

RESEARCH FINDINGS

BASIC AND BEHAVIORAL RESEARCH

Protracted Withdrawal From Cocaine Self-Administration Flips the Switch on 5-HT(1B) Receptor Modulation of Cocaine Abuse-Related Behaviors

The role of serotonin-1B receptors (5-HT(1B)Rs) in modulating cocaine abuse-related behaviors has been controversial due to discrepancies between pharmacological and gene knockout approaches and opposite influences on cocaine self-administration versus cocaine-seeking behavior. The authors hypothesized that modulation of these behaviors via 5-HT(1B)Rs in the mesolimbic pathway may vary depending on the stage of the addiction cycle. To test this hypothesis, they examined the effects of increasing 5-HT(1B)R production by microinfusing a viral vector expressing either green fluorescent protein and 5-HT(1B)R or green fluorescent protein alone into the medial nucleus accumbens shell of rats either during maintenance of cocaine self-administration (i.e., active drug use) or during protracted withdrawal. 5-HT(1B)R receptor gene transfer during maintenance shifted the dose-response curve for cocaine self-administration upward and to the left and increased breakpoints and cocaine intake on a progressive ratio schedule, consistent with enhanced reinforcing effects of cocaine. In contrast, following 21 days of forced abstinence, 5-HT(1B)R gene transfer attenuated breakpoints and cocaine intake on a progressive ratio schedule of reinforcement, as well as cue- and cocaine-primed reinstatement of cocaine-seeking behavior. This unique pattern of effects suggests that mesolimbic 5-HT(1B)Rs differentially modulate cocaine abuse-related behaviors, with a facilitative influence during periods of active drug use, in striking contrast to an inhibitory influence during protracted withdrawal. These findings suggest that targeting 5-HT(1B)Rs may lead to a novel treatment for cocaine dependence and that the therapeutic efficacy of these treatments may vary depending on the stage of the addiction cycle. Pentkowski NS, Cheung TH, Toy WA, Adams MD, Neumaier JF, Neisewander JL. Protracted withdrawal from cocaine self-administration flips the switch on 5-HT(1B) receptor modulation of cocaine abuse-related behaviors. *Biol Psychiatry*. 2012 Sep 1; 72(5): 396-404. doi: 10.1016/j.biopsych.2012.03.024.

The Synthesis and in vivo Evaluation of [18F]PF-9811: A Novel PET Ligand for Imaging Brain Fatty Acid Amide Hydrolase (FAAH)

Fatty acid amide hydrolase (FAAH) is responsible for the enzymatic degradation of the fatty acid amide family of signaling lipids, including the endogenous cannabinoid (endocannabinoid) anandamide. The involvement of the endocannabinoid system in pain and other nervous system disorders has made FAAH an attractive target for drug development. Companion molecular imaging probes are needed, however, to assess FAAH inhibition in the nervous system in vivo. The authors report here the synthesis and in vivo evaluation of [(18F)PF-9811], a novel PET ligand for non-invasive imaging of FAAH in the brain. The potency and selectivity of unlabeled PF-9811 were determined by activity-based protein profiling (ABPP) both in vitro and in vivo. [(18F)PF-9811] was synthesized in a 3-step, one-pot reaction sequence, followed by HPLC purification. Biological evaluation was performed by biodistribution and dynamic PET imaging studies in male rats. The specificity of [(18F)PF-9811] uptake was evaluated by pre-administration of PF-04457845, a potent and selective FAAH inhibitor, 1h prior to radiotracer injection. Biodistribution studies show good uptake (SUV~0.8 at 90 min) of [(18F)PF-9811] in rat brain, with significant reduction of the radiotracer in all brain regions (37%-73% at 90 min) in blocking experiments. Dynamic PET imaging experiments in rat confirmed the heterogeneous uptake of [(18F)PF-9811] in brain regions with high FAAH enzymatic

activity, as well as statistically significant reductions in signal following pre-administration of the blocking compound PF-04457845. The authors conclude that [(18)F]PF-9811 is a promising PET imaging agent for FAAH. Biodistribution and PET imaging experiments show that the tracer has good uptake in brain, regional heterogeneity, and specific binding as determined by blocking experiments with the highly potent and selective FAAH inhibitor, PF-04457845. Skaddan MB, Zhang L, Johnson DS, Zhu A, Zasadny KR, Coelho RV, Kuszpit K, Currier G, Fan KH, Beck EM, Chen L, Drozda SE, Balan G, Niphakis M, Cravatt BF, Ahn K, Bocan T, Villalobos A. The synthesis and in vivo evaluation of [18F]PF-9811: a novel PET ligand for imaging brain fatty acid amide hydrolase (FAAH). *Nucl Med Biol.* 2012 Oct; 39(7): 1058-1067. doi: 10.1016/j.nucmedbio.2012.03.011.

