucleus accumbens neurons, but the underlying signaling events remain unknown. Here the authors show that repeated exposure to cocaine negatively regulates the active form of Rac1, a small GTPase that controls actin remodeling in other systems. Further, they show, using viral-mediated gene transfer, that overexpression of a dominant negative mutant of Rac1 or local knockout of Rac1 is sufficient to increase the density of immature dendritic spines on nucleus accumbens neurons, whereas overexpression of a constitutively active Rac1 or light activation of a photoactivatable form of Rac1 blocks the ability of repeated cocaine exposure to produce this effect. Downregulation of Rac1 activity likewise promotes behavioral responses to cocaine exposure, with activation of Rac1 producing the opposite effect. These findings establish that Rac1 signaling mediates structural and behavioral plasticity in response to cocaine exposure. Dietz DM, Sun H, Lobo MK, Cahill ME, Chadwick B, Gao V, Koo JW, Mazei-Robison MS, Dias C, Maze I, Damez-Werno D, Dietz KC, Scobie KN, Ferguson D, Christoffel D, Ohnishi Y, Hodes GE, Zheng Y, Neve RL, Hahn KM, Russo SJ, Nestler EJ. Rac1 is essential in cocaine-induced structural plasticity of nucleus accumbens neurons. *Nat Neurosci*. 2012 Apr 22. doi: 10.1038/nn.3094. [Epub ahead of print].

Subregional, Dendritic Compartment, and Spine Subtype Specificity In Cocaine Regulation Of Dendritic Spines In The Nucleus Accumbens

Numerous studies have found that chronic cocaine increases dendritic spine density of medium spiny neurons in the nucleus accumbens (NAc). Here, the authors used single-cell microinjections and advanced 3D imaging and analysis techniques to extend these findings in several important ways: by assessing cocaine regulation of dendritic spines in the core versus shell subregions of NAc in the mouse, over a broad time course (4 h, 24 h, or 28 d) of withdrawal from chronic cocaine, and with a particular focus on proximal versus distal dendrites. These data demonstrate subregion-specific, and in some cases opposite, regulation of spines by cocaine on proximal but not distal dendrites. Notably, all observed density changes were attributable to selective regulation of thin spines. At 4 h after injection, the proximal spine density is unchanged in the core but significantly increased in the shell. At 24 h, the density of proximal dendritic spines is reduced in the core but increased in the shell. Such downregulation of thin spines in the core persists through 28 d of withdrawal, whereas the spine density in the shell returns to baseline levels. Consistent with previous results, dendritic tips exhibited upregulation of dendritic spines after 24 h of withdrawal, an effect localized to the shell. The divergence in regulation of proximal spine density in NAc core versus shell by cocaine correlates with recently reported electrophysiological data from a similar drug administration regimen and might represent a key mediator of changes in the reward circuit that drive aspects of addiction. Dumitriu D, Laplant

Q, Grossman YS, Dias C, Janssen WG, Russo SJ, Morrison JH, Nestler EJ. Subregional, dendritic compartment, and spine subtype specificity in cocaine regulation of dendritic spines in the nucleus accumbens. *J Neurosci.* 2012 May 16; 32(20): 6957-6966.

Mice With Reduced NMDA Receptor Expression: More Consistent With Autism Than Schizophrenia?

Reduced NMDA-receptor (NMDAR) function has been implicated in the pathophysiology of neuropsychiatric disease, most strongly in schizophrenia but also recently in autism spectrum disorders (ASD). To determine the direct contribution of NMDAR dysfunction to disease phenotypes, a mouse model with constitutively reduced expression of the obligatory NR1 subunit has been developed and extensively investigated. Adult NR1(neo) (-/-) mice show multiple abnormal behaviors, including reduced social interactions, locomotor hyperactivity, self-injury, deficits in prepulse inhibition, and sensory hypersensitivity, among others. Whereas such phenotypes have largely been interpreted in the context of schizophrenia, these behavioral abnormalities are rather non-specific and are frequently present across models of diseases characterized by negative symptom domains. This study investigated auditory electrophysiological and behavioral paradigms relevant to autism, to determine whether NMDAR hypofunction may be more consistent with adult ASD-like phenotypes. Indeed, transgenic mice demonstrated behavioral deficits relevant to all core ASD symptoms, including decreased social interactions, altered ultrasonic vocalizations, and increased repetitive behaviors. NMDAR disruption recapitulated clinical endophenotypes including reduced prepulse inhibition, auditory-evoked response N1 latency delay, and reduced gamma synchrony. Auditory electrophysiological abnormalities more closely resembled those seen in clinical studies of autism than schizophrenia. These results suggest that NMDA-receptor hypofunction may be associated with a continuum of neuropsychiatric diseases, including schizophrenia and autism. Neural synchrony abnormalities suggest an imbalance of glutamatergic and GABAergic coupling and may provide a target, along with behavioral phenotypes, for preclinical screening of novel therapeutics. Gandal MJ, Anderson RL, Billingslea EN, Carlson GC, Roberts TP, Siegel SJ. Mice with reduced NMDA receptor expression: more consistent with autism than schizophrenia? *Genes Brain Behav.* 2012 Jun 22; 9999(999A). doi: 10.1111/j.1601-183X.2012.00816.x. [Epub ahead of print].

Morphine Administration and Abrupt Cessation Alter The Behavioral Diurnal Activity Pattern

In mammals, there is an underlying mechanism that dictates the organism's biological functions and daily activity schedule, known as circadian rhythms, which play a major role in maintaining steady metabolism, homeostasis, and immunity. Limited research has been done investigating the effects of continuous opiate administration on the circadian rhythm activity pattern. A change in circadian activity pattern is suggested as an experimental model to demonstrate long-term effect of the drug. The objective of this study was to investigate the effects of morphine treatment on the long term activity (24 h) of the animal as well as the activity after abrupt removal, since prescribed medication containing morphine is widely used and abused and its long term effects are not known. Male Sprague-Dawley rats were contained in stable conditions with a standard light/dark cycle recordings taken before, during and after morphine pellet implantation. Cosinor analysis was used to fit a 24-hour curve to the activity pattern. Results indicate that morphine pellet administration alters the mesor, amplitude, the day-time and night-time activity levels, and demonstrates a remarkable change in the maximal circadian rhythm timing during the withdrawal period. The question whether morphine changes the circadian rhythm or a change in circadian rhythm results in tolerance and withdrawal is discussed. Glaser AM, Reyes-Vázquez C, Prieto-Gómez B, Bureau K, Dafny N. Morphine administration and abrupt cessation alter the

behavioral diurnal activity pattern. *Pharmacol Biochem Behav.* 2012 Jun; 101(4): 544-552. Epub 2012 Feb 23.

Regulation Of Presynaptic Neurotransmission By Macroautophagy mTOR is a regulator of cell growth and survival, protein synthesis-dependent synaptic plasticity, and autophagic degradation of cellular components. When triggered by mTOR inactivation, macroautophagy degrades long-lived proteins and organelles via sequestration into autophagic vacuoles. mTOR further regulates synaptic plasticity, and neurodegeneration occurs when macroautophagy is deficient. It is nevertheless unknown whether macroautophagy modulates presynaptic function. The authors find that the mTOR inhibitor rapamycin induces formation of autophagic vacuoles in prejunctional dopaminergic axons with associated decreased axonal profile volumes, synaptic vesicle numbers, and evoked dopamine release. Evoked dopamine secretion was enhanced and recovery was accelerated in transgenic mice in which macroautophagy deficiency was restricted to dopaminergic neurons; rapamycin failed to decrease evoked dopamine release in the striatum of these mice. Macroautophagy that follows mTOR inhibition in presynaptic terminals, therefore, rapidly alters presynaptic structure and neurotransmission. Hernandez D, Torres CA, Setlik W, Cebrián C, Mosharov EV, Tang G, Cheng HC, Kholodilov N, Yarygina O, Burke RE, Gershon M, Sulzer D. Regulation of presynaptic neurotransmission by macroautophagy. *Neuron.* 2012 Apr 26; 74(2): 277-284.

Neurosteroids, Trigger Of The LH Surge Recent experiments from our laboratory are consistent with the idea that hypothalamic astrocytes are critical components of the central nervous system (CNS) mediated estrogen positive feedback mechanism. The "astrocrine hypothesis" maintains that ovarian estradiol rapidly increases free cytoplasmic calcium concentrations ($[Ca^{2+}]_i$) that facilitate progesterone synthesis in astrocytes. This hypothalamic neuroprogesterone along with the elevated estrogen from the ovaries allows for the surge release of gonadotropin-releasing hormone (GnRH) that triggers the pituitary luteinizing hormone (LH) surge. A narrow range of estradiol stimulated progesterone production supports an "off-on-off" mechanism regulating the transition from estrogen negative feedback to estrogen positive feedback, and back again. The rapidity of the $[Ca^{2+}]_i$ response and progesterone synthesis support a non-genomic, membrane-initiated signaling mechanism. In hypothalamic astrocytes, membrane-associated estrogen receptors (mERs) signal through transactivation of the metabotropic glutamate receptor type 1a (mGluR1a), implying that astrocytic function is influenced by surrounding glutamatergic nerve terminals. Although other putative mERs, such as mER β , STX-activated mER-G α (q), and G protein-coupled receptor 30 (GPR30), are present and participate in membrane-mediated signaling, their influence in reproduction is still obscure since female reproduction be it estrogen positive feedback or lordosis behavior requires mER α . The astrocrine hypothesis is also consistent with the well-known sexual dimorphism of estrogen positive feedback. In rodents, only post-pubertal females exhibit this positive feedback. Hypothalamic astrocytes cultured from females, but not males, responded to estradiol by increasing progesterone synthesis. Estrogen autoregulates its own signaling by regulating levels of mER α in the plasma membrane of female astrocytes. In male astrocytes, the estradiol-induced increase in mER α was attenuated, suggesting that membrane-initiated estradiol signaling (MIES) would also be blunted. Indeed, estradiol induced $[Ca^{2+}]_i$ release in male astrocytes, but not to levels required to stimulate progesterone synthesis. Investigation of this sexual differentiation was performed using hypothalamic astrocytes from post-pubertal four core genotype (FCG) mice. In this model, genetic sex is uncoupled from gonadal sex. The authors demonstrated that animals that developed testes (XYM and XXM) lacked estrogen positive feedback, strongly suggesting that the sexual differentiation of progesterone synthesis is driven by the sex steroid

environment during early development. This article is part of a Special Issue entitled 'Neurosteroids'. Kuo J, Micevych P. Neurosteroids, trigger of the LH surge. *J Steroid Biochem Mol Biol.* 2012 Aug; 131(1-2): 57-65. Epub 2012 Feb 2.

Quinpirole Elicits Differential In Vivo Changes In The Pre- and Postsynaptic Distributions Of Dopamine D2 Receptors In Mouse Striatum: Relation To Cannabinoid-1 (CB1) Receptor Targeting

The nucleus accumbens (Acb) shell and caudate-putamen nucleus (CPu) are respectively implicated in the motivational and motor effects of dopamine, which are mediated in part through dopamine D2-like receptors (D2Rs) and modulated by activation of the cannabinoid-1 receptor (CB1R). The dopamine D(2/D3) receptor agonist, quinpirole elicits internalization of D2Rs in isolated cells; however, dendritic and axonal targeting of D2Rs may be highly influenced by circuit-dependent changes in vivo and potentially influenced by endogenous CB1R activation. The authors sought to determine whether quinpirole alters the surface/cytoplasmic partitioning of D2Rs in striatal neurons in vivo. To address this question, they examined the electron microscopic immunolabeling of D2 and CB1 receptors in the Acb shell and CPu of male mice at 1 h following a single subcutaneous injection of quinpirole (0.5 mg/kg) or saline, a time point when quinpirole reduced locomotor activity. Many neuronal profiles throughout the striatum of both treatment groups expressed the D2R and/or CB1R. As compared with saline, quinpirole-injected mice showed a significant region-specific decrease in the plasmalemmal and increase in the cytoplasmic density of D2R-immunogold particles in postsynaptic dendrites without CB1R-immunolabeling in the Acb shell. However, quinpirole produced a significant increase in the plasmalemmal density of D2R immunogold in CB1R negative axons in both the Acb shell and CPu. These results provide in vivo evidence for agonist-induced D2R trafficking that is inversely related to CB1R distribution in postsynaptic neurons of Acb shell and in presynaptic axons in this region and in the CPu. Lane DA, Chan J, Fitzgerald ML, Kearns CS, Mackie K, Pickel VM. Quinpirole elicits differential in vivo changes in the pre- and postsynaptic distributions of dopamine D2 receptors in mouse striatum: relation to cannabinoid-1 (CB1) receptor targeting. *Psychopharmacology (Berl).* 2012 May; 221(1): 101-113. Epub 2011 Dec 8.

Quantitative Unit Classification Of Ventral Tegmental Area Neurons In Vivo

Neurons in the ventral tegmental area (VTA) synthesize several major neurotransmitters, including dopamine (DA), GABA, and glutamate. To classify VTA single-unit neural activity from freely moving rats, the authors used hierarchical agglomerative clustering and probability distributions as quantitative methods. After many parameters were examined, a firing rate of 10 Hz emerged as a transition frequency between clusters of low-firing and high-firing neurons. To form a subgroup identified as high-firing neurons with GABAergic characteristics, the high-firing classification was sorted by spike duration. To form a subgroup identified as putative DA neurons, the low-firing classification was sorted by DA D2-type receptor pharmacological responses to quinpirole and eticlopride. Putative DA neurons were inhibited by the D2-type receptor agonist quinpirole and returned to near-baseline firing rates or higher following the D2-type receptor antagonist eticlopride. Other unit types showed different responses to these D2-type receptor drugs. A multidimensional comparison of neural properties indicated that these subgroups often clustered independently of each other with minimal overlap. Firing pattern variability reliably distinguished putative DA neurons from other unit types. A combination of phasic burst properties and a low skew in the interspike interval distribution produced a neural population that was comparable to the one sorted by D2 pharmacology. These findings provide a quantitative statistical approach for the classification of VTA neurons in unanesthetized animals. Li W, Doyon WM, Dani JA. Quantitative unit

classification of ventral tegmental area neurons in vivo. *J Neurophysiol.* 2012 May; 107(10): 2808-2820. Epub 2012 Feb 29.

Methamphetamine-Induced Dopamine Terminal Deficits In The Nucleus Accumbens Are Exacerbated By Reward-Associated Cues and Attenuated By CB1 Receptor Antagonism

Methamphetamine (METH) exposure is primarily associated with deleterious effects to dopaminergic neurons. While several studies have implicated the endocannabinoid system in METH's locomotor, rewarding and neurochemical effects, a role for this signaling system in METH's effects on dopamine terminal dynamics has not been elucidated. Given that CB1 receptor blockade reduces the acute potentiation of phasic extracellular dopamine release from other psychomotor stimulant drugs and that the degree of acute METH-induced increases in extracellular dopamine levels is related to the severity of dopamine depletion, the authors predicted that pretreatment with the CB1 receptor antagonist rimonabant would reduce METH-induced alterations at dopamine terminals. Furthermore, they hypothesized that administration of METH in environments where reward associated-cues were present would potentiate METH's acute effects on dopamine release in the nucleus accumbens and exacerbate changes in dopamine terminal activity. Fast-scan cyclic voltammetry was used to measure electrically-evoked dopamine release in the nucleus accumbens and revealed markers of compromised dopamine terminal integrity nine days after a single dose of METH. These were exacerbated in animals that received METH in the presence of reward-associated cues, and attenuated in rimonabant-pretreated animals. While these deficits in dopamine dynamics were associated with reduced operant responding on days following METH administration in animals treated with only METH, rimonabant-pretreated animals exhibited levels of operant responding comparable to control. Moreover, dopamine release correlated significantly with changes in lever pressing behavior that occurred on days following METH administration. Together these data suggest that the endocannabinoid system is involved in the subsecond dopaminergic response to METH. Loewinger GC, Beckert MV, Tejada HA, Cheer JF. Methamphetamine-induced dopamine terminal deficits in the nucleus accumbens are exacerbated by reward-associated cues and attenuated by CB1 receptor antagonism. *Neuropharmacology.* 2012 Jun; 62(7): 2192-2201. Epub 2012 Jan 25.

Prior Methamphetamine Self-Administration Attenuates Serotonergic Deficits Induced By Subsequent High-Dose Methamphetamine Administrations

Pre-clinical studies indicate that high-dose, non-contingent methamphetamine (METH) administration both rapidly and persistently decreases serotonergic neuronal function. Despite research indicating the hippocampus plays an important role in METH abuse and is affected by METH use, effects of METH self-administration on hippocampal serotonergic neurons are not well understood, and were thus an important focus of the current study. Because humans often administer METH in a binge-like pattern, effects of prior METH self-administration on a subsequent "binge-like" METH treatment were also examined. Rats were treated as described above, and sacrificed 1 or 8d after self-administration or 1h or 7d after the final binge METH or saline exposure. Hippocampal serotonin (5-hydroxytryptamine; 5HT) content and transporter (SERT) function were assessed. METH self-administration per se had no persistent effect on hippocampal 5HT content or SERT function. However, this treatment attenuated the persistent, but not acute, hippocampal serotonergic deficits caused by a subsequent repeated, high-dose, non-contingent METH treatment administered 1 d the last self-administration session. No attenuation in persistent deficits were seen when the high-dose administration of METH occurred 15d after the last self-administration session. The present findings demonstrate that METH self-administration alters serotonergic neurons so as to engender "tolerance" to the persistent serotonergic deficits caused by a subsequent METH exposure. However, this "tolerance" does not

persist. These data provide a foundation to investigate complex questions including how the response of serotonergic neurons to METH may contribute to contingent-related disorders such as dependence and relapse. McFadden LM, Hunt MM, Vieira-Brock PL, Muehle J, Nielsen SM, Allen SC, Hanson GR, Fleckenstein AE. Prior methamphetamine self-administration attenuates serotonergic deficits induced by subsequent high-dose methamphetamine administrations. *Drug Alcohol Depend.* 2012 May 28. [Epub ahead of print].

Synaptic Cell Adhesion Chemical synapses are asymmetric intercellular junctions that mediate synaptic transmission. Synaptic junctions are organized by trans-synaptic cell adhesion molecules bridging the synaptic cleft. Synaptic cell adhesion molecules not only connect pre- and postsynaptic compartments, but also mediate trans-synaptic recognition and signaling processes that are essential for the establishment, specification, and plasticity of synapses. A growing number of synaptic cell adhesion molecules that include neurexins and neuroligins, Ig-domain proteins such as SynCAMs, receptor phosphotyrosine kinases and phosphatases, and several leucine-rich repeat proteins have been identified. These synaptic cell adhesion molecules use characteristic extracellular domains to perform complementary roles in organizing synaptic junctions that are only now being revealed. The importance of synaptic cell adhesion molecules for brain function is highlighted by recent findings implicating several such molecules, notably neurexins and neuroligins, in schizophrenia and autism. Missler M, Südhof TC, Biederer T. Synaptic cell adhesion. *Cold Spring Harb Perspect Biol.* 2012 Apr 1; 4(4): a005694. doi: 10.1101/cshperspect.a005694.

Δ 9-Tetrahydrocannabinol (Δ 9-THC) Attenuates Mouse Sperm Motility and Male Fecundity

Numerous studies have shown that N-arachidonylethanolamine (AEA) can inhibit sperm motility and function but the ability of cannabinoids to inhibit sperm motility is not well understood. The authors investigated the effects of WIN 55,212-2, a CB(1) cannabinoid receptor agonist, and Δ (9) - tetrahydrocannabinol (Δ (9) -THC) on the ATP levels and motility of murine sperm in vitro. In addition, the effects of acute administration of Δ (9) -THC on male fecundity were determined. Effects of Δ (9) -THC on basal sperm kinematics were determined using computer-assisted sperm analysis (CASA). Stop-motion imaging was performed to measure sperm beat frequency. The effect of Δ (9) -THC on sperm ATP was determined using a luciferase assay. Male fertility was determined by evaluating the size of litters sired by Δ (9) -THC-treated males. Pretreatment of sperm for 15 min with 1 μ M Δ (9) -THC reduced their basal motility and attenuated the ability of bicarbonate to stimulate flagellar beat frequency. Treatment with 5 μ M WIN 55,212-2 or 10 μ M Δ (9) -THC for 30 min reduced sperm ATP levels. In sperm lacking CB(1) receptors this inhibitory effect of WIN 55,212-2 on ATP was attenuated whereas that of Δ (9) -THC persisted. Administration of 50 mg·kg⁻¹ Δ (9) -THC to male mice just before mating caused a 20% decrease in embryonic litter size. Δ (9) -THC inhibits both basal and bicarbonate-stimulated sperm motility in vitro and reduces male fertility in vivo. High concentrations of WIN 55,212-2 or Δ (9) -THC inhibit ATP production in sperm; this effect of WIN 55,212-2 is CB(1) receptor-dependent whereas that of Δ (9) -THC is not. LINKED ARTICLES This article is part of a themed section on Cannabinoids in Biology and Medicine. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2012.165.issue-8>. To view Part I of Cannabinoids in Biology and Medicine visit <http://dx.doi.org/10.1111/bph.2011.163.issue-7>. Morgan DJ, Muller CH, Murataeva NA, Davis BJ, Mackie K. Δ 9-Tetrahydrocannabinol (Δ 9-THC) attenuates mouse sperm motility and male fecundity. *Br J Pharmacol.* 2012 Apr; 165(8): 2575-2583. doi: 10.1111/j.1476-5381.2011.01506.x.

Endogenously Released ACh and Exogenous Nicotine Differentially Facilitate Long-Term Potentiation Induction In The Hippocampal CA1 Region Of Mice

The authors examined the role of $\alpha 7$ - and $\beta 2$ -containing nicotinic acetylcholine receptors (nAChRs) in the induction of long-term potentiation (LTP). Theta-burst stimulation (TBS), mimicking the brain's naturally occurring theta rhythm, induced robust LTP in hippocampal slices from $\alpha 7$ and $\beta 2$ knockout mice. This suggests TBS is capable of inducing LTP without activation of $\alpha 7$ - or $\beta 2$ -containing nAChRs. However, when weak TBS was applied, the modulatory effects of nicotinic receptors on LTP induction became visible. The authors showed that during weak TBS, activation of $\alpha 7$ nAChRs occurs by the release of ACh, contributing to LTP induction. Additionally, bath-application of nicotine activated $\beta 2$ -containing nAChRs to promote LTP induction. Despite predicted nicotine-induced desensitization, synaptically mediated activation of $\alpha 7$ nAChRs still occurs in the presence of nicotine and contributed to LTP induction. Optical recording of single-stimulation-evoked excitatory activity with a voltage-sensitive dye revealed enhanced excitatory activity in the presence of nicotine. This effect of nicotine was robust during high-frequency stimulation, and was accompanied by enhanced burst excitatory postsynaptic potentials. Nicotine-induced enhancement of excitatory activity was observed in slices from $\alpha 7$ knockout mice, but was absent in $\beta 2$ knockout mice. These results suggest that the nicotine-induced enhancement of excitatory activity is mediated by $\beta 2$ -containing nAChRs, and is related to the nicotine-induced facilitation of LTP induction. Thus, our study demonstrates that the activation of $\alpha 7$ - and $\beta 2$ -containing nAChRs differentially facilitates LTP induction via endogenously released ACh and exogenous nicotine, respectively, in the hippocampal CA1 region of mice. Nakauchi S, Sumikawa K. Endogenously released ACh and exogenous nicotine differentially facilitate long-term potentiation induction in the hippocampal CA1 region of mice. *Eur J Neurosci*. 2012 May; 35(9): 1381-1395. doi: 10.1111/j.1460-9568.2012.08056.x. Epub 2012 Mar 30.

Corticotropin-Releasing Factor Modulation Of Forebrain GABAergic Transmission Has A Pivotal Role In The Expression Of Anabolic Steroid-Induced Anxiety In The Female Mouse

Increased anxiety is commonly observed in individuals who illicitly administer anabolic androgenic steroids (AAS). Behavioral effects of steroid abuse have become an increasing concern in adults and adolescents of both sexes. The dorsolateral bed nucleus of the stria terminalis (dlBnST) has a critical role in the expression of diffuse anxiety and is a key site of action for the anxiogenic neuromodulator, corticotropin releasing factor (CRF). Here the authors demonstrate that chronic, but not acute, exposure of female mice during adolescence to AAS augments anxiety-like behaviors; effects that were blocked by central infusion of the CRF receptor type 1 antagonist, antalarmin. AAS treatment selectively increased action potential (AP) firing in neurons of the central amygdala (CeA) that project to the dlBnST, increased the frequency of GABA(A) receptor-mediated spontaneous inhibitory postsynaptic currents (sIPSCs) in dlBnST target neurons, and decreased both c-FOS immunoreactivity (IR) and AP frequency in these postsynaptic cells. Acute application of antalarmin abrogated the enhancement of GABAergic inhibition induced by chronic AAS exposure whereas application of CRF to brain slices of naïve mice mimicked the actions of this treatment. These results, in concert with previous data demonstrating that chronic AAS treatment results in enhanced levels of CRF mRNA in the CeA and increased CRF-IR in the dlBnST neuropil, are consistent with a mechanism in which the enhanced anxiety elicited by chronic AAS exposure involves augmented inhibitory activity of CeA afferents to the dlBnST and CRF-dependent enhancement of GABAergic inhibition in this brain region. Oberlander JG, Henderson LP. Corticotropin-releasing factor modulation of forebrain GABAergic transmission has a pivotal role in the expression of anabolic steroid-induced anxiety in the female mouse.

Neuropsychopharmacology. 2012 May; 37(6): 1483-1499. doi: 10.1038/npp.2011.334. Epub 2012 Feb 1.

Temporally Dependent Changes In Cocaine-Induced Synaptic Plasticity In The Nucleus Accumbens Shell Are Reversed By D1-Like Dopamine Receptor Stimulation

Dopaminergic and glutamatergic inputs to the nucleus accumbens shell have a central role in reward processing. Non-contingent cocaine administration generates a number of long-term AMPA receptor-dependent changes in synaptic efficacy. However, the synaptic consequences of cocaine self-administration and the potential role of dopamine in these processes remain unclear. Here, the authors examined the influence of D1 dopamine receptor (D1DR) activation on excitatory synaptic plasticity in the accumbens shell of adult rats following cocaine self-administration. Their results indicated that during the first 2 days following cocaine exposure both pre- and post-synaptic mechanisms contribute to a net decrease in AMPA receptor-mediated signaling. This is reflected by decreased frequency of miniature EPSCs (mEPSCs) attributable to enhanced cannabinoid receptor activity, decreased mEPSC amplitude, and increased paired-pulse ratio of evoked EPSCs. In contrast, the only changes observed in the shell 3-4 weeks following cocaine self-administration were increased mEPSCs amplitudes and AMPA/NMDA ratios. The authors further found that although these cocaine-induced neuroadaptations during early and late abstinence have different synaptic expression mechanisms, they were normalized by stimulation of D1DRs. Thus, pre-exposure to the D1DR agonist, SKF38393, during the initial period of abstinence increased excitatory synaptic strength, but reduced excitatory signaling after weeks of abstinence. Taken together, these results indicate that the direction of changes in excitatory transmission induced by cocaine self-administration switches over the first few weeks of abstinence. Moreover, D1DRs gate the stability of these cocaine-induced changes at glutamatergic synapses in the accumbens shell by utilizing multiple temporally distinct mechanisms, which has implications for the treatment of cocaine craving and addiction. Ortinski PI, Vassoler FM, Carlson GC, Pierce RC. Temporally dependent changes in cocaine-induced synaptic plasticity in the nucleus accumbens shell are reversed by D1-like dopamine receptor stimulation. *Neuropsychopharmacology*. 2012 Jun; 37(7): 1671-1682. doi: 10.1038/npp.2012.12. Epub 2012 Mar 14.

Sources Contributing To The Average Extracellular Concentration Of Dopamine In The Nucleus Accumbens

Mesolimbic dopamine neurons fire in both tonic and phasic modes resulting in detectable extracellular levels of dopamine in the nucleus accumbens (NAc). In the past, different techniques have targeted dopamine levels in the NAc to establish a basal concentration. In this study, the authors used in vivo fast scan cyclic voltammetry (FSCV) in the NAc of awake, freely moving rats. The experiments were primarily designed to capture changes in dopamine caused by phasic firing - that is, the measurement of dopamine 'transients'. These FSCV measurements revealed for the first time that spontaneous dopamine transients constitute a major component of extracellular dopamine levels in the NAc. A series of experiments were designed to probe regulation of extracellular dopamine. Lidocaine was infused into the ventral tegmental area, the site of dopamine cell bodies, to arrest neuronal firing. While there was virtually no instantaneous change in dopamine concentration, longer sampling revealed a decrease in dopamine transients and a time-averaged decrease in the extracellular level. Dopamine transporter inhibition using intravenous GBR12909 injections increased extracellular dopamine levels changing both frequency and size of dopamine transients in the NAc. To further unmask the mechanics governing extracellular dopamine levels the authors used intravenous injection of the vesicular monoamine transporter (VMAT2) inhibitor, tetrabenazine, to deplete dopamine storage and increase cytoplasmic dopamine in the nerve terminals. Tetrabenazine almost abolished phasic dopamine

release but increased extracellular dopamine to ~500nM, presumably by inducing reverse transport by dopamine transporter (DAT). Taken together, data presented here show that average extracellular dopamine in the NAc is low (20-30nM) and largely arises from phasic dopamine transients. Owesson-White CA, Roitman MF, Sombers LA, Belle AM, Keithley RB, Peele JL, Carelli RM, Wightman RM. Sources contributing to the average extracellular concentration of dopamine in the nucleus accumbens. *J Neurochem.* 2012 Apr; 121(2): 252-262. doi: 10.1111/j.1471-4159.2012.07677.x. Epub 2012 Mar 13.

Glial Cells In (Patho)Physiology Neuroglial cells define brain homeostasis and mount defense against pathological insults. Astroglia regulate neurogenesis and development of brain circuits. In the adult brain, astrocytes enter into intimate dynamic relationship with neurons, especially at synaptic sites where they functionally form the tripartite synapse. At these sites, astrocytes regulate ion and neurotransmitter homeostasis, metabolically support neurons and monitor synaptic activity; one of the readouts of the latter manifests in astrocytic intracellular Ca(2+) signals. This form of astrocytic excitability can lead to release of chemical transmitters via Ca(2+) -dependent exocytosis. Once in the extracellular space, gliotransmitters can modulate synaptic plasticity and cause changes in behavior. Besides these physiological tasks, astrocytes are fundamental for progression and outcome of neurological diseases. In Alzheimer's disease, for example, astrocytes may contribute to the etiology of this disorder. Highly lethal glial-derived tumors use signaling trickery to coerce normal brain cells to assist tumor invasiveness. This review not only sheds new light on the brain operation in health and disease, but also points to many unknowns. Parpura V, Heneka MT, Montana V, Oliet SH, Schousboe A, Haydon PG, Stout RF Jr, Spray DC, Reichenbach A, Pannicke T, Pekny M, Pekna M, Zorec R, Verkhratsky A. Glial cells in (patho)physiology. *J Neurochem.* 2012 Apr; 121(1): 4-27. doi: 10.1111/j.1471-4159.2012.07664.x. Epub 2012 Feb 2.

Role Of Perisynaptic Parameters In Neurotransmitter Homeostasis--Computational Study Of A General Synapse Extracellular neurotransmitter concentrations vary over a wide range depending on the type of neurotransmitter and location in the brain. Neurotransmitter homeostasis near a synapse is achieved by a balance of several mechanisms including vesicular release from the presynapse, diffusion, uptake by transporters, nonsynaptic production, and regulation of release by autoreceptors. These mechanisms are also affected by the glia surrounding the synapse. However, the role of these mechanisms in achieving neurotransmitter homeostasis is not well understood. A biophysical modeling framework was proposed, based on a cortico-accumbens synapse example case, to reverse engineer glial configurations and parameters related to homeostasis for synapses that support a range of neurotransmitter gradients. Model experiments reveal that synapses with extracellular neurotransmitter concentrations in the micromolar range require nonsynaptic neurotransmitter sources and tight synaptic isolation by extracellular glial formations. The model was used to identify the role of perisynaptic parameters on neurotransmitter homeostasis and to propose glial configurations that could support different levels of extracellular neurotransmitter concentrations. Ranking the parameters based on their effect on neurotransmitter homeostasis, nonsynaptic sources were found to be the most important followed by transporter concentration and diffusion coefficient. Pendyam S, Mohan A, Kalivas PW, Nair SS. Role of perisynaptic parameters in neurotransmitter homeostasis--computational study of a general synapse. *Synapse.* 2012 Jul; 66(7): 608-621. doi: 10.1002/syn.21547. Epub 2012 Mar 27.

Levels Of Neural Progenitors In The Hippocampus Predict Memory Impairment And Relapse To Drug Seeking As A Function Of Excessive Methamphetamine Self-Administration

Methamphetamine affects the hippocampus, a brain region crucial for learning and memory, as well as relapse to drug seeking. Rats self-administered methamphetamine for 1 h twice weekly (intermittent-short-I-ShA), 1 h daily (limited-short-ShA), or 6 h daily (extended-long-LgA) for 22 sessions. After 22 sessions, rats from each access group were withdrawn from self-administration and underwent spatial memory (Y-maze) and working memory (T-maze) tests followed by extinction and reinstatement to methamphetamine seeking or received one intraperitoneal injection of 5-bromo-2'-deoxyuridine (BrdU) to label progenitors in the hippocampal subgranular zone (SGZ) during the synthesis phase. Two-hour-old and 28-day-old surviving BrdU-immunoreactive cells were quantified. I-ShA rats performed better on the Y-maze and had a greater number of 2-h-old SGZ BrdU cells than nondrug controls. LgA rats, but not ShA rats, performed worse on the Y- and T-maze and had a fewer number of 2-h-old SGZ BrdU cells than nondrug and I-ShA rats, suggesting that new hippocampal progenitors, decreased by methamphetamine, were correlated with impairment in the acquisition of new spatial cues. Analyses of addiction-related behaviors after withdrawal and extinction training revealed methamphetamine-primed reinstatement of methamphetamine-seeking behavior in all three groups (I-ShA, ShA, and LgA), and this effect was enhanced in LgA rats compared with I-ShA and ShA rats. Protracted withdrawal from self-administration enhanced the survival of SGZ BrdU cells, and methamphetamine seeking during protracted withdrawal enhanced Fos expression in the dentate gyrus and medial prefrontal cortex in LgA rats to a greater extent than in ShA and I-ShA rats. These results indicate that changes in the levels of the proliferation and survival of hippocampal neural progenitors and neuronal activation of hippocampal granule cells predict the effects of methamphetamine self-administration (limited vs extended access) on cognitive performance and relapse to drug seeking and may contribute to the impairments that perpetuate the addiction cycle. Recinto P, Samant AR, Chavez G, Kim A, Yuan CJ, Soleiman M, Grant Y, Edwards S, Wee S, Koob GF, George O, Mandyam CD. Levels of neural progenitors in the hippocampus predict memory impairment and relapse to drug seeking as a function of excessive methamphetamine self-administration. *Neuropsychopharmacology*. 2012 Apr; 37(5): 1275-1287. doi: 10.1038/npp.2011.315. Epub 2011 Dec 28.

Epigenetics Of μ -Opioid Receptors: Intersection With HIV-1 Infection Of The Central Nervous System

The abuse of intravenous drugs, such as heroin, has become a major public health concern due to the increased risk of HIV-1 infection. Opioids such as heroin were originally identified and subsequently abused for their analgesic effects. However, many investigations have found additional effects of opioids, including regulation of the immune system. As such, chronic opioid abuse has been shown to promote HIV-1 pathogenesis and facilitate HIV-1-associated neurocognitive dysfunction. Clinical opioids, such as morphine and methadone, as well as illicit opioids, such as heroin, exert their effects primarily through interactions with the μ -opioid receptor (MOR). However, the mechanisms by which opioids enhance neurocognitive dysfunction through MOR-mediated signaling pathways are not completely understood. New findings in the regulation of MOR expression, particularly epigenetic and transcriptional regulation as well as alternative splicing, sheds new insights into possible mechanisms of HIV-1 and opiate synergy. In this review, the authors identify mechanisms regulating MOR expression and propose novel mechanisms by which opioids and HIV-1 may modulate this regulation. Additionally, they suggest that differential regulation of newly identified MOR isoforms by opioids and HIV-1 has functional consequence in enhancing HIV-1 neurocognitive dysfunction. Regan PM, Dave RS, Datta PK, Khalili K. Epigenetics of μ -opioid receptors: intersection with HIV-1 infection of the central nervous system. *J Cell Physiol*. 2012 Jul; 227(7): 2832-2841. doi: 10.1002/jcp.24004.

S(+)-Amphetamine Induces A Persistent Leak In The Human Dopamine Transporter: Molecular Stent Hypothesis

Wherever they are located, dopamine transporters (DATs) clear dopamine (DA) from the extracellular milieu to help regulate dopaminergic signalling. Exposure to amphetamine (AMPH) increases extracellular DA in the synaptic cleft, which has been ascribed to DAT reverse transport. Increased extracellular DA prolongs postsynaptic activity and reinforces abuse and hedonic behaviour. *Xenopus laevis* oocytes expressing human (h) DAT were voltage-clamped and exposed to DA, R(-)AMPH, or S(+)-AMPH. At -60mV, near neuronal resting potentials, S(+)-AMPH induced a depolarizing current through hDAT, which after removing the drug, persisted for more than 30 min. This persistent leak in the absence of S(+)-AMPH was in contrast to the currents induced by R(-)AMPH and DA, which returned to baseline immediately after their removal. These data suggest that S(+)-AMPH and Na(+) carry the initial S(+)-AMPH-induced current, whereas Na⁺ and Cl⁻ carry the persistent leak current. The authors propose that the persistent current results from the internal action of S(+)-AMPH on hDAT because the temporal effect was consistent with S(+)-AMPH influx, and intracellular S(+)-AMPH activated the effect. The persistent current was dependent on Na(+) and was blocked by cocaine. Intracellular injection of S(+)-AMPH also activated a DA-induced persistent leak current. The authors report a previously unknown action of S(+)-AMPH on hDAT that potentially affects AMPH-induced DA release. They propose that internal S(+)-AMPH acts as a molecular stent that holds the transporter open even after external S(+)-AMPH is removed. Amphetamine-induced persistent leak currents are likely to influence dopaminergic signalling, DA release mechanisms, and amphetamine abuse. Rodriguez-Menchaca AA, Solis E Jr, Cameron K, De Felice LJ. S(+)-amphetamine induces a persistent leak in the human dopamine transporter: molecular stent hypothesis. *Br J Pharmacol*. 2012 Apr; 165(8): 2749-2757. doi: 10.1111/j.1476-5381.2011.01728.x.

Fast Modulation Of M-Opioid Receptor (MOR) Recycling Is Mediated By Receptor Agonists

The μ -opioid receptor (MOR) is a member of the G protein-coupled receptor family and the main target of endogenous opioid neuropeptides and morphine. Upon activation by ligands, MORs are rapidly internalized via clathrin-coated pits in heterologous cells and dissociated striatal neurons. After initial endocytosis, resensitized receptors recycle back to the cell surface by vesicular delivery for subsequent cycles of activation. MOR trafficking has been linked to opioid tolerance after acute exposure to agonist, but it is also involved in the resensitization process. Several studies describe the regulation and mechanism of MOR endocytosis, but little is known about the recycling of resensitized receptors to the cell surface. To study this process, the authors induced internalization of MOR with [D-Ala(2), N-Me-Phe(4), Gly(5)-ol]-enkephalin (DAMGO) and morphine and imaged in real time single vesicles recycling receptors to the cell surface. They determined single vesicle recycling kinetics and the number of receptors contained in them. Then they demonstrated that rapid vesicular delivery of recycling MORs to the cell surface was mediated by the actin-microtubule cytoskeleton. Recycling was also dependent on Rab4, Rab11, and the Ca(2+)-sensitive motor protein myosin Vb. Finally, they showed that recycling is acutely modulated by the presence of agonists and the levels of cAMP. This work identifies a novel trafficking mechanism that increases the number of cell surface MORs during acute agonist exposure, effectively reducing the development of opioid tolerance. Roman-Vendrell C, Yu YJ, Yudowski GA. Fast modulation of μ -opioid receptor (MOR) recycling is mediated by receptor agonists. *J Biol Chem*. 2012 Apr 27; 287(18): 14782-14791. Epub 2012 Feb 29.

NMDA Antagonists Recreate Signal-To-Noise Ratio and Timing Perturbations Present In Schizophrenia

There is increasing evidence that functional deficits in schizophrenia may be driven by a reduction in the signal-to-noise ratio (SNR) and consistent timing of neural signals. This study examined the extent to which exposure to the NMDA receptor antagonists ketamine and MK801, frequently used pharmacological models of schizophrenia, recreate deficits in electrophysiological markers of disturbed brain circuits that are thought to underlie the illness. Furthermore, this study characterizes the specificity of these differences across the frequency spectrum so as to help identify the nature of selective circuit abnormalities that mediate each oscillatory response as relevant to schizophrenia. Mouse EEG was recorded during exposure to repeated auditory stimuli after injection of either vehicle or drug. The dose-response relationship for each electrophysiological measure was determined for ketamine and MK-801. Time-frequency analyses were performed to assess baseline, total, and evoked power and intertrial coherence (ITC) at low (5-10 Hz) and high (35-80 Hz)-frequencies. High frequency evoked and total power was decreased by MK-801 and ketamine in a dose-dependent fashion. High frequency baseline power was increased by MK-801 and ketamine in a dose-dependent fashion. Similar to evoked power, high frequency inter-trial coherence was dose-dependently decreased by both drugs. Low frequency ITC was only decreased by ketamine. Both ketamine and MK-801 cause alterations in high-frequency baseline (noise), total (signal), and evoked (signal) power resulting in a loss of high frequency SNR that is thought to primarily reflect local circuit activity. These changes indicate an inappropriate increase in baseline activity, which can also be interpreted as non-task related activity. Ketamine induced a loss of intertrial coherence at low frequencies, indicating a loss of consistency in low-frequency circuit mechanisms. As a proportion of baseline power, both drugs had a relative shift from low to high frequencies, reflecting a change in the balance of brain activity from coordination of global regions to a pattern of disorganized, autonomous local activity. These changes are consistent with a pattern of fragmented regional brain activity seen in schizophrenia. Saunders JA, Gandal MJ, Siegel SJ. NMDA antagonists recreate signal-to-noise ratio and timing perturbations present in schizophrenia. *Neurobiol Dis.* 2012 Apr; 46(1): 93-100. Epub 2012 Jan 9.

The CB1 Cannabinoid Receptor C-Terminus Regulates Receptor Desensitization In Autaptic Hippocampal Neurones

The cannabinoid CB(1) receptor is the chief mediator of the CNS effects of cannabinoids. In cell culture model systems, CB(1) receptors both desensitize and internalize on activation. Previous work suggests that the extreme carboxy-terminus of this receptor regulates internalization via phosphorylation of residues clustered within this region. Mutational analysis of the carboxy-terminus of CB(1) receptors has demonstrated that the last six serine/threonine residues are necessary for agonist-induced internalization. However, the structural determinants of CB(1) receptor internalization are also dependent on the local cellular environment. The importance of cell context on CB(1) receptor function calls for an investigation of the functional roles of these residues in neurones. To determine the structural requirements of CB(1) internalization in neurones, the authors evaluated the signalling properties of carboxy-terminal mutated CB(1) receptors expressed in cultured autaptic hippocampal neurones, using electrophysiological methods. CB(1) receptors transfected into CB(1) knockout neurones signalled and desensitized as did wild-type neurones, allowing us to test specific CB(1) receptor mutations. Deletion of the last 13 residues yielded a CB(1) receptor that inhibited excitatory postsynaptic currents but did not desensitize. Furthermore, mutation of the final six serine and threonine residues to alanines resulted in a non-desensitizing receptor. In contrast, CB(1) receptors lacking residues 419-460, leaving the last 14 residues intact, did desensitize. The distal thirteen residues of CB(1) receptors are crucial for their desensitization in cultured neurones. Furthermore, this desensitization is likely to follow phosphorylation of serines and threonines within this region. LINKED ARTICLES: This article is part of a themed section on

Cannabinoids in Biology and Medicine. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2012.165.issue-8>. To view Part I of Cannabinoids in Biology and Medicine visit <http://dx.doi.org/10.1111/bph.2011.163.issue-7>. Straiker A, Wager-Miller J, Mackie K. The CB1 cannabinoid receptor C-terminus regulates receptor desensitization in autaptic hippocampal neurones. *Br J Pharmacol*. 2012 Apr; 165(8): 2652-2659. doi: 10.1111/j.1476-5381.2011.01743.x.

Examination Of A Role For Metabotropic Glutamate Receptor 5 In The Medial Prefrontal Cortex In Cocaine Sensitization In Rats

Glutamatergic projection neurons in the medial prefrontal cortex (mPFC) are hyperexcitable in cocaine-sensitized animals, resulting in increased excitatory output to addiction-associated regions such as the ventral tegmental area (VTA) and nucleus accumbens. Evidence suggests that Group I metabotropic glutamate receptor 5 (mGluR5) is necessary for cocaine sensitization, and stimulation of this receptor in the mPFC potentially alters cell excitability directly through glutamate release or indirectly through downstream signaling cascades. Experiments in this report examined the role of mPFC mGluR5 in behavioral sensitization to cocaine. Group I mGluR agonist dihydroxyphenylglycine (DHPG) (15 nmol/side), mGluR5 antagonist 3((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) (15 nmol/side), mGluR1 antagonist YM298198 (15 nmol/side), AMPA receptor antagonist CNQX (1 nmol/side), and/or saline were administered through cannulae implanted 1 mm above the mPFC and/or VTA in male rats. Cocaine (15 mg/kg, i.p.) was systemically administered for four consecutive days to induce sensitization and/or once on test day immediately preceding locomotor monitoring. Intra-mPFC DHPG induced an mGluR5-mediated cross-sensitization to cocaine preventable through the prior administration of an AMPA receptor antagonist in the VTA. Furthermore, mGluR5 blockade in the mPFC failed to prevent the initiation of sensitization. However, intra-mPFC injections of the mGluR5 antagonist MTEP prevented the expression of cocaine sensitization at 21, but not 7, days following daily cocaine injections suggesting a possible role for mPFC mGluR5 in the persistence of the cocaine-sensitized state. These data suggest that stimulation of mGluR5s in the mPFC is sufficient to induce cocaine sensitization and is necessary for the expression of this sensitized response. Timmer KM, Steketee JD. Examination of a role for metabotropic glutamate receptor 5 in the medial prefrontal cortex in cocaine sensitization in rats. *Psychopharmacology (Berl)*. 2012 May; 221(1): 91-100. Epub 2011 Nov 16.

Different Stressors Produce Excitation Or Inhibition Of Mesolimbic Dopamine Neuron

Activity: Response Alteration By Stress Pre-Exposure Stressors can exert a wide variety of responses, ranging from adaptive responses to pathological changes; moreover, recent studies suggest that mild stressors can attenuate the response of a system to major stressful events. The authors have previously shown that 2-week exposure to cold, a comparatively mild inescapable stressor, induced a pronounced reduction in ventral tegmental area (VTA) dopamine (DA) neuron activity, whereas restraint stress increases DA neuron activity. However, it is not known if these stressors differentially impact the VTA in a region-specific manner, if they differentially impact behavioral responses, or whether the effects of such different stressors are additive or antagonistic with regard to their impact on DA neuron firing. To address these questions, single-unit extracellular recordings were performed in anesthetized control rats and rats exposed to chronic cold, and tested after delivery of a 2-h restraint session. Chronic cold stress strongly attenuated the number of DA neurons firing in the VTA, and this effect occurred primarily in the medial and central VTA regions that preferentially project to reward-related ventral striatal regions. Chronic cold exposure also prevented the pronounced increase in DA neuron population activity without affecting the behavioral sensitization to amphetamine produced by restraint stress. Taken together,

these data show that a prolonged inescapable mild stressor can induce plastic changes that attenuate the DA system response to acute stress. Valenti O, Gill KM, Grace AA. Different stressors produce excitation or inhibition of mesolimbic dopamine neuron activity: response alteration by stress pre-exposure. *Eur J Neurosci.* 2012 Apr; 35(8): 1312-1321. doi: 10.1111/j.1460-9568.2012.08038.x.

Phasic Mesolimbic Dopamine Signaling Precedes and Predicts Performance Of A Self-Initiated Action Sequence Task

Sequential reward-seeking actions are readily learned despite the temporal gap between the earliest (distal) action in the sequence and the reward delivery. Fast dopamine signaling is hypothesized to mediate this form of learning by reporting errors in reward prediction. However, such a role for dopamine release in voluntarily initiated action sequences remains to be demonstrated. Using fast-scan cyclic voltammetry, the authors monitored phasic mesolimbic dopamine release, in real time, as rats performed a self-initiated sequence of lever presses to earn sucrose rewards. Before testing, rats received either 0 (n = 11), 5 (n = 11), or 10 (n = 8) days of action sequence training. For rats acquiring the action sequence task at test, dopamine release was strongly elicited by response-contingent (but unexpected) rewards. With learning, a significant elevation in dopamine release preceded performance of the proximal action and subsequently came to precede the distal action. This pre-distal dopamine release response was also observed in rats previously trained on the action sequence task, and the amplitude of this signal predicted the latency with which rats completed the action sequence. Importantly, the dopamine response to contingent reward delivery was not observed in rats given extensive pretraining. Pharmacological analysis confirmed that task performance was dopamine-dependent. These data suggest that phasic mesolimbic dopamine release mediates the influence that rewards exert over the performance of self-paced, sequentially-organized behavior and sheds light on how dopamine signaling abnormalities may contribute to disorders of behavioral control. Wassum KM, Ostlund SB, Maidment NT. Phasic mesolimbic dopamine signaling precedes and predicts performance of a self-initiated action sequence task. *Biol Psychiatry.* 2012 May 15; 71(10): 846-854. Epub 2012 Feb 2.

Ovarian Hormones and Chronic Administration During Adolescence Modify The Discriminative Stimulus Effects Of Delta-9-Tetrahydrocannabinol ($\Delta(9)$ -THC) In Adult Female Rats

Marijuana abuse during adolescence may alter its abuse liability during adulthood by modifying the interoceptive (discriminative) stimuli produced, especially in females due to an interaction with ovarian hormones. To examine this possibility, either gonadally intact or ovariectomized (OVX) female rats received 40 intraperitoneal injections of saline or 5.6mg/kg of $\Delta(9)$ -THC daily during adolescence, yielding 4 experimental groups (intact/saline, intact/ $\Delta(9)$ -THC, OVX/saline, and OVX/ $\Delta(9)$ -THC). These groups were then trained to discriminate $\Delta(9)$ -THC (0.32-3.2mg/kg) from saline under a fixed-ratio (FR) 20 schedule of food presentation. After a training dose was established for the subjects in each group, varying doses of $\Delta(9)$ -THC were substituted for the training dose to obtain dose-effect (generalization) curves for drug-lever responding and response rate. The results showed that: 1) the OVX/saline group had a substantially higher mean response rate under control conditions than the other three groups, 2) both OVX groups had higher percentages of THC-lever responding than the intact groups at doses of $\Delta(9)$ -THC lower than the training dose, and 3) the OVX/ $\Delta(9)$ -THC group was significantly less sensitive to the rate-decreasing effects of $\Delta(9)$ -THC compared to other groups. Furthermore, at sacrifice, western blot analyses indicated that chronic $\Delta(9)$ -THC in OVX and intact females decreased cannabinoid type-1 receptor (CB1R) levels in the striatum, and decreased phosphorylation of cyclic adenosine monophosphate response element binding protein (p-CREB) in the hippocampus. In contrast to the hippocampus, chronic $\Delta(9)$ -THC selectively increased p-CREB in the OVX/saline group in the striatum. Extracellular signal-regulated kinase (ERK) was not significantly affected by

either hormone status or chronic $\Delta(9)$ -THC. In summary, these data in female rats suggest that cannabinoid abuse by adolescent human females could alter their subsequent responsiveness to cannabinoids as adults and have serious consequences for brain development. Winsauer PJ, Filipeanu CM, Bailey EM, Hulst JL, Sutton JL. Ovarian hormones and chronic administration during adolescence modify the discriminative stimulus effects of delta-9-tetrahydrocannabinol ($\Delta(9)$ -THC) in adult female rats. *Pharmacol Biochem Behav.* 2012 Jun 15; 102(3): 442-449. [Epub ahead of print].

Augmentation Of Methamphetamine-Induced Behaviors In Transgenic Mice Lacking The Trace Amine-Associated Receptor 1

The trace amine-associated receptor 1 (TAAR1) is a G protein-coupled receptor that is functionally activated by amphetamine-based psychostimulants, including amphetamine, methamphetamine and MDMA. Previous studies have shown that in transgenic mice lacking the TAAR1 gene (TAAR1 knockout; KO) a single injection of amphetamine can produce enhanced behavioral responses compared to responses evoked in wild-type (WT) mice. Further, the psychostimulant effects of cocaine can be diminished by selective activation of TAAR1. These findings suggest that TAAR1 might be implicated in the rewarding properties of psychostimulants. To investigate the role of TAAR1 in the rewarding effects of drugs of abuse, the psychomotor stimulating effects of amphetamine and methamphetamine and the conditioned rewarding effects of methamphetamine and morphine were compared between WT and TAAR1 KO mice. In locomotor activity studies, both single and repeated exposure to d-amphetamine or methamphetamine generated significantly higher levels of total distance traveled in TAAR1 KO mice compared to WT mice. In conditioned place preference (CPP) studies, TAAR1 KO mice acquired methamphetamine-induced CPP earlier than WT mice and retained CPP longer during extinction training. In morphine-induced CPP, both WT and KO genotypes displayed similar levels of CPP. Results from locomotor activity studies suggest that TAAR1 may have a modulatory role in the behavioral sensitization to amphetamine-based psychostimulants. That methamphetamine-but not morphine-induced CPP was augmented in TAAR1 KO mice suggests a selective role of TAAR1 in the conditioned reinforcing effects of methamphetamine. Collectively, these findings provide support for a regulatory role of TAAR1 in methamphetamine signaling. Achat-Mendes C, Lynch LJ, Sullivan KA, Vallender EJ, Miller GM. Augmentation of methamphetamine-induced behaviors in transgenic mice lacking the trace amine-associated receptor 1. *Pharmacol Biochem Behav.* 2012 Apr; 101(2): 201-207. Epub 2011 Nov 4.

Astrocyte Glypicans 4 and 6 Promote Formation Of Excitatory Synapses Via GluA1 AMPA Receptors

In the developing central nervous system (CNS), the control of synapse number and function is critical to the formation of neural circuits. The authors previously demonstrated that astrocyte-secreted factors powerfully induce the formation of functional excitatory synapses between CNS neurons. Astrocyte-secreted thrombospondins induce the formation of structural synapses, but these synapses are postsynaptically silent. Here they use biochemical fractionation of astrocyte-conditioned medium to identify glypican 4 (Gpc4) and glypican 6 (Gpc6) as astrocyte-secreted signals sufficient to induce functional synapses between purified retinal ganglion cell neurons, and show that depletion of these molecules from astrocyte-conditioned medium significantly reduces its ability to induce postsynaptic activity. Application of Gpc4 to purified neurons is sufficient to increase the frequency and amplitude of glutamatergic synaptic events. This is achieved by increasing the surface level and clustering, but not overall cellular protein level, of the GluA1 subunit of the AMPA (α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) glutamate receptor (AMPA). Gpc4 and Gpc6 are expressed by astrocytes in vivo in the developing CNS, with Gpc4 expression enriched in the hippocampus and Gpc6 enriched in the cerebellum.

Finally, the authors demonstrate that Gpc4-deficient mice have defective synapse formation, with decreased amplitude of excitatory synaptic currents in the developing hippocampus and reduced recruitment of AMPARs to synapses. These data identify glypicans as a family of novel astrocyte-derived molecules that are necessary and sufficient to promote glutamate receptor clustering and receptivity and to induce the formation of postsynaptically functioning CNS synapses. Allen NJ, Bennett ML, Foo LC, Wang GX, Chakraborty C, Smith SJ, Barres BA. Astrocyte glypicans 4 and 6 promote formation of excitatory synapses via GluA1 AMPA receptors. *Nature*. 2012 May 27; 486(7403): 410-414. doi: 10.1038/nature11059.

Association Study Of The B-Arrestin 2 Gene (ARRB2) With Opioid and Cocaine Dependence In A European-American Population The rewarding properties of drugs of abuse are mediated by the mu-opioid receptor (MOR). Genetic variations in MOR and MOR interacting proteins (MORIPs) involved in MOR signaling may increase the risk for drug dependence. The MORIP β -arrestin plays an important role in the regulation of MOR trafficking, thereby highlighting it as a candidate gene for addiction phenotypes. In this case-control association study, DNA samples from cocaine-dependent (n=336) and opioid-dependent (n=335) patients and controls (n=656) were genotyped for seven single nucleotide polymorphisms (rs11868227, rs3786047, rs4522461, rs1045280, rs2271167, rs2036657, and rs4790694) across ARRB2, the gene encoding the β -arrestin 2 protein. No significant differences were observed in genotype or allele frequency between drug-dependent and control individuals for any of the single nucleotide polymorphisms analyzed. Haplotype analysis was similarly negative. Further studies are needed to determine whether variations in ARRB2 (or other MORIPs) are relevant to cocaine or opioid dependence in different ethnic populations or whether they confer a risk that is specific to dependence on other drugs of abuse. Ambrose-Lanci LM, Vaswani M, Clarke TK, Zeng A, Lohoff FW, Ferraro TN, Berrettini WH. Association study of the β -arrestin 2 gene (ARRB2) with opioid and cocaine dependence in a European-American population. *Psychiatr Genet*. 2012 Jun; 22(3): 141-145.

Clusters Of Secretagogin-Expressing Neurons In The Aged Human Olfactory Tract Lack Terminal Differentiation Expanding the repertoire of molecularly diverse neurons in the human nervous system is paramount to characterizing the neuronal networks that underpin sensory processing. Defining neuronal identities is particularly timely in the human olfactory system, whose structural differences from nonprimate macrosmatic species have recently gained momentum. Here, the authors identify clusters of bipolar neurons in a previously unknown outer "shell" domain of the human olfactory tract, which express secretagogin, a cytosolic Ca(2+) binding protein. These "shell" neurons are wired into the olfactory circuitry because they can receive mixed synaptic inputs. Unexpectedly, secretagogin is often coexpressed with polysialylated-neural cell adhesion molecule, β -III-tubulin, and calretinin, suggesting that these neurons represent a cell pool that might have escaped terminal differentiation into the olfactory circuitry. The authors hypothesized that secretagogin-containing "shell" cells may be eliminated from the olfactory axis under neurodegenerative conditions. Indeed, the density, but not the morphological or neurochemical integrity, of secretagogin-positive neurons selectively decreases in the olfactory tract in Alzheimer's disease. In conclusion, secretagogin identifies a previously undescribed cell pool whose cytoarchitectonic arrangements and synaptic connectivity are poised to modulate olfactory processing in humans. Attems J, Alpar A, Spence L, McParland S, Heikenwalder M, Uhlén M, Tanila H, Hökfelt TG, Harkany T. Clusters of secretagogin-expressing neurons in the aged human olfactory tract lack terminal differentiation. *Proc Natl Acad Sci U S A*. 2012 Apr 17; 109(16): 6259-6264. Epub 2012 Apr 2.

Analysis Of Detailed Phenotype Profiles Reveals CHRNA5-CHRNA3-CHRNA4 Gene Cluster Association With Several Nicotine Dependence Traits

The role of the nicotinic acetylcholine receptor gene cluster on chromosome 15q24-25 in the etiology of nicotine dependence (ND) is still being defined. In this study, the authors included all 15 tagging single nucleotide polymorphisms (SNPs) within the CHRNA5-CHRNA3-CHRNA4 cluster and tested associations with 30 smoking-related phenotypes. The study sample was ascertained from the Finnish Twin Cohort study. Twin pairs born 1938-1957 and concordant for a history of cigarette smoking were recruited along with their family members (mainly siblings), as part of the Nicotine Addiction Genetics consortium. The study sample consisted of 1,428 individuals (59% males) from 735 families, with mean age 55.6 years. The authors detected multiple novel associations for ND. DSM-IV ND symptoms associated significantly with the proxy SNP Locus 1 (rs2036527, $p = .000009$) and Locus 2 (rs578776, $p = .0001$) and tolerance factor of the Nicotine Dependence Syndrome Scale (NDSS) showed suggestive association to rs11636753 ($p = .0059$), rs11634351 ($p = .0069$), and rs1948 ($p = .0071$) in CHRNA4. Furthermore, the authors report significant association with DSM-IV ND diagnosis (rs2036527, $p = .0003$) for the first time in a Caucasian population. Several SNPs indicated suggestive association for traits related to ages at smoking initiation. Also, rs11636753 in CHRNA4 showed suggestive association with regular drinking ($p = .0029$) and the comorbidity of depression and ND ($p = .0034$). The authors demonstrate novel associations of DSM-IV ND symptoms and the NDSS tolerance subscale. Their results confirm and extend association findings for other ND measures. They show pleiotropic effects of this gene cluster on multiple measures of ND and also regular drinking and the comorbidity of ND and depression. Broms U, Wedenoja J, Largeau MR, Korhonen T, Pitkäniemi J, Kesitalo-Vuokko K, Häppölä A, Heikkilä KH, Heikkilä K, Ripatti S, Sarin AP, Salminen O, Paunio T, Pergadia ML, Madden PA, Kaprio J, Loukola A. Analysis of detailed phenotype profiles reveals CHRNA5-CHRNA3-CHRNA4 gene cluster association with several nicotine dependence traits. *Nicotine Tob Res.* 2012 Jun; 14(6): 720-733. Epub 2012 Jan 12.

Smoking and Genetic Risk Variation Across Populations Of European, Asian, and African American Ancestry--A Meta-Analysis Of Chromosome 15q25

Recent meta-analyses of European ancestry subjects show strong evidence for association between smoking quantity and multiple genetic variants on chromosome 15q25. This meta-analysis extends the examination of association between distinct genes in the CHRNA5-CHRNA3-CHRNA4 region and smoking quantity to Asian and African American populations to confirm and refine specific reported associations. Association results for a dichotomized cigarettes smoked per day phenotype in 27 datasets (European ancestry (N = 14,786), Asian (N = 6,889), and African American (N = 10,912) for a total of 32,587 smokers) were meta-analyzed by population and results were compared across all three populations. The authors demonstrate association between smoking quantity and markers in the chromosome 15q25 region across all three populations, and narrow the region of association. Of the variants tested, only rs16969968 is associated with smoking ($P < 0.01$) in each of these three populations (odds ratio [OR] = 1.33, 95% CI = 1.25-1.42, $P = 1.1 \times 10^{-17}$) in meta-analysis across all population samples). Additional variants displayed a consistent signal in both European ancestry and Asian datasets, but not in African Americans. The observed consistent association of rs16969968 with heavy smoking across multiple populations, combined with its known biological significance, suggests rs16969968 is most likely a functional variant that alters risk for heavy smoking. The authors interpret additional association results that differ across populations as providing evidence for additional functional variants, but we are unable to further localize the source of this association. Using the cross-population study paradigm provides valuable insights to narrow regions of interest and inform future biological experiments. Chen LS, Saccone NL, Culverhouse RC, Bracci PM, Chen CH, Dueker N, Han Y, Huang H, Jin G, Kohno T, Ma JZ,

Przybeck TR, Sanders AR, Smith JA, Sung YJ, Wenzlaff AS, Wu C, Yoon D, Chen YT, Cheng YC, Cho YS, David SP, Duan J, Eaton CB, Furberg H, Goate AM, Gu D, Hansen HM, Hartz S, Hu Z, Kim YJ, Kittner SJ, Levinson DF, Mosley TH, Payne TJ, Rao DC, Rice JP, Rice TK, Schwantes-An TH, Shete SS, Shi J, Spitz MR, Sun YV, Tsai FJ, Wang JC, Wrensch MR, Xian H, Gejman PV, He J, Hunt SC, Kardia SL, Li MD, Lin D, Mitchell BD, Park T, Schwartz AG, Shen H, Wiencke JK, Wu JY, Yokota J, Amos CI, Bierut LJ. Smoking and genetic risk variation across populations of European, Asian, and African American ancestry--a meta-analysis of chromosome 15q25. *Genet Epidemiol.* 2012 May; 36(4): 340-351. doi: 10.1002/gepi.21627.

Global Hypothesis Testing For High-Dimensional Repeated Measures Outcomes High-throughput technology in metabolomics, genomics, and proteomics gives rise to high dimension, low sample size data when the number of metabolites, genes, or proteins exceeds the sample size. For a limited class of designs, the classic 'univariate approach' for Gaussian repeated measures can provide a reasonable global hypothesis test. The authors derive new tests that not only accurately allow more variables than subjects, but also give valid analyses for data with complex between-subject and within-subject designs. Their derivations capitalize on the dual of the error covariance matrix, which is nonsingular when the number of variables exceeds the sample size, to ensure correct statistical inference and enhance computational efficiency. Simulation studies demonstrate that the new tests accurately control Type I error rate and have reasonable power even with a handful of subjects and a thousand outcome variables. The authors apply the new methods to the study of metabolic consequences of vitamin B6 deficiency. Free software implementing the new methods applies to a wide range of designs, including one group pre-intervention and post-intervention comparisons, multiple parallel group comparisons with one-way or factorial designs, and the adjustment and evaluation of covariate effects. Chi YY, Gribbin M, Lamers Y, Gregory JF 3rd, Muller KE. Global hypothesis testing for high-dimensional repeated measures outcomes. *Stat Med.* 2012 Apr 13; 31(8): 724-742. doi: 10.1002/sim.4435. Epub 2011 Dec 9.

Botch Promotes Neurogenesis By Antagonizing Notch Regulation of self-renewal and differentiation of neural stem cells is still poorly understood. Here the authors investigate the role of a developmentally expressed protein, Botch, which blocks Notch, in neocortical development. Downregulation of Botch in vivo leads to cellular retention in the ventricular and subventricular zones, whereas overexpression of Botch drives neural stem cells into the intermediate zone and cortical plate. In vitro neurosphere and differentiation assays indicate that Botch regulates neurogenesis by promoting neuronal differentiation. Botch prevents cell surface presentation of Notch by inhibiting the S1 furin-like cleavage of Notch, maintaining Notch in the immature full-length form. Understanding the function of Botch expands our knowledge regarding both the regulation of Notch signaling and the complex signaling mediating neuronal development. Chi Z, Zhang J, Tokunaga A, Harraz MM, Byrne ST, Dolinko A, Xu J, Blackshaw S, Gaiano N, Dawson TM, Dawson VL. Botch promotes neurogenesis by antagonizing Notch. *Dev Cell.* 2012 Apr 17; 22(4): 707-720. Epub 2012 Mar 22.

Genome-Wide Association Mapping Of Loci For Antipsychotic-Induced Extrapyrimal Symptoms In Mice Tardive dyskinesia (TD) is a debilitating, unpredictable, and often irreversible side effect resulting from chronic treatment with typical antipsychotic agents such as haloperidol. TD is characterized by repetitive, involuntary, purposeless movements primarily of the orofacial region. In order to investigate genetic susceptibility to TD, the authors used a validated mouse model for a systems genetics analysis geared toward detecting genetic predictors of TD in human patients. Phenotypic data from 27 inbred strains chronically treated with haloperidol and

phenotyped for vacuous chewing movements were subject to a comprehensive genomic analysis involving 426,493 SNPs, 4,047 CNVs, brain gene expression, along with gene network and bioinformatic analysis. Their results identified ~50 genes that they expect to have high prior probabilities for association with haloperidol-induced TD, most of which have never been tested for association with human TD. Among our top candidates were genes regulating the development of brain motor control regions (*Zic4* and *Nkx6-1*), glutamate receptors (*Grin1* and *Grin2a*), and an indirect target of haloperidol (*Drd1a*) that has not been studied as well as the direct target, *Drd2*. Crowley JJ, Kim Y, Szatkiewicz JP, Pratt AL, Quackenbush CR, Adkins DE, van den Oord E, Bogue MA, Yang H, Wang W, Threadgill DW, de Villena FP, McLeod HL, Sullivan PF. Genome-wide association mapping of loci for antipsychotic-induced extrapyramidal symptoms in mice. *Mamm Genome*. 2012 Jun; 23(5-6): 322-335. Epub 2011 Dec 30.

A Comparison Of Methods Sensitive To Interactions With Small Main Effects Numerous genetic variants have been successfully identified for complex traits, yet these genetic factors only account for a modest portion of the predicted variance due to genetic factors. This has led to increased interest in other approaches to account for the "missing" genetic contributions to phenotype, including joint gene-gene or gene-environment analysis. A variety of methods for such analysis have been advocated. However, they have seldom been compared systematically. To facilitate such comparisons, the developers of the multifactor dimensionality reduction (MDR) simulated 100 data replicates for each of 96 two-locus models displaying negligible marginal effects from either locus (16 variations on each of six basic genetic models). The genetic models, based on a dichotomous phenotype, had varying minor allele frequencies and from two to eight distinct risk levels associated with genotype. The basic models were modified to include "noise" from combinations of missing data, genotyping error, genetic heterogeneity, and phenocopies. This study compares the performance of three methods designed to be sensitive to joint effects (MDR, support vector machines (SVMs), and the restricted partition method (RPM)) on these simulated data. In these tests, the RPM consistently outperformed the other two methods for each of the six classes of genetic models. In contrast, the comparison between other two methods had mixed results. The MDR outperformed the SVM when the true model had only a few, well-separated risk classes; while the SVM outperformed the MDR on more complicated models. Of these methods, only MDR has a well-developed user interface. Culverhouse RC. A comparison of methods sensitive to interactions with small main effects. *Genet Epidemiol*. 2012 May; 36(4): 303-311. doi: 10.1002/gepi.21622. Epub 2012 Mar 28.

Inositol Polyphosphate Multikinase: An Emerging Player For The Central Action Of AMP-Activated Protein Kinase AMP-activated protein kinase (AMPK) is an essential enzyme indispensable for energy sensing and metabolic homeostasis at both the cellular and whole-body levels. Phosphorylation of AMPK, a key step for its activation, is known to be regulated by upstream kinases such as liver kinase B1 (LKB1) and calmodulin-dependent protein kinase kinase-beta (CaMKK β). Recent evidence shows that inositol polyphosphate multikinase (IPMK), which possesses both inositol phosphate kinase and lipid inositol kinase activities, can physiologically regulate AMPK signaling in cultured cells and in the arcuate nucleus. IPMK-mediated regulation of AMPK occurs through the dynamic protein interactions of IPMK with AMPK in response to glucose availability. Here the authors review and discuss a novel role for the hypothalamic IPMK signaling in the control of AMPK and central energy homeostasis. Dailey MJ, Kim S. Inositol polyphosphate multikinase: an emerging player for the central action of AMP-activated protein kinase. *Biochem Biophys Res Commun*. 2012 Apr 27; 421(1): 1-3. Epub 2012 Apr 7.

Cluster Cytometry For High-Capacity Bioanalysis Flow cytometry specializes in high-content measurements of cells and particles in suspension. Having long excelled in analytical throughput of single cells and particles, only recently with the advent of HyperCyt sampling technology, flow cytometry's multiexperiment throughput has begun to approach the point of practicality for efficiently analyzing hundreds-of-thousands of samples, the realm of high-throughput screening (HTS). To extend performance and automation compatibility, the authors built a HyperCyt-linked Cluster Cytometer platform, a network of flow cytometers for analyzing samples displayed in high-density, 1,536-well plate format. To assess the performance, they used cell- and microsphere-based HTS assays that had been well characterized in the previous studies. Experiments addressed important technical issues: challenges of small wells (assay volumes 10 μ L or less, reagent mixing, cell and particle suspension), detecting and correcting for differences in performance of individual flow cytometers, and the ability to reanalyze a plate in the event of problems encountered during the primary analysis. Boosting sample throughput an additional fourfold, this platform is uniquely positioned to synergize with expanding suspension array and cell barcoding technologies in which as many as 100 experiments are performed in a single well or sample. As high-performance flow cytometers shrink in cost and size, cluster cytometry promises to become a practical, productive approach for HTS, and other large-scale investigations of biological complexity. Edwards BS, Zhu J, Chen J, Carter MB, Thal DM, Tesmer JJ, Graves SW, Sklar LA. Cluster cytometry for high-capacity bioanalysis. *Cytometry A*. 2012 May; 81(5): 419-429. doi: 10.1002/cyto.a.22039. Epub 2012 Mar 21.

In Vivo Visualization Of Delta Opioid Receptors Upon Physiological Activation Uncovers A Distinct Internalization Profile G-protein-coupled receptors (GPCRs) mediate numerous physiological functions and represent prime therapeutic targets. Receptor trafficking upon agonist stimulation is critical for GPCR function, but examining this process in vivo remains a true challenge. Using knock-in mice expressing functional fluorescent delta opioid receptors under the control of the endogenous promoter, the authors visualized in vivo internalization of this native GPCR upon physiological stimulation. They developed a paradigm in which animals were made dependent on morphine in a drug-paired context. When re-exposed to this context in a drug-free state, mice showed context-dependent withdrawal signs and activation of the hippocampus. Receptor internalization was transiently detected in a subset of CA1 neurons, uncovering regionally restricted opioid peptide release. Importantly, a pool of surface receptors always remained, which contrasts with the in vivo profile previously established for exogenous drug-induced internalization. Therefore, a distinct response is observed at the receptor level upon a physiological or pharmacological stimulation. Altogether, direct in vivo GPCR visualization enables mapping receptor stimulation promoted by a behavioral challenge and represents a powerful approach to study endogenous GPCR physiology. Faget L, Erbs E, Le Merrer J, Scherrer G, Matifas A, Benturquia N, Noble F, Decossas M, Koch M, Kessler P, Vonesch JL, Schwab Y, Kieffer BL, Massotte D. In vivo visualization of delta opioid receptors upon physiological activation uncovers a distinct internalization profile. *J Neurosci*. 2012 May 23; 32(21): 7301-7310.

Systematic Discovery Of Structural Elements Governing Stability Of Mammalian Messenger RNAs Decoding post-transcriptional regulatory programs in RNA is a critical step towards the larger goal of developing predictive dynamical models of cellular behaviour. Despite recent efforts, the vast landscape of RNA regulatory elements remains largely uncharacterized. A long-standing obstacle is the contribution of local RNA secondary structure to the definition of interaction partners in a variety of regulatory contexts, including--but not limited to--transcript stability, alternative splicing and localization. There are many documented instances where the presence of a

structural regulatory element dictates alternative splicing patterns (for example, human cardiac troponin T) or affects other aspects of RNA biology. Thus, a full characterization of post-transcriptional regulatory programs requires capturing information provided by both local secondary structures and the underlying sequence. Here the authors present a computational framework based on context-free grammars and mutual information that systematically explores the immense space of small structural elements and reveals motifs that are significantly informative of genome-wide measurements of RNA behaviour. By applying this framework to genome-wide human mRNA stability data, they reveal eight highly significant elements with substantial structural information, for the strongest of which we show a major role in global mRNA regulation. Through biochemistry, mass spectrometry and in vivo binding studies, we identified human HNRPA2B1 (heterogeneous nuclear ribonucleoprotein A2/B1, also known as HNRNPA2B1) as the key regulator that binds this element and stabilizes a large number of its target genes. The authors created a global post-transcriptional regulatory map based on the identity of the discovered linear and structural cis-regulatory elements, their regulatory interactions and their target pathways. This approach could also be used to reveal the structural elements that modulate other aspects of RNA behaviour. Goodarzi H, Najafabadi HS, Oikonomou P, Greco TM, Fish L, Salavati R, Cristea IM, Tavazoie S. Systematic discovery of structural elements governing stability of mammalian messenger RNAs. *Nature*. 2012 Apr 8; 485(7397): 264-268. doi: 10.1038/nature11013.

HIV Latency: Experimental Systems and Molecular Models Highly active antiretroviral therapy (HAART) has shown great efficacy in increasing the survival of HIV infected individuals. However, HAART does not lead to the full eradication of infection and therefore has to be continued for life. HIV persists in a transcriptionally inactive form in resting T cells in HAART-treated patients and can be reactivated following T-cell activation. These latently infected cells allow the virus to persist in the presence of HAART. Here, the authors review recent advances in the study of the molecular mechanisms of HIV latency. They also review experimental models in which latency is currently studied. They focus on the epigenetic mechanisms controlling HIV transcription and on the role of chromatin and its post-translational modifications. They discuss how small molecule inhibitors that target epigenetic regulators, such as HDAC (histone deacetylase) inhibitors, are being tested for their ability to reactivate latent HIV. Finally, they discuss the clinical potential of these drugs to flush out latently infected cells from HIV-infected patients and to eradicate the virus. Hakre S, Chavez L, Shirakawa K, Verdin E. HIV latency: experimental systems and molecular models. *FEMS Microbiol Rev*. 2012 May; 36(3): 706-716. doi: 10.1111/j.1574-6976.2012.00335.x.

NF- κ B-Mediated Degradation Of The Coactivator RIP140 Regulates Inflammatory Responses and Contributes To Endotoxin Tolerance Tolerance to endotoxins that is triggered by prior exposure to Toll-like receptor (TLR) ligands provides a mechanism with which to dampen inflammatory cytokines. The receptor-interacting protein RIP140 interacts with the transcription factor NF- κ B to regulate the expression of genes encoding proinflammatory cytokines. Here the authors found lipopolysaccharide stimulation of kinase Syk-mediated tyrosine phosphorylation of RIP140 and interaction of the NF- κ B subunit RelA with RIP140. These events resulted in more recruitment of the E3 ligase SCF to tyrosine-phosphorylated RIP140, which degraded RIP140 to inactivate genes encoding inflammatory cytokines. Macrophages expressing nondegradable RIP140 were resistant to the establishment of endotoxin tolerance for specific 'tolerizable' genes. These results identify RelA as an adaptor with which SCF fine tunes NF- κ B target genes by targeting the coactivator RIP140 and show an unexpected role for RIP140 degradation in resolving inflammation and endotoxin tolerance. Ho PC, Tsui YC, Feng X, Greaves DR, Wei LN. NF- κ B-mediated

degradation of the coactivator RIP140 regulates inflammatory responses and contributes to endotoxin tolerance. *Nat Immunol.* 2012 Mar 4; 13(4): 379-386. doi: 10.1038/ni.2238.

Endothelin-1 Promotes Cytoplasmic Accumulation Of RIP140 Through A ET(A)-Plc β -Pkc ϵ Pathway

The physiological signal activating cytoplasmic accumulation of nuclear receptor interacting protein 140 (RIP140) in adipocytes was unclear. The authors uncover that endothelin-1 (ET-1) promotes cytoplasmic accumulation of RIP140 in 3T3-L1 adipocytes. They determine ET-1's signal transduction pathway in adipocytes, which is by activating ET(A) receptor-PLC β -nuclear PKC ϵ . Blocking this pathway in 3T3-L1 adipocyte cultures, by treating cells with an ET(A) antagonist, inhibiting PLC β , or silencing PKC ϵ , reduces ET-1-stimulated cytoplasmic accumulation of RIP140. In a HFD-fed obese mouse model, administration of a selective ET(A) antagonist, ambrisentan, effectively dampens cytoplasmic accumulation of RIP140 in the epididymal adipose tissue and reduces HFD-caused adipocyte dysfunctions. Importantly, ambrisentan improves blood glucose control and reduces the severity of hepatic steatosis in HFD-fed mice. This study reports a physiological signal that stimulates nuclear export of RIP140 in adipocytes and provides evidence for a strategy using selective ET(A) antagonist to treat obesity-induced insulin resistance and, possibly, other metabolic disorders. Ho PC, Tsui YC, Lin YW, Persaud SD, Wei LN. Endothelin-1 promotes cytoplasmic accumulation of RIP140 through a ET(A)-PLC β -PKC ϵ pathway. *Mol Cell Endocrinol.* 2012 Apr 4; 351(2): 176-183. Epub 2011 Dec 19.

Impaired Auditory Discrimination Learning Following Perinatal Nicotine Exposure Or β 2 Nicotinic Acetylcholine Receptor Subunit Deletion

Maternal smoking during pregnancy can impair performance of the exposed offspring in tasks that require auditory stimulus processing and perception; however, the tobacco component(s) responsible for these effects and the underlying neurobiological mechanisms remain uncertain. In this study, the authors show that administration of nicotine during mouse perinatal development can impair performance in an auditory discrimination paradigm when the exposed animals are mature. This suggests that nicotine disrupts auditory pathways via nicotinic acetylcholine receptors (nAChRs) that are expressed at an early stage of development. The authors have also determined that mice which lack nAChRs containing the β 2 subunit (β 2* nAChRs) exhibit similarly compromised performance in this task, suggesting that β 2* nAChRs are necessary for normal auditory discrimination or that β 2* nAChRs play a critical role in development of the circuitry required for task performance. In contrast, no effect of perinatal nicotine exposure or β 2 subunit knockout was found on the acquisition and performance of a differential reinforcement of low rate task. This suggests that the auditory discrimination impairments are not a consequence of a general deficit in learning and memory, but may be the result of compromised auditory stimulus processing in the nicotine-exposed and knockout animals. Horst NK, Heath CJ, Neugebauer NM, Kimchi EY, Laubach M, Picciotto MR. Impaired auditory discrimination learning following perinatal nicotine exposure or β 2 nicotinic acetylcholine receptor subunit deletion. *Behav Brain Res.* 2012 May 16; 231(1): 170-180. Epub 2012 Mar 13.

MicroRNAs In Neuronal Function and Dysfunction

MicroRNAs (miRNAs) are small noncoding RNA transcripts expressed throughout the brain that can regulate neuronal gene expression at the post-transcriptional level. Here, the authors provide an overview of the role for miRNAs in brain development and function, and review evidence suggesting that dysfunction in miRNA signaling contributes to neurodevelopment disorders such as Rett and fragile X syndromes, as well as complex behavioral disorders including schizophrenia, depression and drug addiction. A better understanding of how miRNAs influence the development of neuropsychiatric disorders may reveal fundamental insights into the causes of these devastating illnesses and offer novel targets for

therapeutic development. Im HI, Kenny PJ. MicroRNAs in neuronal function and dysfunction. Trends Neurosci. 2012 May; 35(5): 325-334. Epub 2012 Mar 19.

Plasma Gelsolin Accumulates In Macrophage Nodules In Brains Of Simian Immuno-deficiency Virus Infected Rhesus Macaques

Plasma gelsolin (pGSN), an isoform 1, is secreted by various types of cells in the central nervous system (CNS) and periphery, but not by the liver. pGSN circulates in blood and cerebrospinal fluid (CSF); however, its concentration in CSF is approximately twenty times lower than in plasma. It has been shown that several types of cells such as oligodendrocytes, neurons, and/or astrocytes contribute to the overall pool of pGSN in the CNS. Further, it has been postulated that pGSN plays multiple roles during microbial infection and modulates inflammatory responses; however, the exact mechanism of regulation is not known. The authors previously showed that levels of pGSN in CSF of individuals with advanced neurocognitive impairment due to HIV infection of the brain are decreased. Here, they show that macrophages express significant amounts of pGSN in response to HIV infection in vitro. Using immunohistochemistry of simian immunodeficiency virus infected rhesus monkey brains, the authors show that increased levels of pGSN are present in macrophage nodules creating locally a high level of this protein within the brain. This may not be reflected by the overall decreased level in the distinct CSF compartment. Jagadish T, Pottiez G, Fox HS, Ciborowski P. Plasma gelsolin accumulates in macrophage nodules in brains of simian immunodeficiency virus infected rhesus macaques. J Neurovirol. 2012 Apr; 18(2): 113-119. Epub 2012 Mar 9.

Drosophila Golgi Membrane Protein Ema Promotes Autophagosomal Growth and Function

Autophagy is a self-degradative process in which cellular material is enclosed within autophagosomes and trafficked to lysosomes for degradation. Autophagosomal biogenesis is well described; however mechanisms controlling the growth and ultimate size of autophagosomes are unclear. Here the authors demonstrate that the Drosophila membrane protein Ema is required for the growth of autophagosomes. In an ema mutant, autophagosomes form in response to starvation and developmental cues, and these autophagosomes can mature into autolysosomes; however the autophagosomes are very small, and autophagy is impaired. In fat body cells, Ema localizes to the Golgi complex and is recruited to the membrane of autophagosomes in response to starvation. The Drosophila Golgi protein Lva also is recruited to the periphery of autophagosomes in response to starvation, and this recruitment requires Ema. Therefore, the authors propose that Golgi is a membrane source for autophagosomal growth and that Ema facilitates this process. Clec16A, the human ortholog of Ema, is a candidate autoimmune susceptibility locus. Expression of Clec16A can rescue the autophagosome size defect in the ema mutant, suggesting that regulation of autophagosome morphogenesis may be a fundamental function of this gene family. Kim S, Naylor SA, DiAntonio A. Drosophila Golgi membrane protein Ema promotes autophagosomal growth and function. Proc Natl Acad Sci U S A. 2012 May 1; 109(18): E1072-1081. Epub 2012 Apr 9.

Zebrafish: A Model For The Study Of Addiction Genetics Drug abuse and dependence are multifaceted disorders with complex genetic underpinnings. Identifying specific genetic correlates is challenging and may be more readily accomplished by defining endophenotypes specific for addictive disorders. Symptoms and syndromes, including acute drug response, consumption, preference, and withdrawal, are potential endophenotypes characterizing addiction that have been investigated using model organisms. The authors present a review of major genes involved in serotonergic, dopaminergic, GABAergic, and adrenoceptor signaling that are considered to be directly involved in nicotine, opioid, cannabinoid, and ethanol use and dependence. The zebrafish genome encodes likely homologs of the vast majority of these loci. The authors also review the

known expression patterns of these genes in zebrafish. The information presented in this review provides support for the use of zebrafish as a viable model for studying genetic factors related to drug addiction. Expansion of investigations into drug response using model organisms holds the potential to advance our understanding of drug response and addiction in humans. Klee EW, Schneider H, Clark KJ, Cousin MA, Ebbert JO, Hooten WM, Karpyak VM, Warner DO, Ekker SC. Zebrafish: a model for the study of addiction genetics. *Hum Genet.* 2012 Jun; 131(6): 977-1008. Epub 2011 Dec 30.

The Role Of Transporters In The Toxicity Of Nucleoside and Nucleotide Analogs Two families of nucleoside analogs have been developed to treat viral infections and cancer, but these compounds can cause tissue- and cell-specific toxicity related to their uptake and subcellular activity, which are dictated by host enzymes and transporters. Cellular uptake of these compounds requires nucleoside transporters that share functional similarities but differ in substrate specificity. Tissue-specific cellular expression of these transporters enables nucleoside analogs to produce their tissue-specific toxic effects, a limiting factor in the treatment of retroviruses and cancer. This review discusses the families of nucleoside transporters and how they mediate cellular uptake of nucleoside analogs. Specific focus is placed on examples of known cases of transporter-mediated cellular toxicity and classification of the toxicities resulting. Efflux transporters are also explored as a contributor to analog toxicity and cell-specific effects. Efforts to modulate transporter uptake/clearance remain long-term goals of oncologists and virologists. Accordingly, subcellular approaches that either increase or decrease intracellular nucleoside analog concentrations are eagerly sought and include transporter inhibitors and targeting transporter expression. However, additional understanding of nucleoside transporter kinetics, tissue expression and genetic polymorphisms is required to design better molecules and better therapies. Koczor CA, Torres RA, Lewis W. The role of transporters in the toxicity of nucleoside and nucleotide analogs. *Expert Opin Drug Metab Toxicol.* 2012 Jun; 8(6): 665-676. Epub 2012 Apr 18.

Species-Dependent Posttranscriptional Regulation Of NOS1 By FMRP In The Developing Cerebral Cortex Fragile X syndrome (FXS), the leading monogenic cause of intellectual disability and autism, results from loss of function of the RNA-binding protein FMRP. Here, the authors show that FMRP regulates translation of neuronal nitric oxide synthase 1 (NOS1) in the developing human neocortex. Whereas NOS1 mRNA is widely expressed, NOS1 protein is transiently coexpressed with FMRP during early synaptogenesis in layer- and region-specific pyramidal neurons. These include midfetal layer 5 subcortically projecting neurons arranged into alternating columns in the prospective Broca's area and orofacial motor cortex. Human NOS1 translation is activated by FMRP via interactions with coding region binding motifs absent from mouse *Nos1* mRNA, which is expressed in mouse pyramidal neurons, but not efficiently translated. Correspondingly, neocortical NOS1 protein levels are severely reduced in developing human FXS cases, but not FMRP-deficient mice. Thus, alterations in FMRP posttranscriptional regulation of NOS1 in developing neocortical circuits may contribute to cognitive dysfunction in FXS. Kwan KY, Lam MM, Johnson MB, Dube U, Shim S, Rašin MR, Sousa AM, Fertuzinhos S, Chen JG, Arellano JI, Chan DW, Pletikos M, Vasung L, Rowitch DH, Huang EJ, Schwartz ML, Willemsen R, Oostra BA, Rakic P, Heffer M, Kostović I, Judaš M, Sestan N. Species-dependent posttranscriptional regulation of NOS1 by FMRP in the developing cerebral cortex. *Cell.* 2012 May 11; 149(4): 899-911.

Facets Of Pavlovian and Operant Extinction Research on extinction is of fundamental importance in both Pavlovian and operant approaches to the experimental analysis of learning. Although these approaches are often motivated by different empirical and theoretical questions, extinction has emerged as a research area in which common themes unite the two approaches. In this review, the authors focus on some common considerations in the analysis of Pavlovian and operant extinction. These include methodological challenges and interpretational issues in analyzing behavior during and after extinction. The authors consider the different roles that theory has played in the development of research on extinction in these preparations and conclude with some attention to applications of extinction. Lattal KM, Lattal KA. Facets of Pavlovian and operant extinction. Behav Processes. 2012 May; 90(1): 1-8. Epub 2012 Mar 23.

Acetylation Modulates Cellular Distribution and DNA Sensing Ability Of Interferon-Inducible Protein IFI16 Detection of pathogenic nucleic acids is essential for mammalian innate immunity. IFN-inducible protein IFI16 has emerged as a critical sensor for detecting pathogenic DNA, stimulating both type I IFN and proinflammatory responses. Despite being predominantly nuclear, IFI16 can unexpectedly sense pathogenic DNA in both the cytoplasm and the nucleus. However, the mechanisms regulating its localization and sensing ability remain uncharacterized. Here, the authors propose a two-signal model for IFI16 sensing. They first identify an evolutionarily conserved multipartite nuclear localization signal (NLS). Next, using FISH and immunopurification, they demonstrate that IFI16 detects HSV-1 DNA primarily in the nucleus, requiring a functional NLS. Furthermore, they establish a localization-dependent IFN- β induction mediated by IFI16 in response to HSV-1 infection or viral DNA transfection. To identify mechanisms regulating the secondary cytoplasmic localization, they explored IFI16 posttranslation modifications. Combinatorial MS analyses identified numerous acetylations and phosphorylations on endogenous IFI16 in lymphocytes, in which the authors demonstrate an IFI16-mediated IFN- β response. Importantly, the IFI16 NLS was acetylated in lymphocytes, as well as in macrophages. Mutagenesis and nuclear import assays showed that NLS acetylations promote cytoplasmic localization by inhibiting nuclear import. Additionally, broad-spectrum deacetylase inhibition triggered accumulation of cytoplasmic IFI16, and the authors identify the acetyltransferase p300 as a regulator of IFI16 localization. Collectively, these studies establish acetylation as a molecular toggle of IFI16 distribution, providing a simple and elegant mechanism by which this versatile sensor detects pathogenic DNA in a localization-dependent manner. Li T, Diner BA, Chen J, Cristea IM. Acetylation modulates cellular distribution and DNA sensing ability of interferon-inducible protein IFI16. Proc Natl Acad Sci U S A. 2012 Jun 26; 109(26): 10558-10563. Epub 2012 Jun 12.

Clonally Related Visual Cortical Neurons Show Similar Stimulus Feature Selectivity A fundamental feature of the mammalian neocortex is its columnar organization. In the visual cortex, functional columns consisting of neurons with similar orientation preferences have been characterized extensively, but how these columns are constructed during development remains unclear. The radial unit hypothesis posits that the ontogenetic columns formed by clonally related neurons migrating along the same radial glial fibre during corticogenesis provide the basis for functional columns in adult neocortex. However, a direct correspondence between the ontogenetic and functional columns has not been demonstrated. Here the authors show that, despite the lack of a discernible orientation map in mouse visual cortex, sister neurons in the same radial clone exhibit similar orientation preferences. Using a retroviral vector encoding green fluorescent protein to label radial clones of excitatory neurons, and in vivo two-photon calcium imaging to measure neuronal response properties, the authors found that sister neurons preferred similar orientations whereas

nearby non-sister neurons showed no such relationship. Interestingly, disruption of gap junction coupling by viral expression of a dominant-negative mutant of Cx26 (also known as Gjb2) or by daily administration of a gap junction blocker, carbenoxolone, during the first postnatal week greatly diminished the functional similarity between sister neurons, suggesting that the maturation of ontogenetic into functional columns requires intercellular communication through gap junctions. Together with the recent finding of preferential excitatory connections among sister neurons, these results support the radial unit hypothesis and unify the ontogenetic and functional columns in the visual cortex. Li Y, Lu H, Cheng PL, Ge S, Xu H, Shi SH, Dan Y. Clonally related visual cortical neurons show similar stimulus feature selectivity. *Nature*. 2012 May 2; 486(7401): 118-121. doi: 10.1038/nature11110.

Activation Of Protein Kinase C (PKC) α Or Pkc ϵ As An Approach To Increase Morphine Tolerance In Respiratory Depression and Lethal Overdose

Long-term use of opioids is hindered by respiratory depression and the possibility for fatal overdose in drug abusers. This is attributed to higher levels of tolerance that develops against antinociception than to respiratory depression. Identifying important mechanisms that would increase morphine respiratory depression and overdose tolerance could lead to the safer use of opioids. Because protein kinase C (PKC) activity mediates the development and maintenance of morphine antinociceptive tolerance, the authors hypothesized that activating PKC α or PKC ϵ at the pre-Bötzing complex (preBötC) can increase morphine tolerance in respiration and overdose. Laser microdissection and quantitative reverse transcriptase-polymerase chain reaction were used to compare the relative mRNA abundances of PKC α , γ , and ϵ between ventrolateral periaqueductal gray (vlPAG) and preBötC. To test whether PKC α or ϵ could enhance morphine tolerance in respiratory depression and overdose, lentivirus carrying the wild type, constitutively activated mutants, and small interference RNA against PKC α or ϵ was stereotaxically injected into the preBötC. Expression of constitutively active PKC (CAPKC) α or ϵ , but not wild-type PKC (WTPKC) α or ϵ , at the preBötC allowed rats to develop tolerance to morphine respiratory depression. In terms of lethality, expression of WTPKC ϵ , CAPKC α , or CAPKC ϵ at preBötC increased morphine tolerance to lethal overdose. CAPKC ϵ -expressing rats developed the highest level of respiratory depression tolerance. Furthermore, when CAPKC ϵ lentivirus was injected into the vlPAG, rats were able to develop significant antinociceptive tolerance at low doses of morphine that normally do not cause tolerance. The approach of increasing morphine respiratory depression and lethality tolerance by increasing PKC α or ϵ activity at preBötC could be used to make opioids safer for long-term use. Lin HY, Law PY, Loh HH. Activation of protein kinase C (PKC) α or PKC ϵ as an approach to increase morphine tolerance in respiratory depression and lethal overdose. *J Pharmacol Exp Ther*. 2012 Apr; 341(1): 115-125. Epub 2012 Jan 6.

Connexin 43 Controls The Multipolar Phase Of Neuronal Migration To The Cerebral Cortex

The prospective pyramidal neurons, migrating from the proliferative ventricular zone to the overlying cortical plate, assume multipolar morphology while passing through the transient subventricular zone. Here, the authors show that this morphogenetic transformation, from the bipolar to the multipolar and then back to bipolar again, is associated with expression of connexin 43 (Cx43) and, that knockdown of Cx43 retards, whereas its overexpression enhances, this morphogenetic process. In addition, they have observed that knockdown of Cx43 reduces expression of p27, whereas overexpression of p27 rescues the effect of Cx43 knockdown in the multipolar neurons. Furthermore, functional gap junction/hemichannel domain, and the C-terminal domain of Cx43, independently enhance the expression of p27 and promote the morphological transformation and migration of the multipolar neurons in the SVZ/IZ. Collectively, these results

indicate that Cx43 regulates the passage of migrating neurons through their multipolar stage via p27 signaling and that interference with this process, by either genetic and/or environmental factors, may cause cortical malformations. Liu X, Sun L, Torii M, Rakic P. Connexin 43 controls the multipolar phase of neuronal migration to the cerebral cortex. Proc Natl Acad Sci U S A. 2012 May 22; 109(21): 8280-8285. Epub 2012 May 7.

A Toolbox Of Cre-Dependent Optogenetic Transgenic Mice For Light-Induced Activation and Silencing

Cell type-specific expression of optogenetic molecules allows temporally precise manipulation of targeted neuronal activity. Here the authors present a toolbox of four knock-in mouse lines engineered for strong, Cre-dependent expression of channelrhodopsins ChR2-tdTomato and ChR2-EYFP, halorhodopsin eNpHR3.0 and archaerhodopsin Arch-ER2. All four transgenes mediated Cre-dependent, robust activation or silencing of cortical pyramidal neurons in vitro and in vivo upon light stimulation, with ChR2-EYFP and Arch-ER2 demonstrating light sensitivity approaching that of in utero or virally transduced neurons. The authors further show specific photoactivation of parvalbumin-positive interneurons in behaving ChR2-EYFP reporter mice. The robust, consistent and inducible nature of our ChR2 mice represents a significant advance over previous lines, and the Arch-ER2 and eNpHR3.0 mice are to our knowledge the first demonstration of successful conditional transgenic optogenetic silencing. When combined with the hundreds of available Cre driver lines, this optimized toolbox of reporter mice will enable widespread investigations of neural circuit function with unprecedented reliability and accuracy. Madisen L, Mao T, Koch H, Zhuo JM, Berenyi A, Fujisawa S, Hsu YW, Garcia AJ 3rd, Gu X, Zanella S, Kidney J, Gu H, Mao Y, Hooks BM, Boyden ES, Buzsáki G, Ramirez JM, Jones AR, Svoboda K, Han X, Turner EE, Zeng H. A toolbox of Cre-dependent optogenetic transgenic mice for light-induced activation and silencing. 40. Nat Neurosci. 2012 Mar 25; 15(5): 793-802. doi: 10.1038/nn.3078.

Differential Modulation of Drug-induced Structural and Functional Plasticity of Dendritic Spines

Drug-induced plasticity of excitatory synapses has been proposed to be the cellular mechanism underlying the aberrant learning associated with addiction. Exposure to various drugs of abuse cause both morphological plasticity of dendritic spines and functional plasticity of excitatory synaptic transmission. Chronic activation of μ -opioid receptors (MOR) in cultured hippocampal neurons causes two forms of synaptic plasticity: loss of dendritic spines and loss of synaptic AMPA receptors. Using live imaging, patch clamp electrophysiology, and immunocytochemistry the present study reveals that these two forms of synaptic plasticity are mediated by separate, but interactive, intracellular signaling cascades. The inhibition of Ca(2+)/calmodulin-dependent protein kinase II (CaMKII) with KN-62 blocks MOR-mediated structural plasticity of dendritic spines, but not MOR-mediated cellular redistribution of GluR1 and GluR2 AMPA receptor subunits. In contrast, the inhibition of calcineurin with FK506 blocks both cellular processes. These findings support the idea that drug-induced structural and functional plasticity of dendritic spines are mediated by divergent, but interactive signaling pathways. Miller EC, Zhang L, Dummer BW, Cariveau DR, Loh HH, Law PY, Liao D. Differential Modulation of Drug-induced Structural and Functional Plasticity of Dendritic Spines. Mol Pharmacol. 2012 May 17. [Epub ahead of print]

Varenicline Blocks B2*-nAChR-Mediated Response and Activates B4*-NACHR-Mediated Responses In Mice In Vivo

The smoking cessation aid, varenicline, has higher affinity for the $\alpha 4\beta 2$ -subtype of the nicotinic acetylcholine receptor ($\alpha 4\beta 2$ -nAChR) than for other subtypes of nAChRs by in vitro assays. The mechanism of action of acute varenicline was studied in vivo to determine (a) subtype activation associated with physiological effects and (b) dose relationship as

an antagonist of nicotine. Acute doses of saline, nicotine, and varenicline were given to mice, and locomotor depression and hypothermia were measured. Subunit null mutant mice as well as selective antagonists were used to study mode of action of varenicline as an agonist. Varenicline as an antagonist of nicotine was also investigated. Varenicline evokes locomotor depression and hypothermia at higher doses than necessary for nicotine. Null mutation of the $\alpha 7$ - or $\beta 2$ -nAChR subunit did not decrease the effectiveness of varenicline; however, null mutation of the $\beta 4$ subunit significantly decreased the magnitude of the varenicline effect. Effects of the highest dose studied were blocked by mecamylamine (general nAChR antagonist) and partially antagonized by hexamethonium (largely peripheral nAChR antagonist). No significant block was seen with ondansetron antagonist of 5-hydroxytryptamine 3 receptor. Using a dose of nicotine selective for $\beta 2^*$ -nAChR subtype effects with these tests, dose-dependent antagonism by varenicline was seen. Effective inhibitory doses were determined and appear to be in a range consistent with binding affinity or desensitization of $\beta 2^*$ -nAChRs. Varenicline acts as a functional antagonist of $\beta 2^*$ -nAChRs, blocking certain effects of nicotine. At higher doses, varenicline is an agonist of $\beta 4^*$ -nAChRs producing physiological changes in mice. Ortiz NC, O'Neill HC, Marks MJ, Grady SR. Varenicline blocks $\beta 2^*$ -nAChR-mediated response and activates $\beta 4^*$ -nAChR-mediated responses in mice in vivo. *Nicotine Tob Res.* 2012 Jun; 14(6): 711-719. Epub 2012 Jan 12.

Translational Genetic Approaches To Substance Use Disorders: Bridging The Gap Between Mice and Humans While substance abuse disorders only occur in humans, mice and other model organisms can make valuable contributions to genetic studies of these disorders. In this review, the authors consider a few specific examples of how model organisms have been used in conjunction with studies in humans to study the role of genetic factors in substance use disorders. In some examples genes that were first discovered in mice were subsequently studied in humans. In other examples genes or specific polymorphisms in genes were first studied in humans and then modeled in mice. Using anatomically and temporally specific genetic, pharmacological and other environmental manipulations in conjunction with histological analyses, mechanistic insights that would be difficult to obtain in humans have been obtained in mice. The authors hope these examples illustrate how novel biological insights about the effect of genes on substance use disorders can be obtained when mouse and human genetic studies are successfully integrated. Palmer AA, de Wit H. *Translational genetic approaches to substance use disorders: bridging the gap between mice and humans.* *Hum Genet.* 2012 Jun; 131(6): 931-939. Epub 2011 Dec 15.

Inositol 5-Phosphatases: Insights From The Lowe Syndrome Protein OCRL The precise regulation of phosphoinositide lipids in cellular membranes is crucial for cellular survival and function. Inositol 5-phosphatases have been implicated in a variety of disorders, including various cancers, obesity, type 2 diabetes, neurodegenerative diseases and rare genetic conditions. Despite the obvious impact on human health, relatively little structural and biochemical information is available for this family. Here, the authors review recent structural and mechanistic work on the 5-phosphatases with a focus on OCRL, whose loss of function results in oculocerebrorenal syndrome of Lowe and Dent 2 disease. Studies of OCRL emphasize how the actions of 5-phosphatases rely on both intrinsic and extrinsic membrane recognition properties for full catalytic function. Additionally, structural analysis of missense mutations in the catalytic domain of OCRL provides insight into the phenotypic heterogeneity observed in Lowe syndrome and Dent disease. Pirruccello M, De Camilli P. *Inositol 5-phosphatases: insights from the Lowe syndrome protein OCRL.* *Trends Biochem Sci.* 2012 Apr; 37(4): 134-143. doi: 10.1016/j.tibs.2012.01.002. Epub 2012 Feb 28.

Retrotransposon Profiling Of RNA Polymerase III Initiation Sites Although retroviruses are relatively promiscuous in choice of integration sites, retrotransposons can display marked integration specificity. In yeast and slime mold, some retrotransposons are associated with tRNA genes (tDNAs). In the *Saccharomyces cerevisiae* genome, the long terminal repeat retrotransposon Ty3 is found at RNA polymerase III (Pol III) transcription start sites of tDNAs. Ty1, 2, and 4 elements also cluster in the upstream regions of these genes. To determine the extent to which other Pol III-transcribed genes serve as genomic targets for Ty3, a set of 10,000 Ty3 genomic retrotranspositions were mapped using high-throughput DNA sequencing. Integrations occurred at all known tDNAs, two tDNA relics (iYGR033c and ZOD1), and six non-tDNA, Pol III-transcribed types of genes (RDN5, SNR6, SNR52, RPR1, RNA170, and SCR1). Previous work in vitro demonstrated that the Pol III transcription factor (TF) IIIB is important for Ty3 targeting. However, seven loci that bind the TFIIIB loader, TFIIIC, were not targeted, underscoring the unexplained absence of TFIIIB at those sites. Ty3 integrations also occurred in two open reading frames not previously associated with Pol III transcription, suggesting the existence of a small number of additional sites in the yeast genome that interact with Pol III transcription complexes. Qi X, Daily K, Nguyen K, Wang H, Mayhew D, Rigor P, Forouzan S, Johnston M, Mitra RD, Baldi P, Sandmeyer S. Retrotransposon profiling of RNA polymerase III initiation sites. *Genome Res.* 2012 Apr; 22(4): 681-692. Epub 2012 Jan 27.