Genome-Wide Association Study of d-Amphetamine Response In Healthy Volunteers Identifies Putative Associations, Including Cadherin 13 (CDH13)

Both the subjective response to d-amphetamine and the risk for amphetamine addiction are known to be heritable traits. Because subjective responses to drugs may predict drug addiction, identifying alleles that influence acute response may also provide insight into the genetic risk factors for drug abuse. The authors performed a Genome Wide Association Study (GWAS) for the subjective responses to amphetamine in 381 non-drug abusing healthy volunteers. Responses to amphetamine were measured using a double-blind, placebo-controlled, within-subjects design. They used sparse factor analysis to reduce the dimensionality of the data to ten factors. They identified several putative associations; the strongest was between a positive subjective drug-response factor and a SNP (rs3784943) in the 8(th) intron of cadherin 13 (CDH13; $P = 4.58 \times 10^{-8}$), a gene previously associated with a number of psychiatric traits including methamphetamine dependence. Additionally, they observed a putative association between a factor representing the degree of positive affect at baseline and a SNP (rs472402) in the 1(st) intron of steroid-5-alpha-reductase-alpha-polypeptide-1 (SRD5A1; $P = 2.53 \times 10^{-7}$), a gene whose protein product catalyzes the rate-limiting step in synthesis of the neurosteroid allopregnanolone. This SNP belongs to an LD-block that has been previously associated with the expression of SRD5A1 and differences in SRD5A1 enzymatic activity. The purpose of this study was to begin to explore the genetic basis of subjective responses to stimulant drugs using a GWAS approach in a modestly sized sample. The authors' approach provides a case study for analysis of high-dimensional intermediate pharmacogenomic phenotypes, which may be more tractable than clinical diagnoses. Hart AB, Engelhardt BE, Wardle MC, Sokoloff G, Stephens M, de Wit H, Palmer AA. Genome-wide association study of d-amphetamine response in healthy volunteers identifies putative associations, including cadherin 13 (CDH13). *PLoS One.* 2012; 7(8): e42646.

Peripheral Ammonia as a Mediator of Methamphetamine Neurotoxicity

Ammonia is metabolized by the liver and has established neurological effects. The current study examined the possibility that ammonia contributes to the neurotoxic effects of methamphetamine (METH). The results show that a binge dosing regimen of METH to the rat increased plasma and brain ammonia concentrations that were paralleled by evidence of hepatotoxicity. The role of peripheral ammonia in the neurotoxic effects of METH was further substantiated by the demonstration that the enhancement of peripheral ammonia excretion blocked the increases in brain and plasma ammonia and attenuated the long-term depletions of dopamine and serotonin typically produced by METH. Conversely, the localized perfusion of ammonia in combination with METH, but not METH alone or ammonia alone, into the striatum recapitulated the neuronal damage produced by the systemic administration of METH. Furthermore, this damage produced by the local administration of

ammonia and METH was blocked by the GYKI 52466 [4-(8-methyl-9H-1,3-dioxolo[4,5-h][2,3] benzodiazepin-5-yl)-benzamine hydrochloride], an AMPA receptor antagonist. These findings highlight the importance of ammonia derived from the periphery as a small-molecule mediator of METH neurotoxicity and more broadly emphasize the importance of peripheral organ damage as a possible mechanism that mediates the neuropathology produced by drugs of abuse and other neuroactive molecules. Halpin LE, Yamamoto BK. Peripheral ammonia as a mediator of methamphetamine neurotoxicity. *J Neurosci*. 2012 Sep 19; 32(38): 13155-13163.