The Histone Deacetylase Inhibitor, Sodium Butyrate, Alleviates Cognitive Deficits In Pre-Motor Stage PD Parkinson's disease (PD) patients often times experience impairment in their cognitive abilities early on in the progression of the disease. The reported deficits appear to mainly involve functions that are associated with frontal lobe and frontal-striatal pathways subserving attentional set-shifting, working memory and executive function. The current study explored executive function deficits in a rat model of PD in the pre-motor deficit stage. The rats were lesioned with 12 μg of 6-hydroxydopamine (6-OHDA) in the striatum in a two step process (10 $\mu\text{g}/\mu\text{l}$ followed by 2 $\mu\text{g}/\mu\text{l}$) 48 hours apart. Executive function was tested at 3 weeks post-surgery using a rat analogue of Wisconsin card sorting test called the Extra Dimensional/Intra Dimensional (ED/ID) set-shifting task. The results demonstrated that performance by the pre-motor rat model of PD was equivalent to that of the control groups in the simple and the compound discriminations as well as the intra-dimensional set-shifting. However the PD group exhibited attentional set-shifting deficits similar to those observed in PD patients. Additionally, sodium butyrate, a short chain fatty acid derivative and inhibitor of class I and II histone deacetylase (HDACi), was tested as a potential therapeutic agent to mitigate the pre-motor cognitive deficits in PD. The results indicated that the sodium butyrate treatment not only effectively alleviated the set-shifting deficits, but also improved the attentional set formation in the treated rats. Rane P, Shields J, Heffernan M, Guo Y, Akbarian S, King JA. The histone deacetylase inhibitor, sodium butyrate, alleviates cognitive deficits in pre-motor stage PD. *Neuropharmacology.* 2012 Jun; 62(7): 2409-2412. Epub 2012 Feb 13.

Mouse Delta Opioid Receptors Are Located On Presynaptic Afferents To Hippocampal Pyramidal Cells Delta opioid receptors participate in the control of chronic pain and emotional responses. Recent data have also identified their implication in drug-context associations pointing to a modulatory role on hippocampal activity. The authors used fluorescent knock-in mice that express a functional delta opioid receptor fused at its carboxy terminus with the green fluorescent protein in place of the native receptor to investigate the receptor neuroanatomical distribution in this structure. Fine mapping of the pyramidal layer was performed in hippocampal acute brain slices and organotypic cultures using fluorescence confocal imaging, co-localization with pre- and postsynaptic markers and correlative light-electron microscopy. The different approaches concurred

to identify delta opioid receptors on presynaptic afferents to glutamatergic principal cells. In the latter, only scarce receptors were detected that were confined within the Golgi or vesicular intracellular compartments with no receptor present at the cell surface. In the mouse hippocampus, expression of functional delta opioid receptors is therefore mostly associated with interneurons emphasizing a presynaptic modulatory effect on the pyramidal cell firing rate. Rezaï X, Faget L, Bednarek E, Schwab Y, Kieffer BL, Massotte D. Mouse delta opioid receptors are located on presynaptic afferents to hippocampal pyramidal cells. *Cell Mol Neurobiol*. 2012 May; 32(4): 509-516. Epub 2012 Jan 18.

Prenatal Ablation Of Nicotinic Receptor Alpha7 Cell Lineages Produces Lumbosacral Spina Bifida The Severity Of Which Is Modified By Choline and Nicotine Exposure

Lumbosacral spina bifida is a common debilitating birth defect whose multiple causes are poorly understood. Here, the authors provide the first genetic delineation of cholinergic nicotinic receptor alpha7 (Chrna7) expression and link the ablation of the Chrna7 cell lineage to this condition in the mouse. Using homologous recombination, an IRES-Cre bi-cistronic cassette was introduced into the 3' noncoding region of Chrna7 (Chrna7:Cre) for identifying cell lineages expressing this gene. This lineage first appears at embryonic day E9.0 in rhombomeres 3 and 5 of the neural tube and extends to cell subsets in most tissues by E14.5. Ablation of the Chrna7:Cre cell lineage in embryos from crosses with conditionally expressed attenuated diphtheria toxin results in precise developmental defects including omphalocele (89%) and open spina bifida (SB; 80%). The authors hypothesized that like humans, this defect would be modified by environmental compounds not only folic acid or choline but also nicotine. Prenatal chronic oral nicotine administration substantially worsened the defect to often include the rostral neural tube. In contrast, supplementation of the maternal diet with 2% choline decreased SB prevalence to 38% and dramatically reduced the defect severity. Folic acid supplementation only trended towards a reduced SB frequency. The omphalocele was unaffected by these interventions. These studies identify the Chrna7 cell lineage as participating in posterior neuropore closure and present a novel model of lower SB that can be substantially modified by the prenatal environment. Rogers SW, Tvrđik P, Capecchi MR, Gahring LC. Prenatal ablation of nicotinic receptor alpha7 cell lineages produces lumbosacral spina bifida the severity of which is modified by choline and nicotine exposure. *Am J Med Genet A*. 2012 May; 158A(5): 1135-1144. doi: 10.1002/ajmg.a.35372. Epub 2012 Mar 30.

BioQ: Tracing Experimental Origins In Public Genomic Databases Using A Novel Data Provenance Model

Public genomic databases, which are often used to guide genetic studies of human disease, are now being applied to genomic medicine through in silico integrative genomics. These databases, however, often lack tools for systematically determining the experimental origins of the data. The authors introduce a new data provenance model that we have implemented in a public web application, BioQ, for assessing the reliability of the data by systematically tracing its experimental origins to the original subjects and biologics. BioQ allows investigators to both visualize data provenance as well as explore individual elements of experimental process flow using precise tools for detailed data exploration and documentation. It includes a number of human genetic variation databases such as the HapMap and 1000 Genomes projects. BioQ is freely available to the public at <http://bioq.saclab.net>. Saccone SF, Quan J, Jones PL. BioQ: tracing experimental origins in public genomic databases using a novel data provenance model. *Bioinformatics*. 2012 Apr 15; 28(8): 1189-1191. Epub 2012 Mar 16.

Suicidal Behavior, Smoking, and Familial Vulnerability Smoking is a well-established correlate of suicidal behavior. It is not known if familial risk factors contribute to this association. Data were obtained via semistructured interviews with 1,107 twin fathers, 1,919 offspring between ages 12-32 years, and 1,023 mothers. Familial vulnerability to nicotine dependence and suicidal behavior was modeled via father and maternal self-report of these behaviors. Multinomial logistic regression models were computed with and without familial risk factors to estimate the association between offspring ever smoking, regular smoking, nicotine dependence, and a 4-level offspring suicide variable: (a) none, (b) ideation, (c) ideation + plan, and (d) ideation + plan + attempt or ideation + attempt. All models were stratified by gender and adjusted for sociodemographics, familial risk factors including parental suicidal behavior, nicotine dependence, and conduct disorder, and offspring conduct disorder, depression, alcohol abuse/dependence, and illicit drug abuse/dependence. After adjusting for covariates and familial risk factors, ever smoking was not significantly associated with suicidal behavior in males and females. In males, regular smoking was associated with ideation + plan (odds ratio [OR] = 5.47; 95% CI: 1.05-28.60), and in females, regular smoking was associated with ideation + plan + attempt or ideation + attempt. In both genders, nicotine-dependent smoking was associated with ideation + plan + attempt or ideation + attempt (males: OR = 6.59; 95% CI: 1.91-22.70, females: OR = 3.37; 95% CI: 1.25-9.04). Comparison of models with and without familial risk factors indicated that there is no mediation of smoking status and suicidal behavior by familial risk. Smoking and nicotine dependence are correlated with suicidal behaviour. Contributions from familial risk factors did not significantly alter this association. Scherrer JF, Grant JD, Agrawal A, Madden PA, Fu Q, Jacob T, Bucholz KK, Xian H. Suicidal behavior, smoking, and familial vulnerability. *Nicotine Tob Res.* 2012 Apr; 14(4): 415-424. Epub 2011 Nov 11.

EphBs: An Integral Link Between Synaptic Function and Synaptopathies The assembly and function of neuronal circuits rely on selective cell-cell interactions to control axon targeting, generate pre- and postsynaptic specialization and recruit neurotransmitter receptors. In neurons, EphB receptor tyrosine kinases mediate excitatory synaptogenesis early during development, and then later coordinate synaptic function by controlling synaptic glutamate receptor localization and function. EphBs direct synapse formation and function to regulate cellular morphology through downstream signaling mechanisms and by interacting with glutamate receptors. In humans, defective EphB-dependent regulation of NMDA receptor (NMDAR) localization and function is associated with neurological disorders, including neuropathic pain, anxiety disorders and Alzheimer's disease (AD). Here, the authors propose that EphBs act as a central organizer of excitatory synapse formation and function, and as a key regulator of diseases linked to NMDAR dysfunction. Sheffler-Collins SI, Dalva MB. EphBs: an integral link between synaptic function and synaptopathies. *Trends Neurosci.* 2012 May; 35(5): 293-304. Epub 2012 Apr 18.

Reconsolidation Of Drug Memories Persistent, unwanted memories are believed to be key contributors to drug addiction and the chronic relapse problem over the lifetime of the addict. Contrary to the long-held idea that memories are static and fixed, new studies in the last decade have shown that memories are dynamic and changeable. However, they are changeable only under specific conditions. When a memory is retrieved (reactivated), it becomes labile for a period of minutes to hours and then is reconsolidated to maintain long-term memory. Recent findings indicate that even well-established long-term memories may be susceptible to disruption by interfering with reconsolidation through delivery of certain amnesic agents during memory retrieval. Here the author reviews the growing literature on memory reconsolidation in animal models of addiction, including sensitization, conditioned place preference and self-administration and discusses (a)

several issues that need to be considered in interpreting the findings from reconsolidation studies and (b) future challenges and directions for memory reconsolidation studies in the field of addiction. The findings indicate promise for using this approach as a therapy for disrupting the long-lasting memories that can trigger relapse. Sorg BA. Reconsolidation of drug memories. *Neurosci Biobehav Rev.* 2012 May; 36(5): 1400-1417. Epub 2012 Feb 10.

Hypoxia Disruption Of Vertebrate CNS Pathfinding Through Ephrinb2 Is Rescued By Magnesium

The mechanisms of hypoxic injury to the developing human brain are poorly understood, despite being a major cause of chronic neurodevelopmental impairments. Recent work in the invertebrate *Caenorhabditis elegans* has shown that hypoxia causes discrete axon pathfinding errors in certain interneurons and motorneurons. However, it is unknown whether developmental hypoxia would have similar effects in a vertebrate nervous system. The authors have found that developmental hypoxic injury disrupts pathfinding of forebrain neurons in zebrafish (*Danio rerio*), leading to errors in which commissural axons fail to cross the midline. The pathfinding defects result from activation of the hypoxia-inducible transcription factor (hif1) pathway and are mimicked by chemical inducers of the hif1 pathway or by expression of constitutively active hif1 α . Further, they found that blocking transcriptional activation by hif1 α helped prevent the guidance defects. They identified ephrinB2a as a target of hif1 pathway activation, showed that knock-down of ephrinB2a rescued the guidance errors, and showed that the receptor ephA4a is expressed in a pattern complementary to the misrouting axons. By targeting a constitutively active form of ephrinB2a to specific neurons, they found that ephrinB2a mediates the pathfinding errors via a reverse-signaling mechanism. Finally, magnesium sulfate, used to improve neurodevelopmental outcomes in preterm births, protects against pathfinding errors by preventing upregulation of ephrinB2a. These results demonstrate that evolutionarily conserved genetic pathways regulate connectivity changes in the CNS in response to hypoxia, and they support a potential neuroprotective role for magnesium. Stevenson TJ, Trinh T, Kogelschatz C, Fujimoto E, Lush ME, Piotrowski T, Brimley CJ, Bonkowsky JL. Hypoxia disruption of vertebrate CNS pathfinding through ephrinB2 Is rescued by magnesium. *PLoS Genet.* 2012 Apr; 8(4): e1002638. Epub 2012 Apr 12.

Differential Signalling In Human Cannabinoid CB1 Receptors and Their Splice Variants In Autaptic Hippocampal Neurones

Cannabinoids such as $\Delta(9)$ -tetrahydrocannabinol, the major psychoactive component of marijuana and hashish, primarily act via cannabinoid CB(1) and CB(2) receptors to produce characteristic behavioural effects in humans. Due to the tractability of rodent models for electrophysiological and behavioural studies, most of the studies of cannabinoid receptor action have used rodent cannabinoid receptors. While CB(1) receptors are relatively well-conserved among mammals, human CB(1) (hCB(1)) differs from rCB(1) and mCB(1) receptors at 13 residues, which may result in differential signalling. In addition, two hCB(1) splice variants (hCB(1a) and hCB(1b)) have been reported, diverging in their amino-termini relative to hCB(1) receptors. In this study, the authors have examined hCB(1) signalling in neurones. hCB(1), hCB(1a) hCB(1b) or rCB(1) receptors were expressed in autaptic cultured hippocampal neurones from CB(1) (-/-) mice. Such cells express a complete endogenous cannabinoid signalling system. Electrophysiological techniques were used to assess CB(1) receptor-mediated signalling. Expressed in autaptic hippocampal neurones cultured from CB(1) (-/-) mice, hCB(1), hCB(1a) and hCB(1b) signal differentially from one another and from rodent CB(1) receptors. Specifically, hCB(1) receptors inhibit synaptic transmission less effectively than rCB(1) receptors. These results suggest that cannabinoid receptor signalling in humans is quantitatively very different from that in rodents. As the problems of marijuana and hashish abuse occur in humans, these results highlight the

importance of studying hCB(1) receptors. They also suggest further study of the distribution and function of hCB(1) receptor splice variants, given their differential signalling and potential impact on human health. LINKED ARTICLES: This article is part of a themed section on Cannabinoids in Biology and Medicine. To view the other articles in this section visit <http://dx.doi.org/10.1111/bph.2012.165.issue-8>. To view Part I of Cannabinoids in Biology and Medicine visit <http://dx.doi.org/10.1111/bph.2011.163.issue-7>. Straiker A, Wager-Miller J, Hutchens J, Mackie K. Differential signalling in human cannabinoid CB1 receptors and their splice variants in autaptic hippocampal neurones. *Br J Pharmacol*. 2012 Apr; 165(8): 2660-2671. doi: 10.1111/j.1476-5381.2011.01744.x.

EphA Signaling Impacts Development of Topographic Connectivity in Auditory Corticofugal Systems

Auditory stimulus representations are dynamically maintained by ascending and descending projections linking the auditory cortex (Actx), medial geniculate body (MGB), and inferior colliculus. Although the extent and topographic specificity of descending auditory corticofugal projections can equal or surpass that of ascending corticopetal projections, little is known about the molecular mechanisms that guide their development. Here, the authors used in utero gene electroporation to examine the role of EphA receptor signaling in the development of corticothalamic (CT) and corticollicular connections. Early in postnatal development, CT axons were restricted to a deep dorsal zone (DDZ) within the MGB that expressed low levels of the ephrin-A ligand. By hearing onset, CT axons had innervated surrounding regions of MGB in control-electroporated mice but remained fixed within the DDZ in mice overexpressing EphA7. In vivo neurophysiological recordings demonstrated a corresponding reduction in spontaneous firing rate, but no changes in sound-evoked responsiveness within MGB regions deprived of CT innervation. Structural and functional CT disruption occurred without gross alterations in thalamocortical connectivity. These data demonstrate a potential role for EphA/ephrin-A signaling in the initial guidance of corticofugal axons and suggest that "genetic rewiring" may represent a useful functional tool to alter cortical feedback without silencing Actx. Torii M, Hackett TA, Rakic P, Levitt P, Polley DB. EphA Signaling Impacts Development of Topographic Connectivity in Auditory Corticofugal Systems. *Cereb Cortex*. 2012 Apr 5. [Epub ahead of print].

Functional Proteomics Establishes The Interaction Of SIRT7 With Chromatin Remodeling Complexes and Expands Its Role In Regulation Of RNA Polymerase I Transcription

Among mammalian sirtuins, SIRT7 is the only enzyme residing in nucleoli where ribosomal DNA is transcribed. Recent reports established that SIRT7 associates with RNA Pol I machinery and is required for rDNA transcription. Although defined by its homology to the yeast histone deacetylase Sir2, current knowledge suggests that SIRT7 itself has little to no deacetylase activity. Because only two SIRT7 interactions have been thus far described: RNA Pol I and upstream binding factor, identification of proteins and complexes associating with SIRT7 is critical to understanding its functions. Here, the authors present the first characterization of SIRT7 interaction networks. They have systematically investigated protein interactions of three EGFP-tagged SIRT7 constructs: wild type, a point mutation affecting rDNA transcription, and a deletion mutant lacking the predicted coiled-coil domain. A combinatorial proteomics and bioinformatics approach was used to integrate gene ontology classifications, functional protein networks, and normalized abundances of proteins co-isolated with SIRT7. The resulting refined proteomic data set confirmed SIRT7 interactions with RNA Pol I and upstream binding factor and highlighted association with factors involved in RNA Pol I- and II-dependent transcriptional processes and several nucleolus-localized chromatin remodeling complexes. Particularly enriched were members of the B-WICH complex, such as Mybbp1a, WSTF, and SNF2h. Prominent interactions were validated by a selected reaction

monitoring-like approach using metabolic labeling with stable isotopes, confocal microscopy, reciprocal immunoaffinity precipitation, and co-isolation with endogenous SIRT7. To extend the current knowledge of mechanisms involved in SIRT7-dependent regulation of rDNA transcription, the authors showed that small interfering RNA-mediated SIRT7 knockdown leads to reduced levels of RNA Pol I protein, but not messenger RNA, which was confirmed in diverse cell types. The down-regulation of RNA Pol I protein levels placed in the context of SIRT7 interaction networks led us to propose that SIRT7 plays a crucial role in connecting the function of chromatin remodeling complexes to RNA Pol I machinery during transcription. Tsai YC, Greco TM, Boonmee A, Miteva Y, Cristea IM. Functional proteomics establishes the interaction of SIRT7 with chromatin remodeling complexes and expands its role in regulation of RNA polymerase I transcription. *Mol Cell Proteomics*. 2012 May; 11(5): 60-76.

Serum Response Factor and cAMP Response Element Binding Protein Are Both Required for Cocaine Induction of Δ FosB The molecular mechanism underlying induction by cocaine of Δ FosB, a transcription factor important for addiction, remains unknown. Here, the authors demonstrate a necessary role for two transcription factors, cAMP response element binding protein (CREB) and serum response factor (SRF), in mediating this induction within the mouse nucleus accumbens (NAc), a key brain reward region. CREB and SRF are both activated in NAc by cocaine and bind to the fosB gene promoter. Using viral-mediated Cre recombinase expression in the NAc of single- or double-floxed mice, the authors show that deletion of both transcription factors from this brain region completely blocks cocaine induction of Δ FosB in NAc, whereas deletion of either factor alone has no effect. Furthermore, deletion of both SRF and CREB from NAc renders animals less sensitive to the rewarding effects of moderate doses of cocaine when tested in the conditioned place preference (CPP) procedure and also blocks locomotor sensitization to higher doses of cocaine. Deletion of CREB alone has the opposite effect and enhances both cocaine CPP and locomotor sensitization. In contrast to Δ FosB induction by cocaine, Δ FosB induction in NAc by chronic social stress, which we have shown previously requires activation of SRF, is unaffected by the deletion of CREB alone. These surprising findings demonstrate the involvement of distinct transcriptional mechanisms in mediating Δ FosB induction within this same brain region by cocaine versus stress. These results also establish a complex mode of regulation of Δ FosB induction in response to cocaine, which requires the concerted activities of both SRF and CREB. Vialou V, Feng J, Robison AJ, Ku SM, Ferguson D, Scobie KN, Mazei-Robison MS, Mouzon E, Nestler EJ. Serum response factor and cAMP response element binding protein are both required for cocaine induction of Δ FosB. *J Neurosci*. 2012 May 30; 32(22): 7577-7584.

The Interpretability Of Family History Reports Of Alcoholism In General Community Samples: Findings In A Midwestern U.S. Twin Birth Cohort Although there is a long tradition in alcoholism research of using family history ratings, the interpretability of family history reports of alcoholism from general community samples has yet to be established. Telephone interview data obtained from a large cohort of female like-sex twins (N = 3,787, median age 22) and their biological parents (N = 2,928, assessed at twins' median age 15) were analyzed to determine agreement between parent self-report, parent ratings of coparent, and twin narrow (alcohol problems) and broad (problem or excessive drinking) ratings of each parent. In European ancestry (EA) families, high tetrachoric correlations were observed between twin and cotwin ratings of parental alcohol problems, between twin and parent ratings of coparent alcohol problems using symptom-based and single-item assessments, as well as moderately high correlations between twin and both mother and father self-reports. In African American (AA) families, inter-rater agreement was substantially lower than for EA families, with no cases where father ratings of maternal alcohol

problems agreed with either twin ratings or mother self-report, and both cotwin agreement and mother-twin agreement were reduced. Differences between EA and AA families were not explained by differences in years of cohabitation with father or mother's education; however, underreporting of problems by AA parents may have contributed. Results support the use of family history ratings of parental alcoholism in general community surveys for EA families, but suggest that family history assessment in AA families requires improved methods. Waldron M, Madden PA, Nelson EC, Knopik VS, Glowinski AL, Grant JD, Lynskey MT, Jacob T, Sher KJ, Bucholz KK, Heath AC. The interpretability of family history reports of alcoholism in general community samples: findings in a midwestern U.S. Twin birth cohort. *Alcohol Clin Exp Res.* 2012 Jun; 36(6): 590-597. doi: 10.1111/j.1530-0277.2011.01698.x. Epub 2012 Jan 11.

Nicotine-Taking and Nicotine-Seeking In C57BL/6J Mice Without Prior Operant Training Or Food Restriction The ability to examine genetically engineered mice in a chronic intravenous (IV) nicotine self-administration paradigm will be a powerful tool for investigating the contribution of specific genes to nicotine reinforcement and more importantly, to relapse behavior. Here the authors describe a reliable model of nicotine-taking and -seeking behavior in male C57BL/6J mice without prior operant training or food restriction. Mice were allowed to self-administer either nicotine (0.03mg/kg/infusion) or saline in 2-h daily sessions under fixed ratio 1 (FR1) followed by FR2 schedules of reinforcement. In the nicotine group, a dose-response curve was measured after the nose-poke behavior stabilized. Subsequently, nose-poke behavior was extinguished and ability of cue presentations, priming injections of nicotine, or intermittent footshock to reinstate responding was assessed in both groups. C57BL/6J mice given access to nicotine exhibited high levels of nose-poke behavior and self-administered a high number of infusions as compared to mice given access to saline. After this acquisition phase, changing the unit-dose of nicotine resulted in a flat dose-response curve for nicotine-taking and subsequently reinstatement of nicotine-seeking behavior was achieved by both nicotine-associated light cue presentation and intermittent footshock. Nicotine priming injections only triggered significant reinstatement on the second consecutive day of priming. In contrast, mice previously trained to self-administer saline did not increase their responding under those conditions. These results demonstrate the ability to produce nicotine-taking and nicotine-seeking behavior in naive C57BL/6J mice without both prior operant training and food restriction. Future work will utilize these models to evaluate nicotine-taking and relapsing behavior in genetically-altered mice. Yan Y, Pushparaj A, Gamaledin I, Steiner RC, Picciotto MR, Roder J, Le Foll B. Nicotine-taking and nicotine-seeking in C57BL/6J mice without prior operant training or food restriction. *Behav Brain Res.* 2012 Apr 21; 230(1): 34-39. Epub 2012 Feb 2.

Autosomal Linkage Scan For Loci Predisposing To Comorbid Dependence On Multiple Substances Multiple substance dependence (MSD) trait comorbidity is common, and MSD patients are often severely affected clinically. While shared genetic risks have been documented, so far there has been no published report using the linkage scan approach to survey risk loci for MSD as a phenotype. A total of 1,758 individuals in 739 families [384 African American (AA) and 355 European American (EA) families] ascertained via affected sib-pairs with cocaine or opioid or alcohol dependence were genotyped using an array-based linkage panel of single-nucleotide polymorphism markers. Fuzzy clustering analysis was conducted on individuals with alcohol, cannabis, cocaine, opioid, and nicotine dependence for AAs and EAs separately, and linkage scans were conducted for the output membership coefficients using Merlin-regression. In EAs, the authors observed an autosome-wide significant linkage signal on chromosome 4 (peak lod = 3.31 at 68.3 cM; empirical autosome-wide P = 0.038), and a suggestive linkage signal on chromosome 21 (peak lod = 2.37 at 19.4 cM). In AAs, four suggestive linkage peaks were observed: two peaks on

chromosome 10 (lod = 2.66 at 96.7 cM and lod = 3.02 at 147.6 cM] and the other two on chromosomes 3 (lod = 2.81 at 145.5 cM) and 9 (lod = 1.93 at 146.8 cM). Three particularly promising candidate genes, GABRA4, GABRB1, and CLOCK, are located within or very close to the autosome-wide significant linkage region for EAs on chromosome 4. This is the first linkage evidence supporting existence of genetic loci influencing risk for several comorbid disorders simultaneously in two major US populations. Yang BZ, Han S, Kranzler HR, Farrer LA, Elston RC, Gelernter J. Autosomal linkage scan for loci predisposing to comorbid dependence on multiple substances. *Am J Med Genet B Neuropsychiatr Genet.* 2012 Jun;159B(4):361-9. doi: 10.1002/ajmg.b.32037. Epub 2012 Feb 21.

Conditional and Joint Multiple-SNP Analysis Of GWAS Summary Statistics Identifies Additional Variants Influencing Complex Traits

The authors present an approximate conditional and joint association analysis that can use summary-level statistics from a meta-analysis of genome-wide association studies (GWAS) and estimated linkage disequilibrium (LD) from a reference sample with individual-level genotype data. Using this method, they analyzed meta-analysis summary data from the GIANT Consortium for height and body mass index (BMI), with the LD structure estimated from genotype data in two independent cohorts. They identified 36 loci with multiple associated variants for height (38 leading and 49 additional SNPs, 87 in total) via a genome-wide SNP selection procedure. The 49 new SNPs explain approximately 1.3% of variance, nearly doubling the heritability explained at the 36 loci. The authors did not find any locus showing multiple associated SNPs for BMI. The method they present is computationally fast and is also applicable to case-control data, which they demonstrate in an example from meta-analysis of type 2 diabetes by the DIAGRAM Consortium. Yang J, Ferreira T, Morris AP, Medland SE; Genetic Investigation of ANthropometric Traits (GIANT) Consortium; DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium, Madden PA, Heath AC, Martin NG, Montgomery GW, Weedon MN, Loos RJ, Frayling TM, McCarthy MI, Hirschhorn JN, Goddard ME, Visscher PM. Conditional and joint multiple-SNP analysis of GWAS summary statistics identifies additional variants influencing complex traits. *Nat Genet.* 2012 Mar 18; 44(4): 369-375, S1-3. doi: 10.1038/ng.2213.

Preferential Electrical Coupling Regulates Neocortical Lineage-Dependent Microcircuit Assembly

Radial glial cells are the primary neural progenitor cells in the developing neocortex. Consecutive asymmetric divisions of individual radial glial progenitor cells produce a number of sister excitatory neurons that migrate along the elongated radial glial fibre, resulting in the formation of ontogenetic columns. Moreover, sister excitatory neurons in ontogenetic columns preferentially develop specific chemical synapses with each other rather than with nearby non-siblings. Although these findings provide crucial insight into the emergence of functional columns in the neocortex, little is known about the basis of this lineage-dependent assembly of excitatory neuron microcircuits at single-cell resolution. Here the authors show that transient electrical coupling between radially aligned sister excitatory neurons regulates the subsequent formation of specific chemical synapses in the neocortex. Multiple-electrode whole-cell recordings showed that sister excitatory neurons preferentially form strong electrical coupling with each other rather than with adjacent non-sister excitatory neurons during early postnatal stages. This preferential coupling allows selective electrical communication between sister excitatory neurons, promoting their action potential generation and synchronous firing. Interestingly, although this electrical communication largely disappears before the appearance of chemical synapses, blockade of the electrical communication impairs the subsequent formation of specific chemical synapses between sister excitatory neurons in ontogenetic columns. These results suggest a strong link between lineage-

dependent transient electrical coupling and the assembly of precise excitatory neuron microcircuits in the neocortex. Yu YC, He S, Chen S, Fu Y, Brown KN, Yao XH, Ma J, Gao KP, Sosinsky GE, Huang K, Shi SH. Preferential electrical coupling regulates neocortical lineage-dependent microcircuit assembly. *Nature*. 2012 May 2; 486(7401): 113-117. doi: 10.1038/nature10958.

Variation In Regulator Of G-Protein Signaling 17 Gene (RGS17) Is Associated With Multiple Substance Dependence Diagnoses

RGS17 and RGS20 encode two members of the regulator of G-protein signaling RGS-Rz subfamily. Variation in these genes may alter their transcription and thereby influence the function of G protein-coupled receptors, including opioid receptors, and modify risk for substance dependence. The association of 13 RGS17 and eight RGS20 tag single nucleotide polymorphisms (SNPs) was examined with four substance [dependence diagnoses (alcohol (AD), cocaine (CD), opioid (OD) or marijuana (MjD)) in 1,905 African Americans (AAs: 1,562 cases and 343 controls) and 1,332 European Americans (EAs: 981 cases and 351 controls). Analyses were performed using both chi2 tests and logistic regression analyses that covaried sex, age, and ancestry proportion. Correlation of genotypes and mRNA expression levels was assessed by linear regression analyses. Seven RGS17 SNPs showed a significant association with at least one of the four dependence traits after a permutation-based correction for multiple testing ($0.003 \leq P_{\text{empirical}} \leq 0.037$). The G allele of SNP rs596359, in the RGS17 promoter region, was associated with AD, CD, OD, or MjD in both populations ($0.005 \leq P_{\text{empirical}} \leq 0.019$). This allele was also associated with significantly lower mRNA expression levels of RGS17 in YRI subjects ($P=0.002$) and non-significantly lower mRNA expression levels of RGS17 in CEU subjects ($P=0.185$). No RGS20 SNPs were associated with any of the four dependence traits in either population. This study demonstrated that variation in RGS17 was associated with risk for substance dependence diagnoses in both AA and EA populations. Zhang H, Wang F, Kranzler HR, Anton RF, Gelernter J. Variation in regulator of G-Protein signaling 17 Gene (RGS17) is associated with multiple substance dependence diagnoses. *Behav Brain Funct*. 2012 May 16; 8(1): 23. [Epub ahead of print].

Cognitive and Serum BDNF Correlates Of BDNF Val66Met Gene Polymorphism In Patients With Schizophrenia and Normal Controls

Studies suggest that a functional polymorphism of the brain-derived neurotrophic factor gene (BDNF Val66Met) may mediate hippocampal-dependent cognitive functions. A few studies have reported its role in cognitive deficits in schizophrenia including its association with peripheral BDNF levels as a mediator of these cognitive deficits. The authors assessed 657 schizophrenic inpatients and 445 healthy controls on the repeatable battery for the assessment of neuropsychological status (RBANS), the presence of the BDNF Val66Met polymorphism and serum BDNF levels. They assessed patient psychopathology using the Positive and Negative Syndrome Scale. They showed that visuospatial/constructional abilities significantly differed by genotype but not genotype \times diagnosis, and the Val allele was associated with better visuospatial/constructional performance in both schizophrenic patients and healthy controls. Attention performance showed a significant genotype by diagnosis effect. Met allele-associated attention impairment was specific to schizophrenic patients and not shown in healthy controls. In the patient group, partial correlation analysis showed a significant positive correlation between serum BDNF and the RBANS total score. Furthermore, the RBANS total score showed a statistically significant BDNF level \times genotype interaction. The authors demonstrated an association between the BDNF Met variant and poor visuospatial/constructional performance. Furthermore, the BDNF Met variant may be specific to attentional decrements in schizophrenic patients. The association between decreased BDNF serum levels and cognitive impairment in schizophrenia is dependent on the BDNF Val66Met polymorphism. Zhang XY, Chen da C, Xiu MH, Haile CN, Luo

X, Xu K, Zhang HP, Zuo L, Zhang Z, Zhang X, Kosten TA, Kosten TR. Cognitive and serum BDNF correlates of BDNF Val66Met gene polymorphism in patients with schizophrenia and normal controls. *Hum Genet.* 2012 Jul; 131(7): 1187-1195. Epub 2012 Feb 24.

Identification of CSP α Clients Reveals A Role In Dynamin 1 Regulation Cysteine string protein α (CSP α), a presynaptic cochaperone for Hsc70, is required for synapse maintenance. Deletion of CSP α leads to neuronal dysfunction, synapse loss, and neurodegeneration. The authors utilized unbiased, systematic proteomics to identify putative CSP α protein clients. They found 22 such proteins whose levels are selectively decreased in CSP α knockout synapses. Of these putative CSP α protein clients, two directly bind to the CSP α chaperone complex and are bona fide clients. They are the t-SNARE SNAP-25 and the GTPase dynamin 1, which are necessary for synaptic vesicle fusion and fission, respectively. Using hippocampal cultures, they show that CSP α regulates the stability of client proteins and synaptic vesicle number. Their analysis of CSP α -dynamin 1 interactions reveals unexpectedly that CSP α regulates the polymerization of dynamin 1. CSP α , therefore, participates in synaptic vesicle endocytosis and may facilitate exo- and endocytic coupling. These findings advance the understanding of how synapses are functionally and structurally maintained. Zhang YQ, Henderson MX, Colangelo CM, Ginsberg SD, Bruce C, Wu T, Chandra SS. Identification of CSP α clients reveals a role in dynamin 1 regulation. *Neuron.* 2012 Apr 12; 74(1): 136-150.

Identification Of An Intronic Cis-Acting Element In The Human Dopamine Transporter Gene The human dopamine transporter gene (hDAT) encodes the dopamine transporter in dopamine (DA) neurons to regulate DA transmission. hDAT expression varies significantly from neuron to neuron, and from individual to individual so that dysregulation of hDAT is related to many neuropsychiatric disorders. It is critical to identify hDAT-specific cis-acting elements that regulate the hDAT expression. Previous studies showed that hDAT Intron 1 displayed inhibitory activity for reporter gene expression. Here the authors report that the hDAT Intron 1 contains a 121-bp fragment that down-regulated both SV40 and hDAT promoter activities by 80% in vitro. Subfragments of 121-bp still down-regulated the SV40 promoter but not the hDAT promoter, as supported by nuclear protein-binding activities. Collectively, 121-bp is a silencer in vitro that might coordinate with transcriptional activities both inside and outside 121-bp in regulation of hDAT. Zhao Y, Zhou Y, Xiong N, Lin Z. Identification of an intronic cis-acting element in the human dopamine transporter gene. *Mol Biol Rep.* 2012 May; 39(5): 5393-5399. Epub 2011 Dec 13.

Genotype Calling From Next-Generation Sequencing Data Using Haplotype Information Of Reads Low coverage sequencing provides an economic strategy for whole genome sequencing. When sequencing a set of individuals, genotype calling can be challenging due to low sequencing coverage. Linkage disequilibrium (LD) based refinement of genotyping calling is essential to improve the accuracy. Current LD-based methods use read counts or genotype likelihoods at individual potential polymorphic sites (PPSs). Reads that span multiple PPSs (jumping reads) can provide additional haplotype information overlooked by current methods. In this article, the authors introduce a new Hidden Markov Model (HMM)-based method that can take into account jumping reads information across adjacent PPSs and implement it in the HapSeq program. Their method extends the HMM in Thunder and explicitly models jumping reads information as emission probabilities conditional on the states of adjacent PPSs. Their simulation results show that, compared to Thunder, HapSeq reduces the genotyping error rate by 30%, from 0.86% to 0.60%. The results from the 1000 Genomes Project show that HapSeq reduces the genotyping error rate by 12 and 9%, from 2.24% and 2.76% to 1.97% and 2.50% for individuals with European and African ancestry, respectively. The authors expect their program can improve genotyping qualities of the

large number of ongoing and planned whole genome sequencing projects. CONTACT: dzhi@ms.soph.uab.edu; kzhang@ms.soph.uab.edu. The software package HapSeq and its manual can be found and downloaded at www.ssg.uab.edu/hapseq/. Supplementary data are available at Bioinformatics online. Zhi D, Wu J, Liu N, Zhang K. Genotype calling from next-generation sequencing data using haplotype information of reads. *Bioinformatics*. 2012 Apr 1; 28(7): 938-946. Epub 2012 Jan 27.

Label-Free Quantitation Of Peptide Release From Neurons In A Microfluidic Device With Mass Spectrometry Imaging

Microfluidic technology allows the manipulation of mass-limited samples and when used with cultured cells, enables control of the extracellular microenvironment, making it well suited for studying neurons and their response to environmental perturbations. While matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) provides for off-line coupling to microfluidic devices for characterizing small-volume extracellular releases, performing quantitative studies with MALDI is challenging. Here the authors describe a label-free absolute quantitation approach for microfluidic devices. They optimize device fabrication to prevent analyte losses before measurement and then incorporate a substrate that collects the analytes as they flow through a collection channel. Following collection, the channel is interrogated using MS imaging. Rather than quantifying the sample present via MS peak height, the length of the channel containing appreciable analyte signal is used as a measure of analyte amount. A linear relationship between peptide amount and band length is suggested by modeling the adsorption process and this relationship is validated using two neuropeptides, acidic peptide (AP) and α -bag cell peptide [1-9] (α BCP). The variance of length measurement, defined as the ratio of standard error to mean value, is as low as 3% between devices. The limit of detection (LOD) of our system is 600 fmol for AP and 400 fmol for α BCP. Using appropriate calibrations, the authors determined that an individual *Aplysia* bag cell neuron secretes 0.15 ± 0.03 pmol of AP and 0.13 ± 0.06 pmol of α BCP after being stimulated with elevated KCl. This quantitation approach is robust, does not require labeling, and is well suited for miniaturized off-line characterization from microfluidic devices. Zhong M, Lee CY, Croushore CA, Sweedler JV. Label-free quantitation of peptide release from neurons in a microfluidic device with mass spectrometry imaging. *Lab Chip*. 2012 May 8; 12(11): 2037-2045. Epub 2012 Apr 16.

The Motivation to Self-Administer is Increased After a History of Spiking Brain Levels of Cocaine

Recent attempts to model the addiction process in rodents have focused on cocaine self-administration procedures that provide extended daily access. Such procedures produce a characteristic loading phase during which blood levels rapidly rise and then are maintained within an elevated range for the duration of the session. The present experiments tested the hypothesis that multiple fast-rising spikes in cocaine levels contribute to the addiction process more robustly than constant, maintained drug levels. Here, the authors compared the effects of various cocaine self-administration procedures that produced very different patterns of drug intake and drug dynamics on P_{max} , a behavioral economic measure of the motivation to self-administer drug. Two groups received intermittent access (IntA) to cocaine during daily 6-h sessions. Access was limited to twelve 5-min trials that alternated with 25-min timeout periods, using either a hold-down procedure or a fixed ratio 1 (FR1). Cocaine levels could not be maintained with this procedure; instead the animals experienced 12 fast-rising spikes in cocaine levels each day. The IntA groups were compared with groups given 6-h FR1 long access and 2-h short access sessions and two other control groups. Here, the authors report that cocaine self-administration procedures resulting in repeatedly spiking drug levels produce more robust increases in P_{max} than procedures resulting in maintained high levels of cocaine. These results suggest that rapid spiking of brain-cocaine levels is

sufficient to increase the motivation to self-administer cocaine. Zimmer BA, Oleson EB, Roberts DC. The motivation to self-administer is increased after a history of spiking brain levels of cocaine. *Neuropsychopharmacology*. 2012 Jul; 37(8): 1901-1910. doi: 10.1038/npp.2012.37. Epub 2012 Mar 28.

Genome-Wide Search For Replicable Risk Gene Regions In Alcohol and Nicotine Co-Dependence

The present study searched for replicable risk genomic regions for alcohol and nicotine co-dependence using a genome-wide association strategy. The data contained a total of 3,143 subjects including 818 European-American (EA) cases with alcohol and nicotine co-dependence, 1,396 EA controls, 449 African-American (AA) cases, and 480 AA controls. The authors performed separate genome-wide association analyses in EAs and AAs and a meta-analysis to derive combined P-values, and calculated the genome-wide false discovery rate (FDR) for each SNP. Regions with $P < 5 \times 10^{-7}$ together with $FDR < 0.05$ in the meta-analysis were examined to detect all replicable risk SNPs across EAs, AAs, and meta-analysis. These SNPs were followed with a series of functional expression quantitative trait locus (eQTL) analyses. The authors found a unique genome-wide significant gene region--SH3BP5-NR2C2--that was enriched with 11 replicable risk SNPs for alcohol and nicotine co-dependence. The distributions of $-\log(P)$ values for all SNP-disease associations within this region were consistent across EAs, AAs, and meta-analysis ($0.315 \leq r \leq 0.868$; $8.1 \times 10^{-52} \leq P \leq 3.6 \times 10^{-5}$). In the meta-analysis, this region was the only association peak throughout chromosome 3 at $P < 0.0001$. All replicable risk markers available for eQTL analysis had nominal cis- and trans-acting regulatory effects on gene expression. The transcript expression of the genes in this region was regulated partly by several nicotine dependence (ND)-related genes and significantly correlated with transcript expression of many alcohol dependence- and ND-related genes. The authors concluded that the SH3BP5-NR2C2 region on Chromosome 3 might harbor causal loci for alcohol and nicotine co-dependence. Zuo L, Zhang F, Zhang H, Zhang XY, Wang F, Li CS, Lu L, Hong J, Lu L, Krystal J, Deng HW, Luo X. Genome-wide search for replicable risk gene regions in alcohol and nicotine co-dependence. *Am J Med Genet B Neuropsychiatr Genet*. 2012 Jun; 159B(4): 437-444. doi: 10.1002/ajmg.b.32047. Epub 2012 Apr 4.

Robust Escalation Of Nicotine Intake With Extended Access To Nicotine Self-Administration and Intermittent Periods Of Abstinence

Although established smokers have a very regular pattern of smoking behavior, converging lines of evidence suggest that the escalation of smoking behavior is a critical factor in the development of dependence. However, the neurobiological mechanisms that underlie the escalation of smoking are unknown, because there is no animal model of the escalation of nicotine intake. On the basis of the pattern of smoking behavior in humans and presence of monoamine oxidase inhibitors in tobacco smoke, the authors hypothesized that the escalation of nicotine intake may only occur when animals are given extended-access (21 h per day) self-administration sessions after repeated periods of abstinence (24-48 h), and after chronic inhibition of monoamine oxidase using phenelzine sulfate. Intermittent access (every 24-48 h) to extended nicotine self-administration produced a robust escalation of nicotine intake, associated with increased responding under fixed- and progressive-ratio schedules of reinforcement, and increased somatic signs of withdrawal. The escalation of nicotine intake was not observed in rats with intermittent access to limited (1 h per day) nicotine self-administration or daily access to extended (21 h per day) nicotine self-administration. Moreover, inhibition of monoamine oxidase with daily administration of phenelzine increased nicotine intake by ~50%. These results demonstrate that the escalation of nicotine intake only occurs in animals given intermittent periods

of abstinence with extended access to nicotine, and that inhibition of monoamine oxidase may contribute to the escalation of smoking, thus validating both an animal model of the escalation of smoking behavior and the contribution of monoamine oxidase inhibition to compulsive nicotine-seeking. Cohen A, Koob GF, George O. Robust escalation of nicotine intake with extended access to nicotine self-administration and intermittent periods of abstinence. *Neuropsychopharmacology*. 2012 Aug; 37(9): 2153-2160. doi: 10.1038/npp.2012.67. Epub 2012 May 2.

BASIC BEHAVIORAL RESEARCH

Comparison of the Performance of DBA/2 and C57BL/6 Mice in Transitive Inference and Foreground and Background Contextual Fear Conditioning

DBA/2 mice have altered hippocampal structure and perform poorly in several hippocampus-dependent contextual/spatial learning tasks. The performance of this strain in higher cognitive tasks is less studied. Transitive inference is a hippocampus-dependent task that requires an abstraction to be made from prior rules to form a new decision matrix; performance of DBA/2 mice in this task is unknown, whereas contextual fear conditioning is a hippocampus-dependent task in which DBA/2 mice have deficits. The present study compared DBA/2J and C57BL/6J inbred mice in two different contextual fear conditioning paradigms and transitive inference to test whether similar deficits are seen across these hippocampus-dependent tasks. For background fear conditioning, mice were trained with two paired presentations of an auditory conditioned stimulus (CS, 30 seconds, 85 dB white noise) paired with an unconditioned stimulus (US, 2 seconds, 0.57 mA footshock), the context was a continuous background CS. Mice were tested for contextual learning 24 hours later. Foreground fear conditioning differed in that no auditory CS was presented. For transitive inference, separate mice were trained to acquire a series of overlapping odor discrimination problems and tested with novel odor pairings that either did or did not require the use of transitive inference. DBA/2 mice performed significantly worse than the C57BL/6 in both foreground and background fear conditioning and transitive inference. These results demonstrate that the DBA/2 mice have deficits in higher-cognitive processes and suggest that similar substrates may underlie deficits in contextual learning and transitive inference. André JM, Cordero KA, Gould TJ. Comparison of the performance of DBA/2 and C57BL/6 mice in transitive inference and foreground and background contextual fear conditioning. *Behav Neurosci.* 2012 Apr; 126(2): 249-257. Epub 2012 Feb 6.

Cocaine Hydrolase Encoded In Viral Vector Blocks The Reinstatement Of Cocaine Seeking In Rats For 6 Months

Cocaine dependence is a pervasive disorder with high rates of relapse. In a previous study, direct administration of a quadruple mutant albumin-fused butyrylcholinesterase that efficiently catalyzes hydrolysis of cocaine to benzoic acid and ecgonine methyl ester acutely blocked cocaine seeking in an animal model of relapse. In the present experiments, these results were extended to achieve a long-duration blockade of cocaine seeking with a gene transfer paradigm using a related butyrylcholinesterase-based cocaine hydrolase (CocH). Male and female rats were allowed to self-administer cocaine under a fixed-ratio 1 schedule of reinforcement for approximately 14 days. Following the final self-administration session, rats were injected with CocH vector or a control injection (empty vector or saline), and their cocaine solutions were replaced with saline for 14 days to allow for extinction of lever pressing. Subsequently, they were tested for drug-primed reinstatement by administering intraperitoneal injections of saline (S), cocaine (C) (5, 10, and 15 mg/kg), and d-amphetamine according to the following sequence: S, C, S, C, S, C, S, d-amphetamine. Rats then received cocaine-priming injections once weekly for 4 weeks and, subsequently, once monthly for up to 6 months. Administration of CocH vector produced substantial and sustained CocH activity in plasma that corresponded with diminished cocaine-induced (but not amphetamine-induced) reinstatement responding for up to 6 months following treatment (compared with high-responding control animals). These results demonstrate that viral transfer of CocH may be useful in promoting long-term resistance to relapse to cocaine addiction. Anker JJ, Brimijoin S, Gao Y, Geng L, Zlebnik NE, Parks RJ, Carroll ME. Cocaine hydrolase encoded in viral vector blocks the reinstatement of cocaine seeking in rats for 6 months. *Biol Psychiatry.* 2012 Apr 15; 71(8): 700-705. Epub 2011 Dec 30.

Effects of Progesterone On Escalation Of Intravenous Cocaine Self-Administration In Rats Selectively Bred For High Or Low Saccharin Intake

Progesterone decreases cocaine self-administration in women and in female rats. In a previous study using rats selectively bred for high (HiS) or low (LoS) saccharin intake, HiS rats escalated their cocaine intake compared with LoS rats. The authors goal was to examine the effects of progesterone on the escalation of cocaine self-administration in HiS and LoS rats. Four groups of female rats were compared: HiS P (progesterone treated), LoS P, HiS VEH (vehicle treated), and LoS VEH. Rats were trained to self-administer 0.8 mg/kg cocaine intravenously under a fixed-ratio 1 schedule during daily short-access (ShA) 2-h sessions. Rats then self-administered three randomly-presented doses of cocaine (0.2, 0.4, and 1.6 mg/kg), and then had daily 6-h long-access (LgA) sessions with 0.4 mg/kg of cocaine for 21 days. Cocaine intake was then reassessed with the four doses under the ShA condition. Throughout the experiment, rats were treated with daily subcutaneous injections of progesterone (0.5 mg/kg) or an equal volume of vehicle 30 min before each session. During the initial ShA condition, HiS rats earned more cocaine infusions than LoS rats at all doses, and during the subsequent LgA condition, HiS rats escalated cocaine intake, whereas the LoS rats maintained a steady rate. Progesterone treatment potentiated escalation of cocaine intake in the HiS rats but had an opposite effect on LoS rats, attenuating their cocaine self-administration. Results from the post-LgA dose-response ShA condition indicated that both LoS and HiS vehicle-treated and progesterone-treated rats earned more infusions than pre-LgA, but mainly at low doses. These results suggest that genetic differences in drug abuse vulnerability contribute differentially to treatment outcomes during escalation, a critical phase of the drug abuse process. Anker JJ, Holtz NA, Carroll ME. Effects of progesterone on escalation of intravenous cocaine self-administration in rats selectively bred for high or low saccharin intake. *Behav Pharmacol.* 2012 Apr; 23(2): 205-210.

From Prediction Error To Incentive Salience: Mesolimbic Computation Of Reward

Motivation Reward contains separable psychological components of learning, incentive motivation and pleasure. Most computational models have focused only on the learning component of reward, but the motivational component is equally important in reward circuitry, and even more directly controls behavior. Modeling the motivational component requires recognition of additional control factors besides learning. Here the author discusses how mesocorticolimbic mechanisms generate the motivation component of incentive salience. Incentive salience takes Pavlovian learning and memory as one input and as an equally important input takes neurobiological state factors (e.g. drug states, appetite states, satiety states) that can vary independently of learning. Neurobiological state changes can produce unlearned fluctuations or even reversals in the ability of a previously learned reward cue to trigger motivation. Such fluctuations in cue-triggered motivation can dramatically depart from all previously learned values about the associated reward outcome. Thus, one consequence of the difference between incentive salience and learning can be to decouple cue-triggered motivation of the moment from previously learned values of how good the associated reward has been in the past. Another consequence can be to produce irrationally strong motivation urges that are not justified by any memories of previous reward values (and without distorting associative predictions of future reward value). Such irrationally strong motivation may be especially problematic in addiction. To understand these phenomena, future models of mesocorticolimbic reward function should address the neurobiological state factors that participate to control generation of incentive salience. Berridge KC. From prediction error to incentive salience: mesolimbic computation of reward motivation. *Eur J Neurosci.* 2012 Apr; 35(7): 1124-1143. doi: 10.1111/j.1460-9568.2012.07990.x.

ADH1B Is Associated With Alcohol Dependence and Alcohol Consumption In Populations Of European and African Ancestry

A coding variant in alcohol dehydrogenase 1B (ADH1B) (rs1229984) that leads to the replacement of Arg48 with His48 is common in Asian populations and reduces their risk for alcoholism, but because of very low allele frequencies the effects in European or African populations have been difficult to detect. The authors genotyped and analyzed this variant in three large European and African-American case-control studies in which alcohol dependence was defined by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, and demonstrated a strong protective effect of the His48 variant (odds ratio (OR) 0.34, 95% confidence interval (CI) 0.24, 0.48) on alcohol dependence, with genome-wide significance (6.6×10^{-10}). The hypothesized mechanism of action involves an increased aversive reaction to alcohol; in keeping with this hypothesis, the same allele is strongly associated with a lower maximum number of drinks in a 24-hour period (lifetime), with $P=3 \times 10^{-13}$. The authors also tested the effects of this allele on the development of alcoholism in adolescents and young adults, and demonstrated a significantly protective effect. This variant has the strongest effect on risk for alcohol dependence compared with any other tested variant in European populations. Bierut LJ, Goate AM, Breslau N, Johnson EO, Bertelsen S, Fox L, Agrawal A, Bucholz KK, Grucza R, Hesselbrock V, Kramer J, Kuperman S, Nurnberger J, Porjesz B, Saccone NL, Schuckit M, Tischfield J, Wang JC, Foroud T, Rice JP, Edenberg HJ. ADH1B is associated with alcohol dependence and alcohol consumption in populations of European and African ancestry. *Mol Psychiatry*. 2012 Apr; 17(4): 445-450. doi: 10.1038/mp.2011.124. Epub 2011 Oct 4.

Preclinical Evidence That Activation of Mesolimbic Alpha 6 Subunit Containing Nicotinic Acetylcholine Receptors Supports Nicotine Addiction Phenotype

Nicotine is a major psychoactive ingredient in tobacco yet very few individuals quit smoking with the aid of nicotine replacement therapy. Targeted therapies with more selective action at nicotinic acetylcholine receptors (nAChRs) that contain a $\beta 2$ subunit ($\beta 2^*nAChRs$; *denotes assembly with other subunits) have enjoyed significantly greater success, but exhibit potential for unwanted cardiac, gastrointestinal, and emotive side effects. This literature review focuses on the preclinical evidence that suggests that subclasses of $\beta 2^*nAChRs$ that assemble with the $\alpha 6$ subunit may provide an effective target for tobacco cessation. $\alpha 6\beta 2^*nAChRs$ have a highly selective pattern of neuroanatomical expression in catecholaminergic nuclei including the ventral tegmental area and its projection regions. $\alpha 6\beta 2^*nAChRs$ promote dopamine (DA) neuron activity and DA release in the mesolimbic dopamine system, a brain circuitry that is well-studied for its contributions to addiction behavior. A combination of genetic and pharmacological studies indicates that activation of $\alpha 6\beta 2^*nAChRs$ is necessary and sufficient for nicotine psychostimulant effects and nicotine self-administration. $\alpha 6\beta 2^*nAChRs$ support maintenance of nicotine use, support the conditioned reinforcing effects of drug-associated cues, and regulate nicotine withdrawal. These data suggest that $\alpha 6\beta 2^*nAChRs$ represent a critical pool of high affinity $\beta 2^*nAChRs$ that regulates nicotine dependence phenotype and suggest that inhibition of these receptors may provide an effective strategy for tobacco cessation therapy. Brunzell DH. Preclinical evidence that activation of mesolimbic alpha 6 subunit containing nicotinic acetylcholine receptors supports nicotine addiction phenotype. *Nicotine Tob Res*. 2012 Apr 6. [Epub ahead of print]

Alpha7 Nicotinic Acetylcholine Receptors Modulate Motivation To Self-Administer Nicotine: Implications For Smoking and Schizophrenia

Individuals diagnosed with schizophrenia have an exceptionally high risk for tobacco dependence. Postmortem studies show that these individuals have significant reductions in $\alpha 7$ nicotinic acetylcholine receptors (nAChRs) in several brain areas. Decreased $\alpha 7$ -mediated function might not only be linked to schizophrenia but also to increased

tobacco consumption. The purpose of this study was to determine whether pharmacological blockade of $\alpha 7$ nAChRs would increase motivation of rats to intravenously self-administer nicotine (NIC) during a progressive ratio schedule of reinforcement (PR). Before PR, rats received local infusions of 0, 10, or 20 pmol of a selective $\alpha 7$ nAChR antagonist, α -conotoxin ArIB [V11L,V16D] (ArIB) into the nucleus accumbens (NAc) shell or the anterior cingulate cortex, brain areas that contribute to motivation for drug reward. The authors additionally sought to determine whether local infusion of 0, 10, or 40 nmol of a selective $\alpha 7$ nAChR agonist, PNU 282987, into these brain areas would decrease motivation for NIC use. Infusion of ArIB into the NAc shell and anterior cingulate cortex resulted in a significant increase in active lever pressing, breakpoints, and NIC intake, suggesting that a decrease in $\alpha 7$ nAChR function increases motivation to work for NIC. In contrast, PNU 282987 infusion resulted in reductions in these measures when administered into the NAc shell, but had no effect after administration into the anterior cingulate cortex. These data identify reduction of $\alpha 7$ nAChR function as a potential mechanism for elevated tobacco use in schizophrenia and also identify activation of $\alpha 7$ nAChRs as a potential strategy for tobacco cessation therapy. Brunzell DH, McIntosh JM. Alpha7 nicotinic acetylcholine receptors modulate motivation to self-administer nicotine: implications for smoking and schizophrenia. *Neuropsychopharmacology*. 2012 Apr; 37(5): 1134-1143. doi: 10.1038/npp.2011.299. Epub 2011 Dec 14.

Parent-Adolescent Conflict Interactions and Adolescent Alcohol Use One important factor in adolescents' development of problem alcohol use is their family environment. Yet, the mechanisms that relate parenting to youth alcohol use are not well characterized. This study employed a naturalistic laboratory-based approach to observe parenting behaviors (support, structure, criticism) and adolescents' physiological and emotional responses to parent-adolescent interactions to examine associations with adolescent alcohol use. Fifty eight 10-16year olds and their parents completed a 10minute Parent Adolescent Interaction Task (PAIT) in which they discussed a mutually highly-rated conflict topic. Parental support, structure, and criticism were coded from the interaction. Adolescents' heart rate (HR), blood pressure (BP), reported emotions, and salivary cortisol were assessed before, during, and after the interaction. Findings indicated that lower parental structure and support were associated with youth's greater diastolic BP and anger arousal in response to the PAIT. Furthermore, higher HR, systolic BP, and cortisol responses to the interaction were associated with youth's alcohol use. Findings suggest that heightened emotional and physiological responses to parent-adolescent conflict interactions in youth may be one pathway by which parenting is associated with adolescent alcohol use and risk for abuse. Chaplin TM, Sinha R, Simmons JA, Healy SM, Mayes LC, Hommer RE, Crowley MJ. Parent-adolescent conflict interactions and adolescent alcohol use. *Addict Behav*. 2012 May; 37(5): 605-612. Epub 2012 Jan 13.

Extinction Under A Behavioral Microscope: Isolating The Sources Of Decline In Operant Response Rate Extinction performance is often used to assess underlying psychological processes without the interference of reinforcement. For example, in the extinction/reinstatement paradigm, motivation to seek drug is assessed by measuring responding elicited by drug-associated cues without drug reinforcement. However, extinction performance is governed by several psychological processes that involve motivation, memory, learning, and motoric functions. These processes are confounded when overall response rate is used to measure performance. Based on evidence that operant responding occurs in bouts, this paper proposes an analytic procedure that separates extinction performance into several behavioral components: (1-3) the baseline bout initiation rate, within-bout response rate, and bout length at the onset of extinction; (4-6) their rates of decay

during extinction; (7) the time between extinction onset and the decline of responding; (8) the asymptotic response rate at the end of extinction; (9) the refractory period after each response. Data that illustrate the goodness of fit of this analytic model are presented. This paper also describes procedures to isolate behavioral components contributing to extinction performance and make inferences about experimental effects on these components. This microscopic behavioral analysis allows the mapping of different psychological processes to distinct behavioral components implicated in extinction performance, which may further our understanding of the psychological effects of neurobiological treatments. Cheung TH, Neisewander JL, Sanabria F. Extinction under a behavioral microscope: isolating the sources of decline in operant response rate. *Behav Processes*. 2012 May; 90(1): 111-123. Epub 2012 Mar 15.

Chronic Psychostimulant Exposure To Adult, But Not Periadolescent Rats Reduces Subsequent Morphine Antinociception

Preweanling methylphenidate (MPH) exposure produces a long lasting enhanced sensitivity to opioids. Two important questions are whether this enhancement is specific to the age of psychostimulant exposure and the type of psychostimulant. To answer these questions periadolescent (PD 35) and adult (PD 55) rats received daily injections of saline, MPH, or methamphetamine (METH) for 10 consecutive days. Two weeks later, acute morphine antinociception was assessed on the hot plate using a cumulative dose response procedure. Following acute antinociceptive testing, morphine tolerance was induced in half the animals by administering morphine twice a day over 2 days. Rats pretreated with MPH and METH during the periadolescent period of ontogeny showed no change in acute morphine antinociception, but rats exposed to a relatively high METH dose (3 mg/kg) displayed enhanced morphine tolerance compared to saline pretreated controls. MPH and METH pretreatment during adulthood led to a reduction in morphine antinociceptive potency and an apparent reduction in morphine tolerance. When combined with the authors' previously published findings, these data indicate that the developmental stage during which MPH and METH exposure occurs differentially alters adult morphine responsiveness. That is, psychostimulant exposure to preweanling rats enhances morphine antinociception and facilitates the development of tolerance, whereas psychostimulant exposure to adult rats reduces subsequent morphine antinociception and tolerance. These alterations indicate that it could be important for physicians to know about prior psychostimulant use when prescribing opioids for pain relief. Cyr MC, Ingram SL, Aicher SA, Morgan MM. Chronic psychostimulant exposure to adult, but not periadolescent rats reduces subsequent morphine antinociception. *Pharmacol Biochem Behav*. 2012 Jun; 101(4): 538-543. Epub 2012 Mar 3.

Serum and Plasma Brain-Derived Neurotrophic Factor (BDNF) In Abstinent Alcoholics and Social Drinkers

Although the effects of alcohol on brain-derived neurotrophic factor (BDNF) have been extensively studied in rodents, BDNF levels have rarely been measured in abstinent, alcohol-dependent (AD) individuals. Interpretation of reported group comparisons of serum BDNF levels is difficult due to limited information regarding analytical variance, biological variability, and the relative contribution of platelet and plasma pools to serum BDNF. Analytical variance (intra- and inter-assay coefficients of variation) of the enzyme-linked immunosorbent assay (ELISA) was characterized. Within- and between-subject variability, and group differences in serum and plasma BDNF, was assessed on three separate days in 16, 4-week abstinent AD individuals (7M/9F) and 16 social drinkers (SDs; 8M/8F). Significantly higher mean (\pm sd) serum BDNF levels were observed for the AD group compared to the SD ($p = 0.003$). No significant difference in mean baseline plasma BDNF levels was observed between AD and SD groups. The low analytical variance, high day-to-day within-individual stability and the high degree of individuality demonstrates the potential clinical utility of measuring serum BDNF levels. The low correlations that the authors

observed between plasma and serum levels are congruent with their representing separate pools of BDNF. The observation of higher basal serum BDNF in the AD group without a concomitant elevation in plasma BDNF levels indicates that the elevated serum BDNF in AD patients is not due to greater BDNF exposure. Further research is warranted to fully elucidate mechanisms underlying this alteration and determine the utility of serum BDNF as a predictor or surrogate marker of chronic alcohol abuse. D'Sa C, Dileone RJ, Anderson GM, Sinha R. Serum and plasma brain-derived neurotrophic factor (BDNF) in abstinent alcoholics and social drinkers. *Alcohol*. 2012 May; 46(3): 253-259. Epub 2012 Feb 22.

Which Cue To 'Want'? Opioid Stimulation Of Central Amygdala Makes Goal-Trackers Show Stronger Goal-Tracking, Just As Sign-Trackers Show Stronger Sign-Tracking

Pavlovian cues that have been paired with reward can gain incentive salience. Drug addicts find drug cues motivationally attractive and binge eaters are attracted by food cues. But the level of incentive salience elicited by a cue re-encounter still varies across time and brain states. In an animal model, cues become attractive and 'wanted' in an 'autoshaping' paradigm, where different targets of incentive salience emerge for different individuals. Some individuals (sign-trackers) find a predictive discrete cue attractive while others find a reward contiguous goal cue more attractive (location where reward arrives: goal-trackers). Here the authors assessed whether central amygdala mu opioid receptor stimulation enhances the phasic incentive salience of the goal-cue for goal-trackers during moments of predictive cue presence (expressed in both approach and consummatory behaviors to goal cue), just as it enhances the attractiveness of the predictive cue target for sign-trackers. Using detailed video analysis they measured the approaches, nibbles, sniffs, and bites directed at their preferred target for both sign-trackers and goal-trackers. They report that DAMGO microinjections in central amygdala made goal-trackers, like sign-trackers, show phasic increases in appetitive nibbles and sniffs directed at the goal-cue expressed selectively whenever the predictive cue was present. This indicates enhancement of incentive salience attributed by both goal trackers and sign-trackers, but attributed in different directions: each to their own target cue. For both phenotypes, amygdala opioid stimulation makes the individual's prepotent cue into a stronger motivational magnet at phasic moments triggered by a CS that predicts the reward UCS. DiFeliceantonio AG, Berridge KC. Which cue to 'want'? Opioid stimulation of central amygdala makes goal-trackers show stronger goal-tracking, just as sign-trackers show stronger sign-tracking. *Behav Brain Res*. 2012 May 1; 230(2): 399-408. Epub 2012 Feb 25.

Allostasis and Addiction: Role Of The Dopamine and Corticotropin-Releasing Factor Systems

Allostasis, originally conceptualized to explain persistent morbidity of arousal and autonomic function, is defined as the process of achieving stability through physiological or behavioral change. Two types of biological processes have been proposed to describe the mechanisms underlying allostasis in drug addiction, a within-system adaptation and a between-system adaptation. In the within-system process, the drug elicits an opposing, neutralizing reaction within the same system in which the drug elicits its primary and unconditioned reinforcing actions, while in the between-system process, different neurobiological systems that the one initially activated by the drug are recruited. In this review, the authors focus their interest on alterations in the dopaminergic and corticotropin releasing factor systems as within-system and between-system neuroadaptations respectively, that underlie the opponent process to drugs of abuse. They hypothesize that repeated compromised activity in the dopaminergic system and sustained activation of the CRF-CRF1R system with withdrawal episodes may lead to an allostatic load contributing significantly to the transition to drug addiction. George O, Le Moal M, Koob GF.

Allostasis and addiction: role of the dopamine and corticotropin-releasing factor systems. *Physiol Behav.* 2012 Apr 12; 106(1): 58-64. Epub 2011 Nov 12.

Nicotine Increases Sucrose Self-Administration and Seeking In Rats Associations between nicotine in cigarettes and food consumption may alter the incentive value of food such that food cue-reactivity is exaggerated during abstinence from smoking. This effect may contribute to the weight gain associated with cessation of smoking. The authors examined the effects of nicotine (0.4 mg/kg base subcutaneous) paired (NPD) or unpaired (NUP) with 10% sucrose self-administration (SA; 0.2 ml/delivery, 1 h/day for 10 days) on SA response rate and intake as well as sucrose cue-reactivity following either 1 or 30 days of forced abstinence. Rats were administered the training dose of nicotine prior to a second, consecutive cue-reactivity session. NPD rats responded at over three times the rate for sucrose and earned nearly twice the number of sucrose deliveries as NUP rats or saline controls. Sucrose cue-reactivity was greater after 30 days versus 1 day of forced abstinence for all groups. History of nicotine exposure had no effect on sucrose cue-reactivity. However, the subsequent injection of nicotine increased sucrose cue-reactivity only in the NPD groups. There were no abstinent-dependent effects of nicotine challenge on sucrose cue-reactivity. A study conducted in parallel with water as the reinforcer revealed a less dramatic effect of nicotine on intake. There was no history or abstinence-dependent effects of nicotine on water cue-reactivity. Nicotine increases the reinforcing effects of sucrose and sucrose-paired cues when nicotine is present. An implication of these findings is that relapse to nicotine (cigarettes) could substantially elevate food cue-reactivity. Grimm JW, Ratliff C, North K, Barnes J, Collins S. Nicotine increases sucrose self-administration and seeking in rats. *Addict Biol.* 2012 May; 17(3): 623-633. doi: 10.1111/j.1369-1600.2012.00436.x. Epub 2012 Feb 17.

Circadian Discrimination Of Reward: Evidence For Simultaneous Yet Separable Food- and Drug-Entrained Rhythms In The Rat A unique extra-suprachiasmatic nucleus (SCN) oscillator, operating independently of the light-entrainable oscillator, has been hypothesized to generate feeding and drug-related rhythms. To test the validity of this hypothesis, sham-lesioned (Sham) and SCN-lesioned (SCNx) rats were housed in constant dim-red illumination (LL(red)) and received a daily cocaine injection every 24 h for 7 d (Experiment 1). In a second experiment, rats underwent 3-h daily restricted feeding (RF) followed 12 d later by the addition of daily cocaine injections given every 25 h in combination with RF until the two schedules were in antiphase. In both experiments, body temperature and total activity were monitored continuously. Results from Experiment 1 revealed that cocaine, but not saline, injections produced anticipatory increases in temperature and activity in SCNx and Sham rats. Following withdrawal from cocaine, free-running temperature rhythms persisted for 2-10 d in SCNx rats. In Experiment 2, robust anticipatory increases in temperature and activity were associated with RF and cocaine injections; however, the feeding periodicity (23.9 h) predominated over the cocaine periodicity. During drug withdrawal, the authors observed two free-running rhythms of temperature and activity that persisted for >14 d in both Sham and SCNx rats. The periods of the free-running rhythms were similar to the feeding entrainment (period = 23.7 and 24.0 h, respectively) and drug entrainment (period = 25.7 and 26.1 h, respectively). Also during withdrawal, the normally close correlation between activity and temperature was greatly disrupted in Sham and SCNx rats. Taken together, these results do not support the existence of a single oscillator mediating the rewarding properties of both food and cocaine. Rather, they suggest that these two highly rewarding behaviors can be temporally isolated, especially during drug withdrawal. Under stable dual-entrainment conditions, food reward appears to exhibit a slightly greater circadian influence than drug reward. The ability to generate free-running temperature rhythms of different frequencies following combined food and drug exposures

could reflect a state of internal desynchrony that may contribute to the addiction process and drug relapse. Jansen HT, Sergeeva A, Stark G, Sorg BA. Circadian discrimination of reward: evidence for simultaneous yet separable food- and drug-entrained rhythms in the rat. *Chronobiol Int.* 2012 May; 29(4): 454-468. Epub 2012 Apr 4.

Olanzapine, But Not Fluoxetine, Treatment Increases Survival In Activity-Based Anorexia In Mice

Anorexia nervosa (AN) is an eating disorder characterized by extreme hypophagia, hyperactivity, and fear of weight gain. No approved pharmacological treatments exist for AN despite high mortality rates. The activity-based anorexia (ABA) phenomenon models aspects of AN in rodents, including progressive weight loss, reduced food intake, and hyperactivity. First, the authors optimized the ABA paradigm for mice. The authors compared mouse strains (Balb/cJ, A/J) for susceptibility with ABA, and evaluated the effects of different food access durations (2, 4, 6, 8, and 10 h) on ABA parameters. Balb/cJ mice exhibited significantly shorter survival time (days until 25% bodyweight loss) in the ABA paradigm compared with A/J mice. Furthermore, 6 h of food access reduced survival in mice housed with wheels without reducing survival in mice housed without wheels. They then evaluated the effects of chronic treatment with fluoxetine (4 weeks) or subchronic treatment with olanzapine (OLZ) (1 week) on ABA in BALB/cJ mice. OLZ (12 mg/kg/day) significantly increased survival and reduced food anticipatory activity (FAA). However, OLZ did not alter food intake or running wheel activity during ad-lib feeding (baseline) or restriction conditions, or in mice housed without wheels. Fluoxetine (18 mg/kg/day) increased food intake and reduced FAA, but did not alter survival. Here, the authors report for the first time that OLZ, but not fluoxetine, reduces ABA in mice. These findings indicate further need for clinical investigations into the effects of OLZ, but not selective serotonin reuptake inhibitors, on core features of AN. Klenotich SJ, Seiglie MP, McMurray MS, Roitman JD, Le Grange D, Dugad P, Dulawa SC. Olanzapine, but not fluoxetine, treatment increases survival in activity-based anorexia in mice. *Neuropsychopharmacology.* 2012 Jun; 37(7): 1620-1631. doi: 10.1038/npp.2012.7. Epub 2012 Mar 7.

Effects Of The GABAB Receptor-Positive Modulators CGP7930 and Rac-BHFF In Baclofen- and Γ -Hydroxybutyrate-Discriminating Pigeons

In vivo effects of GABA(B) receptor-positive modulators suggest them to have therapeutic potential to treat central nervous system disorders such as anxiety and drug abuse. Although these effects are thought to be mediated by positive modulation of GABA(B) receptors, such modulation has been examined primarily in vitro. This study further examined the in vivo properties of the GABA(B) receptor-positive modulators 2,6-di-tert-butyl-4-(3-hydroxy-2,2-dimethylpropyl) phenol (CGP7930) and (R,S)-5,7-di-tert-butyl-3-hydroxy-3-trifluoromethyl-3H-benzofuran-2-one (rac-BHFF). In pigeons discriminating baclofen from saline, γ -hydroxybutyrate (GHB) produced 100% baclofen-appropriate responding, and the GABA(B) antagonist 3-aminopropyl (dimethoxymethyl) phosphinic acid (CGP35348) blocked the effects of both drugs. CGP7930 and rac-BHFF produced at most 41 and 74% baclofen-appropriate responding, respectively, and enhanced the discriminative stimulus effects of baclofen, but not of GHB. In pigeons discriminating GHB from saline, CGP7930 and rac-BHFF produced at most 1 and 49% GHB-appropriate responding, respectively, and enhanced the effects of baclofen, but not of GHB. Enhancement of the discriminative stimulus effects of baclofen by rac-BHFF and CGP7930 is further evidence of their effectiveness as GABA(B) receptor-positive modulators in vivo. Furthermore, lack of complete substitution of the positive modulators rac-BHFF and CGP7930 for baclofen and GHB suggests that their discriminative stimulus effects differ from those of GABA(B) receptor agonists. Finally, together with converging evidence that the GABA(B) receptor populations mediating the effects of baclofen and GHB are not identical, the present

findings suggest that these populations differ in their susceptibility to positive modulatory effects. Such differences could allow for more selective therapeutic targeting of the GABA(B) system. Koek W, France CP, Cheng K, Rice KC. Effects of the GABAB receptor-positive modulators CGP7930 and rac-BHFF in baclofen- and γ -hydroxybutyrate-discriminating pigeons. *J Pharmacol Exp Ther*. 2012 May; 341(2): 369-376. Epub 2012 Feb 7.

AMPA-Independent Effect Of Striatal Acamkii Promotes The Sensitization Of Cocaine

Reward Changes in CaMKII-regulated synaptic excitability are a means through which experience may modify neuronal function and shape behavior. While behavior in rodent addiction models is linked with CaMKII activity in the nucleus accumbens (NAc) shell, the key cellular adaptations that forge this link are unclear. Using a mouse strain with striatal-specific expression of autonomously active CaMKII (T286D), the authors demonstrate that while persistent CaMKII activity induces behaviors comparable to those in mice repeatedly exposed to psychostimulants, it is insufficient to increase AMPAR-mediated synaptic strength in NAc shell. However, autonomous CaMKII upregulates A-type K(+) current (IA) and decreases firing in shell neurons. Importantly, inactivating the transgene with doxycycline eliminates both the IA-mediated firing decrease and the elevated behavioral response to cocaine. This study identifies CaMKII regulation of IA in NAc shell neurons as a novel cellular contributor to the sensitization of cocaine reward. Kourrich S, Klug JR, Mayford M, Thomas MJ. AMPAR-independent effect of striatal α CaMKII promotes the sensitization of cocaine reward. *J Neurosci*. 2012 May 9; 32(19): 6578-6586.

Effects Of Hallucinogenic Agents Mescaline and Phencyclidine On Zebrafish Behavior and

Physiology Mescaline and phencyclidine (PCP) are potent hallucinogenic agents affecting human and animal behavior. As their psychotropic effects remain poorly understood, further research is necessary to characterize phenotypes they evoke in various animal models. Zebrafish (*Danio rerio*) are rapidly emerging as a new model organism for neuroscience research. Here, the authors examine the effects of mescaline (5-20mg/l) and PCP (0.5-3mg/l) in several zebrafish paradigms, including the novel tank, open field and shoaling tests. Mescaline and PCP dose-dependently increased top activity in the novel tank test, also reducing immobility and disrupting the patterning of zebrafish swimming, as assessed by ethograms. PCP, but not mescaline, evoked circling behavior in the open field test. At the highest doses tested, mescaline markedly increased, while PCP did not affect, zebrafish shoaling behavior. Finally, 20mg/l mescaline did not alter, and 3mg/l PCP elevated, whole-body cortisol levels. Overall, these studies indicate high sensitivity of zebrafish models to hallucinogenic compounds with complex behavioral and physiological effects. Kyzar EJ, Collins C, Gaikwad S, Green J, Roth A, Monnig L, El-Ounsi M, Davis A, Freeman A, Capezio N, Stewart AM, Kalueff AV. Effects of hallucinogenic agents mescaline and phencyclidine on zebrafish behavior and physiology. *Prog Neuropsychopharmacol Biol Psychiatry*. 2012 Apr 27; 37(1): 194-202. Epub 2012 Jan 9.

(+)-Naloxone, An Opioid-Inactive Toll-Like Receptor 4 Signaling Inhibitor, Reverses Multiple Models Of Chronic Neuropathic Pain In Rats

Previous work demonstrated that both the opioid antagonist (-)-naloxone and the non-opioid (+)-naloxone inhibit toll-like receptor 4 (TLR4) signaling and reverse neuropathic pain expressed shortly after chronic constriction injury. The present studies reveal that the TLR4 contributes to neuropathic pain in another major model (spinal nerve ligation) and to long established (2-4 months) neuropathic pain, not just to pain shortly after nerve damage. Additionally, analyses of plasma levels of (+)-naloxone after subcutaneous administration indicate that (+)-naloxone has comparable pharmacokinetics to (-)-naloxone with a relatively short half-life. This finding accounts for the rapid onset and short duration of allodynia

reversal produced by subcutaneous (+)-naloxone. Given that toll-like receptor 2 (TLR2) has also recently been implicated in neuropathic pain, cell lines transfected with either TLR4 or TLR2, necessary co-signaling molecules, and a reporter gene were used to define whether (+)-naloxone effects could be accounted for by actions at TLR2 in addition to TLR4. (+)-Naloxone inhibited signaling by TLR4 but not TLR2. These studies provide evidence for broad involvement of TLR4 in neuropathic pain, both early after nerve damage and months later. Additionally, they provide further support for the TLR4 inhibitor (+)-naloxone as a novel candidate for the treatment of neuropathic pain. These studies demonstrated that (+)-naloxone, a systemically available, blood-brain barrier permeable, small molecule TLR4 inhibitor can reverse neuropathic pain in rats, even months after nerve injury. These findings suggest that (+)-naloxone, or similar compounds, be considered as a candidate novel, first-in-class treatment for neuropathic pain. Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, Maier SF, Huang Y, Rice KC, Watkins LR. (+)-naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. *J Pain*. 2012 May; 13(5): 498-506. Epub 2012 Apr 20.

What and When To "Want"? Amygdala-Based Focusing Of Incentive Saliency Upon Sugar and Sex

Amygdala-related circuitry helps translate learned Pavlovian associations into appetitive and aversive motivation, especially upon subsequent encounters with cues. The authors asked whether μ -opioid stimulation via microinjections of the specific agonist D-Ala(2), N-MePhe(4), Gly-ol)-enkephalin (DAMGO) in central nucleus of amygdala (CeA), or the adjacent basolateral amygdala (BLA) would magnify sucrose or sex "wanting", guided by available cues. CeA or BLA DAMGO enhancement of cue-triggered "wanting" was assessed using Pavlovian to instrumental transfer (PIT). Unconditioned food "wanting" was measured via intake, and male sexual "wanting" for an estrous female was measured in a sexual approach test. Sucrose hedonic taste "liking" was measured in a taste reactivity test. CeA (but not BLA) DAMGO increased the intensity of phasic peaks in instrumental sucrose seeking stimulated by Pavlovian cues over pre-cue levels in PIT, while suppressing seeking at other moments. CeA DAMGO also enhanced food intake, as well as sexual approach and investigation of an estrous female by males. DAMGO "wanting" enhancements were localized to CeA, as indicated by "Fos plume"-based anatomical maps for DAMGO causation of behavioral effects. Despite increasing "wanting", CeA DAMGO decreased the hedonic impact or "liking" for sucrose in a taste reactivity paradigm. CeA μ -opioid stimulation specifically enhances incentive saliency, which is dynamically guided to food or sex by available cues. Mahler SV, Berridge KC. What and when to "want"? Amygdala-based focusing of incentive saliency upon sugar and sex. *Psychopharmacology (Berl)*. 2012 Jun; 221(3): 407-426. Epub 2011 Dec 14.

The Addicted Brain Craves New Neurons: Putative Role For Adult-Born Progenitors In Promoting Recovery

Addiction is a chronic relapsing disorder associated with compulsive drug taking, drug seeking and a loss of control in limiting intake, reflected in three stages of a recurrent cycle: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation ("craving"). This review discusses the role of adult-born neural and glial progenitors in drug seeking associated with the different stages of the addiction cycle. A review of the current literature suggests that the loss of newly born progenitors, particularly in hippocampal and cortical regions, plays a role in determining vulnerability to relapse in rodent models of drug addiction. The normalization of drug-impaired neurogenesis or gliogenesis may help reverse neuroplasticity during abstinence and, thus, may help reduce the vulnerability to relapse and aid recovery. Mandyam CD, Koob GF. The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. *Trends Neurosci*. 2012 Apr; 35(4): 250-260. Epub 2012 Jan 19.

Sucrose-Predictive Cues Evoke Greater Phasic Dopamine Release Than Saccharin-Predictive Cues Cues that have been paired with food evoke dopamine in nucleus accumbens (NAc) and drive approach behavior. This cue-evoked dopamine signaling could contribute to overconsumption of food. One manner in which individuals try to restrict caloric intake is through the consumption of foods containing artificial (non-nutritive) sweeteners. The authors were interested in whether cues paired with a non-nutritive sweetener (saccharin) would evoke similar dopamine release as cues paired with a nutritive sweetener (sucrose). They trained food-restricted rats to associate distinct cues with sucrose or saccharin pellets. In the first group of rats, training sessions with each pellet took place on different days, maximizing the opportunity for rats to detect nutritional differences. After training, voltammetry recordings in NAc core revealed that sucrose cues evoked greater phasic dopamine release than saccharin cues. In a second group of rats, on each training day, sucrose and saccharin pellets were presented in pseudorandom order within the same session, to mask nutritional differences. In this condition, the difference in dopamine between sucrose and saccharin cues was attenuated, but not abolished. These results suggest that sucrose-paired cues will more powerfully motivate behavior than saccharin-paired cues. The differing responses to each cue seem to be driven by overall preference with both the nutritional value that the pellets predict as well as other factors, such as taste, contributing. McCutcheon JE, Beeler JA, Roitman MF. Sucrose-predictive cues evoke greater phasic dopamine release than saccharin-predictive cues. *Synapse*. 2012 Apr; 66(4): 346-351. doi: 10.1002/syn.21519. Epub 2011 Dec 29.

Model-Based Learning and The Contribution Of The Orbitofrontal Cortex To The Model-Free World Learning is proposed to occur when there is a discrepancy between reward prediction and reward receipt. At least two separate systems are thought to exist: one in which predictions are proposed to be based on model-free or cached values; and another in which predictions are model-based. A basic neural circuit for model-free reinforcement learning has already been described. In the model-free circuit the ventral striatum (VS) is thought to supply a common-currency reward prediction to midbrain dopamine neurons that compute prediction errors and drive learning. In a model-based system, predictions can include more information about an expected reward, such as its sensory attributes or current, unique value. This detailed prediction allows for both behavioral flexibility and learning driven by changes in sensory features of rewards alone. Recent evidence from animal learning and human imaging suggests that, in addition to model-free information, the VS also signals model-based information. Further, there is evidence that the orbitofrontal cortex (OFC) signals model-based information. Here the authors review these data and suggest that the OFC provides model-based information to this traditional model-free circuitry and offer possibilities as to how this interaction might occur. McDannald MA, Takahashi YK, Lopatina N, Pietras BW, Jones JL, Schoenbaum G. Model-based learning and the contribution of the orbitofrontal cortex to the model-free world. *Eur J Neurosci*. 2012 Apr; 35(7): 991-996. doi: 10.1111/j.1460-9568.2011.07982.x.

Adenosine A2A Receptors In The Nucleus Accumbens Bi-Directionally Alter Cocaine Seeking In Rats Repeated cocaine administration enhances dopamine D(2) receptor sensitivity in the mesolimbic dopamine system, which contributes to drug relapse. Adenosine A(2A) receptors are colocalized with D(2) receptors on nucleus accumbens (NAc) medium spiny neurons where they antagonize D(2) receptor activity. Thus, A(2A) receptors represent a target for reducing enhanced D(2) receptor sensitivity that contributes to cocaine relapse. The aim of these studies was to determine the effects of adenosine A(2A) receptor modulation in the NAc on cocaine seeking in rats that were trained to lever press for cocaine. Following at least 15 daily self-administration sessions and 1 week of abstinence, lever pressing was extinguished in daily extinction sessions. The authors

subsequently assessed the effects of intra-NAc core microinjections of the A(2A) receptor agonist, CGS 21680 (4-[2-[[6-amino-9-(N-ethyl-b-D-ribofuranuronamidoyl)-9H-purin-2-yl]amino]ethyl]benzenepropanoic acid hydrochloride), and the A(2A) receptor antagonist, MSX-3 (3,7-dihydro-8-[(1E)-2-(3-methoxyphenyl)ethenyl]-7-methyl-3-[3-(phosphonoxy)propyl]-1-(2-propynyl)-1H-purine-2,6-dione disodium salt hydrate), in modulating cocaine- and quinpirole-induced reinstatement to cocaine seeking. Intra-NAc pretreatment of CGS 21680 reduced both cocaine- and quinpirole-induced reinstatement. These effects were specific to cocaine reinstatement as intra-NAc CGS 21680 had no effect on sucrose seeking in rats trained to self-administer sucrose pellets. Intra-NAc treatment with MSX-3 modestly reinstated cocaine seeking when given alone, and exacerbated both cocaine- and quinpirole-induced reinstatement. Interestingly, the exacerbation of cocaine seeking produced by MSX-3 was only observed at sub-threshold doses of cocaine and quinpirole, suggesting that removing tonic A(2A) receptor activity enables behaviors mediated by dopamine receptors. Taken together, these findings suggest that A(2A) receptor stimulation reduces, while A(2A) blockade amplifies, D(2) receptor signaling in the NAc that mediates cocaine relapse. O'Neill CE, LeTendre ML, Bachtell RK. Adenosine A2A receptors in the nucleus accumbens bidirectionally alter cocaine seeking in rats. *Neuropsychopharmacology*. 2012 Apr; 37(5): 1245-1256. doi: 10.1038/npp.2011.312. Epub 2011 Dec 14.

Data Mining Approaches For Genome-Wide Association Of Mood Disorders Mood disorders are highly heritable forms of major mental illness. A major breakthrough in elucidating the genetic architecture of mood disorders was anticipated with the advent of genome-wide association studies (GWAS). However, to date few susceptibility loci have been conclusively identified. The genetic etiology of mood disorders appears to be quite complex, and as a result, alternative approaches for analyzing GWAS data are needed. Recently, a polygenic scoring approach that captures the effects of alleles across multiple loci was successfully applied to the analysis of GWAS data in schizophrenia and bipolar disorder (BP). However, this method may be overly simplistic in its approach to the complexity of genetic effects. Data mining methods are available that may be applied to analyze the high dimensional data generated by GWAS of complex psychiatric disorders. The authors sought to compare the performance of five data mining methods, namely, Bayesian networks, support vector machine, random forest, radial basis function network, and logistic regression, against the polygenic scoring approach in the analysis of GWAS data on BP. The different classification methods were trained on GWAS datasets from the Bipolar Genome Study (2191 cases with BP and 1434 controls) and their ability to accurately classify case/control status was tested on a GWAS dataset from the Wellcome Trust Case Control Consortium. The performance of the classifiers in the test dataset was evaluated by comparing area under the receiver operating characteristic curves. Bayesian networks performed the best of all the data mining classifiers, but none of these did significantly better than the polygenic score approach. The authors further examined a subset of single-nucleotide polymorphisms (SNPs) in genes that are expressed in the brain, under the hypothesis that these might be most relevant to BP susceptibility, but all the classifiers performed worse with this reduced set of SNPs. The discriminative accuracy of all of these methods is unlikely to be of diagnostic or clinical utility at the present time. Further research is needed to develop strategies for selecting sets of SNPs likely to be relevant to disease susceptibility and to determine if other data mining classifiers that utilize other algorithms for inferring relationships among the sets of SNPs may perform better. Pirooznia M, Seifuddin F, Judy J, Mahon PB; Bipolar Genome Study (BiGS) Consortium, Potash JB, Zandi PP. Collaborators: Kelsoe JR, Greenwood TA, Shilling PD, Nievergelt C, Schork N, Smith EN, Bloss C, Nurnberger J, Edenberg HJ, Foroud T, Gershon E, Liu C, Badner JA, Scheftner WA, Lawson WB, Nwulia EA, Hipolito M, Coryell W, Rice J, Byerley W, McMahon F, Schulze TG, Berrettini W, Potash JB,

Zandi PP, Mahon PB, McInnis MG, Zöllner S, Craig D, Szelinger S. Data mining approaches for genome-wide association of mood disorders. *Psychiatr Genet.* 2012 Apr; 22(2): 55-61.

An Examination Of The Effects Of Subthalamic Nucleus Inhibition Or μ -Opioid Receptor Stimulation On Food-Directed Motivation In The Non-Deprived Rat

The subthalamic nucleus (STN) serves important functions in regulating movement, cognition, and motivation and is connected with cortical and basal ganglia circuits that process reward and reinforcement. In order to further examine the role of the STN on motivation toward food in non-deprived rats, these experiments studied the effects of pharmacological inhibition or μ -opioid receptor stimulation of the STN on the 2-h intake of a sweetened fat diet, the amount of work exerted to earn sucrose on a progressive ratio 2 (PR-2) schedule of reinforcement, and performance on a differential reinforcement of low-rate responding (DRL) schedule for sucrose reward. Separate behavioral groups (N=6-9) were tested following bilateral inhibition of the STN with the GABA(A) receptor agonist muscimol (at 0-5 ng/0.5 μ l/side) or following μ -opioid receptor stimulation with the agonist D-Ala², N-MePhe⁴, Gly-ol-enkephalin (DAMGO; at 0, 0.025 or 0.25 μ g/0.5 μ l/side). Although STN inhibition increased ambulatory behavior during 2-h feeding sessions, it did not significantly alter intake of the sweetened fat diet. STN inhibition also did not affect the breakpoint for sucrose pellets during a 1-h PR-2 reinforcement schedule or impact the number of reinforcers earned on a 1-h DRL-20s reinforcement schedule in non-deprived rats. In contrast, STN μ -opioid receptor stimulation significantly increased feeding on the palatable diet and reduced the reinforcers earned on a DRL-20 schedule, although DAMGO microinfusions had no effect on PR-2 performance. These data suggest that STN inhibition does not enhance incentive motivation for food in the absence of food restriction and that STN μ -opioid receptors play an important and unique role in motivational processes. Pratt WE, Choi E, Guy EG. An examination of the effects of subthalamic nucleus inhibition or μ -opioid receptor stimulation on food-directed motivation in the non-deprived rat. *Behav Brain Res.* 2012 May 1; 230(2): 365-373. Epub 2012 Feb 25.

Chronic Nicotine Exposure Inhibits Estrogen-Mediated Synaptic Functions In Hippocampus Of Female Rats

Nicotine, the addictive agent in cigarettes, reduces circulating estradiol-17 β (E₂) and inhibits E₂-mediated intracellular signaling in hippocampus of female rats. In hippocampus, E₂-signaling regulates synaptic plasticity by phosphorylation of the N-methyl-D-aspartic acid receptor subunit NR2B and cyclic-AMP response element binding protein (pCREB). Therefore, the authors hypothesized that chronic nicotine exposure induces synaptic dysfunction in hippocampus of female rats. Female rats were exposed to nicotine or saline for 16 days followed by electrophysiological analysis of hippocampus. Briefly, population measurements of excitatory post-synaptic field potentials (fEPSPs) were recorded from stratum radiatum of the CA1 hippocampal slice subfield. A strict software-controlled protocol was used which recorded 30 min of baseline data (stimulation rate of 1/min), a paired-pulse stimulation sequence followed by tetanic stimulation, and 1h of post-tetanus recording. EPSP amplitude and the initial EPSP slope were measured off-line. The authors then investigated by Western blot analysis the effects of nicotine on hippocampal estrogen receptor-beta (ER- β), NR2B and pCREB. The results demonstrated significantly decreased post-tetanic potentiation and paired-pulse facilitation at the 40, and 80 ms interval in nicotine-exposed rats compared to the saline group. Western blot analysis revealed that nicotine decreased protein levels of ER- β , NR2B, and pCREB. They also confirmed the role of E₂ in regulating NR2B and pCREB phosphorylation by performing Western blots in hippocampal tissue obtained from E₂-treated ovariectomized rats. In conclusion, chronic nicotine exposure attenuates short-term synaptic plasticity, and the observed synaptic defects might be a consequence of loss of estradiol-17 β -signaling. However, determining the exact molecular mechanisms of chronic nicotine exposure on

synaptic plasticity specific to the female brain require further investigation. Raval AP, Sick JT, Gonzalez GJ, Defazio RA, Dong C, Sick TJ. Chronic nicotine exposure inhibits estrogen-mediated synaptic functions in hippocampus of female rats. *Neurosci Lett*. 2012 May 23;517(1):41-6. Epub 2012 Apr 12.

Synergistic Inhibitory Effect Of Nicotine Plus Oral Contraceptive On Mitochondrial Complex-IV Is Mediated By Estrogen Receptor-B In Female Rats

Chronic nicotine and oral contraceptive (NOC) exposure caused significant loss of hippocampal membrane-bound estrogen receptor-beta (ER- β) in female rats compared with exposure to nicotine alone. Mitochondrial ER- β regulates estrogen-mediated mitochondrial structure and function; therefore, investigating the impact of NOC on mitochondrial ER- β and its function could help delineate the harmful synergism between nicotine and OC. In this study, the authors tested the hypothesis that NOC-induced loss of mitochondrial ER- β alters the oxidative phosphorylation system protein levels and mitochondrial respiratory function. This hypothesis was tested in hippocampal mitochondria isolated from female rats exposed to saline, nicotine, OC or NOC for 16 days. NOC decreased the mitochondrial ER- β protein levels and reduced oxygen consumption and complex IV (CIV) activity by 34% and 26% compared with saline- or nicotine-administered groups, respectively. They also observed significantly low protein levels of all mitochondrial-encoded CIV subunits after NOC as compared with the nicotine or saline groups. Similarly, the silencing of ER- β reduced the phosphorylation of cyclic-AMP response element binding protein, and also reduced levels of CIV mitochondrial-encoded subunits after estrogen stimulation. Overall, these results suggest that mitochondrial ER- β loss is responsible for mitochondrial malfunction after NOC. Raval AP, Dave KR, Saul I, Gonzalez GJ, Diaz F. Synergistic inhibitory effect of nicotine plus oral contraceptive on mitochondrial complex-IV is mediated by estrogen receptor- β in female rats. *J Neurochem*. 2012 Apr; 121(1): 157-167. doi: 10.1111/j.1471-4159.2012.07661.x. Epub 2012 Feb 6.

Glucose-Mediated Control Of Ghrelin Release From Primary Cultures Of Gastric Mucosal Cells

The peptide hormone ghrelin is released from a distinct group of gastrointestinal cells in response to caloric restriction, whereas its levels fall after eating. The mechanisms by which ghrelin secretion is regulated remain largely unknown. Here, the authors have used primary cultures of mouse gastric mucosal cells to investigate ghrelin secretion, with an emphasis on the role of glucose. Ghrelin secretion from these cells upon exposure to different d-glucose concentrations, the glucose antimetabolite 2-deoxy-d-glucose, and other potential secretagogues was assessed. The expression profile of proteins involved in glucose transport, metabolism, and utilization within highly enriched pools of mouse ghrelin cells and within cultured ghrelinoma cells was also determined. Ghrelin release negatively correlated with d-glucose concentration. Insulin blocked ghrelin release, but only in a low d-glucose environment. 2-Deoxy-d-glucose prevented the inhibitory effect of high d-glucose exposure on ghrelin release. mRNAs encoding several facilitative glucose transporters, hexokinases, the ATP-sensitive potassium channel subunit Kir6.2, and sulfonylurea type 1 receptor were expressed highly within ghrelin cells, although neither tolbutamide nor diazoxide exerted direct effects on ghrelin secretion. These findings suggest that direct exposure of ghrelin cells to low ambient d-glucose stimulates ghrelin release, whereas high d-glucose and glucose metabolism within ghrelin cells block ghrelin release. Also, low d-glucose sensitizes ghrelin cells to insulin. Various glucose transporters, channels, and enzymes that mediate glucose responsiveness in other cell types may contribute to the ghrelin cell machinery involved in regulating ghrelin secretion under these different glucose environments, although their exact roles in ghrelin release remain uncertain. Sakata I, Park WM, Walker AK, Piper PK, Chuang JC, Osborne-Lawrence S, Zigman JM. Glucose-mediated control of ghrelin release from primary cultures of

gastric mucosal cells. *Am J Physiol Endocrinol Metab.* 2012 May; 302(10): E1300-310. Epub 2012 Mar 13.

Gender Differences In Craving and Cue Reactivity To Smoking and Negative Affect/Stress Cues

There is evidence that women may be less successful when attempting to quit smoking than men. One potential contributory cause of this gender difference is differential craving and stress reactivity to smoking- and negative affect/stress-related cues. The present human laboratory study investigated the effects of gender on reactivity to smoking and negative affect/stress cues by exposing nicotine dependent women (n = 37) and men (n = 53) smokers to two active cue types, each with an associated control cue: (1) in vivo smoking cues and in vivo neutral control cues, and (2) imagery-based negative affect/stress script and a neutral/relaxing control script. Both before and after each cue/script, participants provided subjective reports of smoking-related craving and affective reactions. Heart rate (HR) and skin conductance (SC) responses were also measured. Results indicated that participants reported greater craving and SC in response to smoking versus neutral cues and greater subjective stress in response to the negative affect/stress versus neutral/relaxing script. With respect to gender differences, women evidenced greater craving, stress and arousal ratings and lower valence ratings (greater negative emotion) in response to the negative affect/stressful script. While there were no gender differences in responses to smoking cues, women trended towards higher arousal ratings. Implications of the findings for treatment and tobacco-related morbidity and mortality are discussed. Saladin ME, Gray KM, Carpenter MJ, LaRowe SD, DeSantis SM, Upadhyaya HP. Gender differences in craving and cue reactivity to smoking and negative affect/stress cues. *Am J Addict.* 2012 May-Jun; 21(3): 210-220. doi: 10.1111/j.1521-0391.2012.00232.x.

Electrode Calibration With A Microfluidic Flow Cell For Fast-Scan Cyclic Voltammetry

Fast-scan cyclic voltammetry (FSCV) is a common analytical electrochemistry tool used to measure chemical species. It has recently been adapted for measurement of neurotransmitters such as dopamine in awake and behaving animals (in vivo). Electrode calibration is an essential step in FSCV to relate observed current to concentration of a chemical species. However, existing methods require multiple components, which reduce the ease of calibrations. To this end, a microfluidic flow cell (μ FC) was developed as a simple device to switch between buffer and buffer with a known concentration of the analyte of interest - in this case dopamine - in a microfluidic Y-channel. The ability to quickly switch solutions yielded electrode calibrations with faster rise times and that were more stable at peak current values. The μ FC reduced the number of external electrical components and produced linear calibrations over a range of concentrations. To demonstrate this, an electrode calibrated with the μ FC was used in FSCV recordings from a rat during the delivery of food reward - a stimulus that reliably evokes a brief increase in current due to the oxidation of dopamine. Using the linear calibration, dopamine concentrations were determined from the current responses evoked during the behavioral task. The μ FC is able to easily and quickly calibrate FSCV electrode responses to chemical species for both in vitro and in vivo experiments. Sinkala E, McCutcheon JE, Schuck MJ, Schmidt E, Roitman MF, Eddington DT. Electrode calibration with a microfluidic flow cell for fast-scan cyclic voltammetry. *Lab Chip.* 2012 Jun 6; 12(13): 2403-2408. Epub 2012 Apr 20.

Involvement Of Metabotropic Glutamate Receptor 5 In Brain Reward Deficits Associated With Cocaine and Nicotine Withdrawal and Somatic Signs Of Nicotine Withdrawal

The involvement of metabotropic glutamate 5 (mGlu5) receptors has been suggested in the reinforcing effects of psychostimulants. However, little is known about the role of these receptors in psychostimulant withdrawal. The role of mGlu5 receptors was assessed in the anhedonic and

somatic aspects of psychostimulant withdrawal. Anhedonia was assessed with the discrete-trial current-intensity intracranial self-stimulation (ICSS) procedure after the termination of cocaine (180 mg kg⁻¹ day⁻¹, salt, 3 days, i.p.) or nicotine (40 mg kg⁻¹ day⁻¹, base, 28 days, s.c.) administration via osmotic minipumps in mGlu5 receptor knockout (mGluR5^{-/-}) and wild-type (mGluR5^{+/+}) mice. Somatic signs were assessed during nicotine withdrawal. The effects of the nicotinic acetylcholine receptor antagonist mecamylamine on ICSS thresholds were assessed during chronic nicotine administration. Nicotine-treated mGluR5^{+/+} and mGluR5^{-/-} mice demonstrated similar threshold elevations during mecamylamine-precipitated withdrawal compared with their saline-treated counterparts. During spontaneous nicotine and cocaine withdrawal, thresholds in drug-withdrawing mGluR5^{+/+}, but not mGluR5^{-/-}, mice were elevated up to 72 h of nicotine/cocaine withdrawal and then returned to baseline, indicating attenuation of withdrawal-induced anhedonia in mGluR5^{-/-} mice. Nicotine-withdrawing mGluR5^{+/+}, but not mGluR5^{-/-}, mice showed increases in somatic signs compared with saline-treated counterparts. mGlu5 receptor null mutation attenuates the anhedonic and somatic effects of psychostimulant withdrawal. This attenuated withdrawal in mGluR5^{-/-} mice may result from the lack of drug-induced adaptations in mGlu5 receptor function that may occur in mGluR5^{+/+} mice with chronic drug administration. Thus, these results suggest the involvement of mGlu5 receptors in psychostimulant dependence and the mediation of the anhedonic and somatic signs of psychostimulant withdrawal. Stoker AK, Olivier B, Markou A. Involvement of metabotropic glutamate receptor 5 in brain reward deficits associated with cocaine and nicotine withdrawal and somatic signs of nicotine withdrawal. *Psychopharmacology (Berl)*. 2012 May; 221(2): 317-327. Epub 2011 Dec 3.

Chronic Corticosterone Exposure During Adolescence Reduces Impulsive Action But Increases Impulsive Choice and Sensitivity To Yohimbine In Male Sprague-Dawley Rats

Chronic stress during adolescence is associated with an increased risk for alcoholism and addictive disorders. Addiction is also associated with increased impulsivity, and stress during adolescence could alter cortical circuits responsible for response inhibition. Therefore, the present study determined the effect of chronic exposure to the stress hormone corticosterone (CORT) during adolescence on tests of impulsivity in adulthood and examined possible biochemical mechanisms. Male Sprague-Dawley rats were exposed to CORT by their drinking water during adolescence (post-natal day 30-50). The rats were then tested in adulthood to assess behavior on the 5-choice serial reaction time task (5CSRTT), stop-signal reaction time task (SSRTT), and the delay-discounting task, which differentially assess attention, impulsive action, and impulsive choice. Yohimbine-induced impulsivity on the 5CSRTT and biochemical analysis of the lateral orbital frontal cortex (IOFC) was also assessed owing to the ability of yohimbine to activate the hypothalamic-pituitary-adrenal axis and influence impulsivity. Adolescent CORT-treated rats were found to behave largely like controls on the 5CSRTT, but did show reduced premature responses when the intertrial interval was increased. Nevertheless, the CORT-treated rats tended to have more yohimbine-induced impulsive responses at low doses on this task, which was not found to be due to increased pCREB in the IOFC, but could be related to a higher expression/activity of the AMPA receptor subunit GluR1. Adolescent CORT-treated rats performed more accurately on the SSRTT, but showed greater impulsivity on the delay-discounting task, as indicated by steeper discounting functions. Therefore, adolescent CORT exposure reduced impulsive action but increased impulsive choice, indicating that chronic stress hormone exposure in adolescence can have long-term consequences on behavior. Torregrossa MM, Xie M, Taylor JR. Chronic corticosterone exposure during adolescence reduces impulsive action but increases impulsive choice and sensitivity to yohimbine in male Sprague-Dawley rats. *Neuropsychopharmacology*. 2012 Jun; 37(7): 1656-1670. doi: 10.1038/npp.2012.11. Epub 2012 Feb 15.

Gender Differences In Smoking Following An Implicit Mood Induction Smoking is significantly associated with negative affect, which may play an especially important role in the smoking behavior of women. The purpose of this laboratory study was to examine the role of gender in the relationship of negative mood and smoking maintenance for male and female smokers following an implicit mood induction using music. Ninety adult smokers (50% female) completed a laboratory session during which they were randomly assigned to a negative mood induction, a positive mood induction, or a neutral mood condition. Latency to smoke and number of cigarettes smoked were assessed during an ad libitum smoking period following the mood induction. Female smokers began smoking more quickly following the negative mood induction when compared with males. There were no gender differences in the number of cigarettes smoked or for cravings to smoke by mood condition. This study demonstrated gender differences in the relationship between negative affect and smoking behavior following an implicit and subtle mood manipulation. A better understanding of gender differences in smoking behavior can provide valuable information about mechanisms that maintain smoking behavior and guide treatment development to help adults quit smoking. Weinberger AH, McKee SA. Gender differences in smoking following an implicit mood induction. *Nicotine Tob Res.* 2012 May; 14(5): 621-625. Epub 2011 Sep 8.

Intrathecal Cannabidiol CB(2)R Agonist, AM1710, Controls Pathological Pain and Restores Basal Cytokine Levels Spinal glial and proinflammatory cytokine actions are strongly implicated in pathological pain. Spinal administration of the anti-inflammatory cytokine interleukin (IL)-10 abolishes pathological pain and suppresses proinflammatory IL-1 β and tumor necrosis factor alpha (TNF- α). Drugs that bind the cannabinoid type-2 receptor (CB(2)R) expressed on spinal glia reduce mechanical hypersensitivity. To better understand the CB(2)R-related anti-inflammatory profile of key anatomical nociceptive regions, the authors assessed mechanical hypersensitivity and protein profiles following intrathecal application of the cannabidiol CB(2)R agonist, AM1710, in 2 animal models; unilateral sciatic nerve chronic constriction injury (CCI), and spinal application of human immunodeficiency virus-1 glycoprotein 120 (gp120), a model of peri-spinal immune activation. In CCI animals, lumbar dorsal spinal cord and corresponding dorsal root ganglia (DRG) were evaluated by immunohistochemistry for expression of IL-10, IL-1 β , phosphorylated p38-mitogen-activated-kinase (p-p38MAPK), a pathway associated with proinflammatory cytokine production, glial cell markers, and degradative endocannabinoid enzymes, including monoacylglycerol lipase (MAGL). AM1710 reversed bilateral mechanical hypersensitivity. CCI revealed decreased IL-10 expression in dorsal spinal cord and DRG, while AM1710 resulted in increased IL-10, comparable to controls. Adjacent DRG and spinal sections revealed increased IL-1 β , p-p38MAPK, glial markers, and/or MAGL expression, while AM1710 suppressed all but spinal p-p38MAPK and microglial activation. In spinal gp120 animals, AM1710 prevented bilateral mechanical hypersensitivity. For comparison to immunohistochemistry, IL-1 β and TNF- α protein quantification from lumbar spinal and DRG homogenates was determined, and revealed increased DRG IL-1 β protein levels from gp120, that was robustly prevented by AM1710 pretreatment. Cannabidiol CB(2)R agonists are emerging as anti-inflammatory agents with pain therapeutic implications. Wilkerson JL, Gentry KR, Dengler EC, Wallace JA, Kerwin AA, Armijo LM, Kuhn MN, Thakur GA, Makriyannis A, Milligan ED. Intrathecal cannabidiol CB(2)R agonist, AM1710, controls pathological pain and restores basal cytokine levels. *Pain.* 2012 May; 153(5): 1091-1106. Epub 2012 Mar 17.

Analgesia Or Addiction?: Implications For Morphine Use After Spinal Cord Injury Opioid analgesics are among the most effective agents for treatment of moderate to severe pain. However, the use of morphine after a spinal cord injury (SCI) can potentiate the development of paradoxical pain symptoms, and continuous administration can lead to dependence, tolerance, and addiction. Although some studies suggest that the addictive potential of morphine decreases when it is used to treat neuropathic pain, this has not been studied in a SCI model. Accordingly, the present studies investigated the addictive potential of morphine in a rodent model of SCI using conditioned place preference (CPP) and intravenous self-administration paradigms. A contusion injury significantly increased the expression of a CPP relative to sham and intact controls in the acute phase of injury. However, contused animals self-administered significantly less morphine than sham and intact controls, but this was dose-dependent; at a high concentration, injured rats exhibited an increase in drug-reinforced responses over time. Exposure to a high concentration of morphine impeded weight gain and locomotor recovery. The authors suggest that the increased preference observed in injured rats reflects a motivational effect linked in part to the drug's anti-nociceptive effect. Further, although injured rats exhibited a suppression of opiate self-administration, when given access to a high concentration, addictive-like behavior emerged and was associated with poor recovery. Woller SA, Moreno GL, Hart N, Wellman PJ, Grau JW, Hook MA. Analgesia or addiction?: Implications for morphine use after spinal cord injury. *J Neurotrauma*. 2012 May 20; 29(8): 1650-1662. Epub 2012 Apr 2.

Genetic Modulation Of Plasma NPY Stress Response Is Suppressed In Substance Abuse: Association With Clinical Outcomes Neuropeptide Y (NPY) is involved in stress regulation. Genetic variations predict plasma NPY and neural correlates of emotion and stress. The authors examined whether the functional NPY haplotype modulates stress-induced NPY and anxiety responses, and if plasma NPY stress responses are associated with substance dependence outcomes. Thirty-seven treatment-engaged, abstinent substance dependent (SD) patients and 28 healthy controls (HCs) characterized on NPY diplotypes (HH: high expression; HLLL: intermediate/low expression) were exposed to stress, alcohol/drug cues and neutral relaxing cues, using individualized guided imagery, in a 3-session laboratory experiment. Plasma NPY, heart rate and anxiety were assessed. Patients were prospectively followed for 90-days post-treatment to assess relapse outcomes. HH individuals showed significantly lower stress-induced NPY with greater heart rate and anxiety ratings, while the HLLL group showed the reverse pattern of NPY, anxiety and heart rate responses. This differential genetic modulation of NPY stress response was suppressed in the SD group, who showed no stress-related increases in NPY and higher heart rate and greater anxiety, regardless of diplotype. Lower NPY predicted subsequent higher number of days and greater amounts of post-treatment drug use. These preliminary findings are the first to document chronic drug abuse influences on NPY diplotype expression where NPY diplotype modulation of stress-related plasma NPY, heart rate and anxiety responses was absent in the substance abuse sample. The finding that lower stress-related NPY is predictive of greater relapse severity provides support for therapeutic development of neuropeptide Y targets in the treatment of substance use disorders. Xu K, Hong KA, Zhou Z, Hauger RL, Goldman D, Sinha R. Genetic modulation of plasma NPY stress response is suppressed in substance abuse: association with clinical outcomes. *Psychoneuroendocrinology*. 2012 Apr; 37(4): 554-564. Epub 2011 Sep 13.

Sex Differences In The Effects Of Social and Physical Environment On Novelty-Induced Exploratory Behavior and Cocaine-Stimulated Locomotor Activity In Adolescent Rats Many factors influence the rewarding effects of drugs such as cocaine. The present study was done to determine whether social and environmental factors alter behavior in adolescent male and female

rats. On postnatal day (PND) 23, rats were housed in one of several same-sex conditions. Both social (number of rats per cage) and environmental (availability of toys) factors were manipulated. Socially isolated rats were housed alone (1 rat/cage) in an environment that either was impoverished (with no toys; II) or enriched (with toys; IE). Standard housing for these studies was social and impoverished, which was 2 rats/cage with no toys (SI2). Other rats were housed 2/cage with toys (SE2), or 3/cage with (SE3) or without (SI3) toys. On PND 37, novelty-induced locomotor activity was measured for 30min. On PND 44-46, locomotor activity in response to an injection of 5mg/kg cocaine was measured for 60min each day. For male rats, only social conditions altered novelty-induced activity. Males housed in groups of three had the most activity, compared to pair-housed and isolated rats. For females, social and environmental enrichment interacted to alter novelty-induced activity. In contrast to males, isolated females had increased activity, compared to group-housed females. Further, isolated females in impoverished environments had more activity than isolated females in enriched environments and group-housed females in impoverished environments. The effect of environmental enrichment on cocaine-stimulated locomotor activity was altered depending upon the number of rats living in a cage for males. For females, only social conditions altered cocaine-stimulated behavior, with activity increasing with the number of rats in the cage, regardless of environmental enrichment. These data show that social and environmental enrichment differentially alter novelty-induced and cocaine-stimulated locomotor activity in adolescent male and female rats. Zakharova E, Starosciak A, Wade D, Izenwasser S. Sex differences in the effects of social and physical environment on novelty-induced exploratory behavior and cocaine-stimulated locomotor activity in adolescent rats. *Behav Brain Res.* 2012 Apr 21; 230(1): 92-99. Epub 2012 Feb 7.

Environmental Enrichment Counters Cocaine Abstinence-Induced Stress and Brain Reactivity To Cocaine Cues But Fails To Prevent The Incubation Effect

Environmental enrichment (EE) during a period of forced abstinence attenuates incentive motivational effects of cocaine-paired stimuli. Here the authors examined whether EE during forced abstinence from cocaine self-administration would prevent time-dependent increases in cue-elicited cocaine-seeking behavior (i.e. the incubation effect). Rats were trained to self-administer cocaine, which was paired with light/tonal cues, for 15 days while living in isolated conditions (IC). Controls received yoked saline infusions. Subsequently, rats were assigned to live in either continued IC or EE for either 1 or 21 days of forced abstinence prior to a test for cocaine-seeking behavior. During testing, responding resulted only in presentation of the light/tonal cues. Contrary to the authors' prediction, cocaine-seeking behavior increased over time regardless of living condition during abstinence; however, EE attenuated cocaine-seeking behavior relative to IC regardless of length of abstinence. Brains were harvested and trunk blood was collected immediately after the 60-minute test and later assayed. Results indicated that short-term EE elevated hippocampal brain-derived neurotrophic factor and reduced plasma corticosterone compared with IC. Furthermore, 21 days of EE during forced abstinence prevented increases in the cue-elicited amygdala phosphorylated extracellular signal-regulated kinase expression that was observed in IC rats. These findings suggest that EE attenuates incentive motivational effects of cocaine cues through a mechanism other than preventing the incubation effect, perhaps involving reduction of stress and neural activity in response to cocaine-paired cues during acute withdrawal. Thiel KJ, Painter MR, Pentkowski NS, Mitroi D, Crawford CA, Neisewander JL. Environmental enrichment counters cocaine abstinence-induced stress and brain reactivity to cocaine cues but fails to prevent the incubation effect. *Addiction Biol.* 2012 Mar; 17(2): 365-377.

Long-Term Effects Of Juvenile Nicotine Exposure On Abstinence-Related Social Anxiety-Like Behavior and Amygdalar Cannabinoid Receptor 1 (CB1R) mRNA Expression In The Novelty-Seeking Phenotype

A rat model of novelty-seeking phenotype predicts vulnerability to nicotine relapse where locomotor reactivity to novelty is used to rank high (HR) versus low (LR) responders. The present study investigates the implication of cannabinoid receptor 1 (CB1R) in the basolateral (BLA) and the central (CeA) nuclei of amygdala in behaviorally sensitizing effects of nicotine and accompanying social anxiety following juvenile nicotine training and a 1- or 3-wk injection-free period in the novelty-seeking phenotype. Sprague-Dawley rats were phenotype screened, and received four, saline (1 ml/kg; s.c) or nicotine (0.35 mg/kg; s.c) injections, followed by a 1- or 3-wk injection-free period. Subsequently, animals were challenged with a low dose of nicotine (0.1 mg/kg; s.c.), subjected to the social interaction test and sacrificed. In situ hybridization histochemistry was used to assess CB1R messenger RNA (mRNA) levels in the amygdala. Nicotine pre-trained HRs displayed expression of locomotor sensitization to nicotine challenge along with enhanced social anxiety compared to saline pre-trained controls following a 1- or 3-wk injection-free period. HR-specific behavioral effects were accompanied by decreased CB1R mRNA levels in the CeA and the BLA following a 1-wk injection-free period. Decreased CB1R mRNA levels in both compartments of the amygdala were also observed following nicotine challenge in saline pre-trained HRs after a 3-wk injection-free period compared to HRs after a 1-wk injection-free period. These findings show robust, long-lasting expression of behavioral sensitization to nicotine in HRs associated with changes in amygdalar CB1R mRNA as a potential substrate for abstinence-related anxiety. Aydin C, Oztan O, Isgor C. Long-term effects of juvenile nicotine exposure on abstinence-related social anxiety-like behavior and amygdalar cannabinoid receptor 1 (CB1R) mRNA expression in the novelty-seeking phenotype. *Behav Brain Res.* 2012 Mar 1; 228(1): 236-239.

Role of $\alpha 7$ - and $\beta 4$ -Containing Nicotinic Acetylcholine Receptors in the Affective and Somatic Aspects of Nicotine Withdrawal: Studies in Knockout Mice

To assess which nicotinic acetylcholine receptors (nAChRs) are involved in the aversive aspects of nicotine withdrawal, brain reward function and the somatic signs of nicotine withdrawal were assessed in mice that lack $\alpha 7$ and $\beta 4$ nAChR subunits. Brain reward function was assessed with the intracranial self-stimulation (ICSS) procedure, in which elevations in ICSS thresholds reflect an anhedonic mood state. At 3–6 h of spontaneous nicotine/saline withdrawal, thresholds were elevated in nicotine-withdrawing $\alpha 7^{+/+}$ and $\beta 4^{+/+}$, but not $\alpha 7^{-/-}$ or $\beta 4^{-/-}$, mice compared with saline-withdrawing mice, indicating a delay in the onset of withdrawal in the knockout mice. From 8 to 100 h of withdrawal, thresholds in $\alpha 7^{+/+}$ and $\alpha 7^{-/-}$ mice were equally elevated, whereas thresholds in $\beta 4^{+/+}$ and $\beta 4^{-/-}$ mice returned to baseline levels. Somatic signs were attenuated in nicotine-withdrawing $\beta 4^{-/-}$, but not $\alpha 7^{-/-}$, mice. Administration of a low dose of the nAChR antagonist mecamylamine induced threshold elevations in $\alpha 7^{-/-}$, but not $\alpha 7^{+/+}$, mice, whereas the highest dose tested only elevated thresholds in $\alpha 7^{+/+}$ mice. Mecamylamine-induced threshold elevations were similar in $\beta 4^{-/-}$ and $\beta 4^{+/+}$ mice. In conclusion, null mutation of the $\alpha 7$ and $\beta 4$ nAChR subunits resulted in a delayed onset of the anhedonic aspects of the spontaneous nicotine withdrawal syndrome. Previous findings of attenuated somatic signs of nicotine withdrawal in $\beta 4^{-/-}$, but not $\alpha 7^{-/-}$, mice were confirmed in the present study, indicating an important role for $\beta 4$ -containing nAChRs in the somatic signs of nicotine withdrawal. The mecamylamine-precipitated withdrawal data suggest that compensatory adaptations may occur in constitutive $\alpha 7^{-/-}$ mice or that mecamylamine may interact with other receptors besides nAChRs in these mice. In summary, the present results indicate an important role for $\alpha 7$ and $\beta 4$ -containing nAChRs in the anhedonic or somatic signs of nicotine withdrawal. Stoker AK, Olivier B, Markou A. Role of $\alpha 7$ - and $\beta 4$ -Containing Nicotinic Acetylcholine Receptors in the Affective and Somatic

Aspects of Nicotine Withdrawal: Studies in Knockout Mice. *Beh Genetics*. 2012 May; 42(3): 423-436.

Enhanced Extinction Of Cocaine Seeking In Brain-Derived Neurotrophic Factor Val66Met Knock-In Mice

The Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene results in alterations in fear extinction behavior in both human populations and mouse models. However, it is not clear whether this polymorphism plays a similar role in extinction of appetitive behaviors. Therefore, the authors examined operant learning and extinction of both food and cocaine self-administration behavior in an inbred genetic knock-in mouse strain expressing the variant BDNF. These mice provide a unique opportunity to relate alterations in aversive and appetitive extinction learning as well as provide insight into how human genetic variation can lead to differences in behavior. BDNF^{Met/Met} mice exhibited a severe deficit in operant learning as demonstrated by an inability to learn the food self-administration task. Therefore, extinction experiments were performed comparing wildtype (BDNF^{Val/Val}) animals to mice heterozygous for the Met allele (BDNF^{Val/Met}), which did not differ in food or cocaine self-administration behavior. In contrast to the deficit in fear extinction previously demonstrated in these mice, we found that BDNF^{Val/Met} mice exhibited more rapid extinction of cocaine responding compared to wildtype mice. No differences were found between the genotypes in the extinction of food self-administration behavior or the reinstatement of cocaine seeking, indicating that the effect is specific to extinction of cocaine responding. These results suggest that the molecular mechanisms underlying aversive and appetitive extinction are distinct from one another and BDNF may play opposing roles in the two phenomena. Briand LA, Lee FS, Blendy JA, Pierce RC. Enhanced extinction of cocaine seeking in brain-derived neurotrophic factor Val66Met knock-in mice. *Eur J Neurosci*. 2012 Mar; 35(6): 932-939.

Cocaine Abstinence Alters Nucleus Accumbens Firing Dynamics During Goal-Directed Behaviors For Cocaine and Sucrose

Distinct subsets of nucleus accumbens (NAc) neurons differentially encode goal-directed behaviors for natural vs. drug rewards [R. M. Carelli et al. (2000) *The Journal of Neuroscience*, 20, 4255–4266], and the encoding of cocaine-seeking is altered following cocaine abstinence [J. A. Hollander & R. M. Carelli (2007) *The Journal of Neuroscience*, 27, 3535–3539]. Here, electrophysiological recording procedures were used to determine if the selective encoding of natural vs. cocaine reward by NAc neurons is: (i) maintained when the natural reinforcer is a highly palatable sweet tastant and (ii) altered by cocaine abstinence. Rats (n = 14) were trained on a multiple schedule of sucrose reinforcement and cocaine self-administration (2–3 weeks) and NAc activity was recorded during the task before and after 30 days of cocaine abstinence. Of 130 cells recorded before abstinence, 82 (63%) displayed patterned discharges (increases or decreases in firing rate, termed phasic activity) relative to operant responding for sucrose or cocaine. As in previous reports, the majority of those cells displayed nonoverlapping patterns of activity during responding for sucrose vs. cocaine. Specifically, only 17 (21%) showed similar patterns of activity (i.e. overlapping activity) across the two reinforcer conditions. After abstinence, this pattern was largely maintained, 23 of 70 phasic cells (33%) were overlapping. However, cocaine abstinence altered the overall percentage of selectively active neurons across reinforcer conditions. Specifically, significantly more neurons became selectively activated during cocaine-directed behaviors than during sucrose-directed behaviors. The results indicate that, although the selective encoding of cocaine and natural rewards is maintained even with a highly palatable substance, 30 days of cocaine abstinence dynamically alters the overall population encoding of natural and drug rewards by NAc neurons. Cameron CM, Carelli RM. Cocaine

abstinence alters nucleus accumbens firing dynamics during goal-directed behaviors for cocaine and sucrose. *Eur J Neurosci.* 2012 Mar; 35(6): 940-951.

Varenicline Dose Dependently Enhances Responding for Nonpharmacological Reinforcers and Attenuates the Reinforcement-Enhancing Effects of Nicotine

Varenicline (VAR), a partial nicotinic agonist, is one of the most effective smoking cessation pharmacotherapies. The therapeutic efficacy of VAR could be partly the result of substituting for and/or blocking the reinforcement-enhancing effects of nicotine (NIC). The authors assessed the effects of VAR alone and in combination with NIC (0.4 mg/kg) while rats pressed the lever for a moderately reinforcing visual stimulus (VS). Rats were injected with placebo (0.9% saline), NIC, VAR (0.1–1 mg/kg), or NIC + VAR. A follow-up study was conducted with a broader dose range of VAR-alone dosages (0.01–3.0 mg/kg). All drug manipulations were conducted in a between-subjects design to prevent confounding effects of repeated exposure. There was a dose-dependent effect of VAR alone. Moderate doses of VAR (0.1 and 1.0 mg/kg) increased the number of VS presentations earned, while lower and higher VAR doses (0.01 and 3.0 mg/kg) did not change responding for the VS. VAR dose dependently attenuated the reinforcement-enhancing effects of NIC, with the highest dose (1.0 mg/kg) exhibiting the greatest antagonist effect. The results of these studies support the assertion that the therapeutic efficacy of VAR may be due to the partial agonist characteristics of the drug, specifically, its ability to partially replace the reinforcement-enhancing effects of NIC as well as antagonize these effects. Levin ME, Weaver MT, Palmatier MI, Caggiula AR, Sved AF, Donny EC. Varenicline dose dependently enhances responding for nonpharmacological reinforcers and attenuates the reinforcement-enhancing effects of nicotine. *Nic Tobacco Res.* 2012 Mar; 14(3): 299-305.

Developmental Effects Of Acute, Chronic, and Withdrawal From Chronic Nicotine

On Fear Conditioning

Pre-adolescence and adolescence are developmental periods associated with increased vulnerability for tobacco addiction, and exposure to tobacco during these periods may lead to long-lasting changes in behavioral and neuronal plasticity. The present study examined the short- and long-term effects of nicotine and nicotine withdrawal on fear conditioning in pre-adolescent, adolescent, and adult mice, and potential underlying substrates that may mediate the developmental effects of nicotine, such as changes in nicotinic acetylcholine receptor (nAChR) binding, CREB expression, and nicotine metabolism. Age related differences existed in sensitivity to the effects of acute nicotine, chronic nicotine and nicotine withdrawal on contextual fear conditioning (no changes in cued fear conditioning were seen); younger mice were more sensitive to the acute effects and less sensitive to the effects of nicotine withdrawal 24 h post treatment cessation. Developmental differences in nAChR binding were associated with the effects of nicotine withdrawal on contextual learning. Developmental differences in nicotine metabolism and CREB expression were also observed, but were not related to the effects of nicotine withdrawal on contextual learning 24 h post treatment. Chronic nicotine exposure during pre-adolescence or adolescence, however, produced long-lasting impairments in contextual learning that were observed during adulthood, whereas adult chronic nicotine exposure did not. These developmental effects could be related to changes in CREB. Overall, there is a developmental shift in the effects of nicotine on hippocampus-dependent learning and developmental exposure to nicotine results in adult cognitive deficits; these changes in cognition may play an important role in the development and maintenance of nicotine addiction. Portugal GS, Wilkinson DS, Turner JR, Blendy JA, Gould TJ. *Neurobiol Learn Mem.* 2012 May; 97(4): 355-494.

Conditioned Response Evoked by Nicotine Conditioned Stimulus Preferentially Induces c-Fos Expression in Medial Regions of Caudate-Putamen

Nicotine has both unconditioned and conditioned stimulus properties. Conditioned stimulus properties of nicotine may contribute to the tenacity of nicotine addiction. The purpose of this experiment was to use neurohistochemical analysis of rapidly developing c-Fos protein to elucidate neurobiological loci involved in the processing of nicotine as an interoceptive conditioned stimulus (CS). Rats were injected (SC) in an intermixed fashion with saline or nicotine (16 sessions of each) and placed in conditioning chambers where they were given one of the three conditions depending on group assignment: (a) nicotine paired 100% of the time with intermittent access to sucrose (nicotine-CS condition), (b) nicotine and saline each paired 50% of the time with sucrose (chamber-CS condition), or (c) no sucrose US control (CS-alone condition). Rats in the nicotine-CS condition acquired the discrimination as evidenced by goal-tracking (ie, increased dipper entries before initial sucrose delivery) only on nicotine sessions. The chamber-CS condition showed goal-tracking on all sessions; no goal-tracking was seen in the CS-alone condition. On the test day, rats in each condition were challenged with saline or nicotine and later assessed for c-Fos immunoreactivity. In concordance with previous reports, nicotine induced c-Fos expression in the majority of areas tested; however, learning-dependent expression was specific to dorsomedial and ventromedial regions of caudate-putamen (dmCPu, vmCPu). Only rats in the nicotine-CS condition, when challenged with nicotine, had higher c-Fos expression in the dmCPu and vmCPu. These results suggest that medial areas of CPu involved in excitatory conditioning with an appetitive nicotine CS. Charntikov S, Tracy ME, Zhao C, Li M, Bevins RA. Conditioned response evoked by nicotine conditioned stimulus preferentially induces c-fos expression in medial regions of caudate-putamen. *Neuropsychopharmacol.* 2012 Mar; 37(4): 876-884.

Attention-Related Pearce-Kaye-Hall Signals in Basolateral Amygdala Require the Midbrain Dopaminergic System

Neural activity in basolateral amygdala has recently been shown to reflect surprise or attention as predicted by the Pearce-Kaye-Hall model (PKH)-an influential model of associative learning. Theoretically, a PKH attentional signal originates in prediction errors of the kind associated with phasic firing of dopamine neurons. This requirement for prediction errors, coupled with projections from the midbrain dopamine system into basolateral amygdala, suggests that the PKH signal in amygdala may depend on dopaminergic input. To test this, the authors recorded single unit activity in basolateral amygdala in rats with 6-hydroxydopamine or sham lesions of the ipsilateral midbrain region. Neurons were recorded as the rats performed a task previously used to demonstrate both dopaminergic reward prediction errors and attentional signals in basolateral amygdala neurons. The authors found that neurons recorded in sham lesioned rats exhibited the same attention-related PKH signal observed in previous studies. By contrast, neurons recorded in rats with ipsilateral 6-hydroxydopamine lesions failed to show attentional signaling. These results indicate a linkage between the neural instantiations of the basolateral complex of the amygdala attentional signal and dopaminergic prediction errors. Such a linkage would have important implications for understanding both normal and aberrant learning and behavior, particularly in diseases thought to have a primary effect on dopamine systems, such as addiction and schizophrenia. Esber GR, Roesch MR, Bali S, Trageser J, Bissonette GB, Puche AC, Holland PC, Schoenbaum G. Attention-related Pearce-Kaye-Hall signals in basolateral amygdala require the midbrain dopaminergic system. *Biol Psychiatry.* 2012 Jul 2. [Epub ahead of print]

Quantifying Individual Variation In The Propensity To Attribute Incentive Salience To Reward Cues

If reward-associated cues acquire the properties of incentive stimuli they can come to powerfully control behavior, and potentially promote maladaptive behavior. Pavlovian incentive stimuli are defined as stimuli that have three fundamental properties: they are attractive, they are themselves desired, and they can spur instrumental actions. The authors have found, however, that there is considerable individual variation in the extent to which animals attribute Pavlovian incentive motivational properties ("incentive salience") to reward cues. The purpose of this paper was to develop criteria for identifying and classifying individuals based on their propensity to attribute incentive salience to reward cues. To do this, the authors conducted a meta-analysis of a large sample of rats (N=1,878) subjected to a classic Pavlovian conditioning procedure. They then used the propensity of animals to approach a cue predictive of reward (one index of the extent to which the cue was attributed with incentive salience), to characterize two behavioral phenotypes in this population: animals that approached the cue ("sign-trackers") vs. others that approached the location of reward delivery ("goal-trackers"). This variation in Pavlovian approach behavior predicted other behavioral indices of the propensity to attribute incentive salience to reward cues. Thus, the procedures reported here should be useful for making comparisons across studies and for assessing individual variation in incentive salience attribution in small samples of the population, or even for classifying single animals. Meyer PJ, Lovic V, Saunders BT, Yager LM, Flagel SB, Morrow JD, Robinson TE. Quantifying individual variation in the propensity to attribute incentive salience to reward cues. PLoS One. 2012; 7(6): e38987. Epub 2012 Jun 22.

Effects Of Acute Administration Of Nicotinic and Muscarinic Cholinergic Agonists and Antagonists On Performance In Different Cost-Benefit Decision Making Tasks In Rats

Alterations in cost-benefit decision making accompany numerous neuropsychiatric conditions, including schizophrenia, attention deficit hyperactivity disorder, and addiction. Central cholinergic systems have been linked to the etiology and/or treatment of many of these conditions, but little is known about the role of cholinergic signaling in cost-benefit decision making. The goal of these experiments was to determine how cholinergic signaling is involved in cost-benefit decision making, using a behavioral pharmacological approach. Male Long-Evans rats were trained in either "probability discounting" or "delay discounting" tasks, in which rats made discrete-trial choices between a small food reward and a large food reward associated with either varying probabilities of omission or varying delays to delivery, respectively. The effects of acute administration of different doses of nicotinic and muscarinic acetylcholine receptor agonists and antagonists were assessed in each task. In the probability discounting task, acute nicotine administration (1.0 mg/kg) significantly increased choice of the large risky reward, and control experiments suggested that this was due to robust nicotine-induced impairments in behavioral flexibility. In the delay discounting task, the muscarinic antagonists scopolamine (0.03, 0.1, and 0.3 mg/kg) and atropine (0.3 mg/kg) both significantly increased choice of the small immediate reward. Neither mecamylamine nor oxotremorine produced reliable effects on either of the decision making tasks. These data suggest that cholinergic receptors play multiple roles in decision making contexts which include consideration of reward delay or probability. These roles should be considered when targeting these receptors for therapeutic purposes. Mendez IA, Gilbert RJ, Bizon JL, Setlow B. Effects of acute administration of nicotinic and muscarinic cholinergic agonists and antagonists on performance in different cost-benefit decision making tasks in rats. Psychopharmacology (Berl). 2012 Jul 4. [Epub ahead of print]

Dopamine Neurons In The Ventral Tegmental Area Fire Faster In Adolescent Rats Than In Adults

Adolescence may be a period of vulnerability to drug addiction. In rats, elevated firing activity of ventral tegmental area (VTA) dopamine neurons predicts enhanced addiction liability. The authors' aim was to determine if dopamine neurons are more active in adolescents than in adults, and to examine mechanisms underlying any age-related difference. VTA dopamine neurons fired faster in adolescents than in adults, measured with in vivo extracellular recordings. Dopamine neuron firing can be divided into non-bursting (single spikes) and bursting activity (clusters of high frequency spikes). Non-bursting activity was higher in adolescents compared with adults. Frequency of burst events did not differ between ages, but bursts were longer in adolescents than in adults. Elevated dopamine neuron firing in adolescent rats was also observed in cell-attached recordings in ex vivo brain slices. Using whole-cell recordings we found that passive and active membrane properties were similar across ages. Hyperpolarization-activated cation currents (I_h) and small conductance calcium-activated potassium (SK) channel currents were also comparable across ages. The authors found no difference in dopamine D2-class autoreceptor function across ages, although the high baseline firing in adolescents resulted in autoreceptor activation being less effective at silencing neurons. Finally, AMPA receptor-mediated sEPSCs occurred at lower frequency in adolescents; GABAA receptor-mediated sIPSCs occurred both at lower frequency and smaller amplitude in adolescents. In conclusion, VTA dopamine neurons fire faster in adolescence, potentially because GABA tone increases as rats reach adulthood. This elevation of firing rate during adolescence is consistent with it representing a vulnerable period for developing drug addiction. McCutcheon JE, Conrad KL, Carr SB, Ford KA, McGehee DS, Marinelli M. Dopamine neurons in the ventral tegmental area fire faster in adolescent rats than in adults. *J Neurophysiol*. 2012 Jun 20. [Epub ahead of print]

Changes In Expression Of C-Fos Protein Following Cocaine-Cue Extinction Learning

Extinguishing abnormally strengthened learned responses to cues associated with drugs of abuse remains a key tactic for alleviating addiction. To assist in developing pharmacotherapies to augment exposure therapy for relapse prevention, investigation into neurobiological underpinnings of drug-cue extinction learning is needed. The authors used regional analyses of c-Fos and GluR2 protein expression to delineate neural activity and plasticity that may be associated with cocaine-cue extinction learning. Rats were trained to self-administer cocaine paired with a light cue, and later underwent a single 2h extinction session for which cocaine was withheld but response-contingent cues were presented (cocaine-cue extinction). Control groups consisted of rats yoked to animals self-administering cocaine and receiving saline non-contingently followed by an extinction session, or rats trained to self-administer cocaine followed by a no-extinction session for which levers were retracted, and cocaine and cues were withheld. Among 11 brain sites examined, extinction training increased c-Fos expression in basolateral amygdala and prelimbic prefrontal cortex of cocaine-cue extinguished rats relative to both control conditions. In dorsal subiculum and infralimbic prefrontal cortex, extinction training increased c-Fos expression in both cocaine-cue and saline-cue extinguished rats relative to the no-extinction control condition. GluR2 protein expression was not altered in any site examined after extinction or control training. Findings suggest that basolateral amygdala and prelimbic prefrontal cortex neurons are activated during acquisition of cocaine-cue extinction learning, a process that is independent of changes in GluR2 abundance. Other sites are implicated in processing the significance of cues that are present early in extinction training. Nic Dhonnchadha BA, Lovascio BF, Shrestha N, Lin A, Leite-Morris KA, Man HY, Kaplan GB, Kantak KM. Changes in expression of c-Fos protein following cocaine-cue extinction learning. *Behav Brain Res*. 2012 Jun 18. [Epub ahead of print].

Bilateral Lesions of the Thalamic Trigeminal Orosensory Area Dissociate Natural From Drug Reward in Contrast Paradigms

Substance abuse and addiction are associated with an apparent devaluation of, and inattention to, natural rewards. This consequence of addiction can be modeled using a reward comparison paradigm where rats avoid intake of a palatable taste cue that comes to predict access to a drug of abuse. Evidence suggests rats avoid intake following such pairings, at least in part, because the taste cue pales in comparison to the highly rewarding drug expected in the near future. In accordance, lesions of the gustatory thalamus or cortex eliminate avoidance of a taste cue when paired with either a drug of abuse or a rewarding sucrose solution, but not when paired with the aversive agent, LiCl. The present study used bilateral ibotenic acid lesions to evaluate the role of a neighboring thalamic structure, the trigeminal orosensory area (TOA), in avoidance of a gustatory cue when paired with sucrose (Experiment 1), morphine (Experiment 2), cocaine (Experiment 3), or LiCl (Experiment 4). The results show that the TOA lesion disrupts, but does not eliminate avoidance of a taste cue that predicts access to a preferred sucrose solution and leaves intact the development of a LiCl-induced conditioned taste aversion. The lesion does, however, eliminate the suppression of intake of a taste cue when paired with experimenter-administered morphine or cocaine using our standard parameters. As such, this is the first manipulation found to dissociate avoidance of a taste cue when mediated by a sweet or by a drug of abuse. Nyland JE, Alexander DN, Liang NC, Grigson PS. Bilateral lesions of the thalamic trigeminal orosensory area dissociate natural from drug reward in contrast paradigms. *Behav Neurosci*. 2012 Jun 11. [Epub ahead of print].

Previous Exposure to Nicotine Enhances the Incentive Motivational Effects of Amphetamine via Nicotine-Associated Contextual Stimuli

The effect of nicotine exposure on the subsequent self-administration of amphetamine, extinction of this behavior, and amphetamine-induced reinstatement of drug seeking was assessed with particular attention to the contribution of contextual stimuli paired or unpaired with nicotine during exposure. Rats were exposed to five injections, one injection every third day, of either saline or nicotine (0.4 mg/kg, IP, base) in three experiments. In one, exposure injections were administered in the home cage. In another, they were administered in the self-administration chambers with the levers retracted. In a third, nicotine was administered either explicitly paired or unpaired with the self-administration chambers using a discrimination learning procedure. Starting 13-15 days later, rats were trained to self-administer amphetamine (100 µg/kg/infusion, IV), tested under a progressive ratio (PR) schedule for 6 days, subjected to up to 20 days of extinction training, and were then tested for reinstatement by non-contingent injections of amphetamine (0, 0.2, 0.4, and 0.75 mg/kg, IP). Nicotine enhanced the self-administration of amphetamine under the PR schedule and amphetamine-induced reinstatement but only when rats were tested in the chamber in which they were previously exposed to nicotine. These effects were not observed in rats exposed to nicotine in the home cage or in rats exposed to nicotine explicitly unpaired with the self-administration chambers. Exposure to nicotine also rendered rats resistant to extinction when amphetamine was withheld but this effect was observed regardless of nicotine exposure context, suggesting a separate consequence of drug exposure. Together, these results show that previous exposure to nicotine can enhance the incentive motivational effects of other psychostimulants like amphetamine and indicate a critical role for nicotine-associated contextual stimuli in the mediation of this effect. These findings have important implications for the treatment of addictions in humans. Cortright JJ, Sampedro GR, Neugebauer NM, Vezina P. Previous exposure to nicotine enhances the incentive motivational effects of amphetamine via nicotine-associated contextual stimuli. *Neuropsychopharmacology*. 2012 May 23. [Epub ahead of print].

Beta Adrenergic Receptor Mediation Of Stress-Induced Reinstatement Of Extinguished Cocaine-Induced Conditioned Place Preference In Mice: Roles For Beta-1 And Beta-2

Adrenergic Receptors

Stress can trigger relapse of drug use in recovering cocaine addicts and reinstatement in rodent models through mechanisms that appear to involve norepinephrine release and beta adrenergic receptor activation. The present study examined the role of beta adrenergic receptor subtypes in the stressor-induced reinstatement of extinguished cocaine-induced (15 mg/kg, ip) conditioned place preference in mice. Forced swim (6 min at 22°C) stress or activation of central noradrenergic neurotransmission by administration the selective alpha-2 adrenergic receptor antagonist, BRL-44,408 (10 mg/kg, ip) induced reinstatement in wild-type but not beta adrenergic receptor-deficient *Adrb1/Adrb2* double-knockout mice. By contrast, cocaine administration (15 mg/kg, ip) resulted in reinstatement in both wild-type and beta adrenergic receptor knockout mice. Stress-induced reinstatement likely involved beta-2 adrenergic receptors. The beta-2 adrenergic receptor antagonist ICI-118,551 (1 or 2 mg/kg, ip) blocked reinstatement by forced swim or BRL-44,408, while administration of the non-selective beta adrenergic receptor agonist, isoproterenol (2 or 4 mg/kg, ip), or the beta-2 adrenergic receptor-selective agonist, clenbuterol (2 or 4 mg/kg, ip), induced reinstatement. Forced swim, but not BRL-44,408, -induced reinstatement was also blocked by a high (20 mg/kg) but not low (10 mg/kg) dose of the beta-1 adrenergic receptor antagonist betaxolol and isoproterenol-induced reinstatement was blocked by pretreatment with either ICI-118,551 or betaxolol, suggesting a potential cooperative role for beta-1 and beta-2 adrenergic receptors in stress-induced reinstatement. Overall, these findings suggest that targeting beta adrenergic receptors may represent a promising pharmacotherapeutic strategy for preventing drug relapse, particularly in cocaine addicts whose drug use is stress-related. Vranjkovic O, Hang S, Baker DA, Mantsch JR. Beta adrenergic receptor mediation of stress-induced reinstatement of extinguished cocaine-induced conditioned place preference in mice: roles for beta-1 and beta-2 adrenergic receptors. *J Pharmacol Exp Ther.* 2012 May 16. [Epub ahead of print].

Alpha-1 Adrenergic Receptors are Localized on Presynaptic Elements in the Nucleus Accumbens and Regulate Mesolimbic Dopamine Transmission

Brainstem noradrenergic neurons innervate the mesocorticolimbic reward pathway both directly and indirectly, with norepinephrine facilitating dopamine (DA) neurotransmission via $\alpha 1$ -adrenergic receptors ($\alpha 1$ ARs). Although $\alpha 1$ AR signaling in the prefrontal cortex (PFC) promotes mesolimbic transmission and drug-induced behaviors, the potential contribution of $\alpha 1$ ARs in other parts of the pathway, such as the ventral tegmental area (VTA) and nucleus accumbens (NAc), has not been investigated before. The authors found that local blockade of $\alpha 1$ ARs in the medial NAc shell, but not the VTA, attenuates cocaine- and morphine-induced locomotion. To determine the neuronal substrates that could mediate these effects, the authors analyzed the cellular, subcellular, and subsynaptic localization of $\alpha 1$ ARs and characterized the chemical phenotypes of $\alpha 1$ AR-containing elements within the mesocorticolimbic system using single and double immunocytochemical methods at the electron microscopic (EM) level. The authors found that $\alpha 1$ ARs are found mainly extra-synaptically in axons and axon terminals in the NAc and are enriched in glutamatergic and dopaminergic elements. $\alpha 1$ ARs are also abundant in glutamatergic terminals in the PFC, and in GABA-positive terminals in the VTA. In line with these observations, microdialysis experiments revealed that local blockade of $\alpha 1$ ARs attenuated the increase in extracellular DA in the medial NAc shell following administration of cocaine. These data indicate that local $\alpha 1$ ARs control DA transmission in the medial NAc shell and behavioral responses to drugs of abuse. Mitrano DA, Schroeder JP, Smith Y, Cortright JJ, Bubula N, Vezina P, Weinshenker D. Alpha-1 adrenergic receptors are localized on presynaptic elements in the nucleus accumbens and regulate mesolimbic dopamine transmission. *Neuropsychopharmacology.* 2012 May 16. [Epub ahead of print].

Effects Of Perinatal Exposure To Palatable Diets On Body Weight and Sensitivity To Drugs Of Abuse In Rats

The aim of the present study was to determine the effects of fat- and sugar-rich diets in utero and during the pre-weaning period on body weight and responses to drugs of abuse. In Exp. 1, dams were fed a balanced control diet or high-fat diet (HFD), and female offspring were cross-fostered to dams consuming the balanced diet. The HFD-exposed offspring, compared to controls, were heavier in body weight, had increased circulating triglyceride levels, and consumed more alcohol and HFD in adulthood. In Exp. 2, dams were fed standard chow alone or standard chow plus a 16% high-fructose corn syrup (HFCS) or 10% sucrose solution. Sets of offspring from each group were cross-fostered to dams in the other groups, allowing for the effects of HFCS or sucrose exposure during the gestational period or pre-weaning period to be determined. The offspring (both female and male) exposed to HFCS or sucrose in utero had higher body weights in adulthood and exhibited increased alcohol intake as shown in female offspring and increased amphetamine-induced locomotor activity as shown in males. Exposure to HFCS or sucrose only during the pre-weaning period had a similar effect of increasing amphetamine-induced locomotor activity in males, but produced no change in circulating triglycerides or alcohol intake. Collectively, these data suggest that prenatal as well as pre-weaning exposure to fat- and sugar-rich diets, in addition to increasing body weight, can affect responses to drugs of abuse. Bocarsly ME, Barson JR, Hauca JM, Hoebel BG, Leibowitz SF, Avena NM. Effects of perinatal exposure to palatable diets on body weight and sensitivity to drugs of abuse in rats. *Physiol Behav.* 2012 May 4. [Epub ahead of print].

Repeated Methamphetamine Administration Differentially Alters Fos Expression In Caudate-Putamen Patch and Matrix Compartments and Nucleus Accumbens

The repeated administration of psychostimulant drugs produces a persistent and long-lasting increase ("sensitization") in their psychomotor effects, which is thought to be due to changes in the neural circuitry that mediate these behaviors. One index of neuronal activation used to identify brain regions altered by repeated exposure to drugs involves their ability to induce immediate early genes, such as c-fos. Numerous reports have demonstrated that past drug experience alters the ability of drugs to induce c-fos in the striatum, but very few have examined Fos protein expression in the two major compartments in the striatum--the so-called patch/striosome and matrix. In the present study, the authors used immunohistochemistry to investigate the effects of pretreatment with methamphetamine on the ability of a subsequent methamphetamine challenge to induce Fos protein expression in the patch and matrix compartments of the dorsolateral and dorsomedial caudate-putamen and in the ventral striatum (nucleus accumbens). Animals pretreated with methamphetamine developed robust psychomotor sensitization. A methamphetamine challenge increased the number of Fos-positive cells in all areas of the dorsal and ventral striatum. However, methamphetamine challenge induced Fos expression in more cells in the patch than in the matrix compartment in the dorsolateral and dorsomedial caudate-putamen. Furthermore, past experience with methamphetamine increased the number of methamphetamine-induced Fos positive cells in the patch compartment of the dorsal caudate putamen, but not in the matrix or in the core or shell of the nucleus accumbens. These data suggest that drug-induced alterations in the patch compartment of the dorsal caudate-putamen may preferentially contribute to some of the enduring changes in brain activity and behavior produced by repeated treatment with methamphetamine. Jedynak JP, Cameron CM, Robinson TE. Repeated methamphetamine administration differentially alters fos expression in caudate-putamen patch and matrix compartments and nucleus accumbens. *PLoS One.* 2012; 7(4): e34227. Epub 2012 Apr 13.

Distinctive Roles For Amygdalar CREB In Reconsolidation and Extinction Of Fear Memory

Cyclic AMP response element binding protein (CREB) plays a critical role in fear memory formation. Here the authors determined the role of CREB selectively within the amygdala in reconsolidation and extinction of auditory fear. Viral overexpression of the inducible cAMP early repressor (ICER) or the dominant-negative mCREB, specifically within the lateral amygdala disrupted reconsolidation of auditory fear memories. In contrast, manipulations of CREB in the amygdala did not modify extinction of fear. These findings suggest that the role of CREB in modulation of memory after retrieval is dynamic and that CREB activity in the basolateral amygdala is involved in fear memory reconsolidation. Tronson NC, Wiseman SL, Neve RL, Nestler EJ, Olausson P, Taylor JR. Distinctive roles for amygdalar CREB in reconsolidation and extinction of fear memory. *Learn Mem.* 2012 Apr 13; 19(5): 178-181.

Differential Effects Of Cocaine Access and Withdrawal On Glutamate Type 1 Transporter Expression In Rat Nucleus Accumbens Core and Shell

Cocaine addiction is characterized by compulsive drug seeking, including relapse after a period of withdrawal. The relapse response requires increased glutamate transmission in the nucleus accumbens (NAc). Consistent with this view, glutamate type 1 transporter (GLT1), the transporter responsible for >90% of glutamate uptake, is downregulated in NAc after several days of withdrawal in rats previously trained to self-administer cocaine under limited access conditions (1-2 h/d). Human addiction, however, appears to be better modeled by extending daily drug access (6-8 h/d) and introducing long periods of withdrawal. Here, the authors determined the combined effects of manipulating cocaine access and withdrawal on GLT1 expression in NAc core and shell. Rats were trained to self-administer cocaine (0.25 mg per intravenous infusion) in daily limited or extended access sessions for 11 days followed by a period of short (1 day) or long (40-45 days) withdrawal. The authors found that although cocaine withdrawal decreases GLT1 expression in both core and shell, only in core is GLT1 downregulation sensitive to both access and withdrawal. In fact, after long withdrawal, GLT1 in core is downregulated more than in shell in either the limited or extended access condition. Thus, glutamate regulation in core appears to be a critical factor in the drug-seeking behavior that follows relatively long periods of cocaine withdrawal. Fischer-Smith KD, Houston AC, Rebec GV. Differential effects of cocaine access and withdrawal on glutamate type 1 transporter expression in rat nucleus accumbens core and shell. *Neuroscience.* 2012 May 17; 210: 333-339.

Assessment Of Ropinirole As A Reinforcer In Rhesus Monkeys

Ropinirole, a D(2)/D(3)/5-HT(1A) agonist, is used for the treatment of Parkinson's disease and restless leg syndrome, and is currently being evaluated as a treatment for cocaine dependence. However, there is little information available on ropinirole's reinforcing effects. The current study tested ropinirole in monkeys (n=7) trained to self administer cocaine on a fixed-ratio 25 (FR 25) schedule of reinforcement to determine if it would function as a reinforcer. In addition, a behavioral economics approach was used in four monkeys to compare the reinforcing effectiveness of ropinirole to cocaine. Cocaine (0.01-0.3mg/kg/injection) functioned as a reinforcer in all monkeys under the FR 25 schedule, and ropinirole (0.01-0.1mg/kg/injection) functioned as a reinforcer in all but one. Furthermore, cocaine was a more effective reinforcer than ropinirole as indexed by demand functions. The current data indicate that ropinirole has reinforcing effects in monkeys, although its effectiveness as a reinforcer is relatively weak. Freeman KB, Heal DJ, McCreary AC, Woolverton WL. Assessment of ropinirole as a reinforcer in rhesus monkeys. *Drug Alcohol Depend.* 2012 Apr 28. [Epub ahead of print]

Sensitivity To Apomorphine-Induced Yawning and Hypothermia In Rats Eating Standard Or High-Fat Chow

Feeding conditions modify sensitivity to indirect- and direct-acting dopamine receptor agonists as well as the development of sensitization to these drugs. This study examined whether feeding condition affects acute sensitivity to apomorphine-induced yawning or changes in sensitivity that occur over repeated drug administration. Quinpirole-induced yawning was also evaluated to see whether sensitization to apomorphine confers cross-sensitization to quinpirole. Drug-induced yawning was measured in different groups of male Sprague Dawley rats (n = 6/group) eating high (34.3%) fat or standard (5.7% fat) chow. Five weeks of eating high-fat chow rendered otherwise drug-naïve rats more sensitive to apomorphine- (0.01-1.0 mg/kg, i.p.) and quinpirole- (0.0032-0.32 mg/kg, i.p.) induced yawning, compared with rats eating standard chow. In other rats, tested weekly with apomorphine, sensitivity to apomorphine-induced yawning increased (sensitization) similarly in rats with free access to standard or high-fat chow; conditioning to the testing environment appeared to contribute to increased yawning in both groups of rats. Food restriction decreased sensitivity to apomorphine-induced yawning across five weekly tests. Rats with free access to standard or high-fat chow and sensitized to apomorphine were cross-sensitized to quinpirole-induced yawning. The hypothermic effects of apomorphine and quinpirole were not different regardless of drug history or feeding condition. Eating high-fat chow or restricting access to food alters sensitivity to direct-acting dopamine receptor agonists (apomorphine, quinpirole), although the relative contribution of drug history and dietary conditions to sensitivity changes appears to vary among agonists. Baladi MG, Thomas YM, France CP. Sensitivity to apomorphine-induced yawning and hypothermia in rats eating standard or high-fat chow. *Psychopharmacology (Berl)*. 2012 Jul; 222(1): 27-36. Epub 2011 Dec 30.

Exercise To Reduce The Escalation Of Cocaine Self-Administration In Adolescent and Adult Rats

Concurrent access to an exercise wheel decreases cocaine self-administration under short access (5 h/day for 5 days) conditions and suppresses cocaine-primed reinstatement in adult rats. The effect of exercise (wheel running) on the escalation of cocaine intake during long access (LgA, 6 h/day for 26 days) conditions was evaluated. Adolescent and adult female rats acquired wheel running, and behavior was allowed to stabilize for 3 days. They were then implanted with an iv catheter and allowed to self-administer cocaine (0.4 mg/kg, iv) during 6-h daily sessions for 16 days with concurrent access to either an unlocked or a locked running wheel. Subsequently, for ten additional sessions, wheel access conditions during cocaine self-administration sessions were reversed (i.e., locked wheels became unlocked and vice versa). In the adolescents, concurrent access to the unlocked exercise wheel decreased responding for cocaine and attenuated escalation of cocaine intake irrespective of whether the locked or unlocked condition came first. However, cocaine intake increased when the wheel was subsequently locked for the adolescents that had initial access to an unlocked wheel. Concurrent wheel access either before or after the locked wheel access did not reduce cocaine intake in adults. Wheel running reduced cocaine intake during LgA conditions in adolescent but not adult rats, and concurrent access to the running wheel was necessary. These results suggest that exercise prevents cocaine seeking and that this effect is more pronounced in adolescents than adults. Zlebnik NE, Anker JJ, Carroll ME. Exercise to reduce the escalation of cocaine self-administration in adolescent and adult rats. *Psychopharmacology (Berl)*. 2012 Jul 3. [Epub ahead of print].

Differential Orexin/Hypocretin Expression In Addiction-Prone and -Resistant Rats Selectively Bred For High (HiS) and Low (LoS) Saccharin Intake

Rats that have been selectively bred for high (HiS) saccharin intake demonstrate elevated drug-seeking behavior in several phases of addiction compared to those bred for low (LoS) saccharin intake. HiS rats also consume greater

amounts of highly palatable substances compared to LoS rats; however, little is known about the neurobiological substrates moderating the divergent behaviors found between the HiS and LoS lines. Orexins are neuropeptides that have been implicated in the conditioned cue aspects of drug abuse and overconsumption of palatable substances, and differential orexin activity in the HiS and LoS phenotypes may enhance our understanding of the close relationship between food and drug reward, and ultimately food and drug addiction. The lateral hypothalamus (LH) and perifornical area (PFA) are brain regions that have been implicated in regulating feeding behavior and addiction processes, and they contain orexinergic neurons that project broadly throughout the brain. Thus, the authors investigated orexin and c-Fos expression in the LH and PFA using immunohistochemistry in HiS and LoS rats following either control or cocaine (15mg/kg) injections. Results indicated that HiS rats have higher orexin-positive cell counts compared to LoS rats in both the LH and PFA, regardless of cocaine (vs. saline) treatment. In contrast, neuronal activity indicated by c-Fos expression did not differ in either of these brain areas in HiS vs. LoS rats. These results suggest that the orexin system may be involved in aspects of genetically-mediated differences in vulnerability to compulsive, reward-driven behaviors. Holtz NA, Zlebnik NE, Carroll ME. Differential orexin/hypocretin expression in addiction-prone and -resistant rats selectively bred for high (HiS) and low (LoS) saccharin intake. *Neurosci Lett.* 2012 Jun 2. [Epub ahead of print].

Cocaine-Induced C-Fos Expression In Rats Selectively Bred For High Or Low Saccharin Intake and In Rats Selected For High Or Low Impulsivity

Sweet preference and impulsivity are predictors of cocaine self-administration; however, no research has been conducted to investigate neuronal activation in key brain reward areas after first time exposure to cocaine in rats that differ in their propensity for cocaine-seeking and -taking behavior. In this study the authors used rats that had been selectively bred for high vs. low saccharin intake and rats selected for high vs. low impulsivity for food. The goal of this study was to investigate whether there are differences of c-Fos reactivity between high and low phenotypes and determine whether these differences are similar between the two animal models. A group of rats was bred for high or low saccharin intake. Another group of rats was selected as high or low impulsive based on performance in a delay-discounting task. Subsequently, rats were given an acute injection of cocaine or saline and then c-Fos expression was observed and analyzed in several brain regions. The low reward-seeking phenotypes showed higher cocaine-induced c-Fos expression in several of these regions. Low saccharin preferring rats showed higher cocaine-induced c-Fos expression in the nucleus accumbens shell, and low impulsive rats showed higher cocaine-induced c-Fos expression in the orbitofrontal cortex and cingulate gyrus 1 area. In addition, both low impulsive and low saccharin rats had higher cocaine-induced c-Fos in the dorsal medial and dorsal lateral caudate putamen. The results indicate that individual differences in neuronal reactivity exist prior to chronic exposure to drugs of abuse. Furthermore, similar differences between the two animal models may be indicative of a common mechanism underlying vulnerability to drugs of abuse. Regier PS, Carroll ME, Meisel RL. Cocaine-induced c-Fos expression in rats selectively bred for high or low saccharin intake and in rats selected for high or low impulsivity. *Behav Brain Res.* 2012 May 18;233(2):271-279. [Epub ahead of print]

Escalation of Methamphetamine Self-Administration In Adolescent and Adult Rats

Methamphetamine (METH) use has increased substantially in the last 10 years and poses a serious health concern, especially for young populations. Drug abuse primarily begins during adolescence, when uninhibited and excessive drug intake is a common occurrence; thus, understanding the developmental patterns of addiction during this critical period is an essential step in its prevention. In the present study, the effect of age on the vulnerability to METH abuse was examined using a rat model of bingeing (i.e., escalation). Adolescent and adult rats were compared during short (ShA, 2-

h) and long-access (LgA, 6-h) to METH self-administration. On postnatal (PN) days 23 (adolescents) and 90 (adults), rats were implanted with i.v. catheters and trained to lever press for infusions of METH (0.05mg/kg) during 2-h sessions. Once the rats reached a steady rate of METH self-administration, they were divided into ShA or LgA groups and allowed to self-administer METH for 15 additional days. Results indicated that adolescent rats earned significantly more infusions than adults under the LgA condition, but the age groups did not differ during ShA. Adolescents, but not adults, also significantly increased (i.e., escalated) METH self-administration across the 15 days of testing under the LgA condition. Further analysis indicated excessive responding during infusions in the LgA METH-exposed adolescents compared to the other groups, suggesting elevated impulsivity or motivation for drug. These results demonstrate that adolescents are more vulnerable to the escalation of METH than adults during LgA. Anker JJ, Baron TR, Zlebnik NE, Carroll ME. Escalation of methamphetamine self-administration in adolescent and adult rats. *Drug Alcohol Depend.* 2012 Jul 1; 124(1-2): 149-153.

Individual Differences In Psychostimulant Responses Of Female Rats Are Associated With Ovarian Hormones and Dopamine Neuroanatomy Ovarian hormones modulate the pharmacological effects of psychostimulants and may enhance vulnerability to drug addiction. Female rats have more midbrain dopamine neurons than males and greater dopamine uptake and release rates. Cocaine stimulates motor behavior and dopamine efflux more in female than male rats, but the mediating mechanisms are unknown. This study investigated individual differences in anatomic, neurochemical, and behavioral measures in female rats to understand how ovarian hormones affect the relatedness of these endpoints. Ovarian hormone effects were assessed by comparing individual responses in ovariectomized (OVX) and sham adult female rats. Locomotion was determined before and following 10mg/kg cocaine. Electrically-stimulated dopamine efflux was assessed using fast cyclic voltammetry in vivo. Dopamine neuron number and density in substantia nigra (SN) and ventral tegmental area (VTA) were determined in the same animals using tyrosine-hydroxylase immunohistochemistry and unbiased stereology. Locomotor behavior and dopamine efflux did not differ at baseline but were greater in sham than OVX following cocaine. Cocaine increased dopamine release rates in both groups but uptake inhibition ($K(m)$) was greater in sham than OVX. Dopamine neuron number and density in SN and VTA were greater in shams. Sham females with the largest uterine weights exhibited the highest density of dopamine neurons in the SN, and the most cocaine-stimulated behavior and dopamine efflux. Ovariectomy eliminated these relationships. The authors postulate that SN density could link ovarian hormones and high-psychostimulant responses in females. Similar mechanisms may be involved in individual differences in the addiction vulnerability of women. Walker QD, Johnson ML, Van Swearingen AE, Arrant AE, Caster JM, Kuhn CM. Individual differences in psychostimulant responses of female rats are associated with ovarian hormones and dopamine neuroanatomy. *Neuropharmacology.* 2012 Jun; 62(7): 2267-2277.

Alcohol Consumption As A Function Of Dietary Restraint and The Menstrual Cycle In Moderate/Heavy ("At-Risk") Female Drinkers Previous research suggests that women who report dietary restraint tend to consume alcohol in greater quantities, however most studies use retrospective data collection, which is often unreliable, and no studies have accounted for this relationship with respect to potential changes in alcohol consumption across the menstrual cycle. Therefore, the present study investigated the relationship between prospectively monitored drinking patterns and dietary restraint across the menstrual cycle among females from the general population whose drinking level (7-20drinks/week) places them at-risk for developing alcohol use disorders. Restrained eaters (RES; N=51) and unrestrained eaters (UN-RES; N=55), per the cognitive restraint

scale scores from the Three-Factor Eating Questionnaire, provided prospective ratings measuring mood, alcohol consumption, and consequences of alcohol use across one full menstrual cycle. Dysphoric mood increased during the late luteal and menstrual phases in both groups. Although overall the RES group did not drink more than the UN-RES group, the RES group drank less than the UN-RES group during the follicular phase, suggesting that among RES women alcohol consumption may be modulated by hormonal fluctuations across the menstrual cycle. The differences between the present findings and previous research may be due to the cohorts sampled; the majority of previous studies sampled college students, where binge drinking and dietary restraint are more common, whereas this study sampled the general population. Future research should replicate prior studies in a college-aged population using the current design of prospective data collection for greater accuracy of self-reported alcohol consumption. Dimatteo J, Reed SC, Evans SM. Alcohol consumption as a function of dietary restraint and the menstrual cycle in moderate/heavy ("at-risk") female drinkers. *Eat Behav.* 2012 Aug;13(3): 285-288.

Effects of Chronic Cocaine Self-Administration on Cognition and Cerebral Glucose

Utilization in Rhesus Monkeys

Chronic cocaine use is associated with neurobiological and cognitive deficits that persist into abstinence, hindering success of behavioral treatment strategies and perhaps increasing likelihood of relapse. The effects of current cocaine use and abstinence on neurobiology and cognition are not well characterized. Adult male rhesus monkeys with an extensive cocaine self-administration history (~5 years) and age-matched control animals (n₄/group) performed cognitive tasks in morning sessions and self-administered cocaine or food in afternoon sessions. Positron emission tomography and [18F]-fluorodeoxyglucose were employed to assess cerebral metabolic rates of glucose utilization during cognitive testing. Cocaine-experienced monkeys required significantly more trials and committed more errors on reversal learning and multidimensional discriminations, compared with control animals. Cocaine-naive, but not cocaine-experienced, monkeys showed greater metabolic rates of glucose utilization during a multidimensional discrimination task in the caudate nucleus, hippocampus, anterior and posterior cingulate, and regions associated with attention, error detection, memory, and reward. Using a delayed match-to-sample task, there were no differences in baseline working memory performance between groups. High-dose cocaine self-administration disrupted delayed match-to-sample performance but tolerance developed. Acute abstinence from cocaine did not affect performance, but by day 30 of abstinence, accuracy increased significantly, while performance of cocaine-naive monkeys was unchanged. These data document direct effects of cocaine self-administration on cognition and neurobiological sequelae underlying cognitive deficits. Improvements in working memory can occur in abstinence, albeit across an extended period critical for treatment seekers, suggesting pharmacotherapies designed to enhance cognition may improve success of current behavioral modification strategies. Gould RW, Gage HD, Nader MA. Effects of chronic cocaine self-administration on cognition and cerebral glucose utilization in rhesus monkeys. *Biol Psychiatry.* 2012 Jun 4. [Epub ahead of print].

Sex Differences In Escalation Of Methamphetamine Self-Administration: Cognitive and Motivational Consequences In Rats

Male rats escalate methamphetamine (meth) intake during long-access meth self-administration, show enhanced reinstatement of meth-seeking, and exhibit meth-induced memory impairments. However, the impact of long-access daily meth self-administration on reinstatement and cognitive dysfunction has not been assessed in females, even though clinical studies on meth addiction have shown differences between men and women. This study determined whether male and freely cycling female rats: (1) escalate meth intake in a 6-h daily-access period relative to 1-h access; (2) show different sensitivity to meth primed

reinstatement after short- and long-access conditions; and (3) show deficits in novel object and object in place recognition memory. Male and female Long-Evans rats self-administered meth in limited (1-h/day) or extended (6-h/day) daily access sessions. After 21 days, meth access was discontinued, and rats entered an abstinence period. On the seventh and 14th days of abstinence, rats were assessed for recognition memory using tests for: (a) novel object recognition memory and (b) object-in-place memory. Rats were tested for reinstatement of meth-seeking following extinction of responding. Female rats self-administered more meth and escalated intake faster than males during extended, but not limited, daily access. Both males and females in the extended, but not limited, access groups showed memory deficits on both tasks. Female rats showed greater reinstatement to meth-seeking with lower doses of meth priming injections than males. Relative to males, females were equally susceptible to meth-induced memory deficits but exhibited higher meth intake and greater relapse to meth-seeking. Reichel CM, Chan CH, Ghee SM, See RE. Sex differences in escalation of methamphetamine self-administration: cognitive and motivational consequences in rats. *Psychopharmacology (Berl)*. 2012 May 17. [Epub ahead of print].

Treatment Of Cocaine Withdrawal Anxiety With Guanfacine: Relationships To Cocaine Intake and Reinstatement Of Cocaine Seeking In Rats

Successful treatment of cocaine addiction is severely impeded by the propensity of users to relapse. Withdrawal severity may serve as a key predictor of susceptibility to relapse. Therefore, the identification and treatment of cocaine withdrawal symptoms such as anxiety may improve addiction treatment outcome. The current study examined the role of anxiety-like behavior during cocaine withdrawal and anxiolytic treatment in reinstatement of cocaine seeking in an animal model of relapse. Male rats experienced daily IV cocaine self-administration. One group of animals received the norepinephrine α -2 agonist, guanfacine, or vehicle prior to anxiety testing 48 h after the last self-administration session. In the second group of rats, relationships between cocaine intake, anxiety-like behavior after withdrawal of cocaine, and reinstatement responding were investigated. The third and fourth groups of animals received guanfacine, yohimbine (norepinephrine α -2 antagonist), or vehicle once per day for 3 days 48 h after cessation of cocaine self-administration, followed by extinction and subsequent reinstatement induced by cocaine injections, cocaine-paired cues, and yohimbine administration. Cocaine-withdrawn rats at 48 h demonstrated higher levels of anxiety-like behavior as measured on a defensive burying task when compared to yoked saline controls, an effect reversed by guanfacine treatment. Cocaine intake was positively correlated with measures of anxiety-like behavior during early withdrawal, and this anxiety-like behavior was significantly correlated with subsequent cocaine-primed reinstatement. Yohimbine treatment during early withdrawal increased reinstatement to conditioned cues, while guanfacine treatment reduced reinstatement to yohimbine. These studies suggest an important role for noradrenergic mediation of anxiety-like behavior that emerges after withdrawal of cocaine and potential risk of relapse as modeled by reinstatement, and suggest that treatment of anxiety symptoms during early abstinence may reduce the risk of relapse. Buffalari DM, Baldwin CK, See RE. Treatment of cocaine withdrawal anxiety with guanfacine: relationships to cocaine intake and reinstatement of cocaine seeking in rats. *Psychopharmacology (Berl)*. 2012 Apr 18. [Epub ahead of print].

Differential Alteration Of The Effects Of MDMA (Ecstasy) On Locomotor Activity and Cocaine Conditioned Place Preference In Male Adolescent Rats By Social and Environmental Enrichment

Ecstasy (MDMA) is used predominately by adolescents and young adults. Young MDMA users are more likely than non-users to use other drugs, including cocaine. The response to stimulant drugs can be affected by environmental factors; however, little information exists about the role that housing plays in mediating effects of MDMA in adolescence. The present experiment

examined whether social and environmental factors alter effects of MDMA on activity and cocaine reward. Male adolescent rats were housed on PND 23. Isolated rats were housed alone (1 rat/cage) in an impoverished environment with no toys (II) or enriched with toys (IE). Social rats were housed three/cage with (SE3) or without (SI3) toys. Starting on PND 29, 5 mg/kg MDMA or saline was injected and activity was measured for 60 min once daily for five consecutive days. On PND 36-40, cocaine CPP was conducted. Saline vehicle-induced activity of II rats was higher than other groups, and all groups became sensitized to the locomotor-stimulant effects of MDMA. In II rats, maximal CPP was increased after MDMA pre-exposure compared to vehicle. Environmental enrichment blocked this; however, dose-effect curves for cocaine CPP shifted to the left in both IE and SE3 rats. In rats with just social enrichment, there were no effects of MDMA on cocaine CPP. Drug prevention and treatment strategies should take into account different environments in which adolescents live. These findings show that MDMA increases cocaine reward in male adolescents, and social enrichment diminishes, while environmental enrichment enhances this. Starosciak AK, Zakharova E, Stagg M, Matos J, Izenwasser S. Differential alteration of the effects of MDMA (ecstasy) on locomotor activity and cocaine conditioned place preference in male adolescent rats by social and environmental enrichment. *Psychopharmacology (Berl)*. 2012 Jul 1. [Epub ahead of print].

Neural Correlates Of Stress and Favorite-Food Cue Exposure In Adolescents: A Functional Magnetic Resonance Imaging Study

Adolescence is a critical period of neurodevelopment for stress and appetitive processing, as well as a time of increased vulnerability to stress and engagement in risky behaviors. This study was conducted to examine brain activation patterns during stress and favorite-food-cue experiences relative to a neutral-relaxing condition in adolescents. Functional magnetic resonance imaging was employed using individualized script-driven guided imagery to compare brain responses with such experiences in 43 adolescents. Main effects of condition and gender were found, without a significant gender-by-condition interaction. Stress imagery, relative to neutral, was associated with activation in the caudate, thalamus, left hippocampus/parahippocampal gyrus, midbrain, left superior/middle temporal gyrus, and right posterior cerebellum. Appetitive imagery of favorite food was associated with caudate, thalamus, and midbrain activation compared with the neutral-relaxing condition. To understand neural correlates of anxiety and craving, subjective (self-reported) measures of stress-induced anxiety and favorite-food-cue-induced craving were correlated with brain activity during stress and appetitive food-cue conditions, respectively. High self-reported stress-induced anxiety was associated with hypoactivity in the striatum, thalamus, hippocampus, and midbrain. Self-reported favorite-food-cue-induced craving was associated with blunted activity in cortical-striatal regions, including the right dorsal and ventral striatum, medial prefrontal cortex, motor cortex, and left anterior cingulate cortex. These findings in adolescents indicate the activation of predominantly subcortical-striatal regions in the processing of stressful and appetitive experiences and link hypoactive striatal circuits to self-reported stress-induced anxiety and cue-induced favorite-food craving. Hommer RE, Seo D, Lacadie CM, Chaplin TM, Mayes LC, Sinha R, Potenza MN. Neural correlates of stress and favorite-food cue exposure in adolescents: A functional magnetic resonance imaging study. *Hum Brain Mapp*. 2012 Apr 16. doi: 10.1002/hbm.22089. [Epub ahead of print].

The Stress Response and Adolescents' Adjustment: The Impact of Child Maltreatment

Experience with and management of stress has implications for adolescents' behavioral and socioemotional development. This study examined the relationship between adolescents' physiological response to an acute laboratory stressor (i.e., Trier Social Stress Test; TSST) and anger regulation and interpersonal competence in a sample of 175 low-income urban adolescents

(51.8% girls). Findings suggested that heightened reactivity as indicated by cortisol, heart rate, and blood pressure was associated with increased interpersonal competence and anger regulation. However, these findings were context dependent such that, for youth high in self-reported child maltreatment, heightened reactivity was associated with decreased interpersonal competence and anger regulation. Results highlight the importance of considering how context may condition the effect of stress reactivity on functioning during adolescence. Cook EC, Chaplin TM, Sinha R, Tebes JK, Mayes LC. *J Youth Adolescence*. 2012 Aug; 41(8): 1067–1077.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

Test of Association between 10 Single Nucleotide Polymorphisms in the Oxytocin Receptor Gene and Conduct Disorder

Animal and human studies have implicated oxytocin in affiliative and prosocial behaviors. The authors tested whether genetic variation in the oxytocin receptor (OXTR) gene is associated with conduct disorder (CD). Utilizing a family-based sample of adolescent probands recruited from an adolescent substance abuse treatment program, control probands and their families (total sample, n=1750), they conducted three tests of association with CD and 10 single nucleotide polymorphisms (SNPs) in the OXTR gene: (a) family-based comparison utilizing the entire sample; (b) within-Whites, case-control comparison of adolescent patients with CD and controls without CD; and (c) within-Whites case-control comparison of parents of patients and parents of controls. Family-based association tests failed to show significant results (no results $P < 0.05$). While strictly correcting for the number of tests ($\alpha = 0.002$), adolescent patients with CD did not differ significantly from adolescent controls in genotype frequency for the OXTR SNPs tested; similarly, comparison of OXTR genotype frequencies for parents failed to differentiate patient and control family type, except a trend association for rs237889 ($P = 0.004$). The authors concluded that in this sample, 10 SNPs in the OXTR gene were not significantly associated with CD. Sakai JT, Crowley TJ, Stallings MC, McQueen M, Hewitt JK, Hopfer C, Hoft NR, Ehringer MA. Test of association between 10 single nucleotide polymorphisms in the oxytocin receptor gene and conduct disorder. *Psychiatr Genet.* 2012 Apr; 22(2): 99-102.

A Behavioral Test of Accepting Benefits that Cost Others: Associations with Conduct Problems and Callous-Unemotionality

Youth with conduct problems (CP) often make decisions which value self-interest over the interests of others. Self-benefiting behavior despite loss to others is especially common among youth with CP and callous-unemotional traits (CU). Such behavioral tendencies are generally measured using self- or observer-report. The authors are unaware of attempts to measure this tendency with a behavioral paradigm. In their AIAn's (altruism-antisocial) game a computer program presents subjects with a series of offers in which they will receive money but a planned actual charity donation will be reduced; subjects decide to accept or reject each offer. They tested (1) whether adolescent patients with CP ($n = 20$) compared with adolescent controls ($n = 19$) differed on AIAn's game outcomes, (2) whether youths with CP and CU differed significantly from controls without CP or CU, and (3) whether AIAn's game outcomes correlated significantly with CP and separately, CU severity. Patients with CP and CU compared with controls without these problems took significantly more money for themselves and left significantly less money in the charity donation; AIAn's game outcomes were significantly correlated with CU, but not CP. In the AIAn's game adolescents with conduct problems and CU traits, compared with controls without CP/CU, are disposed to benefit themselves while costing others even in a novel situation, devoid of peer influences, where anonymity is assured, reciprocity or retribution are impossible, intoxication is absent and when the "other" to be harmed is considered beneficent. AIAn's game outcomes are associated with measures of CU. Results suggest that the AIAn's game provides an objective means of capturing information about CU traits. The AIAn's game, which was designed for future use in the MRI environment, may be used in studies attempting to identify the neural correlates of self-benefiting decision-making. Sakai JT, Dalwani MS, Gelhorn HL, Mikulich-Gilbertson SK, Crowley TJ. A behavioral test of accepting benefits that cost others: associations with conduct problems and callous-unemotionality. *PLoS One.* 2012; 7(4): e36158.

Are Affluent Youth Truly "At Risk"? Vulnerability and Resilience across Three Diverse Samples

Building upon prior findings of elevated problems among East Coast suburban youth through the 11th grade, this study establishes disproportionately high incidence of maladjustment across three disparate samples: East Coast Suburban youth at the end of their senior year in high school, and 11th and 12th graders in (a) a Northwest suburb and (b) an East Coast city. Both East Coast samples showed pronounced elevations in substance use, whereas the Northwest suburban sample showed marked vulnerability in serious internalizing and externalizing symptoms. Across all samples, parents' low perceived containment for substance use (lax repercussions on discovering use) was a major vulnerability factor, followed by parents' knowledge of their teens' activities. Overall, adolescents' symptom levels were more strongly related to their relationships with mothers than with fathers. An exception was boys' apparent vulnerability to fathers', but not mothers', perceived depressive symptoms. As with affluent eighth graders, the authors found that "overscheduling" in extracurriculars is not a critical vulnerability factor among these high school students. Finally, youth reports suggested that most affluent parents do not indiscriminately bail their children out of all problem situations (although a small subset, apparently, do). Results are discussed along with the implications for practice and for future research. Luthar SS, Barkin SH. Are affluent youth truly "at risk"? Vulnerability and resilience across three diverse samples. *Dev Psychopathol.* 2012 May; 24(2): 429-449.

Prenatal Methamphetamine Exposure and Childhood Behavior Problems at 3 and 5 Years of Age

The authors evaluated behavior problems in children who were prenatally exposed to methamphetamine (MA) at ages 3 and 5 years. The Infant Development, Environment, and Lifestyle study, a prospective, longitudinal study of prenatal MA exposure and child outcome, enrolled subjects postpartum in Los Angeles, California; Honolulu, Hawaii; Des Moines, Iowa; and Tulsa, Oklahoma. Prenatal exposure was determined by maternal self-report and/or meconium results. Exposed and comparison groups were matched on race, birth weight, public health insurance, and education. Mothers in the comparison group denied use and had a negative meconium screen for amphetamines. Prenatal exposures to tobacco, alcohol, or marijuana occurred in both groups. At ages 3 and 5 years, 330 children (166 exposed and 164 comparison) were assessed for behavior problems by using the caregiver report on the Child Behavior Checklist. General linear mixed models were used to determine the effects of prenatal MA exposure, including heavy exposure (≥ 3 days per week), age, and the interaction of exposure and age on behavior problems with adjustment for other drugs of abuse and environmental risk factors. MA exposure was associated with increased emotional reactivity and anxious/depressed problems at both ages and externalizing and attention-deficit/hyperactivity disorder problems by age 5 years. Heavy exposure was related to attention problems and withdrawn behavior at both ages. There were no effects of MA on the internalizing or total behavior problems scales. This first report of behavior problems in patients as young as 3 years associated with MA exposure identifies an important public health problem. Continued follow-up can inform the development of preventive intervention programs. LaGasse LL, Derauf C, Smith LM, Newman E, Shah R, Neal C, Arria A, Huestis MA, DellaGrotta S, Lin H, Dansereau LM, Lester BM. Prenatal methamphetamine exposure and childhood behavior problems at 3 and 5 years of age. *Pediatrics.* 2012 Apr; 129(4): 681-688.

Overlapping Neural Substrates Between Intentional and Incidental Down-Regulation of Negative Emotions

Emotion regulation can be achieved in various ways, but few studies have evaluated the extent to which the neurocognitive substrates of these distinct operations overlap. In the study reported here, functional magnetic resonance imaging (fMRI) was used to measure activity in the amygdala and prefrontal cortex of 10 participants who completed two independent

tasks of emotion regulation-reappraisal, measuring intentional emotion regulation, and affect labeling, measuring incidental emotion regulation-with the objective of identifying potential overlap in the neural substrates underlying each task. Analyses focused on a priori regions of interest in the amygdala and inferior frontal gyrus (IFG). For both tasks, fMRI showed decreased amygdala activation during emotion regulation compared with emotion conditions. During reappraisal, this decrease in amygdala activation was accompanied by a proportional decrease in emotional intensity ratings; during affect labeling, the decrease in amygdala activation correlated with self-reported aggression. Importantly, across participants, the magnitude of decrease in amygdala activation during reappraisal correlated with the magnitude of decrease during affect labeling, even though the tasks were administered on separate days, and values indexing amygdala activation during each task were extracted independently of one another. In addition, IFG-amygdala connectivity, assessed via psychophysiological interaction analysis, overlapped between tasks in two regions within the right IFG. The results suggest that the two tasks recruit overlapping regions of prefrontal cortex, resulting in similar reductions in amygdala activation, regardless of the strategy employed. Intentional and incidental forms of emotion regulation, despite their phenomenological differences, may therefore converge on a common neurocognitive pathway. Payer DE, Baicy K, Lieberman MD, London ED. Overlapping neural substrates between intentional and incidental down-regulation of negative emotions. *Emotion*. 2012 Apr; 12(2): 229-235.

Chronic Cocaine Exposure During Pregnancy Increases Postpartum Neuroendocrine Stress Responses

The cycle of chronic cocaine (CC) use and withdrawal results in increased anxiety, depression and disrupted stress-responsiveness. Oxytocin and corticosterone (CORT) interact to mediate hormonal stress responses and can be altered by cocaine use. These neuroendocrine signals play important regulatory roles in a variety of social behaviours, specifically during the postpartum period, and are sensitive to disruption by CC exposure in both clinical settings and preclinical models. To determine whether CC exposure during pregnancy affected behavioural and hormonal stress response in the early postpartum period in a rodent model, Sprague-Dawley rats were administered cocaine daily (30 mg/kg) throughout gestation (days 1-20). Open field test (OFT) and forced swim test (FST) behaviours were measured on postpartum day 5. Plasma CORT concentrations were measured before and after testing throughout the test day, whereas plasma and brain oxytocin concentrations were measured post-testing only. The results obtained indicated increased CORT response after the OFT in CC-treated dams ($P \leq 0.05$). CC-treated dams also exhibited altered FST behaviour ($P \leq 0.05$), suggesting abnormal stress responsiveness. Peripheral, but not central, oxytocin levels were increased by cocaine treatment ($P \leq 0.05$). Peripheral oxytocin and CORT increased after the FST, regardless of treatment condition ($P \leq 0.05$). Changes in stress-responsiveness, both behaviourally and hormonally, may underlie some deficits in maternal behaviour; thus, a clearer understanding of the effect of CC on the stress response system may potentially lead to treatment interventions that could be relevant to clinical populations. Additionally, these results indicate that CC treatment can have long-lasting effects on peripheral oxytocin regulation in rats, similar to changes observed in persistent social behaviour and stress-response deficits in clinical populations. Williams SK, Barber JS, Jamieson-Drake AW, Enns JA, Townsend LB, Walker CH, Johns JM. Chronic cocaine exposure during pregnancy increases postpartum neuroendocrine stress responses. *J Neuroendocrinol*. 2012 Apr; 24(4): 701-711.

Regional Brain Responses in Nulliparous Women to Emotional Infant Stimuli Infant cries and facial expressions influence social interactions and elicit caretaking behaviors from adults. Recent neuroimaging studies suggest that neural responses to infant stimuli involve brain regions that process rewards. However, these studies have yet to investigate individual differences in tendencies

to engage or withdraw from motivationally relevant stimuli. To investigate this, the authors used event-related fMRI to scan 17 nulliparous women. Participants were presented with novel infant cries of two distress levels (low and high) and unknown infant faces of varying affect (happy, sad, and neutral) in a randomized, counter-balanced order. Brain activation was subsequently correlated with scores on the Behavioral Inhibition System/Behavioral Activation System scale. Infant cries activated bilateral superior and middle temporal gyri (STG and MTG) and precentral and postcentral gyri. Activation was greater in bilateral temporal cortices for low- relative to high-distress cries. Happy relative to neutral faces activated the ventral striatum, caudate, ventromedial prefrontal, and orbitofrontal cortices. Sad versus neutral faces activated the precuneus, cuneus, and posterior cingulate cortex, and behavioral activation drive correlated with occipital cortical activations in this contrast. Behavioral inhibition correlated with activation in the right STG for high- and low-distress cries relative to pink noise. Behavioral drive correlated inversely with putamen, caudate, and thalamic activations for the comparison of high-distress cries to pink noise. Reward-responsiveness correlated with activation in the left precentral gyrus during the perception of low-distress cries relative to pink noise. These findings indicate that infant cry stimuli elicit activations in areas implicated in auditory processing and social cognition. Happy infant faces may be encoded as rewarding, whereas sad faces activate regions associated with empathic processing. Differences in motivational tendencies may modulate neural responses to infant cues. Montoya JL, Landi N, Kober H, Worhunsky PD, Rutherford HJ, Mencl WE, Mayes LC, Potenza MN. Regional brain responses in nulliparous women to emotional infant stimuli. *PLoS One*. 2012; 7(5): e36270.

Cigarette Smoking and White Matter Microstructure Diffusion tensor imaging has been used before in testing associations between cigarette smoking and white matter integrity, with inconsistent results. Published reports indicate higher fractional anisotropy (FA, a measure of linear water diffusion) in some brain regions and lower FA in others in adult smokers compared to nonsmokers. Adolescent smokers exhibited elevated FA at several brain regions and a positive correlation of FA in the genu corpus callosum with exposure to smoking (pack-years). To help resolve prior discrepancies, the authors studied adults, sampling multiple brain regions, and testing for relationships to clinical features of nicotine dependence and exposure to smoking. Brain MRI scans (1.5 T) were acquired, and FA and apparent diffusion coefficient (ADC, a measure of random diffusion) were assayed in corpus callosum and prefrontal white matter, corona radiata, internal capsule, cingulum bundle, and hippocampal perforant fibers in 18 smokers (33.7±7.9 years of age) and 18 age- and gender-matched nonsmokers. ADC showed no group difference, but smokers had higher (4.3-21.1%) FA than nonsmokers. The differences were significant in right prefrontal white matter, cingulum, and genu corpus callosum. FA in several regions was negatively correlated with nicotine dependence or cigarettes/day. Combined with earlier findings, these results suggest a model of changing trajectories whereby FA is higher with tobacco exposure during adolescence and declines with continued smoking in adulthood. This notion is supported by the observation that, at multiple sampling sites, participants who had started smoking earlier in life had higher FA than those who had started later. Hudkins M, O'Neill J, Tobias MC, Bartzokis G, London ED. Cigarette smoking and white matter microstructure. *Psychopharmacology (Berl)*. 2012 May; 221(2): 285-295.

Dysregulation Of D₂-Mediated Dopamine Transmission in Monkeys After Chronic Escalating Methamphetamine Exposure Compulsive drug-seeking and drug-taking are important substance-abuse behaviors that have been linked to alterations in dopaminergic neurotransmission and to impaired inhibitory control. Evidence supports the notions that abnormal D₂ receptor-mediated dopamine transmission and inhibitory control may be heritable risk factors for addictions, and that they also reflect drug-induced neuroadaptations. To provide a mechanistic explanation for the drug-

induced emergence of inhibitory-control deficits, this study examined how a chronic, escalating-dose regimen of methamphetamine administration affected dopaminergic neurochemistry and cognition in monkeys. Dopamine D₂-like receptor and dopamine transporter (DAT) availability and reversal-learning performance were measured before and after exposure to methamphetamine (or saline), and brain dopamine levels were assayed at the conclusion of the study. Exposure to methamphetamine reduced dopamine D₂-like receptor and DAT availability and produced transient, selective impairments in the reversal of a stimulus-outcome association. Furthermore, individual differences in the change in D₂-like receptor availability in the striatum were related to the change in response to positive feedback. These data provide evidence that chronic, escalating-dose methamphetamine administration alters the dopamine system in a manner similar to that observed in methamphetamine-dependent humans. They also implicate alterations in positive-feedback sensitivity associated with D₂-like receptor dysfunction as the mechanism by which inhibitory control deficits emerge in stimulant-dependent individuals. Finally, a significant degree of neurochemical and behavioral variation in response to methamphetamine was detected, indicating that individual differences affect the degree to which drugs of abuse alter these processes. Identification of these factors ultimately may assist in the development of individualized treatments for substance dependence. Groman SM, Lee B, Seu E, James AS, Feiler K, Mandelkern MA, London ED, Jentsch JD. Dysregulation of D₂ -mediated dopamine transmission in monkeys after chronic escalating methamphetamine exposure. *J Neurosci*. 2012 Apr 25; 32(17): 5843-5852.

Leveraging Findings from GWAS Meta-Analyses to Test Developmental Hypotheses About Nicotine Consumption

The present study evaluated gene by development interaction in cigarettes smoked per day (CPD) in a longitudinal community-representative sample (N = 3,231) of Caucasian twins measured at ages 14, 17, 20, and 24. Biometric heritability analyses show strong heritabilities and shared environmental influences, as well as cross-age genetic and shared environmental correlations. Single nucleotide polymorphisms (SNPs) previously associated with CPD according to meta-analysis were summed to create a SNP score. At best, the SNP score accounted for 1 % of the variance in CPD. The results suggest developmental moderation with a larger significant SNP score effect on CPD at ages 20 and 24, and smaller non-significant effect at ages 14 and 17. These results are consistent with the notion that nicotine-specific genetic substance use risk is less important at younger ages, and becomes more important as individuals age into adulthood. In a complementary analysis, the same nicotine-relevant SNP score was unrelated to the frequency of alcohol use at ages 14, 17, 20, or 24. These results indicate that the SNP score is specific to nicotine in this small sample and that increased exposure to nicotine at ages 20 and 24 does not influence the extent of concurrent or later alcohol use. Increased sample sizes and replication or meta-analysis are necessary to confirm these results. The methods and results illustrate the importance and difficulty of considering developmental processes in understanding the interplay of genes and environment. Vrieze SI, McGue M, Iacono WG. The interplay of genes and adolescent development in substance use disorders: leveraging findings from GWAS meta-analyses to test developmental hypotheses about nicotine consumption. *Hum Genet*. 2012 Jun; 131(6): 791-801.

Structural Variations in Prefrontal Cortex Mediate the Relationship Between Early Childhood Stress and Spatial Working Memory

A large corpus of research indicates that exposure to stress impairs cognitive abilities, specifically executive functioning dependent on the prefrontal cortex (PFC). The authors collected structural MRI scans (n = 61), well-validated assessments of executive functioning, and detailed interviews assessing stress exposure in humans

to examine whether cumulative life stress affected brain morphometry and one type of executive functioning, spatial working memory, during adolescence—a critical time of brain development and reorganization. Analysis of variations in brain structure revealed that cumulative life stress and spatial working memory were related to smaller volumes in the PFC, specifically prefrontal gray and white matter between the anterior cingulate and the frontal poles. Mediation analyses revealed that individual differences in prefrontal volumes accounted for the association between cumulative life stress and spatial working memory. These results suggest that structural changes in the PFC may serve as a mediating mechanism through which greater cumulative life stress engenders decrements in cognitive functioning. Hanson JL, Chung MK, Avants BB, Rudolph KD, Shirtcliff EA, Gee JC, Davidson RJ, Pollak SD. Structural variations in prefrontal cortex mediate the relationship between early childhood stress and spatial working memory. *J Neurosci*. 2012 Jun 6; 32(23): 7917-7925.

Neural Substrates for Processing Task-Irrelevant Emotional Distracters in Maltreated Adolescents with Depressive Disorders: A Pilot Study

In this pilot study, neural systems related to cognitive and emotional processing were examined using event-related functional magnetic resonance imaging in 5 maltreated youth with depressive disorders and 11 nonmaltreated healthy participants. Subjects underwent an emotional oddball task, where they detected infrequent ovals (targets) within a continual stream of phase-scrambled images (standards). Sad and neutral images were intermittently presented as task-irrelevant distracters. The maltreated youth revealed significantly decreased activation in the left middle frontal gyrus and right precentral gyrus to target stimuli and significantly increased activation to sad stimuli in bilateral amygdala, left subgenual cingulate, left inferior frontal gyrus, and right middle temporal cortex compared to nonmaltreated subjects. Additionally, the maltreated youth showed significantly decreased activation to both attentional targets and sad distracters in the left posterior middle frontal gyrus compared to nonmaltreated subjects. In this exploratory study of dorsal control and ventral emotional circuits, the authors found that maltreated youth with distress disorders demonstrated dysfunction of neural systems related to cognitive control and emotional processing. De Bellis MD, Hooper SR. Neural substrates for processing task-irrelevant emotional distracters in maltreated adolescents with depressive disorders: A pilot study. *J Trauma Stress*. 2012 Apr; 25(2): 198-202.

CLINICAL NEUROSCIENCE RESEARCH

Association of *OPRD1* Polymorphisms with Heroin Dependence in a Large Case-control Series

Genes encoding the opioid receptors (*OPRM1*, *OPRD1* and *OPRK1*) are obvious candidates for involvement in risk for heroin dependence. Prior association studies commonly had samples of modest size, included limited single nucleotide polymorphism (SNP) coverage of these genes and yielded inconsistent results. Participants for the current investigation included 1459 heroin-dependent cases ascertained from maintenance clinics in New South Wales, Australia, 1,495 unrelated individuals selected from an Australian sample of twins and siblings as not meeting DSM-IV criteria for lifetime alcohol or illicit drug dependence (non-dependent controls) and 531 controls ascertained from economically disadvantaged neighborhoods in proximity to the maintenance clinics. A total of 136 *OPRM1*, *OPRD1* and *OPRK1* SNPs were genotyped in this sample. After controlling for admixture with principal components analysis, the authors' comparison of cases to non-dependent controls found four *OPRD1* SNPs in fairly high linkage disequilibrium for which adjusted *P* values remained significant (e.g. rs2236857; OR 1.25; $P = 2.95 \times 10^{-4}$) replicating a previously reported association. A *post hoc* analysis revealed that the two SNP (rs2236857 and rs581111) GA haplotype in *OPRD1* is associated with greater risk (OR 1.68; $P = 1.41 \times 10^{-5}$). No *OPRM1* or *OPRK1* SNPs reached more than nominal significance. Comparisons of cases to neighborhood controls reached only nominal significance. These results replicate a prior report providing strong evidence implicating *OPRD1* SNPs and, in particular, the two SNP (rs2236857 and rs581111) GA haplotype in liability for heroin dependence. Support was not found for similar association involving either *OPRM1* or *OPRK1* SNPs. Nelson EC, Lynskey MT, Heath AC, Wray N, Agrawal A, Shand FL, Henders AK, Wallace L, Todorov AA, Schrage AJ, F. Madden PAF, Degenhardt L, G. Martin NG, Montgomery GW. Association of *OPRD1* polymorphisms with heroin dependence in a large case-control series. *Addict Biol.* 13 APR 2012. [Epub ahead of print].

Denicotinized Versus Average Nicotine Tobacco Cigarette Smoking Differentially Releases Striatal Dopamine

Nicotine has long been recognized as a necessary but insufficient component of tobacco cigarettes to maintain a psychophysiological need to smoke. This study examined venous plasma concentrations effects of nicotine in cigarette smoking after overnight abstinence to release striatal dopamine (DA). Twenty-two male smokers smoked either denicotinized (denic) or average nicotine (nic) cigarettes under single blind conditions. Each was given [¹¹C]raclopride and scanned in a positron emission tomography (PET) facility. Smoking either denic or nic cigarettes released striatal DA. Denic cigarette smoking released DA primarily in the right striatum, whereas nic cigarette smoking released DA in both striata, but especially in the left. Increases in venous plasma nicotine concentrations correlated positively with increased DA release in the left caudate nucleus. Smoking denic cigarettes reduced craving as much as smoking nic cigarettes. Craving reduction after nic tobacco smoking correlated with increases in plasma nicotine. Non-nicotine factors in tobacco smoking produce important right brain effects. Nicotine is a pharmacological factor during tobacco smoking that releases bilateral striatal DA, but more in the left brain. Domino EF, Ni L, Domino JS, Yang W, Evans C, Guthrie S, Wang H, Koeppe RA, Zubieta J-K. Denicotinized versus average nicotine tobacco cigarette smoking differentially releases striatal dopamine. *Nicotine & Tobacco Res.* 2012 April 5. [Epub ahead of print].

Tobacco Smoking Produces Greater Striatal Dopamine Release in G-allele Carriers with Mu Opioid Receptor A118G Polymorphism

The aim of this study was to determine if carriers of the allelic expression of the G variant of the human mu opioid receptor (*OPRM1*) A118G polymorphism have greater increases in striatal dopamine (DA) release after tobacco smoking.

Nineteen of 20 genotyped male tobacco smokers, after overnight abstinence, smoked denicotinized (denic) and average nicotine (nic) containing tobacco cigarettes in a PET brain imaging study using [¹¹C]raclopride. The right striatum had more free D₂ receptors than the left striatum pre- and post-tobacco smoking. After smoking the nic cigarettes, mean decreased DA binding was observed in the left dorsal caudate (− 14 6 11; $t = 3.77$), left and right ventral putamen (− 26 3–8; $t = 4.27$; 28 2 1; $t = 4.25$, respectively), and right caudate (17 18 1; $t = 3.92$). The effects of A118G genotype on the binding potentials for these four regions were then analyzed. Carriers of the G allele had larger magnitudes of DA release in response to nic smoking than those homozygous for the more prevalent AA allele in the right caudate and right ventral pallidum ($t = 3.03$; $p = 0.008$ and $t = 3.91$; $p = 0.001$). A voxel by voxel whole brain SPM analysis using an independent samples t test did not reveal any other differences between genotype groups. In addition, the venous plasma cortisol levels of the volunteers from 8:30 am to 12:00 noon were lower in the AG/GG allele carriers. Nic smoking increased plasma cortisol in both groups, but they were higher in the AA group. This preliminary study indicates a difference in both brain striatal DA release and plasma cortisol in A118G polymorphic male tobacco smokers Domino EF, Evans CL, Ni L, Guthrie SK, Koeppel RA, Zubieta J-K. Tobacco smoking produces greater striatal dopamine release in G-allele carriers with mu opioid receptor A118G polymorphism. *Prog Neuro-Psychopharm Biol Psychiat*. 2012 April 10. [Epub ahead of print].

Associations between Cannabinoid Receptor-1 (CNRI) Variation and Hippocampus and Amygdala Volumes in Heavy Cannabis Users Heavy cannabis users display smaller amygdalae and hippocampi than controls, and genetic variation accounts for a large proportion of variance in liability to cannabis dependence (CD). A single nucleotide polymorphism in the cannabis receptor-1 gene (*CNRI*), rs2023239, has been associated with CD diagnosis and intermediate phenotypes, including abstinence-induced withdrawal, cue-elicited craving, and parahippocampal activation to cannabis cues. This study compared hippocampal and amygdalar volumes (potential CD intermediate phenotypes) between heavy cannabis users and healthy controls, and analyzed interactions between group, rs2023239 variation, and the volumes of these structures. Ninety-four heavy cannabis users participated, of whom 37 (14 men, 23 women; mean age=27.8) were matched to 37 healthy controls (14 men, 23 women; mean age=27.3) for case-control analyses. Controlling for total intracranial volume and other confounding variables, matched cannabis users had smaller bilateral hippocampi (left, $p=0.002$; right, $p=0.001$) and left amygdalae ($p=0.01$) than controls. When genotype was considered in the case-control analyses, there was a group by genotype interaction, such that the rs2023239 G allele predicted lower volume of bilateral hippocampi among cannabis users relative to controls (both $p<0.001$). This interaction persisted when all 94 cannabis users were compared to controls. There were no group by genotype interactions on amygdalar volume. These data replicate previous findings of reduced hippocampal and amygdalar volume among heavy cannabis users, and suggest that *CNRI* rs2023239 variation may predispose smaller hippocampal volume after heavy cannabis use. This association should be tested in future studies of brain volume differences in CD. Schacht JP, Hutchison KE, Filbey FM. Associations between cannabinoid receptor-1 (CNRI) variation and hippocampus and amygdala volumes in heavy cannabis users. *Neuropsychopharmacology* 2012 June 6 2012. [Epub ahead of print].

Neural Correlates of Stress-Induced and Cue-induced Drug Craving: Influences of Sex and Cocaine Dependence Although stress and drug cue exposure each increase drug craving and contribute to relapse in cocaine dependence, no previous research has directly examined the neural correlates of stress-induced and drug cue-induced craving in cocaine-dependent women and men relative to comparison subjects. Functional MRI was used to assess responses to individualized

scripts for stress, drug/alcohol cue and neutral-relaxing-imagery conditions in 30 abstinent cocaine-dependent individuals (16 women, 14 men) and 36 healthy recreational-drinking comparison subjects (18 women, 18 men). Significant three-way interactions between diagnostic group, sex, and script condition were observed in multiple brain regions including the striatum, insula, and anterior and posterior cingulate. Within women, group-by-condition interactions were observed involving these regions and were attributable to relatively increased regional activations in cocaine-dependent women during the stress and, to a lesser extent, neutral-relaxing conditions. Within men, group main effects were observed involving these same regions, with cocaine-dependent men demonstrating relatively increased activation across conditions, with the main contributions from the drug and neutral-relaxing conditions. In men and women, subjective drug-induced craving measures correlated positively with corticostriatal-limbic activations. In cocaine dependence, corticostriatal-limbic hyperactivity appears to be linked to stress cues in women, drug cues in men, and neutral-relaxing conditions in both. These findings suggest that sex should be taken into account in the selection of therapies in the treatment of addiction, particularly those targeting stress reduction. Potenza MN, Hong KI, Lacadie CM, Fulbright RK, Tuit KL, Sinha R. Neural correlates of stress-induced and cue-induced drug craving: influences of sex and cocaine dependence. *Am J Psychiatry*. 2012 Apr; 169(4): 406-414.

Genetic Variation in CYP2A6 Predicts Neural Reactivity to Smoking Cues as Measured Using fMRI Smoking cues trigger craving for cigarettes and relapse. Nicotine metabolism, mediated by the enzyme CYP2A6, also influences smoking behavior. In this study, the authors investigated how nicotine metabolism and genetic variation in CYP2A6 influence the neural response to smoking cues in humans using functional magnetic resonance imaging (fMRI). They hypothesized that individuals with faster rates of nicotine metabolism would have stronger conditioned responses to smoking cues because of closer coupling in everyday life between exposure to cigarettes and surges in blood nicotine concentration. In contrast, individuals with reduced rates of metabolism, who have relatively constant nicotine blood levels throughout the day, should be less likely to develop conditioned responses to cues. The authors screened 169 smokers for their rate of nicotine metabolism and CYP2A6 genotype, and selected 31 smokers with the fastest and slowest rates for fMRI, matched for daily cigarette intake. They measured their neural response to visual smoking and non-smoking cues using fMRI. As predicted, fast metabolizers, by phenotype or genotype, had significantly greater responses to visual cigarette cues than slow metabolizers in the amygdala, hippocampus, striatum, insula, and cingulate cortex. These results support the theory that drug cues are conditioned stimuli, and explain why fast metabolizers who smoke have lower cessation rates. They also provide insight into how genetics can shape human vulnerability to addiction, and have implications for tailoring smoking cessation programs based on individual genetics. Tang DW, Hello B, Mroziewicz M, Fellows LK, Tyndale RF, Dagher A. Genetic variation in CYP2A6 predicts neural reactivity to smoking cues as measured using fMRI. *Neuroimage*. 2012 May 1; 60(4): 2136-2143.

Functional Brain Networks Associated With Cognitive Control, Cocaine Dependence, and Treatment Outcome Individuals with cocaine dependence often evidence poor cognitive control. The purpose of this exploratory study was to investigate networks of functional connectivity underlying cognitive control in cocaine dependence and examine the relationship of the networks to the disorder and its treatment. Independent component analysis (ICA) was applied to fMRI data to investigate if regional activations underlying cognitive control processes operate in functional networks, and whether these networks relate to performance and treatment outcome measures in cocaine dependence. Twenty patients completed a Stroop task during fMRI prior to entering

outpatient treatment and were compared to 20 control participants. ICA identified five distinct functional networks related to cognitive control interference events. Cocaine-dependent patients displayed differences in performance-related recruitment of three networks. Reduced involvement of a "top-down" fronto-cingular network contributing to conflict monitoring correlated with better treatment retention. Greater engagement of two "bottom-up" subcortical and ventral prefrontal networks related to cue-elicited motivational processing correlated with abstinence during treatment. The identification of subcortical networks linked to cocaine abstinence and cortical networks to treatment retention suggests that specific circuits may represent important, complementary targets in treatment development for cocaine dependence. Worhunsky PD, Stevens MC, Carroll KM, Rounsaville BJ, Calhoun VD, Pearlson GD, Potenza MN. Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome. *Psychol Addict Behav.* 2012 Jul 9. [Epub ahead of print].

Striatal Dopamine D₂/D₃ Receptor Availability Correlates with Behavioral Response

Inhibition and Related fMRI BOLD Signal in Frontostriatal Neural Circuitry in Humans

Impulsive behavior is thought to reflect a trait-like characteristic that can have broad consequences for an individual's success and well-being, but its neurobiological basis remains elusive. Although striatal dopamine D₂-like receptors have been linked with impulsive behavior and behavioral inhibition in rodents, a role for D₂-like receptor function in frontostriatal circuits mediating inhibitory control in humans has not been shown. The authors investigated this role in a study of healthy research participants who underwent positron emission tomography with the D₂/D₃ dopamine receptor ligand [¹⁸F]fallypride and BOLD fMRI while they performed the Stop-signal Task, a test of response inhibition. Striatal dopamine D₂/D₃ receptor availability was negatively correlated with speed of response inhibition (stop-signal reaction time) and positively correlated with inhibition-related fMRI activation in frontostriatal neural circuitry. Correlations involving D₂/D₃ receptor availability were strongest in the dorsal regions (caudate and putamen) of the striatum, consistent with findings of animal studies relating dopamine receptors and response inhibition. The results suggest that striatal D₂-like receptor function in humans plays a major role in the neural circuitry that mediates behavioral control, an ability that is essential for adaptive responding and is compromised in a variety of common neuropsychiatric disorders. Ghahremani DG, Lee B, Robertson CL, Tabibnia G, Morgan AT, De Shetler N, Brown AK, Monterosso JR, Aron AR, Mandelkern MA, Poldrack RA, London ED. Striatal dopamine D₂/D₃ receptors mediate response inhibition and related activity in frontostriatal neural circuitry in humans. *J Neurosci.* 2012 May 23; 32(21): 7316-7324.

Cognitive Reappraisal Blunts Amygdala Reactivity and Self-Reported Emotional Intensity in Response to Negative Images

Emotion regulation can be achieved in various ways, but few studies have evaluated the extent to which the neurocognitive substrates of these distinct operations overlap. In the study reported here, functional magnetic resonance imaging (fMRI) was used to measure activity in the amygdala and prefrontal cortex of 10 participants who completed two independent tasks of emotion regulation-reappraisal, measuring intentional emotion regulation, and affect labeling, measuring incidental emotion regulation-with the objective of identifying potential overlap in the neural substrates underlying each task. Analyses focused on a priori regions of interest in the amygdala and inferior frontal gyrus (IFG). For both tasks, fMRI showed decreased amygdala activation during emotion regulation compared with emotion conditions. During reappraisal, this decrease in amygdala activation was accompanied by a proportional decrease in emotional intensity ratings; during affect labeling, the decrease in amygdala activation correlated with self-reported aggression. Importantly, across participants, the magnitude of decrease in

amygdala activation during reappraisal correlated with the magnitude of decrease during affect labeling, even though the tasks were administered on separate days, and values indexing amygdala activation during each task were extracted independently of one another. In addition, IFG-amygdala connectivity, assessed via psychophysiological interaction analysis, overlapped between tasks in two regions within the right IFG. The results suggest that the two tasks recruit overlapping regions of prefrontal cortex, resulting in similar reductions in amygdala activation, regardless of the strategy employed. Intentional and incidental forms of emotion regulation, despite their phenomenological differences, may therefore converge on a common neurocognitive pathway. Payer DE, Baicy K, Lieberman MD, London ED. Overlapping neural substrates between intentional and incidental down-regulation of negative emotions. *Emotion*. 2012 Apr; 12(2): 229-235.

Cooperative Rewards (Reciprocity) are Subject to Delay-Discounting Effects Parties in real-world conflicts often attempt to punish each other's behavior. If this strategy fails to produce mutual cooperation, they may increase punishment magnitude. The present experiment investigated whether delay-reduction - potentially less harmful than magnitude increase - would generate mutual cooperation as interactions are repeated. Participants played a prisoner's dilemma game against a computer that played a tit-for-tat strategy, cooperating after a participant cooperated, defecting after a participant defected. For half of the participants, the delay between their choice and the computer's next choice was long relative to the delay between the computer's choice and their next choice. For the other half, long and short delays were reversed. The tit-for-tat contingency reinforces the other player's cooperation (by cooperating) and punishes the other player's defection (by defecting). Both rewards and punishers are discounted by delay. Consistent with delay discounting, participants cooperated more when the delay between their choice and the computer's cooperation (reward) or defection (punishment) was relatively short. These results suggest that, in real-world tit-for-tat conflicts, decreasing delay of reciprocation or retaliation may foster mutual cooperation as effectively as (or more effectively than) the more usual tactic of increasing magnitude of reciprocation or retaliation. Locey ML, Rachlin H. The temporal dynamics of cooperation. *Behav Decis Mak*. 2012 Jul 1; 25(3): 257-263.

Brief Cognition Screener is Predictive of Drug Abuse Therapy Attendance Neuropsychological impairment among patients with substance use disorders (SUDs) contributes to poorer treatment processes and outcomes. However, neuropsychological assessment is typically not an aspect of patient evaluation in SUD treatment programs because it is prohibitively time and resource consuming. In a previous study, the authors examined the concurrent validity, classification accuracy, and clinical utility of a brief screening measure, the Montreal Cognitive Assessment (MoCA), in identifying cognitive impairment among SUD patients. To provide further evidence of criterion-related validity, MoCA classification should optimally predict a clinically relevant behavior or outcome among SUD patients. The purpose of this study was to examine the validity of the MoCA in predicting treatment attendance. The authors compared previously collected clinical assessment data on 60 SUD patients receiving treatment in a program of short duration and high intensity to attendance data obtained via medical chart review. Though the proportion of therapy sessions attended did not differ between groups, cognitively impaired subjects were significantly less likely than unimpaired subjects to attend all of their group therapy sessions. These results complement previous findings by providing further evidence of criterion-related validity of the MoCA in predicting a clinically relevant behavior (i.e., perfect attendance) among SUD patients. The capacity of the MoCA to predict a clinically relevant behavior provides support for its validity as a brief cognitive screening measure. Copersino ML, Schretlen DJ, Fitzmaurice GM, Lukas SE, Faberman J, Sokoloff J, Weiss RD. Effects of cognitive impairment on substance

abuse treatment attendance: predictive validation of a brief cognitive screening measure. *Am J Drug Alcohol Abuse*. 2012 May; 38(3): 246-250.