FosB Differentially Modulates Nucleus Accumbens Direct and Indirect Pathway Function

Synaptic modifications in nucleus accumbens (NAc) medium spiny neurons (MSNs) play a key role in adaptive and pathological reward-dependent learning, including maladaptive responses involved in drug addiction. NAc MSNs participate in two parallel circuits, direct and indirect pathways that subservise distinct behavioral functions. Modification of NAc MSN synapses may occur in part via changes in the transcriptional potential of certain genes in a cell type-specific manner. The transcription factor FosB is one of the key proteins implicated in the gene expression changes in NAc caused by drugs of abuse, yet its effects on synaptic function in NAc MSNs are unknown. Here, the authors demonstrate that overexpression of FosB decreased excitatory synaptic strength and likely increased silent synapses onto D1 dopamine receptor-expressing direct pathway MSNs in both the NAc shell and core. In contrast, FosB likely decreased silent synapses onto NAc shell, but not core, D2 dopamine receptor-expressing indirect pathway MSNs. Analysis of NAc MSN dendritic spine morphology revealed that FosB increased the density of immature spines in D1 direct but not D2 indirect pathway MSNs. To determine the behavioral consequences of cell type-specific actions of FosB, the authors selectively overexpressed FosB in D1 direct or D2 indirect MSNs in NAc in vivo and found that direct (but not indirect) pathway MSN expression enhances behavioral responses to cocaine. These results reveal that FosB in NAc differentially modulates synaptic properties and reward-related behaviors in a cell type- and subregion-specific fashion. Grueter BA, Robison AJ, Neve RL, Nestler EJ, Malenka RC. FosB differentially modulates nucleus accumbens direct and indirect pathway function. *Proc Natl Acad Sci U S A*. 2013 Jan 14. [Epub ahead of print].

Adolescent Morphine Exposure Affects Long-Term Microglial Function and Later-Life Relapse Liability In A Model Of Addiction

Adolescence in humans represents a unique developmental time point associated with increased risk-taking behavior and experimentation with drugs of abuse. The authors hypothesized that exposure to drugs of abuse during adolescence may increase the risk of addiction in adulthood. To test this, rats were treated with a subchronic regimen of morphine or saline in adolescence, and their preference for morphine was examined using conditioned place preference (CPP) and drug-induced reinstatement in adulthood. The initial preference for morphine did not differ between groups; however, rats treated with morphine during adolescence showed robust reinstatement of morphine CPP after drug re-exposure in adulthood. This effect was not seen in rats pretreated with a subchronic regimen of morphine as adults, suggesting that exposure to morphine specifically during adolescence increases the risk of relapse to drug-seeking behavior in adulthood. The authors have previously established a role for microglia, the immune cells of the brain, and immune molecules in the risk of drug-induced reinstatement of morphine CPP. Thus, they examined the role of microglia within the nucleus accumbens of these rats and determined that rats exposed to morphine during adolescence had a significant increase in Toll-like receptor 4 (TLR4) mRNA and protein expression specifically on microglia. Morphine binds to TLR4 directly, and this increase in TLR4 was associated with exaggerated morphine-

induced TLR4 signaling and microglial activation in rats previously exposed to morphine during adolescence. These data suggest that long-term changes in microglial function, caused by adolescent morphine exposure, alter the risk of drug-induced reinstatement in adulthood. Schwarz JM, Bilbo SD. Adolescent morphine exposure affects long-term microglial function and later-life relapse liability in a model of addiction. *J Neurosci.* 2013 Jan 16; 33(3): 961-971. doi: 10.1523/JNEUROSCI.2516-12.2013.

Assessing the Relative Stability of Dimer Interfaces In G Protein-Coupled Receptors

Considerable evidence has accumulated in recent years suggesting that G protein-coupled receptors (GPCRs) associate in the plasma membrane to form homo- and/or heteromers. Nevertheless, the stoichiometry, fraction and lifetime of such receptor complexes in living cells remain topics of intense debate. Motivated by experimental data suggesting differing stabilities for homomers of the cognate human beta 1- and beta 2-adrenergic receptors, the authors have carried out approximately 160 microseconds of biased molecular dynamics simulations to calculate the dimerization free energy of crystal structure-based models of these receptors, interacting at two interfaces that have often been implicated in GPCR association under physiological conditions. Specifically, results are presented for simulations of coarse-grained (MARTINI-based) and atomistic representations of each receptor, in homodimeric configurations with either transmembrane helices TM1/H8 or TM4/3 at the interface, in an explicit lipid bilayer. These results support a definite contribution to the relative stability of GPCR dimers from both interface sequence and configuration. The authors conclude that beta 1- and beta 2-adrenergic receptor homodimers with TM1/H8 at the interface are more stable than those involving TM4/3, and that this might be reconciled with experimental studies by considering a model of oligomerization in which more stable TM1 homodimers diffuse through the membrane, transiently interacting with other protomers at interfaces involving other TM helices. Johnston JM, Wang H, Provasi D, Filizola M. Assessing the relative stability of dimer interfaces in G protein-coupled receptors. *PLoS Comput Biol.* 2012 Aug; 8(8): e1002649. doi: 10.1371/journal.pcbi.1002649.

Epigenetic Inheritance Of a Cocaine-Resistance Phenotype The authors delineated a heritable phenotype resulting from the self-administration of cocaine in rats. They observed delayed acquisition and reduced maintenance of cocaine self-administration in male, but not female, offspring of sires that self-administered cocaine. Brain-derived neurotrophic factor (BDNF) mRNA and BDNF protein were increased in the medial prefrontal cortex (mPFC), and there was an increased association of acetylated histone H3 with BDNF promoters in only the male offspring of cocaine-experienced sires. Administration of a BDNF receptor antagonist (the TrkB receptor antagonist ANA-12) reversed the diminished cocaine self-administration in male cocaine-sired rats. In addition, the association of acetylated histone H3 with BDNF promoters was increased in the sperm of sires that self-administered cocaine. Collectively, these findings indicate that voluntary paternal ingestion of cocaine results in epigenetic reprogramming of the germline, having profound effects on mPFC gene expression and resistance to cocaine reinforcement in male offspring. Vassoler FM, White, SL, Schmidt, HD, Sadri-Vakili, S, Pierce, RC. Epigenetic inheritance of a cocaine-resistance phenotype. *Nature Neuroscience.* 2013, 16: 42–47. doi:10.1038/nn.3280.

FTO Genotype Is Associated With Phenotypic Variability Of Body Mass Index There is evidence across several species for genetic control of phenotypic variation of complex traits, such that the variance among phenotypes is genotype dependent. Understanding genetic control of variability is important in evolutionary biology, agricultural selection programmes and human

medicine, yet for complex traits, no individual genetic variants associated with variance, as opposed to the mean, have been identified. Here the authors perform a meta-analysis of genome-wide association studies of phenotypic variation using approximately 170,000 samples on height and body mass index (BMI) in human populations. They report evidence that the single nucleotide polymorphism (SNP) rs7202116 at the FTO gene locus, which is known to be associated with obesity (as measured by mean BMI for each rs7202116 genotype), is also associated with phenotypic variability. They show that the results are not due to scale effects or other artifacts, and find no other experiment-wise significant evidence for effects on variability, either at loci other than FTO for BMI or at any locus for height. The difference in variance for BMI among individuals with opposite homozygous genotypes at the FTO locus is approximately 7%, corresponding to a difference of approximately 0.5 kilograms in the standard deviation of weight. These results indicate that genetic variants can be discovered that are associated with variability, and that between-person variability in obesity can partly be explained by the genotype at the FTO locus. The results are consistent with reported FTO by environment interactions for BMI, possibly mediated by DNA methylation. The authors' BMI results for other SNPs and their height results for all SNPs suggest that most genetic variants, including those that influence mean height or mean BMI, are not associated with phenotypic variance, or that their effects on variability are too small to detect even with samples sizes greater than 100,000. Yang J, Loos RJ, Powell JE, Medland SE, Speliotes EK, Chasman DI, Rose LM, Thorleifsson G, Steinthorsdottir V, Magi R, Waite L, Smith AV, Yerges-Armstrong LM, Monda KL, Hadley D, Mahajan A, Li G, Kapur K, Vitart V, Huffman JE, Wang SR, Palmer C, et al. FTO genotype is associated with phenotypic variability of body mass index. *Nature*. 2012 Oct 11; 490(7419): 267-272. Epub 2012 Sep 16.