A Single Administration of Low-Dose Varenicline Saturates $\alpha 4\beta 2^*$ Nicotinic Acetylcholine Receptors in the Human Brain

The primary objective of this project was to determine the $\alpha 4\beta 2^*$ nicotinic acetylcholine receptor (nAChR) occupancy in human brain of a single low dose of varenicline (0.5mg), and to explore the relationship between receptor occupancy by varenicline and tobacco withdrawal symptoms ((*)denoting other putative nAChR subunits). Otherwise healthy smokers (n=9) underwent two positron emission tomography (PET) sessions with the selective $\alpha 4\beta 2^*$ radioligand 2-FA. For the PET sessions, participants received either a low dose of varenicline (0.5mg) or matching placebo pill (double-blind, random order) before imaging. For both sessions, participants received bolus plus continuous infusions of 2-FA, were scanned for 1h after allowing the radiotracer to reach a steady state, smoked to satiety, and were scanned for 2 more hours. The authors estimated the fractional receptor occupancy by a single dose of varenicline (0.5mg) and the corresponding varenicline dissociation constant (K(V)), along with the effect of low-dose varenicline, pill placebo, and smoking-to-satiety on withdrawal rating scales. The data are compatible with 100% occupancy of $\alpha 4\beta 2^*$ nAChRs by a single dose of varenicline, with a 90% lower confidence limit of 89% occupancy for the thalamus and brainstem. The corresponding 90% upper limit on effective K(V) with respect to plasma varenicline was 0.49nM. Smoking to satiety, but not low-dose varenicline, significantly reduced withdrawal symptoms. These findings demonstrate that low-dose varenicline results in saturation of $\alpha 4\beta 2^*$ nAChRs in the thalamus and brainstem without reducing withdrawal symptoms. Lotfipour S, Mandelkern M, Alvarez-Estrada M, L Brody A. A single administration of low-dose varenicline saturates $\alpha 4\beta 2^*$ nicotinic acetylcholine receptors in the human brain. *Neuropsychopharmacology*. 2012 Jun; 37(7): 1738-1748.

Sex Differences in Availability of $\beta 2^*$ -Nicotinic Acetylcholine Receptors in Recently Abstinent Tobacco Smokers

Sex differences exist in the reinforcing effects of nicotine, smoking cessation rates, and response to nicotine therapies. Sex differences in availability of nicotinic acetylcholine receptors containing the $\beta(2)$ subunit ($\beta(2)^*$ -nAChRs) may underlie differential nicotine and tobacco smoking effects and related behaviors in women vs men. To examine $\beta(2)^*$ -nAChR availability in male and female smokers vs nonsmokers and to determine associations among $\beta(2)^*$ -nAChR availability, tobacco smoking characteristics, and female sex steroid hormone levels. Male (n = 26) and female (n = 28) tobacco smokers participated in an iodide 123-labeled 5-iodo-A-85380 ([¹²³I]5-IA) single-photon emission computed tomography (SPECT) imaging session at 7 to 9 days of abstinence. Age-matched male (n = 26) and female (n = 30) nonsmokers participated in a [¹²³I]5-IA SPECT imaging session. All participants completed a magnetic resonance imaging study at an academic imaging center. Tobacco smokers (n = 54) and age- and sex-matched nonsmokers (n = 56). The [¹²³I]5-IA SPECT images were converted to equilibrium distribution volumes and were analyzed using regions of interest. The $\beta(2)^*$ -nAChR availability was significantly higher in male smokers compared with male nonsmokers in striatum, cortex, and cerebellum, but female smokers did not have higher $\beta(2)^*$ -nAChR availability than female nonsmokers in any region. In women, $\beta(2)^*$ -nAChR availability in the cortex and cerebellum was negatively and significantly correlated with progesterone level on the SPECT imaging day. In female smokers on imaging day, the progesterone level was positively and significantly correlated with depressive symptoms, craving for a cigarette, and nicotine withdrawal. The regulatory effects of nicotine in the brain (ie, tobacco smoking-induced upregulation of $\beta(2)^*$ -nAChRs) seem to be distinctly different between men and women, and female sex steroid hormones likely have a role in this regulation. These findings suggest an underlying neurochemical mechanism for the reported

behavioral sex differences. To treat female smokers more effectively, it is critical that nonnicotinic-mediated medications should be explored. Cosgrove KP, Esterlis I, McKee SA, Bois F, Seibyl JP, Mazure CM, Krishnan-Sarin S, Staley JK, Picciotto MR, O'Malley SS. Sex differences in availability of $\beta 2^*$ -nicotinic acetylcholine receptors in recently abstinent tobacco smokers. *Arch Gen Psychiatry*. 2012 Apr; 69(4): 418-427.

Sex, ADHD Symptoms, and Smoking Outcomes: An Integrative Model Both females and individuals with Attention-Deficit/Hyperactivity Disorder (ADHD) have been found to be at increased risk for a range of smoking outcomes, and recent empirical findings have suggested that women with ADHD may be particularly vulnerable to nicotine dependence. On a neurobiological level, the dopamine reward processing system may be implicated in the potentially unique interaction of nicotine with sex and with ADHD status. Specifically, nicotine appears to mitigate core ADHD symptoms through interaction with the dopamine reward processing system, and ovarian hormones have been found to interact with nicotine within the dopamine reward processing system to affect neurotransmitter release and functioning. This article synthesizes data from research examining smoking in women and in individuals with ADHD to build an integrative model through which unique risk for cigarette smoking in women with ADHD can be systematically explored. Based upon this model, the following hypotheses are proposed at the intersection of each of the three variables of sex, ADHD, and smoking: (1) individuals with ADHD have altered functioning of the dopamine reward system, which diminishes their ability to efficiently form conditioned associations based on environmental contingencies; these deficits are partially ameliorated by nicotine; (2) nicotine interacts with estrogen and the dopamine reward system to increase the positive and negative reinforcement value of smoking in female smokers; (3) in adult females with ADHD, ovarian hormones interact with the dopamine reward system to exacerbate ADHD-related deficits in the capacity to form conditioned associations; and (4) during different phases of the menstrual cycle, nicotine and ovarian hormones may interact differentially with the dopamine reward processing system to affect the type and value of reinforcement smoking provides for women with ADHD. Understanding the bio-behavioral mechanisms underlying cigarette addiction in specific populations will be critical to developing effectively tailored smoking prevention and cessation programs for these groups. Overall, the goal of this paper is to examine the interaction of sex, smoking, and ADHD status within the context of the dopamine reward processing system not only to elucidate potential mechanisms specific to female smokers with ADHD, but also to stimulate consideration of how the examination of such individual differences can inform our understanding of smoking more broadly. Van Voorhees EE, Mitchell JT, McClernon FJ, Beckham JC, Kollins SH. Sex, ADHD symptoms, and smoking outcomes: An integrative model. *Med Hypotheses*. 2012 May; 78(5): 585-593.

Varenicline Potentiates Alcohol-Induced Negative Subjective Responses and Offsets Impaired Eye Movements Varenicline (VAR) is a partial nicotinic receptor agonist that is an effective smoking cessation medication. Preliminary evidence indicates that it may also reduce alcohol consumption, but the underlying mechanism is not clear. For example, VAR may reduce alcohol consumption by attenuating its subjectively rewarding properties or by enhancing its aversive effects. In this study, the authors examined the effects of an acute dose of VAR upon subjective, physiological, and objective responses to low and moderate doses of alcohol in healthy social drinkers. Healthy men and women (N = 15) participated in 6 randomized sessions; 3 sessions each with 2 mg VAR and placebo (PL) followed 3 hours later by a beverage containing PL, low-dose alcohol (0.4 g/kg), or high-dose alcohol (0.8 g/kg). Subjective mood and drug effects (i.e., stimulation, drug liking), physiological measures (heart rate, blood pressure), and eye tracking tasks

were administered at various intervals before and after drug and alcohol administration. VAR acutely increased blood pressure, heart rate, ratings of dysphoria and nausea, and also improved eye tracking performance. After alcohol drinking (vs. PL), VAR increased dysphoria and tended to reduce alcohol liking ratings. It also attenuated alcohol-induced eye-tracking impairments. These effects were independent of the drug's effects on nausea before drinking. These data support the theory that VAR may reduce drinking by potentiating aversive effects of alcohol. VAR also offsets alcohol-induced eye movement impairment. The evidence suggests that VAR may decrease alcohol consumption by producing effects, which oppose the rewarding efficacy of alcohol. Childs E, Roche DJ, King AC, de Wit H. Varenicline potentiates alcohol-induced negative subjective responses and offsets impaired eye movements. *Alcohol Clin Exp Res.* 2012 May; 36(5): 906-914.

Patients with Fibromyalgia Display Less Functional Connectivity in the Brain's Pain

Inhibitory Network There is evidence for augmented processing of pain and impaired endogenous pain inhibition in Fibromyalgia syndrome (FM). In order to fully understand the mechanisms involved in FM pathology, there is a need for closer investigation of endogenous pain modulation. In the present study, the authors compared the functional connectivity of the descending pain inhibitory network in age-matched FM patients and healthy controls (HC). They performed functional magnetic resonance imaging (fMRI) in 42 subjects; 14 healthy and 28 age-matched FM patients (2 patients per HC), during randomly presented, subjectively calibrated pressure pain stimuli. A seed-based functional connectivity analysis of brain activity was performed. The seed coordinates were based on the findings from our previous study, comparing the fMRI signal during calibrated pressure pain in FM and HC: the rostral anterior cingulate cortex (rACC) and thalamus. FM patients required significantly less pressure (kPa) to reach calibrated pain at 50 mm on a 0-100 visual analogue scale ($p < .001$, two-tailed). During fMRI scanning, the rACC displayed significantly higher connectivity to the amygdala, hippocampus, and brainstem in healthy controls, compared to FM patients. There were no regions where FM patients showed higher rACC connectivity. Thalamus showed significantly higher connectivity to the orbitofrontal cortex in healthy controls but no regions showed higher thalamic connectivity in FM patients. Patients with FM displayed less connectivity within the brain's pain inhibitory network during calibrated pressure pain, compared to healthy controls. The present study provides brain-imaging evidence on how brain regions involved in homeostatic control of pain are less connected in FM patients. It is possible that the dysfunction of the descending pain modulatory network plays an important role in maintenance of FM pain and our results may translate into clinical implications by using the functional connectivity of the pain modulatory network as an objective measure of pain dysregulation. Jensen KB, Loitole R, Kosek E, Petzke F, Carville S, Fransson P, Marcus H, Williams SC, Choy E, Mainguy Y, Vitton O, Gracely RH, Gollub R, Ingvar M, Kong J. Patients with fibromyalgia display less functional connectivity in the brain's pain inhibitory network. *Mol Pain.* 2012 Apr 26; 8(1): 32.

Dopaminergic Mechanisms of Individual Differences in Human Effort-Based Decision-

Making Preferences for different combinations of costs and benefits are a key source of variability in economic decision-making. However, the neurochemical basis of individual differences in these preferences is poorly understood. Studies in both animals and humans have demonstrated that direct manipulation of the neurotransmitter dopamine (DA) significantly impacts cost/benefit decision-making, but less is known about how naturally occurring variation in DA systems may relate to individual differences in economic behavior. In the present study, 25 healthy volunteers completed a dual-scan PET imaging protocol with [(18)F]fallypride and d-amphetamine to measure DA responsivity and separately completed the effort expenditure for rewards task, a behavioral measure of cost/benefit decision-making in humans. The authors found that individual differences in DA

function in the left striatum and ventromedial prefrontal cortex were correlated with a willingness to expend greater effort for larger rewards, particularly when probability of reward receipt was low. Additionally, variability in DA responses in the bilateral insula was negatively correlated with willingness to expend effort for rewards, consistent with evidence implicating this region in the processing of response costs. These findings highlight the role of DA signaling in striatal, prefrontal, and insular regions as key neurochemical mechanisms underlying individual differences in cost/benefit decision-making. Treadway MT, Buckholtz JW, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Kessler RM, Zald DH. Dopaminergic mechanisms of individual differences in human effort-based decision-making. *J. Neurosci.* 2012 May; 32(18): 6170–6176.

Dose-Related Modulation of Event-Related Potentials to Novel and Target Stimuli by Intravenous Δ^9 -THC In Humans

Cannabinoids induce a host of perceptual alterations and cognitive deficits in humans. However, the neural correlates of these deficits have remained elusive. The current study examined the acute, dose-related effects of delta-9-tetrahydrocannabinol (Δ^9 -THC) on psychophysiological indices of information processing in humans. Healthy subjects (n=26) completed three test days during which they received intravenous Δ^9 -THC (placebo, 0.015 and 0.03 mg/kg) in a within-subject, double-blind, randomized, cross-over, and counterbalanced design. Psychophysiological data (electroencephalography) were collected before and after drug administration while subjects engaged in an event-related potential (ERP) task known to be a valid index of attention and cognition (a three-stimulus auditory “oddball” P300 task). Δ^9 -THC dose-dependently reduced the amplitude of both the target P300b and the novelty P300a. Δ^9 -THC did not have any effect on the latency of either the P300a or P300b, or on early sensory-evoked ERP components preceding the P300 (the N100). Concomitantly, Δ^9 -THC induced psychotomimetic effects, perceptual alterations, and subjective “high” in a dose-dependent manner. Δ^9 -THC-induced reductions in P3b amplitude correlated with Δ^9 -THC-induced perceptual alterations. Lastly, exploratory analyses examining cannabis use status showed that whereas recent cannabis users had blunted behavioral effects to Δ^9 -THC, there were no dose-related effects of Δ^9 -THC on P300a/b amplitude between cannabis-free and recent cannabis users. Overall, these data suggest that at doses that produce behavioral and subjective effects consistent with the known properties of cannabis, Δ^9 -THC reduced P300a and P300b amplitudes without altering the latency of these ERPs. Cannabinoid agonists may therefore disrupt cortical processes responsible for context updating and the automatic orientation of attention, while leaving processing speed and earlier sensory ERP components intact. Collectively, the findings suggest that CB1R systems modulate top-down and bottom-up processing. D’Souza DC, Fridberg DJ, Skosnik PD, Williams A, Roach B, Singh N, Carbuto M, Elander J, Schnakenberg A, Pittman B, Sewell RA, Ranganathan M, Mathalon D. Dose-related modulation of event-related potentials to novel and target stimuli by intravenous Δ^9 -THC in humans. *Neuropsychopharmacology.* 2012 Jun; 37(7): 1632–1646.

Anxiety Sensitivity, Emotional Avoidance, and PTSD Symptom Severity among Crack/Cocaine Dependent Patients in Residential Treatment

High rates of co-occurring posttraumatic stress disorder (PTSD) have been found among patients receiving treatment for substance use disorders (SUD), and there is evidence that this particular co-occurrence is associated with negative SUD treatment outcomes. Thus, there is utility in establishing the role of psychological vulnerabilities related to PTSD within SUD populations, with the goal of ultimately informing targeted interventions and improving clinical outcomes. Anxiety sensitivity (AS) and emotional avoidance (EA) may be two important factors in this regard, as both have been found to demonstrate associations with posttraumatic stress in other clinical and nonclinical populations. To

expand upon this literature, the current study examined the associations between AS and EA and PTSD symptom severity in a sample of traumatic event-exposed crack/cocaine dependent patients in residential SUD treatment (n = 62), as well as the extent to which EA mediated the relation between AS and PTSD symptom severity. As hypothesized, AS and EA were associated with PTSD symptom severity above and beyond the effects of gender and non-specific anxiety symptoms. However, the hypothesis that EA would mediate the relation between AS and PTSD symptom severity was only partially supported. Implications of these findings for understanding and treating co-occurring SUD-PTSD are discussed. Naifeh JA, Tull MT, Gratz KL. Anxiety sensitivity, emotional avoidance, and PTSD symptom severity among crack/cocaine dependent patients in residential treatment. *Cognitive Therapy and Research*. 2012 Jun;36(3): 247–257.

Modulation of Inhibition of Return by the Dopamine D2 Receptor Agonist Bromocriptine

Depends on Individual DAT1 Genotype Involuntary visual spatial attention is captured when a salient cue appears in the visual field. If a target appears soon after the cue, response times to targets at the cue location are faster relative to other locations. However, after longer cue-target intervals, responses to targets at the cue location are slower, due to inhibition of return (IOR). IOR depends on striatal dopamine (DA) levels: It varies with different alleles of the DA transporter gene DAT1 and is reduced in patients with Parkinson's disease, a disease characterized by reduced striatal dopaminergic transmission. The authors examined the role of DA in involuntary attention and IOR by administering the DA D2 receptor-specific agonist bromocriptine to healthy human subjects. There was no effect of either DAT1 genotype or bromocriptine on involuntary attention, but participants with DAT1 alleles predicting higher striatal DA had a larger IOR. Furthermore, bromocriptine increased the magnitude of IOR in participants with low striatal DA but abolished the IOR in subjects with high striatal DA. This inverted U-shaped pattern resembles previously described relationships between DA levels and performance on cognitive tasks and suggests an involvement of striatal DA in IOR that does not include a role in involuntary attention. Rokem A, Landau AN, Prinzmetal W, Wallace DL, Silver MA, D'Esposito M. Modulation of inhibition of return by the dopamine D2 receptor agonist bromocriptine depends on individual DAT1 genotype. *Cereb. Cortex* 2012 May; 22(5): 1133–1138.

Information Content and Reward Processing in the Human Striatum During Performance of a Declarative Memory Task

Negative feedback can signal poor performance, but it also provides information that can help learners reach the goal of task mastery. The primary aim of this study was to test the hypothesis that the amount of information provided by negative feedback during a paired-associate learning task influences feedback-related processing in the caudate nucleus. To do this, the authors manipulated the number of response options: With two options, positive and negative feedback provide equal amounts of information, whereas with four options, positive feedback provides more information than does negative feedback. The authors found that positive and negative feedback activated the caudate similarly when there were two response options. With four options, the caudate's response to negative feedback was reduced. A secondary goal was to investigate the link between brain-based measures of feedback-related processing and behavioral indices of learning. Analysis of the posttest measures showed that trials with positive feedback were associated with higher posttest confidence ratings. Additionally, when positive feedback was delivered, caudate activity was greater for trials with high than with low posttest confidence. This experiment demonstrated the context sensitivity of feedback processing and provided evidence that feedback processing in the striatum can contribute to the strengthening of the representations available within declarative memory. Tricomi E, Fiez JA. Information content and reward

processing in the human striatum during performance of a declarative memory task. *Cogn Affect Behav Neurosci.* 2012 Jun; 12(2): 361–372.

Sustained Recreational Use of Ecstasy is Associated with Altered Pre and Postsynaptic Markers of Serotonin Transmission in Neocortical Areas: A PET Study With [¹¹C]DASB and [¹¹C]MDL 100907

3,4-Methylenedioxymethamphetamine (MDMA), the main psychoactive component of the recreational drug ecstasy, is a potent serotonin (5-HT) releaser. In animals, MDMA induces 5-HT depletion and toxicity in 5-HT neurons. The aim of this study was to investigate both presynaptic (5-HT transporter, SERT) and postsynaptic (5-HT(2A) receptor) markers of 5-HT transmission in recently abstinent chronic MDMA users compared with matched healthy controls. The authors hypothesized that MDMA use is associated with lower SERT density and concomitant upregulation of 5-HT(2A) receptors. Positron emission tomography studies using the SERT ligand [¹¹C]DASB and the 5-HT(2A) receptor ligand [¹¹C]MDL 100907 were evaluated in 13 current and recently detoxified MDMA users and 13 matched healthy controls. MDMA users reported a mean duration of ecstasy use of 8 years, regular exposure, and at least 2 weeks of abstinence before the scans. SERT and 5-HT(2A) receptor availability (binding potential, BP(ND)) were analyzed with a two-tissue compartment model with arterial input function. Current recreational MDMA use was significantly associated with lower SERT BP(ND) and higher 5-HT(2A) receptor BP(ND) in cortical, but not subcortical regions. Decreased SERT BP(ND) was regionally associated with upregulated 5-HT(2A) receptor BP(ND). In light of the animal literature, the most parsimonious interpretation is that repeated exposure to MDMA in humans, even in moderate amounts, leads to damage in 5-HT neuron terminals innervating the cortex. Alterations in mood, cognition, and impulse control associated with these changes might contribute to sustain MDMA use. The reversibility of these changes upon abstinence remains to be firmly established. Urban NB, Girgis RR, Talbot PS, Kegeles LS, Xu X, Frankle WG, Hart CL, Slifstein M, Abi-Dargham A, Laruelle M. Sustained recreational use of ecstasy is associated with altered pre and postsynaptic markers of serotonin transmission in neocortical areas: a PET study with [¹¹C]DASB and [¹¹C]MDL 100907. *Neuropsychopharmacology.* 2012 May; 37(6): 1465–1473.

Dissociable Influences of Opiates and Expectations on Pain Placebo treatments and opiate drugs are thought to have common effects on the opioid system and pain-related brain processes. This has created excitement about the potential for expectations to modulate drug effects themselves. If drug effects differ as a function of belief, this would challenge the assumptions underlying the standard clinical trial. The authors conducted two studies to directly examine the relationship between expectations and opioid analgesia. They administered the opioid agonist remifentanyl to human subjects during experimental thermal pain and manipulated participants' knowledge of drug delivery using an open-hidden design. This allowed us to test drug effects, expectancy (knowledge) effects, and their interactions on pain reports and pain-related responses in the brain. Remifentanyl and expectancy both reduced pain, but drug effects on pain reports and fMRI activity did not interact with expectancy. Regions associated with pain processing showed drug-induced modulation during both Open and Hidden conditions, with no differences in drug effects as a function of expectation. Instead, expectancy modulated activity in frontal cortex, with a separable time course from drug effects. These findings reveal that opiates and placebo treatments both influence clinically relevant outcomes and operate without mutual interference. Atlas LY, Whittington RA, Lindquist MA, Wielgosz J, Sonty N, Wager TD. Dissociable influences of opiates and expectations on pain. *J Neurosci.* 2012 Jun 6; 32(23): 8053-8064.

The Neuroeconomics of Nicotine Dependence: A fMRI Study of Delay Discounting of Monetary and Cigarette Rewards in Smokers

Neuroeconomics integrates behavioral economics and cognitive neuroscience to understand the neurobiological basis for normative and maladaptive decision making. Delay discounting is a behavioral economic index of impulsivity that reflects capacity to delay gratification and has been consistently associated with nicotine dependence. This preliminary study used functional magnetic resonance imaging to examine delay discounting for money and cigarette rewards in 13 nicotine dependent adults. Significant differences between preferences for smaller immediate rewards and larger delayed rewards were evident in a number of regions of interest (ROIs), including the medial prefrontal cortex, anterior insular cortex, middle temporal gyrus, middle frontal gyrus, and cingulate gyrus. Significant differences between money and cigarette rewards were generally lateralized, with cigarette choices associated with left hemisphere activation and money choices associated with right hemisphere activation. Specific ROI differences included the posterior parietal cortex, medial and middle frontal gyrus, ventral striatum, temporoparietal cortex, and angular gyrus. Impulsivity as measured by behavioral choices was significantly associated with both individual ROIs and a combined ROI model. These findings provide initial evidence in support of applying a neuroeconomic approach to understanding nicotine dependence. Mackillop J, Amlung MT, Wier LM, David SP, Ray LA, Bickel WK, Sweet LH. The neuroeconomics of nicotine dependence: A preliminary functional magnetic resonance imaging study of delay discounting of monetary and cigarette rewards in smokers. *Psychiatry Res.* 2012 Apr 30; 202(1): 20-29.

Functional Interactions of HIV-Infection and Methamphetamine Dependence During Motor Programming

Methamphetamine (METH) dependence is frequently comorbid with HIV infection and both have been linked to alterations of brain structure and function. In a previous study, the authors showed that the brain volume loss characteristic of HIV infection contrasts with METH-related volume increases in striatum and parietal cortex, suggesting distinct neurobiological responses to HIV and METH (Jernigan et al., 2005). Functional magnetic resonance imaging (fMRI) has the potential to reveal functional interactions between the effects of HIV and METH. In the present study, 50 participants were studied in four groups: an HIV+ group, a recently METH-dependent group, a dually affected group, and a group of unaffected community comparison subjects. An fMRI paradigm consisting of motor sequencing tasks of varying levels of complexity was administered to examine blood oxygenation level dependent (BOLD) changes. Within all groups, activity increased significantly with increasing task complexity in large clusters within sensorimotor and parietal cortex, basal ganglia, cerebellum, and cingulate. The task complexity effect was regressed on HIV status, METH status, and the HIV×METH interaction term in a simultaneous multiple regression. HIV was associated with less complexity-related activation in striatum, whereas METH was associated with less complexity-related activation in parietal regions. Significant interaction effects were observed in both cortical and subcortical regions; and, contrary to expectations, the complexity-related activation was less aberrant in dually affected than in single risk participants, in spite of comparable levels of neurocognitive impairment among the clinical groups. Thus, HIV and METH dependence, perhaps through their effects on dopaminergic systems, may have opposing functional effects on neural circuits involved in motor programming. Archibald SL, Jacobson MW, Fennema-Notestine C, Ogasawara M, Woods SP, Letendre S, Grant I, Jernigan TL. Functional interactions of HIV-infection and methamphetamine dependence during motor programming. *Psychiatry Res.* 2012 Apr 30; 202(1): 46-52.

EPIDEMIOLOGY RESEARCH

Co-Ingestion Of Prescription Opioids and Other Drugs Among High School Seniors: Results From A National Study

The objective of this study was to determine the past-year prevalence rates and behavioral correlates of co-ingestion of prescription opioids and other drugs among high school seniors in the United States. Nationally representative probability samples of high school seniors in the United States were surveyed as a part of the Monitoring the Future (MTF) study. Data were collected in schools via self-administered paper-and-pencil questionnaires during the spring of each cohort's senior year. The sample consisted of five cohorts (senior years of 2002-2006) made up of 12,441 high school seniors (modal age 18), of which 53% were women. The estimated prevalence of any past-year co-ingestion of prescription opioids and other drugs for these cohorts was 4.4%, and 69.8% among nonmedical users of prescription opioids. The substances most commonly co-ingested with prescription opioids included marijuana (58.5%), alcohol (52.1%), cocaine (10.6%), tranquilizers (10.3%), and amphetamines (9.5%). Nonmedical users who co-ingested prescription opioids with other drugs were more likely to report intranasal administration, recreational motives, oxycodone use, and greater subjective high when using prescription opioids than nonmedical users who did not co-ingest prescription opioids and other drugs. Nearly 7 out of every 10 nonmedical users of prescription opioids reported co-ingestion of prescription opioids and other drugs in the past year. The findings indicate that the co-ingestion of prescription opioids and other drugs by high school seniors in the United States serves as a marker for substance abuse and represents a significant public health concern. McCabe S, West B, Teter C, Boyd C. Co-ingestion of prescription opioids and other drugs among high school seniors: Results from a national study. *Drug Alcohol Depend.* 2012.

Adolescent Nonmedical Users Of Prescription Opioids: Brief Screening and Substance Use Disorders

The objectives of this study are to examine the associations among a positive score on the CRAFFT (a substance use brief screening test for adolescents) and demographic characteristics, diversion sources, routes of administration, substance use behaviors and motivations associated with the use of prescription opioids without a legal prescription. In 2009-2010, a sample of 2,744 middle and high school students from two Midwestern school districts in the United States self-administered a Web-based survey. Approximately 5.6% (n=148) of respondents reported past-year nonmedical use of prescription opioids (NMUPO). Of those reporting NMUPO, approximately 35.1% (n=52) screened positive for substance use disorders based on the CRAFFT. Multiple logistic regression analyses indicated that the odds of buying prescription opioids, obtaining opioids from multiple diversion sources, administering opioids intranasally, and using opioids to get high were greater for nonmedical users with a positive CRAFFT screen as compared to NMUPO with a negative CRAFFT screen. NMUPO with a positive screen was motivated primarily for recreational purposes, while NMUPO with a negative screen was motivated almost exclusively by pain relief. The CRAFFT brief screening test for adolescents can be used to identify a subgroup of NMUPO at the highest risk for a substance use disorder as well as a subgroup of NMUPO who would benefit from appropriate pain management. McCabe S, West B, Teter C, Cranford J, Ross-Durow P, Boyd C. Adolescent nonmedical users of prescription opioids: brief screening and substance use disorders. *Addict Behav.* 2012; 37 (5): 651-656.

Nonmedical Use Of Prescription Stimulants During College: Four-Year Trends In Exposure Opportunity, Use, Motives, and Sources

The objective of this study was to examine trends in nonmedical use of prescription stimulants (NPS), including motives, routes of administration, sources, cost, and risk factors. Participants were 1,253 college students. Data were collected

annually during academic years 2004-2005 through 2008-2009. Generalized estimating equations analyses evaluated longitudinal trends. Logistic regression models evaluated stability of associations between risk factors and NPS over time. Almost two-thirds (61.8% (wt)) were offered prescription stimulants for nonmedical use by Year 4, and 31.0% (wt) used. Studying was the predominant motive (73.8% to 91.5% annually), intranasal administration was modest (< 17% annually), and the most common source was a friend with a prescription (e 73.9% annually). Significant changes over time included decreasing curiosity motives, increasing overuse of one's own prescription, and increasing proportion paying \$5+ per pill. Lower grade point average and alcohol/cannabis use disorders were consistently associated with NPS, holding constant other factors. Prevention opportunities exist for parents, physicians, and college administrators to reduce NPS. Garnier-Dykstra L, Caldeira K, Vincent K, O'Grady K, Arria A. Nonmedical use of prescription stimulants during college: Four-year trends in exposure opportunity, use, motives, and sources. *J Am Coll Health*. 2012; 60 (3): 226-234.

Young Age Predicts Poor Antiretroviral Adherence and Viral Load Suppression Among Injection Drug Users

Previous studies of adherence to antiretroviral therapy (ART) for HIV among young injection drug users (IDU) have been limited because financial barriers to care disproportionately affect youth, thus confounding results. This study examines adherence among IDU in a unique setting where all medical care is provided free-of-charge. From May 1996 to April 2008, we followed a prospective cohort of 545 HIV-positive IDU of 18 years of age or older in Vancouver, Canada. Using generalized estimating equations (GEE), we studied the association between age and adherence (obtaining ARTe95% of the prescribed time), controlling for potential confounders. Using Cox proportional hazards regression, the authors also studied the effect of age on time to viral load suppression (<500 copies per milliliter), and examined adherence as a mediating variable. Five hundred forty-five participants were followed for a median of 23.8 months (interquartile range [IQR]=8.5-91.6 months). Odds of adherence were significantly lower among younger IDU (adjusted odds ratio [AOR]=0.76 per 10 years younger; 95% confidence interval [CI], 0.65-0.89). Younger IDU were also less likely to achieve viral load suppression (adjusted hazard ratio [AHR]=0.75 per 10 years younger; 95% CI, 0.64-0.88). Adding adherence to the model eliminated this association with age, supporting the role of adherence as a mediating variable. Despite absence of financial barriers, younger IDU remain less likely to adhere to ART, resulting in inferior viral load suppression. Interventions should carefully address the unique needs of young HIV-positive IDU. Hadland S, Milloy M, Kerr T, Zhang R, Guillemi S, Hogg R, Montaner J, Wood E. Young age predicts poor antiretroviral adherence and viral load suppression among injection drug users. *AIDS Patient Care STDS*. 2012; 26 (5): 274-280.

Marijuana Use Trajectories During The Post-College Transition: Health Outcomes In Young Adulthood

Despite the relatively high prevalence of marijuana use among college students, little information exists regarding health outcomes associated with different use patterns or trajectories. Seven annual personal interviews (Years 1-7) were administered to 1253 individuals, beginning in their first year in college. Growth mixture modeling was used to identify trajectories of marijuana, alcohol, and tobacco use frequency during Years 1-6. Logistic regression was used to evaluate the relationship between marijuana use trajectories and several Year 7 health outcomes, holding constant Year 1 health, demographics, and alcohol and tobacco use trajectories. Six marijuana use trajectories were identified: Non-Use (71.5%(wt) of students), Low-Stable (10.0%(wt)), Late-Increase (4.7%(wt)), Early-Decline (4.3%(wt)), College-Peak (5.4%(wt)), and Chronic (4.2%(wt)). The six marijuana trajectory groups were not significantly different on Year 1 health-related variables, but differed on all ten Year 7 health outcomes tested, including functional impairment

due to injury, illness, or emotional problems; general health rating; psychiatric symptoms; health-related quality of life; and service utilization for physical and mental health problems. Non-Users fared significantly better than most of the marijuana-using trajectory groups on every outcome tested. Chronic and Late-Increase users had the worst health outcomes. Marijuana use patterns change considerably during college and the post-college period. Marijuana-using students appear to be at risk for adverse health outcomes, especially if they increase or sustain a frequent pattern of use. Caldeira K, O'Grady K, Vincent K, Arria A. Marijuana use trajectories during the post-college transition: Health outcomes in young adulthood. *Drug Alcohol Depend.* 2012.

Physician Experience and Rates Of Plasma HIV-1 RNA Suppression Among Illicit Drug Users: An Observational Study

Despite the availability of antiretroviral therapy (ART), suboptimal treatment outcomes have been observed among HIV-seropositive illicit drug users. As there is an urgent need to improve responses to antiretroviral therapy among this population, the authors undertook this study to evaluate the role of physician experience on rates of plasma HIV-1 RNA suppression following initiation of ART. Using data from a community-recruited cohort of HIV-positive illicit drug users, the authors used Cox proportional hazards regression to model the time to plasma viral HIV RNA < 500 copies/mL among antiretroviral-naïve subjects initiating ART. Physician experience was defined as a continuous variable measured per 100 HIV-infected patients previously enrolled in the province-wide HIV treatment registry by that physician at the time a patient was enrolled. Between May 1996 and December 2008, 267 individuals initiated ART among whom 227 (85%) achieved a plasma HIV RNA < 500 copies/mL during the study period. In a multivariate analysis, greater physician experience was independently associated with higher rates of plasma HIV RNA suppression (adjusted hazard ratio [AHR] = 1.17, 95% confidence interval [CI]: 1.03-1.34) after adjustment for adherence to ART. Other factors associated with viral suppression included engagement in methadone maintenance therapy (AHR = 1.61, 95% CI: 1.23-2.09), e 95% adherence to ART (AHR = 2.42, 95% CI: 1.80-3.26), baseline CD4 count (AHR = 0.89, 95% CI: 0.83-0.96) and baseline plasma HIV-1 RNA (AHR = 0.65, 95% CI: 0.53-0.81). In this setting of universal HIV/AIDS care, illicit drug users with more experienced physicians exhibited faster rates of plasma viral load suppression. These findings argue for specialized services to help optimize HIV treatment outcomes among this population. Sangsari S, Milloy M, Ibrahim A, Kerr T, Zhang R, Montaner J, Wood E. Physician experience and rates of plasma HIV-1 RNA suppression among illicit drug users: An observational study. *BMC Infect Dis.* 2012; 12: 22-28.

Transitions From Injection-Drug-Use-Concentrated To Self-Sustaining Heterosexual HIV Epidemics: Patterns In The International Data

Injecting drug use continues to be a primary driver of HIV epidemics in many parts of the world. Many people who inject drugs (PWID) are sexually active, so it is possible that high-seroprevalence HIV epidemics among PWID may initiate self-sustaining heterosexual transmission epidemics. Fourteen countries that had experienced high seroprevalence (<20%) HIV epidemics among PWID and had reliable data for injection drug use (IDU) and heterosexual cases of HIV or AIDS were identified. Graphs of newly reported HIV or AIDS cases among PWID and heterosexuals were constructed to identify temporal relationships between the two types of epidemics. The year in which newly reported cases among heterosexuals surpassed newly reported cases among PWID, aspects of the epidemic curves, and epidemic case histories were analyzed to assess whether it was "plausible" or "highly unlikely" that the HIV epidemic among PWID might have initiated the heterosexual epidemic in each country. Transitions have occurred in 11 of the 14 countries. Two types of temporal relationships between IDU and heterosexual HIV epidemics were identified, rapid high incidence transitions vs. delayed, low incidence transitions. In six countries it appears "plausible" that the IDU epidemic initiated a

heterosexual epidemic, and in five countries it appears "highly unlikely" that the IDU epidemic initiated a heterosexual epidemic. A rapid decline in incidence among PWID after the peak year of new cases and national income were the best predictors of the "highly unlikely" initiation of a heterosexual epidemic. Transitions from IDU concentrated epidemics to heterosexual epidemics are common in countries with high seroprevalence among PWID though there are distinct types of transitions. Interventions to immediately reduce HIV incidence among PWID may reduce the likelihood that an IDU epidemic may initiate a heterosexual epidemic. Des Jarlais D, Feelemyer J, Modi S, Arasteh K, Mathers B, Degenhardt L, Hagan H. Transitions from injection-drug-use-concentrated to self-sustaining heterosexual hiv epidemics: Patterns in the international data. *PLoS One*. 2012; 7(3): e31227-e31235.

Estimates of the Population Prevalence of Injection Drug Users among Hispanic Residents of Large US Metropolitan Areas

Little information exists on the population prevalence or geographic distribution of injection drug users (IDUs) who are Hispanic in the USA. Here, the authors present yearly estimates of IDU population prevalence among Hispanic residents of the 96 most populated US metropolitan statistical areas (MSAs) for 1992-2002. First, yearly estimates of the proportion of IDUs who were Hispanic in each MSA were created by combining data on (1) IDUs receiving drug treatment services in Substance Abuse and Mental Health Services Administration (SAMHSA)'s Treatment Entry Data System, (2) IDUs being tested in the Centers for Disease Control and Prevention (CDC) HIV-Counseling and Testing System, and (3) incident AIDS diagnoses among IDUs, supplemented by (4) data on IDUs who were living with AIDS. Then, the resulting proportions were multiplied by published yearly estimates of the number of IDUs of all racial/ethnic groups in each MSA to produce Hispanic IDU population estimates. These were divided by Hispanic population data to produce population prevalence rates. Time trends were tested using mixed-effects regression models. Hispanic IDU prevalence declined significantly on average (1992 mean = 192, median = 133; 2002 mean = 144, median = 93; units are per 10,000 Hispanics aged 15-64). The highest prevalence rates across time tended to be in smaller northeastern MSAs. Comparing the last three study years to the first three, prevalence decreased in 82% of MSAs and increased in 18%. Comparisons with data on drug-related mortality and hepatitis C mortality supported the validity of the estimates. Generally, estimates of Hispanic IDU population prevalence were higher than published estimates for non-Hispanic White residents and lower than published estimates for non-Hispanic Black residents. Further analysis indicated that the proportion of IDUs that was Hispanic decreased in 52% and increased in 48% of MSAs between 2002 and 2007. The estimates resulting from this study can be used to investigate MSA-level social and economic factors that may have contributed to variations across MSAs and to help guide prevention program planning for Hispanic IDUs within MSAs. Future research should attempt to determine to what extent these trends are applicable to Hispanic national origin subgroups. Pouget E, Friedman S, Cleland C, Tempalski B, Cooper H. Estimates of the population prevalence of injection drug users among Hispanic residents of large US metropolitan areas. *J Urban Health*. 2012; 1-38.

Parental Monitoring at Age 11 and Subsequent Onset of Cannabis Use up to Age 17: Results from a Prospective Study

Smoking cannabis before adulthood is associated with subsequent adverse psychiatric outcomes and might be prevented via parenting interventions such as programs to increase parents' effective monitoring of their children. The aim of this study was to estimate the influence of parental monitoring assessed at age 11 on the initiation of cannabis use before age 18. Data are from a longitudinal study of 823 children randomly selected from 1983 to 1985 newborn discharge lists from two major hospitals in southeast Michigan. Parental monitoring was assessed at age 11 via a standardized 10-item scale, and the parental monitoring-cannabis initiation relationship

was estimated for the 638 children with complete data. Poisson regression with robust error variances was used to estimate the association that links levels of parental monitoring at age 11 with the risk of cannabis use up to age 17, adjusting for other important covariates. Higher levels of parental monitoring at age 11 were associated with a reduced risk of cannabis initiation from ages 11 to 17 (adjusted estimated relative risk = 0.96; 95% CI [0.93, 0.98]). This prospective investigation found that higher levels of parental monitoring were associated with a reduced occurrence of cannabis initiation from ages 11 to 17 years. Consistent with evidence reported elsewhere, these findings from prospective research lend further support to theories about parenting and familial characteristics that might exert long-lasting influences on a child's risk of starting to use drugs. Bohnert K, Anthony J, Breslau N. Parental monitoring at age 11 and subsequent onset of cannabis use up to age 17: results from a prospective study. *J Stud Alcohol Drugs*. 2012; 73(2): 173-177.

Incidence and Risk Factors For Non-Fatal Overdose Among A Cohort Of Recently Incarcerated Illicit Drug Users

Release from prison is associated with a markedly increased risk of both fatal and non-fatal drug overdose, yet the risk factors for overdose in recently released prisoners are poorly understood. The aim of this study was to identify risk and protective factors for non-fatal overdose (NFOD) among a cohort of illicit drug users in Vancouver, Canada, according to recent incarceration. The study employed a prospective cohort of 2,515 community-recruited illicit drug users in Vancouver, Canada, followed from 1996 to 2010. The authors examined factors associated with NFOD in the past six months separately among those who did and did not also report incarceration in the last six months. One third of participants (n=829, 33.0%) reported at least one recent NFOD. Among those recently incarcerated, risk factors independently and positively associated with NFOD included daily use of heroin, benzodiazepines, cocaine or methamphetamine, binge drug use, public injecting and previous NFOD. Older age, methadone maintenance treatment and HIV seropositivity were protective against NFOD. A similar set of risk factors was identified among those who had not been incarcerated recently. Among this cohort, and irrespective of recent incarceration, NFOD was associated with a range of modifiable risk factors including more frequent and riskier patterns of drug use. Not all ex-prisoners are at equal risk of overdose and there remains an urgent need to develop and implement evidence-based preventive interventions, targeting those with modifiable risk factors in this high risk group. Kinner S, Milloy M, Wood E, Qi J, Zhang R, Kerr T. Incidence and risk factors for non-fatal overdose among a cohort of recently incarcerated illicit drug users. *Addict Behav*. 2012; 37(6): 691-696.

Temporal and Geographic Shifts In Urban and Non-urban Cocaine-Related Fatal Overdoses In British Columbia, Canada

Illicit drug overdose is a leading cause of premature mortality. The authors sought to examine fatal overdose trends from 2001 to 2005 in urban and nonurban areas of British Columbia, Canada. They conducted a review of all provincial coroner files in which drug overdose was the cause of death between January 1, 2001, and December 31, 2005. They compared cocaine and non-cocaine-related overdoses and examined temporal changes in cocaine-related mortality rates in urban and non-urban areas. Multilevel mixed effects models were used to determine the independent risk factors for cocaine-related death. Spatial analyses were conducted to identify clusters of these cases. During the study period, 904 illicit drug overdoses were recorded, including 369 (40.8%) in non-urban areas and 532 (58.9%) related to cocaine consumption. In a multilevel model, we observed a significant interaction (p = .010) between population density and year, indicating a considerable and differential increase in the likelihood of cocaine-related deaths in non-urban areas. Cocaine-related deaths were clustered in the southeast region of the province. Cocaine-related overdoses in non-urban areas should be a public health concern. Evidence-based

interventions to reduce the risks associated with cocaine consumption and reach drug users in nonurban settings are needed. Marshall B, Milloy M, Wood E, Galea S, Kerr T. Temporal and geographic shifts in urban and non-urban cocaine-related fatal overdoses in British Columbia, Canada. *Ann Epidemiol.* 2012; 22(3): 198-206.

Patterns Of Heroin and Cocaine Injection and Plasma HIV-1 RNA Suppression Among A Long-Term Cohort Of Injection Drug Users

Previous studies suggest that active drug use may compromise HIV treatment among HIV-positive injection drug users (IDU). However, little is known about the differential impacts of cocaine injection, heroin injection, and combined cocaine and heroin injection on plasma HIV-1 RNA suppression. Data were derived from a longstanding open prospective cohort of HIV-positive IDU in Vancouver, Canada. Kaplan-Meier methods and Cox proportional hazards regression were used to examine the impacts of different drug use patterns on rates of plasma HIV-1 RNA suppression. Between May 1996 and April 2008, 267 antiretroviral (ART) naïve participants were seen for a median follow-up duration of 50.6 months after initiating ART. The incidence density of HIV-1 RNA suppression was 65.2 (95%CI: 57.0-74.2) per 100 person-years. In Kaplan-Meier analyses, compared to those who abstained from injecting, individuals injecting heroin, cocaine, or combined heroin/cocaine at baseline were significantly less likely to achieve viral suppression (all $p < 0.01$). However, none of the drug use categories remained associated with a reduced rate of viral suppression when considered as time-updated variables (all $p > 0.05$). Active injecting at the time of ART initiation was associated with lower plasma HIV-1 RNA suppression rates; however, there was no difference in suppression rates when drug use patterns were examined over time. These findings imply that adherence interventions for active injectors should optimally be applied at the time of ART initiation. Kerr T, Marshall B, Milloy M, Zhang R, Guillemi S, Montaner J, Wood E. Patterns of heroin and cocaine injection and plasma HIV-1 RNA suppression among a long-term cohort of injection drug users. *Drug Alcohol Depend.* 2012; 1-5.

A Varying-Coefficient Method For Analyzing Longitudinal Clinical Trials Data With Nonignorable Dropout

Dropout is common in longitudinal clinical trials and when the probability of dropout depends on unobserved outcomes even after conditioning on available data, it is considered missing not at random and therefore nonignorable. To address this problem, mixture models can be used to account for the relationship between a longitudinal outcome and dropout. The authors propose a Natural Spline Varying-coefficient mixture model (NSV), which is a straightforward extension of the parametric Conditional Linear Model (CLM). They assume that the outcome follows a varying-coefficient model conditional on a continuous dropout distribution. Natural cubic B-splines are used to allow the regression coefficients to semiparametrically depend on dropout and inference is therefore more robust. Additionally, this method is computationally stable and relatively simple to implement. The authors conduct simulation studies to evaluate performance and compare methodologies in settings where the longitudinal trajectories are linear and dropout time is observed for all individuals. Performance is assessed under conditions where model assumptions are both met and violated. In addition, the authors compare the NSV to the CLM and a standard random-effects model using an HIV/AIDS clinical trial with probable nonignorable dropout. The simulation studies suggest that the NSV is an improvement over the CLM when dropout has a nonlinear dependence on the outcome. Forster JE, MaWhinney S, Ball EL, Fairclough D. A varying-coefficient method for analyzing longitudinal clinical trials data with nonignorable dropout. *Contemp Clin Trials.* 2012; 33(2): 378-385.

Evaluating Consistency in Repeat Surveys of Injection Drug Users Recruited by Respondent-Driven Sampling in the Seattle Area: Results from the NHBS-IDU1 and NHBS-IDU2 Surveys

The authors compared data from two respondent-driven sampling (RDS) surveys of Seattle-area injection drug users (IDU) to evaluate consistency in repeat RDS surveys. The RDS-adjusted estimates for 16 key sociodemographic, drug-related, sexual behavior, and HIV- and hepatitis C virus-related variables were compared in the 2005 and the 2009 National HIV Behavioral Surveillance system surveys (NHBS-IDU1 and NHBS-IDU2). Time trends that might influence the comparisons were assessed by the use of data from reported HIV cases in IDU, surveys of needle exchange users, and two previous IDU studies. NHBS-IDU2 participants were more likely than NHBS-IDU1 participants to report older age, heroin as their primary injection drug, male-to-male sex, unprotected sex with a partner of nonconcordant HIV status, and to self-report HIV-positive status. NHBS-IDU2 participants were less likely to report residence in downtown Seattle, amphetamine injection, and a recent HIV test. Time trends among Seattle-area IDU in age, male-to-male sex, and HIV testing could have influenced these differences. The number and magnitude of the estimated differences between the two RDS surveys appeared to describe materially different populations. This could be a result of changes in the characteristics of Seattle-area IDU over time, of accessing differing subpopulations of Seattle IDU, or of high variability in RDS measurements. Burt R, Thiede H. Evaluating consistency in repeat surveys of injection drug users recruited by respondent-driven sampling in the Seattle area: Results from the NHBS-IDU1 and NHBS-IDU2 Surveys. *Ann Epidemiol.* 2012; 1-10.

Association Between Obstructive Lung Disease and Markers Of HIV Infection In A High-Risk Cohort

Evidence suggests an association between HIV infection and the presence of obstructive lung disease (OLD). However, the associations between specific markers of HIV infection and OLD remain unclear. A study was undertaken to determine the independent associations of HIV infection, CD4 cell count and plasma HIV viral load with the presence of OLD in an urban cohort. Clinical, laboratory and spirometric data from the AIDS Linked to the Intravenous Experience (ALIVE) study, an observational study of current and former injection drug users in Baltimore, Maryland, were analyzed. Multivariable logistic regression models were generated to identify HIV infection indices independently associated with OLD. Of 1,077 participants (mean±SD age 48±8 years), 89% were African-American, 65% were men and 86% were current smokers. A total of 303 (28%) were HIV infected and 176 (16%) had spirometry-defined OLD. Higher viral load was independently associated with OLD. HIV-infected individuals with viral load >200,000 copies/ml had a 3.4-fold increase in the odds of OLD compared with HIV-negative participants (95% CI 1.24 to 9.39; p=0.02). The association between higher HIV viral load and OLD persisted after accounting for antiretroviral therapy use (OR 4.06, 95% CI 1.41 to 11.7; p=0.01). No association was observed between HIV serostatus or CD4 cell count and the presence of OLD. In a cohort at risk for OLD and HIV infection, high viral load but not CD4 cell count was associated with an increased prevalence of spirometry-defined OLD. These findings suggest that higher viral load may contribute mechanistically to the increased risk of OLD in patients with HIV infection. Drummond M, Kirk G, Astemborski J, Marshall M, Mehta S, McDyer J, Brown R, Wise R, Merlo C. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax.* 2012; 67(4): 309-314.

Risk of Anal Cancer In HIV-Infected and HIV-Uninfected Individuals in North America

Anal cancer is one of the most common cancers affecting individuals infected with human immunodeficiency virus (HIV), although few have evaluated rates separately for men who have sex with men (MSM), other men, and women. There are also conflicting data regarding calendar trends.

In a study involving 13 cohorts from North America with follow-up between 1996 and 2007, the authors compared anal cancer incidence rates among 34,189 HIV-infected (55% MSM, 19% other men, 26% women) and 114 260 HIV-uninfected individuals (90% men). Among men, the unadjusted anal cancer incidence rates per 100,000 person-years were 131 for HIV-infected MSM, 46 for other HIV-infected men, and 2 for HIV-uninfected men, corresponding to demographically adjusted rate ratios (RRs) of 80.3 (95% confidence interval [CI], 42.7-151.1) for HIV-infected MSM and 26.7 (95% CI, 11.5-61.7) for other HIV-infected men compared with HIV-uninfected men. HIV-infected women had an anal cancer rate of 30/100,000 person-years, and no cases were observed for HIV-uninfected women. In a multivariable Poisson regression model, among HIV-infected individuals, the risk was higher for MSM compared with other men (RR, 3.3; 95% CI, 1.8-6.0), but no difference was observed comparing women with other men (RR, 1.0; 95% CI, 0.5-2.2). In comparison with the period 2000-2003, HIV-infected individuals had an adjusted RR of 0.5 (95% CI, .3-.9) in 1996-1999 and 0.9 (95% CI, .6-1.2) in 2004-2007. Anal cancer rates were substantially higher for HIV-infected MSM, other men, and women compared with HIV-uninfected individuals, suggesting a need for universal prevention efforts. Rates increased after the early antiretroviral therapy era and then plateaued. Silverberg M, Lau B, Justice A, Engels E, Gill M, Goedert J, Kirk G, D'Souza G, Bosch R, Brooks J, Napravnik S, Hessol N, Jacobson L, Kitahata M, Klein M, Moore R, Rodriguez B, Rourke S, Saag M, Sterling T, Gebo K, Press N, Martin J, Dubrow R, Dubrow R. Risk of anal cancer in HIV-infected and HIV-uninfected individuals in North America. *Clin Infect Dis*. 2012; 54(7): 1026-1034.

Sexual, Behavioral, and Quality Of Life Characteristics Of Healthy Weight, Overweight, and Obese Gay and Bisexual Men: Findings From A Prospective Cohort Study

While there have been attempts to explore the association of obesity and risky sexual behaviors among gay men, findings have been conflicting. Using a prospective cohort of gay and bisexual men residing in Pittsburgh, the authors performed a semi-parametric, group-based analysis to identify distinct groups of trajectories in body mass index slopes over time from 1999 to 2007 and then correlated these trajectories with a number of psychosocial and behavioral factors, including sexual behaviors. They found many men were either overweight (41.2%) or obese (10.9%) in 1999 and remained stable at these levels over time, in contrast to recent increasing trends in the general population. Correlates of obesity in our study replicated findings from the general population. However, they found no significant association between obesity and sexual risk-taking behaviors, as suggested from several cross-sectional studies of gay men. While there was not a significant association between obesity and sexual risk-taking behaviors, they found high prevalence of overweight and obesity in this population. Gay and bisexual men's health researchers and practitioners need to look beyond HIV and STI prevention and also address a broader range of health concerns important to this population. Guadamuz T, Lim S, Marshal M, Friedman M, Stall R, Silvestre A. Sexual, behavioral, and quality of life characteristics of healthy weight, overweight, and obese gay and bisexual men: Findings from a prospective cohort study. *Arch Sex Behav*. 2012; 41(2): 385-389.

Social and Environmental Predictors Of Plasma HIV RNA Rebound Among Injection Drug Users Treated With Antiretroviral Therapy

Evidence is needed to improve HIV treatment outcomes for individuals who use injection drugs (IDU). Although studies have suggested higher rates of plasma viral load (PVL) rebound among IDU on antiretroviral therapy (ART), risk factors for rebound have not been thoroughly investigated. The authors used data from a long-running community-recruited prospective cohort of IDU in Vancouver, Canada, linked to comprehensive ART and clinical monitoring records. Using proportional hazards methods, they modeled the time to confirmed PVL rebound above 1000 copies per milliliter among IDU on ART with sustained

viral suppression, defined as 2 consecutive undetectable PVL measures. Between 1996 and 2009, 277 individuals had sustained viral suppression. Over a median follow-up of 32 months, 125 participants (45.1%) experienced at least 1 episode of virologic failure for an incidence of 12.6 [95% confidence interval (CI): 10.5 to 15.0] per 100 person-years. In a multivariate model, PVL rebound was independently associated with sex-trade involvement [adjusted hazard ratio (AHR) = 1.40, 95% CI: 1.08 to 1.82) and recent incarceration (AHR = 1.83, 95% CI: 1.33 to 2.52). Methadone maintenance therapy (AHR = 0.79, 95% CI: 0.66 to 0.94) was protective. No measure of illicit drug use was predictive. In this setting of free ART, several social and environmental factors predicted higher risks of viral rebound among IDU, including sex-trade involvement and incarceration. These findings should help inform efforts to identify individuals at risk of viral rebound and targeted interventions to treat and retain individuals in effective ART. Milloy M, Kerr T, Buxton J, Rhodes T, Krusi A, Guillemi S, Hogg R, Montaner J, Wood E. Social and environmental predictors of plasma HIV RNA rebound among injection drug users treated with antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012; 59(4): 393-399.

Longitudinal Associations Between Adolescent Alcohol Use and Adulthood Sexual Risk Behavior and Sexually Transmitted Infection In the United States: Assessment Of Differences By Race

The authors examined race differences in the longitudinal associations between adolescent alcohol use and adulthood sexually transmitted infection (STI) risk in the United States. They estimated multivariable logistic regression models using Waves I (1994-1995: adolescence) and III (2001-2002: young adulthood) of the National Longitudinal Study of Adolescent Health (n = 10,783) to estimate associations and assess differences between Whites and African Americans. In adjusted analyses, adolescent alcohol indicators predicted adulthood inconsistent condom use for both races but were significantly stronger, more consistent predictors of elevated partnership levels for African Americans than Whites. Among African Americans but not Whites, self-reported STI was predicted by adolescent report of any prior use (adjusted odds ratio [AOR] = 1.47; 95% confidence interval [CI] = 1.00, 2.17) and past-year history of getting drunk (AOR = 1.53; 95% CI = 1.01, 2.32). Among Whites but not African Americans, biologically confirmed STI was predicted by adolescent report of past-year history of getting drunk (AOR = 1.68; 95% CI = 1.07, 2.63) and consistent drinking (AOR = 1.65; 95% CI = 1.03, 2.65). African American and White adolescent drinkers are priority populations for STI prevention. Prevention of adolescent alcohol use may contribute to reductions in adulthood STI risk. Khan M, Berger A, Wells B, Cleland C. Longitudinal associations between adolescent alcohol use and adulthood sexual risk behavior and sexually transmitted infection in the United States: Assessment of differences by race. *Am J Public Health*. 2012; 102(5): 867-876.

Exploring the Ecological Association Between Crime and Medical Marijuana Dispensaries

Routine activities theory purports that crime occurs in places with a suitable target, motivated offender, and lack of guardianship. Medical marijuana dispensaries may be places that satisfy these conditions, but this has not yet been studied. The current study examined whether the density of medical marijuana dispensaries is associated with crime. An ecological, cross-sectional design was used to explore the spatial relationship between density of medical marijuana dispensaries and two types of crime rates (violent crime and property crime) in 95 census tracts in Sacramento, CA, during 2009. Spatial error regression methods were used to determine associations between crime rates and density of medical marijuana dispensaries, controlling for neighborhood characteristics associated with routine activities. Violent and property crime rates were positively associated with percentage of commercially zoned areas, percentage of one-person households, and unemployment rate. Higher violent crime rates were associated with concentrated disadvantage. Property crime

rates were positively associated with the percentage of population 15-24 years of age. Density of medical marijuana dispensaries was not associated with violent or property crime rates. Consistent with previous work, variables measuring routine activities at the ecological level were related to crime. There were no observed cross-sectional associations between the density of medical marijuana dispensaries and either violent or property crime rates in this study. These results suggest that the density of medical marijuana dispensaries may not be associated with crime rates or that other factors, such as measures dispensaries take to reduce crime (i.e., doormen, video cameras), may increase guardianship such that it deters possible motivated offenders. Kepple N, Freisthler B. Exploring the ecological association between crime and medical marijuana dispensaries. *J Stud Alcohol Drugs*. 2012; 73(4): 523-530.

Cigarette Smoking Among College Students: Longitudinal Trajectories and Health Outcomes

Light and intermittent patterns of cigarette smoking are prevalent among U.S. college-aged individuals. It is unclear whether intermittent smokers maintain their use over time or are transitioning to daily use or nonuse, and whether they experience more adverse health outcomes than nonsmokers. This study examined the trajectories of tobacco cigarette smoking, their predictors, and health outcomes among students (N = 1,253) assessed during their first year of college (Y(1)) and annually thereafter (Y(2), Y(3), and Y(4)). In Y(1), 3.4% smoked daily and 4.1% exhibited signs of dependence (first cigarette within 30 min of waking). Growth curve modeling identified five distinct smoking trajectories. After stable nonsmokers (71.5%(wt)), the low-stable smoking trajectory was the most common (13.3%(wt)), outnumbering both low-increasing (6.5%(wt)) and high-stable smokers (5.5%(wt)) by 2:1 and high-decreasing smokers (3.2%(wt)) by 4:1. The likelihood of maintaining a low level of smoking over time was inversely related to Y(1) smoking frequency. Few demographic, smoking, and alcohol use characteristics measured in Y(1) distinguished low-increasers from low-stable smokers or high-decreasers from high-stable smokers. By Y(4), high-stable smokers rated their health significantly worse than all others except low-increasers. High-stable smokers had the most Y(4) health problems (i.e., provider visits for health problems and days of illness-related impairment), but only among nonWhites. Many college students smoke, but few smoke daily or are nicotine dependent. Intermittent smoking patterns are often stable throughout college and are associated with adverse health outcomes. Prevention strategies should be designed to mitigate the possible long-term health consequences of light and intermittent smoking. Caldeira K, O'Grady K, Garnier-Dykstra L, Vincent K, Pickworth W, Arria A. Cigarette smoking among college students: Longitudinal trajectories and health outcomes. *Nicotine Tob Res*. 2012.

Medical and Nonmedical Use of Prescription Opioids Among High School Seniors in the United States

The objectives of this study were to determine the prevalence of medical and nonmedical use of prescription opioids among high school seniors in the United States and to assess substance use behaviors based on medical and nonmedical use of prescription opioids. Nationally representative samples of high school seniors (modal age 18 years) were surveyed during the spring of their senior year via self-administered questionnaires. Data were collected in public and private high schools. The sample consisted of 7,374 students from 3 independent cohorts (2007, 2008, and 2009). Outcome measures collected included self-reports of medical and nonmedical use of prescription opioids and other substance use. An estimated 17.6% of high school seniors reported lifetime medical use of prescription opioids, while 12.9% reported nonmedical use of prescription opioids. Sex differences in the medical and nonmedical use were minimal, while racial/ethnic differences were extensive. More than 37% of nonmedical users reported intranasal administration of prescription opioids. An estimated 80% of nonmedical users with an earlier history of medical

use had obtained prescription opioids from a prescription they had previously. The odds of substance use behaviors were greater among individuals who reported any history of nonmedical use of prescription opioids relative to those who reported medical use only. Nearly 1 in every 4 high school seniors in the United States has ever had some exposure to prescription opioids either medically or non-medically. The quantity of prescription opioids and number of refills prescribed to adolescents should be carefully considered and closely monitored to reduce subsequent nonmedical use of leftover medication. McCabe S, West B, Teter C, Boyd C. Medical and nonmedical use of prescription opioids among high school seniors in the United States. *Arch Pediatr Adolesc Med*. 2012.

Condom Use Trajectories in Adolescence and the Transition to Adulthood: The Role of Mother and Father Support

Few studies have investigated how mother and father support differ on predicting youths' sexual risk behavior. The authors therefore examined the influence of parental support on condom use trajectories and its correlates in a predominantly African American sample [(N=627; 53% female; M = 14.86 years (SD=. 64)] from adolescence to young adulthood. They used hierarchical growth curve modeling to examine the relationship between condom use, substance use, psychological distress and parental support prospectively. They found that consistent condom use decreased over time and was associated negatively with psychological distress and substance use. Furthermore, both maternal and paternal supports were associated with more condom use over time. The authors discuss the implications of their findings for HIV prevention programs. Pingel E, Bauermeister J, Elkington K, Fergus S, Caldwell C, Zimmerman M. Condom use trajectories in adolescence and the transition to adulthood: The role of mother and father support. *J Res Adolesc*. 2012; 22(2): 350-366.

Low Dead-Space Syringes For Preventing HIV Among People Who Inject Drugs: Promise and Barriers

This review examines evidence regarding the differential effects of high dead-space syringes (HDSS) and low dead-space syringes (LDSS) on HIV transmission among people who inject drugs (PWID). It also identifies areas for additional research and examines potential barriers to interventions that promote LDSS. Results of laboratory experiments and cross-sectional bio-behavioral surveys provide circumstantial evidence that the probability of HIV transmission associated with sharing LDSS is less than the probability of HIV transmission associated with sharing HDSS. Mathematical models suggest that LDSS may prevent injection-related HIV epidemics among PWID. Circumstantial evidence suggests that LDSS may substantially reduce HIV transmission among PWID, who share syringes. Additional research that links LDSS to reductions in HIV incidence is needed. Most currently available LDSS are 1 ml or smaller and have fixed needles. These cannot be used by PWID 'injecting' larger volumes of fluid and they may be rejected by PWID, who prefer syringes with detachable needles. Nonetheless, LDSS represent a potentially promising intervention that deserves serious consideration. Zule W. Low dead-space syringes for preventing hiv among people who inject drugs: Promise and barriers. *Curr Opin HIV AIDS*. 2012; 7(4): 369-375.

Double Jeopardy--Drug and Sex Risks Among Russian Women Who Inject Drugs: Initial Feasibility and Efficacy Results Of A Small Randomized Controlled Trial

With HIV prevalence estimated at 20% among female injecting drug users (IDUs) in St. Petersburg, Russia, there is a critical need to address the HIV risks of this at-risk population. This study characterized HIV risks associated with injecting drug use and sex behaviors and assessed the initial feasibility and efficacy of an adapted Woman-Focused intervention, the Women's CoOp, relative to a Nutrition control to reduce HIV risk behaviors among female IDUs in an inpatient detoxification drug

treatment setting. Women (N = 100) were randomized into one of two one-hour long intervention conditions--the Woman-Focused intervention (n = 51) or a time and attention-matched Nutrition control condition (n = 49). The results showed that 57% of the participants had been told that they were HIV-positive. At 3-month follow-up, both groups showed reduced levels of injecting frequency. However, participants in the Woman-Focused intervention reported, on average, a lower frequency of partner impairment at last sex act and a lower average number of unprotected vaginal sex acts with their main sex partner than the Nutrition condition. The findings suggest that improvements in sexual risk reduction are possible for these at-risk women and that more comprehensive treatment is needed to address HIV and drug risks in this vulnerable population. Wechsberg W, Krupitsky E, Romanova T, Zvartau E, Kline T, Browne F, Ellerson R, Bobashev G, Zule W, Jones H. Double jeopardy--drug and sex risks among Russian women who inject drugs: Initial feasibility and efficacy results of a small randomized controlled Trial. *Subst Abuse Treat Prev Policy*. 2012; 7: 1-1.

Resilience Among IDUs: Planning Strategies to Help Injection Drug Users to Protect Themselves and Others From HIV/HCV Infections

Many long-term injection drug users (IDUs) engage in planning strategies. In this pilot study, the authors examine the relation of one planning strategy to IDUs' engaging in safer injection practices. Sixty-eight IDUs were recruited in 2010 from a New York City (NYC) needle exchange program and referrals to participate in an innovative Staying Safe Intervention that teaches strategies to stay HIV/HCV uninfected. Responses to a baseline 185-item survey were analyzed using correlations and odds ratios. Planning ahead to have steady access to clean equipment was correlated with both individually based and networks-based safety behaviors including storing clean needles; avoiding sharing needles, cookers, and filters with other injectors; and providing clean needles to sex partners. Implications related to resilience in IDUs are discussed and the study's limitations have been noted. Sirikantraporn S, Mateu-Gelabert P, Friedman S, Sandoval M, Torruella R. Resilience among IDUs: Planning strategies to help injection drug users to protect themselves and others from HIV/HCV infections. *Subst Use Misuse*. 2012.

Access To Health Services and Sexually Transmitted Infections In A Cohort Of Relocating African American Public Housing Residents: An Association Between Travel Time and Infection

High incidence and prevalence of sexually transmitted infection (STI) in blacks have been attributed to multiple factors. However, few articles have discussed spatial access to healthcare as a driver of disparities. The objective of this analysis was to evaluate the relationship between travel time to a healthcare provider and the likelihood of testing positive for 1 of 3 STIs in a sample of adults living in public housing. One hundred and eight black adults in Atlanta, GA from November 2008 to June 2009, completed a survey that queried sexual behavior and healthcare use and had urine tested for *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* by molecular methods. Travel time was a continuous variable capturing the number of minutes it took to reach the place where participants received most of their care. Multivariate analyses tested the hypothesis that individuals reporting longer travel times would be more likely to test positive for an STI. Travel time was squared to linearize its relationship to the outcome. Thirty-six residents (37.5%) tested positive for e1 STI. A curvilinear relationship existed between travel time and STI status. When travel time was <48 minutes, a positive relationship existed between travel time and the odds of testing positive for an STI. An inverse relationship existed when travel time was e48 minutes. Residents of impoverished communities experience a curvilinear relationship between travel time and STI status. The authors discuss possible factors that might have created this curvilinear relationship, including voluntary social isolation. Bonney L, Cooper H, Caliendo A, Del

Rio C, Hunter-Jones J, Swan D, Rothenberg R, Druss B. Access to health services and sexually transmitted infections in a cohort of relocating African American public housing residents: An association between travel time and infection. *Sex Transm Dis.* 2012; 39 (2): 116-121.

Evaluation Of Respondent-Driven Sampling Respondent-driven sampling is a novel variant of link-tracing sampling for estimating the characteristics of hard-to-reach groups, such as HIV prevalence in sex workers. Despite its use by leading health organizations, the performance of this method in realistic situations is still largely unknown. The authors evaluated respondent-driven sampling by comparing estimates from a respondent-driven sampling survey with total population data. Total population data on age, tribe, religion, socioeconomic status, sexual activity, and HIV status were available on a population of 2402 male household heads from an open cohort in rural Uganda. A respondent-driven sampling (RDS) survey was carried out in this population, using current methods of sampling (RDS sample) and statistical inference (RDS estimates). Analyses were carried out for the full RDS sample and then repeated for the first 250 recruits (small sample). The authors recruited 927 household heads. Full and small RDS samples were largely representative of the total population, but both samples underrepresented men who were younger, of higher socioeconomic status, and with unknown sexual activity and HIV status. Respondent-driven sampling statistical inference methods failed to reduce these biases. Only 31%-37% (depending on method and sample size) of RDS estimates were closer to the true population proportions than the RDS sample proportions. Only 50%-74% of respondent-driven sampling bootstrap 95% confidence intervals included the population proportion. Respondent-driven sampling produced a generally representative sample of this well-connected non-hidden population. However, current respondent-driven sampling inference methods failed to reduce bias when it occurred. Whether the data required to remove bias and measure precision can be collected in a respondent-driven sampling survey is unresolved. Respondent-driven sampling should be regarded as a (potentially superior) form of convenience sampling method, and caution is required when interpreting findings based on the sampling method. McCreesh N, Frost S, Seeley J, Katongole J, Tarsh M, Ndunguse R, Jichi F, Lunel N, Maher D, Johnston L, Sonnenberg P, Copas A, Hayes R, White R. Evaluation of respondent-driven sampling. *Epidemiology.* 2012; 23(1): 138-147.

Reciprocal Sex Partner Concurrency and STDs among Heterosexuals at High-Risk of HIV Infection Inconsistent findings on the relationship of sex partner concurrency to infection with HIV and other sexually transmitted diseases (STDs) may result from differences in how sex partner concurrency is conceptualized. The authors examine the relationship of reciprocal sex partner concurrency (RSPC) to diagnosed STDs among heterosexuals. Heterosexually active adults (N = 717) were recruited for a cross-sectional study using respondent-driven sampling (RDS) from high-HIV-risk areas in New York City (NYC, 2006-2007) and interviewed about their sexual risk behaviors, number of sex partners, last sex partners, and STD diagnoses (prior 12 months). RSPC was when both the participant and her/his last sex partner had sex with other people during their sexual relationship. Odds ratios (OR), adjusted odds ratios (aOR), and 95 % confidence intervals (95%CI) were estimated by logistic regression. The sample was 52.4 % female, 74.3 % Black; median age was 40 years. RSPC was reported by 40.7 % and any STD diagnoses by 23.4 %. Any STDs was reported by 31.5 % of those reporting RSPC vs. 17.9 % of those who did not (OR = 2.11, 95%CI = 1.49-3.0). Any STDs was independently associated with RSPC (aOR = 1.54, 95%CI = 1.02-2.32), female gender (aOR = 2.15, 95%CI = 1.43-3.23), having more than three sex partners (aOR = 1.72, 95%CI = 1.13-2.63), and unprotected anal sex (aOR = 1.65, 95%CI = 1.12-2.42). Heterosexuals in high-HIV-risk neighborhoods in sexual partnerships that involve RSPC are at greater risk of STDs and, potentially, HIV. RSPC, in addition to sexual risk behaviors and the

number of sex partners, may facilitate the heterosexual spread of HIV through STD cofactors and linkage into larger STD/HIV sexual transmission networks. Neaigus A, Jenness S, Hagan H, Murrill C, Wendel T. Reciprocal sex partner concurrency and STDs among heterosexuals at high-risk of HIV infection. *J Urban Health*. 2012.

Racial and Ethnic Disparities and Implications For The Prevention Of HIV Among Persons Who Inject Drugs

There are now an estimated 16 million people who inject drugs (PWID) throughout the world, 3 million of whom are estimated to be infected with HIV. In many countries, substantial proportions of PWID belong to racial/ethnic/nationality minority groups, and are at increased likelihood of being infected with HIV. This article reviews current evidence on ethnic disparities in HIV infection among PWID and assesses the issues that would need to be addressed to reduce these disparities. An ongoing systematic review of ethnic disparities has found that, in a pooled weighted odds ratio, ethnic minority PWID are twice as likely to be HIV seropositive than ethnic majority, PWID from the same geographic area. If implemented with sufficient quality and coverage, current HIV prevention programs probably have the capability of ending HIV transmission among both ethnic majority and minority PWID. Large-scale, evidence-based prevention programs need to be implemented in the contexts of patterns of injecting drug use that continue to evolve-with injecting practices spreading to new areas, changes in drugs injected, and some transitions from injecting to non-injecting drug use. Lack of financial resources and policies against evidence-based programming are increasingly important problems that are likely to have particularly adverse effects on ethnic minority PWID. Racial/ethnic/nationality disparities in HIV infection are quite common among PWID. Addressing these disparities will be a fundamental challenge within a human rights approach to public health. Jarlais D, Cooper H, Bramson H, Deren S, Hatzakis A, Hagan H. Racial and ethnic disparities and implications for the prevention of HIV among persons who inject drugs. *Curr Opin HIV AIDS*. 2012; 7(4): 354-361.

Are Females Who Inject Drugs At Higher Risk For HIV Infection Than Males Who Inject Drugs: An International Systematic Review Of High Seroprevalence Areas

There are multiple reasons why females who inject drugs may be more likely to become infected with HIV than males who inject drugs. Where this is the case, special HIV prevention programs for females would be needed. This is an international systematic review and meta-analysis of studies across 14 countries. Countries with high seroprevalence (>20%) HIV epidemics among persons who inject drugs (PWID) were identified from the Reference Group to the UN on HIV and Injecting Drug Use. Systematic literature reviews collected data on HIV prevalence by gender for these countries. Non-parametric and parametric tests along with meta-analytic techniques examined heterogeneity and differences in odds ratios (OR) across studies. Data were abstracted from 117 studies in 14 countries; total sample size N=128,745. The mean weighted OR for HIV prevalence among females to males was 1.18 [95% CI 1.10-1.26], with high heterogeneity among studies (I(2)=70.7%). There was a Gaussian distribution of the log ORs across studies in the sample. There was a significantly higher HIV prevalence among females compared to males who inject drugs in high seroprevalence settings, but the effect size is extremely modest. The high level of heterogeneity and the Gaussian distribution suggest multiple causes of differences in HIV prevalence between females and males, with a specific difference determined by local factors. Greater understanding of factors that may protect females from HIV infection may provide insights into more effective HIV prevention for both females and males who inject drugs. Des Jarlais D, Feelemyer J, Modi S, Arasteh K, Hagan H. Are females who inject drugs at higher risk for HIV infection than males who inject drugs: An international systematic review of high seroprevalence areas. *Drug Alcohol Depend*. 2012; 124 (1-2): 95-107.

Meta-Analysis Of Hepatitis C Seroconversion In Relation To Shared Syringes and Drug Preparation Equipment

The authors conducted a systematic review of studies reporting seroincidence of hepatitis C infection (HCV) in relation to shared syringes and drug preparation equipment among injection drug users (IDUs). They identified published and unpublished studies that met inclusion criteria. They estimated the relative contributions of shared syringes and drug preparation equipment to HCV transmission using random-effects meta-analysis, and analyzed potential sources of heterogeneity of effects among studies. Syringe sharing was associated with HCV seroconversion [pooled risk ratio (PRR) = 1.94, 95% confidence interval (CI) 1.53, 2.46], as was sharing drug preparation containers (PRR = 2.42, 95% CI 1.89, 3.10), filters (PRR = 2.61, 95% CI 1.91, 3.56), rinse water (PRR = 1.98, 95% CI 1.54, 2.56), combinations of this equipment (PRR = 2.24, 95% CI 1.28, 3.93) and 'backloading', a syringe-mediated form of sharing prepared drugs (PRR = 1.86, 95% CI 1.41, 2.44). Meta-regression results showed that the association between syringe sharing and seroconversion was modified by HCV seroprevalence in the IDU populations. The risk of hepatitis C infection through shared syringes is dependent upon hepatitis C infection seroprevalence in the population. The risk of hepatitis C infection through shared drug preparation equipment is similar to that of shared syringes. Because the infection status of sharing partners is often unknown, it is important for injection drug users to consistently avoid sharing unsterile equipment used to prepare, divide or inject drugs and avoid backloading with an unsterile syringe. Pouget E, Hagan H, Des Jarlais D. Meta-analysis of hepatitis c seroconversion in relation to shared syringes and drug preparation equipment. *Addiction*. 2012; 107(6): 1057-1065.

Drug-Related Arrest Rates and Spatial Access To Syringe Exchange Programs In New York City Health Districts: Combined Effects On the Risk Of Injection-Related Infections Among Injectors

Drug-related law enforcement activities may undermine the protective effects of syringe exchange programs (SEPs) on local injectors' risk of injection-related infections. The authors explored the spatial overlap of drug-related arrest rates and access to SEPs over time (1995-2006) in New York City health districts, and used multilevel models to investigate the relationship of these two district-level exposures to the odds of injecting with an unsterile syringe. Districts with better SEP access had higher arrest rates, and arrest rates undermined SEPs' protective relationship with unsterile injecting. Drug-related enforcement strategies targeting drug users should be de-emphasized in areas surrounding SEPs. Cooper H, Des Jarlais D, Tempalski B, Bossak B, Ross Z, Friedman S. Drug-related arrest rates and spatial access to syringe exchange programs in New York City health districts: Combined effects on the risk of injection-related infections among injectors. *Health Place*. 2012; 18(2): 218-228.

Social and Structural Factors Associated With HIV Disease Progression Among Illicit Drug Users: A Systematic Review

The objective of this study was to systematically review factors associated with HIV disease progression among illicit drug users, focusing on exposures exogenous to individuals that likely shape access and adherence to HIV treatment. A systematic review of peer-reviewed English-language studies among HIV-seropositive illicit drug users was conducted with at least one of these endpoint of interest: a diagnosis of AIDS; death; changes/differences in CD4 cell counts; or changes/differences in plasma HIV-1 RNA levels. Articles were included if they reported factors associated with an outcome of interest among a group of illicit drug users. Studies were identified, screened and selected using systematic methods. Of 2,668 studies matching the search criteria, 58 (2%) met the inclusion criteria, all but one from North America or Western Europe. Overall, 41 (71%) studies contained significant individual-level clinical characteristics or behaviours (e.g., illicit drug use) associated with disease progression. Fifteen studies (26%) identified significant social, physical, economic or policy-level exposures, including

incarceration, housing status or lack of legal income. While past studies demonstrate important environmental exposures that appear to shape access to care and subsequent disease progression, the limited literature to examine these factors demonstrates the need for future research to consider risk environment characteristics and the role they may play in shaping health outcomes from HIV infection among drug users through determining access and adherence to evidence-based care. Milloy M, Marshall B, Kerr T, Buxton J, Rhodes T, Montaner J, Wood E. Social and structural factors associated with HIV disease progression among illicit drug users: A systematic review. *AIDS*. 2012; 26(9): 1049-1063.

Injection Drug Use and HIV Antiretroviral Therapy Discontinuation in A Canadian Setting

The authors investigated whether drug-related behaviors predicted antiretroviral therapy (ART) discontinuation among a cohort of injection drug users (IDU) in a Canadian setting. Cox regression analyses were used to investigate the impact of drug use patterns on rates of ART discontinuation among a sample of HIV-positive IDU in Vancouver, Canada between May 1996 and April 2008. In total, 408 HIV-positive IDU initiated ART during the study period, among whom 257 (63.0%) discontinued ART at least once. Rates of ART discontinuation were not significantly elevated among those who reported ongoing injection of heroin, cocaine, or other illicit drugs in comparison to those who reported not injecting drugs. However, public drug use was significantly predictive of ART discontinuation. These findings may contribute to a reconsideration of the role of active drug use in determining retention in ART programs among IDU. Werb D, Milloy M, Kerr T, Zhang R, Montaner J, Wood E. Injection drug use and HIV antiretroviral therapy discontinuation in a Canadian setting. *AIDS Behav*. 2012; 1-6.

PREVENTION RESEARCH

Internalizing Symptoms: Effects of a Preventive Intervention on Developmental Pathways from Early Adolescence to Young Adulthood

This study examined the mediated and moderated effects of a universal family-focused preventive intervention, delivered during young adolescence, on internalizing symptoms assessed in young adulthood. Sixth grade students (N = 446; 52% female; 98% White) and their families from 22 rural Midwestern school districts were randomly assigned to the experimental conditions in 1993. Self-report questionnaires were administered at seven time points (pre-test to young adulthood-age 21) to those receiving the Iowa Strengthening Families Program (ISFP) and to the control group. Results showed that growth factors of adolescent internalizing symptoms (grades 6-12) were predicted by ISFP condition and risk status (defined as early substance initiation). Moderation of the condition effect by risk status was found, with higher-risk adolescents benefitting more from the ISFP. Results also supported the hypothesis that the ISFP's effect on internalizing symptoms in young adulthood was mediated through growth factors of adolescents' internalizing symptoms; risk moderation, however, was only marginally significant in young adulthood. The relative reduction rate on clinical or subclinical levels of young adult internalizing symptoms was 28%, indicating that for every 100 young adults displaying clinical or subclinical levels of internalizing symptoms from school districts not offering an intervention, there could be as few as 72 displaying those levels of symptoms in school districts that offered middle school prevention programming. These findings highlight how the positive effects of family-focused universal interventions can extend to non-targeted outcomes and the related potential public-health impact of scaling up these interventions. Trudeau L, Spoth R, Randall G, Mason W, Shin C. Internalizing symptoms: Effects of a preventive intervention on developmental pathways from early adolescence to young adulthood. *J Youth Adolesc.* 2011; Published online Dec 10, 2011.

Behavioral Control in At-Risk Toddlers: The Influence of the Family Check-up

This study examines the role of one component of emotion regulation, behavioral control, in the growth of children's early behavior problems by examining whether increases in parental positive behavior support brought about by a family-centered intervention were associated with greater child behavioral control, and whether greater behavioral control at age 3 mediated the association between improvements in aspects of positive behavior support from ages 2 to 3 and decreases in growth of behavior problems from ages 2 to 4. The sample included 713 at-risk children (50% female) and their primary caregivers (50% European American, 28% African American, 13% biracial, 9% other) who were randomly assigned to the intervention or control group. Children had a mean age of 29.91 months at the initial assessment. Data were collected through home visits at child ages 2 to 4, which involved questionnaires for primary caregivers and structured and unstructured play activities for children with primary and alternative caregivers and siblings. Results indicated that the intervention improved parental positive behavior support and reduced growth of child behavior problems. One dimension of positive behavior support, proactive parenting, was modestly associated with behavioral control at age 3, which in turn was significantly associated with growth in behavior problems from ages 2 to 4, with greater behavioral control related to lower levels of growth in behavior problems. Results provide support for the notion that proactive parenting is an important factor in the development of children's behavioral control and that behavioral control plays an important role in the growth of behavior problems. Shelleby E, Shaw D, Cheong J, Chang H, Gardner F, Dishion T, Wilson M. Behavioral control in at-risk toddlers: The influence of the family check-up. *J Clin Child Adolescent Psychol.* 2012; 41(3): 288-301.

Benefits Of Universal Intervention Effects On A Youth Protective Shield 10 Years After Baseline

An earlier randomized controlled study found that a universal, family-focused preventive intervention produced protective shield effects-reduced adolescent exposures to illicit substance opportunities-among adolescents in grade 12. This study examined a follow-up assessment of the sample during young adulthood. A randomized controlled trial evaluated the Iowa Strengthening Families Program that was implemented in 22 rural schools (N = 446 families) when the participants were in grade six. Measures included adolescent exposure to illicit substance use and young adult lifetime substance use (age 21; N = 331). Growth curve modeling examined indirect intervention effects through growth factors of adolescent exposure. Findings from this study confirm protective shield effects that mediate long-term reduction of illicit substance use ($R^2 = .14$, $p = .02$, Relative Reduction Rate = 28.2%). The benefits of decreasing exposure to substance use during adolescence through universal interventions were supported, with positive effects extending into young adulthood. Spoth R, Trudeau L, Guyll M, Shin C. Benefits of universal intervention effects on a youth protective shield 10 years after baseline. *J Adolescent Health*. 2012; 50(4): 414-417.

Assessing the Effectiveness Of Antiretroviral Regimens In Cohort Studies Involving HIV-Positive Injection Drug Users

The authors compared the effectiveness of different HAART regimens considering, separately, history of injection drug use (IDU) (yes/no). Participants comprised a total of 1,163 HIV-infected patients initiated HAART between January 1, 2000 and February 28, 2009 in British Columbia, Canada, and were followed until February 28, 2010. HAART effectiveness was measured by the ability to achieve viral suppression < 50 copies/mL at 6 months. The authors compared HAART regimens containing efavirenz and boosted atazanavir. They developed logistic regression models using different techniques to control for potential confounders. Among the 1,163 patients, 796 (68%) achieved viral suppression at 6 months (32% reporting a history of IDU). Different confounding models yielded very similar odds ratios for achieving viral suppression. Boosted atazanavir-based HAART demonstrated to be the most effective regimen, showing a surprisingly higher benefit for patients with a history of IDU (odds ratios from different models ranged from 1.74-1.95 versus 1.45-1.51). The literature has conflicting results regarding the effectiveness of highly active antiretroviral treatment (HAART) to treat HIV infection among those with a history of injection drug use (IDU). The authors have shown that most patients, with and without a history of IDU, were able to achieve viral suppression at 6 months. Boosted atazanavir-based HAART was the most resilient regimen and it was more effective than efavirenz-based HAART among IDU. Given the limited inclusion of IDU in clinical trials of HAART's efficacy, a randomized clinical trial comparing different first-line HAART regimens among IDU is warranted based on these results. Lima V, Nosyk B, Wood E, Kozai T, Zhang W, Chan K, Montaner J. Assessing the effectiveness of antiretroviral regimens in cohort studies involving HIV-positive injection drug users. *AIDS*. 2012; Epub.

Family Relationships and Parental Monitoring During Middle School as Predictors Of Early Adolescent Problem Behavior

The middle school years are a period of increased risk for youths' engagement in antisocial behaviors, substance use, and affiliation with deviant peers (Dishion & Patterson, 2006). This study examined the specific role of parental monitoring and of family relationships (mother, father, and sibling) that are all critical to the deterrence of problem behavior in early adolescence. The study sample comprised 179 ethnically diverse 6th-grade (46% female) students who were followed through 8th grade. Results indicated that parental monitoring and father-youth connectedness were associated with reductions in problem behavior over time, and conflict with siblings was linked with increases in problem behaviors. No associations were found

for mother-youth connectedness. These findings did not differ for boys and for girls, or for families with resident or nonresident fathers. Fosco G, Stormshak E, Dishion T, Winter C. Family relationships and parental monitoring during middle school as predictors of early adolescent problem behavior. *J Clin Child Adolesc Psychol.* 2012; 41(2): 202-213.

The Mothers and Toddlers Program, An Attachment-Based Parenting Intervention For Substance-Using Women: Results At 6-Week Follow-Up in a Randomized Clinical Pilot

Previously, the authors reported post treatment findings from a randomized pilot study testing a new attachment-based parenting intervention for mothers enrolled in substance-use treatment and caring for children ages birth to 3 years (N.E. Suchman, C. DeCoste, N. Castiglioni, T. McMahon, B. Rounsaville, & L. Mayes, 2010). The Mothers and Toddlers Program (MTP) is a 12-session, weekly individual parenting therapy that aims to enhance maternal capacity for reflective functioning and soften harsh and distorted mental representations of parenting. In a randomized pilot study, 47 mothers who were enrolled in outpatient substance-abuse treatment and caring for children between birth and 3 years of age were randomized to the MTP versus the Parent Education Program (PE), a comparison intervention that provided individual case management and developmental guidance. At the end of treatment, mothers in the MTP condition demonstrated better reflective functioning, representation quality and caregiving behavior than did mothers in the PE condition. In this investigation, the authors examined whether the benefits of MTP at post treatment were sustained at the 6-week follow-up. Recently, they also identified two components of parental reflective functioning: (a) a self-focused component representing the parent's capacity to mentalize about strong personal emotions (e.g., anger, guilt, or pain) and their impact on the child and (b) a child-focused component representing the parent's capacity to mentalize about the child's emotions and their impact on the mother (N. Suchman, C. DeCoste, D. Leigh, & J. Borelli, 2010). In this study, the authors reexamined post treatment outcomes using these two related, but distinct, constructs. Suchman N, Decoste C, McMahon T, Rounsaville B, Mayes L. The Mothers And Toddlers Program, an attachment-based parenting intervention for substance-using women: Results at 6-week follow-up in a randomized clinical pilot. *Infant Ment Health J.* 2011; 32(4): 427-449.

Family-Centered Program Deters Substance Use, Conduct Problems, and Depressive Symptoms In Black Adolescents

The present research addressed the following important question in pediatric medicine: Can participation in a new family-centered preventive intervention, the Strong African American Families-Teen (SAAF-T) program, deter conduct problems, substance use, substance use problems, and depressive symptoms among rural black adolescents across 22 months? Data were collected from 502 black families in rural Georgia, assigned randomly to SAAF-T or an attention control condition. The prevention condition consisted of 5 consecutive meetings at community facilities with separate, concurrent sessions for caregivers and adolescents followed by a caregiver-adolescent session in which families practiced skills they learned in the separate sessions. Adolescents self-reported conduct problem behaviors, substance use, substance use problems, and depressive symptoms at ages 16 years (pretest) and 17 years 10 months (long-term assessment). Adolescents who participated in SAAF-T evinced lower increases in conduct problem behavior, substance use, substance use problems, and depressive symptom frequencies than did adolescents in the attention control condition across the 22 months between pretest and long-term assessment. This is the first study to demonstrate efficacy in a prevention program designed to deter conduct problems, substance use, substance use problems, and depressive symptoms among rural black adolescents. Because SAAF-T is a manualized, structured program, it can be easily disseminated to public health agencies, schools, churches, boys' and girls' clubs, and other community organizations. Brody G, Chen Y, Kogan S, Yu T, Molgaard V, DiClemente R,

Wingood G. Family-centered program deters substance use, conduct problems, and depressive symptoms in Black adolescents. *Pediatrics*. 2012; 129(1): 108-115.

Using Consumer Preference Information to Increase the Reach and Impact of Media-Based Parenting Interventions in a Public Health Approach to Parenting Support

Within a public health approach to improving parenting, the mass media offer a potentially more efficient and affordable format for directly reaching a large number of parents with evidence-based parenting information than do traditional approaches to parenting interventions that require delivery by a practitioner. Little is known, however, about factors associated with parents' interest in and willingness to watch video messages about parenting. Knowledge of consumer preferences could inform the effective design of media interventions to maximize parental engagement in the parenting messages. This study examined parents' preferred formats for receiving parenting information, as well as family sociodemographic and child behavior factors that predict parents' ratings of acceptability of a media-based parenting intervention. An ethnically diverse sample of 162 parents of children ages 3-6 years reported their preferences for various delivery formats for parenting information and provided feedback on a prototype episode of a video-format parenting program based on the Triple P Positive Parenting Program. Parents reported the strongest preference for self-administered delivery formats such as television, online programs, and written materials; the least preferred formats were home visits, therapists, and multiweek parenting groups. Parents' ratings of engagement, watchability, and realism of the prototype parenting episode were quite strong. Parents whose children exhibited clinical levels of problem behaviors rated the episode as more watchable, engaging, and realistic. Mothers also rated the episodes as more engaging and realistic than did fathers. Lower income marginally predicted higher watchability ratings. Minority status and expectations of future problems did not predict acceptability ratings. The results suggest that the episode had broad appeal across groups. Metzler C, Sanders M, Rusby J, Crowley R. Using consumer preference information to increase the reach and impact of media-based parenting interventions in a public health approach to parenting support. *Behav Ther*. 2012; 43(2): 257-270.

The Natural Course of Nicotine Dependence Symptoms among Adolescent Smokers

Few studies have investigated the natural course of nicotine dependence prospectively from the earliest experiences with smoking. Drawing on a cohort of 9th- and 10th-grade adolescents followed over 48 months, survival analyses were conducted to evaluate the cumulative probability, following smoking initiation, for the development of nicotine dependence symptoms. Although each nicotine dependence symptom was significantly more prevalent among adolescents who had smoked more than 100 cigarettes by the end of the follow-up assessment, 20% of adolescents smoking fewer than 100 cigarettes reported experiencing "smoking to relieve restlessness and irritability" and "smoking a lot more now to be satisfied compared to when first smoked". Nicotine dependence symptoms were also reported before reaching 100 cigarettes for a substantial number of adolescents (between 9.4% and 58.8% for individual symptoms). Endorsement of nicotine dependence symptoms prospectively predicted past-week smoking (odds ratios [ORs] between 3.18 and 14.62 for significant symptoms) and past-month daily smoking (significant symptoms' ORs between 3.52 and 10.68) at the 48-month assessment even when controlling for amount of previous smoking. The present study adds to the growing body of literature on the natural course of nicotine dependence from earliest experiences with smoking by showing that symptoms of nicotine dependence may develop soon after initiation and/or at low levels of smoking. These findings suggest that novice adolescent smokers should not be neglected in smoking cessation intervention and that screening and effective intervention for early emerging symptoms among adolescent smokers may be an important target in preventing chronic smoking. Zhan W, Dierker L, Rose J, Selya A, Mermelstein

R. The natural course of nicotine dependence symptoms among adolescent smokers. *Nicotine Tob Res.* 2012.

Engaging Parents in the Family Check-Up in Middle School: Longitudinal Effects on Family Conflict and Problem Behavior through the High School Transition

Adolescence is a time of significant developmental change. During this period, levels of problem behavior that had been relatively innocuous may escalate in the company of peers, with simultaneous reductions in parental monitoring and involvement. In this article, the authors report the results of a randomized controlled trial of the Family Check-Up (FCU), a family-centered, school-based intervention designed to forestall the escalation of adolescent problem behavior by promoting and motivating skillful parenting through the transition to high school. In this study, 593 ethnically diverse families were randomized to be offered the FCU when their youth were in seventh and eighth grades of middle school. The authors used complier average causal effect analysis to examine change in family conflict, antisocial behavior, involvement with deviant peers, and alcohol use from sixth through ninth grades. Analyses revealed that when compared with a matched control group, youths whose parents had engaged in the FCU demonstrated significantly lower rates of growth in family conflict ($p = .052$), antisocial behavior, involvement with deviant peers, and alcohol use. These results extend current research on the FCU and provide support for theory that links family conflict with a variety of youth problem behavior. These results and the extant research on the FCU suggest that traditional school-based service delivery models that focus on the individual child may benefit from a shift in perspective to engage parents and families. Van Ryzin M, Stormshak E, Dishion T. Engaging parents in the family check-up in middle school: Longitudinal effects on family conflict and problem behavior through the high school transition. *J Adolesc Health.* 2012; 50(6): 627-633.

At The Edge? HIV Stigma and Centrality In A Community's Social Network In Namibia

Social network analysis was used to examine the relationship between HIV/AIDS stigmatization, perceived risk, and centrality in the community network (via participation in community groups). The findings from respondents in Keetmanshoop, Namibia ($N = 375$) showed an interaction between stigma and risk perceptions. Those who perceived higher HIV risk and stronger HIV stigma participated in fewer community groups and participated in groups with members who participated less widely across the network. In contrast, those who perceived higher HIV risk and weaker HIV stigma participated more, and were in community groups that are located on a greater share of the paths between entities in the network. Taboo, secrecy, resistance, knowing a person living with HIV/AIDS, and desire for diagnosis secrecy were also related to centrality. Findings suggest that the interaction of perceived HIV risk and HIV stigma are related to structural-level features of community networks based on participation in community groups. Smith R, Baker M. At the edge? HIV stigma and centrality in a community's social network in Namibia. *AIDS Behav.* 2012.

Girls in Foster Care: Risk and Promotive Factors for School Adjustment across the Transition to Middle School

Girls in foster care may face difficulties across the transition to middle school. Latent growth curve modeling was employed to examine trajectories and predictors of academic competence and aggression from and against peers for 75 girls in foster care from the end of elementary school to the 2nd year of middle school. Across the transition to middle school, academic competence increased. Poor self-regulation was associated with decreased academic competence, and higher caregiver support was associated with increased academic competence. Frequency of aggression from peers decreased across the transition, with perceived school competence predicting smaller decreases. Aggression against peers dropped initially and then

increased to pretransition levels by the end of the 2(nd) year of middle school. Lower caregiver support was associated with higher rates of aggression against peers at the end of the 1(st) year of middle school. The results are discussed in terms of implications for interventions for girls in foster care. Pears K, Kim H, Leve L. Girls in foster care: Risk and promotive factors for school adjustment across the transition to middle school. *Child Youth Serv Rev.* 2012; 34(1): 234-243.

Translating Family-Focused Prevention Science Into Public Health Impact Underage drinking is a pervasive problem in the United States, with serious consequences for youth, families, communities, and society as a whole. Family-focused preventive interventions for children and adolescents have shown potential for reducing underage drinking and other problem behaviors. Research findings indicate that clear advances have been made, in terms of both the number of evidence-based interventions available, and in the quality of the methods used to evaluate them. To fully reap the benefits of such preventive interventions and achieve public health impact, the findings of family-focused preventive intervention science must be translated into real-world, community practices. This type of translation can be enhanced through four sets of translational impact factors-effectiveness of interventions, extensiveness of their population coverage, efficiency of interventions, and engagement of eligible populations, with sustained quality intervention implementation. Findings from studies conducted by researchers at the Partnerships in Prevention Science Institute and other empirical work highlight the importance of these factors. A model for community- university partnerships has been developed that potentially can facilitate the dissemination and public health impact of universal interventions to prevent underage drinking and other problem behaviors. This model fits well within a comprehensive strategic framework for promoting effective prevention. Spoth R, Schainker L, Hiller-Sturmhöefel S. Translating family-focused prevention science into public health impact. *Alcohol Res Health.* 2011; 34(2): 188-203.

Needle Exchange and the HIV Epidemic In Vancouver: Lessons Learned From 15 Years Of Research During the mid-1990s, Vancouver experienced a well characterized HIV outbreak among injection drug users (IDU) and many questioned how this could occur in the presence of a high volume needle exchange program (NEP). Specific concerns were fuelled by early research demonstrating that frequent needle exchange program attendees were more likely to be HIV positive than those who attended the NEP less frequently. Since then, some have misinterpreted this finding as evidence that NEPs are ineffective or potentially harmful. In light of continuing questions about the Vancouver HIV epidemic, the authors review 15 years of peer-reviewed research on Vancouver 's NEP to describe what has been learned through this work. This review demonstrates that: (1) NEP attendance is not causally associated with HIV infection, (2) frequent attendees of Vancouver 's NEP have higher risk profiles which explain their increased risk of HIV seroconversion, and (3) a number of policy concerns, as well as the high prevalence of cocaine injecting contributed to the failure of the NEP to prevent the outbreak. Additionally, the authors highlight several improvements to Vancouver's NEP that contributed to declines in syringe sharing and HIV incidence. Vancouver's experience provides a number of important lessons regarding NEP. Keys to success include refocusing the NEP away from an emphasis on public order objectives by separating distribution and collection functions, removing syringe distribution limits and decentralizing and diversifying NEP services. Additionally, our review highlights the importance of context when implementing NEPs, as well as ongoing evaluation to identify factors that constrain or improve access to sterile syringes. Hyshka E, Strathdee S, Wood E, Kerr T. Needle exchange and the HIV epidemic in Vancouver: Lessons learned from 15 years of research. *Int J Drug Policy.* 2012.

Do Peers' Parents Matter? A New Link Between Positive Parenting and Adolescent Substance Use

Although studies have demonstrated that an adolescent's parents and friends both influence adolescent substance use, it is not known whether the parenting experienced by one's friends also affects one's own use. Drawing on conceptions of shared parenting and the tenets of coercion theory, the authors investigated the extent to which three domains of parenting behaviors (parental knowledge, inductive reasoning, and consistent discipline) influenced the alcohol, cigarette, and marijuana use of not only their own adolescent children but also of members of their adolescents' friendship groups. Analyses of friendship nominations within each of two successive ninth-grade cohorts in 27 Iowa and Pennsylvania schools (N = 7,439 students, 53.6% female) were used to identify 897 friendship groups. Hierarchical logistic regression models were used to examine prospective associations between 9th-grade friendship group-level parenting behaviors and adolescent self-reported alcohol, cigarette, and marijuana use in 10th grade. Adolescent substance use in 10th grade was significantly related to parenting behaviors of friends' parents, after controlling for adolescents' reports of their own substance use and their own parents' behaviors at the 9th grade level. These associations were particularly strong for parents' knowledge about their children and use of inconsistent discipline strategies. Significant interaction effects indicated that these relationships were strongest when adolescents received positive parenting at home. Some, but not all, of the main effects of friends' parents' parenting became non-significant after friends' substance use in ninth grade was included in the model. The findings suggest that the parenting style in adolescents' friends' homes plays an important role in determining adolescent substance use. Implications of the joint contribution of parents and peers for prevention and intervention are discussed. Cleveland M, Feinberg M, Osgood D, Moody J. Do peers' parents matter? A new link between positive parenting and adolescent substance use. *J Stud Alcohol Drugs*. 2012; 73(3): 423-433.

Identifying the HIV Transmission Bridge: Which Men Are Having Unsafe Sex with Female Sex Workers and with their Own Wives or Steady Partners?

The objective of this study was to gain insights into bridging behaviors and their correlates among male clients of female sex workers (FSWs). Men aged 18 years and older who recently paid or traded for sex with FSWs were recruited in Tijuana in 2008-2009. Participants underwent interviews and testing for HIV, chlamydia, syphilis, and gonorrhea. Logistic regression compared "bridgers" (clients who had unprotected sex with FSWs and with a wife or steady partner) with men who did not. Of 383 men, 134 (35%) had a steady partner. Half (n = 70) of those had unprotected sex with both FSWs and the steady partner. Prevalence of any STI or HIV was 16.5% among bridgers and 2.3% among non-bridgers. Compared to other clients, bridgers were more likely to use drugs during sex with FSWs (81.4% versus 46.9%, $p < 0.0001$), had higher sensation-seeking ($p < 0.0001$) and misogyny scores ($p = 0.05$), and were more likely to offer FSWs extra money for unprotected sex (34.4% versus 1.6%, $p < 0.0001$). Factors independently associated with bridging were: using drugs during sex with FSWs (adjusted odds ratio (AOR): 3.4, $p = 0.007$), sensation-seeking (AOR: 4.3 per unit increase, $p = 0.05$), and offering FSWs more money for unprotected sex (AOR: 24.5, $p = 0.003$). Sensation-seeking clients who use drugs during sex and coerce FSWs into unprotected sex may be less responsive to standard risk reduction interventions. Interventions are needed that target clients rather than rely on FSWs to change behaviors that may not be under their control. Patterson T, Volkmann T, Gallardo M, Goldenberg S, Lozada R, Semple S, Anderson C, Strathdee S. Identifying the HIV transmission bridge: which men are having unsafe sex with female sex workers and with their own wives or steady partners?. *J Acquir Immune Defic Syndr*. 2012.

Longitudinal Predictors of School-Age Academic Achievement: Unique Contributions of Toddler-Age Aggression, Oppositionality, Inattention, and Hyperactivity

This project examined the unique predictive validity of parent ratings of toddler-age aggression, oppositionality, inattention, and hyperactivity-impulsivity to academic achievement at school-age in a sample of 566 high-risk children and families. The study also investigated potential indirect effects of the Family Check-Up on school-age academic achievement through changes in child behavior problems. The results demonstrated that toddler-age aggression was most consistently associated with school-age academic achievement, albeit modestly. Moreover, findings showed that the intervention predicted greater decreases in aggression from ages 2-3 to 4-5 compared to controls. The results suggest that in high-risk toddler-aged children, aggression may be a more consistent predictor of school-age academic achievement than other externalizing dimensions, which has implications for early identification and efforts to promote children's adaptation. Brennan L, Shaw D, Dishion T, Wilson M. Longitudinal predictors of school-age academic achievement: Unique contributions of toddler-age aggression, oppositionality, inattention, and hyperactivity. *J Abnorm Child Psychol*. 2012; epub ahead of print.

A Six-Year Predictive Test of Adolescent Family Relationship Quality and Effortful Control Pathways to Emerging Adult Social and Emotional Health

This longitudinal study examined how a multimethod (youth report, parent report, direct observation) assessment of family relationship quality (cohesion and conflict) in adolescence (age 16-17) predicted growth and maintenance of effortful control across ages 17, 22, and 23 years old, and, ultimately, subjective well-being, emotional distress, and aggressive behavior in emerging adulthood (23). A diverse sample of 792 youth at age 17 and their families, and youth at ages 22 and 23, were studied to examine family cohesion and conflict and the growth and maintenance of effortful control as predictors of emerging adult social and emotional health. Results indicated that family cohesion and conflict during late adolescence and mean-level effortful control at age 22 each served as unique pathways to emerging adult adjustment. These findings underscore the importance of family functioning during adolescence and the maintenance of effortful control into emerging adulthood for understanding adjustment during the emerging adulthood period. (PsycINFO Database Record (c) 2012 APA, all rights reserved). Fosco G, Caruthers A, Dishion T. A six-year predictive test of adolescent family relationship quality and effortful control pathways to emerging adult social and emotional health. *J Fam Psychol*. 2012.

Perceived Discrimination and Longitudinal Increases In Adolescent Substance Use: Gender Differences and Mediation Pathways

This study was designed to test hypotheses about the prospective association of adolescents' perceptions of discrimination with increases in substance use and the processes that mediate this association. African American youths residing in rural Georgia (n = 573; mean age = 16.0 years) provided longitudinal data on their experiences with discrimination, substance use, school engagement, and affiliations with substance-using peers. For male youths, perceived discrimination was significantly related to increases in substance use, and, as hypothesized, this association was mediated by the contributions of perceived discrimination to decreases in school engagement and increases in affiliations with substance-using peers. Analyses also indicated that discrimination influences substance use rather than vice versa. Results are consistent with the hypothesis that high levels of discrimination are linked to increases in substance use for African American male adolescents. Brody G, Kogan S, Chen Y. Perceived discrimination and longitudinal increases in adolescent substance use: Gender differences and mediational pathways. *Am J Public Health*. 2012; 102(5): 1006-1011.

The Adults in the Making Program: Long-Term Protective Stabilizing Effects on Alcohol Use and Substance Use Problems For Rural African American Emerging Adults

This report addresses the long-term efficacy of the Adults in the Making (AIM) prevention program on deterring the escalation of alcohol use and development of substance use problems, particularly among rural African American emerging adults confronting high levels of contextual risk. African American youths (M age, pretest = 17.7 years) were assigned randomly to the AIM (n = 174) or control (n = 173) group. Past 3-month alcohol use, past 6-month substance use problems, risk taking, and susceptibility cognitions were assessed at pretest and at 6.4, 16.6, and 27.5 months after pretest. Pretest assessments of parent-child conflict, affiliations with substance-using companions, and perceived racial discrimination were used to construct a contextual risk factor index. A protective stabilizing hypothesis was supported; the long-term efficacy of AIM in preventing escalation of alcohol use and substance use problems was greater for youths with higher pretest contextual risk scores. Consistent with a mediation-moderation hypothesis, AIM-induced reductions over time in risk taking and susceptibility cognitions were responsible for the AIM × contextual risk prevention effects on alcohol use and substance use problems. Training in developmentally appropriate protective parenting processes and self-regulatory skills during the transition from adolescence to emerging adulthood for rural African Americans may contribute to a self-sustaining decreased interest in alcohol use and a lower likelihood of developing substance use problems. Brody G, Yu T, Chen Y, Kogan S, Smith K. The adults in the making program: Long-term protective stabilizing effects on alcohol use and substance use problems for rural African American emerging adults. *J Consult Clin Psychol*. 2012; 80(1): 17-28.

Adaptations to the Coping Power Program's Structure, Delivery Settings, and Clinician Training

This article describes the conceptual framework for the Coping Power program that has focused on proximal risk factors that can actively alter preadolescent children's aggressive behavior. The results of initial controlled efficacy trials are summarized. However, consistent with the theme of this special section, some clinicians and workshop participants have indicated barriers to the implementation of the Coping Power program in their service settings. In response to these types of concerns, three key areas of programmatic adaptation of the program that serve to address these concerns are then described in the article. First, existing and in-process studies of variations in how the program can be delivered are presented. Existing findings indicate how the child component fares when delivered by itself without the parent component, how simple monthly boosters affect intervention effects, and whether the program can be reduced by a third of its length and still be effective. Research planned or in progress on program variations examines whether group versus individual delivery of the program affects outcomes, whether the program can be adapted for early adolescents, whether the program can be delivered in an adaptive manner with the use of the Family Check Up, and whether a brief, efficient version of the program in conjunction with Internet programming can be developed and be effective. Second, the program has been and is being developed for use in different settings, other than the school-based delivery in the efficacy trials. Research has examined its use with aggressive deaf youth in a residential setting, with Oppositional Defiant Disorder and Conduct Disorder children in outpatient clinics, and in after-school programs. Third, the article reports how variations in training clinicians affect their ability to effectively use the program. (PsycINFO Database Record (c) 2012 APA, all rights reserved). Lochman J, Powell N, Boxmeyer C, Andrade B, Stromeyer S, Jimenez-Camargo L. Adaptations to the coping power program's structure, delivery settings, and clinician training. *Psychotherapy (Chic)*. 2012; 49(2): 135-142.

Negative Urgency, Distress Tolerance, and Substance Abuse Among College Students

Negative affect has been consistently linked with substance use/problems in prior research. The present study sought to build upon these findings by exploring how an individual's characteristic responding to negative affect impacts substance abuse risk. Trait negative affect was examined in relation to substance abuse outcomes along with two variables tapping into response to negative affect: Distress Tolerance, an individual's perceived ability to tolerate negative affect, and Negative Urgency, the tendency to act rashly while experiencing distress. Participants were 525 first-year college students (48.1% male, 81.1% Caucasian), who completed self-report measures assessing personality traits and alcohol-related problems, and a structured interview assessing past and current substance use. Relations were tested using Zero-Inflated Negative Binomial regression models, and each of the personality variables was tested in a model on its own, and in a model where all three traits were accounted for. Negative Urgency emerged as the best predictor, relating to every one of the substance use outcome variables even when trait negative affect and Distress Tolerance were accounted for. These findings suggest that Negative Urgency is an important factor to consider in developing prevention and intervention efforts aimed at reducing substance use and problems. Kaiser AJ, Milich R, Lynam DR, Charnigo RJ. Negative urgency, distress tolerance, and substance abuse among college students. *Addict Behav.* 2012; Epub.

Substance Misuse Prevention and Economic Analysis: Challenges and Opportunities

Regarding International Utility Economic analyses of substance misuse prevention assess the intervention cost necessary to achieve a particular outcome, and thereby provide an additional dimension for evaluating prevention programming. This article reviews several types of economic analysis, considers how they can be applied to substance misuse prevention, and discusses challenges to enhancing their international relevance, particularly their usefulness for informing policy decisions. Important first steps taken to address these challenges are presented, including the disease burden concept and the development of generalized cost-effectiveness, advances that facilitate international policy discussions by providing a common framework for evaluating health care needs and program effects. Guyll M, Spoth R, Cornish M. Substance misuse prevention and economic analysis: Challenges and opportunities regarding international utility. *Subst Use Misuse.* 2012; 47(8-9): 877-888.

A Model of School Problems, Academic Failure, Alcohol Initiation, and the Relationship to Adult Heroin Injection

The current study uses structural equation modeling to investigate factors associated with alcohol initiation and injection heroin use. Baseline data from the NEURO-HIV Epidemiologic Study in Baltimore, Maryland, were used. Participants were 404 injection heroin users (M(age) = 32.72) with a history of regular injection in their lifetime. Latent variables were created for self-reported school problems and academic failure. The final model indicated that greater school problems were associated with earlier alcohol initiation ($\beta = -0.22$, $p < .001$) and earlier alcohol initiation was associated with greater frequency of recent heroin use ($\beta = -0.12$, $p < .05$). Academic failure was directly related to greater frequency of recent heroin injection ($\beta = 0.15$, $p < .01$). The results expand research investigating the relationship between adolescent behavior and illicit drug use in adulthood. Trenz R, Harrell P, Scherer M, Mancha B, Latimer W. A model of school problems, academic failure, alcohol initiation, and the relationship to adult heroin injection. *Subst Use Misuse.* 2012; Epub.

The Role of Acculturation and Family Functioning in Predicting HIV Risk Behaviors Among Hispanic Delinquent Youth

The present study examined the relationship between Berry's acculturation typology and HIV risk behaviors and whether family functioning mediated any such effects. A total of 235 high risk Hispanic adolescents were categorized into one of Berry's four acculturation typologies through the use of cut-off scores on measures of Hispanicism and Americanism. Structural equation modeling was used to examine the effects of acculturation typology on HIV risk behaviors and the indirect effects of acculturation typology on HIV risk behaviors through family functioning. Acculturation typology was related to HIV risk behaviors. Family functioning partially mediated the effects of acculturation typology on the HIV risk behavior outcomes. These findings suggest that both Americanism and Hispanicism play an important role in the etiology of HIV risk behaviors among Hispanic youth and that both, along with family functioning, are important to consider when designing preventive interventions for this population. Farrelly C, Cordova D, Huang S, Estrada Y, Prado G. The role of acculturation and family functioning in predicting HIV risk behaviors among Hispanic delinquent youth. *J Immigr Minor Health*. 2012.

Boosting A Teen Substance Use Prevention Program With Motivational Interviewing

A brief motivational interviewing (MI) intervention may be a viable adjunct to school-based substance abuse prevention programs. This article describes the development and implementation of a brief MI intervention with 573 adolescents (mean age 16.8; 40.3% female, 68% Latino) enrolled in eight continuation high schools in Southern California. Study participants were assigned to the MI condition in a randomized controlled trial of Project Toward No Drug Abuse. Data are provided on dosage, topics discussed, and quality of MI determined with the Motivational Interviewing Skill Code (MISC). Results suggest that the protocol was feasible and implemented with adequate fidelity. The study's limitations are noted. Barnett E, Spruijt-Metz D, Unger J, Sun P, Rohrbach L, Sussman S. Boosting a teen substance use prevention program with motivational interviewing. *Subst Use Misuse*. 2012; 47(4): 418-428.

Predicting Condom Use Attitudes, Norms, and Control Beliefs in Hispanic Problem Behavior Youth: The Effects of Family Functioning and Parent-Adolescent Communication about Sex on Condom Use

Hispanic problem behavior youth are at an increased risk of engaging in HIV risk behaviors, including low condom use. However, relatively little research has examined factors that affect condom use in this population. Although research indicates that family processes, such as higher levels of family functioning and open parent-adolescent communication about sex, and condom use attitudes, norms, and control beliefs as depicted by the theory of planned behavior have an effect on condom use behaviors, the combination of the two factors has received minimal attention. The purpose of this study was to examine the effect of family functioning on condom use intentions and behaviors through communication about sex and condom use attitudes, parental norms, and control beliefs. A cross-sectional study of 171 predominately male (73.1%) sexually active Hispanic problem behavior adolescents (mean age = 14.88 years) was conducted. Structural equation modeling was used to test the study hypothesis. Findings largely support the overall model and suggest that family functioning had an indirect effect on condom use intention and behavior through communication about sex, condom use attitudes, and control beliefs. Family functioning, however, did not have an indirect effect on condom use intention and behavior through communication about sex and parental norms. Implications for prevention science and future research are discussed. Malcolm S, Huang S, Cordova D, Freitas D, Arzon M, Jimenez G, Pantin H, Prado G. Predicting condom use attitudes, norms, and control beliefs in Hispanic problem behavior

youth: The effects of family functioning and parent-adolescent communication about sex on condom use. *Health Educ Behav.* 2012.

The Effects of Language Brokering Frequency and Feelings on Mexican-Heritage Youth's Mental Health and Risky Behaviors

Language brokering is the communication process where individuals with no formal training (often children of immigrant families) linguistically mediate for 2 or more parties (usually adult family members and individuals from mainstream culture). This study examined the direct and indirect effects of language brokering on mental health and risky behaviors. Mexican-heritage youth (N = 684) from schools in Phoenix, AZ, completed surveys at 3 waves from 7th through 8th grades. Language brokering frequency and negative brokering feelings were positively associated with family-based acculturation stress, which was positively associated with alcohol use and other risky behaviors. Yet, brokering frequency was negatively associated with other risky behaviors, and positive brokering feeling was negatively associated with cigarette use. Implications for these findings are discussed. Kam JA. The effects of language brokering frequency and feelings on Mexican-heritage youths mental health and risky behaviors. *Journal of Communication.* 2011; 61: 455-475.

Long-Term Effects of Self-Control On Alcohol Use and Sexual Behavior among Urban Minority Young Women

High risk alcohol use and sexual behaviors peak in young adulthood and often occur in the same individuals. Alcohol use has been found to impair decision-making and contribute to high risk sexual activity. However, the association between alcohol use and risky sexual behavior may also reflect enduring individual differences in risk taking, sociability, self-control, and related variables. Both behaviors can serve similar functions related to recreation, interpersonal connection, and the pursuit of excitement or pleasure. The present study examined the extent to which high risk drinking and sexual behavior clustered together in a sample of urban minority young adult women, a demographic group at elevated risk for negative outcomes related to sexual health. The authors tested whether psychosocial functioning measured at the beginning of high school predicted classes of risk behaviors when girls were tracked longitudinally into young adulthood. Latent class analysis indicated three distinct profiles based on high risk drinking and sexual behavior (i.e., multiple sex partners) in young adulthood. The largest class (73% of the sample) reported low levels of risky drinking and sexual behavior. The next largest class (19%) reported high risk drinking and low risk sexual behavior, and the smallest class (8%) reported high levels of both behaviors. Compared to women from other racial/ethnic groups, black women were more likely to be categorized in the high risk drinking/low risk sex class. Multinomial logistic regression indicated that self-control in adolescence had a broad and enduring protective effect on risk behaviors eight years later and was associated with a greater probability of being in the low risk drinking/low risk sex class. Findings are discussed in terms of understanding the phenotypic expressions of risk behavior as they relate to early psychosocial development and the long-term protective function of self-control in reducing high risk drinking and sexual behaviors. Griffin K, Scheier L, Acevedo B, Grenard J, Botvin G. Long-term effects of self-control on alcohol use and sexual behavior among urban minority young women. *Int J Environ Res Public Health.* 2012; 9(1): 1-23.

Improved Adherence To Modern Antiretroviral Therapy Among HIV-Infected Injecting Drug Users

Adherence to antiretroviral therapy (ART) among injecting drug users (IDUs) is often suboptimal, yet little is known about changes in patterns of adherence since the advent of highly active antiretroviral therapy in 1996. The authors sought to assess levels of optimal adherence to ART among IDUs in a setting of free and universal HIV care. Data were collected through a

prospective cohort study of HIV-positive IDUs in Vancouver, British Columbia. They calculated the proportion of individuals achieving at least 95% adherence in the year following initiation of ART from 1996 to 2009. Among 682 individuals who initiated ART, the median age was 37 years (interquartile range 31-44 years) and 248 participants (36.4%) were female. The proportion achieving at least 95% adherence increased over time, from 19.3% in 1996 to 65.9% in 2009 (Cochrane-Armitage test for trend: $P < 0.001$). In a logistic regression model examining factors associated with 95% adherence, initiation year was statistically significant (odds ratio 1.08; 95% confidence interval 1.03-1.13; $P < 0.001$ per year after 1996) after adjustment for a range of drug use variables and other potential confounders. The proportion of IDUs achieving at least 95% adherence during the first year of ART has consistently increased over a 13-year period. Although improved tolerability and convenience of modern ART regimens probably explain these positive trends, by the end of the study period a substantial proportion of IDUs still had suboptimal adherence, demonstrating the need for additional adherence support strategies. Mann B, Milloy M, Kerr T, Zhang R, Montaner J, Wood E. Improved adherence to modern antiretroviral therapy among HIV-infected injecting drug users. *HIV Med.* 2012.

Living In the Here and Now: Interrelationships Between Impulsivity, Mindfulness, and Alcohol Misuse

Impulsivity and mindfulness both emphasize orientation to the present, and both have been linked to alcohol misuse, but the relationship between the two is not clearly understood. The objectives of this study are to examine the relationships between elements of impulsivity and mindfulness and to examine both variables in relation to alcohol misuse. Young adults ($N = 116$) were assessed for alcohol use, mindfulness, and impulsivity using psychometrically validated measures. Numerous significant associations were present among the facets of impulsivity and mindfulness. All impulsivity facets and three facets of mindfulness were related to alcohol consumption and adverse consequences from drinking. After controlling for other variables, only the impulsivity domains of Negative Urgency (NU), Positive Urgency, and delay discounting were significantly related to alcohol consumption and only Lack of Premeditation and NU were significantly associated with drinking-related consequences. There was considerable overlap between some elements of impulsivity and mindfulness while the overlap was negligible for other facets. The associations between mindfulness and alcohol misuse were entirely a function of impulsivity. In particular, acting on impulses while experiencing a negative affect was significantly associated with level of alcohol consumption and level of alcohol-related risk. Steep discounting of future rewards was associated with alcohol consumption while poor premeditation was associated with adverse drinking consequences. These findings illustrate the importance of jointly studying impulsivity when examining mindfulness traits. Murphy C, Mackillop J. Living in the here and now: Interrelationships between impulsivity, mindfulness, and alcohol misuse. *Psychopharmacology (Berl)*. 2012; 219(2): 527-536.

Relationship Proximity To Victims Of Witnessed Community Violence: Associations With Adolescent Internalizing and Externalizing Behaviors

Witnessing community violence has been linked with several adverse outcomes for adolescents, including emotional and behavioral problems. Among youth who have witnessed community violence, proximity to the victim of community violence is one factor that may determine, in part, the nature of adolescents' responses to community violence exposure. The present study examines whether relationship proximity to the victim of community violence is associated with internalizing and externalizing behaviors among a sample of urban and predominantly African American adolescents ($N=501$) who have witnessed community violence. In 10th grade, participants reported whether they had witnessed 10 community violence events during the past year, and, if so, whether the victim of the violence was a family member,

close friend, acquaintance, or stranger. Witnessed community violence against a family member or close friend was associated with depressive symptoms, and witnessed community violence against known individuals was associated with anxiety symptoms. Witnessing community violence against familiar persons and strangers was linked with aggressive behavior. Gender differences in these associations and implications for assessment and intervention with community violence-exposed youth are discussed. Lambert S, Boyd R, Cammack N, Ialongo N. Relationship proximity to victims of witnessed community violence: associations with adolescent internalizing and externalizing behaviors. *Am J Orthopsychiatry*. 2012; 82(1): 1-9.

Multilevel Mediation Analysis: The Effects Of Omitted Variables In The 1-1-1 Model

Multilevel mediation analysis examines the indirect effect of an independent variable on an outcome achieved by targeting and changing an intervening variable in clustered data. The authors study analytically and through simulation the effects of an omitted variable at level 2 on a 1-1-1 mediation model for a randomized experiment conducted within clusters in which the treatment, mediator, and outcome are all measured at level 1. When the residuals in the equations for the mediator and the outcome variables are fully orthogonal, the two methods of calculating the indirect effect (ab , $c - c'$) are equivalent at the between- and within-cluster levels. Omitting a variable at level 2 changes the interpretation of the indirect effect and will induce correlations between the random intercepts or random slopes. The equality of within-cluster ab and $c - c'$ no longer holds. Correlation between random slopes implies that the within-cluster indirect effect is conditional, interpretable at the grand mean level of the omitted variable. Tofighi D, West S, Mackinnon D. Multilevel mediation analysis: the effects of omitted variables in the 1-1-1 model. *Br J Math Stat Psychol*. 2012; Epub.

Longitudinal Association Between Childhood Impulsivity and Bulimic Symptoms In African American Adolescent Girls

Using a longitudinal design, the authors of this study examined the relationship between externalizing problems and impulsivity in early childhood and symptoms of disordered eating in late adolescence. Participants were urban, African American first-grade girls ($N = 119$) and their parents who were participating in a longitudinal study examining the prevention of disruptive behaviors. Impulsivity, conduct problems, and oppositional defiant behavior were assessed by parent report via structured interview questions. At 9-year follow-up, bulimic symptoms were measured by the Eating Disorder Inventory. A hierarchical regression analysis was conducted to determine the longitudinal association among impulsivity, conduct problems, and oppositional defiant behavior and bulimic symptoms. Parental report of impulsivity in first-grade girls, but not conduct problems or oppositional defiant behavior, was associated with self-reported bulimic symptoms in the girls in late adolescence ($p < .04$). These results extend previous findings of a concurrent relationship between impulsivity and dysfunctional eating behaviors to a minority sample and further indicate that behavioral impulsivity in early childhood may be used to identify children for targeted prevention of disordered eating. Bodell L, Joiner T, Ialongo N. Longitudinal association between childhood impulsivity and bulimic symptoms in African American adolescent girls. *J Consult Clin Psychol*. 2012; 80(2): 313-316.

Life Events and Depressive Symptoms In African American Adolescents: Do Ecological Domains and Timing Of Life Events Matter?

Considerable research has documented associations between adverse life events and internalizing symptoms in adolescents, but much of this research has focused on the number of events experienced, with less attention to the ecological context or timing of events. This study examined life events in three ecological domains relevant to adolescents (i.e., family, peers, themselves) as predictors of the course of depressive symptoms

among a community epidemiologically defined sample of 419 (47.2% females) urban African American adolescents. Given that youth depressive symptoms change over time, grade level was examined as a moderator. For males, the strength of associations between life events happening to participants, family life events, and peer life events and depressive symptoms did not change from grades 6-9. For females, the strength of the association between peer life events and depressive symptoms did not change over time, but the strength of associations between life events happening to participants and family life events and females' depressive symptoms decreased over time. Implications of the findings and directions for future research are discussed. Sanchez Y, Lambert S, Ialongo N. Life events and depressive symptoms in african american adolescents: Do ecological domains and timing of life events matter?. *J Youth Adolesc.* 2012; 41(4): 438-448.

Genetic Moderation Of Contextual Effects On Negative Arousal and Parenting In African-American Parents A three-stage context amplification model was tested with a sample of 345 African-American parent-child dyads. The model combined the conceptual structure of stress generation with recent findings regarding genetic susceptibility. Because the 7R + allele of the dopamine transporter (DRD4) has the potential to enhance contextual priming and arousal, this allele was examined as a potential moderator of each stage of the amplification process. Particular attention was given to the hypothesized influence of parental negative arousal on valence of parent-child interactions. The literature on genetic susceptibility led to the hypothesis that DRD4 would moderate each stage of the model in a "for better or for worse" manner. The model was partially supported. DRD4 moderated effects at all three stages of the model and, as hypothesized, DRD4 moderated contextual effects on negative arousal in a "for better or for worse" manner. Effects on parent-child interaction, however, were moderated in a "for worse" manner only. These results indicate that parenting interactions may amplify the effects of positive and negative contexts in a stress-generating manner, and that a susceptibility framework captures the way in which DRD4 moderates the impact of context on negative arousal. Beach S, Lei M, Brody G, Simons R, Cutrona C, Philibert R. Genetic moderation of contextual effects on negative arousal and parenting in African-American parents. *J Fam Psychol.* 2012; 26(1): 46-55.

Life Stress, The Dopamine Receptor Gene, and Emerging Adult Drug Use Trajectories: A Longitudinal, Multilevel, Mediated Moderation Analysis This study was designed to examine the prospective relations of life stress and genetic status with increases in drug use. African Americans (N=399) in rural Georgia (Wave 1 mean age=17 years) provided three waves of data across 27.5 months and a saliva sample from which the dopamine receptor D4 (DRD4) gene was genotyped. Multilevel growth curve modeling analysis indicated that emerging adults manifested the highest escalations in drug use when they reported high life stress and carried an allele of DRD4 with 7 or more repeats (7 β R allele). In addition, emerging adults who reported high life stress and carried the 7 β R allele evinced the largest increases in two proximal risk factors for drug use: affiliations with drug-using companions and drug use vulnerability cognitions. Furthermore, when the Gene X Environment interaction effects on the increases in affiliations with drug-using companions and vulnerability cognitions were entered into the model forecasting drug use, the Life Stress X DRD4 Status interaction on drug use became nonsignificant in the presence of the risk mechanisms. This finding provides an example of "second generation" Gene X Environment interaction research in which the interaction's effects on proximal risk mechanisms account for its effects on outcomes. Brody GH, Chen YF, Yu T, Beach SRH, Kogan SM, Simons RL, Windle M, Philibert RA. *Development and Psychopathology* 2012; 24: 941-951.

Substance Use and Delinquency Among Middle School Girls in Foster Care: A Three-Year Follow-Up of a Randomized Controlled Trial

The present study evaluated the efficacy of the Middle School Success intervention (MSS) for reducing substance use and delinquency among girls in foster care, using a randomized controlled trial design. The program was designed to fill a service gap during the summer prior to the middle school transition and to prevent delinquency, substance use, and related problems. One hundred girls in foster care and their caregivers were randomly assigned either to the intervention (n=48) or to a regular foster care control (n=52) condition. The girls completed a baseline (T1) assessment and follow-up assessments at 6 months (T2), 12 months (T3), 24 months (T4), and 36 months (T5) postbaseline. Caregivers participated in assessments from T1 through T4. This study is a follow-up to Smith, Leve, and Chamberlain's (2011) study, which examined immediate outcomes at T2. Girls in the intervention condition showed significantly lower levels of substance use than did girls in the control condition at 36 months postbaseline. The group difference was only marginally significant for delinquency. Further analyses indicated significant indirect effects of the intervention through increased prosocial behaviors that led to decreased internalizing and externalizing symptoms and then to lower levels of substance use. The direct effect of the intervention on substance use remained significant in the presence of the indirect effects. For delinquency, the intervention had positive effects mainly through increased prosocial skills. Findings highlight the importance of providing preventive intervention services for early adolescent girls in foster care. Kim HK, Leve LD. *Journal of Consulting and Clinical Psychology* 2011;79(6):740–750.

Coordinated Changes In AHRR Methylation In Lymphoblasts and Pulmonary Macrophages From Smokers

Smoking is associated with a wide variety of adverse health outcomes including cancer, chronic obstructive pulmonary disease, diabetes, depression, and heart disease. Unfortunately, the molecular mechanisms through which these effects are conveyed are not clearly understood. To examine the potential role of epigenetic factors in these processes, the authors examined the relationship of smoking to genome wide methylation and gene expression using biomaterial from two independent samples, lymphoblast DNA and RNA (n = 119) and lung alveolar macrophage DNA (n = 19). They found that in both samples current smoking status was associated with significant changes in DNA methylation, in particular at the aryl hydrocarbon receptor repressor (AHRR), a known tumor suppressor. Both baseline DNA methylation and smoker associated DNA methylation signatures at AHRR were highly correlated (r = 0.94 and 0.45, respectively). DNA methylation at the most differentially methylated AHRR CpG residue in both samples, cg0557592, was significantly associated with AHRR gene expression. Pathway analysis of lymphoblast data (genes with most significant methylation changes) demonstrated enrichment in protein kinase C pathways and in TGF beta signaling pathways. For alveolar macrophages, pathway analysis demonstrated alterations in inflammation-related processes. The authors conclude that smoking is associated with functionally significant genome wide changes in DNA methylation in both lymphoblasts and pulmonary macrophages and that further integrated investigations of these epigenetic effects of smoking on carcinogenesis and other related co-morbidities are indicated. Monick M, Beach S, Plume J, Sears R, Gerrard M, Brody G, Philibert R. Coordinated changes in AHRR methylation in lymphoblasts and pulmonary macrophages from smokers. *Am J Med Genet B Neuropsychiatr Genet.* 2012; 159B(2): 141-151.

Correlates and Contexts of US Injection Drug Initiation among Undocumented Mexican Migrant Men Who Were Deported from the United States

Preventing the onset of injection drug use is important in controlling the spread of HIV and other blood borne infections. Undocumented migrants in the United States face social, economic, and legal stressors that may

contribute to substance abuse. Little is known about undocumented migrants; drug abuse trajectories including injection initiation. To examine the correlates and contexts of US injection initiation among undocumented migrants, the authors administered quantitative surveys (N = 309) and qualitative interviews (N = 23) on migration and drug abuse experiences to deported male injection drug users in Tijuana, Mexico. US injection initiation was independently associated with ever using drugs in Mexico pre-migration, younger age at first US migration, and US incarceration. Participants' qualitative interviews contextualized quantitative findings and demonstrated the significance of social contexts surrounding US injection initiation experiences. HIV prevention programs may prevent/delay US injection initiation by addressing socio-economic and migration-related stressors experienced by undocumented migrants. Robertson A, Lozada R, Pollini R, Rangel G, Ojeda V. Correlates and contexts of US injection drug initiation among undocumented Mexican Migrant men who were deported from the United States. *AIDS Behav.* 2012; Epub Jan 2012.

Resource Consumption Of A Diffusion Model For Prevention Programs: The PROSPER Delivery System

To prepare public systems to implement evidence-based prevention programs for adolescents, it is necessary to have accurate estimates of programs' resource consumption. When evidence-based programs are implemented through a specialized prevention delivery system, additional costs may be incurred during cultivation of the delivery infrastructure. Currently, there is limited research on the resource consumption of such delivery systems and programs. In this article, the authors describe the resource consumption of implementing the PROSPER (PROmoting School-Community-University Partnerships to Enhance Resilience) delivery system for a period of 5 years in one state, and how the financial and economic costs of its implementation affect local communities as well as the Cooperative Extension and University systems. The authors used a six-step framework for conducting cost analysis, using a Cost-Procedure-Process-Outcome Analysis model (Yates, Analyzing costs, procedures, processes, and outcomes in human services: An introduction, 1996; Yates, 2009). This method entails defining the delivery System; bounding cost parameters; identifying, quantifying, and valuing systemic resource Consumption, and conducting sensitivity analysis of the cost estimates. The authors' analyses estimated both the financial and economic costs of the PROSPER delivery system. Evaluation of PROSPER illustrated how costs vary over time depending on the primacy of certain activities (e.g., team development, facilitator training, program implementation). Additionally, this work describes how the PROSPER model cultivates a complex resource infrastructure and provides preliminary evidence of systemic efficiencies. This work highlights the need to study the costs of diffusion across time and broadens definitions of what is essential for successful implementation. In particular, cost analyses offer innovative methodologies for analyzing the resource needs of prevention systems. Crowley D, Jones D, Greenberg M, Feinberg M, Spoth R. Resource consumption of a diffusion model for prevention programs: The PROSPER delivery system. *J Adolesc Health.* 2012; 50(3): 256-263.

Romantic Relationship Characteristics and Alcohol Use: Longitudinal Associations with Dual Method Contraception Use

Dual method contraception use, or the use of one type of contraceptive intended to prevent pregnancy combined with another type intended to reduce the risk of sexually transmitted infection, may be the most effective method to prevent both unintended pregnancy and sexually transmitted infection. This study tested the association between relationship length, relationship type (married, cohabiting, dating but not cohabiting), global alcohol use, and situational alcohol use and the probability of dual method contraception use from 20 to 23 years of age. Hierarchical linear modeling analyses were conducted using longitudinal data from 754 sexually active male and female young adults aged 20-23 years. Dependent variables included both any dual method contraception use and consistent dual method contraception use. Between 15%

and 20% of respondents reported consistent dual method contraception use at each time point. Longer relationship length and more committed relationship type were associated with a lower probability of both any and consistent dual method contraception use. Situational alcohol use (drinking before sex), but not global alcohol use, also was related to a lower probability of both any and consistent dual method contraception use. Increasing age was associated with a lower probability of any dual method contraception use, but was not related to consistent dual method use. Efforts to promote dual method contraception among young adults should include messages discouraging drinking before sex and supporting dual method use even in the context of committed relationships. Bailey J, Fleming C, Catalano R, Haggerty K, Manhart L. Romantic relationship characteristics and alcohol use: longitudinal associations with dual method contraception use. *J Adolesc Health*. 2012; 50(5): 450-455.

The Nonlinear Dynamics of Family Problem Solving in Adolescence: The Predictive Validity of a Peaceful Resolution Attractor In this study the authors examined the videotaped family interactions of a community sample of adolescents and their parents. Youths were assessed in early to late adolescence on their levels of antisocial behavior. At age 16-17, youths and their parents were videotaped interacting while completing a variety of tasks, including family problem solving. The interactions were coded and compared for three developmental patterns of antisocial behavior: early onset, persistent; adolescence onset; and typically developing. The mean duration of conflict bouts was the only interaction pattern that discriminated the 3 groups. In the prediction of future antisocial behavior, parent and youth reports of transition entropy and conflict resolution interacted to account for antisocial behavior at age 18-19. Families with low entropy and peaceful resolutions predicted low levels of youth antisocial behavior at age 18-19. These findings suggest the need to study both attractors and repellers to understand family dynamics associated with health and social and emotional development. Dishion T, Forgatch M, Van Ryzin M, Winter C. The nonlinear dynamics of family problem solving in adolescence: the predictive validity of a peaceful resolution attractor. *Nonlinear Dynamics Psychol Life Sci*. 2012; 16(3): 331-352.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

Front-loaded versus Weekly Counseling for Treatment of Tobacco Addiction Approximately 60%-70% of cigarette smokers who try to quit relapse by 2 weeks postcessation. The authors tested the efficacy of a front-loaded (FL) counseling intervention whose goal was to increase the likelihood of successful early abstinence and subsequent long-term abstinence. They randomized 278 adult smokers to an FL or weekly behavioral smoking cessation counseling schedule. The total number of sessions across treatment was the same for both groups. However, those assigned to the FL schedule received 6 counseling sessions in the first 2 weeks postcessation, while those in the weekly condition received 2 sessions. Participants in both groups also received standard nicotine patch treatment. At 1 year postcessation, FL participants were significantly less likely to have relapsed when continuous abstinence was used as the definition of abstinence/relapse (11.7% abstinent vs. 6.3%, hazard ratio [HR] = 0.69, $p = .007$); and there were nonsignificant trends for FL subjects to have better outcomes when abstinence was defined as never smoking for 7 or more consecutive days nor for 7 or more consecutive episodes (18.4% abstinent vs. 14.8%, HR = 0.83, $p = .20$) and as point prevalence abstinence (15.6% abstinent vs. 12.9%, $p = .11$). The relationship between FL counseling treatment and continuous abstinence was partially mediated by higher postcessation levels of social support perceived from counseling and greater use of cessation-related coping strategies. The authors conclude that FL counseling is a promising treatment model that should be evaluated further, perhaps using modifications of the FL schedule used in this study. Garvey AJ, Kalman D, Hoskinson RA Jr, Kinnunen T, Wadler BM, Thomson CC, Rosner B. Front-loaded versus weekly counseling for treatment of tobacco addiction. *Nicotine Tob Res.* 2012 14; (5): 578-585.

Temporal and Probability Discounting by Cigarette Smokers Following Acute Smoking

Abstinence Given the lack of consensus regarding changes in temporal and probability discounting as a function of smoking abstinence in cigarette smokers, the present study comprehensively examined possible changes in these processes following a period of acute smoking abstinence consistent with elevated withdrawal symptoms and craving. Computerized temporal and probability discounting assessments were collected from cigarette smokers following normal smoking and 24-hr smoking abstinence, with the order of normal smoking and abstinence sessions counterbalanced across participants. Other conditions included commodity (money and cigarettes), sign (gains and losses), and magnitude (\$50 and \$1,000). Twenty four-hour smoking abstinence resulted in a reduction in expired carbon monoxide to near-zero levels and increases in withdrawal and craving. Examination of discounting parameters as a function of smoking abstinence revealed a general pattern of increase in the temporal discounting of monetary gains and losses following abstinence but not in the temporal discounting of cigarettes or probability discounting of money or cigarettes. Pearson correlations also revealed an expected pattern of significant relationships. The present study is a comprehensive examination of temporal and probability discounting following smoking abstinence and reveals a generalized change in intertemporal decision making for monetary rewards. Yi R, Landes RD. Temporal and probability discounting by cigarette smokers following acute smoking abstinence. *Nicotine Tob Res.* 2012 May; 14(5): 547-558.

A Randomized Trial of Computer-Delivered Brief Intervention and Low-Intensity Contingency Management for Smoking During Pregnancy

Implementation of evidence-based interventions for smoking during pregnancy is challenging. The authors developed 2 highly replicable interventions for smoking during pregnancy: (a) a computer-delivered 5As-based brief intervention (CD-5As) and (b) a computer-assisted, simplified, and low-intensity contingency

management (CM-Lite). A sample of 110 primarily Black pregnant women reporting smoking in the past week were recruited from prenatal care clinics and randomly assigned to CD-5As (n = 26), CM-Lite (n = 28), CD-5As plus CM-Lite (n = 30), or treatment as usual (n = 26). Self-report of smoking, urine cotinine, and breath CO were measured 10 weeks following randomization. Participants rated both interventions highly (e.g., 87.5% of CD-5As participants reported increases in likelihood of quitting), but most CM-Lite participants did not initiate reinforcement sessions and did not show increased abstinence. CD-5As led to increased abstinence as measured by cotinine (43.5% cotinine negative vs. 17.4%; odds ratio [OR] = 10.1, p = .02) but not for CO-confirmed 7-day point prevalence (30.4% abstinent vs. 8.7%; OR = 5.7, p = .06). Collapsing across CM-Lite status, participants receiving the CD-5As intervention were more likely to talk to a doctor or nurse about their smoking (60.5% vs. 30.8%; OR = 3.0, p = .02). Low-intensity participant-initiated CM did not affect smoking in this sample, but the CD-5As intervention was successful in increasing abstinence during pregnancy. Further research should seek to replicate these results in larger and more diverse samples. Should CD-5As continue to prove efficacious, it could greatly increase the proportion of pregnant smokers who receive an evidence-based brief intervention. Ondersma SJ, Svikis DS, Lam PK, Connors-Burge VS, Ledgerwood DM, Hopper JA. A randomized trial of computer-delivered brief intervention and low-intensity contingency management for smoking during pregnancy. *Nicotine Tob Res.* 2012 Mar; 14(3): 351-360.

Tobacco Cessation Intervention During Pregnancy Among Alaska Native Women This paper describes a community-based participatory research program with Alaska Native people addressing a community need to reduce tobacco use among pregnant women and children. Tobacco use during pregnancy among Alaska Native women is described along with development of a community partnership, findings from a pilot tobacco cessation intervention, current work, and future directions. Among Alaska Native women residing in the Yukon Kuskokwim Delta region of western Alaska, the prevalence of tobacco use (cigarette smoking and/or use of smokeless tobacco) during pregnancy is 79%. Results from a pilot intervention study targeting pregnant women indicated low rates of participation and less than optimal tobacco abstinence outcomes. Developing alternative strategies to reach pregnant women and to enhance the efficacy of interventions is a community priority, and future directions are offered. Patten CA. Tobacco cessation intervention during pregnancy among Alaska Native women. *J Cancer Educ.* 2012 Apr; 27 Suppl 1: S86-90.

A Preliminary Study of the Neural Effects of Behavioral Therapy for Substance Use Disorders

The mechanisms by which behavioral therapies for substance use disorders (SUDs) exert their effects and the components of treatment that contribute most to substance use outcome remain unclear. Disruptions to aspects of impulse control and attention have been hypothesized to contribute to the development and maintenance of addiction; moreover, alterations in these processes may underlie responses to treatment. Individuals participating in a randomized clinical trial evaluating computer-assisted cognitive behavioral therapy (CBT) for substance abuse participated in fMRI Stroop before and after treatment. A non-substance-using comparison group performed the same task under test-retest conditions. The patient group demonstrated decreased Stroop-related BOLD signal in regions including the anterior cingulate, inferior frontal gyrus and midbrain at post-treatment relative to pre-treatment, and displayed a greater decrease in the subthalamic nucleus and surrounding regions compared to healthy controls following test-retest. Behavioral therapies may be associated with reduction in substance use and effects on neural systems involved in cognitive control, impulsivity, motivation and attention. DeVito EE, Worhunsky PD, Carroll KM, Rounsaville BJ, Kober H, Potenza MN. A preliminary study of the

neural effects of behavioral therapy for substance use disorders. *Drug Alcohol Depend.* 2012 May 1; 122(3): 228-235.

Varenicline Versus Bupropion XL for Smoking Cessation in Older Adolescents Despite tremendous potential public health impact, little work has focused on development of evidence-based smoking cessation treatments for adolescents, including pharmacotherapies. No prior studies have explored the feasibility and safety of varenicline and bupropion XL, 2 potentially promising pharmacotherapies, as smoking cessation treatments in adolescents. Treatment-seeking older adolescent smokers (ages 15-20) were randomized (double-blind) to varenicline (n = 15) or bupropion XL (n = 14), with 1-week titration and active treatment for 7 weeks. Structured safety, tolerability, and efficacy assessments (cotinine-confirmed 7-day point prevalence abstinence) were conducted weekly. There were no serious adverse events. Two participants discontinued bupropion XL due to adverse effects, and none discontinued varenicline. Over the course of treatment, participants receiving varenicline reduced from 14.1 ± 6.3 (mean \pm SD) to 0.9 ± 2.1 cigarettes/day (CPD, 4 achieved abstinence), while those receiving bupropion XL reduced from 15.8 ± 4.4 to 3.1 ± 4.0 CPD (2 achieved abstinence). These preliminary results support the feasibility and safety of conducting adequately powered, placebo-controlled efficacy studies of varenicline and bupropion XL for adolescent smoking cessation. Gray KM, Carpenter MJ, Lewis AL, Klintworth EM, Upadhyaya HP. Varenicline versus bupropion XL for smoking cessation in older adolescents: A randomized, double-blind pilot trial. *Nicotine Tob Res.* 2012 Feb; 14(2): 234-239.

Contingent Incentives Reduce Cigarette Smoking Among Pregnant, Methadone-Maintained Women This study examined the feasibility and efficacy of behavioral incentives for reducing cigarette smoking among pregnant methadone-maintained patients. Participants (n = 102) were assigned randomly to: (i) contingent behavioral incentives (CBI: n = 42); (ii) non-contingent behavioral incentives (NCBI: n = 28); or (iii) treatment as usual (TAU: n = 32). Study procedures were implemented at the Center for Addiction and Pregnancy in Baltimore, MD. Participants Study participants were pregnant, methadone-maintained women enrolled in substance use disorder treatment. Baseline carbon monoxide (CO) levels were calculated for each participant. Subsequently, breath samples were tested three times weekly to measure changes in smoking behavior. CBI participants received incentives for target reductions from baseline: any reduction (week 1); 10% reduction (weeks 2–4), 25% reduction (weeks 5–7), 50% reduction (weeks 8–9), 75% reduction (week 10–11); and abstinence [CO < 4 parts per million (p.p.m.)] (week 12 until delivery). NCBI participants received incentives independent of smoking CO measurement results. TAU participants received no incentives, the standard treatment at the program. CBI condition participants submitted significantly lower mean CO values than the NCBI and TAU conditions over the course of the intervention ($P < 0.0001$). Nearly half (48%) of the CBI participants met the 75% smoking reduction target and one-third (31%) met the abstinence target at week 12. In contrast, none of the NCBI met either the 75% or abstinence targets. Only 2% of the TAU participants met the 75% reduction and none of the TAU participants met the abstinence targets. These smoking behavior reductions did not yield significant differences in birth outcomes. Cigarette smoking may be reduced significantly among pregnant, methadone-maintained women through the use of contingent reinforcement for gradual reductions in breath carbon monoxide levels. Tuten M, Fitzsimons H, Chisolm MS, Nuzzo PA, Jones HE. Contingent incentives reduce cigarette smoking among pregnant, methadone-maintained women: Results of an initial feasibility and efficacy randomized clinical trial. *Addiction.* 2012 Jun 21. doi: 10.1111/j.1360-0443.2012.03923.x. [Epub ahead of print].

Delay Discounting Predicts Adolescent Substance Abuse Treatment Outcome The purpose of the current study was to identify predictors of delay discounting among adolescents receiving treatment for marijuana abuse or dependence, and to test delay discounting as a predictor of treatment outcome. Participants for this study were 165 adolescents (88% male) between the ages of 12 and 18 (mean age = 15.8 years; standard deviation = 1.3 years) who enrolled in a clinical trial comparing three behavioral treatments for adolescent marijuana abuse or dependence. Participants completed a delay discounting task at treatment onset for \$100 and \$1,000 of hypothetical money and marijuana. Overall, smaller magnitude rewards were discounted more than larger magnitude rewards. Delay discounting rates were concurrently related to demographic variables (socioeconomic status, race). Delay discounting of \$1,000 of money predicted during treatment abstinence outcomes among adolescent marijuana abusers, over and above the effects of type of treatment received. Teens who show higher levels of discounting of the future may be an important subgroup to identify at treatment onset. Youth with a greater tendency to discount the future may require different intervention strategies that address their impulsivity (e.g., targeting executive function or inhibitory control) and/or different schedules of reinforcement to address their degree of preference for immediate rewards. Stanger C, Ryan SR, Fu H, Landes RD, Jones BA, Bickel WK, Budney AJ. Delay discounting predicts adolescent substance abuse treatment outcome. *Exp Clin Psychopharmacol.* 2012 Jun; 20(3): 205-212.

The Role of Family Affect in Juvenile Drug Court Offenders' Substance Use and HIV Risk Family-based interventions targeting parenting factors, such as parental monitoring and parent-child communication, have been successful in reducing adolescent offenders' substance use and delinquency. This pilot, exploratory study focuses on family and parenting factors that may be relevant in reducing juvenile offenders' substance use and sexual risk taking behavior, and in particular examines the role of family emotional involvement and responsiveness in young offenders' risk-taking behaviors. Participants included 53 juvenile drug court offenders and their parents. Results indicate that poor parent-child communication is associated with marijuana use and unprotected sexual activity for young offenders; however, family affective responsiveness is also a significant unique predictor of unprotected sexual activity for these youth. Findings suggest that interventions focused on improving parent-child communication may reduce both marijuana use and risky sexual behavior among court-involved youth, but a specific intervention focused on improving parents and young offenders' ability to connect with and respond to one another emotionally may provide a novel means of reducing unprotected sexual risk behaviors. Tolou-Shams M, Hadley W, Conrad SM, Brown LK. The role of family affect in juvenile drug court offenders' substance use and HIV risk. *J Child Fam Stud.* 2012 Jun 1; 21(3): 449-456.

Depression as a Mediator of the Association between Substance Abuse and Negative Parenting of Fathers The role of substance abuse (SA) and depression on paternal parenting has recently gained attention in the research literature. Both SA and depression have been associated with negative parenting in fathers, but studies to date have not examined the mediating role that depression may play in the association of SA and fathering. SA, depression, and parenting data were reported by 87 fathers presenting for SA evaluation. Bootstrap mediation modeling was conducted to determine the role of depression on the association between SA and negative parenting. Depression is a significant mediator of the relationship between the severity of fathers' drug use and hostile-aggressive parenting behaviors. Fathers who had concerns about parenting or wanted help to improve the parent-child relationship had significantly higher symptoms of depression. Depressive symptoms in fathers entering SA treatment have implications for both the severity of drug abuse and negative parenting behaviors. Stover CS, Urdahl A, Easton C.

Depression as a mediator of the association between substance abuse and negative parenting of fathers. *Am J Drug Alcohol Abuse*. 2012 Jul; 38(4): 344-349.

Validation of the Delinquent Activities Scale for Incarcerated Adolescents This study examined the validity of the delinquent activities scale (DAS), based in part on the self reported delinquency (SRD) scale. Participants were 190 incarcerated adolescents (85.8% male; average age 17 years) at a juvenile correctional facility in the Northeast. While incarcerated, they were asked about substance use and delinquent activities in the 1 year prior to incarceration, as well as parental, peer, and demographic information. They were tracked at three months post-release, given the DAS, and assessed for post-release substance use. Three factors of the DAS assess general, alcohol-involved, and marijuana-involved delinquent activities. Principal components analysis was used to develop subscales within each factor. Support was found for concurrent and predictive incremental validities of these factors and their subscales in predicting substance use, with stronger findings for the general and the alcohol-involved factors. Subscales related to stealing showed lower validity than those related to more aggressive behaviors. These analyses suggest that the factors and empirically derived subscales offer researchers and clinicians a psychometrically sound approach for the assessment of adolescent misbehaviors. Reavy R, Stein LA, Paiva A, Quina K, Rossi JS. Validation of the delinquent activities scale for incarcerated adolescents. *Addict Behav*. 2012 Jul; 37(7): 875-879.

Preliminary Web-Based Measures Development for GHB: Expectancies, Functions, and Withdrawal Much of what is understood regarding gamma hydroxybutyrate (GHB) treatment is based on hospital case studies for overdose and withdrawal, and there are currently no measures developed specifically for GHB or its analogs (e.g., gamma butyrolactone and 1,4-butanediol) to assess drug effect expectancies, reasons for starting use, withdrawal effects, and knowledge and opinions about use. This pilot study (N = 61) was conducted to begin measures development to assess experiences, functions of use, and opinions regarding use as indicated by respondents taking a Web-based survey. Minimum average partial correlation and parallel analysis procedures are employed to create scales. Scales were developed to assess expectancies, reasons for use, withdrawal, and knowledge/opinions of use with median $\alpha = .79$ and that account for 8.69-24.17% of the variance. Scales have relatively good psychometric properties and replication is needed. GHB-specific measures may greatly assist in furthering our understanding of protective and risk factors for use, and withdrawal phenomena. Stein LA, Lebeau R, Clair M, Martin R, Bryant M, Storti S. Preliminary web-based measures development for GHB: Expectancies, functions, and withdrawal. *Am J Drug Alcohol Abuse*. 2012 Mar; 38(2): 121-129.

A Developmental Perspective on Neuroeconomic Mechanisms of Contingency Management

This paper provides a developmental overview of relevant theory and research on delay discounting and neuroeconomics, and their implications for contingency management (CM) approaches to treatment. Recent advances in the neuroscience of decision making have the potential to inform treatment development for adolescent substance use in general, and CM treatments in particular. CM interventions may be informed by research on delay discounting, a type of decision making that reflects how individuals value immediate versus delayed rewards. Delay discounting reliably distinguishes substance abusers from nonabusers and is a significant predictor of individual differences in response to substance use treatments. Discounting may also be important in predicting response to CM, as CM attempts to directly influence this decision-making process, shifting the preference from the immediate rewards of use to delayed rewards for choosing not to use. Multiple neural processes underlie decision making, and those processes have implications for

adolescent substance abuse. There are significant neurodevelopmental processes that differentiate adolescents from adults. These processes are implicated in delay discounting, suggesting that adolescence may reflect a period of plasticity in temporal decision making. Understanding the neural mechanisms of delay discounting has led to promising working memory interventions directly targeting the executive functions that underlie individual choices. These interventions may be particularly helpful in combination with CM interventions that offer immediate rewards for brief periods of abstinence, and may show particular benefit in adolescence due to the heightened neural plasticity of systems that underlie temporal discounting in adolescence. Stanger C, Budney AJ, Bickel WK. A developmental perspective on neuroeconomic mechanisms of contingency management. *Psychology of Addictive Behaviors*. 2012 June. [Epub ahead of print].

Intervention for Homeless, Substance Abusing Mothers: Findings from a Non-Randomized Pilot

Little empirically-based information is available regarding how best to intervene with substance-abusing homeless mothers. This study pilot-tested a comprehensive intervention with 15 homeless women and their 2- to 6-year-old children, recruited from a local family shelter. All participants were offered integrated intervention with three major components. The first component was housing which included 3 months of rental and utility assistance, and these services were not contingent upon women's abstinence from drugs or alcohol. The second and third components included 6 months of case management services and an evidence-based substance abuse treatment (Community Reinforcement Approach; CRA). Analysis revealed that women showed reductions in substance use ($F(2,22) = 3.63; p < .05$), homelessness ($F(2,24) = 25.31; p < .001$), and mental health problems ($F(2,20) = 8.5; p < .01$). Further, women reported reduced internalizing ($F(2,22) = 4.08; p < .05$) and externalizing problems ($F(2,24) = 7.7; p = .01$) among their children. The findings suggest that the intervention is a promising approach to meet the multiple needs of this vulnerable population. These positive outcomes support the need for future research to replicate the findings with a larger sample using a randomized design. Slesnick N, Erdem G. Intervention for homeless, substance abusing mothers: Findings from a non-randomized pilot. *Behav Med*. 2012 Apr; 38(2): 36-48.

Knowledge of HIV Transmission through Breast Milk among Drug-Dependent Pregnant Women

The current study examined the correlates of knowledge about human immunodeficiency virus (HIV) transmission through breast milk among drug-dependent pregnant women. There is a tremendous need to examine the knowledge about HIV transmission through breastfeeding among this largely understudied, but high-risk subset of pregnant women in order to minimize the extent to which they pass HIV to their children after giving birth. Participants included 97 pregnant women from Baltimore, MD, USA. Prevalence of drug use over the last 6 months included 37.1% reporting smoking marijuana, 36.1% injecting heroin, and 67.0% smoking crack. When asked whether HIV could be transmitted through breast milk, 72 women (74.2%) answered correctly. These results indicate that the overall knowledge about transmission through breast milk is relatively low. Furthermore, participants who smoked crack during the past 6 months and participants who were white were significantly less likely to have correct knowledge about this topic. These findings have important implications with regard to preventive interventions for this population. Future research is needed to determine how to best modify these interventions to address the specific needs of drug-dependent pregnant women, and how to specifically target white women and women who smoke crack. Zur J, Dunne E, Rose J, Latimer W. Knowledge of HIV transmission through breast milk among drug-dependent pregnant women. *AIDS Care*. 2012 Sep; 24(9): 1145-1149.

Computer-Facilitated Substance Use Screening and Brief Advice for Teens in Primary Care: An International Trial

Primary care providers need effective strategies for substance use screening and brief counseling of adolescents. The authors examined the effects of a new computer-facilitated screening and provider brief advice (cSBA) system. They used a quasi-experimental, asynchronous study design in which each site served as its own control. From 2005 to 2008, 12- to 18-year-olds arriving for routine care at 9 medical offices in New England (n = 2096, 58% females) and 10 in Prague, Czech Republic (n = 589, 47% females) were recruited. Patients completed measurements only during the initial treatment-as-usual study phase. They then conducted 1-hour provider training, and initiated the cSBA phase. Before seeing the provider, all cSBA participants completed a computerized screen, and then viewed screening results, scientific information, and true-life stories illustrating substance use harms. Providers received screening results and "talking points" designed to prompt 2 to 3 minutes of brief advice. The authors examined alcohol and cannabis use, initiation, and cessation rates over the past 90 days at 3-month follow-up, and over the past 12 months at 12-month follow-up. Compared with treatment as usual, cSBA patients reported less alcohol use at follow-up in New England (3-month rates 15.5% vs 22.9%, adjusted relative risk ratio [aRRR] = 0.54, 95% confidence interval 0.38-0.77; 12-month rates 29.3% vs 37.5%, aRRR = 0.73, 0.57-0.92), and less cannabis use in Prague (3-month rates 5.5% vs 9.8%, aRRR = 0.37, 0.17-0.77; 12-month rates 17.0% vs 28.7%, aRRR = 0.47, 0.32-0.71). Computer-facilitated screening and provider brief advice appears promising for reducing substance use among adolescent primary care patients. Harris SK, Csémy L, Sherritt L, Starostova O, Van Hook S, Johnson J, Boulter S, Brooks T, Carey P, Kossack R, Kulig JW, Van Vranken N, Knight JR. Computer-facilitated substance use screening and brief advice for teens in primary care: An international trial. *Pediatrics*. 2012 Jun; 129(6): 1072-1082.

Identifying Provider Beliefs Related to Contingency Management Adoption Using the Contingency Management Beliefs Questionnaire

Contingency management (CM) is a widely recognized empirically-supported addiction treatment; however, dissemination and adoption of CM into routine clinical practice has been slow. Assessment of beliefs about CM may highlight key barriers and facilitators of adoption and inform dissemination efforts. In the present study, the authors developed a 35-item questionnaire (contingency management beliefs questionnaire; CMBQ) assessing CM beliefs and examined the relation of these beliefs to clinician characteristics and clinical practices. The web-based study was completed by 617 substance abuse treatment providers. They examined the factor structure using exploratory factor analysis (EFA) in a randomly selected half-sample (n=318) and evaluated the generalizability of the solution using confirmatory factor analysis (CFA) in the second half-sample (n=299). EFA results suggested a 3-factor solution with 32 items retained; factors represented general barriers, training-related barriers, and pro-CM items. CFA results supported the solution, and reliability was good within each half-sample ($\alpha=0.88$ and 0.90). Therapeutic approach, years experience in addictions field, perception of CM's research support, prior CM training, and CM adoption interest were significantly associated with the factors. Overall, participants viewed CM favorably yet endorsed barriers, indicating a need for more extensive and targeted response to the most common misperceptions in dissemination efforts. Rash CJ, Petry NM, Kirby KC, Martino S, Roll J, Stitzer ML. Identifying provider beliefs related to contingency management adoption using the contingency management beliefs questionnaire. *Drug Alcohol Depend*. 2012 Mar 1; 121(3): 205-212.

Naltrexone in the Treatment of Opioid-Dependent Pregnant Women: The Case for a Considered and Measured Approach to Research

The present paper considers naltrexone to treat opioid dependence during pregnancy. The public health problem of opioid dependence and its treatment during pregnancy is reviewed first. Next, the naltrexone and opioid dependence treatment literature is summarized, with overviews of the pre-clinical and clinical research on prenatal naltrexone exposure. Finally, considerations and recommendations for future medication research for the treatment of opioid dependence in pregnant women are provided. The efficacy of long-acting injectable naltrexone relative to placebo, its blockade of opioid agonist euphoric effects, its lack of abuse and tolerance development and its modest adverse effect profile make it a potential medication for opioid-dependent pregnant women. However, it is not without seriously concerning potential drawbacks, including the difficulty surrounding medication induction that may lead to vulnerability with regard to relapse, physical dependence re-establishment, increased risk behaviors, treatment dropout and resulting opioid overdose. Before embarking on future research with this medication, the benefits and risks for the mother-embryo/fetus/child dyad should be weighed carefully. Should future research be conducted, a multi-level commitment to proactive ethical research is needed to reach the ultimate goal of improving the lives of women and children affected by opioid dependence. Jones HE, Chisolm MS, Jansson LM, Terplan M. Naltrexone in the treatment of opioid-dependent pregnant women: The case for a considered and measured approach to research. *Addiction*. 2012 Apr 4. doi: 10.1111/j.1360-0443.2012.03811.x. [Epub ahead of print].

Adolescent and Caregiver Reports of ADHD Symptoms among Inner-City Youth: Agreement, Perceived Need for Treatment, and Behavioral Correlates

This study investigated adolescent and caregiver reports of ADHD symptoms in a sample of clinically referred inner-city adolescents. Participants (N = 168) included youth ages 12-18 (54% male, 98% ethnic minority) and their caregivers who each completed diagnostic interviews of ADHD symptoms and assessments of perceived need for ADHD treatment and correlated behavior problems. Informants showed poor agreement on DSM-IV diagnostic categories and also dimensional scales, Inattention/Disorganization (I/D) and Hyperactivity/Impulsivity (H/I). Both caregiver and adolescent reports of I/D symptoms, but not H/I symptoms, were related to perceived need for ADHD treatment. Caregiver reports were linked to behavioral correlates typically associated with ADHD: I/D symptoms correlated with planning/organization and socioemotional deficits, and H/I symptoms correlated with externalizing and behavior regulation deficits. In contrast, adolescent reports of I/D were related to internalizing and externalizing problems, and their reports of H/I correlated with externalizing only. Few gender effects were found. Study results underscore the developmental salience of I/D symptoms and have implications for ADHD diagnosis and treatment planning for adolescents. Hogue A, Dauber S, Lichvar E, Spiewak G. Adolescent and caregiver reports of ADHD symptoms among inner-city youth: Agreement, perceived need for treatment, and behavioral correlates. *J Atten Disord*. 2012 Apr 27. [Epub ahead of print].

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Enhanced Attenuation Of Nicotine Discrimination In Rats By Combining Nicotine-Specific Antibodies With A Nicotinic Receptor Antagonist

Tobacco addiction requires activation by nicotine of a variety of central nicotinic acetylcholine receptors (nAChRs). In animals, both nAChR antagonists and immunization against nicotine can reduce nAChR activation by nicotine and block a variety of addiction-relevant behaviors. However, clinical use of nAChR antagonists for smoking cessation is limited by dose-related side effects, and immunization does not reliably produce sufficient antibody levels in smokers to enhance smoking cessation rates. Combining these approaches may be one way of addressing the limitations of each while enhancing overall efficacy. This study examined the individual and combined effects of passive immunization with the monoclonal nicotine-specific antibody Nic311 and the nicotinic receptor antagonist mecamylamine (MEC) on nicotine's discriminative stimulus effects. Rats were trained to discriminate 0.4 mg/kg of nicotine from saline using a two-lever operant discrimination procedure. Antagonism of nicotine discrimination by Nic311 (160 mg/kg i.v.) and ascending doses of MEC (0.03, 0.1, 0.3, and 1.0 mg/kg s.c.) was assessed across four consecutive daily 2-min extinction test sessions using a 2×2 design. Nic311 alone produced a 24-48% reduction in % nicotine-lever responding (%NLR) across all four test sessions. MEC produced a dose-dependent decrease in %NLR, with no effect at the two lowest doses and 80-93% attenuation at the two highest doses. Nic311 combined with MEC significantly suppressed %NLR at every MEC dose (85-92% reduction across all four test sessions). Very low doses of MEC that were ineffective alone completely blocked nicotine discrimination when combined with Nic311. These data demonstrate that nicotine-specific antibodies and MEC can work synergistically to suppress the subjective effects of nicotine and suggest that low doses of MEC may significantly enhance the efficacy of immunotherapy. LeSage MG, Shelley D, Pravetoni M, Pentel PR. Enhanced attenuation of nicotine discrimination in rats by combining nicotine-specific antibodies with a nicotinic receptor antagonist. *Pharmacol Biochem Behav.* 2012 Jul; 102(1): 157-162. Epub 2012 Apr 4.

AAVrh.10-Mediated Expression Of An Anti-Cocaine Antibody Mediates Persistent Passive Immunization That Suppresses Cocaine-Induced Behavior

Cocaine addiction is a major problem affecting all societal and economic classes for which there is no effective therapy. The authors hypothesized an effective anti-cocaine vaccine could be developed by using an adeno-associated virus (AAV) gene transfer vector as the delivery vehicle to persistently express an anti-cocaine monoclonal antibody in vivo, which would sequester cocaine in the blood, preventing access to cognate receptors in the brain. To accomplish this, they constructed AAVrh.10antiCoc. Mab, an AAVrh.10 gene transfer vector expressing the heavy and light chains of the high affinity anti-cocaine monoclonal antibody GNC92H2. Intravenous administration of AAVrh.10antiCoc. Mab to mice mediated high, persistent serum levels of high-affinity, cocain-specific antibodies that sequestered intravenously administered cocaine in the blood. With repeated intravenous cocaine challenge, naive mice exhibited hyperactivity, while the AAVrh.10antiCoc.Mab-vaccinated mice were completely resistant to the cocaine. These observations demonstrate a novel strategy for cocaine addiction by requiring only a single administration of an AAV vector mediating persistent, systemic anti-cocaine passive immunity. Rosenberg JB, Hicks MJ, De BP, Pagovich O, Frenk E, Janda KD, Wee S, Koob GF, Hackett NR, Kaminsky SM, Worgall S, Tignor N, Mezey JG, Crystal RG. Mediated expression of an anti-cocaine antibody mediates persistent passive immunization that suppresses cocaine-induced behavior. *Hum Gene Ther.* 2012 May; 23(5): 451-459.

Effects Of The Specific $\alpha 4\beta 2$ nAChR Antagonist, 2-Fluoro-3-(4-Nitrophenyl)

Deschloroepibatidine, On Nicotine Reward-Related Behaviors In Rats and Mice

Alleviating addiction to tobacco products could prevent millions of deaths. Investigating novel compounds selectively targeting $\alpha 4\beta 2$ nAChRs hypothesized to have a key role in the rewarding effects of nicotine may be a useful approach for future treatment. The present study was designed to evaluate 2-fluoro-3-(4-nitrophenyl) deschloroepibatidine (4-nitro-PFEB), a potent competitive antagonist of neuronal $\alpha 4\beta 2$ nAChRs, in several animal models related to nicotine reward: drug discrimination, intracranial self-stimulation (ICSS), conditioned place preference, and limited access to self-administration. Long Evans rats were trained in a two-lever discrimination procedure to discriminate 0.4 mg/kg nicotine (s.c.) from saline. Male Sprague-Dawley rats were stereotaxically implanted with electrodes and trained to respond for direct electrical stimulation of the medial forebrain bundle. ICR mice were evaluated using an unbiased place preference paradigm, and finally, male Wistar rats were implanted with intrajugular catheters and tested for nicotine self-administration under limited access (1 h/day). 4-Nitro-PFEB attenuated the discriminative stimulus effects of nicotine, but alone did not produce nicotine-like discriminative stimulus effects. Nicotine-induced facilitation of ICSS reward thresholds was reversed by 4-nitro-PFEB, which alone had no effect on thresholds. 4-Nitro-PFEB also blocked the conditioned place preference produced by nicotine, but alone had no effect on conditioned place preference. Finally, 4-nitro-PFEB dose-dependently decreased nicotine self-administration. These results support the hypothesis that neuronal $\alpha 4\beta 2$ nAChRs play a key role in mediating the rewarding effects of nicotine and further suggest that targeting $\alpha 4\beta 2$ nAChRs may yield a potential candidate for the treatment of nicotine dependence. Tobey KM, Walentiny DM, Wiley JL, Carroll FI, Damaj MI, Azar MR, Koob GF, George O, Harris LS, Vann RE. Effects of the specific $\alpha 4\beta 2$ nAChR antagonist, 2-fluoro-3-(4-nitrophenyl) deschloroepibatidine, on nicotine reward-related behaviors in rats and mice. *Psychopharmacology (Berl)*. 2012 Apr 22.

An Antidote For Acute Cocaine Toxicity

Not only has immunopharmacotherapy grown into a field that addresses the abuse of numerous illicit substances, but also the treatment methodologies within immunopharmacotherapy have expanded from traditional active vaccination to passive immunization with anti-drug monoclonal antibodies, optimized mAb formats, and catalytic drug-degrading antibodies. Many laboratories have focused on transitioning distinct immunopharmacotherapeutics to clinical evaluation, but with respect to the indication of cocaine abuse, only the active vaccine TA-CD, which is modeled after our original cocaine hapten GNC, has been carried through to human clinical trials. The successful application of murine mAb GNC92H2 to the reversal of cocaine overdose in a mouse model prompted investigations of human immunoglobulins with the clinical potential to serve as cocaine antidotes. The authors now report the therapeutic utility of a superior clone, human mAb GNCgzk ($K(d) = 0.18$ nM), which offers a 10-fold improvement in cocaine binding affinity. The GNCgzk manifold was engineered for rapid cocaine clearance, and administration of the $F(ab')_2$ and Fab formats even after the appearance of acute behavioral signs of cocaine toxicity granted nearly complete prevention of lethality. Thus, contrary to the immunopharmacotherapeutic treatment of drug self-administration, minimal antibody doses were shown to counteract the lethality of a molar excess of circulating cocaine. Passive vaccination with drug-specific antibodies represents a viable treatment strategy for the human condition of cocaine overdose. Treweek JB Janda KD. An antidote for acute cocaine toxicity. *Mol Pharm*. 2012 Apr 2; 9(4): 969-978.

Synthesis, Radioiodination And *In Vitro* And *In Vivo* Sigma Receptor Studies Of N-1-Allyl-N'-4-Phenethylpiperazine Analogs Sigma-1 (Σ (1))

Receptor radioligands are useful for basic pharmacology studies and for imaging studies in neurology, psychiatry and oncology. The authors derived a hybrid structure, N-1-allyl-N'-4-phenethylpiperazine, from known ligands TPCNE and SA4503 for use as a scaffold for development of radioiodinated σ (1) receptor ligands. E- and Z-N-1-(3'-iodoallyl)-N'-4-(3'',4''-dimethoxyphenethyl)-piperazine (E-1 and Z-1), N-1-allyl-N'-4-(3',4'-dimethoxyphenethyl)-piperazine (2) and E-N-1-(3'-iodoallyl)-N'-4-(3''-methoxy-4'-hydroxyphenethyl)-piperazine (3) were synthesized. Affinities for σ (1) and σ (2) receptors were determined. [(125)I]E-1 and [(125)I]Z-1 were prepared and evaluated *in vivo* in mice. [(125)I]E-1 was further evaluated in σ (1) receptor binding assays *in vitro*. E-1 displayed moderately high apparent affinity (15 nM) for σ (1) sites and 84-fold selectivity against σ (2) sites. Z-1 showed similar σ (1) affinity, but only 23-fold selectivity. In contrast, 2 exhibited poor binding to both subtypes, while 3 had good affinities but poor selectivity. E-1 profiled as a probable antagonist in the phenytoin shift assay. [(125)I]E-1 and [(125)I]Z-1 were prepared in good yields and with high specific radioactivities. Log D(7.4) values (2.25 and 2.27) fall within the optimal range for *in vivo* studies. Both radioligands selectively labeled σ (1) receptors in mouse brain and peripheral organs *in vivo*. [(125)I]E-1 showed a higher level of specific binding than [(125)I]Z-1 and displayed good metabolic stability. Further, [(125)I]E-1 selectively labeled σ (1) receptors in mouse brain homogenates (K(d) 3.79 nM; B(max)=599 fmol/mg protein). [(125)I]E-1 is a selective σ (1) receptor radioligand that exhibits properties amenable to *in vitro* and *in vivo* studies, with possible extension to single photon emission computed tomography using iodine-123. Lever SZ, Xu R, Fan KH, Ferguson-Cantrell EA, Carmack TL, Watkinson LD, Lever JR. Synthesis, radioiodination and *in vitro* and *in vivo* sigma receptor studies of n-1-allyl-n'-4-phenethylpiperazine analogs sigma-1 (σ (1)). Nucl Med Biol. 2012 Apr; 39(3): 401-414.

Influence Of Chronic Dopamine Transporter Inhibition By RTI-336 On Motor Behavior, Sleep, and Hormone Levels In Rhesus Monkeys Dopamine Transporter (DAT)

Inhibitors have been developed as a promising treatment approach for cocaine dependence. However, the stimulant effects of DAT inhibitors have the potential to disrupt sleep patterns, and the influence of long-term treatment on dopamine neurochemistry is still unknown. The objectives of this study were to (1) explore the stimulant-related effects of chronic DAT inhibitor (RTI-336) treatment on motor activity and sleep-like measures in male rhesus monkeys (*Macaca mulatta*; n = 4) and (2) to determine the effect of drug treatment on prolactin and cortisol levels. Subjects were fitted with a collar-mounted activity monitor to evaluate their motor activity, with 4 days of baseline recording preceding 21 days of daily saline or RTI-336 (1 mg/kg/day; intramuscular) injections. Blood samples were collected immediately prior to and following chronic treatment to assess hormone levels. RTI-336 produced a significant increase in locomotor activity at the end of the daytime period compared to saline administration. During the 3-week treatment period, sleep efficiency was decreased and the fragmentation index and latency to sleep onset were significantly increased. Hormone levels were not changed throughout the study. Chronic treatment with RTI-336 has a mild but significant stimulant effect, as evidenced by the significant increase in activity during the evening period which may cause minor disruptions in sleep measures. Andersen ML, Sawyer EK, Carroll FI, Howell LL. Influence of chronic dopamine transporter inhibition by rti-336 on motor behavior, sleep, and hormone levels in rhesus monkeys dopamine transporter (dat). Exp Clin Psychopharmacol. 2012 Apr; 20(2): 77-83.

A Double-Blind Randomized Controlled Trial Of N-Acetylcysteine In Cannabis-Dependent Adolescents

Preclinical findings suggest that the over-the-counter supplement N-acetylcysteine (NAC), via glutamate modulation in the nucleus accumbens, holds promise as a pharmacotherapy for substance dependence. The authors investigated NAC as a novel cannabis cessation treatment in adolescents, a vulnerable group for whom existing treatments have shown limited efficacy. In an 8-week double-blind randomized placebo-controlled trial, treatment-seeking cannabis-dependent adolescents (ages 15-21 years; N=116) received NAC (1200 mg) or placebo twice daily as well as a contingency management intervention and brief (<10 minutes) weekly cessation counseling. The primary efficacy measure was the odds of negative weekly urine cannabinoid test results during treatment among participants receiving NAC compared with those receiving placebo, in an intent-to-treat analysis. The primary tolerability measure was frequency of adverse events, compared by treatment group. Participants receiving NAC had more than twice the odds, compared with those receiving placebo, of having negative urine cannabinoid test results during treatment (odds ratio=2.4, 95% CI=1.1-5.2). Exploratory secondary abstinence outcomes favored NAC but were not statistically significant. NAC was well tolerated, with minimal adverse events. This is the first randomized controlled trial of pharmacotherapy for cannabis dependence in any age group to yield a positive primary cessation outcome in an intent-to-treat analysis. Findings support NAC as a pharmacotherapy to complement psychosocial treatment for cannabis dependence in adolescents. Gray KM, Carpenter MJ, Baker NL, Desantis SM, Kryway E, Hartwell KJ, McRae-Clark AL, Brady KT. A double-blind randomized controlled trial of N-Acetylcysteine in cannabis-dependent adolescents. *Am J Psychiatry*. 2012 Jun 15. [Epub ahead of print]

A Retrospective Analysis of Two Randomized Trials of Bupropion for Methamphetamine Dependence: Suggested Guidelines for Treatment Discontinuation/Augmentation

Two clinical trials have shown efficacy for bupropion in treating methamphetamine (MA) dependence among those with moderate baseline MA use. However, treatment response is highly variable and it is unclear what duration of treatment is necessary to determine if maintaining the treatment course is indicated or if discontinuation or augmentation is appropriate. The present study assessed the relationship among early bupropion treatment response for moderate MA users and end-of-treatment (EOT) abstinence. These data provide estimates of the duration of treatment and the degree of responsiveness required to persist in bupropion treatment. Participants with moderate baseline MA use in the bupropion condition of two randomized double-blind placebo controlled trials were included. The relationship between early treatment response and EOT outcomes was assessed with Receiver Operating Characteristic (ROC) curves. With thrice weekly urine drug testing, excellent predictive power was established in the first two weeks of treatment. The inability to achieve at least three MA negative samples in the first two weeks is associated with greater than 90% likelihood of treatment failure. More closely approximating clinical settings, once-weekly testing featured reliable predictive power within three weeks, suggesting that the failure to produce at least two clean samples in the first three weekly visits confers high risk of treatment failure. The findings provide preliminary evidence to guide clinical decisions for moderate MA users receiving bupropion. The results are consistent with data from the smoking cessation literature and may highlight the importance of early response in addiction treatment. Brensilver M, Heinzerling KG, Swanson AN, Shoptaw SJ. A retrospective analysis of two randomized trials of bupropion for methamphetamine dependence: Suggested guidelines for treatment discontinuation/augmentation. *Drug Alcohol Depend*. 2012 Apr 23. [Epub ahead of print]

A Proof-Of-Concept Randomized Controlled Study Of Gabapentin: Effects On Cannabis Use Withdrawal and Executive Function Deficits In Cannabis-Dependent Adults

There are no FDA-approved pharmacotherapies for cannabis dependence. Cannabis is the most widely used illicit drug in the world and patients seeking treatment for primary cannabis dependence represent 25% of all substance use admissions. The authors conducted a phase IIa proof-of-concept pilot study to examine the safety and efficacy of a calcium channel/GABA modulating drug gabapentin for the treatment of cannabis dependence. A 12-week randomized double-blind placebo-controlled clinical trial was conducted in 50 unpaid treatment-seeking male and female outpatients aged 18-65 years diagnosed with current cannabis dependence. Subjects received either gabapentin (1200 mg/day) or matched placebo. Manual-guided abstinence-oriented individual counseling was provided weekly to all participants. Cannabis use was measured by weekly urine toxicology and by self-report using the Timeline Followback Interview. Cannabis withdrawal symptoms were assessed using the Marijuana withdrawal Checklist. Executive function was measured using subtests from the Delis-Kaplan Executive Function System. Relative to placebo, gabapentin significantly reduced cannabis use as measured both by urine toxicology ($p=0.001$) and by the Timeline Followback Interview ($p=0.004$) and significantly decreased withdrawal symptoms as measured by the Marijuana withdrawal Checklist ($p<0.001$). Gabapentin was also associated with significantly greater improvement in overall performance on tests of executive function ($p=0.029$). This POC pilot study provides preliminary support for the safety and efficacy of gabapentin for treatment of cannabis dependence that merits further study and provides an alternative conceptual framework for treatment of addiction aimed at restoring homeostasis in brain stress systems that are dysregulated in drug dependence and withdrawal. Mason BJ, Crean R, Goodell V, Light JM, Quello S, Shadan F, Buffkins K, Kyle M, Adusumalli M, Begovic A, Rao S. A proof-of-concept randomized controlled study of gabapentin: Effects on cannabis use withdrawal and executive function deficits In cannabis-dependent adults. *Neuropsychopharmacology* 2012 Jun; (7): 1689-1698.

Pharmacodynamic Profile Of Tramadol In Humans: Influence Of Naltrexone Pretreatment

Tramadol is a prescription analgesic that activates mu opioid and monoamine receptor systems. Tramadol is thought to have limited abuse potential compared to mu opioid agonists, but laboratory data indicate that it shares some of their pharmacodynamic effects. This study evaluated the effect of mu opioid receptor blockade with naltrexone on the pharmacodynamic action of tramadol in humans. This inpatient, double-blind, randomized, within-subject study examined the effects of oral placebo, tramadol (87.5, 175, and 350 mg), and hydromorphone (4 and 16 mg; positive control) after 1 h pretreatment with oral naltrexone (0 and 50 mg). Ten recreational opioid users completed the study. Pharmacodynamic effects were measured before and for 7 h after initial drug administration. Lower doses of tramadol and hydromorphone were generally placebo-like. Hydromorphone (16 mg) produced prototypic mu opioid agonist-like effects that were blocked by naltrexone. Tramadol (350 mg) produced miosis and increased ratings of "Good Effects" and "Liking" but also increased ratings of "Bad Effects." Naltrexone reversed tramadol-induced physiological effects and mydriasis emerged, but unlike results with hydromorphone, naltrexone only partially attenuated tramadol's positive subjective effects and actually enhanced several unpleasant subjective ratings. Naltrexone can be used to disentangle the mixed neuropharmacological actions of tramadol. High-dose tramadol produces a mixed profile of effects. These data suggest that both mu and non-mu opioid actions play a role in tramadol's subjective profile of action. Stoops WW, Lofwall MR, Nuzzo PA, Craig LB, Siegel AJ, Walsh SL. Pharmacodynamic profile of tramadol in humans: influence of naltrexone pretreatment. *Psychopharmacology (Berl)*. 2012 May 24. [Epub ahead of print]

next 2 days: (1) subjects could work for the test dose over 7 trials (1/7th of total dose/trial), and (2) subjects could work for either a portion of the dose (1/7th) or money (\$3) over 7 trials. Physiological and subjective measures were collected before and after drug administration for all sessions. Subjects never worked to self-administer placebo regardless of whether money was available. In both self-administration sessions, oxycodone self-administration was dose-dependent. Subjects worked less for drug (28 mg oxycodone) when money was available but only modestly so. Oxycodone dose-dependently increased VAS ratings of positive drug effects (e.g., "like") during sample sessions ($p < .05$). These reports were positively correlated with self-administration behavior (e.g., "like," $r = .65$). These data suggest that both procedures are sensitive for detecting the reinforcing properties of intranasal oxycodone and may be used to further explore the characteristics of opioid compounds and potential pharmacotherapies for treatment. Middleton LS, Lofwall MR, Nuzzo PA, Siegel AJ, Walsh SL. Intranasal oxycodone self-administration in non-dependent opioid abusers. *Exp Clin Psychopharmacol*. 2012 Jun 11. [Epub ahead of print]

Effects Of Repeated Oxycodone Administration On Its Analgesic and Subjective Effects In Normal, Healthy Volunteers Tolerance to the analgesic effects of opioids has been demonstrated in laboratory animals after repeated drug administration; yet, this effect has been studied less frequently under controlled laboratory conditions in humans. This within-subject, double-blind, placebo-controlled study was designed to determine whether tolerance developed to the analgesic, subjective, and physiological effects of the commonly prescribed opioid oxycodone when it was administered daily for 5 days. The effects of oxycodone (0, 5, and 20 mg/70 kg, orally) were compared, using a within-session cumulative dosing procedure, on the first and fifth days of the 'daily' dosing phase to assess for tolerance; active oxycodone was administered on the second and fourth days of the daily dosing phase. Changes in the effects of oxycodone were also compared when the medication was only administered on the first and the fifth day of a 5-day 'intermittent' dosing phase; placebo medication was administered on the second and fourth days of the intermittent dosing phase. A 9-day 'washout' period occurred between phases during which no medication was administered. Healthy volunteers (N=10) with no history of drug dependence or current drug use participated in this outpatient study. Analgesia was assessed using the cold pressor test, pain and drug effects were measured using a variety of questionnaires, and pupil diameter was monitored as an index of physiological effects. When administered daily, no differences were observed in oxycodone-induced analgesia between the first and the fifth days, but tolerance did develop to some of the positive subjective effects of oxycodone. In contrast, oxycodone-induced analgesia and participant ratings of some positive subjective drug effects were greater on the fifth compared with the first day of the intermittent dosing phase. No differences in the miotic effects of oxycodone between the first and the fifth days of either dosing phase were detected. Although obtained under limited experimental conditions, these findings suggest that tolerance may not develop to the analgesic effects of therapeutic doses of oxycodone under short-term daily dosing conditions, even though some of its subjective effects may decrease. These data also suggest that intermittent administration may enhance the analgesic effects of oxycodone, while also increasing some of the drug's positive subjective effects related to abuse liability. Cooper ZD, Sullivan MA, Vosburg SK, Manubay JM, Haney M, Foltin RW, Evans SM, Kowalczyk WJ, Saccone PA, Comer SD. Effects of repeated oxycodone administration on its analgesic and subjective effects in normal, healthy volunteers. *Behav Pharmacol*. 2012 Jun; 23(3): 271-279.

A Human Laboratory Study Investigating the Effects Of Quetiapine On Marijuana Withdrawal and Relapse In Daily Marijuana Smokers

Marijuana withdrawal contributes to the high relapse rates in individuals seeking treatment for marijuana-use disorders. Quetiapine, an atypical antipsychotic, reduces characteristic symptoms of marijuana withdrawal in a variety of psychiatric conditions, including mood lability, sleep disruption and anorexia. This human laboratory study investigated the effectiveness of quetiapine to decrease marijuana withdrawal and relapse to marijuana use in non-treatment-seeking marijuana smokers. Volunteers were maintained on placebo or quetiapine (200mg/day) in this double-blind, counter-balanced, within-subject study consisting of two 15-day medication phases, the last 8 days of which were in-patient. On the first in-patient day, active marijuana [6.2% delta (9)-tetrahydrocannabinol (THC)] was repeatedly smoked under controlled conditions. For the next 3 days, inactive marijuana (0.0% THC) was available for self-administration (withdrawal). On the subsequent 4 days, active marijuana (6.2% THC) was available for self-administration (relapse). Volunteers (n=14) who smoked an average of 10 marijuana cigarettes/day, 7 days/week, completed the study. Under placebo, withdrawal was marked by increased subjective ratings of negative mood, decreased sleep quality, and decreased caloric intake and weight loss. Compared with placebo, quetiapine improved sleep quality, increased caloric intake and decreased weight loss. However, quetiapine increased marijuana craving and marijuana self-administration during the relapse phase. These data do not suggest that quetiapine shows promise as a potential treatment for marijuana dependence. Cooper ZD, Foltin RW, Hart CL, Vosburg SK, Comer SD, Haney M. A human laboratory study investigating the effects of quetiapine on marijuana withdrawal and relapse in daily marijuana smokers. *Addict Biol.* 2012 Jun 28. doi: 10.1111/j.1369-1600.2012.00461.x. [Epub ahead of print]

Galantamine Attenuates Some Of The Subjective Effects Of Intravenous Nicotine and Improves Performance On A Go No-Go Task In Abstinent Cigarette Smokers: A Preliminary Report

Galantamine (GAL), a reversible and competitive inhibitor of acetylcholinesterase, is used clinically in the treatment of Alzheimer's dementia. Some preclinical and clinical studies support the potential efficacy of cholinesterase inhibitors for smoking cessation, although their effects on the behavioral and physiological responses to nicotine have not been examined. The goal of this study was to characterize GAL's actions on multiple outcomes, including withdrawal severity and cognitive performance, as well as subjective and physiological responses to nicotine administered intravenously. A total of 12 smokers participated in a double-blind, placebo-controlled, crossover study. Smokers had two 4-day treatment periods, assigned in random sequence, to GAL (8 mg/day) or placebo treatment. On day 4 of each treatment phase, smokers had an experimental session in which they received an intravenous (IV) dose of saline or 1 mg/70 kg nicotine, 1 h apart, in a random order. GAL attenuated the self-reported rating of "craving for cigarettes" and prevented decrements in performance in a Go/No-Go task. In response to IV nicotine, GAL treatment attenuated the self-report ratings of "like the drug effects," "good drug effects," "bad drug effects," and "stimulated." These findings support the potential utility of GAL as a treatment for smoking cessation. Sofuoglu M, Herman AI, Li Y, Waters AJ. Galantamine attenuates some of the subjective effects of intravenous nicotine and improves performance on a Go No-Go task in abstinent cigarette smokers: A preliminary report. *Psychopharmacology (Berl)*. 2012 Jun 15. [Epub ahead of print]

Smoking and Genetic Risk Variation Across Populations Of European, Asian, and African American Ancestry – A Meta-Analysis Of Chromosome 15q25

Recent meta-analyses of European ancestry subjects show strong evidence for association between smoking quantity and multiple genetic variants on chromosome 15q25. This meta-analysis extends the examination of association between distinct genes in the CHRNA5-CHR3A-CHRNA3-CHRNA4 region and smoking

Influence Of Acute Bupropion Pre-Treatment On The Effects Of Intranasal Cocaine The aim of this experiment was to determine the influence of acute bupropion pre-treatment on subject-rated effects and choice of intranasal cocaine versus money. The study was a randomized, within-subject, placebo-controlled, double-blind experiment conducted in an out-patient research unit. Participants were eight cocaine-using adults. Subjects completed nine experimental sessions in which they were pre-treated with 0, 100 or 200 mg oral immediate release bupropion. Ninety minutes later they sampled an intranasal cocaine dose [4 (placebo), 15 or 45 mg] and made six choices between that dose and an alternative reinforcer (US\$0.25), available on independent, concurrent progressive ratio schedules. Subjects also completed a battery of subject-rated, performance and physiological measures following the sample doses of cocaine. After 0 mg bupropion, the high dose of cocaine (45 mg) was chosen five of six times on average compared to 2.25 of six choices for placebo cocaine (4 mg) ($P < 0.05$). Active bupropion reduced choice of 45 mg cocaine to 3.13 (100 mg) or 4.00 (200 mg) out of six drug choices on average. Bupropion also consistently enhanced positive subject-rated effects of cocaine (e.g. good effects; willing to take again) while having no effects of its own. The atypical antidepressant, bupropion, acutely appears to reduce preference for intranasal cocaine versus a small amount of money but to increase reported positive experiences of the drug. Stoops WW, Lile JA, Glaser PE, Hays LR, Rush CR. Influence of acute bupropion pre-treatment on the effects of intranasal cocaine. *Addiction*. 2012 Jun; 107(6): 1140-1147.

Guanfacine Effects On Stress, Drug Craving and Prefrontal Activation In Cocaine Dependent Individuals: Preliminary Findings Cocaine dependence is associated with increased stress and drug cue-induced craving and physiological arousal but decreased prefrontal activity to emotional and cognitive challenge. As these changes are associated with relapse risk, we investigated the effects of α_2 receptor agonist guanfacine on these processes. Twenty-nine early abstinent treatment-seeking cocaine dependent individuals were randomly assigned to either daily placebo or guanfacine (up to 3 mg) for four weeks. In a laboratory experiment, all patients were exposed to three 10-min guided imagery conditions (stress/stress, drug cue/drug cue, stress/drug cue), one per day, consecutively in a random, counterbalanced order. Subjective craving, anxiety and arousal as well as cardiovascular output were assessed repeatedly. Brain response to stress, drug cue and relaxing imagery was also assessed during a functional magnetic resonance (fMRI) imaging session. In the current study, guanfacine was found to be safe and well-tolerated. Lower basal heart rate and blood pressure was observed in the guanfacine versus placebo group. Guanfacine lowered stress and cue-induced nicotine craving and cue-induced cocaine craving, anxiety and arousal. The guanfacine group also showed increased medial and lateral prefrontal activity following stress and drug cue exposure compared with placebo. Data suggest further exploration of guanfacine is warranted in terms of its potential for reducing stress-induced and cue-induced drug craving and arousal. Fox HC, Seo D, Tuit K, Hansen J, Kimmerling A, Morgan PT, Sinha R. Guanfacine effects on stress, drug craving and prefrontal activation in cocaine dependent individuals: preliminary findings. *J Psychopharmacol*. 2012 Jul; 26(7): 958-972. Epub 2012 Jan 9.

Intranasal Oxycodone Self-Administration In Non-Dependent Opioid Abusers Oxycodone, an opioid with known abuse liability, is misused by the intranasal route. The authors' objective was to develop a model of intranasal oxycodone self-administration useful for assessing the relative reinforcing effects of opioids and potential pharmacotherapies for opioid use disorders. Healthy, sporadic intranasal opioid abusers ($n = 8$; 7 M, 1 F) completed this inpatient 2.5-week, randomized, double-blind, placebo-controlled, crossover study. Each intranasal oxycodone dose (0, 14 & 28 mg) was tested in a separate 3-day block of sessions. The first day of each block was a sample session in which the test dose was given. Two randomized progressive ratio sessions were conducted on the

quantity to Asian and African American populations to confirm and refine specific reported associations. Association results for a dichotomized cigarettes smoked per day phenotype in 27 datasets (European ancestry (N = 14,786), Asian (N = 6,889), and African American (N = 10,912) for a total of 32,587 smokers) were meta-analyzed by population and results were compared across all three populations. The authors demonstrate association between smoking quantity and markers in the chromosome 15q25 region across all three populations, and narrow the region of association. Of the variants tested, only rs16969968 is associated with smoking ($P < 0.01$) in each of these three populations (odds ratio [OR]=1.33, 95% CI=1.25-1.42, $P=1.1 \times 10^{-17}$ in meta-analysis across all population samples). Additional variants displayed a consistent signal in both European ancestry and Asian datasets, but not in African Americans. The observed consistent association of rs16969968 with heavy smoking across multiple populations, combined with its known biological significance, suggests rs16969968 is most likely a functional variant that alters risk for heavy smoking. The authors interpret additional association results that differ across populations as providing evidence for additional functional variants, but were unable to further localize the source of this association. Using the cross-population study paradigm provides valuable insights to narrow regions of interest and inform future biological experiments. Chen LS, Saccone NL, Culverhouse RC, Bracci PM, Chen CH, Dueker N, Han Y, Huang H, Jin G, Kohno T, Ma JZ, Przybeck TR, Sanders AR, Smith JA, Sung YJ, Wenzlaff AS, Wu C, Yoon D, Chen YT, Cheng YC, Cho YS, David SP, Duan J, Eaton CB, Furberg H, Goate AM, Gu D, Hansen HM, Hartz S, Hu Z, Kim YJ, Kittner SJ, Levinson DF, Mosley TH, Payne TJ, Rao DC, Rice JP, Rice TK, Schwantes-An TH, Shete SS, Shi J, Spitz MR, Sun YV, Tsai FJ, Wang JC, Wrensch MR, Xian H, Gejman PV, He J, Hunt SC, Kardina SL, Li MD, Lin D, Mitchell BD, Park T, Schwartz AG, Shen H, Wiencke JK, Wu JY, Yokota J, Amos CI, Bierut LJ. Smoking and genetic risk variation across populations of European, Asian, and African American ancestry--a meta-analysis of chromosome 15q25. *Genet Epidemiol.* 2012 May; 36(4): 340-351.

μ -Opioid Receptor Availability In The Amygdala Is Associated With Smoking For Negative Affect Relief

The perception that smoking relieves negative affect contributes to smoking persistence. Endogenous opioid neurotransmission, and the μ -opioid receptor (MOR) in particular, plays a role in affective regulation and is modulated by nicotine. The authors examined the relationship of MOR binding availability in the amygdala to the motivation to smoke for negative affect relief and to the acute effects of smoking on affective responses. Twenty-two smokers were scanned on two separate occasions after overnight abstinence using [(11)C]carfentanil positron emission tomography imaging: after smoking a nicotine-containing cigarette and after smoking a denicotinized cigarette. Self-reports of smoking motives were collected at baseline, and measures of positive and negative affect were collected pre- and post- cigarette smoking. Higher MOR availability in the amygdala was associated with motivation to smoke to relieve negative affect. However, MOR availability was unrelated to changes in affect after smoking either cigarette. Increased MOR availability in amygdala may underlie the motivation to smoke for negative affective relief. These results are consistent with previous data highlighting the role of MOR neurotransmission in smoking behavior. Falcone M, Gold AB, Wileyto EP, Ray R, Ruparel K, Newberg A, Dubroff J, Logan J, Zubieta JK, Blendy JA, Lerman C. M-opioid receptor availability in the amygdala is associated with smoking for negative affect relief. *Psychopharmacology (Berl)*. 2012 Mar 3. [Epub ahead of print]

Pharmacogenetic Association Of the Galanin Receptor (GALR1) SNP Rs2717162 With Smoking Cessation

Galanin modulates dopaminergic neurotransmission in the mesolimbic dopamine system, thereby influencing the rewarding effects of nicotine. Variants in the galanin receptor 1 (GALR1) gene have been associated with retrospective craving severity and heaviness of smoking in prior research. The authors investigated pharmacogenetic associations of the previously studied GALR1 polymorphism, rs2717162, in 1217 smokers of European ancestry who participated in one of three pharmacogenetic smoking cessation clinical trials and were treated with nicotine patch (n=623), nicotine nasal spray (n=189), bupropion (n=213), or placebo (n=192). The primary endpoint was abstinence (7-day point prevalence, biochemically confirmed) at the end of treatment. Cravings to smoke were assessed on the target quit day (TQD). The longitudinal regression model revealed a significant genotype by treatment interaction (P=0.03). There was a reduced odds of quitting success with the presence of at least one minor (C) allele in the bupropion-treated group (OR=0.43; 95% CI=0.22-0.77; P=0.005) but equivalent quit rates by genotype in the nicotine-replacement therapy groups. This genotype by treatment interaction was reproduced in a Cox regression model of time to relapse (P=0.04). In the bupropion trial, smokers carrying the C allele also reported more severe TQD cravings. Further research to identify functional variants in GALR1 and to replicate pharmacogenetic associations is warranted. Gold AB, Wileyto EP, Lori A, Conti D, Cubells JF, Lerman C. Pharmacogenetic association of the galanin receptor (galr1) SNP rs2717162 with smoking cessation. *Neuropsychopharmacology*. 2012 Jun; 37(7): 1683-1688.

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

Retention on Buprenorphine Is Associated with High Levels of Maximal Viral Suppression among HIV-Infected Opioid Dependent Released Prisoners HIV-infected prisoners lose viral suppression within the 12 weeks after release to the community. This prospective study evaluates the use of buprenorphine/naloxone (BPN/NLX) as a method to reduce relapse to opioid use and sustain viral suppression among released HIV-infected prisoners meeting criteria for opioid dependence (OD). From 2005–2010, 94 subjects meeting DSM-IV criteria for OD were recruited from a 24-week prospective trial of directly administered antiretroviral therapy (DAART) for released HIV-infected prisoners; 50 (53%) selected BPN/NLX and were eligible to receive it for 6 months; the remaining 44 (47%) selected no BPN/NLX therapy. Maximum viral suppression (MVS), defined as HIV-1 RNA < 50 copies/mL, was compared for the BPN/NLX and non-BPN/NLX (N = 44) groups. The two groups were similar, except the BPN/NLX group was significantly more likely to be Hispanic (56.0% v 20.4%), from Hartford (74.4% v 47.7%) and have higher mean global health quality of life indicator scores (54.18 v 51.40). MVS after 24 weeks of being released was statistically correlated with 24-week retention on BPN/NLX [AOR = 5.37 (1.15, 25.1)], having MVS at the time of prison-release [AOR = 10.5 (3.21, 34.1)] and negatively with being Black [AOR = 0.13 (0.03, 0.68)]. Receiving DAART or methadone did not correlate with MVS. In recognition that OD is a chronic relapsing disease, strategies that initiate and retain HIV-infected prisoners with OD on BPN/NLX is an important strategy for improving HIV treatment outcomes as a community transition strategy. Springer SA, Qiu J, Saber-Tehrani SA, Altice FL. Retention on buprenorphine is associated with high levels of maximal viral suppression among HIV-infected opioid dependent released prisoners. *PLoS ONE* May 2012; 7(5): e38335.

Early Identification of HIV: Empirical Support for Jail-Based Screening Although routine HIV testing is recommended for jails, little empirical data exist describing newly diagnosed individuals in this setting. Client-level data (CLD) are available on a subset of individuals served in EnhanceLink, for the nine of the 10 sites who enrolled newly diagnosed persons in the client level evaluation. In addition to information about time of diagnosis, the authors analyzed data on initial CD4 count, use of antiretroviral therapy (ART), and linkage to care post discharge. Baseline data from newly diagnosed persons were compared to data from persons whose diagnoses predated jail admission. CLD were available for 58 newly diagnosed and 708 previously diagnosed individuals enrolled between 9/08 and 3/11. Those newly diagnosed had a significantly younger median age (34 years) when compared to those previously diagnosed (41 years). In the 30 days prior to incarceration, 11% of those newly diagnosed reported injection drug use and 29% reported unprotected anal intercourse. Median CD4 count at diagnosis was 432 cells/mL (range: 22–1,453 cells/mL). A minority (21%, N = 12) of new diagnoses started antiretroviral treatment (ART) before release; 74% have evidence of linkage to community services. Preliminary results from a cross-sectional analysis of this cohort suggest testing in jails finds individuals early on in disease progression. Most HIV⁺ detainees did not start ART in jail; therefore screening may not increase pharmacy costs for jails. Detainees newly diagnosed with HIV in jails can be effectively linked to community resources. Jail-based HIV testing should be a cornerstone of “test and treat” strategies. De Voux A, Spaulding AC, Beckwith C, Avery A, Williams C, Messina LC, Ball S, Altice FL. Early identification of HIV: Empirical support for jail-based screening. *PLoS ONE* May 2012; 7(5): e37603.

Establishment, Retention, and Loss to Follow-Up in Outpatient HIV Care For optimal clinical benefit, HIV-infected patients should receive periodic outpatient care indefinitely. However, initially establishing HIV care and subsequent retention in care are problematic. This study examines establishment, retention, and loss to follow-up (LTFU) in a large multi-site cohort over a 2-8 year period. Medical record data were reviewed for 22,984 adult HIV patients receiving care at 12 clinics in the HIV Research Network between 2001 and 2009. Three dichotomous outcome measures were based on each patient's history of outpatient visits. Establishment reflects whether the patient made outpatient visits for longer than 6 months after initial enrollment. The retention measure reflects whether the patient had at least 2 outpatient visits separated by 90 days in each year in care. LTFU reflects whether the patient had no outpatient visits for more than 12 months without returning. Multiple logistic regression examined demographic and clinical correlates of each outcome and the combined outcome of meeting all 3 measures. Overall, 21.7% of patients never established HIV care after an initial visit. Among established patients, 57.4% did not meet the retention criterion in all years, and 34.9% were LTFU. Only 20.4% of all patients met all 3 criteria. The odds of successfully meeting all 3 criteria were higher for women, for older patients, for Hispanics compared with whites, and for those with CD4 levels ≤ 50 cells per cubic millimeter. These data highlight the need to improve establishment and retention in HIV care. Fleishman JA, Yehia BR, Moore RD, Korthuis PT, Gebo K, for the HIV Research Network. Establishment, retention, and loss to follow-up in outpatient HIV care. *J AIDS* 2012; 60(3): 249-259.

Estimating the Effects of Multiple Time-varying Exposures Using Joint Marginal Structural Models: Alcohol Consumption, Injection Drug Use, and HIV Acquisition The joint effects of multiple exposures on an outcome are frequently of interest in epidemiologic research. In 2001, Hernan et al (*J Am Stat Assoc.* 2001;96:440-448) presented methods for estimating the joint effects of multiple time-varying exposures subject to time-varying confounding affected by prior exposure using joint marginal structural models. Nonetheless, the use of these joint models is rare in the applied literature. Minimal uptake of these joint models, in contrast to the now widely used standard marginal structural model, is due in part to a lack of examples demonstrating the method. In this paper, the authors review the assumptions necessary for unbiased estimation of joint effects as well as the distinction between interaction and effect measure modification. They demonstrate the use of marginal structural models for estimating the joint effects of alcohol consumption and injection drug use on HIV acquisition, using data from 1525 injection drug users in the AIDS Link to Intravenous Experience cohort study. In the joint model, the hazard ratio (HR) for heavy drinking in the absence of any drug injections was 1.58 (95% confidence interval = 0.67-3.73). The HR for any drug injections in the absence of heavy drinking was 1.78 (1.10-2.89). The HR for heavy drinking and any drug injections was 2.45 (1.45-4.12). The P values for multiplicative and additive interaction were 0.7620 and 0.9200, respectively, indicating a lack of departure from effects that multiply or add. The authors could not rule out interaction on either scale due to imprecision. Howe CJ, Cole SR, Mehta SH Kirk GD. Estimating the effects of multiple time-varying exposures using joint marginal structural models: Alcohol consumption, injection drug use, and HIV acquisition. *Epidemiology* 2012; 23(4): 574-582.

Vitamin D Deficiency Is Associated With The Development Of Subclinical Coronary Artery Disease In African Americans With HIV Infection: A Preliminary Study Premature coronary artery disease (CAD) is a major concern in human immunodeficiency virus (HIV)-infected African Americans. The objectives of the study were to estimate the incidence of subclinical CAD, defined by the presence of coronary plaque and/or calcification on cardiac computed tomography (CT), and to identify the associated risk factors in this vulnerable population. Between August 2003 and

September 2010, 188 HIV-infected African Americans without known, or symptoms of, CAD underwent cardiac CT. The subset without demonstrable disease underwent a second cardiac CT approximately 2 years later. The incidence of disease over that period and the effects of antiretroviral treatment and other known and hypothesized risk factors were investigated. Sixty-nine of these 188 African Americans had evidence of subclinical disease on the initial cardiac CT, confirming prior high prevalence reports. A second cardiac CT was performed on 119 African Americans without disease approximately 2 years later. The total person-years of follow-up was 284.4. Subclinical CAD was detected in 14 of these, yielding an overall incidence of 4.92/100 person-years (95% confidence interval, 2.69-8.26). Among the factors investigated, only male sex and vitamin D deficiency were independently associated with the development of subclinical CAD. The study did not find significant associations between CD4 count, HIV viral load, antiretroviral treatment use, or cocaine use and the incidence of subclinical CAD. The incidence of subclinical CAD in African Americans with HIV infection is provocatively high. Larger studies are warranted to confirm the role of vitamin D deficiency in the development of CAD in HIV-infected African Americans. Lai H, Detrick B, Fishman EK, Gerstenblith G, Brinker JA, Hollis BW, Bartlett J, Cofrancesco J Jr, Tong W, Tai H, Chen S, Bhatia S, Lai S. Vitamin D deficiency is associated with the development of subclinical coronary artery disease in African Americans with HIV infection: A preliminary study. *J Investig Med.* 2012 Jun; 60(5): 801-807.

Cholesterol Is Associated With The Presence Of A Lipid Core In Carotid Plaque Of Asymptomatic, Young-To-Middle-Aged African Americans With and Without HIV Infection and Cocaine Use Residing In Inner-City Baltimore, MD, USA

Stroke remains a leading cause of death in the United States. While stroke-related mortality in the USA has declined over the past decades, stroke death rates are still higher for blacks than for whites, even at younger ages. The purpose of this study was to estimate the frequency of a lipid core and explore risk factors for its presence in asymptomatic, young-to-middle-aged urban African American adults recruited from inner-city Baltimore, MD, USA. Between August 28, 2003, and May 26, 2005, 198 African American participants aged 30-44 years from inner-city Baltimore, MD, were enrolled in an observational study of subclinical atherosclerosis related to HIV and cocaine use. In addition to clinical examinations and laboratory tests, B-mode ultrasound for intima-media thickness of the internal carotid arteries was performed. Among these 198, 52 were selected from the top 30th percentile of maximum carotid intima-media thickness by ultrasound, and high-resolution black blood MRI images were acquired through their carotid plaque before and after the intravenous administration of gadodiamide. Of these 52, 37 with maximum segmental thickness by MRI >1.0 mm were included in this study. Lumen and outer wall contours were defined using semiautomated analysis software. The frequency of a lipid core in carotid plaque was estimated and risk factors for lipid core presence were explored using logistic regression analysis. Of the 37 participants in this study, 12 (32.4%) were women. The mean age was 38.7 ± 4.9 years. A lipid core was present in 9 (17%) of the plaques. Seventy percent of the study participants had a history of cigarette smoking. The mean total cholesterol level was 176.1 ± 37.3 mg/dl, the mean systolic blood pressure was 113.1 ± 13.3 mm Hg, and the mean diastolic blood pressure was 78.9 ± 9.5 mm Hg. There were 5 participants with hypertension (13.5%). Twelve (32%) participants had a history of chronic cocaine use, and 23 (62%) were HIV positive. Among the factors investigated, including age, sex, blood pressure, cigarette smoking, C-reactive protein, fasting glucose, triglycerides, serum total cholesterol, coronary calcium, cocaine use, and HIV infection, only total cholesterol was significantly associated with the presence of a lipid core. This study revealed an unexpectedly high rate of the presence of lipid core in carotid plaque and highlights the importance of cholesterol lowering to prevent cerebrovascular disease in this population. Further population-based studies are

warranted to confirm these results. Du J, Wasserman BA, Tong W, Chen S, Lai S, Malhotra S, Lai H. Cholesterol is associated with the presence of a lipid core in carotid plaque of asymptomatic, young-to-middle-aged African Americans with and without HIV infection and cocaine use residing in inner-city Baltimore, MD, USA. *Cerebrovasc Dis.* 2012; 33(3): 295-301. doi: 10.1159/000334661. Epub 2012 Feb 8.