Within-Family Environmental Transmission of Drug Abuse: A Swedish National Study Drug abuse (DA) strongly runs in families. Does this result solely from genetic factors or does the family environment contribute? The objective of this study was to determine the familial environmental contribution to the risk for DA. The study design was a follow-up in 9 public databases (1961-2009) in siblings and spouses. The study was conducted in Sweden. Participants comprised a total of 137,199 sibling pairs and 7,561 spousal pairs containing a proband with DA and matched control probands. Main outcomes measures were drug abuse recorded in medical, legal, or pharmacy registry records. In the best-fit model, which contained significant linear, quadratic, and cubic effects, among full sibling pairs containing a proband with DA, the relative risk for DA in the sibling declined from more than 6.0 for siblings born within 2 years of each other to less than 4.5 when born 10 years apart. Controlling for age differences in full sibling pairs, the hazard rate for DA in a sibling when the affected proband was older vs younger was 1.42 (95% CI, 1.31-1.54). In the best-fit model, which contained significant linear, quadratic, and cubic effects, among spousal pairs containing a proband with DA, the relative risk for DA in the spouse declined from more than 25.0 within 1 year of proband DA registration to 6.0 after 5 years. The authors concluded that controlling for genetic effects by examining only full siblings, sibling resemblance for the risk for DA was significantly greater in pairs closer vs more distant in age. Older siblings more strongly transmitted the risk for DA to their younger siblings than vice versa. After one spouse is registered for DA, the other spouse has a large short-lived increase in DA risk. These results support strong familial environmental influences on DA at various life stages. A complete understanding of the familial transmission of DA will require knowledge of how genetic and familial environmental risk factors act and interact over development. Kendler KS, Ohlsson H, Sundquist K, Sundquist J. Within-family environmental transmission of drug abuse: A Swedish national study. *Arch Gen Psychiatry*. 2012 Dec 10:1-8. doi: 10.1001/jamapsychiatry.2013.276. [Epub ahead of print].

Human Dorsal Anterior Cingulate Cortex Neurons Mediate Ongoing Behavioural Adaptation

The ability to optimize behavioural performance when confronted with continuously evolving environmental demands is a key element of human cognition. The dorsal anterior cingulate cortex (dACC), which lies on the medial surface of the frontal lobes, is important in regulating cognitive control. Hypotheses about its function include guiding reward-based decision making, monitoring for conflict between competing responses and predicting task difficulty. Precise mechanisms of dACC function remain unknown, however, because of the limited number of human neurophysiological studies. Here the authors use functional imaging and human single-neuron recordings to show that the firing of individual dACC neurons encodes current and recent cognitive load. They demonstrate that the modulation of current dACC activity by previous activity produces a behavioural adaptation that accelerates reactions to cues of similar difficulty to previous ones, and retards reactions to cues of different difficulty. Furthermore, this conflict adaptation, or Gratton effect, is abolished after surgically targeted ablation of the dACC. These results demonstrate that the dACC provides a continuously updated prediction of expected cognitive demand to optimize future behavioural responses. In situations with stable cognitive demands, this signal promotes efficiency by hastening responses, but in situations with changing demands, it engenders accuracy by delaying responses. Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, Bush G, Eskandar EN. Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. *Nature*. 2012 Aug 9; 488(7410): 218-221.

In Vivo Genome Editing Using A High-Efficiency TALEN System

The zebrafish (*Danio rerio*) is increasingly being used to study basic vertebrate biology and human disease with a rich array of in vivo genetic and molecular tools. However, the inability to readily modify the genome in a targeted fashion has been a bottleneck in the field. Here the authors show that improvements in artificial transcription activator-like effector nucleases (TALENs) provide a powerful new approach for targeted zebrafish genome editing and functional genomic applications. Using the GoldyTALEN modified scaffold and zebrafish delivery system, they show that this enhanced TALEN toolkit has a high efficiency in inducing locus-specific DNA breaks in somatic and germline tissues. At some loci, this efficacy approaches 100%, including biallelic conversion in somatic tissues that mimics phenotypes seen using morpholino-based targeted gene knockdowns. With this updated TALEN system, the authors successfully used single-stranded DNA oligonucleotides to precisely modify sequences at predefined locations in the zebrafish genome through homology-directed repair, including the introduction of a custom-designed EcoRV site and a modified loxP (mloxP) sequence into somatic tissue in vivo. They further show successful germline transmission of both EcoRV and mloxP engineered chromosomes. This combined approach offers the potential to model genetic variation as well as to generate targeted conditional alleles. Bedell VM, Wang Y, Campbell JM, Poshusta TL, Starker CG, Krug RG 2nd, Tan W, Penheiter SG, Ma AC, Leung AY, Fahrenkrug SC, Carlson DF, Voytas DF, Clark KJ, Essner JJ, Ekker SC. In vivo genome editing using a high-efficiency TALEN system. *Nature*. 2012 Nov 1; 491(7422): 114-118. Epub 2012 Sep 23.