Rapid HIV Testing In Large Urban Jails HIV prevalence is higher in jails than in the community, yet many jails do not conduct HIV testing. Jails in Baltimore, Maryland; Philadelphia, Pennsylvania; and the District of Columbia have implemented innovative rapid HIV testing programs. The authors have summarized the results of these programs, including the numbers of persons tested, rapid and confirmatory HIV test results, and numbers of persons newly diagnosed with HIV. They have described facilitators and challenges of implementation. These programs confirmed that rapid HIV testing in jails was feasible and identified undiagnosed HIV infection. Challenges included limited space to provide confidential rapid HIV testing and rapid turnover of detainees. Implementation required collaboration between local governments, health agencies, and correctional institutions. These programs serve as models for expanding rapid HIV testing in jails. Beckwith CG, Nunn A, Baucom S, Getachew A, Akinwumi A, Herdman B, DiBartolo P, Spencer S, Brown D, Lesansky H, Kuo I. Rapid HIV testing in large urban jails. *Am J Public Health.* 2012 May; 102 Suppl 2: S184-186. Epub 2012 Mar 8.

Disulfiram Metabolite S-Methyl-N,N-Diethylthiocarbamate Quantitation In Human Plasma With Reverse Phase Ultra Performance Liquid Chromatography and Mass Spectrometry

Disulfiram has been used extensively for alcohol abuse and may have a role in treatment for cocaine addiction. Recent data suggest that disulfiram may also reactivate latent HIV in reservoirs. Disulfiram has complex pharmacokinetics with rapid metabolism to active metabolites, including S-methyl-N,N-diethylthiocarbamate (DET-Me) which is formed from cytochrome P450 (CYP450). Assessing disulfiram in HIV-infected individuals with a CYP450 inducing drug (e.g., efavirenz) or a CYP450 inhibiting drug (e.g., HIV-1 protease inhibitors) requires an assay that can measure a metabolite that is formed directly via CYP450 oxidation. Therefore, an assay to measure concentrations of DET-Me in human plasma was validated. DET-Me and the internal standard, S-ethylpropylthiocarbamate (EPTC) were separated by isocratic ultra performance liquid chromatography using a Waters Acquity HSS T3 column (2.1 mm × 100 mm, 1.8 μm) and detection via electrospray coupled to a triple quadrupole mass spectrometer. Multiple reaction monitoring in positive mode was used with DET-Me at 148/100 and the internal standard at 190/128 with a linear range of 0.500-50.0 ng/mL with a 5 min run time. Human plasma (500 μL) was extracted using a solid phase procedure. The interassay variation ranged from 1.86 to 7.74% while the intra assay variation ranged from 3.38 to 5.94% over three days. Representative results are provided from samples collected from subjects receiving daily doses of disulfiram 62.5mg or 250 mg. Hochreiter J, McCance-Katz F, Lapham J, Ma Q, Morse GD. Disulfiram metabolite S-methyl-N,N-diethylthiocarbamate quantitation in human plasma with reverse phase ultra performance liquid chromatography and mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2012 May 15; 897: 80-84. Epub 2012 Apr 1.

Targeting Strategies For Human Immunodeficiency Virus: A Combinatorial Approach The battle between human and the Human Immunodeficiency Virus (HIV) is on, with both of them rapidly improving their attacking and defense strategies. Many therapeutic agents for HIV infection have been designed and developed, However there are various aspects, like novel targets against HIV, which are yet to be unfolded with a goal of designing and developing novel drug molecules

against HIV. This article reviews the current status and innovative new options for antiretroviral therapy for HIV and also discusses the various mechanisms of action for each class of drugs, and the problems yet to be solved with respect to HIV as a target for improvised treatment against AIDS. Saxena SK, Gupta A, Bhagyashree K, Saxena R, Arora N, Banerjee AK, Tripathi AK, Chandrasekar MJ, Gandhi N, Nair MP. Targeting strategies for Human Immunodeficiency Virus: A combinatorial approach. *Mini Rev Med Chem.* 2012 Mar; 12(3): 236-254.

Hepatitis C Virus Clearance, Reinfection, and Persistence, With Insights From Studies Of Injecting Drug Users: Towards A Vaccine

Hepatitis C virus (HCV) was discovered more than two decades ago, but progress towards a vaccine has been slow. HCV infection will spontaneously clear in about 25% of people. Studies of spontaneous HCV clearance in chimpanzees and human beings have identified host and viral factors that could be important in the control of HCV infection and the design of HCV vaccines. Although data from studies of chimpanzees suggest that protection against reinfection is possible after spontaneous clearance, HCV is a human disease. Results from studies of reinfection risk after spontaneous clearance in injecting drug users are conflicting, but some people seem to have protection against HCV persistence. To guide future vaccine development, the authors assess data from studies of HCV reinfection after spontaneous clearance, discuss flaws in the methods of previous human studies, and suggest essential components for future investigations of control of HCV infection. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, Page K, Lloyd AR, Dore GJ; International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC3). Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: Towards a vaccine. *Lancet Infect Dis.* 2012 May; 12(5): 408-414.

The More You Look, The More You Find: Effects Of Hepatitis C Virus Testing Interval On Reinfection Incidence and Clearance and Implications For Future Vaccine Study Design

Studies have explored whether spontaneous clearance of hepatitis C virus (HCV) infection decreases the likelihood of reinfection or increases the probability of clearance. This analysis investigates whether the conflicting findings from these studies could be due to differences in frequency of HCV RNA testing. A model simulated the dynamics of HCV reinfection and clearance among a cohort of injection drug users. For different reinfection incidence and clearance rates, the model evaluated the accuracy of epidemiological studies that used different HCV testing frequencies. Experimental estimates for the reinfection incidence and clearance probability will be accurate (<20% error) if the testing interval is less than the reinfection clearance duration. Otherwise, experimental estimates can greatly underestimate the real values ($\leq 66\%$ error if reinfection duration is 1 month and the testing interval is 3 months). Uncertainty in experimental estimates also increases at lower reinfection incidences, whereas for lower clearance probabilities the uncertainty in the estimated clearance probability increases but estimated reinfection incidence decreases. Differences in HCV testing interval could account for most between-study variability in the estimated probability of clearing reinfections and is likely to have biased reinfection incidence estimates. These findings suggest that a high reinfection clearance probability (>75%) is consistent with data. Vickerman P, Grebely J, Dore GJ, Sacks-Davis R, Page K, Thomas DL, Osburn WO, Cox AL, Aitken CK, Hickman M, Hellard M; InC Collaborative Group. The more you look, the more you find: Effects of Hepatitis C virus testing interval on reinfection incidence and clearance and implications for future vaccine study design. *J Infect Dis.* 2012 May 1; 205(9): 1342-1350. Epub 2012 Mar 29.

Injecting Risk Behavior Among Traveling Young Injection Drug Users: Travel Partner and City Characteristics

Young injection drug users (IDUs), a highly mobile population, engage in high levels of injecting risk behavior, yet little is understood about how such risk behavior may vary by the characteristics of the cities to which they travel, including the existence of a syringe exchange program (SEP), as well as travel partner characteristics. In 2004-2005, the authors conducted a 6-month prospective study to investigate the risk behavior of 89 young IDUs as they traveled, with detailed information gathered about 350 city visits. In multivariable analyses, travel to larger urban cities with a population of 500,000-1,000,000 was significantly associated with injecting drugs (adjusted odds ratio (AOR)= 3.71; 95 % confidence interval (CI), 1.56-8.82), ancillary equipment sharing (AES; AOR=7.05; 95 % CI, 2.25-22.06) and receptive needle sharing (RNS; AOR=5.73; 95 % CI, 1.11-27.95), as compared with visits to smaller cities with populations below 50,000. Region of the country, and the existence of a SEP within the city visited, were not independently associated with injecting drugs, AES, or RNS during city visits. Traveling with more than one injecting partner was associated with injecting drugs during city visits (AOR=2.77; 95 % CI, 1.46-5.27), when compared with traveling alone. Additionally, both non-daily and daily/almost daily alcohol use during city visits were associated with AES (AOR=3.37; 95 % CI, 1.42-7.68; AOR=3.03; 95 % CI, 1.32-6.97, respectively) as compared with no alcohol consumption. Traveling young IDUs are more likely to inject when traveling with other IDUs and to engage in higher risk injection behavior when they are in large cities. Risk behavior occurring in city visits, including equipment sharing and alcohol consumption, suggests further need for focused interventions to reduce risk for viral infection among this population. Montgomery ME, Fatch RS, Evans JL, Yu M, Davidson PJ, Page K, Hahn JA. Injecting risk behavior among traveling young injection drug users: Travel partner and city characteristics. *J Urban Health*. 2012 Jun 29. PubMed PMID: 22744293.

Primary Care-Based Interventions Are Associated With Increases In Hepatitis C Virus Testing For Patients At Risk

An estimated 3.2 million persons are chronically infected with the hepatitis C virus (HCV) in the U.S. Effective treatment is available, but approximately 50% of patients are not aware that they are infected. Optimal testing strategies have not been described. The Hepatitis C Assessment and Testing Project (HepCAT) was a serial cross-sectional evaluation of two community-based interventions designed to increase HCV testing in urban primary care clinics in comparison with a baseline period. The first intervention (risk-based screener) prompted physicians to order HCV tests based on the presence of HCV-related risks. The second intervention (birth cohort) prompted physicians to order HCV tests on all patients born within a high-prevalence birth cohort (1945-1964). The study was conducted at three primary care clinics in the Bronx, New York. Both interventions were associated with an increased proportion of patients tested for HCV from 6.0% at baseline to 13.1% during the risk-based screener period (P<0.001) and 9.9% during the birth cohort period (P<0.001). Two simple clinical reminder interventions were associated with significantly increased HCV testing rates. These findings suggest that HCV screening programs, using either a risk-based or birth cohort strategy, should be adopted in primary care settings so that HCV-infected patients may benefit from antiviral treatment. Litwin AH, Smith BD, Drainoni ML, McKee D, Gifford AL, Koppelman E, Christiansen CL, Weinbaum CM, Southern WN. Primary care-based interventions are associated with increases in hepatitis C virus testing for patients at risk. *Dig Liver Dis*. 2012 Jun; 44(6): 497-503. Epub 2012 Feb 18.

Hip Bone Geometry In HIV/HCV-Co-Infected Men and Healthy Controls People with both HIV and hepatitis C are more likely than those with HIV alone to have wrist, hip, and spine fractures. The authors compared hip strength between HIV/HCV-co-infected men and healthy men

and found that HIV/HCV-co-infected men had decreased hip strength due to lower lean body mass. Hepatitis C co-infection is a risk factor for fragility fracture among HIV-infected populations. Whether bone strength is compromised in HIV/HCV-co-infected patients is unknown. The authors compared dual-energy x-ray absorptiometry (DXA)-derived hip geometry, a measure of bone strength, in 88 HIV/HCV-co-infected men from the Johns Hopkins HIV Clinic to 289 men of similar age and race and without HIV or HCV from the Boston Area Community Health Survey/Bone Survey. Hip geometry was assessed at the narrow neck, intertrochanter, and shaft using hip structural analysis. Lean body mass (LBM), total fat mass (FM), and fat mass ratio (FMR) were measured by whole-body DXA. Linear regression was used to identify body composition parameters that accounted for differences in bone strength between cohorts. HIV/HCV-co-infected men had lower BMI, LBM, and FM and higher FMR compared to controls (all $p < 0.05$). At the narrow neck, significant differences were observed between HIV/HCV-co-infected men and controls in bone mineral density, cross-sectional area, section modulus, buckling ratio, and centroid position. After adjustment for race, age, smoking status, height, and weight, only buckling ratio and centroid position remained significantly different between cohorts (all $p < 0.05$). Substituting LBM, FM, and FMR for weight in the multivariate model revealed that differences in LBM, but not FM or FMR, accounted for differences in all narrow neck parameters between cohorts, except buckling ratio and centroid position. HIV/HCV-co-infected men have compromised hip strength at the narrow neck compared to uninfected controls, which is attributable in large part to lower lean body mass. Walker Harris V, Sutcliffe CG, Araujo AB, Chiu GR, Trivison TG, Mehta S, Sulkowski MS, Higgins Y, Thomas DL, Dobs AS, Beck TJ, Brown TT. Hip bone geometry in HIV/HCV-co-infected men and healthy controls. *Osteoporosis Int.* 2012 Jun; 23(6): 1779-1787.

Effect Of Pegylated Interferon-A-2a Treatment On Mental Health During Recent Hepatitis C Virus Infection

Pegylated interferon (PEG-IFN) treatment for hepatitis C virus (HCV) infection has neuropsychiatric side effects. Data on the effect of HCV treatment on mental health among injecting drug users (IDUs) are limited. The authors assessed mental health during treatment of recently acquired HCV, within a predominantly IDU population. Participants with HCV received PEG-IFN- α -2a (180 μ g/week) for 24 weeks; HCV/HIV received PEG-IFN with ribavirin. Depression was assessed using the Mini-International Neuropsychiatric Interview (MINI). Logistic regression was used to identify factors associated with depression at enrolment and during treatment. Also, the effect of depression prior to and during treatment on sustained virological response (SVR) was assessed. Of 163 participants, 111 received treatment (HCV, $n = 74$; HCV/HIV, $n = 37$), with 76% ever reporting IDU. At enrollment, 16% had depression ($n = 25$). In adjusted analysis, depression at enrollment occurred less often in participants full-/part-time employed (adjusted odds ratio [AOR] 0.23; 95% confidence interval [CI]: 0.06, 0.82, $P = 0.023$) and more often in recent IDUs (AOR 3.04; 95% CI: 1.19, 7.72, $P = 0.019$). During treatment, 35% ($n = 31$) developed new-onset depression. In adjusted analysis, poorer social functioning (higher score) was associated with new-onset depression (score ≤ 9 vs score ≥ 17 ; OR 5.69; 95% CI: 1.61, 20.14, $P = 0.007$). SVR was similar among participants with and without depression at enrollment (60% vs 61%, $P = 0.951$) and in those with and without new-onset depression (74% vs 63%, $P = 0.293$). Although depression at enrollment and during treatment was common among participants with recent HCV, neither influenced SVR. Participants with poor social functioning may be most at risk of developing depression during HCV therapy. Alavi M, Grebely J, Matthews GV, Petoumenos K, Yeung B, Day C, Lloyd AR, Van Beek I, Kaldor JM, Hellard M, Dore GJ, Haber PS; ATAHC Study Group. Effect of pegylated interferon- α -2a treatment on mental health during recent hepatitis C virus infection. *J Gastroenterol Hepatol.* 2012 May; 27(5): 957-965. doi: 10.1111/j.1440-1746.2011.07035.x.

Knowledge and Barriers Associated With Assessment and Treatment For Hepatitis C Virus Infection Among People Who Inject Drugs

Uptake of treatment for hepatitis C virus (HCV) infection among people who inject drugs is low. Further understanding is required of the relationship between HCV knowledge and treatment willingness, assessment and treatment in this population. A cross-sectional self-administered survey was conducted with clients of four opioid substitution therapy (OST) clinics and the Medically Supervised Injecting Centre in Sydney, Australia. Of 132 participants, 85 (64%) self-reported having HCV infection. HCV knowledge was mixed (mean 6.5, range 0-12) and was relatively lower on items measuring knowledge of factors impacting HCV-related disease progression. The likelihood of being in a higher knowledge category was associated with being female [adjusted odds ratio (AOR) = 3.78, 95% confidence interval (CI) (1.79, 7.98)], higher formal education [AOR = 3.28, 95% CI (1.57, 6.88)], being on a current OST program [AOR = 2.61, 95% CI (1.10, 6.19)] and being older [AOR = 1.04, 95% CI (1.01, 1.09)]. Participants receiving OST were more likely to report higher willingness to have HCV treatment [OR = 4.45, 95% CI (2.23, 8.17)]. Having been assessed for HCV treatment was associated with younger age [AOR = 0.93; CI 95% (0.88, 1.00)] and higher formal education [AOR = 7.81; 95% CI (1.62, 37.71)]. Overall, knowledge scores were mid-range. Knowledge of modifiable factors influencing HCV-related liver disease progression was particularly low indicating the need for ongoing education. Education should also be targeted at older people and those not on OST, and be inclusive of those with lower literacy levels. Treloar C, Hull P, Dore GJ, Grebely J. Knowledge and barriers associated with assessment and treatment for Hepatitis C virus infection among people who inject drugs *Drug Alcohol Rev.* 2012 May 21. *Lancet Infect Dis.* 2012 May; 12(5): 408-414.

Management Of Patients Coinfected With HCV and HIV: A Close Look At The Role For Direct-Acting Antivirals

With the development of effective therapies against human immunodeficiency virus (HIV), hepatitis C virus (HCV) infection has become a major cause of morbidity and mortality among patients with both infections (coinfection). In addition to the high prevalence of chronic HCV, particularly among HIV-infected injection drug users, the rate of incident HIV infections is increasing among HIV-infected men who have sex with men, leading to recommendations for education and screening for HCV in this population. Liver disease is the second leading and, in some cases, a preventable cause of death among coinfecting patients. Those at risk for liver disease progression are usually treated with a combination of interferon (IFN) and ribavirin (RBV), which is not highly effective; it has low rates of sustained virologic response (SVR), especially for coinfecting patients with HCV genotype 1 and those of African descent. Direct-acting antivirals might overcome factors such as immunodeficiency that can reduce the efficacy of IFN. However, for now it remains challenging to treat coinfecting patients due to interactions among drugs, additive drug toxicities, and the continued need for combination therapies that include pegylated IFN. Recently developed HCV protease inhibitors such as telaprevir and boceprevir, given in combination with pegylated IFN and RBV, could increase the rate of SVR with manageable toxicity and drug interactions. The authors review the latest developments and obstacles to treating coinfecting patients. Naggie S, Sulkowski MS. Management of patients coinfecting with HCV and HIV: A close look at the role for direct-acting antivirals. *Gastroenterology.* 2012 May; 142(6): 1324-1334.e3.

High Rates Of Serum Selenium Deficiency Among HIV- and HCV-Infected and Uninfected Drug Users In Buenos Aires, Argentina

To describe the prevalence of low serum Se and determine whether HIV, Hepatitis C virus (HCV) and/or the types of drugs used are associated with serum Se in a cohort of infected and uninfected drug users. Independent correlates of low serum Se

levels based on data collected from food recalls, physical examinations and clinical questionnaires were identified using multivariate regression analysis. The study setting was Buenos Aires, Argentina. Participants were a total of 205 (twenty-five female and 180 male) former and current drug users. Drug users had an average serum Se level of 69.8 (sd 32.8) µg/dl, and 82 % were considered deficient (<85 µg/dl). Multivariate analyses found that HIV- and/or HCV-infected individuals had lower mean Se compared with healthy, uninfected drug users (HIV/HCV co-infection: -25.3 µg/l (se 7.6), P = 0.001; HIV alone: -28.9 µg/l (se 6.9), P < 0.001; HCV alone: -19.4 µg/l (se 7.1), P = 0.006). Current and previous drug use was associated with higher serum Se. Cigarette smoking and heavy alcohol consumption were not found to be associated with Se status. Low serum Se levels are highly prevalent among drug users in Buenos Aires, Argentina. Se supplementation and/or dietary interventions may be warranted in drug users who are at high risk for HIV and/or HCV infection. Sheehan HB, Benetucci J, Muzzio E, Redini L, Naveira J, Segura M, Weissenbacher M, Tang AM. High rates of serum selenium deficiency among HIV- and HCV-infected and uninfected drug users in Buenos Aires, Argentina. *Public Health Nutr.* 2012 Mar; 15(3): 538-545. Epub 2011 Jul 11.

Immunogenicity and Cross-Reactivity Of A Representative Ancestral Sequence In Hepatitis C Virus Infection

Vaccines designed to prevent or to treat hepatitis C viral infection must achieve maximum cross-reactivity against widely divergent circulating strains. Rational approaches for sequence selection to maximize immunogenicity and minimize genetic distance across circulating strains may enhance vaccine induction of optimal cytotoxic T cell responses. The authors assessed T cell recognition of potential hepatitis C virus (HCV) vaccine sequences generated using three rational approaches: combining epitopes with predicted tight binding to the MHC, consensus sequence (most common amino acid at each position), and representative ancestral sequence that had been derived using bayesian phylogenetic tools. No correlation was seen between peptide-MHC binding affinity and frequency of recognition, as measured by an IFN-γ T cell response in HLA-matched HCV-infected individuals. Peptides encoding representative, consensus, and natural variant sequences were then tested for the capacity to expand CD8 T cell populations and to elicit cross-reactive CD8 T cell responses. CD8(+) T cells expanded with representative sequence HCV generally more broadly and robustly recognized highly diverse circulating HCV strains than did T cells expanded with either consensus sequence or naturally occurring sequence variants. These data support the use of representative sequence in HCV vaccine design. Burke KP, Munshaw S, Osburn WO, Levine J, Liu L, Sidney J, Sette A, Ray SC, Cox AL. Immunogenicity and cross-reactivity of a representative ancestral sequence in hepatitis C virus infection. *J Immunol.* 2012 May 15; 188(10): 5177-5188. Epub 2012 Apr 16.

Computational Reconstruction Of Bole1a, A Representative Synthetic Hepatitis C Virus Subtype 1a Genome

Hepatitis C virus (HCV) research is hampered by the use of arbitrary representative isolates in cell culture and immunology. The most replicative isolate in vitro is a subtype 2a virus (JFH-1); however, genotype 1 is more prevalent worldwide and represents about 70% of infections in the United States, and genotypes differ from one another by 31% to 33% at the nucleotide level. For phylogenetic and immunologic analyses, viruses H77 and HCV-1 (both subtype 1a) are commonly used based on their historic importance. In an effort to rationally design a representative subtype 1a virus (Bole1a), the authors used Bayesian phylogenetics, ancestral sequence reconstruction, and covariance analysis on a curated set of 390 full-length human HCV 1a sequences from GenBank. By design, Bole1a contains variations present in widely circulating strains and matches more epitope-sized peptides in a full-genome comparison to subtype 1a isolates than any other sequence studied. Parallel analyses confirm that selected epitopes from the Bole1a

genome were able to elicit a robust T cell response. In a proof of concept for infectivity, the envelope genes (E1 and E2) of Bole1a were expressed in an HIV pseudoparticle system containing HCV envelope genes and HIV nonenvelope genes with luciferase expression. The resulting Bole1a pseudoparticle robustly infected Hep3B cells. In this study, the authors demonstrate that a rationally designed, fully synthetic HCV genome contains representative epitopes and envelope genes that assemble properly and mediate entry into target cells. Munshaw S, Bailey JR, Liu L, Osburn WO, Burke KP, Cox AL, Ray SC. Computational reconstruction of Bole1a, a representative synthetic hepatitis C virus subtype 1a genome. *J Virol.* 2012 May; 86(10): 5915-5921. Epub 2012 Mar 21.

Public Health and The Epidemic Of Incarceration An unprecedented number of Americans have been incarcerated in the past generation. In addition, arrests are concentrated in low-income, predominantly nonwhite communities where people are more likely to be medically underserved. As a result, rates of physical and mental illnesses are far higher among prison and jail inmates than among the general public. The authors review the health profiles of the incarcerated; health care in correctional facilities; and incarceration's repercussions for public health in the communities to which inmates return upon release. The review concludes with recommendations that public health and medical practitioners capitalize on the public health opportunities provided by correctional settings to reach medically underserved communities, while simultaneously advocating for fundamental system change to reduce unnecessary incarceration. Dumont DM, Brockmann B, Dickman S, Alexander N, Rich JD. Public health and the epidemic of incarceration. *Annu Rev Public Health.* 2012 Apr; 33: 325-339. Epub 2012 Jan 3.

Mechanism Of Efavirenz Influence On Methadone Pharmacokinetics and Pharmacodynamics Mechanisms by which efavirenz diminishes methadone plasma concentrations are unknown. This investigation determined efavirenz influence on clinical methadone disposition and miosis, intravenous and oral alfentanil clearance (hepatic and intestinal cytochrome P450 3A4/5 (CYP3A4/5) activity), fexofenadine disposition (intestinal transporters activity), and efavirenz clearance and 8-hydroxylation (CYP2B6 activity), and human hepatocyte effects. Efavirenz induced systemic and oral alfentanil clearances two- to fivefold and induced efavirenz 8-hydroxylation. Efavirenz stereoselectively decreased methadone plasma concentrations 50-70%. Methadone systemic and oral clearances, hepatic clearance and extraction ratio, N-demethylation, and metabolite formation clearance were stereoselectively increased two- to threefold. Bioavailability decreased. Efavirenz shifted methadone concentration-miosis curves leftward and upward. Efavirenz induced hepatocyte CYP2B6 and CYP3A4 expression, activity, and methadone N-demethylation. Results show that efavirenz coinduced hepatic CYP2B6 and CYP3A4/5, coinduced hepatic and intestinal CYP3A4/5, and coinduced gastrointestinal CYP3A4/5 and efflux transporters. Methadone disposition was most consistent with efavirenz induction of hepatic CYP2B6-mediated methadone N-demethylation. Efavirenz may alter methadone pharmacodynamics. Kharasch ED, Whittington D, Ensign D, Hoffer C, Bedynek PS, Campbell S, Stubbert K, Crafford A, London A, Kim T. Mechanism of efavirenz influence on methadone pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther.* 2012 Apr; 91(4): 673-684. doi: 10.1038/clpt.2011.276. Epub 2012 Mar 7.

Patterns Of Salivary Cortisol Levels Can Manifest Work Stress In Emergency Care Providers To develop objective assessments of work fatigue, the authors investigated the patterns of changes in salivary cortisol levels in emergency care providers working extended work shifts. Fourteen subjects, comprising seven physicians and seven physician assistants, provided unstimulated saliva samples at regular intervals over the course of a 24-h work shift and over their subsequent free day.

There was a significant time effect, with early morning cortisol levels being significantly attenuated following the work shift. Native diurnal variations varied by gender, with the female subjects manifesting greater cortisol levels. Physicians also had higher cortisol profiles even though their wake-rest cycles were similar to those of the physician assistants. Results suggest that temporal changes, as well as diurnal similarities, in the salivary cortisol patterns can reflect work-related stress and recovery. In particular, early morning cortisol levels may manifest individual reactivity to work stressors as well as sleep deprivation. Nakajima Y, Takahashi T, Shetty V, Yamaguchi M. Patterns of salivary cortisol levels can manifest work stress in emergency care providers. *J Physiol Sci.* 2012 May; 62(3): 191-197. Epub 2012 Feb 19.

Illicit Use Of Androgens and Other Hormones: Recent Advances The purpose of this review was to summarize recent advances in studies of illicit use of androgens and other hormones. Androgens and other appearance-enhancing and performance-enhancing substances are widely abused worldwide. Three notable clusters of findings have emerged in this field in recent years. First, studies almost unanimously find that androgen users engage in polypharmacy, often ingesting other hormones (e.g., human growth hormone, thyroid hormones, and insulin), ergo/thermogenic drugs (e.g., caffeine, ephedrine, and clenbuterol), and classical drugs of abuse (e.g., cannabis, opiates, and cocaine). Second, reports of long-term psychiatric and medical adverse effects of androgens continue to accumulate. In cardiovascular research particularly, controlled studies have begun to supersede anecdotal evidence, strengthening the case that androgens (possibly acting synergistically with other abused drugs) may cause significant morbidity and even mortality. Third, it is increasingly recognized that androgen use may lead to a dependence syndrome with both psychological and physiological origins. Androgen dependence likely affects some millions of individuals worldwide, and arguably represents the least studied major class of illicit drug dependence. Given mounting evidence of the adverse effects of androgens and associated polypharmacy, this topic will likely represent an expanding area of research and an issue of growing public health concern. Kanayama G, Pope HG Jr. Illicit use of androgens and other hormones: recent advances. *Curr Opin Endocrinol Diabetes Obes.* 2012 Jun; 19(3): 211-219.

SERVICES RESEARCH

Randomized Trial of Standard Methadone Treatment Compared to Initiating Methadone without Counseling: 12-Month Findings

This study aimed to determine the relative effectiveness of 12 months of interim methadone (IM; supervised methadone with emergency counseling only for the first 4 months of treatment), standard methadone treatment (SM; with routine counseling) and restored methadone treatment (RM: routine counseling with smaller case-loads). A randomized controlled trial was conducted comparing IM, SM and RM treatment. IM lasted for 4 months, after which participants were transferred to SM. The study was conducted in two methadone treatment programs in Baltimore, MD, USA. The study included 230 adult methadone patients newly admitted through waiting-lists. The authors administered the Addiction Severity Index and a supplemental questionnaire at baseline, 4 and 12 months post-baseline. Measurements included retention in treatment, self-reported days of heroin and cocaine use, criminal behavior and arrests and urine tests for heroin and cocaine metabolites. At 12 months, on an intent-to-treat basis, there were no significant differences in retention in treatment among the IM, SM and RM groups (60.6%, 54.8% and 37.0%, respectively). Positive urine tests for the three groups declined significantly from baseline ($P_s < 0.001$ and 0.003 , for heroin and cocaine metabolites, respectively) but there were no significant group x time interactions for these measures. At least one arrest was reported by 30.6% of the sample during the year, but there were no significant between-group effects. Limited availability of drug counseling services should not be a barrier to providing supervised methadone to adults dependent on heroin—at least for the first 4 months of treatment. Schwartz R, Kelly S, O'Grady K, Gandhi D, Jaffe J. Randomized trial of standard methadone treatment compared to initiating methadone without counseling: 12-month findings. *Addiction*. 2012; 107(5): 943-952.

A Randomized Controlled Trial of a Brief Intervention for Illicit Drugs Linked to the Alcohol, Smoking and Substance Involvement Screening Test in Primary Health-Care Settings in Four Countries

This study evaluated the effectiveness of a brief intervention (BI) for illicit drugs (cannabis, cocaine, amphetamine-type stimulants and opioids) linked to the World Health Organization (WHO) Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). The ASSIST screens for problem or risky use of 10 psychoactive substances, producing a score for each substance that falls into either a low-, moderate- or high-risk category. The study design was a prospective, randomized controlled trial in which participants were either assigned to a 3-month waiting-list control condition or received brief motivational counseling lasting an average of 13.8 minutes for the drug receiving the highest ASSIST score. Settings comprised primary health-care settings in four countries: Australia, Brazil, India, and the United States. Participants were 731 males and females scoring within the moderate-risk range of the ASSIST for cannabis, cocaine, amphetamine-type stimulants or opioids. Measurements obtained were ASSIST-specific substance involvement scores for cannabis, stimulants or opioids and ASSIST total illicit substance involvement score at baseline and 3 months post-randomization. Omnibus analyses indicated that those receiving the BI had significantly reduced scores for all measures, compared with control participants. Country-specific analyses showed that, with the exception of the site in the United States, BI participants had significantly lower ASSIST total illicit substance involvement scores at follow-up compared with the control participants. The sites in India and Brazil demonstrated a very strong brief intervention effect for cannabis scores ($P < 0.005$ for both sites), as did the sites in Australia ($P < 0.005$) and Brazil ($P < 0.01$) for stimulant scores and the Indian site for opioid scores ($P < 0.01$). The Alcohol, Smoking and Substance Involvement Screening Test-linked brief intervention aimed at reducing illicit substance use and related risks is effective, at least in the short term, and the effect generalizes across countries. Humeniuk R, Ali R, Babor T, Souza-Formigoni

MO, Boerngen de Lacerda R, Ling W, McRee B, Newcombe D, Pal H, Poznyak V, Simon S, Vendetti J. A randomized controlled trial of a brief intervention for illicit drugs linked to the alcohol, smoking and substance involvement screening test (ASSIST) in clients recruited from primary health-care settings in four countries. *Addiction*. 2012; 107(5): 957-966.

Developing a Modified Directly Observed Therapy Intervention for Hepatitis C Treatment in a Methadone Maintenance Program: Implications for Program Replication

Hepatitis C virus (HCV) is a prevalent chronic blood-borne infection among opioid-dependent patients on methadone maintenance treatment (MMT). Despite case reports and case-control studies, a randomized controlled trial (RCT) examining HCV treatment adherence in methadone-maintained patients is lacking and was the impetus for this ongoing RCT examining modified directly administered therapy for HCV treatment integrated within a MMT. Subjects were randomized 1:1 to receive HCV treatment as modified directly observed therapy (mDOT) into the MMT program or at a liver specialty clinic as self-administered therapy (SAT). Randomization was stratified based on HIV status and HCV genotype. Twenty-one subjects to date have enrolled in this pilot study. The mDOT subjects have had greater success in starting treatment and 10 of the 12 mDOT subjects achieved early virologic response (EVR) at week 12 and 6 of those 10 achieved sustained virologic response (SVR). Of the nine SAT subjects, only three achieved EVR at week 12 and only one achieved SVR despite not completing the treatment. Hepatitis C treatment can be successfully integrated into a methadone maintenance clinic, and mDOT can be implemented with a methadone clinic's existing nursing and medical staff. Patients struggling with concurrent substance use and mental illness co morbidity may be successfully addressed in such settings and facilitate access to and completion of treatment through the utilization of on-site clinical services for HCV treatment and adherence support with mDOT. The exact importance of site of services and adherence support remains a significant area for future investigation. Bruce DR, Eiserman J, Acosta A, Gote C, Lim JK, Altice FL. Developing a modified directly observed therapy intervention for hepatitis C treatment in a methadone maintenance program: Implications for program replication. *Am J Drug Alcohol Abuse*. 2012; 38(3): 206-212. (2): 151-158.

Hepatitis C among Methadone Maintenance Treatment Patients in Shanghai and Kunming, China

This study aims to: (1) document the prevalence of Hepatitis C virus (HCV) among methadone maintenance treatment (MMT) patients in Kunming and Shanghai; (2) examine risk factors for HCV by comparing those who tested positive with those who were negative and (3) examine if HCV serostatus is related to attitudes toward MMT. Using data collected from 306 patients admitted to MMT in 2009-2010 in Shanghai and Kunming, the authors compared HCV-positive and HCV-negative patients (based on clinical records) on their HCV knowledge and risk behaviors and attitudes toward MMT. The HCV seropositive rate was 53.3% (51.3% in Shanghai and 55.5% in Kunming) and a majority of patients did not know their serostatus. Patients scored on average fewer than 6 correct out of the 20 items in the HCV knowledge questionnaire. Recent injection use and length of opiate use were strong predictors of HCV status, while no differences were found between HCV-positive and HCV-negative individuals in sexual risks or HCV knowledge. Both groups expressed similar views toward MMT. The high HCV prevalence and the general lack of knowledge about HCV infection, transmission and treatment suggest the need to provide HCV education and health promotion programs among patients in MMT. Hser Y, Du J, Li J, Zhao M, Chang Y, Peng C, Evans E. Hepatitis C among methadone maintenance treatment patients in Shanghai and Kunming, China. *J Public Health (Oxf)*. 2012; 34(1): 24-31.

Hepatitis C Knowledge and Alcohol Consumption among Patients Receiving Methadone Maintenance Treatment in Shanghai, China

The aim was to investigate hepatitis C virus (HCV) knowledge and alcohol consumption among patients (n = 114) in a methadone maintenance treatment (MMT) clinic in Shanghai. A cross-sectional survey was carried out in an MMT clinic. Structured questionnaires (HCV Knowledge Scale and Alcohol Use Disorders Identification Test (AUDIT)) and some open-ended questions were used to assess (i) HCV knowledge, (ii) HCV treatment received, (iii) awareness of HCV status, and (iv) alcohol consumption. Findings revealed the HCV-positive rate was 57.0%. There were significant gaps in knowledge about HCV and HCV treatment received. The group mean score of HCV knowledge was 11.3 out of 20 (SD = 2.1) and the mean score on the AUDIT was 3.2 (SD = 5.4). Most participants (68.4%) reported not knowing their HCV status. Among HCV-positive participants, only 15.3% had received HCV antiviral treatment and 18.4% expressed a need for counseling about HCV infection. Considering the limited HCV knowledge and low level of HCV treatment received, effective HCV education and intervention strategies should be developed to target patients in China's MMT clinics. Moreover, alcohol screening should also be part of the routine assessments within MMT programs. This study reveals the importance of HCV testing and education among drug users in MMT clinics. Du J, Wang Z, Xie B, Zhao M. Hepatitis C knowledge and alcohol consumption among patients receiving methadone maintenance treatment in Shanghai, China. *Am J Drug Alcohol Abuse*. 2012; 38(3): 228-232.

Increasing the Effectiveness of In-Prison Treatment May Yield Cost-Saving to the Criminal Justice System

Reflecting drug use patterns and criminal justice policies throughout the 1990s and 2000s, prisons hold a disproportionate number of society's drug abusers. Approximately 50% of state prisoners meet the criteria for a diagnosis of drug abuse or dependence, but only 10% receive medically based drug treatment. Because of the link between substance abuse and crime, treating substance abusing and dependent state prisoners while incarcerated has the potential to yield substantial economic benefits. In this paper, the authors' simulate the lifetime costs and benefits of improving prison-based substance abuse treatment and post-release aftercare for a cohort of state prisoners. Their model captures the dynamics of substance abuse as a chronic disease; estimates the benefits of substance abuse treatment over individuals' lifetimes; and tracks the costs of crime and criminal justice costs related to policing, adjudication, and incarceration. They estimate net societal benefits and cost savings to the criminal justice system of the current treatment system and five policy scenarios. They find that four of the five policy scenarios provide positive net societal benefits and cost savings to the criminal justice system relative to the current treatment system. This study demonstrates the societal gains to improving the drug treatment system for state prisoners. Cowell AJ, Hicks KA, Mills MJ, Belenko S, Dunlap LJ, Houser KA, Keys V. Benefits and costs of substance abuse treatment programs for state prison inmates: Results from a lifetime simulation model. *Health Econ*. 2012; 21: 633-652.

Enhancing the Effectiveness of Juvenile Drug Courts by Integrating Evidence-Based Practices

The primary purpose of this study was to test a relatively efficient strategy for enhancing the capacity of juvenile drug courts (JDC) to reduce youth substance use and criminal behavior by incorporating components of evidence-based treatments into their existing services. Six JDCs were randomized to a condition in which therapists were trained to deliver contingency management in combination with family engagement strategies (CM-FAM) or to continue their usual services (US). Participants included 104 juvenile offenders (average age = 15.4 years; 83% male; 57% White, 40% African American, 3% Biracial). Eighty-six percent of the youths met criteria for at least 1 substance use disorder, and co-occurring psychiatric diagnoses were highly prevalent. Biological

and self-report measures of substance use and self-reported delinquency were assessed from baseline through 9 months post recruitment. CM-FAM was significantly more effective than US at reducing marijuana use, based on urine drug screens, and at reducing both crimes against persons and property offenses. Such favorable outcomes, however, were not observed for the self-report measure of substance use. Although some variation in outcomes was observed between courts, the outcomes were not moderated by demographic characteristics or co-occurring psychiatric disorders. The findings suggest that JDC practices can be enhanced to improve outcomes for participating juvenile offenders. A vehicle for promoting such enhancements might pertain to the development and implementation of program certification standards that support the use of evidence-based interventions by JDCs. Such standards have been fundamental to the successful transport of evidence-based treatments of juvenile offenders. Henggeler S, McCart M, Cunningham P, Chapman J. Enhancing the effectiveness of juvenile drug courts by integrating evidence-based practices. *J Consult Clin Psychol.* 2012; 80(2): 264-275.

Adaptive Programming Improves Outcomes in Drug Court: An Experimental Trial Prior studies in drug courts have reported improved outcomes when participants were matched to schedules of judicial status hearings based on their criminological risk level. The current experiment determined whether incremental efficacy could be gained by periodically adjusting the schedule of status hearings and clinical case management sessions in response to participants' ensuing performance in the program. The adjustments were made pursuant to a priori criteria specified in an adaptive algorithm. Results confirmed that participants in the full adaptive condition ($n = 62$) were more than twice as likely as those assigned to baseline matching only ($n = 63$) to be drug abstinent during the first 18 weeks of the program; however, graduation rates and the average time to case resolution were not significantly different. The positive effects of the adaptive program appear to have stemmed from holding noncompliant participants more accountable for meeting their attendance obligations in the program. Directions for future research and practice implications are discussed. Marlowe DB, Festinger DS, Dugosh KL, Benasutti KM, Fox G, Croft JR. Adaptive programming improves outcomes in drug court: An experimental trial. *Crim Justice Behav.* 2012; 39(4): 514-532.

Dissection of the Phenotypic and Genotypic Associations with Nicotinic Dependence Strong evidence demonstrates that nicotine dependence is associated with 4 genetic variants rs16969968, rs6474412, rs3733829, and rs1329650 in large-scale Genome-Wide Association Studies. The authors examined how these identified genetic variants relate to nicotine dependence defined by different categorical and dimensional measures. Four genetic variants were analyzed in 2,047 subjects of European descent (1,062 cases and 985 controls). Nicotine dependence was assessed with multiple smoking measures, including the Fagerström Test for Nicotine Dependence, the Diagnostic and Statistical Manual for Mental Disorders-IV (DSM-IV) nicotine dependence, the Nicotine Dependence Syndrome Scale, and the Wisconsin Inventory of Smoking Dependence Motives. Single-item measures of cigarettes per day (CPD) and time to first cigarette (TTF) in the morning were also examined. Among the variants, association effect sizes were largest for rs16969968, with measures of craving and heavy smoking, especially cigarettes smoked per day, showing the largest effects. Significant but weaker associations were found for rs6474412 and rs3733729 but not for rs1329650. None of the more comprehensive measures of smoking behaviors yielded stronger genetic associations with these variants than did CPD. CPD is an important simple measure that captures in part the genetic associations of CHRNA5 and nicotine dependence, even when other more comprehensive measures of smoking behaviors are examined. The CHRNA5 gene is associated with heavy compulsive smoking and craving; this should inform the mission to

improve the diagnostic validity of DSM-V. Chen L, Baker T, Grucza R, Wang J, Johnson E, Breslau N, Hatsukami D, Smith S, Saccone N, Saccone S, Rice J, Goate A, Bierut L. Dissection of the phenotypic and genotypic associations with nicotinic dependence. *Nicotine Tob Res.* 2012; 14 (4): 425-433.

DSM Criteria for Tobacco Use Disorder and Tobacco Withdrawal: A Critique and Proposed Revisions for DSM-5

This paper aims to identify appropriate criteria for tobacco dependence assessment, evaluate relevant research and suggest revisions that may be incorporated into DSM-5. Desirable conceptual and psychometric features of tobacco dependence assessments were identified; including the types of outcomes against which such assessment should be validated. DSM-IV criteria were matched against these criteria and compared with other dependence measures. DSM-IV criteria were found to be ambiguous; little used in tobacco research, and has relatively low predictive validity. Other dependence measures were found to have greater validity in the prediction of important dependence features such as relapse likelihood. Strength of urges to smoke on typical smoking days and during abstinence, markers of nicotine intake or frequency of smoking and latency to smoke soon after waking were found to be useful dependence measures. The use and utility of DSM-5 will be enhanced by eliminating most DSM-IV criteria and adding new ones based on smoking pattern, smoking heaviness, and the severity of craving during periods of smoking and withdrawal. Baker T, Breslau N, Covey L, Shiffman S. DSM criteria for tobacco use disorder and tobacco withdrawal: A critique and proposed revisions for DSM-5. *Addiction.* 2012; 107(2): 263-275.

Smoking Cessation and Quality of Life: Changes in Life Satisfaction Over 3 Years Following a Quit Attempt

There has been limited research addressing changes in subjective well-being as a result of quitting smoking. The purpose of this study was to use longitudinal data to determine the relation between smoking cessation and subjective measures of well-being, including global quality of life (QOL), health-related QOL (HR-QOL), affect, relationship satisfaction, and stressor occurrence. As part of a randomized, placebo-controlled smoking cessation trial, 1,504 participants (58.2% women, 83.9% white) completed assessments and had their smoking status biochemically confirmed at baseline and years 1 and 3 post-quit. Compared with continuing smokers, quitters showed improved global QOL, HR-QOL, and affect at years 1 and 3 and fewer stressors by year 3. Smoking status did not influence marital relationship satisfaction. Successful quitters, in contrast to continuing smokers, reported improved subjective well-being, which could be used to motivate quit attempts by individuals with concerns about what life will be like without cigarettes. Piper M, Kenford S, Fiore M, Baker T. Smoking cessation and quality of life: Changes in life satisfaction over 3 years following a quit attempt. *Ann Behav Med.* 2012; 43(2): 262-270.

Patterns of Tobacco Use and Tobacco-Related Psychiatric Morbidity and Substance Use among Middle-Aged and Older Adults in the United States

The purpose of this study was to examine prevalence of tobacco use and identify psychiatric symptoms and substance use correlates of tobacco use comparing adults 50-64 years of age with those 65+ years of age (N = 10,891). Data were from the 2008-2009 US National Surveys on Drug Use and Health. Past-year tobacco use was one-half as frequent among adults aged 65+ years (14.1%) compared to adults aged 50-64 years (30.2%); the latter group surpassed the former in rates of cigarette smoking (24.8% vs. 10.6%), daily cigarette smoking (16.5% vs. 7.1%), cigar smoking (7.4% vs. 2.3%), and smokeless tobacco use (2.5% vs. 1.7%). Increased odds of cigarette smoking were noted among men, whites, African Americans, and those who had less education, had lower income, were not currently married, or were binge drinkers or illicit/non-medical drug users. In controlled analyses, odds ratio in those 65+

years of age who had smoked during the past year was 2.2 for binge drinking and 3.5 for illicit or non-medical drug use. Odds ratio of binge drinking among those 65+ years of age for cigar smokers during the past year was 3.1. Past-year cigarette smoking was not associated with reports of symptoms of depression or anxiety in the 65+ age group. Tobacco use is less prevalent among adults 65+ years of age yet continues to be strongly associated with binge drinking and illicit or non-medical drug use. Preventive efforts to decrease these substance use problems should include programs to decrease tobacco use. Blazer D, Wu L. Patterns of tobacco use and tobacco-related psychiatric morbidity and substance use among middle-aged and older adults in the United States. *Aging Ment. Health.* 2012; 16(3): 296-304.

Gambling, Disordered Gambling and Their Association with Major Depression and

Substance Use: A Web-Based Cohort and Twin-Sibling Study

Relatively little is known about the environmental and genetic contributions to gambling frequency and disordered gambling (DG), the full continuum of gambling-related problems that includes pathological gambling (PG). A web-based sample (n=43,799 including both members of 609 twin and 303 sibling pairs) completed assessments of number of lifetime gambling episodes, DSM-IV criteria for PG, alcohol, nicotine and caffeine intake, and nicotine dependence (ND) and DSM-III-R criteria for lifetime major depression (MD). Twin modeling was performed using Mx. In the entire cohort, symptoms of DG indexed a single dimension of liability. Symptoms of DG were weakly related to caffeine intake and moderately related to MD, consumption of cigarettes and alcohol, and ND. In twin and sibling pairs, familial resemblance for number of times gambled resulted from both familial-environmental ($c^2=42\%$) and genetic factors ($a^2=32\%$). For symptoms of DG, resemblance resulted solely from genetic factors ($a^2=83\%$). Bivariate analyses indicated a low genetic correlation between symptoms of DG and MD ($r(a)=+0.14$) whereas genetic correlations with DG symptoms were substantially higher with use of alcohol, caffeine and nicotine, and ND (ranging from +0.29 to +0.80). The results were invariant across genders. Whereas gambling participation is determined by shared environmental and genetic factors, DG constitutes a single latent dimension that is largely genetically determined and more closely related to externalizing than internalizing behaviors. Because these findings are invariant across genders, they suggest that the etiological factors of DG are likely to be similar in men and women. Blanco C, Myers J, Kendler K. Gambling, disordered gambling and their association with major depression and substance use: A web-based cohort and twin-sibling study. *Psychol Med.* 2012; 42(3): 497-508.

The Relationship between Perceptions of Organizational Functioning and Voluntary

Counselor Turnover: A Four-Wave Longitudinal Study

Using data from a nationwide study, the authors annually track a cohort of 598 substance use disorder counselors over a four-wave period to (a) document the cumulative rates of voluntary turnover and (b) examine how counselor perceptions of the organizational environment (procedural justice, distributive justice, perceived organizational support, and job satisfaction) and clinical supervisor leadership effectiveness (relationship quality, in-role performance, extra-role performance) predict voluntary turnover over time. Survey data were collected from counselors in Year 1, and actual turnover data were collected from organizational records in Years 2, 3, and 4. Findings reveal that 25% of the original counselors turned over by Year 2, 39% by Year 3, and 47% by Year 4. Counselors with more favorable perceptions of the organizational environment are between 13.8% and 22.8% less likely to turn over than those with less favorable perceptions. None of the leadership effectiveness variables are significant. Eby L, Rothrauff-Laschober T. The relationship between perceptions of organizational functioning and voluntary counselor turnover: A four-wave longitudinal study. *J Subst Abuse Treat.* 2012; 42.

A Preliminary Study of the Effects of Patient Feedback on Treatment Outcomes The purpose of this study was to examine the effects of feedback provided to counselors on the outcomes of patients treated at community based substance abuse treatment programs. A version of the Outcome Questionnaire (OQ-45), adapted to include drug and alcohol use, was administered to patients (N = 304) in 3 substance abuse treatment clinics. Phase I of the study consisted only of administration of the assessment instruments. Phase II consisted of providing feedback reports to counselors based on the adapted OQ-45 at every treatment session up to Session 12. Patients who were found to not be progressing at an expectable rate (i.e., “off-track”) were administered a questionnaire that was used as a second feedback report for counselors. For off-track patients, feedback compared with no feedback led to significant linear reductions in alcohol use throughout treatment and also in OQ-45 total scores and drug use from the point of the second feedback instrument to Session 12. The effect for improving mental health functioning was evident at only 1 of the 3 clinics. These results suggest that a feedback system adapted to the treatment of substance use problems is a promising approach that should be tested in a larger randomized trial. Crits-Christoph P, Ring-Kurtz S, Hamilton JL, Lambert MJ, Gallop R, McClure B, Kulaga A, Rotrosen J. A preliminary study of the effects of individual patient-level feedback in outpatient substance abuse treatment programs. *J Subst Abuse Treat.* 2012; 42: 301-309.

Treatment Staff Turnover in Organizations Implementing Evidence-Based Practices: Turnover Rates and Their Association with Client Outcomes High staff turnover has been described as a problem for the substance use disorder treatment field. This assertion is based primarily on the assumption that staff turnover adversely impacts treatment delivery and effectiveness. This assumption, however, has not been empirically tested. In this study, the authors computed annualized rates of turnover for treatment staff (N = 249) participating in an evidence-based practice implementation initiative and examined the association between organizational-level rates of staff turnover and client-level outcomes. Annualized rates of staff turnover were 31% for clinicians and 19% for clinical supervisors. In addition, multilevel analyses did not reveal the expected relationship between staff turnover and poorer client-level outcomes. Rather, organizational-level rates of staff turnover were found to have a significant positive association with two measures of treatment effectiveness: less involvement in illegal activity and lower social risk. Possible explanations for these findings are discussed. Garner B, Hunter B, Modisette K, Ihnes P, Godley S. Treatment staff turnover in organizations implementing evidence-based practices: Turnover rates and their association with client outcomes. *J Subst Abuse Treat.* 2012; 42(2): 134-142.

Counselor Perception of Workplace Stress Linked to Client Participation in Treatment This article explores the impact of organizational attributes on client engagement within substance abuse treatment. Previous research has identified organizational features, including small size, accreditation, and workplace practices, that impact client engagement (KM Broome, PM Flynn, DK Knight, DD Simpson, 2007). This study sought to explore how aspects of the work environment impact client engagement. The sample included 89 programs located in 9 states across the United States. Work environment measures included counselor perceptions of stress, burnout, and work satisfaction at each program, whereas engagement measures included client ratings of participation, counseling rapport, and treatment satisfaction. Using multiple regressions, tests of moderation and mediation revealed that staff stress negatively predicted client participation in treatment. Burnout was related to stress but was not related to participation. Two additional organizational measures—workload and influence—moderated the positive relationship between staff stress and burnout. Implications for drug treatment programs are discussed. Landrum B, Knight DK, Flynn PM. The

impact of organizational stress on burnout and client engagement. *J Subst Abuse Treat.* 2012; 42(2): 222-230.

Higher Staff Turnover Rates Linked to Increased Workplace Demands and Decreased Perceptions of Support among Those Remaining

The purpose of this study was to examine the impact of staff turnover on perceptions of organizational demands and support among staff that remained employed in substance abuse treatment programs. The sample consisted of 353 clinical staff from 63 outpatient agencies. Two scales from the Survey of Organizational Functioning measured work environment demands (stress and inadequate staffing), and 3 measured supportive work relationships (communication, cohesion, and peer collaboration). Results from a series of multilevel models documented that counselors working in programs that had previously experienced high staff turnover perceived higher demands and lower support within their organization, even after controlling for other potentially burdensome factors such as budget, census, and individual measures of workload. Two individual-level variables, caseload and tenure, were important determinants of work environment demands but were not related to supportive work relationships. Findings suggest that staff turnover increases workplace demands, decreases perceptions of support, and underscores the need to reduce stress and minimize subsequent turnover among clinical staff. Knight DK, Becan JE, Flynn PM. Organizational consequences of staff turnover in outpatient substance abuse treatment programs. *J Subst Abuse Treat.* 2012; 42(2): 143-150.

Program-level Orientation towards Change Associated with Quitting among Counselors

Although evidence suggests that turnover rates are higher in high-stress/high-needs work environments, it is unclear whether agencies' attempts at improving practices influence individuals' decisions to stay at or leave a job. The purpose of this study was to examine whether program needs and change orientation influence individual decisions to quit. A sample of 206 counselors from 25 outpatient substance abuse treatment programs completed the Survey of Organizational Functioning, rating the organization on program needs, leadership, and change. They also rated themselves on stress, burnout, and job satisfaction. Multilevel modeling indicated a significant interaction between program needs and change orientation, even after controlling for stress, burnout, job satisfaction, tenure, and selected program characteristics. When perceptions of program needs were high, counselors were more likely to stay if they felt that the organization was making progress toward change. These findings suggest that an orientation toward change can counteract negative effects of perceived need within the workplace. Knight DK, Becan JE, Flynn PM. Program needs and change orientation: Implications for counselor turnover. *J Subst Abuse Treat.* 2012; 42(2): 159-168.

Innovation Adoption as Facilitated by a Change-Oriented Workplace

One of the unique contributions of this study is a glimpse into the process by which counselors decide to try new innovations in their clinical work. Data were collected from 421 counseling staff from 71 outpatient treatment programs in 4 U.S. regions. Using hierarchical linear modeling, results reveal that the propensity to adopt workshop-based interventions is facilitated by two important mechanisms: (a) an innovative organization with creative leadership and (b) change-oriented staff attributes (i.e., seeking professional growth, efficacy, adaptability, and influence on others). Innovative leaders and a climate receptive to change also bolster the development of these change-oriented attributes. One implication of these findings is the cascading effect of leaders' support of innovative thinking and action resulting in employees strengthening their own adaptive skills and carrying this innovative

thinking into individual adoption. Becan J, Knight D, Flynn P. Innovation adoption as facilitated by a change-oriented workplace. *J Subst Abuse Treat.* 2012; 42(2): 179-190.

Resources and Training in Outpatient Substance Abuse Treatment Facilities The exposure to new clinical interventions through formalized training and the utilization of strategies learned through training are two critical components of the program change process. This study considers the combined influence of actual program fiscal resources and counselors' perceptions of workplace resources on two mechanisms of training: exposure and utilization. Data were collected from 323 counselors nested within 59 programs located in nine states. Multilevel analysis revealed that training exposure and training utilization represent two distinct constructs that are important at different stages in the Program Change Model. Training exposure is associated primarily with physical and financial resources, whereas utilization is associated with professional community and job burnout. These results suggest that financial resources are important in initial exposure to new interventions but that successful utilization of new techniques depends in part on the degree of burnout and collaboration experienced by counselors. Lehman W, Becan J, Joe G, Knight D, Flynn P. Resources and training in outpatient substance abuse treatment facilities. *J Subst Abuse Treat.* 2012; 42(2): 169-178.

Predictors of Highly Active Antiretroviral Therapy Utilization for Behaviorally HIV-1-infected Youth: Impact of Adult versus Pediatric Clinical Care Site The authors evaluated highly active antiretroviral therapy (HAART) utilization in youth infected with HIV through risk behaviors who met treatment criteria for HAART. They assessed the impact of receiving care at an adult or pediatric HIV clinical site on initiation and discontinuation of the first HAART regimen in behaviorally infected youth (BIY). This was a retrospective analysis of treatment-naïve BIY, aged 12-24 years, who enrolled in the HIV Research Network between 2002 and 2008 and who met criteria for HAART. The outcomes were time from meeting criteria to initiation of HAART and time to discontinuation of the first HAART regimen. Analyses were conducted using Cox proportional hazards regression. Of 287 treatment-eligible youth, 198 (69%) received HAART; of these 198 youth, 58 (29.3%) subsequently discontinued HAART. In multivariable analyses, there was no significant difference in the time between meeting treatment criteria and initiating HAART for BIY followed at adult or pediatric HIV clinical sites. However, BIY followed at adult sites discontinued HAART sooner than BIY followed at pediatric HIV clinical sites (adjusted hazard ratio [AHR]: 3.19 [1.26-8.06]). Two-thirds of treatment-eligible BIY in the HIV Research Network cohort initiated HAART; however, one-third who initiated HAART discontinued it during the study period. Identifying factors associated with earlier HAART initiation and sustainability can inform interventions to enhance HAART utilization among treatment-eligible youth. The finding of earlier HAART discontinuation for youth at adult care sites deserves further study. Agwu A, Siberry G, Ellen J, Fleishman J, Rutstein R, Gaur A, Korthuis P, Warford R, Spector S, Gebo K. Predictors of highly active antiretroviral therapy utilization for behaviorally HIV-1-infected youth: Impact of adult versus pediatric clinical care site. *J Adolesc Health.* 2012; 50(5): 471-477.

Comparing Different Measures of Retention in Outpatient HIV Care The US National HIV/AIDS Strategy identifies retention in care as an important quality performance measure. There is no gold standard to measure retention in care. This study is the first to compare different measures of retention, using a large geographically diverse sample. The study examined a prospective cohort of 17,425 HIV-infected adults enrolled in care at 12 US HIV clinics between 2001 and 2008. The authors compared three measures of retention for each patient: proportion of time not spent in a gap of more than 6 months between successive outpatient visits; proportion of

91-day quarters in which at least one visit occurred; proportion of years in which two or more visits separated by at least 90 days occurred. Associations among measures and effects of sociodemographic and clinical characteristics were examined. The three measures of retention were moderately to strongly correlated. Averaging across patients, 71% of time in care was not spent in a gap more than 6 months; 73% of all quarters had at least one visit; and 75% of all years had at least two visits separated by at least 90 days. For all measures, retention was significantly higher for women, whites, older individuals, men who had sex with men (MSM)-related HIV transmission, and initial CD4 cell counts 50 cell/ μ l or less. This is one of the first studies to provide a national estimate of retention in HIV care in the US, which ranged from 71 to 75% using any of the accepted retention measures. Future studies should assess how well different measures predict clinical outcomes and establish acceptable target levels for retention. Yehia B, Fleishman J, Metlay J, Korthuis P, Agwu A, Berry S, Moore R, Gebo K, Gebo K. Comparing different measures of retention in outpatient HIV care. *AIDS*. 2012; 26(9): 1131-1139.

Attitudes toward Opioid Agonist Treatment among Buprenorphine Patients Understanding the attitudes of opioid-dependent individuals in the United States toward buprenorphine and methadone may help fashion approaches to increase treatment entry and improve patient outcomes. This secondary analysis study compared attitudes toward methadone and buprenorphine of opioid-dependent adults entering short-term buprenorphine treatment (BT) with opioid-dependent adults who are either entering methadone maintenance treatment or not entering treatment. The 417 participants included 132 individuals entering short-term BT, 191 individuals entering methadone maintenance, and 94 individuals not seeking treatment. Participants were administered an Attitudes toward Methadone scale and its companion Attitudes toward Buprenorphine scale. Demographic characteristics for the three groups were compared using χ^2 tests of independence and one-way analysis of variance. A repeated-measures multivariate analysis of variance with planned contrasts was used to compare mean attitude scores among the groups. Participants entering BT had significantly more positive attitudes toward buprenorphine than toward methadone ($p < .001$) and more positive attitudes toward BT than methadone-treatment (MT) participants and out-of-treatment (OT) participants ($p < .001$). In addition, BT participants had less positive attitudes toward methadone than participants entering MT ($p < .001$). Participants had a clear preference for a particular medication. Offering a choice of medications to OT individuals might enhance their likelihood of entering treatment. Treatment programs should offer a choice of medications when possible to new patients, and future comparative effectiveness research should incorporate patient preferences into clinical trials. Kelly SM, Brown BS, Katz EC, O'Grady KE, Mitchell SG, King S, Schwartz RP. A Comparison of attitudes toward opioid agonist treatment among short-term buprenorphine patients. *Am J Drug Alcohol Abuse*. 2012; 38: 233-238.

Benefits and Costs Associated with Mutual-Help Community-Based Recovery Homes: The Oxford House Model The authors used data from a randomized controlled study of Oxford House (OH), a self-run, self-supporting recovery home, to conduct a cost-benefit analysis of the program. Following substance abuse treatment, individuals that were assigned to an OH condition ($n=68$) were compared to individuals assigned to a usual care condition ($n=61$). Economic cost measures were derived from length of stay at an Oxford House residence, and derived from self-reported measures of inpatient and outpatient treatment utilization. Economic benefit measures were derived from self-reported information on monthly income, days participating in illegal activities, binary responses of alcohol and drug use, and incarceration. Results suggest that OH compared quite favorably to usual care: the net benefit of an OH stay was estimated to be roughly \$29,000 per person on average. Bootstrapped standard errors suggested that the net benefit was statistically

significant. Costs were incrementally higher under OH, but the benefits in terms of reduced illegal activity, incarceration and substance use substantially outweighed the costs. The positive net benefit for Oxford House is primarily driven by a large difference in illegal activity between OH and usual care participants. Using sensitivity analyses, under more conservative assumptions the authors still arrived at a net benefit favorable to OH of \$17,830 per person. Lo Sasso A, Byro E, Jason L, Ferrari J, Olson B. Benefits and costs associated with mutual-help community-based recovery homes: The Oxford House Model. *Eval Program Plann.* 2012; 35(1): 47-53.

A Dimensional Approach to Understanding Severity Estimates and Risk Correlates of Marijuana Abuse and Dependence in Adults

While item response theory (IRT) research shows a latent severity trait underlying response patterns of substance abuse and dependence symptoms, little is known about IRT-based severity estimates in relation to clinically relevant measures. In response to increased prevalence of marijuana-related treatment admissions, an elevated level of marijuana potency, and the debate on medical marijuana use, the authors applied dimensional approaches to understand IRT-based severity estimates for marijuana use disorders (MUDs) and their correlates while simultaneously considering gender- and race/ethnicity-related differential item functioning (DIF). Using adult data from the 2008 National Survey on Drug Use and Health (N = 37,897), Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for MUDs among past-year marijuana users were examined by IRT, logistic regression, and multiple indicators-multiple causes (MIMIC) approaches. Among 6,917 marijuana users, 15% met criteria for a MUD; another 24% exhibited sub threshold dependence. Abuse criteria were highly correlated with dependence criteria (correlation = 0.90), indicating unidimensionality; item information curves revealed redundancy in multiple criteria. MIMIC analyses showed that MUD criteria were positively associated with weekly marijuana use, early marijuana use, other substance use disorders, substance abuse treatment, and serious psychological distress. African Americans and Hispanics showed higher levels of MUDs than Whites, even after adjusting for race/ethnicity-related DIF. The redundancy in multiple criteria suggests an opportunity to improve efficiency in measuring symptom-level manifestations by removing low-informative criteria. Elevated rates of MUDs among African Americans and Hispanics require research to elucidate risk factors and improve assessments of MUDs for different racial/ethnic groups. Wu L, Woody G, Yang C, Pan J, Reeve B, Blazer D. A dimensional approach to understanding severity estimates and risk correlates of marijuana abuse and dependence in adults. *Int J Methods Psychiatr Res.* 2012 (epub ahead of print).

Alcohol Use and Crime: Findings from a Longitudinal Sample of U.S. Adolescents and Young Adults

A positive relationship between alcohol use and criminal activity has been well documented among adults, but fewer studies explore this relationship among adolescents. Using data from 4 waves of the National Longitudinal Study of Adolescent Health (Add Health), the authors examine alcohol use patterns and criminal activity from adolescence to young adulthood. Fixed-effects models partially address the potential endogeneity of alcohol use, and, because numerous studies indicate that males are more likely than females to engage in drinking and criminal activity, the analyses are segmented by gender. Findings show a strong positive relationship between alcohol consumption, the commission of crimes, and criminal victimization for both genders. Various sensitivity analyses and robustness checks support this core finding. These results have important policy implications, as public policy tools that aim to reduce drinking among adolescents could also reduce criminal activity. Moreover, effective alcohol abuse treatment may indirectly reduce delinquency and thus have greater long-term economic benefits than previously estimated. Popovici

I. Alcohol use and crime: Findings from a longitudinal sample of U.S. adolescents and young adults. *Alcoholism: Clinical and Experimental Research*. 2012; 36(3): 532-543.

Most Clients in an ATI Program Cite Logistical Barriers to Health and Psychosocial Services

Receipt The high levels of health and psychosocial needs among correctional populations strongly shape the well-being of the urban communities from which a large number of criminal justice-involved individuals come or to which they return. The benefits of providing services to correction-involved individuals and linking them to providers such as with alternative to incarceration (ATI) programs may be limited if they encounter difficulties accessing such services. This study identified the types of barriers that have prevented entrants into ATI programs from receiving health and psychosocial services. The authors then tested the association between number of prior incarcerations and number of barriers by gender. From a random sample of adults (N=322; 83 women and 239 men) entering ATI programs in New York City, data were collected via structured interviews that elicited self-reported sociodemographics, substance use, prior incarcerations, and barriers that had actually prevented a participant from visiting or returning to a service provider. Participants reported an average of 3.0 barriers that have prevented them from receiving health and psychosocial services. The most prevalent barriers predominantly concerned service providers' inability to accommodate constraints on participants' time availability or flexibility, transportation, and money. Compared to women, men had a significantly different association that was in the adverse direction—i.e., more prior incarcerations was associated with more barriers—between prior incarcerations and encountering service barriers. Findings indicate that ATI program entrants experience many barriers that have prevented them from receiving health and/or psychosocial services. Furthermore, men with more extensive incarceration histories particularly are disadvantaged. ATI programs can improve the public health of urban communities if such programs are prepared and resourced to facilitate the receipt of services among program participants, especially men who have more extensive incarceration histories. Wu E, El-Bassel N, Gilbert L, Hess L, Lee H, Rowell TL. Prior incarceration and barriers to receipt of services among entrants to alternative to incarceration programs: A gender-based disparity. *J Urban Health*. 2012; 89(2): 384-395.

A Randomized Clinical Trial of Methadone Maintenance for Prisoners: Prediction of Treatment Entry and Completion in Prison

The present report is an intent-to-treat analysis involving secondary data drawn from the first randomized clinical trial of prison-initiated methadone in the United States. This study examined predictors of treatment entry and completion in prison. A sample of 211 adult male prerelease inmates with pre-incarceration heroin dependence were randomly assigned to one of three treatment conditions: counseling only (counseling in prison; n = 70); counseling plus transfer (counseling in prison with transfer to methadone maintenance treatment upon release; n = 70); and counseling plus methadone (methadone maintenance in prison, continued in a community-based methadone maintenance program upon release; n = 71). Entered prison treatment ($p < .01$), and completed prison treatment ($p < .001$) were significantly predicted by the set of 10 explanatory variables and favored the treatment conditions receiving methadone. The present results indicate those individuals who are older in age and have longer prison sentences may have better outcomes than younger individuals with shorter sentences, meaning they are more likely to enter and complete prison-based treatment. Furthermore, implications for the treatment of prisoners with prior heroin dependence and for conducting clinical trials may indicate the importance of examining individual characteristics and the possibility of the examination of patient preference. Gordon MS, Kinlock TW, Couvillion KA, Schwartz RP, O'Grady K. A randomized

clinical trial of methadone maintenance for prisoners: Prediction of treatment entry and completion in prison. *J Offender Rehabil.* 2012; 51(4): 222-238.

An Evaluation of Six Brief Interventions that Target Drug-Related Problems in Correctional Populations

Finding brief effective treatments for criminal justice populations is a major public need. The CJ-DATS Targeted Intervention for Corrections (TIC), which consists of six brief interventions (Communication, Anger, Motivation, Criminal Thinking, Social Networks, and HIV/Sexual Health), were tested in separate federally-funded randomized control studies. In total, 1,573 criminal justice-involved individuals from 20 correction facilities participated (78% males; 54% white). Multi-level repeated measures analyses found significant gains in knowledge, attitudes, and psychosocial functioning (criteria basic to Knowledge, Attitude, and Practices (KAP) and TCU Treatment Process Models). While improvements were less consistent in criminal thinking, overall evidence supported efficacy for the TIC interventions. Joe G, Knight K, Simpson D, Flynn P, Morey J, Bartholomew N, Tindall M, Burdon W, Hall E, Martin S, O'Connell D. An evaluation of six brief interventions that target drug-related problems in correctional populations. *J Offender Rehabil.* 2012; 51 (1-2): 9-33.

Review of Buprenorphine-Mediated Transitions from Opioid Agonist to Antagonist

Treatment Constant refinement of opioid dependence (OD) therapies is a condition to promote treatment access and delivery. Among other applications, the partial opioid agonist buprenorphine has been studied to improve evidence-based interventions for the transfer of patients from opioid agonist to antagonist medications. This paper summarizes PubMed-searched clinical investigations and conference papers on the transition from methadone maintenance to buprenorphine and from buprenorphine to naltrexone, discussing challenges and advances. The majority of the 26 studies we examined were uncontrolled investigations. Many small clinical trials have demonstrated the feasibility of in- or outpatient transfer to buprenorphine from low to moderate methadone doses (up to 60-70 mg). Results on the conversion from higher methadone doses, on the other hand, indicate significant withdrawal discomfort, and need for ancillary medications and inpatient treatment. Tapering high methadone doses before the transfer to buprenorphine is not without discomfort and the risk of relapse. The transition buprenorphine-naltrexone has been explored in several pilot studies, and a number of treatment methods to reduce withdrawal intensity warrant further investigation, including the co-administration of buprenorphine and naltrexone. Outpatient transfer protocols using buprenorphine, and direct comparisons with other modalities of transitioning from opioid agonist to antagonist medications are limited. Given its potential salience, the information gathered should be used in larger clinical trials on short and long-term outcomes of opioid agonist-antagonist transition treatments. Future studies should also test new pharmacological mechanisms to help reduce physical dependence, and identify individualized approaches, including the use of pharmacogenetics and long-acting opioid agonist and antagonist formulations. Mannelli P, Peindl K, Lee T, Bhatia K, Wu L. Buprenorphine-mediated transition from opioid agonist to antagonist treatment: State of the art and new perspectives. *Curr Drug Abuse Rev.* 2012 Mar; 5(1): 52-63.

Do 12-Step Meeting Attendance Trajectories over 9 Years Predict Abstinence?

This study grouped treatment-seeking individuals (n = 1825) by common patterns of 12-step attendance using 5 waves of data (75% interviewed Year 9) to isolate unique characteristics and use-related outcomes distinguishing each class profile. The "high" class reported the highest attendance and abstinence. The "descending" class reported high baseline alcohol severity, long treatment episodes, and high initial attendance and abstinence, but by Year 5, their attendance and abstinence dropped. The "early-drop" class, which started with high attendance and abstinence but with low problem

severity, reported no attendance after Year 1. The "rising" class, with fairly high alcohol and psychiatric severity throughout, reported initially low attendance, followed by increasing attendance paralleling their abstinence. Last, the "low" and "no" classes, which reported low problem severity and very low/no attendance, had the lowest abstinence. Female gender and high alcohol severity predicted attendance all years. Consistent with a sustained benefit for 12-step exposure, abstinence patterns aligned much like attendance profiles. Witbrodt J, Mertens J, Kaskutas L, Bond J, Chi F, Weisner C. Do 12-step meeting attendance trajectories over 9 years predict abstinence? *J Subst Abuse Treat.* 2012; 43(1): 30-43. *Curr Drug Abuse Rev.* 2012; 5: 52-63.

Many States Will Need to Modify Children's Health Insurance Program Benefit Design to Comply with Federal Parity Legislation The Children's Health Insurance Program (CHIP) plays a vital role in financing behavioral health services for low-income children. This study examines behavioral health benefit design and management in separate CHIP programs on the eve of federal requirements for behavioral health parity. Even before parity implementation, many state CHIP programs did not impose services limits or costs sharing for behavioral health benefits. However, a substantial share of states imposed limits or cost sharing that might hinder access to care. The majority of states used managed care to administer behavioral health benefits. It is important to monitor how states adapt to programs to comply with parity. Garfield RL, Beardslee WR, Greenfield SF, Meara EM. Behavioral health services in separate CHIP programs on the eve of parity. *Adm Policy Ment Health.* 2012; 39: 147-157.

Economic Grand Rounds: The Price is Right? Changes in The Quantity of Services Used and Prices Paid in Response to Parity The impact of parity coverage on the quantity of behavioral health services used by enrollees and on the prices of these services was examined in a set of Federal Employees Health Benefit (FEHB) Program plans. After parity implementation, the quantity of services used in the FEHB plans declined in five service categories, compared with plans that did not have parity coverage. The decline was significant for all service types except inpatient care. Because a previous study of the FEHB Program found that total spending on behavioral health services did not increase after parity implementation, it can be inferred that average prices must have increased over the period. The finding of a decline in service use and increase in prices provides an empirical window on what might be expected after implementation of the federal parity law and the parity requirement under the health care reform law. Goldman H, Barry C, Normand S, Azzone V, Busch A, Huskamp H. Economic grand rounds: The price is right? Changes in the quantity of services used and prices paid in response to parity. *Psychiatr Serv.* 2012; 63(2): 107-109.

Identifying the Necessary and Sufficient Number of Risk Factors for Predicting Academic Failure Identifying the point at which individuals become at risk for academic failure (grade point average [GPA] < 2.0) involves an understanding of which and how many factors contribute to poor outcomes. School-related factors appear to be among the many factors that significantly impact academic success or failure. This study focused on 12 school-related factors. Using a thorough 5-step process, the authors identified which unique risk factors place one at risk for academic failure. Academic engagement, academic expectations, academic self-efficacy, homework completion, school relevance, school safety, teacher relationships (positive relationship), grade retention, school mobility, and school misbehaviors (negative relationship) were uniquely related to GPA even after controlling for all relevant covariates. Next, a receiver operating characteristic curve was used to determine a cutoff point for determining how many risk factors predict academic failure (GPA < 2.0). Results yielded a cutoff point of 2 risk factors for predicting academic failure, which provides

a way for early identification of individuals who are at risk. Further implications of these findings are discussed. Lucio R, Hunt E, Bornovalova M. Identifying the necessary and sufficient number of risk factors for predicting academic failure. *Dev Psychol.* 2012; 48(2): 422-428.

Injection Behaviors among Injection Drug Users in Treatment: The Role of Hepatitis C

Awareness Injection drug use (IDU) is a primary vector for blood-borne infections. Awareness of Hepatitis C virus (HCV) infection status may affect risky injection behaviors. This study determines the prevalence of risky injection practices and examines associations between awareness of positive HCV status and risky injection behaviors. The authors surveyed individuals seeking treatment for substance use at 12 community treatment programs as part of a national HIV screening trial conducted within the National Drug Abuse Treatment Clinical Trials Network. Participants reported socio-demographic characteristics, substance use, risk behaviors, and HCV status. The authors used multivariable logistic regression to test associations between participant characteristics and syringe/needle sharing. The 1281 participants included 244 (19.0%) individuals who reported injecting drugs in the past 6 months and 37.7% of IDUs reported being HCV positive. During the six months preceding baseline assessment, the majority of IDUs reported obtaining sterile syringes from pharmacies (51.6%) or syringe exchange programs (25.0%), but fewer than half of IDUs always used a sterile syringe (46.9%). More than one-third (38.5%) shared syringe/needles with another injector in the past 6 months. Awareness of positive HCV vs. negative/unknown status was associated with increased recent syringe/needle sharing (aOR 2.37, 95% CI 1.15, 4.88) in multivariable analysis. Risky injection behaviors remain prevalent and awareness of HCV infection was associated with increased risky injection behaviors. New approaches are needed to broadly implement HCV prevention interventions for IDUs seeking addiction treatment. Korthuis TP, Feaster DI, Gomez ZL, Das M, Tross S, Wiest K, Douaihy A, Mandler R. Injection behaviors among injection drug users in treatment: The role of hepatitis C awareness. *Addict Behav.* 2012; 37(4): 552-555.

Patterns of Water-Pipe and Cigarette Smoking Initiation in Schoolchildren: Irbid

Longitudinal Smoking Study Tobacco use remains a major public health problem worldwide. Water-pipe smoking is spreading rapidly and threatening to undermine the successes achieved in tobacco control. A school-based longitudinal study in the city of Irbid, Jordan, was performed from 2008 to 2010. All seventh-grade students in 19 randomly selected schools, out of a total of 60 schools in the city, were enrolled at baseline and surveyed annually. Of the 1,781 students enrolled at baseline 1,701 (95.5%) were still in the study at the end of the second year of follow-up (869 boys, median age at baseline 13 years). Ever and current water-pipe smoking were higher than those of cigarette smoking at baseline (ever smoking: 25.9% vs. 17.6% and current smoking: 13.3% vs. 5.3% for water-pipe and cigarette smoking, respectively; $p < .01$ for both) but cigarette smoking caught up by the second year of follow-up (ever smoking: 46.4% vs. 44.7%; $p = .32$ and current smoking: 18.9% vs. 14.9%; $p < .01$). Water pipe-only smokers at baseline were twice as likely to become current cigarette smokers after 2 years compared with never smokers (relative risk (RR) = 2.1; 95% CI = 1.2, 3.4). A similar pattern was observed for cigarette-only smokers at baseline (RR = 2.0; 95% CI = 0.9, 4.8). Prevalence of water-pipe and cigarette smoking increased dramatically over the 2-year follow-up period with similar patterns in boys and girls, although girls had lower prevalence in all categories. Water-pipe smoking at baseline predicted the progress to cigarette smoking in the future and vice versa. Mzayek F, Khader Y, Eissenberg T, Al Ali R, Ward K, Maziak W. Patterns of water-pipe and cigarette smoking initiation in schoolchildren: Irbid Longitudinal Smoking Study. *Nicotine Tob Res.* 2012; 14(4): 448-454.

Gender Differences in Physical and Mental Health Outcomes among an Aging Cohort of Individuals with a History of Heroin Dependence

This paper examines the health status and functioning of an aging cohort of individuals with a history of heroin dependence with a focus on gender differences. Study subjects were originally sampled from methadone maintenance clinics in California in the 1970s and completed follow-up interviews in 2005-2009. Out of the original study sample (N=914), 343 participants (44.3% female) were interviewed (70.6% of those not deceased). Bivariate analyses examined gender differences in participants' overall health status and physical and mental health problems. Scores on SF-36 scales were compared with general population norms by gender and age, as well as between participants in the study sample who did and did not report past-year drug use. Average age of the study sample was 58.3 (SD=4.9) years for males and 55.0 (SD=4.1) years for females. There were no significant gender differences in past-year drug use (38% of sample) or injection drug use (19%). Women reported significantly more chronic health problems and psychological distress compared with men, and overall poorer health and functioning compared with general population norms. Men under 65 had poorer physical health and social functioning compared with population norms. Men in the study sample reporting past-year substance use had poorer physical functioning, but less bodily pain, than non-users, whereas women with past-year substance use had poorer mental health than other women. Individuals with a history of heroin dependence have poorer health and functioning than their counterparts in the general population. At a younger age, women reported poorer overall health status and more chronic health and mental health problems than men. Study findings may inform interventions for this population, particularly related to gender-specific treatment needs. Grella C, Lovinger K. Gender differences in physical and mental health outcomes among an aging cohort of individuals with a history of heroin dependence. *Addict Behav.* 2012; 37(3): 306-312.

Attendance and Substance Use Outcomes for The Seeking Safety Program: Sometimes Less is More

This study uses data from the largest effectiveness trial to date on treatment of co-occurring posttraumatic stress and substance use disorders, using advances in statistical methodology for modeling treatment attendance and membership turnover in rolling groups. Women receiving outpatient substance abuse treatment (N = 353) were randomized to 12 sessions of Seeking Safety or a health education control condition. Assessments were completed at baseline and at 1 week, 3, 6, and 12 months post treatment. Outcome measures were alcohol and cocaine use in the prior 30 days captured using the Addiction Severity Index. Latent class pattern mixture modeling (LCPMM) was used to estimate attendance patterns and to test for treatment effects within and across latent attendance patterns and group membership turnover. Across LCPMM analyses for alcohol and cocaine use, similar treatment attendance patterns emerged: Completers never decreased below an 80% probability of attendance, droppers never exceeded a 41% probability of attendance, and titrators demonstrated a 50% to 80% probability of attendance. Among completers, there were significant decreases in alcohol use from baseline to 1-week post treatment, followed by non-significant increases in alcohol during follow-up. No differences between treatment conditions were detected. Titrators in Seeking Safety had lower rates of alcohol use from 1-week through 12-month follow-up compared with control participants. Droppers had non-significant increases in alcohol during both study phases. Cocaine use findings were similar but did not reach significance levels. The impact of client self-modulation of treatment dosage and group membership composition may influence behavioral treatment outcomes among this population. Hien D, Morgan-Lopez A, Campbell A, Saavedra L, Wu E, Cohen L, Ruglass L, Nunes E. Attendance and substance use outcomes for the seeking safety program: Sometimes less is more. *J Consult Clin Psychol.* 2012; 80 (1): 29-42.

Comparison of the Addiction Severity Index (ASI) and the Global Appraisal of Individual Needs (GAIN) in Predicting the Effectiveness of Drug Treatment Programs for Pregnant and Postpartum Women

This study conducts a within-subject comparison of the Addiction Severity Index (ASI) and the Global Appraisal of Individual Needs (GAIN) to assess change in alcohol and other drug treatment outcomes for pregnant and postpartum women. Data are from 139 women who were pregnant or who had children under 11 months old and were admitted to residential drug treatment, then re-interviewed 6 months post discharge (83% follow-up rate). The ASI and GAIN change measures were compared on their ability to detect changes in alcohol and drug use, medical and HIV risk issues, employment issues, legal problems, family and recovery environment characteristics, and psychological/emotional issues. The measures were similar in their ability to detect treatment outcomes, and ASI and GAIN change scores were moderately correlated with each other. The GAIN scales had equal or slightly higher coefficient alpha values than the ASI composite scores. The GAIN also includes an HIV risk scale, which is particularly important for pregnant and postpartum women. These results suggest that the GAIN is comparable with the ASI and can be used for treatment research with pregnant and postpartum women. Coleman-Cowger V, Dennis M, Funk R, Godley S, Lennox R. Comparison of the Addiction Severity Index (ASI) and the Global Appraisal of Individual Needs (GAIN) in predicting the effectiveness of drug treatment programs for pregnant and postpartum women. *J Subst Abuse Treat.* 2012 March 19. (e-pub ahead of print).

Alcohol Use after Combat-Acquired Traumatic Brain Injury: What We Know and Don't Know

Military personnel engage in unhealthy alcohol use at rates higher than their same age, civilian peers, resulting in negative consequences for the individual and jeopardized force readiness for the armed services. Among those returning from combat deployment, unhealthy drinking may be exacerbated by acute stress reactions and injury, including traumatic brain injury (TBI). Combat-acquired TBI is common among personnel in the current conflicts. Although research suggests that impairments due to TBI leads to an increased risk for unhealthy drinking and consequences among civilians, there has been little research to examine whether TBI influences drinking behaviors among military personnel. This article examines TBI and drinking in both civilian and military populations and discusses implications for clinical care and policy. Adams R, Corrigan J, Larson M. Alcohol use after combat-acquired traumatic brain injury: What we know and don't know. *J Soc Work Pract Addict.* 2012; 12(1): 28-51.

Influence of Co-Morbid Mental Disorders on Time to Seeking Treatment for Major Depressive Disorder

Although treatment of depression has increased in recent years, long delays commonly separate disorder onset from first treatment contact. This study evaluates the effects of psychiatric co-morbidities and sociodemographic characteristics on lifetime treatment seeking and speed to first treatment contact for major depressive disorder (MDD). A cross-sectional epidemiological survey including retrospective structured assessments of DSM-IV MDD and other psychiatric disorders, respondent age at disorder onset, and age at first treatment contact. A nationally representative sample of 5,958 adults aged at least 18 years residing in households and group quarters who met lifetime criteria for MDD. The percentage of respondents with lifetime MDD who reported ever seeking treatment is reported overall and stratified by sociodemographic characteristics. Unadjusted and adjusted hazard ratios (AHRs) are presented on time to first depression treatment seeking by sociodemographic characteristics and co-morbid psychiatric disorders. A majority (61.3%) of respondents with MDD reported having sought treatment for depression at some point in their lives. Time to first depression treatment contact was significantly related to the occurrence of co morbid panic disorder [AHR=2.01, 95% confidence interval (CI), 1.69-2.39], generalized anxiety disorder (AHR=1.55; 95% CI, 1.33-1.81), drug dependence

(AHR=1.54; 95% CI, 1.06-2.26), dysthymic disorder (AHR=1.54; 95% CI, 1.35-1.76), and posttraumatic stress disorder (AHR=1.34; 95% CI, 1.13-1.59) and inversely related to male sex (AHR=0.74; 95% CI, 0.66-0.82) and black race/ethnicity (AHR=0.69, 95% CI, 0.59-0.81). Co-morbid psychiatric disorders, especially panic, generalized anxiety, substance use, and dysthymic disorders, appear to play an important role in accelerating treatment seeking for MDD. Outreach efforts should include a focus on depressed individuals without complicating psychiatric co morbidities. Olfson M, Liu S, Grant B, Blanco C. Influence of co morbid mental disorders on time to seeking treatment for major depressive disorder. *Med Care*. 2012; 50(3): 227-232.

Epidemiology of Major Depression with Atypical Features: Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

The purpose of this study was to examine prevalence, correlates, co morbidity and treatment-seeking among individuals with a lifetime major depressive episode (MDE) with and without atypical features. Data were derived from the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions, a large cross-sectional survey of a representative sample (N = 43,093) of the US population that assessed psychiatric disorders using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version (AUDADIS-IV). Comparison groups were defined based on the presence or absence of hypersomnia or hyperphagia in individuals who met criteria for lifetime DSM-IV MDE. The presence of atypical features during an MDE was associated with greater rates of lifetime psychiatric co morbidity, including alcohol abuse, drug dependence, dysthymia, social anxiety disorder, specific phobia, and any personality disorder (all P values < .05), except antisocial personality disorder, than MDE without atypical features. Compared with the latter group, MDE with atypical features was associated with female gender, younger age at onset, more MDEs, greater episode severity and disability, higher rates of family history of depression, bipolar I disorder, suicide attempts, and larger mental health treatment-seeking rates (all P values < .05). These data provide further evidence for the clinical significance and validity of this depressive specifier. Based on the presence of any of the 2 reversed vegetative symptoms during an MDE, most of the commonly cited validators of atypical depression were confirmed in this study. Major depressive episode with atypical features may be more common, severe, and impairing than previously documented. Blanco C, Vesga-López O, Stewart J, Liu S, Grant B, Hasin D. Epidemiology of major depression with atypical features: Results from The National Epidemiologic Survey On Alcohol And Related Conditions (NESARC). *J Clin Psychiatry*. 2012; 73(2): 224-232.

Gender, HIV Status, and Psychiatric Disorders: Results from The National Epidemiologic Survey on Alcohol and Related Conditions

More than 30 years after the onset of the human immunodeficiency virus (HIV) epidemic, there is no information on the prevalence of psychiatric disorders among HIV-positive individuals in the general population. The authors sought to compare the prevalence of 12-month psychiatric disorders among HIV-positive and HIV-negative adults stratified by sex and to examine the differential increase in risk of a psychiatric disorder as a function of the interaction of sex and HIV status. Face-to-face interviews were conducted between 2004 and 2005 with participants in the National Epidemiologic Survey on Alcohol and Related Conditions Wave 2, a large nationally representative sample of US adults (34,653). The diagnostic interview used was the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. When compared with their HIV-negative same-sex counterparts, HIV-positive men were more likely to have any mood disorder (odds ratio [OR] = 6.10; 95% confidence interval [CI], 2.99-12.44), major depressive disorder/dysthymia (OR = 3.77; 95% CI, 1.16-12.27), any anxiety disorder (OR = 4.02; 95% CI, 2.12-7.64), and any personality disorder (OR = 2.50; 95% CI, 1.34-4.67). In relation to their same-sex HIV-negative counterparts, the effect of HIV status on the odds

of any mood disorder (OR = 7.17; 95% CI, 2.52-20.41), any anxiety disorder (OR = 3.45; 95% CI, 1.27-9.38), and any personality disorder (OR = 2.66; 95% CI, 1.16-6.10) was significantly greater for men than women. HIV status was significantly more strongly associated with psychiatric disorders in men than in women. HIV-positive men had a higher prevalence than HIV-negative men of most psychiatric disorders. By contrast, HIV-positive women were not significantly more likely than HIV-negative women to have psychiatric disorders. Lopes M, Olfson M, Rabkin J, Hasin D, Alegría A, Lin K, Grant B, Blanco C. Gender, HIV status, and psychiatric disorders: Results from the National Epidemiologic Survey On Alcohol and Related Conditions. *J Clin Psychiatry*. 2012; 73 (3): 384-391.

Methodological Reporting in Qualitative, Quantitative, and Mixed Methods Health Services

Research Articles Methodologically sound mixed methods research can improve our understanding of health services by providing a more comprehensive picture of health services than either method can alone. This study describes the frequency of mixed methods in published health services research and compares the presence of methodological components indicative of rigorous approaches across mixed methods, qualitative, and quantitative articles. All empirical articles (n = 1,651) published between 2003 and 2007 from four top-ranked health services journals were compiled. All mixed methods articles (n = 47) and random samples of qualitative and quantitative articles were evaluated to identify reporting of key components indicating rigor for each method, based on accepted standards for evaluating the quality of research reports (e.g., use of p-values in quantitative reports, description of context in qualitative reports, and integration in mixed method reports). The authors used chi-square tests to evaluate differences between article types for each component. Mixed methods articles comprised 2.85 percent (n = 47) of empirical articles, quantitative articles 90.98 percent (n = 1,502), and qualitative articles 6.18 percent (n = 102). There was a statistically significant difference ($\chi^2(1) = 12.20, p = .0005, \text{Cramer's } V = 0.09, \text{odds ratio} = 1.49 [95\% \text{ confidence interval} = 1.27, 1.74]$) in the proportion of quantitative methodological components present in mixed methods compared to quantitative papers (21.94 versus 47.07 percent, respectively) but no statistically significant difference ($\chi^2(1) = 0.02, p = .89, \text{Cramer's } V = 0.01$) in the proportion of qualitative methodological components in mixed methods compared to qualitative papers (21.34 versus 25.47 percent, respectively). Few published health services research articles use mixed methods. The frequency of key methodological components is variable. Suggestions are provided to increase the transparency of mixed methods studies and the presence of key methodological components in published reports. Wisdom J, Cavaleri M, Onwuegbuzie A, Green C. Methodological reporting in qualitative, quantitative, and mixed methods health services research articles. *Health Serv Res*. 2012; 47(2): 721-745.

Hepatitis A/B Vaccine Completion among Homeless Adults with History of Incarceration

Hepatitis B virus (HBV) vaccination rates for incarcerated adults remain low despite their high risk for infection. This study determined predictors of vaccine completion in homeless adults (N= 297) who reported histories of incarceration and who participated in one of three nurse-led hepatitis programs of different intensity. Moreover time since release from incarceration was also considered. Just over half of the former prisoners completed the vaccine series. Older age (e40), having a partner and chronic homelessness were associated with vaccine completion. Recent research has documented the difficulty in providing vaccine services to younger homeless persons and homeless males at risk for HBV. Additional strategies are needed to achieve HBV vaccination completion rates greater than 50% for formerly incarcerated homeless men. Nyamathi A, Marlow E, Branson C, Marfisee M, Nandy K. Hepatitis A/B vaccine completion among homeless adults with history of incarceration. *J Forensic Nurs*. 2012; 8(1): 13-22.

Eating Disorders, Normative Eating Self-Efficacy and Body Image Self-Efficacy: Women in Recovery Homes

Although eating disorders (EDs) and ED symptoms are common among individuals in recovery for substance abuse (SA), long-term SA treatment programmes rarely address these problems. The present study examined the prevalence of EDs among women residing in Oxford Houses--low-cost, self-governed recovery homes for SA. Further, among women both with and without an ED diagnosis, the association between duration of Oxford House residency and eating-related self-efficacy scores was examined as an indicator of potential treatment effects on ED symptoms. During a telephone assessment, participants were administered the Structured Clinical Interview for DSM-IV-TR Axis I Disorders and the Eating Disorder Recovery Self-Efficacy Questionnaire. Results indicated that 12 of the 31 women analyzed met criteria for an ED (bulimia nervosa, 2; ED not otherwise specified, 10). Differential findings were evident for eating-related self-efficacy measures depending on ED diagnostic status and duration of residency. Potential interpretations, limitations and implications are discussed. Czarlinski J, Aase D, Jason L. Eating disorders, normative eating self-efficacy and body image self-efficacy: Women in recovery homes. *Eur Eat Disord Rev.* 2012; 20(3): 190-195.

Motives for Using: A Comparison Of Prescription Opioid, Marijuana and Cocaine Dependent Individuals

Identification of the motives for drug use is critical to the development of effective interventions. Furthermore, consideration of the differences in motives for drug use across substance dependent populations may assist in tailoring interventions. To date, few studies have systematically compared motives for substance use across drug classes. The current study examined motives for drug use between non-treatment seeking individuals with current prescription opioid, marijuana, or cocaine dependence. Participants (N=227) completed the Inventory of Drug-Taking Situations (IDTS; Annis, Turner & Sklar,1997), which contains eight subscales assessing motives for drug use. The findings revealed that prescription opioid dependent individuals scored significantly higher than all other groups on the Physical Discomfort, Testing Personal Control and Conflict with Others subscales. Both the prescription opioid and cocaine dependent groups scored significantly higher than the marijuana group on the Urges or a Temptation to Use subscale. In contrast, marijuana dependent individuals scored highest on the Pleasant Emotions and Pleasant Times with Others subscales. The marked differences revealed in motives for drug use could be used in the development and implementation of specific treatment interventions for prescription opioid, marijuana and cocaine dependent individuals. Hartwell K, Back S, McRae-Clark A, Shaftman S, Brady K. Motives for using: A comparison of prescription opioid, marijuana and cocaine dependent individuals. *Addict Behav.* 2012; 37(4): 373-378.

Conduct Disorder and Adult Psychiatric Diagnoses: Associations and Gender Differences in the U.S. Adult Population

The authors' objective was to examine the presence of Axis I and II psychiatric disorders among adult males and females with a history in childhood and/or adolescence of conduct disorder (CD). Data were derived from a large national sample of the U.S. population. Face-to-face interviews of more than 34,000 adults ages 18 years and older were conducted during 2004-2005 using the Alcohol Use Disorder and Associated Disabilities Interview Schedule eDSM-IV Version. After adjusting for sociodemographic characteristics and psychiatric co-morbidity, CD was associated with all Axis I and II disorders, particularly substance use disorders (SUD), bipolar disorder, and histrionic personality disorders. After adjusting for gender differences in the general population, men had significantly greater odds of social anxiety disorder and paranoid personality disorder, whereas women were more likely to have SUD. Furthermore, there was dose-response relationship between number of CD symptoms and risk for most psychiatric disorders. From a clinical standpoint, knowledge of the gender differences in associations of CD with other

psychiatric disorders in adulthood may be informative of developmental pathways of the disorder, and of possible gender-specific risk factors. Early recognition and treatment of CD may help prevent the development of adult-onset disorders. Morcillo C, Duarte CS, Sala R, Lejuez CW, Kerridge BT, Blanco C. Conduct disorder and adult psychiatric diagnoses: Associations and gender differences in the U.S. adult population. *J Psychiatr Res.* 2012; 46: 323-330.

A Compilation of Strategies for Implementing Clinical Innovations in Health and Mental Health

Efforts to identify, develop, refine, and test strategies to disseminate and implement evidence-based treatments have been prioritized in order to improve the quality of health and mental health care delivery. However, this task is complicated by an implementation science literature characterized by inconsistent language use and inadequate descriptions of implementation strategies. This article brings more depth and clarity to implementation research and practice by presenting a consolidated compilation of discrete implementation strategies, based on a review of 205 sources published between 1995 and 2011. The resulting compilation includes 68 implementation strategies and definitions, which are grouped according to six key implementation processes: planning, educating, financing, restructuring, managing quality, and attending to the policy context. This consolidated compilation can serve as a reference to stakeholders who wish to implement clinical innovations in health and mental health care and can facilitate the development of multifaceted, multilevel implementation plans that are tailored to local contexts. Powell BJ, McMillen CJ, Proctor EK, Carpenter CR, Griffey RT, Bunger AC, Glass JE, York JL. A compilation of strategies for implementing clinical innovations in health and mental health. *Med Care Res Rev.* 2012; 69(2): 123-157.

The Impact of Intimate Partner Violence on Women's Condom Negotiation Efficacy

HIV prevention efforts promote the use of condoms to prevent the spread of HIV and other STDs. Thus, a woman's agency to practice healthy sexual behaviors necessarily involves negotiation with another person. This poses unique challenges for women who have limited power in relationships. The current study explores how the experience of intimate partner violence (IPV) impacts a woman's confidence in her ability to negotiate condom use with a sexual partner (i.e., condom use self-efficacy), using data from incarcerated females in three states, who were interviewed just prior to release back into the community. The direct effect of experiencing IPV as an adult, controlling for other risk factors, on condom use self-efficacy has not previously been empirically tested. Results show that IPV experiences among women significantly decreases their confidence in negotiating condom use with a partner, putting them at a higher risk of HIV infection than women who do not report having recently experienced IPV. Swan H, O'Connell DJ. The impact of intimate partner violence on women's condom negotiation efficacy. *J Interpers Violence.* 2012; 27(4): 775-792.

The Short Inventory of Problems-Modified for Drug Use (SIP-DU): Validity in a Primary Care Sample

Primary care physicians can help drug-dependent patients mitigate adverse drug use consequences; instruments validated in primary care to measure these consequences would aid in this effort. This study evaluated the validity of the Short Inventory of Problems-Alcohol and Drugs modified for Drug Use (SIP-DU) among subjects recruited from a primary care clinic (n= 106). SIP-DU internal consistency was evaluated using Cronbach's alphas, convergent validity by correlating the total SIP-DU score with the DAST-10, and construct validity by analyzing the factor structure. The SIP-DU demonstrated high internal consistency (Cronbach's alpha for overall scale .95, subscales .72-.90) comparable with other SIP versions and correlated well with the DAST-10 (r= .70). Confirmatory factor analysis suggested an unacceptable fit of previously proposed factors;

exploratory factor analyses suggested a single factor of drug use consequences. The SIP-DU offers primary care clinicians a valid and practical assessment tool for drug use consequences.

Allensworth-Davies D, Cheng D, Smith P, Samet J, Saitz R. The Short Inventory of Problems-Modified for Drug Use (SIP-DU): Validity in a primary care sample. *Am J Addict.* 2012; 21(3): 257-262.

Does Switching to a Tobacco-Free Water Pipe Product Reduce Toxicant Intake? A Crossover Study Comparing CO, NO, PAH, Volatile Aldehydes

Water pipe (hookah, narghile, shisha) use has become a global phenomenon, with numerous product variations. One variation is a class of products marketed as "tobacco-free" alternatives for the "health conscious user". In this study, toxicant yields from water pipes smoked using conventional tobacco-based and tobacco-free preparations were compared. A human-mimic water pipe smoking machine was used to replicate the puffing sequences of 31 human participants who completed two double-blind ad libitum smoking sessions in a controlled clinical setting: once with a tobacco-based product of their choosing and once with a flavor-matched tobacco-free product. Outcome measures included yields of carbon monoxide, nitric oxide, volatile aldehydes, nicotine, tar, and polycyclic aromatic hydrocarbons. Smoke from both water pipe preparations contained substantial quantities of toxicants. Nicotine yield was the only outcome that differed significantly between preparations. These findings contradict advertising messages that "herbal" water pipe products are a healthy alternative to tobacco products. Shihadeh A, Salman R, Jaroudi E, Saliba N, Sepetdjian E, Blank M, Cobb C, Eissenberg T. Does switching to a tobacco-free water pipe product reduce toxicant intake? A crossover study comparing CO, NO, PAH, volatile aldehydes. *Food Chem Toxicol.* 2012; 50(5): 1494-1498.

Relationship of Substance Abuse to Dependence in The U.S. General Population

The diagnostic categories of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, for substance abuse and dependence are commonly used in clinical work and research studies, but whether abuse and dependence represent two different syndromes has been debated. The purpose of this article is to investigate the relationship of substance abuse and dependence for cannabis, cocaine, stimulants and sedatives among lifetime users of these substances in the National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative survey conducted in 2001-2002. The multiple indicators multiple causes (MIMIC) model addresses three sets of relationships: those between (1) diagnostic criteria and latent factors, (2) latent factors and covariates, and (3) criteria and covariates. This approach allows for the detection of and compensation for non-invariance of the measurement of criteria across subgroups. Compared with one-factor models, two-factor models (factors roughly corresponding to abuse and dependence) fit significantly better across all substances, with abuse and dependence factors highly correlated. The MIMIC model indicated that race/ethnicity, age, income, and marital status showed some differential relationships across substance groups, although most covariates showed similar associations to dependence and abuse factors. Noninvariance of criteria measurement by demographic covariates was most pronounced for cannabis abuse and dependence criteria. The general relationship of abuse to dependence was consistent across substances. Results were equivocal on the value of retaining separate factors; therefore, investigating the relationships of specific genetic variants and treatment outcomes to dimensional indicators of abuse, dependence, and measures combining these criteria is warranted. Measurement of cannabis abuse and dependence criteria appears most affected by demographic characteristics. Saha T, Harford T, Goldstein R, Kerridge B, Hasin D. Relationship of substance abuse to dependence in the U.S. general population. *J Stud Alcohol Drugs.* 2012; 73(3): 368-378.

A Broad Symmetry Criterion for Nonparametric Validity of Parametrically Based Tests in Randomized Trials Pilot phases of a randomized clinical trial often suggest that a parametric model may be an accurate description of the trial's longitudinal trajectories. However, parametric models are often not used for fear that they may invalidate tests of null hypotheses of equality between the experimental groups. Existing work has shown that when, for some types of data, certain parametric models are used, the validity for testing the null is preserved even if the parametric models are incorrect. Here, the authors provide a broader and easier to check characterization of parametric models that can be used to (i) preserve nonparametric validity of testing the null hypothesis, i.e., even when the models are incorrect, and (ii) increase power compared to the non- or semi-parametric bounds when the models are close to correct. They demonstrate these results in a clinical trial of depression in Alzheimer's patients. Shinohara RT, Frangakis CE, Lyketsos CG. A broad symmetry criterion for nonparametric validity of parametrically based tests in randomized trials. *Biometrics*. 2012; 68(1): 85-91.

Screening For Alcohol and Drug Use Disorders in Primary Care: A Review The Patient Protection and Affordable Care Act of 2010 supports integration of substance abuse interventions and treatments into the mainstream health care system. Thus, effective screening and intervention for substance use disorders in health care settings is a priority. This paper reviews the prevalence of alcohol and drug use disorders (abuse or dependence) in primary care settings and emergency departments, as well as current screening tools and brief interventions. MEDLINE was searched using the following keywords: alcohol use, alcohol use disorder, drug use, drug use disorder, screening, primary care, and emergency departments. Using the related-articles link, additional articles were screened for inclusion. This review focuses on alcohol and drug use and related disorders among adults in primary care settings. Screening, brief intervention, and referral for treatment are feasible and effective in primary care settings, provided that funding for screening is available, along with brief interventions and treatment facilities to which patients can be referred and treated promptly. Pilowsky DJ, Wu L. Screening for alcohol and drug use disorders among adults in primary care: A review. *Subst Abuse Rehabil*. 2012; 3: 25-34.

Relationship of Episode Costs to Clinical Intensity Positive But Not Proportional This study investigates how average costs for an episode of care in outpatient drug-free (ODF) treatment related to clinical intensity (length of stay and weekly counseling hours) and program structure (e.g. size, staffing), controlling for prices paid and selected client measures. Based on cost assessments from a naturalistic sample of 67 programs located across the United States (using the Treatment Cost Analysis Tool), robust regression techniques showed that programs having 10% longer treatment stays had episode costs 7% higher, those having 10% more weekly counseling hours per client had 4% higher episode costs. Other important factors included wages, amount of counselors' time conducting sessions, and serving more clients referred from the criminal justice system. The study provides valuable information on treatment program features that relate to costs. Broome KM, Knight DK, Joe GW, Flynn PM. Treatment program operation and costs. *J Subst Abuse Treat*. 2012; 42(2): 125-133.

CTN-RELATED RESEARCH

Implementing Rapid HIV Testing With Or Without Risk-Reduction Counseling In Drug Treatment Centers: Results Of A Randomized Trial

The authors examined the effectiveness of risk reduction counseling and the role of on-site HIV testing in drug treatment. Between January and May 2009, they randomized 1,281 HIV-negative (or status unknown) adults who reported no past-year HIV testing to (1) referral for off-site HIV testing, (2) HIV risk-reduction counseling with on-site rapid HIV testing, or (3) verbal information about testing only with on-site rapid HIV testing. The authors defined 2 primary self-reported outcomes a priori: receipt of HIV test results and unprotected anal or vaginal intercourse episodes at 6-month follow-up. The combined on-site rapid testing participants received more HIV test results than off-site testing referral participants ($P < .001$; Mantel-Haenszel risk ratio=4.52; 97.5% confidence interval [CI] =3.57, 5.72). At 6 months, there were no significant differences in unprotected intercourse episodes between the combined on-site testing arms and the referral arm ($P = .39$; incidence rate ratio [IRR]=1.04; 97.5% CI=0.95, 1.14) or the 2 on-site testing arms ($P = .81$; IRR=1.03; 97.5% CI=0.84, 1.26). This study demonstrated on-site rapid HIV testing's value in drug treatment centers and found no additional benefit from HIV sexual risk-reduction counseling. Metsch LR, Feaster DJ, Gooden L, Matheson T, Mandler RN, Haynes L, Tross S, Kyle T, Gallup D, Kosinski AS, Douaihy A, Schackman BR, Das M, Lindblad R, Erickson S, Korhuis PT, Martino S, Sorensen JL, Szapocznik J, Walensky R, Branson B, Colfax GN. Implementing rapid HIV testing with or without risk-reduction counseling in drug treatment centers: Results of a randomized trial. *Am J Public Health*. 2012 Jun; 102(6): 1160-1167. Epub 2012 Apr 19.

Stimulant Abuser Groups To Engage In 12-Step: A Multisite Trial In The National Institute On Drug Abuse Clinical Trials Network

The study evaluated the effectiveness of an 8-week combined group plus individual 12-step facilitative intervention on stimulant drug use and 12-step meeting attendance and service. The study design was a multisite randomized controlled trial, with assessments at baseline, mid-treatment, end of treatment, and 3- and 6-month post-randomization follow-ups (FUs) conducted in intensive outpatient substance treatment programs. Participants were individuals with stimulant use disorders ($n = 471$) randomly assigned to treatment as usual (TAU) or TAU into which the Stimulant Abuser Groups to Engage in 12-Step (STAGE-12) intervention was integrated. Measurements included urinalysis and self-reports of substance use and 12-step attendance and activities. Group sessions focused on increasing acceptance of 12-step principles; individual sessions incorporated an intensive referral procedure connecting participants to 12-step volunteers. Compared with TAU, STAGE-12 participants had significantly greater odds of self-reported stimulant abstinence during the active 8-week treatment phase; however, among those who had not achieved abstinence during this period, STAGE-12 participants had more days of use. STAGE-12 participants had lower Addiction Severity Index Drug Composite scores at and a significant reduction from baseline to the 3-month FU, attended 12-step meetings on a greater number of days during the early phase of active treatment, engaged in more other types of 12-step activities throughout the active treatment phase and the entire FU period, and had more days of self-reported service at meetings from mid-treatment through the 6-month FU. The present findings are mixed with respect to the impact of integrating the STAGE-12 intervention into intensive outpatient drug treatment compared with TAU on stimulant drug use. However, the results more clearly indicate that individuals in STAGE-12 had higher rates of 12-step meeting attendance and were engaged in more related activities throughout both the active treatment phase and the entire 6-month FU period than did those in TAU. Donovan DM, Daley DC, Brigham GS, Hodgkins CC, Perl HI, Garrett SB, Doyle SR, Floyd AS, Knox PC, Botero C, Kelly TM, Killeen TK, Hayes C,

Kau'ibaumhofer N, Seamans C, Zammarelli L. Stimulant abuser groups to engage in 12-Step: A multisite trial in the National Institute on Drug Abuse Clinical Trials Network. *J Subst Abuse Treat.* 2012 May 30. [Epub ahead of print].

Frontal Systems Deficits In Stimulant-Dependent Patients: Evidence Of Pre-Illness

Dysfunction and Relationship To Treatment Response Frontal systems dysfunction is present in stimulant-dependent patients. However, it is unclear whether this dysfunction is a pre-morbid risk factor or stimulant-induced, is severe enough to be clinically relevant, and if it is relevant to treatment response. These questions were addressed using the Frontal Systems Behavior Scale (FrSBe), a reliable and valid self-report assessment of three neurobehavioral domains associated with frontal systems functioning (Apathy, Disinhibition, and Executive Dysfunction, summed for a Total), that assesses both pre- and post-morbid functioning, and has a specific cutoff for defining clinically significant abnormalities. The study employed six sites evaluating 12-step facilitation for stimulant abusers obtained the FrSBe from 180 methamphetamine- and/or cocaine-dependent participants. Dichotomous treatment response measures included self-reported stimulant use, stimulant urine drug screens, and treatment completion. A substantial percentage of participants retrospectively reported clinically significant neurobehavioral abnormalities prior to lifetime stimulant abuse initiation (e.g., 67.5% on FrSBe-Total) with a significant increase in the proportion reporting such abnormalities for current functioning (86% on FrSBe-Total; $p < 0.0001$). Treatment response was significantly worse for participants with, relative to those without, clinically significant Disinhibition as measured by treatment non-completion (31.6% vs. 15.6%, OR=2.51) and self-reported stimulant use during treatment (40.5% vs. 16.7%, OR=3.40). These findings suggest that frontal systems dysfunction is present prior to stimulant-abuse onset and worsens with stimulant use. Disinhibition may be a prime target for intervention in stimulant-dependent individuals. Winhusen TM, Somoza EC, Lewis DF, Kropp FB, Horigian VE, Adinoff B. Frontal systems deficits in stimulant-dependent patients: Evidence of pre-illness dysfunction and relationship to treatment response. *Drug Alcohol Depend.* 2012 Jul 6. [Epub ahead of print].

The Short Inventory Of Problems - Revised (SIP-R): Psychometric Properties Within A Large, Diverse Sample Of Substance Use Disorder Treatment Seekers

Assessment of the adverse consequences of substance use serves an important function in both clinical and research settings, yet there is no universally agreed upon measure of consequences relevant to multiple types of substance use disorders. One of the most commonly used measures, the Short Inventory of Problems (SIP), has been adapted and evaluated in several specific populations, but evidence is needed of its reliability and validity across broader samples of persons with substance use disorders. This study evaluated the psychometric properties of a revised version of the SIP (SIP-R) in a large combined sample of alcohol and drug use disorder treatment seekers, with participants pooled from two national, multisite, randomized clinical trials. A total of 886 participants across 10 outpatient treatment facilities completed a common assessment battery that included the SIP-R, Addiction Severity Index (ASI), University of Rhode Island Change Assessment (URICA), HIV Risk Behavior Scale (HRBS), and a substance use calendar. Results supported the SIP-R's internal reliability ($\alpha = .95$). Confirmatory factor analysis demonstrated that the hypothesized 5-factor model with one higher-order factor produced the best fit. Convergent validity was evident through the SIP-R's correlation with several composite scores from the ASI and the URICA, and analyses supported its conceptual distinction from quantity indices of drug/alcohol use. The SIP-R also demonstrated an ability to predict treatment retention, with higher scores associated with poorer retention. These results provide support for the SIP-R's psychometric properties as a measure of consequences across a broad sample of treatment-seeking drug and alcohol users. (PsycINFO Database Record (c) 2012

APA, all rights reserved). Kiluk BD, Dreifuss JA, Weiss RD, Morgenstern J, Carroll KM. The Short Inventory of Problems - Revised (SIP-R): Psychometric properties within a large, diverse sample of substance use disorder treatment seekers. *Psychol Addict Behav.* 2012 May 28. [Epub ahead of print].

Predictors Of Attrition With Buprenorphine/Naloxone Treatment In Opioid Dependent

Youth In opioid dependent youth there is substantial attrition from medication-assisted treatment. If youth at risk for attrition can be identified at treatment entry or early in treatment, they can be targeted for interventions to help retain them in treatment. Opioid dependent adolescents and young adults (n=152), aged 15-21, were randomized to 12weeks (BUP, n=74) or 2weeks of detoxification (DETOX, n=78) with buprenorphine/naloxone (Bup/Nal), both in combination with 12weeks of psychosocial treatment. Baseline and early treatment related predictors of treatment attrition were identified in each group using bivariate and multivariate logistic regression. In the DETOX group 36% left between weeks 2 and 4, at the end of the dose taper, while in the BUP group only 8% left by week 4. In the BUP group, early adherence to Bup/Nal, early opioid negative urines, use of any medications in the month prior to treatment entry, and lifetime non-heroin opioid use were associated with retention while prior 30-day hallucinogen use was associated with attrition. In the DETOX group, only use of sleep medications was associated with retention although not an independent predictor. A broad range of other pre-treatment characteristics was unrelated to attrition. Prompt attention to those with early non-adherence to medication or an early opioid positive urine, markers available in the first 2weeks of treatment, may improve treatment retention. Extended Bup/Nal treatment appeared effective in improving treatment retention for youth with opioid dependence across a wide range of demographics, and pre-treatment clinical characteristics. Warden D, Subramaniam GA, Carmody T, Woody GE, Minhajuddin A, Poole SA, Potter J, Fishman M, Bogenschutz M, Patkar A, Trivedi MH. Predictors of attrition with buprenorphine/naloxone treatment in opioid dependent youth. *Addict Behav.* 2012 Sep; 37(9): 1046-1053. Epub 2012 May 8.

Predictors Of Relationship Power Among Drug-Involved Women Gender-based relationship power is frequently linked to women's capacity to reduce sexual risk behaviors. This study offers an exploration of predictors of relationship power, as measured by the multidimensional and theoretically grounded sexual relationship power scale, among women in outpatient substance abuse treatment. Linear models were used to test nine predictors (age, race/ethnicity, education, time in treatment, economic dependence, substance use, sexual concurrency, partner abuse, and sex role orientation) of relationship power among 513 women participating in a multi-site HIV risk reduction intervention study. Significant predictors of relationship control included having a non-abusive male partner, only one male partner, and endorsing traditional masculine (or both masculine and feminine) sex role attributes. Predictors of decision-making dominance were interrelated, with substance use \times partner abuse and age \times sex role orientation interactions. Results contribute to the understanding of factors which may influence relationship power and to their potential role in HIV sexual risk reduction interventions. Campbell AN, Tross S, Hu MC, Pavlicova M, Nunes EV. Predictors of relationship power among drug-involved women. *AIDS Behav.* 2012 May 22. [Epub ahead of print].

Evaluation Of Buspirone For Relapse-Prevention In Adults With Cocaine Dependence: An Efficacy Trial Conducted In The Real World Cocaine dependence is a significant public health problem for which there are currently no FDA-approved medications. Hence, identifying candidate compounds and employing an efficient evaluation process is crucial. This paper describes key

design decisions made for a National Institute on Drug Abuse (NIDA) Clinical Trials Network (CTN) study that uses a novel two-stage process to evaluate bupirone (60mg/day) for cocaine-relapse prevention. The study includes pilot (N=60) and full-scale (estimated N=264) trials. Both trials will be randomized, double-blind, and placebo-controlled and both will enroll treatment-seeking cocaine-dependent participants engaged in inpatient/residential treatment and scheduled for outpatient treatment post-discharge. All participants will receive contingency management in which incentives are given for medication adherence as evaluated by the Medication Events Monitoring System (MEMS). The primary outcome measure is maximum days of continuous cocaine abstinence, as assessed by twice-weekly urine drug screens (UDS) and self-report, during the 15-week outpatient treatment phase. Drug-abuse outcomes include cocaine use as assessed by UDS and self-report of cocaine use, other substance use as assessed by UDS and self-report of substance use (i.e., alcohol and/or illicit drugs), cocaine bingeing, HIV risk behavior, quality of life, functioning, and substance abuse treatment attendance. Unique aspects of the study include conducting an efficacy trial in community treatment programs, a two-stage process to efficiently evaluate bupirone, and an evaluation of mediators by which bupirone might exert a beneficial effect on relapse prevention. Winhusen T, Brady KT, Stitzer M, Woody G, Lindblad R, Kropp F, Brigham G, Liu D, Sparenborg S, Sharma G, Vanveldehuisen P, Adinoff B, Somoza E. Evaluation of bupirone for relapse-prevention in adults with cocaine dependence: An efficacy trial conducted in the real world. *Contemp Clin Trials*. 2012 May 19. [Epub ahead of print].

Web-Based, Psychosocial Treatment For Substance Use Disorders In Community Treatment Settings The purpose of this multisite clinical trial was to evaluate the effectiveness of a web-based version of the Community Reinforcement Approach, plus motivational incentives, within community-based, outpatient substance abuse treatment. This ongoing study is being conducted within the National Drug Abuse Treatment Clinical Trials Network, funded by the National Institute on Drug Abuse. Midway through the enrollment of 500 participants, the study is being implemented in 10 treatment programs across the United States. Information is provided on design, sample, intervention and technology, and preliminary lessons learned. Campbell AN, Miele GM, Nunes EV, McCrimmon S, Ghitza UE. Web-based, psychosocial treatment for substance use disorders in community treatment settings. *Psychol Serv*. 2012 May; 9(2): 212-214.

Pre-Treatment Change In A Randomized Trial With Pregnant Substance-Abusing Women In Community-Based Outpatient Treatment Participants in clinical trials of interventions for substance use frequently show substantial pre-treatment reductions in use. However, pre-treatment change has not been studied among pregnant women, a group with unique motivational characteristics. It is also not clear whether pre-treatment reduction in substance use can be clearly linked to research activities such as pre-treatment assessment, or if it is the result of more general factors such as the decision to seek treatment. Using an interrupted longitudinal design, the authors evaluated pre-treatment change among 148 pregnant women, all of whom had completed a clinical trial comparing motivational enhancement therapy to treatment as usual. When baseline period was compared to the period after randomization and before treatment, the change in substance use was substantial (dropping from an average of substance use on 30.5% of days during baseline to 16.7% of days during the pre-treatment phase; $p < .001$), and was greater in magnitude than change following initiation of study-related treatment. Further, this reduction was significant after controlling for a longitudinal time effect and did not apply to tobacco use. These findings suggest that change following pre-treatment research activities is independent of the decision to seek treatment and is present even among pregnant women, many of whom have already reduced their substance use. These findings also suggest the possible need for re-evaluation of the nature and

causes of behavior change, as well as trial design, in clinical trials for substance abuse. Ondersma SJ, Winhusen T, Lewis DF. Pre-treatment change in a randomized trial with pregnant substance-abusing women in community-based outpatient treatment. *Contemp Clin Trials*. 2012 Jun 16. [Epub ahead of print].

INTRAMURAL RESEARCH

Molecular Targets and Medications Discovery Research Branch

Medicinal Chemistry Section

R-Modafinil (Armodafinil): A Unique Dopamine Uptake Inhibitor and Potential Medication For Psychostimulant Abuse

(±)-Modafinil has piqued interest as a treatment for ADHD and stimulant dependence. (±)-, R- and S-Modafinil bind to the DAT and inhibit dopamine uptake less potently than cocaine, with R-modafinil having ~3-fold higher affinity than its S-enantiomer. Molecular docking studies revealed subtle differences in binding modes for the enantiomers. R-modafinil was significantly less potent in the DAT Y156F mutant compared to wild-type DAT, whereas S-modafinil was affected less. Studies with the Y335A DAT mutant showed that the R- and S-enantiomers tolerated the inward facing conformation better than cocaine, which was further supported by MTSET reactivity on the DAT E2C I159C. Microdialysis studies demonstrated that both R- and S-modafinil produced increases in extracellular DA concentrations in the NAc shell less efficaciously than cocaine, and with a longer duration of action. Both enantiomers fully substituted in mice trained to discriminate cocaine from saline. R-modafinil displays an in vitro profile different from cocaine. Future trials with R-modafinil as a substitute therapy with the potential benefit of cognitive enhancement for psychostimulant addiction are warranted. Loland CJ, Mereu M, Okunola OM, Cao J, Prisinzano TE, Mazier S, Kopajtic T, Shi L, Katz JL, Tanda G, Newman AH. R-Modafinil (armodafinil): A unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. *Biol. Psychiatry* 2012, e-pub April 24, 2012.

Metabotropic Glutamate Receptor 5 Negative Allosteric Modulators As Novel Tools For In Vivo Investigation

Negative allosteric modulators (NAMs) of metabotropic glutamate receptor subtype 5 (mGluR5) have shown promising results in preclinical models for anxiety and drug abuse. Here IRP scientists describe a series of aryl-substituted alkynyl analogues of the prototypic mGluR5 NAM 2-methyl-6-(phenylethynyl)pyridine (MPEP, 1). Displacement of [³H]1 binding in rat brain membranes showed that several of these novel compounds displayed high affinity binding ($K_i < 10$ nM) for mGluR5, with up to a 24-fold increase in affinity over 1. Replacements of the 2-position Me on the pyridyl ring of 1 along with various 3'-CN, 5'-substitutions were generally well tolerated. All of the active analogues in this series had cLogP values in the 2-5 range and displayed inverse agonist characteristics in an ELISA-based assay of G_qα-mediated IP₃ production. Compounds 7i and 7j produced in vivo effects in mouse models of anxiety-like behaviors more potently than 1 or 3-((2-methyl-1,3-thiazol-4-yl)ethynyl)pyridine (MTEP, 2), supporting their utility as in vivo tools. Keck TM, Zou M-F, Zhang P., Rutledge RP, Newman AH. Metabotropic glutamate receptor 5 negative allosteric modulators as novel tools for in vivo investigation. *ACS Med Chem Lett* 2012, e-pub May 23, 2012.

Molecular Determinants of Selectivity and Efficacy at the Dopamine D3 Receptor The dopamine D3 receptor (D3R) has been implicated in substance abuse and other neuropsychiatric disorders. The high sequence homology between the D3R and D2R, especially within the orthosteric binding site (OBS) that binds dopamine, has made the development of D3R-selective compounds challenging. Here, IRP investigators deconstruct into pharmacophoric elements a series of D3R-selective substituted-4-phenylpiperazine compounds, and use computational simulations and binding and activation studies to dissect the structural bases for D3R selectivity and efficacy. They find that selectivity arises from divergent interactions within a second binding pocket (SBP)

separate from the OBS, whereas efficacy depends on the binding mode in the OBS. These findings reveal structural features of the receptor that are critical to selectivity and efficacy that can be used to design highly D3R-selective ligands with targeted efficacies. These findings are generalizable to other GPCRs in which the SBP can be targeted by bitopic or allosteric ligands. Newman AH, Beuming T, Banala AK, Donthamsetti P, Pongetti K, LaBounty A, Levy B, Cao J, Michino M, Luedtke RR, Javitch JA, Shi L. Molecular determinants of selectivity and efficacy at the dopamine D3 receptor. *J Med Chem* 2012, e-pub May 25, 2012.

Cellular Neurobiology Research Branch

Behavioral Neurophysiology Science Section

Willingness To Wait and Altered Encoding of Time-Discounted Reward in the Orbitofrontal Cortex With Normal Aging Normal aging has been associated with cognitive changes, including shifts in responding for time-discounted rewards. The orbitofrontal cortex, an area previously associated with aging-related cognitive changes, is critical for normal discounting. Previously IRP scientists have shown in a choice task that rats prefer immediate over delayed reward and that neural representations of delayed reward in orbitofrontal cortex were attenuated, whereas immediate reward elicited strong responses. Changes in choice performance were correlated with changes in firing rate in orbitofrontal neurons, suggesting that these reward representations were critical to the rats' ability to wait for reward. Here the authors asked whether age-dependent changes in discounting behavior were related to changes in the representation of delayed reward in the orbitofrontal cortex. Young (3-6 months) and aged (22-26 months) rats were trained on the same discounting paradigm used previously. They found that aged rats showed less sensitivity to increasing delay preceding reward delivery, shifting behavior away from the delayed reward more slowly than younger rats. This sensitivity was specific to delay, since choice performance did not differ between the two groups when delay was held constant and reward size varied. Aged rats exhibited a corresponding increase in the prevalence of neurons that fired more strongly for delayed reward. Again this change was specific to delay; there was no change in encoding of different-sized rewards. These results suggest that natural aging results in altered representations of reward in orbitofrontal cortex. These changes may relate to the increased ability to delay gratification and reduced impulsivity associated with aging. Roesch MR, Bryden DW, Cerri DH, Haney ZR, Schoenbaum G. Willingness to wait and altered encoding of time-discounted reward in the orbitofrontal cortex with normal aging. *J Neurosci.* 2012 Apr 18; 32(16): 5525-5533.

Surprise! Neural Correlates Of Pearce-Hall and Rescorla-Wagner Coexist Within The Brain

Learning theory and computational accounts suggest that learning depends on errors in outcome prediction as well as changes in processing of or attention to events. These divergent ideas are captured by models, such as Rescorla-Wagner (RW) and temporal difference (TD) learning on the one hand, which emphasize errors as directly driving changes in associative strength, vs. models such as Pearce-Hall (PH) and more recent variants on the other hand, which propose that errors promote changes in associative strength by modulating attention and processing of events. Numerous studies have shown that phasic firing of midbrain dopamine (DA) neurons carries a signed error signal consistent with RW or TD learning theories, and recently we have shown that this signal can be dissociated from attentional correlates in the basolateral amygdala and anterior cingulate. Here the authors review these data along with new evidence: (i) implicating habenula and

striatal regions in supporting error signaling in midbrain DA neurons; and (ii) suggesting that the central nucleus of the amygdala and prefrontal regions process the amygdalar attentional signal. However, while the neural instantiations of the RW and PH signals are dissociable and complementary, they may be linked. Any linkage would have implications for understanding why one signal dominates learning in some situations and not others, and also for appreciating the potential impact on learning of neuropathological conditions involving altered DA or amygdalar function, such as schizophrenia, addiction or anxiety disorders. Roesch MR, Esber GR, Li J, Daw ND, Schoenbaum G. Surprise! Neural correlates of Pearce-Hall and Rescorla-Wagner coexist within the brain. *Eur J Neurosci.* 2012; Apr; 35(7): 1190-1200.

Electrophysiology Research Section

Blockade Of B-Cell K(ATP) Channels By The Endocannabinoid, 2-Arachidonoylglycerol

The endocannabinoid system has been demonstrated to be active in the pancreatic β -cell. However the effects of the endocannabinoids (ECs) on insulin secretion are not well defined and may vary depending on the metabolic state of the β -cell. Specifically it is not known whether the effects of the ECs occur by activation of the cannabinoid receptors or via their direct interaction with the ion channels of the β -cell. To begin to delineate the effects of ECs on β -cell function, IRP researchers examined how the EC, 2-AG influences β -cell ion channels in the absence of glucose stimulation. The mouse insulinoma cell line R7T1 was used to survey the effects of 2-AG on the high voltage activated (HVA) calcium, the delayed rectifier (K(v)), and the ATP-sensitive K (K(ATP)) channels by whole cell patch clamp recording. At 2mM glucose, 2-AG inhibited the HVA calcium (the majority of which are L-type channels), K(v), and K(ATP) channels. The channel exhibiting the most sensitivity to 2-AG blockade was the K(ATP) channel, where the IC(50) for 2-AG was 1 μ M. Pharmacological agents revealed that the blockade of all these channels was independent of cannabinoid receptors. These results provide a mechanism for the previous observations that CB1R agonists increase insulin secretion at low glucose concentrations through CB1R independent blockade of the K(ATP) channel. Spivak CE, Kim W, Liu QR, Lupica CR, Doyle ME. Blockade of β -cell K(ATP) channels by the endocannabinoid, 2-arachidonoylglycerol. *Biochem Biophys Res Commun.* 2012 Jun 22; 423(1): 13-18.

Molecular Neuropsychiatry Research Branch

Role Of Oxidative Stress In Methamphetamine-Induced Dopaminergic Toxicity Mediated By Protein Kinase C δ

This study examined the role of protein kinase C (PKC) isozymes in methamphetamine (MA)-induced dopaminergic toxicity. Multiple-dose administration of MA did not significantly alter PKC α , PKC β I, PKC β II, or PKC ζ expression in the striatum, but did significantly increase PKC δ expression. Gö6976 (a co-inhibitor of PKC α and β), hispidin (PKC β inhibitor), and PKC ζ pseudosubstrate inhibitor (PKC ζ inhibitor) did not significantly alter MA-induced behavioral impairments. However, rottlerin (PKC δ inhibitor) significantly attenuated behavioral impairments in a dose-dependent manner. In addition, MA-induced behavioral impairments were not apparent in PKC δ knockout (-/-) mice. MA-induced oxidative stress (i.e., lipid peroxidation and protein oxidation) was significantly attenuated in rottlerin-treated mice and was not apparent in PKC δ (-/-) mice. Consistent with this, MA-induced apoptosis (i.e., terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling-positive apoptotic cells) was significantly attenuated in rottlerin-treated mice. Furthermore, MA-induced increases in the

dopamine (DA) turnover rate and decreases in tyrosine hydroxylase (TH) activity and the expression of TH, dopamine transporter (DAT), and vesicular monoamine transporter 2 (VMAT2) were not significantly observed in roflumetinol-treated or PKC δ (-/-) mice. These results suggest that PKC δ gene expression is a key mediator of oxidative stress and dopaminergic damage induced by MA. Thus, inhibition of PKC δ may be a useful target for protection against MA-induced neurotoxicity. Shin EJ, Duong CX, Nguyen XK, Li Z, Bing G, Bach JH, Park DH, Nakayama K, Ali SF, Kanthasamy AG, Cadet JL, Nabeshima T, Kim HC. Role of oxidative stress in methamphetamine-induced dopaminergic toxicity mediated by protein kinase C δ . *Behav Brain Res.* 232(1): 98-113. Epub 2012.

Methamphetamine Causes Differential Alterations In Gene Expression and Patterns of Histone Acetylation/Hypoacetylation In the Rat Nucleus Accumbens

Methamphetamine (METH) addiction is associated with several neuropsychiatric symptoms. Little is known about the effects of METH on gene expression and epigenetic modifications in the rat nucleus accumbens (NAC). This study investigated the effects of a non-toxic METH injection (20 mg/kg) on gene expression, histone acetylation, and the expression of the histone acetyltransferase (HAT), ATF2, and of the histone deacetylases (HDACs), HDAC1 and HDAC2, in that structure. Microarray analyses done at 1, 8, 16 and 24 hrs after the METH injection identified METH-induced changes in the expression of genes previously implicated in the acute and longterm effects of psychostimulants, including immediate early genes and corticotropin-releasing factor (Crf). In contrast, the METH injection caused time-dependent decreases in the expression of other genes including Npas4 and cholecystokinin (Cck). Pathway analyses showed that genes with altered expression participated in behavioral performance, cell-to-cell signaling, and regulation of gene expression. PCR analyses confirmed the changes in the expression of c-fos, fosB, Crf, Cck, and Npas4 transcripts. To determine if the METH injection caused post-translational changes in histone markers, the authors used western blot analyses and identified METH-mediated decreases in histone H3 acetylated at lysine 9 (H3K9ac) and lysine 18 (H3K18ac) in nuclear sub-fractions. In contrast, the METH injection caused time-dependent increases in acetylated H4K5 and H4K8. The changes in histone acetylation were accompanied by decreased expression of HDAC1 but increased expression of HDAC2 protein levels. The histone acetyltransferase, ATF2, showed significant METH-induced increased in protein expression. These results suggest that METH-induced alterations in global gene expression seen in rat NAC might be related, in part, to METH-induced changes in histone acetylation secondary to changes in HAT and HDAC expression. The causal role that HATs and HDACs might play in METH-induced gene expression needs to be investigated further. Martin TA, Jayanthi S, McCoy MT, Brannock C, Ladenheim B, Garrett T, Lehrmann E, Becker KG, Cadet JL. Methamphetamine causes differential alterations in gene expression and patterns of histone acetylation/hypoacetylation in the rat nucleus accumbens. *PLoS One.* 7(3):e34236. Epub 2012.

Chemical Biology Research Branch

Drug Design and Synthesis Section

Antagonism Of Sigma-1 Receptors Blocks Compulsive-Like Eating Binge eating disorder is an addiction-like disorder characterized by episodes of rapid and excessive food consumption within discrete periods of time which occur compulsively despite negative consequences. This study was aimed at determining whether antagonism of Sigma-1 receptors (Sig-1Rs) blocked compulsive-like

binge eating. The authors trained male Wistar rats to obtain a sugary, highly palatable diet (Palatable group) or a regular chow diet (Chow control group), for 1h a day under fixed ratio 1 operant conditioning. Following intake stabilization, they evaluated the effects of the selective Sig-1R antagonist BD-1063 on food responding. Using a light/dark conflict test, they also tested whether BD-1063 could block the time spent and the food eaten in an aversive, open compartment, where the palatable diet was offered. Furthermore, they measured Sig-1R mRNA and protein expression in several brain areas of the two groups, 24h after the last binge session. Palatable rats rapidly developed binge-like eating, escalating the 1h intake by four times, and doubling the eating rate and the regularity of food responding, compared to Chow rats. BD-1063 dose-dependently reduced binge-like eating and the regularity of food responding, and blocked the increased eating rate in Palatable rats. In the light/dark conflict test, BD-1063 antagonized the increased time spent in the aversive compartment and the increased intake of the palatable diet, without affecting motor activity. Finally, Palatable rats showed reduced Sig-1R mRNA expression in prefrontal and anterior cingulate cortices, and a two-fold increase in Sig-1R protein expression in anterior cingulate cortex compared to control Chow rats. These findings suggest that the Sig-1R system may contribute to the neurobiological adaptations driving compulsive-like eating, opening new avenues of investigation towards pharmacologically treating binge eating disorder. Cottone P, Wang X, Park JW, Valenza M, Blasio A, Kwak J, Iyer MR, Steardo L, Rice KC, Hayashi T, Sabino V. Antagonism of sigma-1 receptors blocks compulsive-like eating. *Neuropsychopharmacology* 2012 Jun 20. doi: 10.1038/npp.2012.89.

Interaction Between Mu and Delta Opioid Receptor Agonists In An Assay Of Capsaicin-Induced Thermal Allodynia In Rhesus Monkeys

Delta opioid agonists enhance antinociceptive effects of mu-opioid agonists in many preclinical assays of acute nociception, but delta/mu interactions in preclinical models of inflammation-associated pain have not been examined. This study examined interactions between the delta agonist SNC80 [(+)-4-[(α R)- α -((2S,5R)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-N,N-diethylbenzamide] and the mu agonist analgesics methadone, morphine, and nalbuphine in an assay of capsaicin-induced thermal allodynia in rhesus monkeys. Thermal allodynia was produced by topical application of capsaicin to the tail. Antiallodynic effects of methadone, morphine, and nalbuphine were evaluated alone or in combination with fixed proportions of SNC80 identical to proportions previously shown to enhance acute thermal antinociceptive effects of these mu agonists in rhesus monkeys (0.9:SNC80/methadone; 0.29:1 SNC80/morphine; 3.6:1SNC80/nalbuphine). Methadone, morphine, and nalbuphine each produced dose-dependent antiallodynia. SNC80 produced partial antiallodynia up to the highest dose tested (5.6mg/kg). SNC80 produced a modest, enantioselective, and naltrindole-reversible enhancement of methadone-induced antiallodynia. However, SNC80 did not enhance morphine antiallodynia and only weakly enhanced nalbuphine antiallodynia. Overall, SNC80 produced modest or no enhancement of the antiallodynic effects of the three mu agonists evaluated. These results suggest that delta agonist-induced enhancement of mu agonist antiallodynia may be weaker and less reliable than previously demonstrated enhancement of mu agonist acute thermal nociception. Interaction between mu and delta opioid receptor agonists in an assay of capsaicin-induced thermal allodynia in rhesus monkeys. Negus SS, Morrissey EM, Folk JE, Rice KC. *Pain Res Treat.* 2012; 867067. Epub 2012 May 14.

Dopamine Mediates Cocaine-Induced Conditioned Taste Aversions As Demonstrated With Cross-Drug Preexposure To GBR 12909

Although cocaine readily induces taste aversions, little is known about the mechanisms underlying this effect. It has been suggested that its inhibitory effects at one of the monoamine transporters may be mediating this suppression. Using the cross-

drug preexposure preparation, the present series of studies examined a possible role of dopamine (DA) in this effect. Male Sprague-Dawley rats were exposed to cocaine (18mg/kg; Experiment 1) or the selective DA transporter (DAT) inhibitor GBR 12909 (50mg/kg; Experiment 2) prior to the pairing of a novel saccharin solution with injections of GBR 12909 (32mg/kg), cocaine (18mg/kg) or vehicle in a conditioned taste aversion (CTA) procedure. Preexposure to cocaine attenuated aversions induced by itself but not aversions induced by GBR 12909 (Experiment 1). Conversely, preexposure to GBR 12909 attenuated aversions induced by itself and cocaine (Experiment 2). This asymmetry suggests that cocaine and GBR 12909 induce CTAs via similar, but non-identical, mechanisms. These data are discussed in the context of previous work demonstrating roles for dopamine, norepinephrine and serotonin in cocaine-induced CTAs. Serafine KM, Briscione MA, Rice KC, Riley AL. Dopamine mediates cocaine-induced conditioned taste aversions as demonstrated with cross-drug preexposure to GBR 12909 *Pharmacol Biochem Behav.* 2012 Aug; 102(2): 269-274. Epub 2012 May 3.

(+)-Naloxone, An Opioid-Inactive Toll-Like Receptor 4 Signaling Inhibitor, Reverses Multiple Models Of Chronic Neuropathic Pain In Rats

Previous work demonstrated that both the opioid antagonist (-)-naloxone and the non-opioid (+)-naloxone inhibit toll-like receptor 4 (TLR4) signaling and reverse neuropathic pain expressed shortly after chronic constriction injury. The present studies reveal that the TLR4 contributes to neuropathic pain in another major model (spinal nerve ligation) and to long established (2-4 months) neuropathic pain, not just to pain shortly after nerve damage. Additionally, analyses of plasma levels of (+)-naloxone after subcutaneous administration indicate that (+)-naloxone has comparable pharmacokinetics to (-)-naloxone with a relatively short half-life. This finding accounts for the rapid onset and short duration of allodynia reversal produced by subcutaneous (+)-naloxone. Given that toll-like receptor 2 (TLR2) has also recently been implicated in neuropathic pain, cell lines transfected with either TLR4 or TLR2, necessary co-signaling molecules, and a reporter gene were used to define whether (+)-naloxone effects could be accounted for by actions at TLR2 in addition to TLR4. (+)-Naloxone inhibited signaling by TLR4 but not TLR2. These studies provide evidence for broad involvement of TLR4 in neuropathic pain, both early after nerve damage and months later. Additionally, they provide further support for the TLR4 inhibitor (+)-naloxone as a novel candidate for the treatment of neuropathic pain. These studies demonstrated that (+)-naloxone, a systemically available, blood-brain barrier permeable, small molecule TLR4 inhibitor can reverse neuropathic pain in rats, even months after nerve injury. These findings suggest that (+)-naloxone, or similar compounds, be considered as a candidate novel, first-in-class treatment for neuropathic pain. Lewis SS, Loram LC, Hutchinson MR, Li CM, Zhang Y, Maier SF, Huang Y, Rice KC, Watkins LR. (+)-naloxone, an opioid-inactive toll-like receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats. *J Pain.* 2012 May; 13(5): 498-506. Epub 2012 Apr 20.

Corticotropin-Releasing Factor Receptor-Dependent Effects Of Repeated Stress On Tau Phosphorylation, Solubility, and Aggregation

Exposure and/or sensitivity to stress have been implicated as conferring risk for development of Alzheimer's disease (AD). Although the basis for such a link remains unclear, IRP scientists previously reported differential involvement of corticotropin-releasing factor receptor (CRFR) 1 and 2 in acute stress-induced tau phosphorylation (tau-P) and solubility in the hippocampus. Here they examined the role of CRFRs in tau-P induced by repeated stress and the structural manifestations of altered tau solubility. Robust tau-P responses were seen in WT and CRFR2 null mice exposed to repeated stress, which were sustained at even 24 h after the final stress exposure. A portion of phosphorylated tau in these mice was sequestered in detergent-soluble cellular fractions. In contrast, CRFR1 and CRFR double-KO mice did not exhibit

repeated stress-induced alterations in tau-P or solubility. Similarly, treatment with CRFR1 antagonist attenuated repeated stress-induced tau-P. Using histochemical approaches in a transgenic CRFR1 reporter mouse line, the authors found substantial overlap between hippocampal CRFR1 expression and cells positive for phosphorylated tau after exposure to repeated stress. Ultrastructural analysis of negatively stained extracts from WT and CRFR2 null mice identified globular aggregates that displayed positive immunogold labeling for tau-P, as well as conformational changes in tau (MC1) seen in early AD. Given that repeated stress exposure results in chronic increases in hippocampal tau-P and its sequestration in an insoluble (and potentially prepathogenic) form, these data may define a link between stress and an AD-related pathogenic mechanism. Rissman RA, Staup MA, Lee AR, Justice NJ, Rice KC, Vale W, Sawchenko PE. Corticotropin-releasing factor receptor-dependent effects of repeated stress on tau phosphorylation, solubility, and aggregation. *Proc Natl Acad Sci U S A*. 2012 Apr 17; 109(16): 6277-6282. Epub 2012 Mar 26.

Neurobiological Changes Mediating the Effects Of Chronic Fluoxetine On Cocaine Use Acute SSRI (selective serotonin reuptake inhibitor) treatment has been shown to attenuate the abuse-related effects of cocaine; however, SSRIs have had limited success in clinical trials for cocaine abuse, possibly due to neurobiological changes that occur during chronic administration. In order to better understand the role of serotonin (5HT) in cocaine abuse and treatment, IRP researchers examined the effects of chronic treatment with the SSRI fluoxetine at clinically relevant serum concentrations on cocaine-related neurobiology and behavior. Rhesus macaques self-administering cocaine underwent a 6-week dosing regimen with fluoxetine designed to approximate serum concentrations observed in humans. Self-administration and reinstatement were monitored throughout the treatment and washout period. In vivo microdialysis was used to assess changes in dopaminergic and serotonergic neurochemistry. Positron emission tomography was used to assess changes in the 5HT transporter and 2A receptor binding potential (BP). Functional output of the 5HT system was assessed using prolactin levels. Cocaine-primed reinstatement and cocaine-elicited dopamine overflow were significantly suppressed following chronic fluoxetine treatment. 5HT_{2A} receptor BP was increased in the frontal cortex following treatment while prolactin release was blunted, suggesting desensitization of the 5HT_{2A} receptor. These effects persisted after a 6-week washout period. Measures of pre-synaptic serotonergic function and cocaine self-administration were unaffected. These data demonstrate that acute and chronic fluoxetine treatments exert different effects on cocaine-related behavior. Furthermore, chronic fluoxetine treatment causes alterations in 5HT_{2A} receptors in the frontal cortex that may selectively disrupt cocaine-primed reinstatement. Fluoxetine may not be useful for treatment of ongoing cocaine abuse but may be useful in relapse prevention. Sawyer EK, Mun J, Nye JA, Kimmel HL, Voll RJ, Stehouwer JS, Rice KC, Goodman MM, Howell LL. Neurobiological changes mediating the effects of chronic fluoxetine on cocaine use. *Neuropsychopharmacology*. 2012 Jul; 37(8): 1816-1824. doi: 10.1038/npp.2012.29. Epub 2012 Mar 21.

Effects Of the Delta Opioid Receptor Agonist SNC80 On Pain-Related Depression Of Intracranial Self-Stimulation (ICSS) In Rats The delta opioid receptor agonist SNC80 produces both antinociceptive and antidepressant effects in rodents. This profile suggests that SNC80 may also reverse prodepressant effects of pain. Accordingly, this study compared SNC80 effects in complementary assays of pain-stimulated and pain-depressed behavior in rats. Intraperitoneal injection of dilute acid served as an acute noxious visceral stimulus in rats to stimulate abdominal stretching (a pain-stimulated behavior) or depress intracranial self-stimulation of the medial forebrain bundle (ICSS; a pain-depressed behavior). When administered once per week to minimize acute tolerance, SNC80 (1-10 mg/kg IP) decreased acid-stimulated stretching but had little effect on

acid-induced depression of ICSS. More frequent SNC80 administration produced tolerance to SNC80 effects on acid-stimulated stretching, but unmasked antinociception in the assay of acid-depressed ICSS. SNC80 did not facilitate ICSS in the absence of pain, and effects of SNC80 were not duplicated by ARM390, a reputed delta agonist congener of SNC80 that does not internalize delta receptors. These findings support continued consideration of delta agonists as candidate analgesics to treat prodepressant effects of pain and illustrate the potential for diametrically opposite effects of drug treatments on preclinical measures of pain-stimulated and pain-depressed behavior. The delta opioid agonist SNC80 blocked pain-related depression of intracranial self-stimulation in rats, suggesting that delta agonists may be useful to treat prodepressant effects of pain. Repeated SNC80 produced tolerance to SNC80 antinociception in a conventional assay of pain-stimulated behavior but unmasked SNC80 antinociception in an assay of pain-depressed behavior. Negus SS, Rosenberg MB, Altarifi AA, O'Connell RH, Folk JE, Rice KC. Effects of the delta opioid receptor agonist SNC80 on pain-related depression of intracranial self-stimulation (ICSS) in rats. *J Pain*. 2012 Apr; 13(4): 317-327. Epub 2012 Mar 15.

Behavioral Neuroscience Branch

Behavioral Neuroscience Section

Role Of Projections From Ventral Medial Prefrontal Cortex To Nucleus Accumbens Shell In Context-Induced Reinstatement Of Heroin Seeking In humans, exposure to contexts previously associated with heroin use can provoke relapse. In rats, exposure to heroin-paired contexts after extinction of drug-reinforced responding in different contexts reinstates heroin seeking. This effect is attenuated by inhibition of glutamate or dopamine transmission in nucleus accumbens shell, or inactivation of ventral medial prefrontal cortex (vmPFC). Here, IRP scientists used an anatomical asymmetrical disconnection procedure to demonstrate that an interaction between glutamatergic projections from vmPFC to accumbens shell and local dopamine D₁ postsynaptic receptors contributes to context-induced reinstatement of heroin seeking. They also combined the marker of neuronal activity, Fos, with the retrograde tracer Fluoro-Gold (FG) to assess activation in this pathway during context-induced reinstatement. Rats were trained to self-administer heroin for 12 days; drug infusions were paired with a discrete tone-light cue. Lever-pressing was subsequently extinguished in a non-drug-associated context in the presence of the discrete cue. Rats were then tested in the heroin- or extinction-associated contexts under extinction conditions. Injections of muscimol+baclofen into vmPFC in one hemisphere and D₁-family receptor antagonist SCH 23390 into the contralateral or ipsilateral accumbens shell decreased context-induced reinstatement. Unilateral injections of muscimol+baclofen into vmPFC or SCH 23390 into the accumbens shell had no effect. Context-induced reinstatement was associated with increased Fos expression in vmPFC neurons, including those projecting to accumbens shell, with higher double-labeling in the ipsilateral projection than in the contralateral projection. The results demonstrate that activation of glutamatergic projections from ventral mPFC to accumbens shell, previously implicated in inhibition of cocaine relapse, promotes heroin relapse. Bossert JM, Stern AL, Theberge FR, Marchant MJ, Wang HL, Morales M, Shaham Y. Role of projections from ventral medial prefrontal cortex to nucleus accumbens shell in context-induced reinstatement of heroin seeking. *Journal of Neuroscience*. 2011; 32: 4982-4991.

Medial Prefrontal Cortex Neuronal Activation and Synaptic Alterations After Stress-Induced Reinstatement Of Palatable Food Seeking: A Study Using C-Fos-GFP Transgenic Female

Rats Relapse to maladaptive eating habits during dieting is often provoked by stress and there is evidence for a role of ovarian hormones in stress responses and feeding. IRP scientists studied the role of these hormones in stress-induced reinstatement of food seeking and medial prefrontal cortex (mPFC) neuronal activation in *c-fos*-GFP transgenic female rats, which express green fluorescent protein (GFP) in strongly activated neurons. Food-restricted ovariectomized or sham-operated *c-fos*-GFP rats were trained to lever-press for palatable food pellets. Subsequently, lever-pressing was extinguished and reinstatement of food seeking and mPFC neuronal activation was assessed after injections of the pharmacological stressor yohimbine (0.5-2 mg/kg) or pellet priming (1-4 non-contingent pellets). Estrous cycle effects on reinstatement were also assessed in wild-type rats. Yohimbine- and pellet-priming-induced reinstatement was associated with Fos and GFP induction in mPFC; both reinstatement and neuronal activation were minimally affected by ovarian hormones in both *c-fos*-GFP and wild-type rats. *c-fos*-GFP transgenic rats were then used to assess glutamatergic synaptic alterations within activated GFP-positive and non-activated GFP-negative mPFC neurons following yohimbine-induced reinstatement of food seeking. This reinstatement was associated with reduced AMPAR/NMDAR current ratios and increased paired-pulse facilitation in activated GFP-positive but not GFP-negative neurons. Together, while ovarian hormones do not appear to play a role in stress-induced relapse of food seeking in our rat model, this reinstatement was associated with unique synaptic alterations in strongly activated mPFC neurons. This paper introduces the *c-fos*-GFP transgenic rat as a new tool to study unique synaptic changes in activated neurons during behavior. Cifani C, Koya E, Navarre BM, Calu DJ, Baumann MH, Marchant NJ, Liu Q-R, Khuc T, Pickel J, Lupica CR, Shaham Y, Hope BT. Medial prefrontal cortex neuronal activation and synaptic alterations after stress-induced reinstatement of palatable food seeking: a study using *c-fos*-GFP transgenic female rats. *Journal of Neuroscience* 2012; 32(25): 8480-8490.

Preclinical Pharmacology Section

Effects Of Environmental Enrichment On the Incubation Of Cocaine Craving Recent studies have demonstrated that exposure to environmental enrichment (EE) during withdrawal periods reduces the risks of relapse to drug-seeking behavior. In this study, the authors investigated whether EE could prevent the development of time-dependent increases in cocaine-seeking behavior (incubation of craving). In addition, they investigated whether EE could eliminate already developed incubation and whether the effects of EE would last when enrichment is discontinued. For this, they allowed rats to self-administer cocaine for 10 daily 6 h sessions and measured cocaine-seeking 1, 30 and 60 days after the last self-administration session. In between these tests, rats were kept in forced abstinence and housed either in EE or standard environments (SE). Between day 30 and 60 of withdrawal, half of the rats in each group were maintained in their original environmental condition and the other half was switched to the other environmental condition. The authors found that exposure to EE prevents development of incubation of cocaine craving and eliminates already developed incubation. In addition, contrary to their expectations, when EE was discontinued, its positive effects on incubation of craving disappeared. These results indicate that EE can reduce cocaine seeking but only temporarily and questions the hypothesis that EE can permanently eliminate the neural consequences of exposure to drugs of abuse. Therefore, stimulating environments could have positive effects on the treatment of cocaine addiction only if they are maintained for long periods of abstinence that encompass the time-frame during which

addicts are most vulnerable to relapse. Chauvet C, Goldberg SR, Jaber M, Solinas M. Effects of environmental enrichment on the incubation of cocaine craving. *Neuropharmacology*, 2012 May. [Epub ahead of print] PMID: 22634364.

Novel Use Of A Lipid-Lowering Fibrate Medication To Prevent Nicotine Reward and

Relapse: Preclinical Findings

Experimental drugs that activate α -type peroxisome proliferator-activated receptors (PPAR α) have recently been shown to reduce the rewarding effects of nicotine in animals, but these drugs have not been approved for human use. The fibrates are a class of PPAR α -activating medications that are widely prescribed to improve lipid profiles and prevent cardiovascular disease, but these drugs have not been tested in animal models of nicotine reward. Here, the authors examine the effects of clofibrate, a representative of the fibrate class, on reward-related behavioral, electrophysiological, and neurochemical effects of nicotine in rats and squirrel monkeys. Clofibrate prevented the acquisition of nicotine-taking behavior in naive animals, substantially decreased nicotine taking in experienced animals, and counteracted the relapse-inducing effects of re-exposure to nicotine or nicotine-associated cues after a period of abstinence. In the central nervous system, clofibrate blocked nicotine's effects on neuronal firing in the ventral tegmental area and on dopamine release in the nucleus accumbens shell. All of these results suggest that fibrate medications might promote smoking cessation. The fact that fibrates are already approved for human use could expedite clinical trials and subsequent implementation of fibrates as a treatment for tobacco dependence, especially in smokers with abnormal lipid profiles. Panlilio LV, Justinova Z, Mascia P, Pistis M, Luchicchi A, Lecca S, Barnes C, Redhi GH, Adair J, Heishman SJ, Yasar S, Aliczki M, Haller J, Goldberg SR. Novel use of a lipid-lowering fibrate medication to prevent nicotine reward and relapse: preclinical findings. *Neuropsychopharmacology*, 2012 Jul; 37(8): 1838-1847.

PROGRAM ACTIVITIES

New NIDA RFAs

On May 11, 2012, NIDA issued an RFA entitled **Identifying Health Outcomes Associated with Changes in Use of Illicit Drugs (R01)** [RFA-DA-13-007](#). The National Institute on Drug Abuse (NIDA) is soliciting grant (R01) applications to test the hypothesis that reductions in illicit drug use are associated with improved health outcomes in patients. This FOA will support both prospective and retrospective studies, which may include, but not limited to, identification and characterization of beneficial health outcomes that are associated with reduced levels of drug use. Such studies may focus on identification and or validation of strategies, methods, and tools (including biomarkers) that can assess the salutary consequences resulting from reduced use of a particular illicit drug. Open date: July 22, 2012. Application due date: August 22, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On May 15, 2012, NIDA issued an RFA entitled **Synthesis and Preclinical Evaluation of Medications to Treat Substance Use Disorders (SUDs) (R01)** [RFA-DA-13-004](#). The National Institute on Drug Abuse (NIDA) is soliciting grant (R01) applications to support the synthesis and preclinical evaluation of new molecular entities as potential treatments for Substance Use Disorders (SUDs). The goal is to identify candidate compounds and advance them towards Investigational New Drug (IND) submission. Open date: July 15, 2012. Application due date: August 15, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On June 14, 2012, NIDA issued an RFA entitled **Advancing Exceptional Research on HIV/AIDS (R01)** [RFA-DA-13-008](#). This FOA will support highly innovative R01 applications on HIV/AIDS and drug abuse and will complement the Avant-Garde program. This FOA focuses on innovative research projects that have the potential to open new areas of HIV/AIDS research and/or lead to new avenues for prevention and treatment of HIV/AIDS among drug abusers. Open date: November 17, 2012. Application due date: December 17, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On July 13, 2012, NIDA issued an RFA entitled **Translational Research on Interventions for Adolescents in the Legal System: TRIALS (U01)** [RFA-DA-13-009](#). The National Institute on Drug Abuse (NIDA) invites applications for cooperative agreement participants (multiple Research Centers and one coordinating center) to collaborate in developing and testing implementation strategies and associated measures to improve the continuum of substance abuse prevention and treatment services delivered to youth under juvenile justice supervision. Open date: October 28, 2012. Application due date: November 28, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On August 24, 2012, NIDA issued an RFA entitled **The Interplay of Substance Abuse and HIV-1 Infection on Glial Cell Function (R01)** [RFA-DA-13-010](#) (R21) [RFA-DA-13-011](#). This Funding Opportunity Announcement (FOA) issued by the National Institute on Drug Abuse (NIDA) solicits basic and pre-clinical research applications that study the combined and interactive effects of substance abuse and HIV-1 infection on glial cell biology. The goal of this FOA is to encourage research to determine the molecular and cellular consequences of substance abuse, HIV-1 infection, and their interactions on glial cells within the central nervous system (CNS). Open date: October 19,

2012. Application due date: November 19, 2012, by 5:00 PM local time of applicant organization.
AIDS application due date: Not applicable.

New NIDA Program Announcements

On June 8, 2012, NIDA issued a PAR entitled **Research Education Grants for Statistical and Computational Training in the Genetics of Addiction (R25) [PAR-12-199](#)**. The purpose of this opportunity is to encourage applications focused on research education in statistical and computational models to address genetics-based problems in addiction. Open date: August 14, 2012. Application due date: September 14, 2012, August 21, 2013, August 21, 2014, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On June 29, 2012, NIDA issued a PAR entitled **Cohort Studies of HIV/AIDS and Substance Use (U01) [PAR-12-222](#)**. This FOA will support the development and maintenance of new cohorts or the expansion of existing cohorts to address the natural and treated history of HIV infection in at-risk populations where substance use is a central factor. The intent of the FOA is to provide a strong resource platform for current and future collaborative efforts with other investigators to address emerging questions related to HIV infection, prevention, and treatment in the context of substance abuse, as well as to foster the creativity and efficiency of investigator-initiated research goals. Open date: November 11, 2012. Application due date(s): December 11, 2012, April 9, 2013, December 11, 2013, April 9, 2014, December 11, 2014, and April 9, 2015, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On July 6, 2012, NIDA issued a PA entitled **Development and Testing of Novel Interventions to Improve HIV Prevention, Care, and Program Implementation (R34) [PA-12-231](#)**. This FOA is issued by the National Institute on Drug Abuse (NIDA), National Institutes of Health for R34 applications, and provides resources to support (a) pilot or feasibility studies of new or adapted interventions to prevent HIV infection among populations where substance use may be a contributing factor; (b) pilot or feasibility studies of new or adapted interventions to improve the care of HIV infection among populations where substance use is prevalent, including interventions that integrate treatment for substance use disorders and HIV infection; or (c) pilot or feasibility studies to increase the scale, uptake, delivery, and/or quality of HIV prevention or care interventions with established evidence of efficacy. Both primary and secondary prevention will be supported. Open date: August 7, 2012. Application due date(s): Not applicable. AIDS application due date: [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On July 16, 2012, NIDA issued a PAR entitled **Development of Minimally-Invasive Bioassays to Support Outpatient Clinical Trials of Therapeutics for Substance Use Disorders (R01) [PAR-12-239](#); (R21) [PAR-12-238](#)**. The announcement has two main aims. The first aim is to encourage the development of devices / techniques that will improve estimations of a subject's consumption of an abused drug (i.e. both quantity and frequency of consumption) during an outpatient clinical trial. The second aim of this FOA is to develop new, improved markers to evaluate a subject's adherence to the study medication. Open date: September 5, 2012 (R01); September 16, 2012 (R21). Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date: [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On July 26, 2012, NIDA issued a PAR entitled **Behavioral Science Track Award for Rapid Transition (B/START) (R03) [PAR-12-251](#)**. This FOA will use the NIH Small Research Grant (R03) award mechanism and seeks to facilitate the entry of beginning investigators into the field of behavioral science research related to drug abuse. To be appropriate for a B/START award, research must be primarily focused on behavioral processes and research questions. Open date: September 16, 2012. Application due date(s): Not applicable. AIDS application due date: [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

New FOAs Issued by the NIH Roadmap

On June 13, 2012, the NIH Common Fund issued a Roadmap RFA entitled **Human Heredity and Health in Africa (H3Africa): Ethical, Legal, and Societal Issues (ELSI) Research Program (U01) [RFA-RM-12-005](#)**. This Funding Opportunity Announcement (FOA) encourages applications to study the ethical, legal and societal issues (ELSI) of human genome research in African populations. Of particular interest are projects that propose focused bioethical, legal, and social science analyses of new or emerging issues. Open date: September 29, 2012. Application due date(s): October 29, 2012, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On June 13, 2012, the NIH Common Fund issued a Roadmap RFA entitled **NIH Director's Transformative Research Awards (R01) [RFA-RM-12-017](#)**. The NIH Director's Transformative Research Awards complements NIH's traditional, investigator-initiated grant programs by supporting individual scientists or groups of scientists proposing groundbreaking, exceptionally innovative, original and/or unconventional research with the potential to create new scientific paradigms, establish entirely new and improved clinical approaches, or develop transformative technologies. Open date: August 21, 2012. Application due date(s): September 21, 2012, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On June 13, 2012, the NIH Common Fund issued a Roadmap RFA entitled **NIH Director's Early Independence Awards (DP5) [RFA-RM-12-018](#)**. The NIH Director's Early Independence Award Program supports exceptional investigators who wish to pursue independent research directly after completion of their terminal doctoral/research degree or clinical residency, thereby forgoing the traditional post-doctoral training period. Open date: December 30, 2012. Application due date(s): January 30, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 22, 2012, the NIH Common Fund issued a Roadmap RFA entitled **Human Heredity and Health in Africa (H3Africa): Collaborative Centers (U54) [RFA-RM-12-006](#)**. The purpose of this FOA is to call for applications for U54 Collaborative Centers that will provide funding to support multi-project research programs that address the goals of H3Africa and that involve two or more collaborations with investigators from outside the applicant institution. Application due date(s): October 29, 2012, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 22, 2012, the NIH Common Fund issued a Roadmap RFA entitled **Human Heredity and Health in Africa (H3Africa): H3Africa Research Grants (U01) [RFA-RM-12-007](#)**. The purpose of this NIH FOA is to invite applications from Institutions in African countries for

Research Projects (U01 cooperative agreements) that address one or more goals of the Human Heredity and Health in Africa (H3Africa) initiative. H3Africa is an NIH initiative in partnership with the Wellcome Trust with the goals of developing the study of genomic/genetic/environmental contributors to human health and disease within Africa using cutting-edge genomic research tools, increasing capacity for biomedical research in Africa, in terms of building the infrastructure needed for genomic research (including data and research resources), and increasing the genomic proficiency of researchers and trainees in Africa. Open date: September 28, 2012. Application due date(s): October 29, 2012, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On August 22, 2012, the NIH Common Fund issued a Roadmap RFA entitled **Human Heredity and Health in Africa (H3Africa): H3Africa Biorepository Grants. (UH2/UH3) [RFA-RM-12-008](#)**. The purpose of this FOA is to call for applications for UH2/UH3 cooperative agreements that will provide funding to develop plans for an H3Africa Biorepository, building upon existing infrastructure. Applications should include plans for initial two-year UH2 Phase I studies (Phase I) as well as plans for an additional four years of support for implementing a full-scale H3Africa Biorepository (Phase II), beginning in 2014. Open date: September 28, 2012. Application due date(s): October 29, 2012, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

New Administrative Supplement Program Announcements Issued by NIH

On June 13, 2012, NIDA, in collaboration with numerous other NIH components, issued an administrative supplement entitled **Establish Sharing of Human Brain Image Data Relevant to Drug Addiction (Admin Supp) [PAR-12-204](#)**. This program is intended to supplement NIDA funded projects to enable investigators to standardize and disseminate brain image data from patient (current or former drug abusers or subjects with risk factors) and/or healthy comparison subjects. Open date: July 9, 2012. Application due date(s): August 9, 2012, November 9, 2012, February 9, 2013, May 9, 2013, August 9, 2013, by 5:00 PM local time of applicant organization. AIDS application due date: not applicable.

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

On June 13, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **U.S. India Bilateral Collaborative Research Partnerships (CRP) on the Prevention of HIV/AIDS and Co-morbidities (R21) [RFA-AI-12-033](#)**. The U.S.-India Bilateral CRP Program is designed to develop collaborations between scientists and institutions in the U.S. and India to conduct high quality HIV/AIDS prevention research of mutual interest and benefit to both countries while developing the basis for future institutional and individual scientific collaborations. This FOA will utilize the research capacities of the institutions and scientists in both countries to advance the field of HIV/AIDS prevention and to develop preliminary data that may support a more extensive future research proposal to test an HIV/AIDS prevention program. Open date: August 4, 2012. Application due date(s): September 4, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: September 4, 2012, by 5:00 PM local time of applicant organization.

On July 5, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Advancing Community-level Approaches to Reduce HIV Infection in Highly Impacted Communities (R34) [RFA-MH-13-092](#); (R21) [RFA-MH-13-091](#); (R01) [RFA-MH-13-090](#)**. This Funding Opportunity Announcement (FOA) seeks research to advance our understanding of community-level HIV-prevention and care interventions within geographic locations and specific populations highly impacted by HIV. In targeting communities, this FOA invites applications to address the need for efficacious interventions that simultaneously impact a large number of individuals. Open date: December 11, 2012. Application due date(s): Not applicable. AIDS application due date: January 11, 2013, by 5:00 PM local time of applicant organization.

On August 23, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **TaRGET I: Chromatin Structure, Genomics, and Transcriptional Responses to the Environment (R01) [RFA-ES-12-008](#)**. The purpose of this FOA is to encourage research applications that will potentially move the field from descriptive and correlative studies to an enhanced mechanistic understanding of how environmental exposures affect the proteins and functional genomic elements involved in establishing and maintaining gene expression patterns and chromatin states. Open date: October 19, 2012. Application due date(s): November 19, 2012, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

New PAs Issued with Other NIH/HHS Components in which NIDA is a participant

On June 19, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **NIH Support for Conferences and Scientific Meetings (Parent R13/U13) [PA-12-212](#)**. The purpose of the NIH Research Conference (R13) Grant and NIH Research Conference Cooperative Agreement (U13) Programs is to support high quality conferences that are relevant to the public health and to the scientific mission of the participating Institutes and Centers. Open date: July 12, 2012. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date: [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On June 21, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Women's Mental Health During Pregnancy and the Postpartum Period (R01) [PA-12-216](#); (R21) [PA-12-215](#)**. The purpose of this Funding Opportunity Announcement (FOA) is to outline priority areas for research related to women's mental health during pregnancy and the postpartum period. Priority areas include basic and clinical neuroscience, studies of clinical course, epidemiological factors and risk factors, as well as interventions and services research. Open date: September 5, 2012. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date: [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On July 5, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Research on Children in Military Families: The Impact of Parental Military Deployment and Reintegration on Child and Family Functioning (R13) [PA-12-223](#)**. The purpose of this funding opportunity announcement (FOA) is to encourage interdisciplinary conferences and meetings to examine critical questions regarding the impact of parental military deployment, combat-related stress and reintegration with the family on child social and affective development outcomes as well as on family functioning. Open date: July 12, 2012. Application due

date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date: [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On July 24, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Ethical Issues in Research on HIV/AIDS and its Co-morbidities (R01)** [PAR-12-244](#); **(R21)** [PAR-12-243](#). This Funding Opportunity Announcement (FOA) invites applications addressing ethical issues in research relevant to populations with HIV and associated co-morbidities, and populations at high risk of HIV acquisition. Open date: November 7, 2012. Application due date(s): January 7, 2013; January 7, 2014; January 7, 2015, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

On August 24, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Successor-in-Interest (Type 6 Parent)** [PA-12-269](#). The National Institutes of Health (NIH) hereby notify grantee organizations holding specific types of NIH research grants, listed in the full Funding Opportunity Announcement (FOA), that applications for change of grantee organization status, often referred to in this announcement as Successor-In-Interest, may be submitted in response to this FOA. Open date: August 24, 2012. Application due date(s): A successor-in-interest request must be made before the anticipated start date at the new organization and preferably several months in advance. AIDS application due date: Not applicable.

On August 24, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Change of Grantee Organization (Type 7 Parent)** [PA-12-270](#). The National Institutes of Health (NIH) hereby notify grantee organizations holding specific types of NIH grants, listed in the full Funding Opportunity Announcement (FOA), that applications for change of grantee organization may be submitted in response to this FOA. Open date: August 24, 2012. Application due date(s): A change of grantee organization request must be made before the anticipated start date at the new organization and preferably several months in advance. AIDS application due date: Not applicable.

New NIH FOAs Issued in Collaboration with the FDA Center for Tobacco Products

On July 10, 2012, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued a Request for Application entitled **Tobacco Centers of Regulatory Science for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (P50)** [RFA-DA-13-003](#). The Tobacco Centers of Regulatory Science (TCORS) program objective is to conduct programs of multidisciplinary research that will inform tobacco product regulation and address the research priorities related to the regulatory authority of the Food and Drug Administration (FDA) Center for Tobacco Products (CTP). Application due date: November 14, 2012. Start Date: September 2013.

On August 19, 2011, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued a Program Announcement entitled **FDA Small Scientific Conference Grant Program (R13)** [PA-11-310](#). The purpose of this PA is to facilitate the provision of federal financial assistance in support of scientific conferences clearly aligned with the FDA mission. Application due date: October 15; January 15; April 15; July 15, by 5:00 PM local time of applicant organization. Start Date: October 15 - December 1; January 15 - March 1; April 15 - June 1; July 15 - September 1. **Note:** Earliest start date depends on objective review date and may not

occur as listed above. Applicants are strongly encouraged to pursue funding for their small scientific conference well in advance of the anticipated meeting date.

On August 23, 2012, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Tobacco Control Regulatory Research (R21) [PAR-12-266 \(R01\)](#) [PAR-12-267 \(R03\)](#) [PAR-12-268](#)**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage biomedical, behavioral, and social science research that will inform the development and evaluation of regulations on tobacco product manufacturing, distribution, and marketing. Open date: October 1, 2012. Application due date(s): November 1, 2012; January 16, 2013; June 18, 2013; January 15, 2014; June 17, 2014; January, 16, 2015, by 5:00 PM local time of applicant organization. AIDS application due date: Not applicable.

Other Program Activities

CTN Update

A total of 50 protocols have been initiated since 2001, including multi-site clinical trials (36), multi-site surveys (3), studies in special populations (5), and secondary analyses of data across various trials (6). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Nearly 15,000 participants have been enrolled in CTN studies.

Information on protocols can be found at:

<http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies>

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

Receipt, Referral, and Review

NIDA received 1436 applications, including both primary and dual assignments, for which the Office of Extramural Affairs (OEA) managed the programmatic referral process during this Council cycle. Of these, NIDA received the primary assignment on 897 applications.

OEA arranged and managed 9 grant review meetings in which 197 applications were evaluated. OEA's reviews included applications in a chartered, standing review committee and Special Emphasis Panels (SEPs). In addition, OEA staff arranged and managed 10 review meetings dealing either with contract proposals or contract concepts.

NIDA has one standing chartered committee, NIDA-K, which reviewed Career Development applications and Institutional Training Grant applications (T32). There were also 8 Special Emphasis Panels to review grant applications for a variety of reasons:

- Behavioral Science Track Award for Rapid Transition (B/START)
- Imaging Science Track Award for Research Transition (I/START)
- Conference Grants (R13)
- Collaborative Clinical Trials In Drug Abuse (Collaborative R01)
- Grand Opportunity In Medications Development For Substance-Related Disorders (U01)
- Loan Repayment Program
- Requests for Applications (RFAs)

OEA managed the following RFA review:

DA12-011 FY12 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1)

Completed contract-related review activity from the Contracts Review Branch since the last Council includes:

SBIR Phase II

N44DA-12-1206 Rapid Portable Devices to Measure Drug Uses

SBIR Phase II (Resubmissions)

N44DA-12-5567 E-Technology Tools for Extending the Reach of Prevention Interventions in Rural and Remote Locations

N44DA-12-5560 SecuRX: Preventing Prescription Drug Diversion

Contract Reviews (R&D and non-R&D)

NO1DA-12-8902 Regulatory Filing Support for the Development of Medications

NO1DA-12-2229 Data, Statistics, and Information Technology Support for NIDA

NO1DA-12-8905 Pharmacokinetic and Pharmacodynamic Studies for Medications Development

Concept Reviews (SBIR Phase I)

N43DA-13-2233	A Mobile Application to Help Patients Take their Pill Medications as Prescribed (Improving Medication Adherence)
N43DA-13-7786	Development of Predictive in vivo Screening Systems for Phenotypic Drug Discovery
N43DA-13-4417	Video Game Targeting Relapse Prevention in Youth with Substance Use Disorders
N43DA-13-4418	A Clean, Green System for at-Home Destruction of Leftover Prescription Medicines

The CTN Data and Safety Monitoring Board(s) met:

- May 14, 2012 to review protocol CTN 0053, Achieving Cannabis Cessation-Evaluating N-Acetylcysteine Treatment (ACCENT)
- May 16, 2012 to discuss progress of protocol CTN 0037, Exercise as a Treatment for Substance Use Disorders
- June 5, 2012 to discuss progress of protocol CTN 0048, Cocaine Use Reduction with Buprenorphine (CURB)
- August 27, 2012 to review protocol CTN 0054, Combination Pharmacotherapy for Methamphetamine Dependence: Extended Release Depot Naltrexone + Bupropion vs. Matched Placebos (ADAPT-MD).

Certificates of Confidentiality

Between April 5 and July 16, 2012, OEA processed 87 Certificate of Confidentiality applications, including 17 amendments for either extension of expiration date or protocol change.

Staff Training and Development

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations that included presentations about the *PhenX Toolkit for Human Subjects' Research*, presented by Kevin Conway, Ph.D., Deputy Director, DESPR; *NIH Review Appeals Process*, presented by Teresa Levitin, Ph.D., Director, OEA; *New Policy: Human Subjects in NIH Contract Proposals*, presented by Dr. Jerry McLaughlin, OEA, and Mr. Kenneth Goodling, CMB; and *Diversity Supplements*, presented by Pamela Goodlow, Special Populations Office.

CONGRESSIONAL AFFAIRS SECTION
(Prepared August 8, 2012)

APPROPRIATIONS/BUDGET

In the President's Fiscal Year 2013 budget, the request for NIH is \$30.62 billion, identical to the enacted level in FY 2012 of 30.62 billion. For NIDA, the Fiscal Year 2013 request is \$1.054 billion, compared to an enacted level in FY 2012 of \$1.052 billion.

The Senate appropriations committee reported out its Labor-HHS-Education bill in June. That bill provides NIH with \$30,731,459,000, \$100 million over the President's request, including \$1.057 billion for NIDA.

The House Labor-HHS-Education appropriations subcommittee reported out its bill in July. The bill provides NIH with \$30,631,459,000, equal to the FY 2012 level. This would include \$1.052 billion for NIDA. The full committee has yet to consider the bill. There have already been significant policy arguments about several sections of the bill. A complete summary is available for anyone interested in those details.

- **Special Issue: Sequestration.** (Some text excerpted from Congressional Quarterly) On August 7, President Obama signed into law H.R. 5872, a bill that requires the administration to detail within 30 days how it would implement the looming spending cuts in domestic and defense programs. The "sequester transparency measure," as it is called, directs the White House to spell out what kinds of reductions at the "program, project and activity level" would result from allowing slated across-the-board cuts to take place. Leaders in both parties have said that federal law should be changed to derail these currently mandated \$109 billion cuts, known as the sequester, but Democrats and Republicans remain deeply split about how to find an alternative plan for deficit reduction.
- **Special Issue: Continuing Resolution.** (text from NIH/OLPA) On July 31, 2012, Senator Harry Reid (D-NV), Senate Majority Leader, announced that he and Representative John Boehner (R-OH), Speaker of the House, had reached an agreement on a six-month Continuing Resolution for FY2013, which would be written during the August recess and voted on in September. Most continuing resolutions maintain flat-line funding from one fiscal year into the next. However, under this agreement, funding would be consistent with the \$1.047 trillion level for fiscal 2013 set forth in last year's Budget Control Act, and above the \$1.028 trillion called for by Representative Paul Ryan's (R-WI) budget proposal. It is also above the \$1.043 trillion level for the current fiscal year called for by the law.

CONGRESSIONAL BRIEFINGS/MEETINGS OF INTEREST

Women and Smoking.

On June 8, NIDA Director Dr. Nora Volkow participated in a Congressional briefing on women and smoking. The briefing was cosponsored and organized by Women's Policy, Inc., Legacy, and the Women's Health Task Force of the House Women's Caucus. Also presenting was Cheryl Heulton, Legacy's CEO. Dr. Volkow presented research on and discussed the unique and specific difficulties faced by women who try to quit smoking.

Friends of NIDA Congressional briefing on HIV/AIDS.

On July 18, the Friends of the National Institute on Drug Abuse (NIDA) in conjunction with the Congressional Addiction, Treatment and Recovery Caucus hosted a congressional briefing titled "Treatment as Prevention: HIV/AIDS and Substance Abuse." The briefing, seventeenth in the Charles R. Schuster Congressional Briefing Series, was co-sponsored by 20 member organizations of the Friends of NIDA coalition and drew an audience of over 70 including 19 congressional staff. The briefing, for which the American Psychological Association provided significant logistical support, featured presentations by NIDA director Dr. Nora Volkow and three other scientists whose research is funded by the institute.

Dr. Nora Volkow presented on the shift in direction of HIV/AIDS research since the 2011 breakthrough discovery that early antiretroviral therapy prevented transmission, likely by suppressing HIV viral load. She presented statistics on the prevalence and the outcomes of treatment with highly active antiretroviral therapy (HAART), including that injection drug users are much less likely to receive the treatment than are other HIV positive patients. The Institute currently supports research on new therapeutics for injection drug users, including long lasting medications to improve compliance, medications not based on opioid substitution, and vaccines and other immunotherapies, as well as on implementation of Seek, Test, Treat and Retain (STTR) mode of care for high risk, hard to reach drug abusing groups who have not been recently tested for HIV.

Dr. Marguerita Lightfoot, co-director of the Center for AIDS Prevention Studies and director of the Technology and Information Exchange Core at the UCSF Department of Medicine, presented her research on expansion of HIV testing among vulnerable populations, including text messaging interventions with teens. Dr. Frederick Altice, professor of medicine and of epidemiology microbial diseases at Yale University and director of the HIV in Prisons Program, presented his research on STTR in the criminal justice system and highlighted problems including insufficient access to antiretroviral therapy after incarceration. Dr. Carlos Del Rio, professor and chair of the Rollins School of Public Health' Hubert Department of Global Health and professor of medicine at the Emory School of Medicine's Division of Infection Diseases, presented on the "cascade of care" phenomenon, emphasizing that the three biggest problems with HIV treatment and prevention in the US are delays in testing, delays in care, and early dropout. Dr. Del Rio discussed the National HIV/AIDS Strategy goals for 2015 and new clinical guidelines.

LAWS ENACTED

Reauthorization of FDA programs. On July 9, 2012, the President signed S. 3187, the Food and Drug Administration Safety and Innovation Act (P.L. 112-144). The bill authorizes for five years the FDA's user fee program for prescription drugs and devices, establishes user fee programs for generic drugs and biosimilars, among other provisions. Section 1122 focuses on prescription drug abuse and requires a report to Congress reviewing current federal initiatives and identification of gaps and opportunities in addressing this significant problem.

BILLS OF INTEREST

H.R. 866 – On March 1, 2011, Representative Ed Whitfield (R-TN) introduced the National All Schedules Prescription Electronic Reporting Reauthorization Act of 2011, to amend and reauthorize the controlled substance monitoring program under section 3990 of the Public Health Service Act. The bill was referred to the House Energy and Commerce Committee, Subcommittee on Health.

H.R. 1065 – On March 14, 2011, Representative Vern Buchanan (R-FL) introduced the Pill Mill Crackdown Act of 2011, to amend the Controlled Substances Act to provide for increased penalties for operators of pill mills, and for other purposes. The bill was referred to the House Committees on the Judiciary and Energy and Commerce Subcommittee on Health. See S. 1760.

H.R. 1562 – On April 14, 2011, Representative Lucille Roybal-Allard (D-CA) introduced the Sober Truth on Preventing Underage Drinking Reauthorization Act, to provide for programs and activities with respect to the prevention of underage drinking. The bill was referred to the House Committee on Energy and Commerce, Subcommittee on Health. See also S. 854.

H.R. 1729 – On May 4, 2011, Representative Dutch Ruppersberger (R-MD) introduced the Opiate Addiction Treatment Act of 2011, to amend the Controlled Substances Act to authorize certain practitioners other than physicians to dispense certain narcotic drugs in schedule III, IV, and V for maintenance treatment or detoxification treatment without obtaining annually a separate registration for that purpose. The bill was referred to the House Energy and Commerce (Subcommittee on Health) and Judiciary Committees (Subcommittee on Crime, Terrorism and Homeland Security).

H.R. 1925 - On March 8, 2011, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2011, to focus on consumer and practitioner education, opioid treatment programs, prescription monitoring programs, and mortality reporting. The bill was referred to the House Judiciary Committee (Subcommittee on Crime, Terrorism and Homeland Security) and Energy and Commerce Committee (Subcommittee on Health). See also S. 507.

H.R. 1983 – On May 2, 2011, Representative Barney Frank (D-MA) introduced the States' Medical Marijuana Patient Protection Act, to provide for the rescheduling of marijuana and for the medical use of marijuana in accordance with the laws of the various States. The bill was referred to the Committee on Energy and Commerce, Subcommittee on Health.

H.R. 2119 – On June 3, 2011, Representative Mary Bono Mack (R-CA) introduced the Ryan Crendon Act of 2011, to amend the Controlled Substances Act to require practitioners to obtain particular training or special certification, approved by the Attorney General, on addiction to and abuse of controlled substances and appropriate and safe use of controlled substances. The bill was referred to the House Judiciary Committee (Subcommittee on Crime, Terrorism and Homeland Security) and House Energy and Commerce Committee (Subcommittee on Health).

H.R. 2306 – On June 23, 2011, Representative Barney Frank (D-MA) introduced the Ending Federal Marijuana Prohibition Act of 2011, to limit the application of Federal laws to the distribution and consumption of marijuana. The bill was referred to the House Judiciary Committee (Subcommittee on Crime, Terrorism and Homeland Security) and the Energy and Commerce Committee (Subcommittee on Health).

H.R. 2334 – On June 23, 2011, Representative Jim Moran (D-VA) introduced the Comprehensive Problem Gambling Act of 2011, to include in SAMHSA programs activities to research, prevent and treat the harmful consequences of pathological and other problem gambling, and for other purposes. The bill was referred to the House Energy and Commerce Committee, Subcommittee on Health.

H.R. 2376 -- On June 24, 2011, Representative Diana DeGette (D-CO) introduced the Stem Cell Research Advancement Act of 2011. Similar to legislation Representative DeGette introduced in the 111th Congress, H.R. 2376 would amend the Public Health Service Act to provide for human stem cell research, including human embryonic stem cell research. The bill would establish criteria for the use of human embryonic stem cells in research; require the Secretary of HHS to maintain and update guidelines applicable to the conduct and support of embryonic stem cell research; prohibit funding for human cloning; and require that a section on stem cells be added to the NIH Biennial Report. H.R. 2376 was referred to the House Committee on Energy and Commerce, Subcommittee on Health.

H.R. 2689 – On July 28, 2011, Representative Gwen Moore (D-WI) introduced the SAFE Teen Act, to amend the Safe and Drug Free Schools and Communities Act to authorize the use of grant funds for violence prevention and other purposes. The bill was referred to the House Committee on Education and the Workforce, Subcommittee on Early Childhood, Elementary, and Secondary Education. See also S. 1447.

H.R. 3433 – On November 16, 2011, Representative James Lankford (R-OK) introduced H.R. 3433, the Grant Reform and New Transparency Act of 2011. The bill would amend title 31, United States Code, to provide transparency and require certain standards in the award of federal grants, and for other purposes. Among the provisions in the bill are requirements for posting grant award information for each competitive grant awarded by a federal agency on a public web site. Specifically, the bill would require the posting of the full grant application, award decision documentation and rankings, justification for deviating from rankings, and disclosure of information on individuals who served as peer reviewers on the grant. In addition, the bill would require the posting of grant performance information within 60 days after the end of the period for completion of the grant. The bill was reported out of committee (Oversight and Government Reform) on November 17 and awaits further action.

H.R. 3699 – On December 16, 2011, Representatives Darrell Issa (R-CA) and Carolyn Maloney (D-NY) introduced H.R. 3699, the Research Works Act, which would prohibit any Federal agency, including NIH, from requiring that investigators make any research paper arising from research funds publicly accessible via the Internet without the prior consent of the publisher. The bill would also prevent government agencies from including in its grant and contract agreements a prospective requirement that the results of the research be made publicly available on the Internet. The bill would effectively prevent NIH from posting peer-reviewed papers arising from NIH funds to PubMed Central as required by Division G, Title II, Section 218 of P.L. 110-161. The bill was referred to the House Committee on Oversight and Government Reform.

NOTE: On February 27, 2012, Representatives Darrell Issa (R-CA) and Carolyn Maloney (D-NY) submitted identical statements supporting continued dialogue about open access publishing and intellectual property, and expressions by each of their intent to stop pursuing legislative action on this bill.

H.R. 4292 – On March 28, Representative Harold Rogers (D-KY) introduced the ID MEDS Act (Interstate Drug Monitoring Efficiency and Data Sharing Act of 2012), to direct the Attorney General to establish uniform standards for the exchange of controlled substance and prescription information for the purpose of preventing diversion, fraud, and abuse of controlled substances and other prescription drugs. The bill was referred to the Committee on Energy and Commerce. See also S. 2254.

H.R. 5856 – On July 19, 2012, the House passed, by a vote of 326-90, H.R. 5856, the Department of Defense (DOD) Appropriations bill for FY 2013. The bill contains a number of items of interest to NIH, including several amendments approved on the House floor that would shift funding from defense operations to support research within the Congressionally Directed Medical Research Programs at DOD. The report accompanying the bill includes a focus on prescription drug abuse and neuroscience research:

- Prescription Drug Abuse – The Committee remains concerned with pain management prescription medication dependency among service members, and encourages the Secretary of DOD to make curtailing prescription drug abuse a priority.
- Federal Neuroscience Working Group – The Committee is aware that the Office of Science and Technology Policy, within the Executive Office of the President, is establishing an interagency working group under the auspices of the National Science and Technology Council (NSTC) to coordinate investments in neuroscience research across the Federal Government and leverage the potential for significant, transformative advances in our fundamental understanding of learning, brain development, and brain health and recovery. The Committee supports the activities of the NSTC Neuroscience Working Group and urges DOD to play an active role.

H.R. 6187 – On July 25, 2012, Representative Jim Himes (D-CT) introduced H.R. 6187, the Cure for AIDS Act. Provisions would establish an accelerated research program within the DOD Congressionally Directed Medical Research Program to find a cure for HIV/AIDS. Provisions would also require the Secretary of Defense to (1) collaborate with the Directors of NIH and the NIAID, and the heads of a Federal agency deems appropriate by the Secretary, (2) ensure that highly targeted research is conducted to address seven specific questions and priorities, (3) collaborate with at least one nonprofit entity, and (4) involve the selected nonprofit in establishing research priorities for peer-reviewed funded research. Authorized, but not appropriated, would be \$20 million for each of the fiscal years 2013 through 2017. H.R. 6187 was jointly referred to the Committees on Armed Services and Energy and Commerce.

H.R. 6214 – On July 26, 2012, Representative Joe Barton (R-TX) introduced H.R. 6214, the HHS Employee Compensation Reform Act of 2012. The bill would (1) limit the use of the Title 42 hiring authority mechanism to only the Department of Health and Human Services (HHS), (2) limit the total Title 42 employees at HHS to five percent of total employees, (3) limit the pay of Title 42 employees by designating a salary cap equal to 150 percent of the annual rate of pay for Level 1 of the Executive Schedule (Level 1 pay is \$199,700), (4) require HHS to annually report to Congress the number of Title 42 employees and break the numbers down by agency, and (5) provide that at any time, up to 50 individuals serving pursuant to this subsection may be paid without regard to the limitation on compensation if the Secretary finds that each such individual's service is vital to support the activities of HHS. H.R. 6214 was referred to the House Committee on Energy and Commerce.

H.R. 6272 – On August 2, 2012, Representative Edward Markey (D-MA) introduced H.R. 6272, the Trial and Experimental Studies Transparency (TEST) Act of 2012. The TEST Act is cosponsored by Representatives Henry Waxman (D-CA), Rosa DeLauro (D-CT), and Jan Schakowsky (D-IL). H.R. 6272 would expand upon the Food and Drug Administration Amendments Act of 2007 as it relates to clinical trials registration and results reporting on clinicaltrials.gov. Provisions would amend Section 402(j) of the PHS Act to (1) require all interventional biomedical studies on humans to be registered with the clinical trial registry data base

before the first participant is enrolled in the trial; (2) require that results from all covered trials are posted on the database within one year of completion of the trial; (3) provide for delayed submission of results (up to two years after trial completion) for trials on medical interventions that have never before been approved for any use; (4) instruct the Secretary of HHS to undergo rulemaking to require foreign trials that are used to support an application for marketing in the United States to comply with the registration and reporting requirements of the database; and (5) instruct NIH and the FDA to provide a report to Congress regarding the implementation and compliance with the database requirements. H.R. 6272 was referred to the Committee on Energy and Commerce.

S. 507 – On March 8, 2011, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2011, to focus on consumer and practitioner education, opioid treatment programs, prescription monitoring programs, and mortality reporting. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 1925.

S. 660 – On March 29, 2011, Senator Jon Kyle (R-AZ) introduced the Preserving Access to Targeted, Individualized, and Effective New Treatments and Services (PATIENTS) Act of 2011. S. 660 states that notwithstanding any other provisions of law, the Secretary of Health and Human Services (HHS) shall not use data obtained from the conduct of Comparative Effectiveness Research (CER), including such research that is conducted or supported using funds appropriated under the American Recovery and Reinvestment Act of 2009 or authorized or appropriated under the Patient Protection and Affordable Care Act, to deny or delay coverage of an item or service under a Federal health care program. In addition, the bill would require the Secretary of HHS to ensure that CER conducted or supported by the Federal government accounts for factors contributing to differences in treatment response and treatment preferences of patients, including patient-reported outcomes, genomics of personalized medicine, the unique needs of health disparity populations, and indirect patient benefits. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S. 810 – On July 25, 2012, the Senate Environment and Public Works Committee (Senator Barbara Boxer, [D-CA], chairman), favorably reported S. 810, the Great Ape Protection and Cost Savings Act, as amended, out of Committee by voice vote. Senator James Inhofe (R-OK) voiced his concern that the bill went further than the IOM report and voted “no”. During the Committee mark-up, Senators Boxer and Cardin (D-MD) offered a substitute amendment. S. 810 would prohibit invasive research on great apes, including chimpanzees, and would require that all federally owned and supported chimpanzees be retired and moved to sanctuaries. The amendment provides a contingency exemption for research should an emerging or reemerging condition arise in the future, although it retains the requirement that all federally owned chimpanzees must be retired and sent to sanctuaries where no research can be preformed. The amendment would also create a Task Force to review funding proposals that include the use of chimpanzees.

S. 854 – On April 14, 2011, Senator Frank Lautenberg (D-NJ) introduced the Sober Truth on Preventing Underage Drinking Reauthorization Act, to provide for programs and activities with respect to the prevention of underage drinking. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 1562.

S. 882 – On May 4, 2011, Senator Sherrod Brown (D-OH) introduced the STOP Act, to prevent misuse, overutilization, and trafficking of prescription drugs by limiting access to such drugs for Medicare and Medicaid beneficiaries who have been identified as high-risk prescription drug users. The bill was referred to the Committee on Finance.

S. 1231 – On June 20, 2011, Senator Patrick Leahy (D-VT) introduced the Second Chance Reauthorization Act of 2011. First passed in 2007, the Second Chance Act provides resources to states, local governments and nonprofit organization to improve outcomes for people returning to communities from prisons and jails. The bill was reported out of Committee on July 21 and placed on the Senate calendar.

S. 1234 – On June 20, 2011, Senator Charles Grassley (R-IA) introduced the Partners for Stable Families and Foster Youth Affected by Methamphetamine or Other Substance Abuse Act, to amend the Social Security Act to reauthorize grants to assist children affected by methamphetamine or other substance use under the promoting safe and stable families program. The bill was referred to the Committee on Finance.

S. 1447 – On July 28, 2011, Senator Mike Crapo (R-ID) introduced the SAFE Teen Act, to amend the Safe and Drug Free Schools and Communities Act to authorize the use of grant funds for violence prevention and other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 2689.

S. 1760 -- On October 20, 2011, Senator Joe Manchin (D-WV) introduced the Pill Mill Crackdown Act of 2011, to amend the Controlled Substances Act to provide for increased penalties for operators of pill mills, and for other purposes. The bill was referred to the Judiciary Committee. See H.R. 1065.

S. 2254 - On March 29, Senator Rob Portman (R-OH) introduced the ID MEDS Act (Interstate Drug Monitoring Efficiency and Data Sharing Act of 2012), to direct the Attorney General to establish uniform standards for the exchange of controlled substance and prescription information for the purpose of preventing diversion, fraud, and abuse of controlled substances and other prescription drugs. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also H.R. 4292.

S. 2262 – On March 29, Senator Tim Johnson (D-SD) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the Fetal Alcohol Syndrome prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

INTERNATIONAL ACTIVITIES

Research Funding

Funding Opportunities for International Research

NIDA and NIH have recently issued several funding opportunity announcements of interest to the international drug abuse research community:

FY13 NIDA Avant-Garde Award Program for HIV/AIDS Research (DP1) RFA-DA-13-002

The NIDA Avant-Garde Award Program for HIV/AIDS Research is now open to international scientists. This award is designed to support individual scientists of exceptional creativity who propose cutting-edge—and possibly transformative—approaches to major challenges in biomedical and behavioral research on HIV/AIDS that are relevant to drug abuse. The award is intended to support high-impact research that will open new areas of HIV/AIDS research and/or lead to new avenues for treatment and prevention of HIV/AIDS among drug abusers. Proposed research should reflect ideas and approaches that are substantially different from those already being studied by the investigator or others. Avant-Garde awardees are required to commit at least 35% of their research effort to activities supported by the Avant-Garde Award. Pre-application is required.

Tobacco Centers of Regulatory Science (P50; RFA-DA-13-003) NIDA is among the NIH Institutes that have issued an RFA in conjunction with the Food and Drug Administration to provide up to \$40 million to support as many as 12 Tobacco Centers of Regulatory Science (TCORS) for fiscal year 2013. TCORS conduct multidisciplinary research to inform tobacco product regulation and are expected to cooperate with other centers in the research network. Applications must include a plan for research training. Foreign institutions are eligible to apply.

U.S.–India Bilateral Collaborative Research Partnerships on the Prevention of HIV/AIDS and Co-morbidities (R21; RFA-AI-12-033) NIDA is among the NIH Institutes that have issued a Request for Applications (RFA) committing approximately \$3 million in fiscal year 2013 to fund 8 to 10 applications to support research partnerships in the field of HIV/AIDS prevention or in preventing, treating, or ameliorating HIV-related co-morbidities. The lead Indian agencies are the Indian Council of Medical Research (ICMR) and India's Department of Biotechnology. U.S. and Indian collaborating investigators should work together to submit corresponding applications to NIH and ICMR. The U.S. applicants may request support for 2-year projects with direct costs of \$275,000 or less.

NIH/USAID Partnerships for Enhanced Engagement in Research (PEER) Health The U.S. Agency on International Development (USAID) and NIH have issued a Request for Applications to support implementation science research collaborations between NIH-funded researchers in the United States and researchers from 33 eligible countries. Each award will provide up to \$450,000 over 3 years to support collaborations that address morbidity and mortality among children under age 5. Additional funds are available to support research in Indonesia.

Norwegian Collaborative Projects With Research Groups in the U.S. Up to \$10 million NOK is available to cover the Norwegian costs of collaborative research projects between Norwegian researchers and NIH-funded U.S. researchers investigating mental health, alcohol, or drug abuse.

Research Results

International Researchers Brief Clinical Trials Network Steering Committee

Five INVEST/Clinical Trials Network (CTN) Fellows reported on their mentored research projects, and representatives of three other international initiatives reported on their activities during an international report session at the April 17, 2012, CTN Steering Committee meeting in Atlanta. The international initiatives discussed included the Clinical Intervention Network in Addiction being created by the Institute of Neurosciences, Mental Health and Addiction at the Canadian Institutes of Health Research; development of a CTN-type organization in Mexico; and research into heroin substitution treatment for opioid dependence in Switzerland, part of a fellowship project conducted by Gabriel Thorens, M.D., University Hospital of Geneva. Dr. Thorens's mentor is John Rotrosen, M.D., New York University. The INVEST/CTN Fellows included:

- Cecile Denis, Ph.D., France, who participated in field trials of diagnostic severity measures proposed for the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) and researched assessment tools, such as the Addiction Severity Index, and treatment outcome measures at the University of Pennsylvania. Her mentors are John Cacciola, Ph.D., and Charles O'Brien, M.D., Ph.D.
- Sergii Dvoriak, M.D., Ph.D., Ukraine, who—with his mentor, George Woody, M.D., University of Pennsylvania, and colleagues in Russia—is comparing the costs and outcomes of the different treatment models for opioid dependence that have been developed in Russia and Ukraine despite the similarities in the two countries' HIV epidemics, cultures, and economies. The team has received a 5-year grant from NIDA.
- Maria de L.Garcia-Anaya, M.D., Ph.D., Mexico, whose fellowship is part of the initiative to develop a Mexican network similar to the CTN. Her mentors are Edward V. Nunes, M.D., Columbia University and New York State Psychiatric Institute, and Jose Szapocznik, Ph.D., University of Miami.
- Wang Xuyi, M.D., China, who is testing the effects of contingency management techniques on psychosocial function and treatment for methamphetamine dependence with his mentor, Walter L. Ling, M.D., University of California, Los Angeles.
- Effatalsadat M. Khoei, Ph.D., Iran, who is working with Kathleen Brady, M.D., Ph.D., at the Medical University of South Carolina to develop gender-sensitive prevention programs for female drug users and sex workers. She described the drug situation in Iran, treatment options for various drugs of abuse that are available in the country, and characteristics of Iranian women who abuse drugs.

Chinese Researchers Document Prevalence of ATS Use, HCV, and HIV

A team of researchers including former NIDA INVEST and DISCA fellow Min Zhao, M.D., Ph.D., has found that 43.5 percent of amphetamine-type stimulant (ATS) users in six Chinese provinces have been exposed to hepatitis C (HCV). They found that prevalence of HIV was high among ATS users in Yunnan province (20.3 percent) but quite rare elsewhere. Writing in the *Journal of Acquired Immune Deficiency Syndromes* (1 August 2012; 60[4]:438–446; doi: 10.1097/QAI.0b013e31825694f2HIV) they concluded that their findings emphasize the need for

new prevention strategies for this at-risk population. HIV infection was independently associated with living in Yunnan province [adjusted odds ratio = 15.8; 95% confidence interval (CI): 2.0 to 125.1), polydrug use (adjusted odds ratio = 2.6; 95% CI: 1.3 to 5.4), increased frequency of sexual behavior (adjusted odds ratio = 2.0; 95% CI: 1.1 to 4.1), history of sex with sexually transmitted infection-positive persons (adjusted odds ratio = 11.4; 95% CI: 1.3 to 98.9), and HCV infection (adjusted odds ratio = 2.8; 95% CI: 1.2 to 6.7). HCV was associated with study site, marital status, unemployment (adjusted odds ratio = 1.8; 95% CI: 1.3 to 2.4), a longer duration of ATS use, and history of injection use of ATS.

NIDA-Supported Meetings

NIDA International Forum Focuses on New and Emerging Psychoactive Substances

More than 260 participants from 61 countries attended the 17th Annual NIDA International Forum, which was held June 8 – 11, 2012, in Palm Springs, California. The meeting focused on the growing public health problem of new and emerging psychoactive substances, which are mostly unregulated compounds that are specifically designed to circumvent drug laws and mimic the effects of illicit drugs by slightly altering the chemical structure of a known drug. A joint College on Problems of Drug Dependence (CPDD)/NIDA International Forum poster session featured presentations by 160 U.S. and international researchers.

IP Director Steven W. Gust, Ph.D., chaired the meeting, which was planned jointly by the IP, DESPR, and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). OSPC and the NIDA Asian American/Pacific Islander Researchers and Scholars Work Group also provided financial support for the 2012 NIDA International Forum.

NIDA International Awards of Excellence, which recognize individuals for outstanding contributions to international cooperation in drug abuse research and training, were presented to Clyde B. McCoy, Ph.D., University of Miami, for excellence in mentoring, and Paul Griffiths M.Sc., EMCDDA, for excellence in international leadership.

The opening plenary session featured updates from the White House Office on National Drug Control Policy (ONDCP), EMCDDA, and the U.S. Drug Enforcement Administration (DEA). Cecelia McNamara Spitznas, Ph.D., ONDCP, said strengthening international partnerships in both demand and supply reduction efforts remains a priority for ONDCP. She also described the U.S. National Drug Control Strategy as a balance of public health and public safety concerns and reported that every dollar invested in an evidence-based prevention program could reduce costs related to substance use disorders by \$2 to \$18. Mr. Griffiths described how the European Union response to emerging psychoactive substances relies on real-time information exchange and scientific risk assessment tools to quickly develop evidence-based policy responses that are intended to be faster and more effective than previous policy initiatives and focus on the added value delivered by European Union-level cooperation. He concluded that globalization, reliance on the Internet as a source of medical information, younger populations who are more willing to experiment with new substances, and cost efficiencies in manufacturing and adapting products have created a dynamic and fluid situation that presents a growing challenge for monitoring, responding to, and controlling the use of new psychoactive substances. Michelle D. Walker, Ph.D., Drug Enforcement Administration (DEA), described the legal steps the agency can use to limit use of these new psychoactive substances, which she noted are reportedly more addictive, dangerous, and may cause more powerful highs compared to chemically similar substances.

NIDA Acting Deputy Director David A. Shurtleff, Ph.D., chaired a plenary session panel of researchers who discussed the latest research findings on detecting new compounds, assessing their effects, and monitoring use trends. During that panel Michael Baumann, Ph.D., IRP, described the Institute's Designer Drugs Initiative and described recent studies of "bath salts." OSPC Acting Director Susan Weiss, Ph.D., chaired a breakout session that featured international research reports on using electronic media to track drug use trends, assessing the prevalence of prescription drug misuse among adolescents, treating opioid dependence with naltrexone or buprenorphine, instituting drug courts, and identifying factors that inhibit injection drug users from participating in voluntary HIV testing. IP Associate Director Dale Weiss chaired a session designed for NIDA International Fellowships Program alumni that featured DBNBR Acting Director Joni Rutter, Ph.D., who discussed international research opportunities in genetics. Other speakers in the fellowships session introduced online resources for researchers from developing countries, a writing mentor program sponsored by the International Society of Addiction Journal Editors, and the NIDA Hubert H. Humphrey Drug Abuse Research Fellowships. Moira O'Brien, DESPR, planned a workshop that focused on network-based models for monitoring drug abuse trends, providing practical information and examples regarding: (1) establishing, operating, and maintaining networks; (2) adapting to address new/emerging drugs, issues, and technologies; and (3) using network information. The final breakout session explored cross-national patterns of drugged driving, issues in measurement and interpretation of drug-impaired driving, the range of policy responses, and gaps in the relevant evidence base.

NIDA Joins Prevention Researchers To Promote Healthy Living

NIDA supported a poster session, roundtable discussion, and International Networking Forum at the Society for Prevention Research (SPR) Annual Meeting, which was held in Washington, DC, from May 29 to June 1, 2012. The meeting attracted more than 800 researchers, policymakers, and practitioners to discuss prevention science research results and evidence-based policies that can be implemented to promote healthy living. To open the SPR meeting, the NIDA IP and DESPR cosponsored the Fifth NIDA International Poster Session, with support from the National Institute on Alcohol Abuse and Alcoholism. IP Associate Director Dale S. Weiss and SPR President Deborah Gorman-Smith, Ph.D., University of Chicago, welcomed participants. Ms. Weiss called the poster session an important way to highlight the outstanding and varied research conducted globally and a way to encourage collaborative international research. She also introduced the new Acting Chief of the DESPR Prevention Research Branch, Harold I. Perl, Ph.D. The poster session featured 11 scientists who received travel awards to present the results of drug abuse prevention research completed in international settings, including the following:

- Gabriel Andreuccetti, University of São Paulo Medical School, Brazil
- Sawitri Assanangkornchai, Prince of Songkla University, Thailand
- Anneke Buehler, IFT Institut für Therapieforschung, Germany
- Heather Clark, Canadian Centre on Substance Abuse, Canada
- Andrea Fogarasi-Grenczer, Semmelweis University, Hungary
- Johanna Gripenberg-Abdon, Karolinska Institutet, Sweden
- Hanna Heikkila, United Nations Office on Drugs and Crime (UNODC), Austria
- Joachim Jacobs, University of the Western Cape, South Africa
- Krzysztof Ostaszewski, Institute of Psychiatry and Neurology, Poland
- Valeriy Ryabukha, United Nations Development Programme in Ukraine, Ukraine
- Shreeletha Solomon, Institute for Child and Adolescent Health Research, India.

The NIDA IP organized a roundtable discussion session for SPR participants, where representatives from five NIH components reviewed funding opportunities and the international missions, activities, and prevention research priorities of their organizations. IP Director Steven W. Gust, Ph.D., opened the session by reviewing the types of NIH funding opportunities, including the types of NIH grants that can be used to support international research, and the advantages of international teams seeking NIH funding through domestic grants with a foreign component. Dr. Perl described the DESPR Prevention Research Branch focus on the whole person within different contexts and across the lifespan. Representatives from NICHD, NIMH, NIAAA, and the Fogarty International Center also participated.

Before the SPR meeting opened, about 20 researchers from around the world gathered for the SPR International Networking Forum. Participants discussed the UNODC effort to establish international prevention standards, a draft registry of international collaborative research that the group is developing, funding models and sources to support international prevention research partnerships, and potential uses of social media to inform International Networking Forum members of activities and opportunities. Brenda A. Miller, Ph.D., Pacific Institute for Research and Evaluation, chaired the International Networking Forum.

ASAM Features International Symposium on Comorbid Addiction and Mental Illness

The breadth of dual-diagnosis issues found internationally and how they are manifest in three different national settings was the focus of a symposium at the American Society of Addiction Medicine (ASAM) 43rd Medical-Scientific Conference, which was held April 19–22, 2012, in Atlanta. Carlos Roncero, M.D., Ph.D., associate professor of psychiatry at the Autonomous University of Barcelona and chief of the drug addiction unit at Vall d’Hebron University Hospital, described the issues and treatment approaches in Spain. Giuseppe Carra, M.D., M.Sc., Ph.D., Monza Mental Health University Trust, Italy, described the dual-diagnosis treatment, service models, and research that have been developed in Italy over the past two decades. Haim Mell, M.D., head of treatment and rehabilitation at the Israeli National Anti-Drug Authority, discussed dual diagnosis in Israel. Other speakers included NIDA IP Director Steven W. Gust, Ph.D.; Marc Galanter, M.D., New York University; and Jag Khalsa, Ph.D., DPMCD. Dr. Galanter, Dr. Khalsa, and Petros Levounis, M.D., M.A., The Addiction Institute of New York, organized the symposium.

IP Joins Johns Hopkins Workshop for Burmese Officials

NIDA IP Director Steven W. Gust, Ph.D., participated in an April 10 workshop at Johns Hopkins University for a delegation of government officials from Burma (Myanmar). The Burmese delegation, which was lead by the Minister of Health, Dr. Pe Thet Khin, included representatives from the Office of the President; Ministries of Health, Education, Justice, and Science and Technology; and the nongovernmental organization Mingalar Myanmar. In addition to meeting with Dr. Gust, the delegation learned about opioid dependence treatment research conducted at the university from Eric C. Strain, M.D., who directs the university’s Center for Substance Abuse Treatment and Research. The workshop also focused on health systems; maternal, child, and women’s health; nutrition; infectious diseases; and mental health.

Online Conference Features U.S.–Mexico Border Drug Issues

The University of Texas at El Paso hosted a conference, *U.S.–Mexico Border Drug Issues*, May 22–23, 2012, that featured presentations by behavioral health providers and researchers to discuss program strategies and research findings for populations along the U.S.–Mexico border. In addition to the in-person sessions, the conference was streamed live and can be viewed by anyone with access to an Internet connection for approximately 1 year. The U.S. Counties Along the Mexican Border Initiative and the NIDA-funded Vulnerability Issues in Drug Abuse (VIDA) Program cosponsored the conference.

Fellowships

New NIDA IP Fellowship Application Deadlines

The NIDA IP has announced new application deadlines for its three postdoctoral training fellowships. The deadlines are being adjusted to streamline the application receipt and review processes. Application deadlines for the following fellowships are now April 1:

- INVEST Drug Abuse Research Fellowship
- INVEST/CTN Drug Abuse Research Fellowship
- U.S.–Mexico Drug Abuse Prevention Research Fellowship

International AIDS Society, NIDA Select New Fellows

The International AIDS Society (IAS) and NIDA have awarded postdoctoral fellowships to scientists from Bangladesh, Greece, and Iran and professional development fellowships to scientists from Iran and Tajikistan. IAS and NIDA cosponsor the fellowships. The postdoctoral awards provide 18 months of training with an expert in drug abuse-related HIV to advance scientific understanding of the linkages between drug use and HIV while fostering multinational research. The professional development awards provide 8 months of training in HIV-related drug use research for well-established HIV or drug use scientists.

The 2012 IAS/NIDA postdoctoral fellows are:

- Salequl Islam, Ph.D., Bangladesh, who will study mechanisms and implications of injection and inflammation among HIV/HCV-coinfected drug users in the *AIDS Linked to the IntraVenous Experience (ALIVE)* study. His mentor is Gregory D. Kirk, M.D., Johns Hopkins University. Building on Dr. Islam’s microbiology and HIV basic science expertise, the fellowship combines epidemiological and mechanistic investigation of the contributions made by injecting behavior and HIV/HCV infections to chronic inflammation and the role of inflammation on progression of HIV/HCV-related liver disease.
- Georgios Nikolopoulos, Ph.D., Greece, will develop measures to study how macro-level economic and social changes may have affected HIV risk among Greek injecting drug users. His mentor is Samuel Friedman, Ph.D., National Development and Research Institutes, Inc. Dr. Nikolopoulos will spend the first part of his fellowship studying behavioral and social risk research methods and the second part conducting ethnographic research in Greece. He and his mentor expect that these Greek data, collected in the contexts of ongoing turmoil related to the economic crisis and an HIV epidemic among injection drug users, will greatly improve methods to conduct research in other crisis-involved countries and monitor crisis-involved countries for emerging HIV risk situations.
- Mehrak Javadi Paydar, Ph.D., Iran, will analyze the neuroprotective effects of estrogen/soy isoflavones against development of HIV-induced neurodegeneration. Her mentor is Rosemarie

Booze, Ph.D., University of South Carolina. They will modulate the dopamine transmission system of cocaine-sensitized rats and hope to determine the potential protective effects of estrogenic compounds on concomitant cocaine/HIV neurotoxicity.

The 2012 IAS/NIDA professional development fellows are:

- Seyed Ramin Radfar, M.D., M.P.H., Iran, will analyze the prevalence of amphetamine-type stimulant (ATS) use among patients receiving methadone or buprenorphine maintenance treatment and the effects of ATS use on HIV risk-related behaviors in Isfahan, Iran. His mentor is Richard Rawson, Ph.D., University of California, Los Angeles. Dr. Radfar will use a mixed method, qualitative-quantitative study to provide local health authorities with recommendations for reducing ATS-related harms among drug users in Isfahan.
- Makhbatsho Bakhromov, Tajikistan, M.D., M.S., will examine the linkage between temporary labor migration, substance abuse, and HIV risk among Tajik male migrants in Moscow. His mentor is Judith Levy, Ph.D., University of Illinois at Chicago. Dr. Bakhromov will explore the role of socioeconomic marginalization, psychosocial factors, and lessening of normative sanctions in encouraging risky behavior and develop for later testing a culturally appropriate and contextually suitable HIV prevention model for Tajik migrant workers who inject drugs.