Severe Stress Switches CRF Action in the Nucleus Accumbens From Appetitive To Aversive

Stressors motivate an array of adaptive responses ranging from 'fight or flight' to an internal urgency signal facilitating long-term goals. However, traumatic or chronic uncontrollable stress promotes the onset of major depressive disorder, in which acute stressors lose their motivational properties and are perceived as insurmountable impediments. Consequently, stress-induced depression is a debilitating human condition characterized by an affective shift from engagement of the environment to withdrawal. An emerging neurobiological substrate of depression and associated

pathology is the nucleus accumbens, a region with the capacity to mediate a diverse range of stress responses by interfacing limbic, cognitive and motor circuitry. Here the authors report that corticotropin-releasing factor (CRF), a neuropeptide released in response to acute stressors and other arousing environmental stimuli, acts in the nucleus accumbens of naive mice to increase dopamine release through coactivation of the receptors CRFR1 and CRFR2. Remarkably, severe-stress exposure completely abolished this effect without recovery for at least 90 days. This loss of CRF's capacity to regulate dopamine release in the nucleus accumbens is accompanied by a switch in the reaction to CRF from appetitive to aversive, indicating a diametric change in the emotional response to acute stressors. Thus, the current findings offer a biological substrate for the switch in affect which is central to stress-induced depressive disorders. Lemos JC, Wanat MJ, Smith JS, Reyes BA, Hollon NG, Van Bockstaele EJ, Chavkin C, Phillips PE. Severe stress switches CRF action in the nucleus accumbens from appetitive to aversive. *Nature*. 2012 Oct 18; 490(7420): 402-406. doi: 10.1038/nature11436. Epub 2012 Sep 19.

Constitutive Knockout of the Membrane Cytoskeleton Protein Beta Adducin Decreases Mushroom Spine Density In the Nucleus Accumbens But Does Not Prevent Spine Remodeling In Response To Cocaine

The adducin family of proteins associates with the actin cytoskeleton in a calcium-dependent manner. Beta adducin (betaAdd) is involved in synaptic plasticity in the hippocampus; however, the role of betaAdd in synaptic plasticity in other brain areas is unknown. Using diolistic labeling with the lipophilic dye DiI, the authors found that the density of mature mushroom-shaped spines was significantly decreased in the nucleus accumbens (NAc) in brain slices from betaAdd-knockout (KO) mice as compared to their wildtype (WT) siblings. The effect of 10 days of daily cocaine (15 mg/kg) administration on NAc spine number and locomotor behavior was also measured in betaAdd WT and KO mice. As expected, there was a significant increase in overall spine density in NAc slices from cocaine-treated WT mice at this time-point; however, there was a greater increase in the density of mushroom spines in betaAdd-KO animals following chronic cocaine administration than in WT. In addition, betaAdd-KO mice showed elevated locomotor activity in response to cocaine treatment compared to WT siblings. These results indicate that betaAdd is required for stabilising mature spines under basal conditions in the NAc, but that lack of this protein does not prevent synaptic remodeling following repeated cocaine administration. In addition, these data are consistent with previous studies suggesting that betaAdd may normally be involved in stabilising spines once drug- or experience-dependent remodeling has occurred. Jung Y, Mulholland PJ, Wiseman SL, Judson Chandler L, Picciotto MR. Constitutive knockout of the membrane cytoskeleton protein beta adducin decreases mushroom spine density in the nucleus accumbens but does not prevent spine remodeling in response to cocaine. *Eur J Neurosci*. 2012 Oct 29. [Epub ahead of print].