NIDA Selects Former Humphrey Fellow for INVEST Fellowship

Former Hubert H. Humphrey Fellow Tetiana Kiriazova, Ph.D., Ukraine, has been selected as a NIDA INVEST Fellow. Her mentor is Jeffrey H. Samet, M.D. M.A., M.P.H, Boston Medical Center. The director of HIV/AIDS programs at the Odessa Regional Charity Foundation “Future Without AIDS,” Dr. Kiriazova is the Ukrainian principal investigator on Dr. Samet’s NIDA-funded project, *Linking Russian Narcology and HIV Care to Enhance Treatment, Retention, and Outcomes*, and a senior investigator on a Ukrainian Ministry of Health-funded project to analyze the local HIV and tuberculosis epidemics. During her fellowship, she will conduct a secondary analysis of factors associated with participant attrition in a completed randomized controlled trial of an HIV risk reduction intervention that Dr. Samet conducted in Russia. They hypothesize that injection drug use, HIV stigma, HIV disclosure, and depression will be associated with likelihood of attrition. If this hypothesis is supported, they will suggest ways that clinical research and practice could be modified to minimize attrition in future studies. Dr. Kiriazova spent her 2009-2010 Humphrey Fellowship in HIV/AIDS Policy and Prevention at Emory University.

Dutch Researcher Uses DISCA Award To Explore Prevention Research

Harrie Jonkman, Dr.S., Verwey-Jonker Institute, The Netherlands, has received a NIDA Distinguished International Scientist Collaboration Award (DISCA) to extend his collaboration with J. David Hawkins, Ph.D., University of Washington in Seattle. With previous support from the NIDA IP and the Dutch Organisation for Health Research and Development (ZonMw) through the U.S.–Netherlands Binational Agreement, the two have collaborated on implementing and assessing the outcomes of the Communities That Care prevention intervention in 10 Dutch and 12 U.S. cities. During the DISCA exchange, Drs. Jonkman and Hawkins will explore three topics: (1) sharing experiences on research assessing the impact of prevention programs; (2) comparing implementation research in both countries; and (3) preparing a multinational, longitudinal research plan to investigate alcohol use and other problem behaviors in adolescents that would be modeled on a University of Washington in Seattle program with Australian researchers. Dr. Jonkman’s research proposal would translate, cognitively pretest, pilot, and develop the capacity in six

European nations (Austria, Croatia, Cyprus, Germany, The Netherlands, and United Kingdom) to standardize data collection and sampling procedures and examine the effects of school, state, and national policies on drug use by youth. Dr. Jonkman also is completing a book on prevention and impact research.

South African Investigator Receives International Traveling Fellowship Award

The World Health Organization, NIDA, and the College on Problems of Drug Dependence (CPDD) have selected the 2012 International Traveling Fellow. Hetta Gouse, Ph.D., University of Cape Town, South Africa, received the award based on her research into the investigation of the effects of methamphetamine in a South African sample using detailed neuropsychological testing and a functional magnetic resonance imaging reward task. The award enabled Dr. Gouse to make a 1-week research visit with a NIDA-supported research grantee and participate in the NIDA International Forum and the CPDD Annual Scientific Meeting in June 2012. Dr. Gouse is an early-career investigator who is building an innovative program of research to examine the clinical relevance of neuropsychological function in substance abuse treatment outcomes as well as HIV prevention and care. She visited Adam W. Carrico, Ph.D., and others in the Department of Psychiatry, University of California, San Francisco, where they discussed potential collaborative research to examine the clinical relevance of neuropsychological function for HIV prevention among methamphetamine users.

Former NIDA Humphrey Fellow Organizes Meeting About Drug Courts in Brazil

Former NIDA Hubert H. Humphrey Fellow Mario Sobrinho, Public Ministry of São Paulo, Brazil, helped organize a 2-day seminar on therapeutic justice for government and police officials, prosecutors, psychologists, and psychiatrists. Dr. Sobrinho worked with officials at the U.S. Consulate in São Paulo as part of a series of meetings organized to discuss ways to improve the performance of government in relation to drugs. Secretary of Justice Eloisa Alvarez de Souza opened the event at the São Paulo State Prosecutor's Office by stating that drugs have become a principal problem for the state and officials do not know how to cope with the problem. Ronaldo Laranjeira, M.D., Ph.D., a psychiatrist at the Federal University of São Paulo, attributed the increasing number of addicts in Brazil to "a phenomenal network for narcotics distribution and cheap prices." Tara Kunkel, management consultant at the National Center for State Courts in Virginia, told participants that drug courts separate nonviolent drug users from the criminal system by offering drug treatment instead of incarceration. She added that more than 2,400 drug courts function in the United States. Dr. Sobrinho focused on drug courts during his Hubert H. Humphrey Fellowship professional affiliation at the National Center for State Courts. The meeting was held May 17–18, 2012, in São Paulo.

NIDA Humphrey Fellows Celebrate With Graduation Ceremonies and Retreat

NIDA Hubert H. Humphrey Drug Abuse Research Fellows at Virginia Commonwealth University (VCU) and Johns Hopkins University (JHU) marked the end of their fellowships at the Humphrey Fellowship Year-End Retreat, May 6–8, 2012, in Rocky Gap, Maryland. The retreat gathered all 204 Hubert H. Humphrey Fellows who had participated in 1 of the 18 host university programs. Brian Morales of the U.S. Department of State Bureau of International Narcotics and Law Enforcement encouraged the substance abuse fellows to put the networking skills they learned as Hubert H. Humphrey Fellows to use in making connections when they returned home. Fellows received certificates signed by President Barak Obama and Secretary of State Hilary Clinton. Penny Jessop, M.P.H., the Tulane University Hubert H. Humphrey Fellowships coordinator since 1979, was honored on her retirement. IP Associate Director Dale Weiss and Fellowships Administrator

Lisa Jordre of IQ Solutions attended the year-end retreat as well as graduation ceremonies at the VCU and JHU campuses. Ms. Weiss spoke at the May 22 JHU ceremony, telling the fellows that NIDA appreciates the difficulty of completing a Hubert H. Humphrey Fellowship, and looks forward to the fellows' contributions to the international drug abuse research community.

Travel Support

NIDA International Program Supports AIDS Treatment as Prevention Workshop Participants

The NIDA IP supported the participation of scientists from Argentina, Peru, and South Africa at the 2nd International HIV Treatment as Prevention Workshop, which was held April 22–25, 2012, in Vancouver, Canada. The meeting was organized by Julio S.G. Montaner, M.D., University of British Columbia, and featured a keynote address by U.S. Global AIDS Coordinator Ambassador Eric Goosby about the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) perspective on treatment as prevention. NIDA Director Nora Volkow, M.D., spoke at an opening plenary session roundtable discussion that also featured representatives from the National Institute of Allergy and Infectious Diseases, Joint United Nations Programme on HIV/AIDS, World Health Organization, and the French Agence Nationale de Recherche sur le Sida. The IP supported Stephen D. Lawn, M.D., South Africa, Maria Eugenia Socias, M.D., Argentina, and Carlos F. Caceres, M.D., Ph.D., Peru, who joined academic, policy, industry, and community representatives at the meeting. Participants reviewed emerging data and identified priority areas for research and action related to the impact of combination antiretroviral therapy (ART) use among HIV-infected individuals on the transmission of HIV infection. Dr. Lawn, who works at the Desmond Tutu HIV Centre at the University of Cape Town, discussed the impact of ART on tuberculosis control during an oral presentation. Dr. Socias, who works at the infectious diseases unit of the Hospital Juan A. Fernández in Buenos Aires, discussed a pilot study investigating provider-initiated HIV testing on hospital admission during an oral presentation session on initial results of Small Business Technology Transfer outcomes.

NIDA Awards Tuition Waiver to Dutch Summer Institute

Thanks to a tuition waiver provided by the NIDA International Program, Allison Valentine Schlosser, a doctoral student in medical anthropology at Case Western Reserve University, attended the Dutch Summer Institute on Alcohol, Drugs and Addiction. Ms. Schlosser began conducting addiction research in 2005 as a social worker. She hopes to conduct international comparative addiction research integrating anthropological and health services research when she completes her degree. The University of Amsterdam sponsors the 2-week, multidisciplinary institute. The 2012 course focused on the intersection of policy models, prevention, evidence-based treatment, and bridging the gap between research, treatment practice, and policy. Dennis McCarty, Ph.D., Oregon Health & Science University, is academic director of the Dutch Summer Institute.

NIDA Supports Latin American Scientists at Regional Workshop

The NIDA IP supported three participants in a Regional Grant Writing and Scientific Peer Review Workshop that was held June 27–29, 2012, in Bogotá, Colombia. The workshop, which was organized by U.S. and Latin American officials, provided guidance on identifying training and funding opportunities, developing grant applications, establishing collaborations, the grant review process, and understanding confidentiality and conflict of interest. Ivan Montoya, M.D., DPMCD, was one of the U.S. faculty members and made several presentations during the meeting. The NIDA-supported participants included 2001-2002 NIDA Humphrey Fellow Ines Bustamante, Ph.D., Peru; Franco Romani, M.D., Peru; and Maria Isabel Roldos, D.Ph., Ecuador. In addition to NIDA,

the workshop was supported by the U.S. Department of Health and Human Services; NIH; Fogarty International Center; National Cancer Institute; National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Disease; *Eunice Kennedy Shriver* National Institute of Child Health and Human Development; U.S. Centers for Disease Control and Prevention; Pan American Health Organization; Colombian Ministry of Health and Social Protection; and the Colombian National Institute of Health.

CTN INVEST Fellows

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) jointly offer fellowships to non-U.S. scientists. The international researcher works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention. To date, nine scientists have completed their fellowships and have successfully continued their research in their countries; four are currently working on their projects and one will start by the end of 2012.

On June 25, 2012, Drs. Annette Sogaard Nielsen and Kjeld Andersen, from the Drug and Alcohol Treatment Center, and the University of Southern Denmark, visited NIDA and met with CCTN staff to discuss their current projects and opportunities for collaboration.

Other Activities

Dr. Cheryl Anne Boyce participated in the 30th International Congress of Psychology in Capetown, South Africa held July 22-27, 2012 and presented at the invited Translational Policy Research Lecture on "International Research on Addiction and Mental Health: Fostering Collaborations."

Dr. Ivan Montoya, DPMCDA, participated in a trans-NIH "Grant Writing and Peer Review" workshop that took place in Bogota, Colombia on June 27-29, 2012. The workshop was organized by the Ministry of Health of Colombia, Pan American Health Organization, and several NIH Institutes including NCI, NIAID, NHLBI, NICHD, Fogarty International Center, and NIDA. The participants included scientists from El Salvador, Guatemala, Costa Rica, Panama, Venezuela, Peru, Ecuador, and Colombia.

Dr. Wilson M. Compton, Director, DESPR, presented "Unemployment and Substance Outcomes in the United States: Changes During an Economic Recession" at the 6th Albatros Days International Congress of Addictology, Paris, France, June 7, 2012.

Dr. Eve Reider, DESPR, was invited by the Drug Prevention and Health Branch of the United Nations Office on Drugs and Crime to attend a meeting and provide technical consultation for developing International Standards on Drug Use Prevention. This meeting was held at UNODC Headquarters in Vienna, Austria, June 12-13, 2012.

Dr. Jonathan Pollock, DBNBR, attended the Cellular Biology Addiction Meeting at the University of Pompeu Fabra, Barcelona, Spain, in collaboration with Cold Spring Harbor Laboratory, July 19-23 where he gave a lecture on International Funding Opportunities for Substance Abuse Research.

MEETINGS/CONFERENCES

The **College on Problems of Drug Dependence (CPDD) Annual Meeting** was held June 9-14, 2012 in Palm Springs, CA. As a part of this meeting OSPC coordinated a **NIDA Grant-Writing and Career Workshop** and a **NIDA/CPDD Training Networking Event**. Drs. David Shurtleff, Eliane Lazar-Wesley, Linda Cottler (University of Florida), and Frances Levin (Columbia University) provided information on NIDA research priorities, funding opportunities, review procedures, and training on grantsmanship and other career-building skills. The Training Networking Event provided a forum for training directors, trainees, and NIDA staff to learn about the different training programs that NIDA supports and for trainees to find future training and employment opportunities.

Twenty **Director's Travel Awards** were given to National Research Service Award (NRSA) trainees and fellows and Diversity Supplement recipients to present at this year's CPDD meeting and attend the NIDA Grant-Writing and Career Workshop. In addition, NIDA's Women & Sex/Gender Differences Research Program gave 28 **Women & Gender Junior Investigator Travel Awards** consisting of \$750 travel support to first author junior investigators who make presentations on the topic of women and/or sex/gender differences. These travel awards have been made annually beginning in 1999, and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. To further promote research in this field, NIDA published a mini-program book, Focus on Women & Sex/Gender Differences, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. The program also contains a listing of all awardees since 1999, information about the Women & Gender Junior Investigator Travel Awardees presentations, announcement of the travel award program for CPDD 2013, and information on current NIDA funding opportunity announcements in this area. These efforts were led by Dr. Samia Noursi with the support of Drs. Cora Lee Wetherington, Lynda Erinoff and Joe Frascella.

The National Institute on Drug Abuse (NIDA) organized a program at the **2012 American Psychological Association (APA) Annual Meeting** in Orlando, Florida, August 2-5. NIDA staff and grantees participated in a number of sessions on a wide range of topics related to addiction research, such as symposia on increasing implementation of evidence-based interventions by computerizing treatments and how innovations in neuroscience can spur innovations for adolescent drug abuse treatment. NIDA also co-sponsored an Early Career Investigator Poster Session with APA's Divisions 28 and 50 and the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as part of the two Divisions' Social Hour.

DCNBR NIDA hosted the **ACYF Neuroscience and Child Maltreatment Expert Panel Meeting** on May 3-4, 2012 in Rockville, MD convened by Commissioner Bryan Samuels at the Administration on Children, Youth and Families (ACYF) DHHS in collaboration with NIDA, NICHD, and the Robert Wood Johnson Foundation.

NIDA's Child and Adolescent Workgroup (CAWG) facilitated an interagency visit with staff from NIDA, NIAAA, DHHS Administration on Children, Youth and Families and White House Office of National Drug Control Policy (ONDCP) White House Office of National Drug Control Policy (ONDCP) to NIDA's Intramural Research Program (IRP), hosted in collaboration with Dr. Marilyn Huestis (NIDA IRP) and Dr. Anto Bonci (Scientific Director, NIDA IRP) on May 9, 2012.

NIDA DCNBR funded travel through the Division logistics contract for seven students to participate in the **Young Investigators Special Symposia at the International Behavioral Neuroscience Society Annual Meeting** which was held in Kailua-Kona, Hawaii, June 5-10, 2012.

On April 23-24, 2012, The "**NIDA Special Populations Research Development Seminar Series**" workshop was convened in Bethesda, Maryland for new investigators interested in becoming funded through NIDA and the NIH. Chaired by Flair Lindsey, Program Analyst, Special Populations Office, during the two-day session new investigators met with funded NIDA investigators and senior NIDA program officials, received feedback on research concept papers and learned about the NIH grants submission and review processes.

The inaugural "**NIDA SPO Translational Research Speaker Series: Promoting Diversity and Moving Toward Health Equity**," which was centered on the theme of HIV and Drug Abuse from Lab to Clinic, convened on Thursday, June 21, 2012 at the Neuroscience Center in Rockville, Maryland. Dr. Benjamin Chen of Mount Sinai School of Medicine, the first guest speaker, presented on HIV and Drug Abuse from Lab to Clinic.

NIDA's Special Populations Office convened its fifth annual "**Addiction Research Training Institute**," at the Morehouse School of Medicine in Atlanta, Georgia, July 16-19, 2012. The four-day workshop provided grants writing, research training, and valuable mentoring to early career investigators interested in research careers in substance abuse and HIV/AIDS. Pamela Goodlow, Public Health Analyst, Special Populations Office and Dionne Jones, Deputy, Services Research Branch, DESPR, participated in the workshop.

Flair Lindsey, Special Populations Office, presented on NIDA/NIH research training and funding opportunities before early career professionals and graduate students at the 3rd Annual Association of Black Psychologists (ABPsi) Writer's Bootcamp on July 16 during the ABPsi 44th Annual Convention at the Westin Hotel in Los Angeles, California.

Dr. Susan Weiss, Acting Director, OSPC, gave the keynote address, entitled "The Science of Drug Addiction: Implications for Treatment" at the Chief Resident Immersion Training/Fellow Immersion Training Program in Addiction Medicine May 2, 2012, in Cape Cod, Massachusetts.

Dr. Susan Weiss gave a lecture entitled "NIDA Priorities and How to Get Beyond the K: Early Career Funding Opportunities and Keys to Success" at the American Academy of Child and Adolescent Psychiatry (AACAP) K-12 retreat on June 8, 2012, in Palm Springs, California.

Dr. Susan Weiss gave a presentation: "Overview of Opiates" at the ONDCP Interagency Meeting on Heroin Abuse on June 28, 2012, in Washington, D.C.

Dr. Ruben Baler, OSPC, gave a lecture entitled "Where do addictions come from?" at the 17th Annual Employee Assistance Program (EAPA) Regional Spring Conference on April 19, 2012, in Richmond, Virginia.

Dr. Da-Yu Wu, DBNBR, represented NIDA at the Common Fund Single Cell Analysis Program and participated in completing the first phase funding plan for the three initiatives of this program. Dr. Da-Yu Wu is participating in the subgroup to draft the second phase RFA.

Dr. Da-Yu Wu was invited to present a talk on NIDA's programmatic interest and funding opportunities on cell and molecular research of substance abuse and addiction at the 18th International Neuroscience and Biological Psychiatry Conference held at New Orleans, LA from June 22 to 24.

Dr. John Satterlee, DBNBR, planned and participated in NIH Roadmap Epigenomics Program Investigator's meeting, May 14-15, 2012 Rockville, MD.

Dr. John Satterlee attended trans-NIH GTEx meeting, Rockville, MD, June 13-14, 2012.

Dr. Rao Rapaka, DBNBR, organized a Minisymposium on the "Recent Advances in X-Ray Crystallographic Studies of the Opiate Receptors". The symposium took place July 13 at Masur Auditorium, NIH Campus, Bethesda, MD.

Dr. Rao Rapaka organized a conference on Spice and Bath Salts: A Discussion on June 26, 2012, at NSC. Drs. Brian Thomas and Jenny Wiley were the presenters.

Dr. Vishnudutt Purohit and Dr. David Thomas, DBNBR, organized a symposium on Gender/Sex Differences in Pain and Opioid Analgesia at the American Pain Society's 31st Annual Scientific Meeting, May 16-19, 2012 in Honolulu, HI. The following topics were discussed by three speakers at the meeting: 1) An overview of human research findings related to sex differences and hormonal influences on pain and analgesia (Dr. Roger B. Fillingim, University of Florida); 2) Role of PAG mu receptors in sexually dimorphic action of morphine (Dr. Anne Z. Murphy, Georgia State University); and 3) Sex-related differences in antinociception and antihyperalgesia produced by activation of opioid receptor like-1 receptor (Dr. Sukhbir S. Mokha, Meharry Medical College).

Dr. Vishnudutt Purohit and Dr. Rao Rapaka organized a symposium on Role of Cannabinoid System in Nicotine Addiction at the International Cannabinoid Research Society (ICRS) meeting, Freiburg, Germany, July 22-27, 2012. The following topics were covered by four speakers at the meeting: 1) Proteomics of Nicotine-Dependent Brain (Dr. Sherry Niessen, Scripps Research Institute); 2) FAAH Inhibitors as Potential Leads for Smoking Cessation (Dr. Daniele Piomelli, University of California); 3) Modulating Nicotine Reward and Dependence through the Endogenous Cannabinoid System (Dr. Aron Lichtman, Virginia Commonwealth University); and 4) Targeting the CB1 Receptor to Treat Nicotine Addiction (Dr. Dr. Raphael Maldonado, Barcelona, Spain)

Dr. David Thomas, DBNBR, served as the discussant at a session titled, “Virtual Reality and Pain Management” at the 31st Annual Scientific Meeting of the American Pain Society, May 17, 2012, Honolulu, HI.

Dr. David Thomas served as a moderator in at a session titled, “Gender/Sex Differences in Pain and Opioid Analgesia” at the 31st Annual Scientific Meeting of the American Pain Society, May 17th, 2012, Honolulu, HI.

Dr. David Thomas chaired a session titled “Novel Approaches in Opioid Analgesic Development and Use” at the 7th Annual Pain Consortium Symposium on Advances in Pain Research, held at Natcher Auditorium, May 29th and 30th, 2012, Bethesda, MD.

Dr. David Thomas chaired a session titled “The Basic Science of Pain” at the FDA “Assessment of Analgesic Treatment of Chronic Pain: A Scientific Workshop” held at Natcher Auditorium, May 30th and 31st, 2012, Bethesda, MD.

Dr. David Thomas chaired the NIH Pain Consortium’s Centers of Excellence in Pain Education Kick-Off Meeting July 10th and 11th, 2012 in Bethesda, MD.

Dr. David Thomas made a presentation titled: Chronic Pain: Clinical issues and NIH Research Support, to the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Advisory Board on Medical Rehabilitation Research, May, 4, 2012 in Bethesda MD.

Dr. David Thomas made a presentation on the NIH grant funding process in a session titled “Successful Grant Writing and Funding Opportunities in Pain Research” at the 31st Annual Scientific Meeting of the American Pain Society, May 18th, 2012, Honolulu, HI.

Dr. Samia Noursi, DBNBR and Deputy Coordinator, Women and Sex/Gender Differences Research and Dr. Dionne, Jones, DESPR, chaired a guided discussion at the Johns Hopkins Women’s Health Research Group 5th Annual Spring Symposium, May 21, 2012. The discussion included information on federal efforts in funding opportunities focused on women’s health.

Dr. Samia Noursi presented a poster at the Johns Hopkins Women’s Health Research Group 5th Annual Spring Symposium, May 21, 2012. The poster covered highlights of violence against women research conducted at NIH.

Dr. Samia Noursi presented at a breakout session entitled “Women’s Health Research at the National Institutes of Health” at the SAMHSA 5th National Conference on Behavioral Health for Women and Girls, July 17-19, 2012 in San Diego, CA.

Dr. Cora Lee Wetherington, DBNBR and Women and Sex/Gender Differences Research Coordinator, was an invited participant in the Working Conference on Sex/Gender and the Use of Psychoactive Substances held at the University of Michigan, May 22-23.

Dr. Cora Lee Wetherington gave the invited luncheon keynote address, “Sex/Gender Differences in Drug Abuse & Implications for Gender-Focused Treatment,” 2012 International Women’s Fifth Meeting and Conference, Palm Springs, CA, June 8, 2012.

Dr. Cora Lee Wetherington chaired, along with Dr. Wendy Lynch (University of Virginia), the symposium “Triggers, Treatments & Sex Differences in Models of Relapse and Translational Implications,” at the American Psychological Association annual meeting held in Orlando, FL, August 2-5, 2012. Speakers were Ronald See (Medical University of South Carolina), Marilyn Carroll, University of Minnesota, Wendy Lynch, University of Virginia and Rajita Sinha, Yale University.

Dr. Minda Lynch, DBNBR, co-organized and co-chaired a combined Common Fund/OppNet grantees meeting in June, with Dr. John King from NIA. Investigators supported by NIH’s Common Fund “Science of Behavior Change” initiative and NIH’s Opportunity Network for Basic Behavioral and Social Science Research “Basic Mechanisms Influencing Behavioral Maintenance” RFA met to discuss overlapping science and discoveries in at the forefront of behavioral change and maintaining healthy behavior.

In July 2012, Dr. Minda Lynch co-organized a NIH Opportunity Network for Basic Behavioral and Social Science Research meeting of experts in the area of Animal Behavioral Models. Along with Dr. Deb Olster from NIH’s Office of Behavioral and Social Science Research, over 20 experts discussed challenges to modeling complex human behavioral and social processes, and barriers to translation from animal to human research.

Dr. Joe Frascella, Director, DCNBR, participated in the University of Texas at El Paso first annual conference entitled “U.S. – Mexico Border Issues. He participated in a panel designed to highlight federal perspectives on drug use along the U.S. – Mexico border and presented highlights of NIDA’s related research programs and also gave a presentation on NIH grant writing. The conference was held at the University of Texas at El Paso May 22 – 23, 2012.

Dr. Joe Frascella participated in the Interdisciplinary Research Training Institute on Hispanic Drug Abuse at the University of Southern California and gave a presentation on grant writing for the fellows – June 19, 2012.

Drs. Jim Bjork and Joe Frascella, DCNBR, co-chaired Dys-Connectivity of the Brain in Addiction and Pain, a symposium presented at the American Psychiatric Association Annual Meeting-Philadelphia, PA; May 7, 2012.

Dr. Yu (Woody) Lin, DCNBR, co-chaired with Dr. Linda Chang (U. Hawaii) a symposium entitled “NeuroImmune Pharmacology Research in Hawaii” at the 18th annual scientific conference of the Society on NeuroImmune Pharmacology in Honolulu, Hawaii on April 24 -- 28, 2012.

Dr. Steven Grant, DCNBR, represented NIDA at the 9th International Symposium on Functional Neuroreceptor Mapping of the Living Brain (NRM12) in Baltimore, Maryland on August 9 -11, 2012.

Dr. Cheryl Anne Boyce, DCNBR, presented at the Annual Convention of the American Psychological Association in Orlando, FL on “Building Federal and Research Careers in Psychology” at the American Psychological Association of Graduate Students (APAGS) morning session co-sponsored by the Clinical Psychology of Ethnic Minorities (APA Division 12, Section VI).

Also at the Annual Convention of the American Psychological Association Drs. Cheryl Anne Boyce (NIDA) and Sarah Lynne Landsman, (University of Florida) co-chaired the symposium entitled “Innovations in Neuroscience to Innovations for Adolescent Drug Abuse Treatment” highlighting grantees from the NIDA funded funding opportunities in this area.

Dr. Karen Sirocco, DCNBR, and Dr. Mariela Shirley, NIAAA, organized a joint session on “Stimulant Medication, ADHD, and Substance Use Outcomes.” at the Annual Convention of the American Psychological Association in Orlando, FL in August 2012.

Dr. Cheryl Anne Boyce organized two remote symposium sessions with assistance from NIDA IRMB for participants attending the Society for the Psychological Study of Ethnic Minority Issues (Division 45): Second Biennial Conference held on May 24-26, 2012 at the University of Michigan in Ann Arbor. On Thursday, May 24, 2012 the symposium on “Early Career Research Funding Opportunities for Behavioral Scientists” included Dr. Cheryl Anne Boyce, Lauren Hill (NIMH), Dr. Mariela Shirley (NIAAA), Dr. Valerie Maholmes, (NICHD), Dr. Alfiee Breland Noble (Georgetown University) and Ms. Ericka Wells (NIDA Grants Management). On May 25, 2012, the panel on “Research Priorities Opportunities for Health Disparities” included Dr. Cheryl Anne Boyce, Dr. Alfiee Breland Noble (Georgetown University) and Ms. Ericka Wells (NIDA Grants Management).

On Tuesday, May 29th at the Johns Hopkins Bloomberg School of Public Health in Baltimore, MD, Dr. Cheryl Anne Boyce presented on “Career Trajectories at NIH” for underrepresented students from across the nation interested in public health as part of the NIH panel during the orientation for the CDC funded Maternal Child Health Careers / Research Initiatives for Student Enhancement-Undergraduate Program (MCHC/RISE-UP) and Ferguson Fellowship Programs.

On June 5, 2012 in Washington, DC, Dr. Cheryl Anne Boyce attended the DHHS Office of Adolescent Health’s Advancing the Prevention of Mental, Emotional, and Behavioral Disorders in Adolescence: A Science to Service Symposium which was designed around the framework of the 2009 Institute of Medicine (IOM) report, Preventing Mental, Emotional, and Behavioral Disorders in Young People: Progress and Possibilities.

Dr. Cheryl Anne Boyce and Dr. Mariela Shirley (NIAAA) attended the National Academy of Sciences (NAS) meeting Seeking Solutions: Maximizing American Talent by Advancing Women of Color in Academia Conference on June 7-8, 2012 in Washington, DC.

On June 26, 2012 in Baltimore, MD, Dr. Cheryl Anne Boyce presented an invited lecture co-sponsored by the Neurobehavioral Teratology Society (NBTS) at the Teratology Society (TS) 52nd Annual Meeting on “Addiction: A Developmental Disorder” to provide an NIH perspective on the effects of prenatal methamphetamine. She also co-chaired the joint TS/NBTS symposium with Gregg D. Stanwood (Vanderbilt University) on the “Effects of Prenatal Methamphetamine: Clinical, Preclinical, and Translation Aspects” which included presentations by NIDA and NIH grantees Dr. Lynne Smith (UCLA), Dr. Linda Chang (University of Hawaii), Dr. Charles V. Vorhees, (Cincinnati Children’s Hospital Medical Center), and Peter G. Wells (University of Toronto).

Dr. Cheryl Anne Boyce chaired the 2012 NIDA Summer Intern Panel on Paths and Opportunities for a Science Career organized in collaboration with Montrue Nelson (OM/NIDA) on June 28, 2012. Drs. Will Aklin (BITB/DCNBR), Karen Sirocco (BBDB/DCNBR), James Bjork (CNB/DCNBR) and special guest James Griffin (NICHD) participated on the panel to share their personal research career paths and advice for building a career in health science.

Dr. Cheryl Anne Boyce participated in the International Conference on Health in the African Diaspora - ICHAD 2012, July 5-8, 2012 in Baltimore, MD along with Dr. Lula Beatty, SPO.

Dr. Cheryl Anne Boyce presented on “How to Give a Dynamic Presentation” on July 9, 2012 in Washington, D.C. at the American Psychological Association Minority Fellowship Program Psychology Summer Institute (PSI) which provides educational, professional development and mentoring experiences to advanced doctoral students of psychology and psychologists who are in the early stage of their careers.

Dr. Cheryl Anne Boyce and Dr. Eve Reider (DESPR/NIDA) attended the public open session of the first meeting of the Institute of Medicine Board on Children, Youth and Families Committee on Child Maltreatment Research, Policy, and Practice for the Next Decade on July 17, 2012 in Washington, DC. This committee will provide recommendations for research priorities for the next decade, including new areas of research that should be funded by public and private agencies and suggestions regarding fields that are no longer a priority for funding.

Dr. Karen Sirocco, DCNBR and Dr. Mariela Shirley, NIAAA, attended several Networking receptions to facilitate interactions between NIH and the students attending the Quantitative Training for Underrepresented Groups (QTUG) 9th Annual Conference in Orlando, FL held July 29 -August 1, 2012.

Dr. Lisa Onken, DCNBR, gave a presentation entitled, “Redefining the Vision for Clinical Science,” as part of a panel, “Redefining Clinical Science Training: Progress Report on the Delaware Project,” on May 24th at the Association for Psychological Science annual convention in Chicago, Illinois.

Dr. Lisa Onken gave a presentation on NIDA, “Behavioral Economics and Research Priorities at NIDA,” at the June 5-6, 2012 meeting of the Penn CMU Roybal P30 Center in Behavioral Economics and Health in Philadelphia, Pennsylvania.

Dr. Lisa Onken moderated a panel, “Science of Behavior Change III” at the NIH Science of Behavior Change and OppNet Annual Meeting of Investigators on June 20-21, 2012 in Rockville, MD.

Drs. Lisa Onken and Will Aklin chaired a symposium, “Increasing implementability by computerizing treatments - Where, when, and for whom?” at the American Psychological Association meeting in Orlando, Florida, on August 2, 2012. At the symposium, Dr. Kathleen Carroll discussed the potential benefits and risks of computerized treatment for addiction.” Dr. Lisa Marsch gave a presentation on technology-based treatments for addiction and models for implementation with various populations and in various settings. Dr. Steve Ondersma talked about screening and brief intervention for drug abuse in pregnant women. Dr. Michelle Craske gave a presentation on new directions in computerizing treatments for anxiety disorders.

Dr. Lisa Onken gave a presentation entitled, “The NIH Stage Model of Intervention Development: Going back to move forward” as part of a panel on “Models of psychotherapy development: Putting contextual behavioral science strategies in their larger context,” at the Association for Contextual Behavioral Science annual meeting in Bethesda, Maryland, July 23-25, 2012.

Dr. Wilson M. Compton, Director, DESPR, continues to participate in the White House Office of National Drug Control Policy Interagency Workgroup on a continuing basis.

Dr. Wilson M. Compton continues to participate in two interagency workgroups for the Department of Health and Human Services: The Behavioral Health Coordinating Committee (particularly the Prescription Drug Abuse Subcommittee) and the Tobacco Control Steering Committee (including co-chairing the Data/Research Subcommittee) on a continuing basis. As part of these efforts, Dr. Compton chaired a panel at a meeting jointly sponsored by FDA, NIDA and CDC on the potential for expanded access to naloxone for opioid overdose prevention.

Dr. Wilson M. Compton continues to participate in the NIH Opportunity Network for Basic Behavioral and Social Science Research (OppNet) as a member of the Steering Committee and as an alternate for the Coordinating Committee on a continuing basis.

Dr. Wilson M. Compton continues to participate in the DSM-V Task Force and DSM-V Substance Use Disorders Workgroup meetings on a continuing basis.

Dr. Wilson M. Compton presented Understanding Addiction as a Brain Disease: Implications for the Drug-Crime Nexus at the Maryland Public Defenders Conference, Catonsville, Maryland, May 24, 2012.

Dr. Wilson M. Compton presented in the new investigators satellite program and then co-chaired and presented in a panel on comorbidity at the 52nd NCDEU: An Annual Meeting Sponsored by the American Society of Clinical Psychopharmacology, Scottsdale, Arizona, May 28-30, 2012.

Dr. Wilson M. Compton presented on Drugs, Delinquency and Prevention: A Health-based Approach to the Committee on Law and Justice, National Academies of Science, May 25, 2012 and Prescription Drug Abuse: It’s Not What the Doctor Ordered the Board on Health Sciences Policy, Institute of Medicine of the National Academies, June 21, 2012, Washington, District of Columbia.

Drs. Wilson M. Compton and Elizabeth Robertson, DESPR, presented on “What is the Extent of the Prescription Drug Abuse Problem?” and “What are the Key Elements of Drug Prevention?” respectively in the Office of National Drug Control Policy sponsored webinar called “It’s Epidemic:

Prescription Drug Abuse and How to Prevent It” to the Department of Agriculture Cooperative Extension Service, May 23, 2012.

Dr. Wilson M. Compton presented in a panel on driving under the influence of drugs and served as discussant in a panel on the Community Youth Development Study at the 2012 Society for Prevention Research Conference, May 30-June 1, 2012.

Dr. Wilson M. Compton presented “Prescription Drug Abuse: It’s Not What the Doctor Ordered” at the Harold Rogers Prescription Drug Monitoring Program National Meeting, Washington, District of Columbia, June 4, 2012.

Dr. Wilson M. Compton presented drug abuse health services research at the UCLA Center for Advancing Longitudinal Drug Abuse Research (CALDAR) Summer Institute, August 13, 2012, Los Angeles, California.

Drs. Elizabeth Robertson, Eve Reider and Wilson Compton, DESPR, were members of a program planning committee for the DHHS multi-agency meeting “Domestic and International Adoption: Strategies to Improve Health Outcomes for Youth and their Families” that was held August 29-30, 2012 at SAMHSA. Drs. Robertson and Reider organized the panel on “Behavioral Health Services for Adopted Youth and Their Families.”

Dr. Redonna K. Chandler, DESPR, presented on “Addiction, the Brain, and Evidence Based Treatment” at the National Institute of Justice “Real World” Seminar Series, Washington DC, March 5, 2012.

Dr. Redonna K. Chandler presented a plenary on “Addressing Addiction as a Chronic Disease: What Does Research Tell Us?” at the annual meeting of the Baltimore Buprenorphine Initiative, Baltimore, MD, May 17, 2012.

Dr. Redonna K. Chandler presented “Evidence Based Approaches to Address Drug Abuse in Criminal Justice Settings at the annual training event for the Maryland Public Defenders, Baltimore, MD, May 24, 2012.

Dr. Redonna K. Chandler presented a plenary on “Addressing Addiction as a Chronic Disease: What Does Research Tell us About Recovery?” at the SAMHSA Satellite Session “Exploring the Dimensions of Recovery and Recovery Support Services” of the 74th Annual Scientific Meeting of the CPDD, Palm Beach, CA, June 9, 2012.

Dr. Redonna K. Chandler is chairing an NIH workgroup exploring the role of community engagement projects within the NIH Clinical and Translational Science Awards.

Drs. Redonna Chandler, Shoshana Kahana, Will Aklin, Bennett Fletcher and Dionne Jones, DESPR, presented a poster in July, 2012 entitled “Data harmonization efforts across the Seek, Test, Treat and Retain paradigm at the National Institute on Drug Abuse” at the XIX International AIDS Conference, Washington, DC.

Dr. Harold Perl, DESPR, organized and chaired a panel entitled "Targeted Contingency Management and Skillful Motivational Interviewing: 2 Evidence-Based Methods to Reduce Substance Abuse Problems in Your Caseload" at the 18th National TASC Conference on Drugs, Crime and Reentry in Baltimore, MD on March 22, 2012. Dr. Perl also gave a talk entitled "NIDA's Clinical Trials Network: Science, Practice & Reality" as part of that panel.

Dr. Harold Perl organized and co-taught a Technical Assistance workshop entitled "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application & Improve Your Chance at Success" at the 120th Annual Convention of the American Psychological Association, in Orlando, FL on August 1, 2012.

Dr. Harold Perl gave the presentation entitled "STAGE-12: A combined group/individual intervention to treat stimulant abuse" as part of a symposium entitled "Implications of NIDA CTN Behavioral Research for Evidenced Based Practice" at the 120th Annual Convention of the American Psychological Association, in Orlando, FL on August 3, 2012.

Dr. Dionne Jones, DESPR, made a presentation on "Research Initiatives and Activities in DESPR/NIDA" at the NIDA Special Populations Research Development Seminar Series Workshop on April 23, 2012.

Lori Ducharme, DESPR, organized a panel and presented early findings from the CJDATS medication assisted treatment implementation trial at the 2012 meetings of the American Association for the Treatment of Opioid Dependence (AATOD), Las Vegas.

The US Army Medical Research and Materiel Command (USAMRMC) Clinical and Rehabilitative Medicine Research Program (CRM RP) has invited Richard Denisco M.D., DESPR, to serve as a member of the Pain Scientific Steering Committee (SSC) from 2012 to 2014.

Richard Denisco organized a panel and presented new findings on Hepatitis C Virus testing and treatment in Methadone Maintenance Clinics at the 2012 meetings of the American Association for the Treatment of Opioid Dependence (AATOD), Las Vegas on April 25, 2012.

Dr. Shoshana Y. Kahana, DESPR, was a discussant on a panel entitled "Extending the reach of behavioral treatments for drug-abusing populations through mobile-based interventions: Are we overselling a bill of goods?" in June 2012 at 74th Annual Meeting - College on Problems of Drug Dependence, Palm Springs, CA.

Dr. Shoshana Y. Kahana served as moderator for a panel on Substance use and ART adherence presented at the 7th International Conference on HIV Treatment Adherence, Miami, FL in June 2012.

Dr. Eve Reider, DESPR, represents NIDA on a Federal Interagency Committee on Traumatic Brain Injury and attended a meeting that was held March 23, 2012 at the Westin Hotel, Alexandria, Virginia.

Dr. Eve Reider was invited by Dr. Alan Guttmacher, Director, NICHD, and Dr. Thomas Insel, Director, NIMH, to participate in a meeting with Commissioner Bryan Samuels and Deputy Commissioner Clare Anderson, ACYF, on April 4, 2012. The purpose of the meeting was to discuss current collaborations and future opportunities between ACYF, NICHD, NIMH and NIDA, including: 1) Substance Abuse, Parenting Capacities and Child Functioning Interventions, a) Regional Partnership Grants, b) Family Supportive Housing Grants, 2) HHS High Priority Goal – Addressing Trauma in Children Known to the Child Welfare System, and 3) Applying Neuroscience to the Child Welfare System.

Dr. Eve Reider presented on “Substance Use Disorders in the Military: The NIDA Perspective” and served as discussant for the symposium “Understanding and Reducing Substance Use in the U.S. Military” which was held May 31, 2012 at the 20th Annual Meeting for the Society for Prevention Research in Washington D.C..

Dr. Eve Reider was invited by Military Operational Medicine Research Program (MOMRP)/Joint Program Committee for Military Operational Medicine (JPC5) to serve as a subject matter expert for its 3rd annual In-Progress Review (IPR) of Defense Health Program funded research. The meeting focused on Psychological Resilience research was held August 29-30, 2012 and the meeting focused on Families was held August 1-2, 2012 in Frederick, Maryland.

Drs. Elizabeth Robertson, Eve Reider and Belinda Sims, DESPR, organized and presented at a half-day workshop at the 2012 Society for Prevention Research Meeting; May 29, 2012 in Washington, D.C. titled “Emerging Principles of Drug Abuse Prevention: Program Delivery”.

Dr. Eve Reider was invited by the Institute of Medicine to be an external reviewer of the Institute’s draft report by the Committee; June 22, 2012 on “Prevention, Diagnosis, Treatment and Management of Substance Use Disorders in the U.S. Armed Forces.”

Dr. Aria Crump, DESPR, organized a symposium entitled “The Art, Science, and Philosophy of Developing Culturally Adapted Programs for Substance Abuse and HIV Prevention” for the Annual Meeting of the Society for Prevention Research, May 30, 2012, in Washington D.C.

Dr. Augusto Diana, DESPR, presented a keynote address, and a follow-up panel titled, “Prevention of Problem Behavior: What the Research Says about Prescription Drugs,” to the Natrona County Coalition Meth and Substance Abuse Conference, in Casper, WY, on April 26, 2012.

Dr. Augusto Diana presented a keynote address, and a follow-up panel titled, “Prevention of Problem Behavior: Our Knowledge about Inhalant Abuse,” to the Natrona County Coalition Meth and Substance Abuse Conference, in Casper, WY, on April 27, 2012

Dr. Augusto Diana presented a keynote address, and a follow-up panel titled, “Prevention of Problem Behavior: What the Research Has Shown Us,” to the Virginia Association of Community Service Boards, in Williamsburg, VA, on May 2, 2012.

Dr. Jacqueline Lloyd, DESPR, chaired a symposium at the 2012 Society for Prevention Research Meeting in Washington D.C; May 30, 2012, titled “Interventions to Prevent Multiple Risk Behaviors in High Risk Youth: Challenges, Opportunities and Implications”.

Drs. Belinda Sims and Jacqueline Lloyd, DESPR, co-chaired a panel titled “Prevention Infrastructure” at the Advancing the Prevention of Mental Emotional and Behavioral Disorders in Adolescence: A Science to Service Symposium,” June 5, 2012 in Washington D.C.

Dr. Belinda Sims chaired a research roundtable session at the 2012 Society for Prevention Research Meeting in Washington, D.C., May 30, 2012, titled “The Intervention Works, Now What? Opportunities for Research and Research & Development”.

Dr. Belinda Sims was a presenter on a symposium at the 2012 Society for Prevention Research Meeting in Washington, D.C, May 30, 2012, titled “Reducing Mortality and Morbidity from Suicide: How can we get there?”

Dr. Belinda Sims was a discussant during a research brown-bag at the 2012 Society for Prevention Research Meeting in Washington, D.C., May 31, 2012, titled “Research on the Prevention of Bullying.”

Drs. Belinda Sims and Aria Crump co-chaired a panel at the 2012 Society for Prevention Research Meeting in Washington, D.C., May 31, 2012, titled “Ask the Feds: An Open Forum on Federal Funding.” Participants included Dr. Elizabeth Ginexi, NCI; Dr. Lynne Haverkos, NICHD; Dr. Marcia Scott, NIAAA; Dr. Susannah Allison, NIMH; Dr. Patty Mabry, NIH/OBSSR; Wilma Peterman Cross, NIH/ODP; Dr. Lauren Supplee, Administration for Children and Families; Dr. Greta Massetti, Centers for Disease Control and Prevention.

Dr. Kristopher Bough, DPMCD, organized and co-chaired a pre-conference workshop entitled “Biomarker Development for Substance-Use Disorders”. This full-day satellite meeting was convened as part of the College on Problems of Drug Dependence annual meeting in Palm Springs, CA on June 8, 2012. Participants included academic, government (FDA and NIDA), and industry experts. Among the topics covered were: (1) existing cardiovascular- and neuroimaging potential biomarkers for cocaine-dependent subjects, (2) discovery approaches for new biomarkers associated with SUDs, and (3) the regulatory steps that would be required for assay validation / qualification of identified biomarkers.

Dr. Jag Khalsa, DPMCD, presented/co-chaired three and helped organize three other symposia at the Annual Conference of the American Society of Addiction Medicine (ASAM), April 19-22, 2012, held in Atlanta. The symposia: “Drug-Drug Interactions: Role of Individualized Medicine”, “An International Perspective on Combined Addiction and Mental Illness (ASAM/ISAM/NIDA Collaboration on Treatment Modalities in International Settings”, and “Prenatal Care and Neonatal Withdrawal Approaches in Opiate Dependence” were very well received by the audience. Dr. Khalsa also participated in the ASAM Medical Science Program Committee that plans for symposia for the next annual conference. Importantly, for the first time NIDA co-sponsored 6 of the 11 symposia at this year’s ASAM conference.

Dr. Jag Khalsa participated in the Annual meeting of the Society of NeuroImmune Pharmacology (SNIP), and co-chaired the NIH workshop on Mentoring and Funding Opportunities, Honolulu, Hawaii, April 24-28, 2012.

Dr. Guifang Lao, DPMCD, participated in a Pre-Conference Workshop on “Biomarker Development for Substance-Use Disorders” at the Annual CPDD meeting, La Quinta Resort & Club, Palm Springs, CA, USA. Saturday, June 9, 2012.

Dr. David McCann, DPMCD, and Dr. Wilson Compton, DESPR, chaired a panel session entitled “Common Targets for the Treatment of Substance Use Disorders and Co-occurring Psychiatric Disorders” at the NCDEU meeting on May 29, 2012 in Phoenix, Arizona. Dr. Compton presented on “Substance Use Disorders and Co-occurring Psychiatric Disorders: Prevalence and Current Treatment Approaches.” Dr. McCann presented on “Bupropion: Beyond Smoking Cessation and Depression,” Dr. Lawrence Toll (Torrey Pines Institute for Molecular Studies) presented on “NOP Receptors as Targets for the Treatment of Drug Addiction and Co-occurring Psychiatric Disorders,” and Dr. Linda Rorick-Kehn (Lilly Research Laboratories) presented on “Preclinical Pharmacological Characterization of Structurally Unique, Potent, Kappa Opioid Receptor Antagonists in Animal Models of Alcohol.”

Drs. Jane Acri, Nathan Appel, and David White, DPMCD, presented a workshop entitled “NIDA Medications Development Workshop -Early Drug Development: Predicting and Assessing Safety” at the College on Problems of Drug Dependence (CPDD) meeting on June 11, 2012 in Palm Springs, California. The workshop focused on predictive safety profiling of candidate medications and drug interactions studies required for compounds used to treat substance use disorders.

Drs. David McCann and Jane Acri organized and chaired a symposium entitled “Recent Advances in Medications Development for the Treatment of Substance Use Disorders” at the College on Problems of Drug Dependence (CPDD) meeting on June 12, 2012 in Palm Springs, California. Presenters provided updates on projects to develop medications for substance use disorders, and included Michel Steiner from Actelion Pharmaceuticals, Merav Bassan from Teva Pharmaceuticals, Linda Rorick Kehn from Eli Lilly and Company, and Steven Miller from Catalyst Pharmaceutical partners.

Drs. Ivan Montoya, DPMCD, and Lori Ducharme, DESPR, participated in the organizing committee of a Consensus Panel Meeting led by SAMHSA to develop guidelines on “Treatment of Alcohol Use Disorders” and “Naltrexone for Opioid Dependence.” The meeting was held in Washington DC on July 16-18, 2012. The meeting participants included academic scientists, representatives from government agencies, as well as from organizations involved in providing drug abuse treatment in the United States.

Dr. Geetha Subramaniam, CCTN, presented a poster at the Joint Meeting of Adolescent Treatment Effectiveness held April 10-12, 2012 in Washington, DC. Poster title: “Comparisons of Treatment Outcomes for Adolescents with Problem Use of Heroin Versus Non-heroin Opioids.”

The 165th Annual Meeting of the **American Psychiatric Association** was held May 5-9, 2012 in Philadelphia, Pennsylvania. NIDA CCTN staff presented the following:

- 1) On May 8th, Dr. Petra Jacobs chaired a symposium entitled “Assessment of Substance Use Disorder (SUD) Patient Outcomes Using Longitudinal Registry/EMR Data”. The presenters were Roberto Mollica (Italy), Matt Hickman (UK), Fred Blow (US), Don Stablein (US), and Li-Tzy Wu (US). The panel discussed how large databases (including EMR) could be used to assess treatment outcomes.

- 2) Dr. Geetha Subramaniam chaired a symposium entitled, “Adolescent Substance Use Disorders: Clinical Updates and New Developments in Treatment.” Dr. Paula Riggs from the CTN Florida Node Alliance was a collaborator.

The **Society for Clinical Trials (SCT)** 33rd Annual Meeting was held in Miami, FL, May 20-23, 2012. NIDA CCTN staff presented the following:

- 1) Carmen Rosa organized and chaired a session entitled, “Ethical, Regulatory and Recruitment Issues in Vulnerable Populations: Substance Use Trials as a Case Study”. Presenters included Drs. Emily Anderson, Loyola University, Aimee Campbell, Columbia University and Jennifer Sharpe-Potter from the University of Texas.
- 2) Dr. Paul Wakim and Ms. Michele Straus organized a session entitled, “Dealing with Treatment Compliance in Clinical Trials on Inherently Low-compliant Populations: What to do at the Design, Monitoring and Analysis Stages.”
- 3) Dr. Paul Wakim organized, chaired and presented at a half-day workshop on “Practical Statistical Reasoning in Clinical Trials for Non-Statisticians.”

The 74th Annual Meeting of the **College on Problems of Drug Dependence (CPDD)** was held in Palm Springs, CA, June 9-14, 2012. NIDA CCTN staff presented the following:

- 1) Dr. Petra Jacobs chaired a symposium entitled, “Deaths during and after Opioid Treatment: Results from Studies in the US, the EU and Australia.” The symposium was co-chaired by Walter Ling and the presenters were Mathew Hickman (UK), Louisa Degenhardt (Australia), Yih-ing Hser, Frederic Blow, Mary Jeanne Kreek (US). The symposium showed how mortality rates in the various countries are associated with different phases of opioid treatment as well as patients’ characteristics.
- 2) Dr. Petra Jacobs chaired a symposium entitled, “What’s New in NIDA’s National Drug Abuse Treatment Clinical Trials Network? Findings and Observations from Recent Trials.” The presenters were Andrew Saxon, Edward Nunes, Dennis Donovan and Theresa Winhusen from the Clinical Trials Network. The panel presented results and updates from three of CTN’s multisite trials, and discussed how to select the most suitable primary outcome measures.
- 3) Dr. Geetha Subramaniam chaired a symposium entitled, “Is Abstinence the Only Meaningful Endpoint? Results for Secondary Analyses of Cocaine Treatment Studies.” Dr. George Woody was the co-chair. Both he and Dr. Kathleen Carroll (both CTN PIs) presented at this session.
- 4) Dr. Geetha Subramaniam presented a poster with Drs. Betty Tai and Udi Ghitza as co-authors: A clinical decision support model for screening and management of substance use disorders in electronic health records in general medical settings.
- 5) Dr. Steve Sparenborg presented the poster, Pre-existing psychiatric severity did not affect likelihood of success in the Prescription Opiate Addiction Treatment Study (POATS).

Dr. Betty Tai, Director, CCTN, was the keynote speaker at the pre-Conference workshop of The Seventh Annual Texas Conference on Health Disparities held July 11-13, 2012 in Fort Worth, Texas. This NIDA-sponsored Workshop was titled “Tobacco Smoking, HIV/AIDS and Cancer in Health Disparity Populations.”

Drs. Teri Levitin, Meena Hiremath, and Eliane Lazar-Wesley, all of OEA co-chaired a workshop “What’s New at NIDA and NIH: Peer Review and Other Policies that Affect Applicants” at the annual meeting of the College on Problems of Drug Dependence (CPDD), in Palm Springs, California, June 9-14, 2012.

Dr. Levitin co-organized a workshop on NIH research funding and the grants review process for the 120th annual meeting of the American Psychological Association in Orlando, Florida, August 2-5, 2012. Dr. Gerald McLaughlin taught this workshop with Dr. Harold Perl.

Dr. Gerald McLaughlin, OEA, chaired a workshop “Career Development: A Perspective from Junior and Senior Researchers” with panel members Elise Weerts, Richard De La Garza, William L. Dewey, and Mary Jeanne Kreek at the annual meeting of the College on Problems of Drug Dependence June 9-14 in Palm Springs, CA,

Dr. Eliane Lazar-Wesley, OEA, presented “The Peer-Review Process” as part of a grant writing workshop at the annual meeting of the College on Problems of Drug Dependence in Palm Springs, CA, June 9-14, 2012.

Dr. Amy Newman, IRP, gave invited lectures in the School of Pharmacy, Florida A&M University, Tallahassee, FL, in February, the School of Pharmacy, University of Kansas, Lawrence KS, in April, and was the plenary lecturer at the 12th Annual Mercy Medical Symposium at St Vincent’s Mercy Hospital, Toledo, OH, in May 2012.

MEDIA AND EDUCATION ACTIVITIES

SCIENCE EDUCATION ACTIVITIES

NIDA participated in the first **NIH K-12 Lessons About Biology (LAB) Challenge**, a national call-to-action asking individuals, groups, organizations, and scientists to submit procedures for engaging, hands-on health- and life-science-related experiments for grades K-12. Activities needed to: (1) be geared towards grades K-12; (2) use safe, easily available, and inexpensive materials; (3) take 90 minutes (or less) of in-class time; (4) have at least one clear learning objective; and (5) be related to the NIH mission. An overwhelming number of engaging submissions were received. These submissions were carefully reviewed and the experiments were tried by NIH staff and in classrooms. The winners are being announced over the next few months. Winners receive an official, electronic NIH Challenge badge to display online.

OTHER EDUCATIONAL ACTIVITIES

NIDA's new **Easy-To-Read website** (<http://easyread.drugabuse.gov/>) has won several awards including a ClearMark Award of Distinction from the Center for Plain Language and a Merit Award from "Web Health Awards: Honoring the Best Digital Health Resources." In addition, an abstract entitled "NIDA's 'Easy-to-Read Drug Facts' website: Reaching low-literacy audiences online" was selected for a poster presentation at the 2012 APHA Annual Meeting.

Drs. James Bjork, Steven Grant, and Mary Kautz of DCNBR staffed the NIDA exhibit at the 2nd USA Science & Engineering Festival at the Washington, D.C Convention Center on April 27 -29, 2012.

As part of the CCTN Seminar Series, on June 19, Drs. Robin Conwit and Scott Janis, Program Directors in the Office of Clinical Research at the National Institute of Neurological Disorders and Stroke (NINDS), presented "The NINDS Experience with the Neurological Emergencies Treatment Trials (NETT) Network." NINDS established NETT in 2006 as a large network of clinical sites with centralized coordinating centers, dedicated to the study of acute injuries and illnesses affecting the brain, spinal cord, and peripheral nervous system.

MEDIA SUPPORT OF EVENTS AND MEETINGS

NIDA Director Dr. Nora Volkow Featured on 60 Minutes

A piece profiling Dr. Nora Volkow titled "Hooked: Why Bad Habits are Hard to Break" aired on *60 Minutes* on Sunday, April 29th. *60 Minutes Overtime* also produced four accompanying stories titled *Are You Addicted to Food?; A Cure for Addiction?; Addiction, Ethnicity and Environment;* and *The Most Dangerous Drugs?* The following evening, *60 Minutes* conducted its first ever Live Facebook Chat featuring Dr. Volkow. As a result of the promotion surrounding the profile piece and chat, NIDA reached over 12 million people on Twitter and nearly 5 million people on Facebook.

Addiction Inc.

NIDA hosted a screening of *Addiction Inc.*, a major motion picture about Dr. Victor DeNoble, a former research scientist for Philip Morris who testified before Congress in 1994 about his research showing the addictive nature of nicotine. More than 300 NIH staff attended the showing and panel discussion which featured Dr. Volkow, Dr. DeNoble, Charles Evans Jr., the film's producer/director, and Dr. Paul Mele, a researcher also in the film.

Spanish Language Videos

NIDA is creating a resource teachers can use to educate Spanish-speaking teens on drug abuse and addiction. Portions from Dr. Volkow's meeting with high school students in Mexico and an instructional kit will be available online in time for National Drug Facts Week in January 2013.

National Prescription Drug Abuse Summit

Dr. Nora Volkow presented a keynote entitled "It's Not What the Doctor Ordered" at the first national meeting devoted to addressing prescription drug abuse, held on April 10th and 11th in Florida. Several NIDA grantees participated in sessions related to healthcare, prevention, and treatment. NIDA exhibited our PEERx and NIDAMED materials, and hosted a train-the-trainer workshop to help communities learn how to implement the use of PEERx materials.

Aspen Ideas Festival

Dr. Volkow participated in the Aspen Ideas Festival July 2 in Aspen, Colorado. The festival, in its eighth year, is presented by the Aspen Institute and *The Atlantic*, and is a gathering of the world's foremost thought leaders.

PRESS RELEASES

March 21, 2012

Study provides clues for designing new anti-addiction medications

Scientists are now one step closer to developing anti-addiction medications, thanks to new research that provides a better understanding of the properties of the only member of the opioid receptor family whose activation counteracts the rewarding effects of addictive drugs. The study was supported by the National Institute on Drug Abuse (NIDA), the National Institute of General Medical Sciences and the National Institute of Mental Health, all components of the National Institutes of Health.

"Drug abuse and addiction remain devastating public health challenges in the United States," said NIDA Director Dr. Nora D. Volkow. "This research could aid in the development of effective medications for the treatment of drug addiction, particularly to stimulants like cocaine, for which there are no medications currently available. It may also be valuable for the development of safer pain medications."

Unlike the other opioid receptor subtypes, the kappa opioid receptor (KOR) is not associated with the development of physical dependence or the abuse potential of opiate drugs (e.g., heroin, morphine). Therefore, medications that act at the KOR could have broad therapeutic potential for addressing addiction, pain, as well as other mental disorders. The leading compound in this context

is JDTic because its specific binding to the KOR has been shown to reduce relapse to cocaine seeking in animal models.

In this new study, scientists produced a high resolution three-dimensional image of JDTic bound to the human KOR. By mapping all the points of contact between JDTic and the human KOR, researchers were able to see how the two fit together. The emerging picture reveals critical new information that helps explain why JDTic binds so tightly and specifically to this particular opioid receptor. This advance opens the door to the development of compounds targeting the KOR with improved therapeutic profiles, including that of non-addictive pain medications.

The study by Wu et al., can be found at: www.nature.com, please review our disclaimer.. For information on prescription drug abuse, go to: www.drugabuse.gov/drugs-abuse/prescription-medications.

May 18, 2012

Optogenetics project takes top NIDA Addiction Science Award

A project that maps dopamine circuits in the prefrontal cortex through optogenetic manipulation was given top honors in this year's annual Addiction Science Awards at the 2012 Intel International Science and Engineering Fair (ISEF)—the world's largest science competition for high school students. The awards were presented by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, and Friends of NIDA, a coalition that supports NIDA's mission. The Intel ISEF Addiction Science Awards were presented at a ceremony Thursday night at the David L. Lawrence Convention Center in Pittsburgh.

Among the 2012 Addiction Science Award winners, first place distinction went to John Edward Solder, a senior at Staples High School in Westport CT, for his project, Optogenetic Interrogation of Prefrontal Cortex Dopamine D1 Receptor-Containing Neurons as a Technique to Restore Timing: A Novel Approach to Treat Prefrontal Disorders. The 18-year-old was able to specifically control behavioral timing in mice that were genetically modified to activate dopamine neurons in the prefrontal cortex, a region involved in higher order functions such as impulsivity and self-control, in response to a light stimulus. His research, which provides another example of the power of optogenetics (a technique that activates specific neurons just by shining light onto them) to modify neural activity in discrete brain areas at will, brings us one step closer to the development of novel therapies for a wide range of psychiatric disorders. He plans to attend Yale University in the fall.

“This young scientist used optogenetics to directly activate dopamine neurons in the prefrontal cortex to influence behavior in the mouse, providing a proof of principle for an approach that could be used one day to restore disease-impaired functions in the brain,” said NIDA Director Dr. Nora D. Volkow. “His work highlights the versatility of the optogenetic technique for mapping out the circuits that underlie discrete behaviors and that are disrupted in brain disorders that involve the prefrontal cortex, including Parkinson's disease, addiction and schizophrenia. His impressive command of the principles, mechanics and implications of this promising technology should enable Mr. Solder to make significant and long-lasting contributions to the field of neuroscience.”

Second place distinction went to Benjamin Jake Kornick, a 17-year-old at Roslyn High School in Roslyn Heights, NY, for his project OMG: Look Who Joined Facebook! The Relationship between Parenting and Adolescent Risk Behaviors. He became interested in the prevention of hurtful online behaviors after being the target of cyber-bullying in middle school. For his project, he conducted a 74-item survey of more than 130 teens about their relationship with their parents as well as their risky behaviors online and offline. His detailed statistical analysis allowed him to construct a novel model of the complex relationships between parental knowledge and their children's undesirable or risky behaviors. The high school senior will attend Columbia University next year.

“In this new world of cyberspace and social networking, Mr. Kornick delved into highly nuanced and often overlooked aspects of the relationship between parents and their children,” said Dr. Susan Weiss, NIDA's head judge and acting director of the Office of Science Policy and Communications. “He determined that stricter control of teen activities online and parent-child closeness are the best predictors of their knowledge about what their child does while unsupervised. And yes, he recommends that parents ‘friend’ their teens’ Facebook pages.”

Winning third place distinction was L. Elisabeth Burton from Rio Rancho High School in Rio Rancho, NM, for her study of body image in both boys and girls, and how it affects their perceptions and health behaviors, which she titled A Big Fat Deal, Phase III: Attributions of Body Talk, Risk Assessments of Steroid/Dietary Supplement Use, Perceptions of Media Images, and Self-Esteem. The 16-year-old sophomore became interested in body image when a friend committed suicide after a long battle with an eating disorder. Burton developed and conducted a survey of nearly 200 teenage boys and girls to determine how their internal self image and self esteem affected eating disorders, steroid use and potentially dangerous use of dietary supplements. While girls aspire to look “skinny” like fashion models and boys want to look “buff” like the athletes they see in magazines, few teens realized that many of the highly stylized body portrayals in the media are altered images, and are unrealistic to attain safely.

For the first time, the judges awarded an honorable mention, to 15-year-old Zarin Ibnat Rahman, a sophomore at Brookings High School in Brookings, SD, for her project, Boosting the ADHD Brain: Effects of Gum Chewing and Caffeine on Cognition and Memory in Adolescents with ADHD. Based on recent brain imaging research, she hypothesized that the act of chewing may boost key aspects of cognition (e.g., memory and attention), and decided to test this hypothesis conducting a study of teens who have been diagnosed with ADHD. She tested the effects of chewing sugarless gum and/or caffeine (from dark chocolate) on their performance on a series of cognitive tests. Her results are consistent with the notion that chewing gum can improve attention and memory, although it did not appear to affect concentration.

Friends of NIDA provides funding for the awards as part of its ongoing support of research into the causes, consequences, and treatment of drug abuse and addiction. “We are thrilled at the broad range of research topics explored by the students this year,” said Dr. William Dewey, Louis S. and Ruth S. Harris Professor and Chair, Department of Pharmacology and Toxicology, Virginia Commonwealth University, Richmond, and president and chair of the Executive Committee, Friends of NIDA. “From optogenetics to Facebook, these young winners really showcase the breadth of addiction science. By sponsoring this competition, Friends of NIDA hopes that these bright students will be encouraged to pursue a career in drug abuse research.”

This year, about 1,500 students from 70 countries participated in the Intel ISEF competition, coordinated by the Society for Science and the Public. The nonprofit organization Society for Science and the Public partners with Intel—along with dozens of other corporate, academic, government and science-focused sponsors—to provide support and awards each year. Winners receive cash awards provided by Friends of NIDA, with a \$2,500 scholarship for the first-place honoree. NIDA has developed a special section on its website, which includes other resources on addiction science, to highlight the winning projects and to help science fair entrants understand the criteria for the awards: The NIDA Science Fair Award for Addiction Science.

May 21, 2012

NIH selects 11 Centers of Excellence in Pain Education

The National Institutes of Health Pain Consortium has selected 11 health professional schools as designated Centers of Excellence in Pain Education (CoEPEs). The CoEPEs will act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing and pharmacy schools to enhance and improve how health care professionals are taught about pain and its treatment. Twenty institutes, centers and offices at NIH are involved in the consortium.

"Virtually all health professionals are called upon to help patients suffering from pain," said NIH Director Francis S. Collins, M.D., Ph.D. "These new centers will translate current research findings about pain management to fill what have been recognized as gaps in curricula so clinicians in all fields can work with their patients to make better and safer choices about pain treatment."

The new Centers of Excellence in Pain Education were selected by the NIH Pain Consortium after a contract solicitation process and review. The awardees are the University of Washington, Seattle; the University of Pennsylvania Perelman School of Medicine, Philadelphia; Southern Illinois University, Edwardsville; the University of Rochester, N.Y.; the University of New Mexico, Albuquerque; the Harvard School of Dental Medicine, Boston; the University of Alabama at Birmingham; the Thomas Jefferson University School of Medicine, Philadelphia; the University of California, San Francisco; the University of Maryland, Baltimore; and the University of Pittsburgh. Many of the new CoEPEs will build curricula across several of their health professional schools.

"We were impressed with the scope and breadth of the proposals that came in from academic centers around the country---all recognizing the need for a more coordinated approach to the treatment of pain," said Dr. Story C. Landis, Ph.D., director of the National Institute of Neurological Disorders and Stroke (NINDS), and chair of the consortium. "We are confident that these eleven centers will lead the way in improving pain education for health care professionals, and ultimately, the quality of care for people who suffer from chronic pain."

Chronic pain affects approximately 100 million Americans, costing up to \$635 billion in medical treatment and lost productivity, and producing immeasurable suffering for people of every age. Yet, pain treatment is not taught extensively in many health professional schools, and clinical approaches can be inconsistent. The curricula developed by the CoEPEs will advance the assessment, diagnosis, and safe treatment of a wide variety of pain conditions while minimizing the

abuse of opioid pain relievers. They will include multiple case-based scenarios, many taught in video or electronic formats popularly used in contemporary academic settings. Types of pain of particular interest to the NIH Pain Consortium are rehabilitation pain, arthritis and musculoskeletal pain, neuropathic pain, and headache pain. In addition, the curricula will teach about the pathophysiology and pharmacology of pain and its treatment, the latest research in complementary and integrative pain management, factors that contribute to both under- and over-prescribing of pain medications, and how pain manifests itself differently by gender, in children, in older adults and in diverse populations.

NIH institutes and centers funding the CoEPEs include the National Institute on Drug Abuse (NIDA), which is coordinating the project; the Eunice Kennedy Shriver National Institute of Child Health and Human Development; the National Center for Complementary and Alternative Medicine; the National Institute of Dental and Craniofacial Research; the National Institute of Nursing Research; the National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute on Aging; the Office of Behavioral and Social Sciences Research; the Office of Research on Women's Health; and NINDS. Other NIH institutes and centers that are part of the consortium will act as technical advisors to the project. The full list of the consortium members can be found at: <http://painconsortium.nih.gov/members.html>.

"While opioid pain medications have improved the quality of life for millions who suffer from pain, they can also produce harmful consequences, including addiction," said NIDA Director Nora D. Volkow, M.D., a member of the consortium's executive committee. "These new CoEPEs can help prevent negative outcomes by designing curricula that promote appropriate screening and management of chronic pain patients, along with education about the risks of prescription drug abuse."

NIH supports the full spectrum of pain research from basic understanding of pain mechanisms through translation of discoveries into treatments and prevention strategies. In FY 2011, NIH supported \$386 million in research focused on chronic pain, not including the related diseases that often cause chronic pain, such as cancer, arthritis, diabetes, and stroke. The details of individual pain-focused grants are publicly available on the NIH RePORTER website. Enhancing education of pain care professionals was highlighted in the June 2011 Institute of Medicine report, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, please review our disclaimer.

May 30, 2012

Odds of quitting smoking affected by genetics

Genetics can help determine whether a person is likely to quit smoking on his or her own or need medication to improve the chances of success, according to research published in today's American Journal of Psychiatry. Researchers say the study moves health care providers a step closer to one day providing more individualized treatment plans to help patients quit smoking.

The study was supported by multiple components of the National Institutes of Health, including the National Institute on Drug Abuse (NIDA), the National Human Genome Research Institute, the

National Cancer Institute, and the Clinical and Translational Science Awards program, administered by the National Center for Advancing Translational Sciences.

“This study builds on our knowledge of genetic vulnerability to nicotine dependence, and will help us tailor smoking cessation strategies accordingly,” said NIDA Director Nora D. Volkow, M.D. “It also highlights the potential value of genetic screening in helping to identify individuals early on and reduce their risk for tobacco addiction and its related negative health consequences.”

Researchers focused on specific variations in a cluster of nicotinic receptor genes, CHRNA5-CHRNA3-CHRNA4, which prior studies have shown contribute to nicotine dependence and heavy smoking. Using data obtained from a previous study supported by the National Heart Lung and Blood Institute, researchers showed that individuals carrying the high-risk form of this gene cluster reported a 2-year delay in the median quit age compared to those with the low-risk genes. This delay was attributable to a pattern of heavier smoking among those with the high risk gene cluster. The researchers then conducted a clinical trial, which confirmed that persons with the high-risk genes were more likely to fail in their quit attempts compared to those with the low-risk genes when treated with placebo. However, medications approved for nicotine cessation (such as nicotine replacement therapies or bupropion) increased the likelihood of abstinence in the high risk groups. Those with the highest risk had a three-fold increase in their odds of being abstinent at the end of active treatment compared to placebo, indicating that these medications may be particularly beneficial for this population.

“We found that the effects of smoking cessation medications depend on a person’s genes,” said first author Li-Shiun Chen, M.D., of the Washington University School of Medicine, St. Louis. “If smokers have the risk genes, they don't quit easily on their own and will benefit greatly from the medications. If smokers don't have the risk genes, they are likely to quit successfully without the help of medications such as nicotine replacement or bupropion.”

According to the Centers for Disease Control and Prevention, tobacco use is the single most preventable cause of disease, disability, and death in the United States. Smoking or exposure to secondhand smoke results in more than 440,000 preventable deaths each year -- about 1 in 5 U.S. deaths overall. Another 8.6 million live with a serious illness caused by smoking. Despite these well-documented health costs, over 46 million U.S. adults continue to smoke cigarettes.

The study can be found at: <http://ajp.psychiatryonline.org/article.aspx?articleID=1169679>. For information on tobacco addiction, go to: www.drugabuse.gov/drugs-abuse/tobacco-addiction-nicotine. For more information on tools and resources to help quit smoking, go to: www.smokefree.gov.

This work was partially funded by NIDA under grant numbers DA19706, DA026911, DA021237 and DA030398.

SCIENCE SPOTLIGHTS/ANNOUNCEMENTS

March 28, 2012 — A NIDA study showed that clofibrate — widely prescribed to treat high cholesterol and cardiovascular disease — reduces nicotine’s effects in animal models. Specifically, the medication prevented nicotine-taking in animals never before exposed, greatly reduced it in experienced animals, and countered a return to drug-seeking in a model of relapse. Because clofibrate is already FDA-approved for reducing risk of heart disease, clinical trials for smoking cessation could be expedited. For a copy of the article by Panlilio et al., go to www.nature.com/npp/index.html.

April 19, 2012 — Drug use is associated with an increased risk of HIV infection, yet the majority of drug treatment programs in the U.S. do not offer on-site HIV testing. New research by NIDA-funded scientists showed that providing on-site HIV testing at drug treatment centers, rather than referrals to off-site HIV testing, increases the likelihood that people will receive their test results. This same study found no additional benefit from HIV risk reduction counseling and also no differences in sexual risk behaviors among the study groups. For a copy of the article by Metsch et al., go to <http://ajph.aphapublications.org/toc/ajph/0/0>.

May 3, 2012 — As part of its Blending initiative, NIDA developed two new products to help healthcare providers integrate the latest substance abuse research into their practices. One of the products, “Prescription Opioid Addiction Treatment Study (POATS),” is based on results from a large-scale study conducted by NIDA’s Clinical Trial Network. The POATS product provides training materials on the effective use of buprenorphine treatment for adults addicted to prescription painkillers. The other, “HIV Rapid Testing in Substance Abuse Treatment Programs,” describes best practices for implementing on-site rapid HIV testing and is based on the results of a NIDA-funded study, published April 19. More information on the Blending products, as well as the Blending initiative, can be found on www.drugabuse.gov/publications/nidasamhsa-blending-initiative. Blending Team Products are developed through a collaborative effort between NIDA researchers, members of the Substance Abuse and Mental Health Services Administration’s (SAMHSA) Center for Substance Abuse Treatment, and community-based practitioners.

Monday, May 7, 2012 — A study, funded by NIDA and the National Institute on Alcohol Abuse and Alcoholism, showed that a computer-facilitated Screening and Brief Advice system tested with teens in the United States and Prague promoted reductions in use of alcohol and marijuana, respectively, for up to one year. Teens completed a computerized screening questionnaire and viewed the results as well as scientific information and real-life stories illustrating substance use harms before a healthcare provider office visit. Clinicians then received screening results and talking points to assist in providing the patient brief advice during the visit. For the article by Harris et al., go to <http://pediatrics.aappublications.org/content/early/recent>.

June 7, 2012 — The number of 50- to 59-year-olds reporting past-month abuse of illicit drugs — including the nonmedical use of prescription drugs — more than doubled from 2002 to 2010, going from 907,000 to 2,375,000, or from 2.7 to 5.8 percent in this population. Among those 65 and older, 414,000 used illicit drugs in 2010. A new topic, Prescription and Illicit Drug Abuse, available on NIHSeniorHealth.gov, describes this disturbing trend and the effects of medication and drug abuse on older adults.

MEDIA ADVISORIES

April 3, 2012

NIH's "PEERx" for teens to be showcased at Rx Drug Abuse Summit

A unique, new campaign targeting teens was on exhibit at the first national summit addressing the prescription drug abuse epidemic. NIDA showcased "PEERx," a NIDA initiative that uses interactive videos and other tools to educate teens about the dangers of prescription drug abuse and help them to spread the word. Teen leaders from SADD (Students Against Destructive Decisions) assisted NIDA in exhibiting PEERx and hosted a train-the-trainer workshop for state and national leaders, law enforcement officials, medical professionals, community advocates, treatment experts, educators, private industry leaders, and others attending the event. NIDA also exhibited NIDAMED, a collection of tools and resources to assist health care providers in detecting drug abuse early, preventing escalation to addiction, and referring patients to treatment when necessary.

April 16, 2012

Blending conference translates substance abuse research into practice

Experts shared the latest clinical research with addiction treatment professionals, healthcare providers, policy makers, and others during the April 19th Blending Conference in Atlanta, Georgia. The program is supported by the NIDA in collaboration with the American Society of Addiction Medicine Annual Medical-Scientific Conference as part of an ongoing initiative to accelerate research findings into practice.

May 3, 2012

Actress Dianne Wiest to raise the curtain in NIDA's Addiction Performance Project

Dianne Wiest led an impressive cast in the Addiction Performance Project, an innovative continuing medical education (CME) program for doctors and other health providers, on May 9 in Philadelphia, Pa. The performance is a project of NIDA and is designed to help doctors and other health professionals better identify and help drug-abusing patients in primary care settings, and to break down the stigma associated with drug addiction.

INTERVIEW HIGHLIGHTS: April 2012 – June 2012

60 Minutes — Dr. Nora Volkow was interviewed for a profile piece.

Associated Press-TV — Dr. David Shurtleff was interviewed about newborn withdrawal from opioids.

Tampa Bay Times — Dr. Richard Denisco was interviewed about effects of cocaine on the heart.

The New York Times — Dr. Volkow was interviewed about PET scans.

International Business Times — Dr. Steven Grant was interviewed about MDMA.

Seattle Times — Dr. Marilyn Huestis was interviewed about marijuana use testing.

Drs. Steven Grant of DCNBR and Ruben Baler of OSPC were interviewed on July 10, 2012 for a telecast produced by the Center for Public Safety Innovation (CPSI) for the Multijurisdictional Counterdrug Task Force Training on the "**Origins of Addiction**" to be aired in February, 2013.

RECENT AND UPCOMING CONFERENCES/EXHIBITS

American Psychological Association Annual Convention
Orlando, FL -- 8/2-5/12

PLANNED MEETINGS

Dr. Cheryl Anne Boyce, DCNBR, is a member of the interagency planning committee for the DHHS Administration for Children, Youth and Families (ACYF), Office of Planning, Research, and Evaluation (OPRE) **Methodological Advancement Meeting: Innovative Directions in Estimating Impact** to be held on September 6-7, 2012.

Dr. Cheryl Anne Boyce is a federal member on the planning committee for **Translational Research on Child Neglect Consortium: Final Meeting** to be held on September 20-21, 2012 at the NIH Neuroscience Center in Rockville, MD. An evening poster session highlighting early investigators and travel awardees will be held on September 20, 2012.

Dr. Lisa Onken, DCNBR, in collaboration with the NIH Science of Behavior Change Work Group, is planning a meeting on October 9-10, 2012, "**Revisiting Pasteur's Quadrant: Fostering Use-Inspired Basic Research.**" This meeting, to be held in the Washington D.C. area, will explore how basic science questions about how behavioral interventions work can be asked within applied or clinical research studies on these interventions. The proximal goal of such research is to determine how an intervention exerts its effects, with the ultimate goal of modifying the intervention to become more potent, streamlined, efficient, and implementable. Specifically, this workshop will examine how to conduct basic research-- within the context of intervention studies—so that efficacious but difficult-to-implement interventions can be modified (ultimately) to be implementable ("community-friendly") interventions within the existing health care delivery system.

The NIDA Mini-Convention Frontiers in Addiction Research will be held at the **Annual Meeting of the Society for Neuroscience (SfN)** on Friday, October 12, 2012 in New Orleans, LA. Sessions to be included are:

- (1) Ghrelin, Leptin, and Insulin Modulated Reward
- (2) Jacob P. Waletzky Memorial Lecture
- (3) Role of Phagocytes in Synaptic Plasticity and Remodeling of Tissues in the Nervous System
- (4) Early Career Poster Session
- (5) Brain Energies and Neurotransmission: Fueling Neurons and Glia
- (6) Central Nervous System Immune Signaling and Addiction

Other tentatively scheduled NIDA-sponsored activities during the SfN meeting include:

Toni S. Shippenberg Memorial Symposium

Friday, October 12, 2012, 6:00 p.m. – 7:30 p.m.

Julius Axelrod Lecture and Poster Session

Sunday, October 14, 2012, 6:30 p.m. – 9:30 p.m.

NIDA/INSERM Workshop on US-France Collaboration on Drug Abuse and Addiction Research

Monday, October 15, 2012, 6:30 p.m. – 9:00 p.m.

NIH Grant Workshop for Early Career Investigators

Tuesday, October 16, 2012, 6:30 p.m. – 9:00 p.m.

The next **National CTN Steering Committee Meetings** will be held March 12-15, 2013 in Bethesda, Maryland.

PUBLICATIONS

NIDA PUBLICATIONS

Research Report Series: Drug Abuse and HIV (In Press)

NIH Pub. No.: 12-5760

This research report is designed to highlight the state of the science and to raise awareness of the link between HIV/AIDS and drug abuse – not just injection drug use but drug abuse in general. This update was released to coincide with the XIX International AIDS Conference held in Washington, DC in July 2012. The report details NIDA's multifaceted approach towards ending this disease and the ongoing research strategies to prevent and treat it.

Research Report Series: Inhalant Abuse (In Press)

NIH Pub. No.: 12-3818

This report is based on research on the use and prevalence of inhalants, presents information on the different types of inhalants, the consequences of their use, who is abusing inhalants, and how to recognize inhalant abuse.

Research Report Series: Marijuana Abuse (In Press)

NIH Pub. No.: 12-3859

This report summarizes what the science tells us about marijuana abuse in the United States and its effects on the brain and body. It includes an extensive review of the latest research literature presented for a general audience interested in learning more about marijuana's consequences for physical, mental, and emotional health.

Research Report Series: Tobacco Addiction (In Press) (English and Spanish)

NIH Pub. No.: 12-4342

This report describes tobacco, presents current epidemiological research data regarding its use, and reports on the medical consequences of tobacco use. Emphasizes the effects on the brain as well as current research findings about use during pregnancy. Includes treatment approaches.

Brain Power! The NIDA Junior Scientist Program: Grade 2-3 (Revised) (In Press)

NIH Pub. No.: 12-4575

This package is designed to interest and educate students in an age-appropriate manner about their brains, why they should protect them, and how drugs such as nicotine and inhalants can hurt their brains. The parent' guide describes activities that can be done with the whole family and includes a listing of resources. This package also includes a DVD.

Brain Power! The NIDA Junior Scientist Program: Grade 4-5 (Revised) (In Press)

NIH Pub. No.: 12-5730

This package introduces students in grades 4-5 to the human brain and to the effects of abused drugs on the brain. It explores how different regions of the brain work, and how various drugs affect the brain. The last module introduces students to addiction and the drug abuse problem in the United States and allows students to explore the impact of drug use on society and the differences between legal and illegal drugs. This package also includes a DVD.

Mind Over Matter: The Brain's Response to Methamphetamine (In Press)

NIH Pub. No.: 12-4394

Explains how methamphetamine acts in the body and the brain, with an emphasis on harmful effects. Uses drug information to teach scientific principles and encourage interest in science, while increasing awareness of significant drug dangers.

CTN-RELATED PUBLICATIONS

Seven editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 27 CTN studies are now available on the NIDA Data Sharing Web Site <http://www.nida.nih.gov/CTN/Data.html>. Over 1,500 data sets have been downloaded by researchers from 28 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The CTN Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

INTERNATIONAL PROGRAM-RELATED PUBLICATIONS

NIDA International Program E-News

- *April 2012* – This issue reported on NIDA participation in the Italian School on Addiction, part of the binational agreement between NIDA and the Italian Department for Anti-Drug Policies, and the journal supplement (*Substance Abuse and Rehabilitation* 2012; 3[S1]) published by International Women's and Children's Health and Gender Research Group (InWomen), a multidisciplinary research working group organized through a NIDA IP initiative. Other stories announced the 2012 WHO/NIDA/CPDD International Traveling Fellow and IP participation in a Johns Hopkins University workshop for Burmese officials.
- *June 2012* – This issue reported that international researchers are now eligible to apply for the NIDA Avant-Garde Award in HIV/AIDS Research. The issue also described NIDA activities at the Society for Prevention Research Annual Meeting, the American Society of Addiction Medicine 43rd Medical-Scientific Conference, and the 2nd International HIV Treatment as Prevention Workshop. Other stories reported on a new open-access journal that was partially supported by the NIDA IP, the *International Journal of Alcohol and Drug Research*, and new online tools for researchers.

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STAFF HIGHLIGHTS

Staff Honors and Awards

Dr. Rao Rapaka, DBNBR, received the ICRS 2012 Lifetime Achievement Award, Frieberg, Germany.

Dr. Rao Rapaka received a Lifetime Achievement Award from ATA for achievements in the area of Biomedical Science.

Dr. Cheryl Anne Boyce, DCNBR, was elected as member-at-large to the membership Society for Clinical Psychology (Division 12, American Psychological Association).

Dr. Scott Chen, OEA, now serves as a Technology Review consultant/volunteer in a group that aims to 1) Educate the consultant/volunteer on commercial analysis methodology, 2) Perform commercial and technical analysis individually and as a team, and 3) Arrive at a documented Go/No Go decision for each of the technologies evaluated. It is anticipated that the “Go” decisions will result in an opportunity to create a new company or license to already existing companies.

Dr. Wilson M. Compton, DESPR, received the 2012 Leveraging Collaboration Award, Food and Drug Administration.

Dr. Kathy Etz, DESPR, received the Native Research Network’s (NRN) Dr. Phil Smith Award, an given to a Federal employee that's shown exemplary support to research in Native communities through direct funding or facilitating mechanisms, policy or training. The award was presented at the NRN annual conference in Seattle, WA, July 19, 2012.

Dr. Thomas Keck, IRP, received a 2012 NIH FARE Travel Award.

Dr. Eliane Lazar-Wesley, OEA, was appointed to the Staff Advisory Team for Extramural Operations (SATEO) group: representatives of each division/office meet to discuss and propose solutions to issues applicable to NIDA personnel.

Dr. Teri Levitin, Director, OEA, has joined the newly-formed NIH-wide New Investigators Evaluation Working Group. This group will be assessing the extent to which the NIH New Investigators program is meeting its stated goals.

Dr. Lisa Onken, DCNBR, was elected a Fellow of the Association for Psychological Science.

Dr. Geetha Subramaniam, CCTN, received the award for Best Scientific Poster at the Joint Meeting of Adolescent Treatment Effectiveness held April 10-12, 2012 in Washington, DC. Title: “Comparisons of Treatment Outcomes for Adolescents with Problem Use of Heroin versus Non-heroin Opioids.”

2012 NIH DIRECTOR'S AWARDS

The NIDA Population Assessment of Tobacco and Health (PATH) Study Team

For outstanding contributions to science and public health in launching a landmark longitudinal study on tobacco and health with FDA's Center for Tobacco Products.

Wilson Compton, M.D., M.P.E.

Kevin Conway, Ph.D.

Kathy Etz, Ph.D.

John Hamill

Donna M. Jones

Elizabeth Y. Lambert, M.Sc.

Marsha Lopez, Ph.D., M.H.S.

Brian H. O'Laughlin, M.P.A.

James L. Quinn, III, J.D.

Kay Wanke, Ph.D., M.P.H.

Surgeon General Call to Action on Prescription Drug Abuse Among Youth

In recognition of exceptional and sustained leadership to produce a U.S. Surgeon General's Call to Action to Prevent Prescription Drug Abuse Among Youth.

Jessica Cotto, M.P.H.

Gaya Dowling, Ph.D.

Jennifer Elcano, M.A.

Carol M. Krause

Anna Staton, M.P.A.

Isabelle Thibau

Eric Wargo, Ph.D.

Susan Weiss, Ph.D.

Elizabeth Y. Lambert, M.Sc. and **Tisha Wiley Ph.D.**, DESPR, received an NIH Director's Award for their participation in the NIH Lesbian, Gay, Bisexual, and Transgender Research Coordinating Committee.

2012 NIDA DIRECTOR'S AWARDS

NIDA Director's Innovator Award

Mark Fleming

In recognition for your innovative redesign of NIDA's Web site to provide complete mobile access, thus broadening public access to scientific information about drug abuse and addiction.

Center for the Clinical Trials Network

Paul Wakim

In recognition of your dedication, contributions, and support to meet the mission of NIDA

NIDA Information Technology and Data Management Acquisition Planning Workgroup

Christine Colvis

Carol Cushing

Kenneth Goodling

Richard Kline

Jan Leahey

David McCann

Ivan Montoya

Susan Nsangou

James Quinn,

Joseph Tam Lung

Robert Walsh

In recognition of your dedication, contributions, and support to meet the mission of NIDA

NIDA CCTN Common Data Elements for Electronic Health Records Task Force

Udi Ghitza

Geetha Subramaniam

Betty Tai

In recognition of your extraordinary leadership in the Development of Expert defined, consensus-based Common Data Elements for Use in the National Electronic Health Records for Substance Use Disorder

Division of Basic Neuroscience and Behavioral Research

Rao Rapaka

In recognition of your dedication and creative contributions to advance NIDA's mission

ARRA Analysis Team

Mark Caulder

Christine Colvis

Jonathan Pollock

Dena Procaccini

Joni Rutter,

John Satterlee

Isabelle Thibau

Paul Wakim

In recognition of your creative and outstanding analytic efforts to support the mission of NIDA

Division of Clinical Neuroscience & Behavioral Research

James Bjork

In recognition of your dedication, contributions, and support to meet the mission of NIDA in programmatic efforts to advance the ability to conduct brain imaging in pediatric populations

Woody Lin

In recognition of your dedication to the NIDA mission through leadership of the Asian American and Pacific Islander Workgroup

Lisa Onken

In recognition of your outstanding sustained scientific leadership and vision at NIH that have advanced public health through behavioral treatment research for drug abuse, addiction, and related fields

Division of Epidemiology, Services and Prevention Research

Elizabeth Robertson

In recognition of your exemplary and innovative leadership of the Prevention Research Branch

Adolescent Treatment Group

Ericka Boone

Cheryl Boyce

Redonna Chandler

Richard Denisco

Gayathri Dowling

Jennifer Elcano

Petra Jacobs

Jacqueline Lloyd

Geetha Subramaniam

Eric Wargo

Susan Weiss

In recognition for leadership in developing and disseminating evidence-based interventions, including adolescent SBIRT and NIDA Principles of Effective Treatment for Adolescents

Division of Pharmacotherapies and Medical Consequences of Drug Abuse

The DPMCD A Abuse Liability Evaluation and Controlled Substance Scheduling Group

Jane Acri

Nathan Appel

Carol Hubner

David McCann

David White

In recognition of your contributions to meet the mission of NIDA

Intramural Research Program

Brandon Harvey

In recognition of your dedication, contributions, and support to meet the mission of NIDA

NIDA IRP Scientific PMAP Working Group

Agnes Coffay

Sergi Ferre

William Freed

Steven Goldberg

Marilyn Huestis

Jonathan Katz

Irina Krasnova

Mary Lee

Toni Shippenberg

Tsung-Ping Su

George Uhl

Massoud Vahabzadeh

Amina Woods

Susan Harrelson

Janice Carico

Debra Alexander

In recognition of efforts to develop a guide to assist scientific supervisors to more effectively manage, motivate and mentor highly performing scientific employees

NIDA Office of the Director

NIDA Electronic Health Records (EHR) Development Task Force

Ericka Boone

Wilson Compton

Gayathri Dowling

Sarah Duffy

Udi Ghitza

Steven Sparenborg

Geetha Subramaniam

Betty Tai

Susan Weiss

In recognition of your performance to support the development of electronic health records

The NIDA Product Development Partnership (PDP/MITD) Task Force

Kristopher Bough

Scott Chen

Udi Ghitza

Elena Koustova

Jonathan Pollock

Geetha Subramaniam

In recognition of your contribution, dedication, and support of Medication Initiative for Tobacco Dependence

Office of Extramural Affairs

Advisory Council Management Team

Cikena Reid

Julius Diggs

In recognition of exceptional work in managing, innovating and improving Council administration

FOA Development Assistance Team

Loretta Beuchert

Scott Chen

Lyle Furr

Eliane Lazar-Wesley

Minna Liang

Nadine Rogers

Jose Ruiz

In recognition of sustained and outstanding contributions to NIDA program announcement development and publication

Office of Management

David Daubert

In recognition of your sustained exceptional support of the NIDA mission, execution of innovative initiatives, and outstanding NIH corporate citizenship

James Quinn

In recognition of your sustained exceptional acquisition support services contributing to NIDA's effectiveness in meeting its goals and objectives

Berhane Yibarek

In recognition of your dedication, reliability, customer service, and commitment to meet the mission of NIDA

Office of Science Policy and Communications

Mobile NIDA Web Site Team

Mark Fleming

Carol Krause

Jan Lipkin

Rich Panzer

Paulina Puig

In recognition of NIDA's pioneering innovation to create a completely mobile web site, broadening public access to scientific information about drug abuse and addiction

NIDA Director's Award for Plain Language Writing

NIDA Easy-Read Drug Facts Web Site Team

Gayathri Dowling

Mark Fleming

Carol Krause

Jan Lipkin

Cathrine Sasek

Susan Weiss

In recognition of your leadership in advancing NIDA's mission by developing a Web site geared to adults with limited literacy skills.

NIDA Director's Award for EEO, Diversity and Quality of Worklife

Quandra Scudder

In recognition of your efforts to promote a healthy lifestyle for NIDA employees as Chair of the NIDA Work life Advisory Committee's Wellness Subcommittee

30 Years of Government Service Awards

Deborah Battle Dudley

Annette Carter

Christine Kidd

Jan Lipkin

Juanita Nelson

Stephanie Powell

Amy Siller

Dale Weiss

40 Years of Government Service Award

David Jones

50 Years of Government Service Award

Ana Anders

Staff Changes

New Employees

Ms. Jessica Henry has joined the CCTN for a summer internship. Jessica is currently a doctoral student in Clinical/Community Psychology at The George Washington University in Washington, D.C. In 2006, she received her M.A. in Clinical Psychology from Teachers College, Columbia University, and she graduated summa cum laude from Howard University in 2005, with a B.S. in Psychology. Jessica already has an extensive list of publications, honors, awards, and clinical and research experience that includes work with Trauma-Focused CBT; Research Assistant positions with NIMH, Howard, Yale, Columbia, and Brown; and internships with NIDA in OSPC and DESPR.

New Roles within NIDA

Dr. Susan Weiss has accepted a new position in the OD as Associate Director for Scientific Affairs, where she will serve as a senior advisor to the NIDA Director. Previously at NIDA, Dr. Weiss served as the Chief of the Science Policy Branch, overseeing the preparation of scientific and policy communications for members of Congress and the public, along with outreach and education programs for elementary school students and training of young scientists and new grantees. Most recently, she served as the Acting Director, Office of Science Policy and Communications, providing leadership and oversight for all of NIDA's interactions with its diverse stakeholders. Before coming to NIDA, Dr. Weiss supervised a research program in the Biological Psychiatry Branch of the National Institute of Mental Health (NIMH) focused on characterizing the evolving nature of psychiatric and neurologic illnesses to inform the development of novel treatment options for patients with affective, anxiety, and substance use disorders.

Anita LoMonico, IRMB, OM has been selected to serve as NIDA's Acting CIO. Anita has served as the Deputy CIO since her arrival at NIDA in January of 2010 and brings almost 30 years of NIH lab, IT and administrative experience to the position.

Janet Linton, OSPC, became a Federal employee in June of 2012 and serves as an IT Specialist with NIDA's web team. She has been working in OSPC under a contract since 2009 and will continue to provide web support to the NIDA Webmaster. Her primary tasks include, but are not limited to: ensuring NIDA's content is compliant with section 508, overseeing NIDA's Facebook, Flickr, and YouTube accounts, and maintaining the National Drug Facts Week site. Prior to joining OSPC, Ms. Linton was a lead operator, training and overseeing employees, at the PNC Bank Operation Center in Baltimore, MD. She holds a Bachelor of Science degree in Animation from Westwood College.

New Appointments

Jack B. Stein, MSW, Ph.D. joined NIDA in August 2012 as the new Director of the NIDA Office of Science Policy and Communications (OSPC). Jack has over two decades of professional experience in leading national drug and HIV-related research, practice, and policy initiatives for NIDA, the Substance Abuse and Mental Health Services Administration (SAMHSA) and the Office of National Drug Control Policy (ONDCP) where, before coming back to NIDA, he served as the Chief of the Prevention Branch.

Departures

Christine Colvis, Ph.D., Director of Program Integration, left NIDA in July 2012 to accept a position at the newly formed National Center for Advancing Translational Sciences (NCATS), where she is leading their Therapeutics Discovery Program. Christine joined the Genetics and Molecular Neurobiology Research Branch in DBNBR in 2001. She had been doing proteomics research as a Research Fellow at the National Eye Institute prior to coming to NIDA. At NIDA, she helped build the proteomics portfolio, and when she saw the potential importance that epigenetics could play in addiction, she began building the epigenetics portfolio as well. Christine was well-known to the staff of the Common Fund serving on several project teams for Roadmap and the Common Fund since the program began. In 2008, Christine moved to the OD in NIDA where she worked with the Director on a number of projects including ARRA.

Jan Leahey, Deputy Director of NIDA's Office of Acquisitions (OA), has recently accepted a Program Analyst position in the Food and Drug Administration (FDA), Center for Tobacco Products. Ms. Leahey has worked as both an acquisition official and program manager in various Agencies throughout Health and Human Services (HHS) during her federal career. In 2001, Ms. Leahey joined the National Institute of Child Health and Human Development (NICHD), where she participated in the start-up of the National Children's Study (NCS). In addition to supporting the NCS, Ms. Leahey worked as a Program Manager in the Obstetric and Pediatric Pharmacology Branch, where she supported the Best Pharmaceuticals for Children Act. Ms. Leahey has worked in NIDA since 2010, providing support to acquisition and program staff, as they implemented various government initiatives, including the most recent Efficient Spending Policy.

Jeff Weiner, NIDA's Chief Information Officer left in July to help oversee business improvement processes at the Center for Tobacco Products at FDA. Jeff has been at NIH for twenty years and joined NIDA three years ago to help the IRMB group and NIDA improve our IT programs. His efforts helped solidify our IT operations, mature our IT portfolio activities, and expand community involvement in NIDA IT decisions. His commitment to enhancing the NIH and NIDA missions through IT services is greatly appreciated.

Retirements

Dr. Bennett Fletcher retired on September 1, 2012. Bennett joined NIDA in 1987. His first assignment was to establish a study to evaluate treatment outcomes, which became the Drug Abuse Treatment Outcome Studies (DATOS), a prospective follow-up study of patients in drug abuse treatment that ran from 1989 until about 2008. DATOS resulted in more than 85 peer-reviewed publications and laid the groundwork for research on the organization and delivery of treatment services. Dr. Fletcher was also instrumental in building a research demonstration program on drug abuse treatment to prevent HIV/AIDS, which produced a number of important studies, including DATAR (PI D. Dwayne Simpson, TCU) and the Key-Crest studies (PI James Inciardi, U. Delaware). From 1996 until 2004, Dr. Fletcher was chief of the Services Research Branch. He expanded the role of health services research to include studies of the economics and financing of treatment, research on special populations, and research on the organization and management of treatment services. In 1992, he established a research program focused on the interaction between drug abuse treatment and the criminal justice system. This program led to the Criminal Justice – Drug Abuse Treatment Studies (CJ-DATS), an ongoing cooperative research program that has expanded NIDA’s focus on the science of implementation and how evidence-based treatment is effectively integrated into the criminal justice system. Dr. Fletcher worked with NIDA colleagues to produce and publish several widely-distributed publications, including the *Principles of Drug Addiction Treatment* and the *Principles of Drug Abuse Treatment for Criminal Justice Populations*. From 2002 until his retirement, Dr. Fletcher was the Science Officer on CJ-DATS.

Karen Skinner, Ph.D., retired from NIDA on June 30th, 2012. Prior to her retirement, Dr. Karen Skinner had been with NIH, including NIDA, for over 36 years, and her many contributions have been far reaching; from developing novel, high impact programs to bringing high caliber investigators to the area of drug abuse and addiction. Her commitment and dedication to our shared mission, and her love of science have inspired us. Karen sees the big picture and the molecular details as well – after all she is a chemist. As a carryover from her days as a writer at Chemistry and Engineering News, she encouraged plain language and clear writing for all NIDA documents before it became fashionable at the NIH and government-wide levels. Her ability to see the connections among otherwise disparate programs and her intuition for where the science is going next are among her strengths. Karen has always had her hand on the pulse of technology and has always been “out front” to lead us into the areas that are barely visible on the horizon. Her discerning eye and her breadth of knowledge have identified key developments in areas of science that could be made relevant to the mission of NIDA. Karen was instrumental in establishing the Basic Neuroscience Program at NIDA. She was the first to recognize the importance of the BMAP—Brain Molecular Anatomy Project—which later morphed into the Neuroscience Blueprint. She envisioned the Neuroscience Information Framework (NIF), created the initiative and shepherded it through its gestation. Karen created the NIDA Neuroscience Consortium and, while Acting Director of DBNBR, instituted DBNBR’s Science Friday meetings and facilitated the incorporation of the internet into the everyday activities of NIDA/DBNBR staff. She insisted on having an on-site library or reading room, which became the Roger Brown room, named in memory of a DBNBR program officer. She would cold-call researchers (often prominent prize winners) to get them to apply to NIDA - Sidney Brenner, Paul Greengard, David Bredt, Richard Zare and Mark Wightman to name a few. She hired and mentored Jonathan Pollock and selected David Shurtleff as her deputy. Her impact on NIDA has been significant and her imprint is still evident in all we do. As is typical of Karen’s character—she will be serving as a volunteer at NIDA to continue to have her fingerprints on a variety of programs that are of interest to her.

GRANTEE HONORS

Dr. Marilyn E. Carroll, University of Minnesota, was the recipient of the Marian W. Fischman Memorial Award given by the College on Problems of Drug Dependence at its annual meeting, June 9-14, 2012, Palm Springs, CA. In 1991 Dr. Carroll became NIDA's 12th MERIT awardee and the 3rd female recipient, and she is a current NIDA K05 awardee. Dr. Carroll has had continuous NIDA grant support since 1980 for her research on drug self-administration using the rodent and non-human primate models. She is nationally and internationally recognized for identifying and studying factors that affect vulnerability to drug abuse throughout the major phases of drug addiction (i.e., acquisition, escalation, maintenance, extinction and relapse), studying behavioral and pharmacologic interventions targeting those phases, and studying sex differences in self-administration outcomes and the contribution of gonadal hormones, especially estrogen and progesterone.

Mike Dennis and **Chris Scott** received the Dan Anderson Award for recovery related research at the National Association of Addiction Treatment Providers (NAATP) annual conference (May 21, 2012).

Brian Hicks, Ph.D. was awarded the Fulker Award at the 2012 meeting of the Behavior Genetics Association for his "particularly meritorious paper" in the journal Behavior Genetics, Hicks BM, Schalet BD, Malone SM, Iacono WG, McGue M (2011) Psychometric and genetic architecture of substance use disorder and behavioral disinhibition measures for gene association studies. Behav. Genet. 41: 459-475

Dr. Krista M. Lisdahl, a Principal Investigator at the University of Wisconsin-Milwaukee, was selected as one of 20 NIH recipients of the 2011 Presidential Early Career Award in Science and Engineering (PECASE).

Jason Burrow Sanchez, University of Utah, was awarded the 1st Place Early Career Poster Award at the 2012 Summer APA Convention.

Dr. Terrence Thornberry's paper (Smith CA, Ireland TOI, Park A, Thornberry TOI, Elwyn L. 2011; Intergenerational continuities and discontinuities in intimate partner violence: A two generational prospective study. Journal of Interpersonal Violence, 26, 3720-3752) was selected as among the "Best of 2011 Violence Research" July 2012, by an invited panel convened for Psychology of Violence.

Dr. Lisa Metsch, Co-Principal Investigator of the CTN Florida Node Alliance (FNA), is the first incumbent of the Stephen Smith Professorship and the new Chair of the Department of Sociomedical Sciences (SMS) at Columbia University's Mailman School of Public Health. Lisa will continue to be actively involved in all of the research being carried out with the CTN.

CTN 0028 study (Paula Riggs, M.D. and Theresa Winhusen, Ph.D., Co-Principle Investigators) received the 2012 Elaine Schlosser Lewis Award for research on Attention Deficit Disorder by the American Academy of Child and Adolescent Psychiatry (AACAP). Dr Riggs will be giving the Honor's presentation of study and clinician implications at the upcoming Annual AACAP meeting

in October, 2012. In addition, the Journal of the American Academy of Child and Adolescent Psychiatry (JAACAP) will recognize the CTN 0028 flagship paper as the best research paper on ADHD published in the JAACAP in the past year. JAACAP is the primary journal reaching the field of child/adolescent psychiatry as well as pediatricians and mental health professionals working in this field.”

Ed Johnson, Southeast ATTC South Carolina Program Manager and CTN collaborator, was one of eight individuals who received the 2012 Nyswander-Dole Award from the American Association for the Treatment of Opioid Dependence (AATOD). The award is named after Drs. Marie Nyswander and Vincent Dole, who pioneered the use of medication in the treatment of opioid dependence, and acknowledges efforts in patient advocacy, stigma reduction, improving quality of care and increasing access to care.

Lisa R. Thomas, Ph.D., CTN Research Scientist at the University of Washington, received the Young Investigator Award for Excellence in Research from the Native Research Network, Inc. The award was presented at the 2012 Annual Native Health Research Conference held July 16-19, 2012 in Seattle, Washington.

IN MEMORIAM

Dr. Toni Shippenberg, a highly respected IRP scientist, died after a long struggle with cancer. She was recognized both within NIDA and throughout the larger scientific community as an influential and distinguished researcher in the field of neuroscience, focusing for the past 2 decades on addiction research in support of NIDA's mission. Toni elegantly combined genetics with behavioral pharmacology to uncover the pivotal role that the dynorphin/ κ -opioid receptor system plays in the control of dopamine dynamics in the brain's reward center and, secondarily, in mood, motivation, and cognitive functions. Thanks to her seminal discoveries, the kappa opioid system has become a major focus of translational research that could lead to the development of novel medications for the treatment of several psychiatric disorders, including addiction. Her contributions to neuroscience and neuropharmacology leave an outstanding legacy that extends throughout this country and internationally, with achievements that include appointments to the prestigious Senior Biomedical Research Service (SBRS) and an honorary professorship at the University of Queensland in Australia. Dr. Shippenberg received numerous awards throughout her career and will be remembered not only as a distinguished neuroscientist, but also as a devoted mentor to many in our community who have gone on to achieve successful scientific careers of their own, all over the world.