Circadian Rhythm Of Redox State Regulates Excitability In Suprachiasmatic Nucleus

Neurons Daily rhythms of mammalian physiology, metabolism, and behavior parallel the day-night cycle. They are orchestrated by a central circadian clock in the brain, the suprachiasmatic nucleus (SCN). Transcription of clock genes is sensitive to metabolic changes in reduction and oxidation (redox); however, circadian cycles in protein oxidation have been reported in anucleate cells, where no transcription occurs. The authors investigated whether the SCN also expresses redox cycles and how such metabolic oscillations might affect neuronal physiology. They detected self-sustained circadian rhythms of SCN redox state that required the molecular clockwork. The redox oscillation could determine the excitability of SCN neurons through nontranscriptional modulation of multiple potassium (K(+)) channels. Thus, dynamic regulation of SCN excitability appears to be

closely tied to metabolism that engages the clockwork machinery. Wang TA, Yu YV, Govindaiah G, Ye X, Artinian L, Coleman TP, Sweedler JV, Cox CL, Gillette MU. Circadian rhythm of redox state regulates excitability in suprachiasmatic nucleus neurons. *Science*. 2012 Aug 17; 337(6096): 839-842. Epub 2012 Aug 2.

Transcriptional Architecture and Chromatin Landscape of the Core Circadian Clock In Mammals

The mammalian circadian clock involves a transcriptional feedback loop in which CLOCK and BMAL1 activate the Period and Cryptochrome genes, which then feed back and repress their own transcription. The authors have interrogated the transcriptional architecture of the circadian transcriptional regulatory loop on a genome scale in mouse liver and find a stereotyped, time-dependent pattern of transcription factor binding, RNA polymerase II (RNAPII) recruitment, RNA expression, and chromatin states. They find that the circadian transcriptional cycle of the clock consists of three distinct phases: a poised state, a coordinated de novo transcriptional activation state, and a repressed state. Only 22% of messenger RNA (mRNA) cycling genes are driven by de novo transcription, suggesting that both transcriptional and posttranscriptional mechanisms underlie the mammalian circadian clock. The authors also find that circadian modulation of RNAPII recruitment and chromatin remodeling occurs on a genome-wide scale far greater than that seen previously by gene expression profiling. Koike N, Yoo SH, Huang HC, Kumar V, Lee C, Kim TK, Takahashi JS. Transcriptional architecture and chromatin landscape of the core circadian clock in mammals. *Science*. 2012 Oct 19; 338(6105): 349-354. doi: 10.1126/science.1226339. Epub 2012 Aug 30.

Alzheimer Amyloid-Beta Oligomer Bound To Postsynaptic Prion Protein Activates Fyn To Impair Neurons

Amyloid-beta (Abeta) oligomers are thought to trigger Alzheimer's disease pathophysiology. Cellular prion protein (PrP(C)) selectively binds oligomeric Abeta and can mediate Alzheimer's disease-related phenotypes. The authors examined the specificity, distribution and signaling of Abeta-PrP(C) complexes, seeking to understand how they might alter the function of NMDA receptors (NMDARs) in neurons. PrP(C) is enriched in postsynaptic densities, and Abeta-PrP(C) interaction leads to Fyn kinase activation. Soluble Abeta assemblies derived from the brains of individuals with Alzheimer's disease interacted with PrP(C) to activate Fyn. Abeta engagement of PrP(C)-Fyn signaling yielded phosphorylation of the NR2B subunit of NMDARs, which was coupled to an initial increase and then a loss of surface NMDARs. Abeta-induced dendritic spine loss and lactate dehydrogenase release required both PrP(C) and Fyn, and human familial Alzheimer's disease transgene-induced convulsive seizures did not occur in mice lacking PrP(C). These results delineate an Abeta oligomer signal transduction pathway that requires PrP(C) and Fyn to alter synaptic function, with deleterious consequences in Alzheimer's disease. Um JW, Nygaard HB, Heiss JK, Kostylev MA, Stagi M, Vortmeyer A, Wisniewski T, Gunther EC, Strittmatter SM. Alzheimer amyloid-beta oligomer bound to postsynaptic prion protein activates Fyn to impair neurons. *Nat Neurosci*. 2012. Sep; 15(9): 1227-1235. Epub 2012 Jul 22.

Coactivation of Multiple Tightly Coupled Calcium Channels Triggers Spontaneous Release Of GABA

Voltage-activated Ca(2+) channels (VACCs) mediate Ca(2+) influx to trigger action potential-evoked neurotransmitter release, but the mechanism by which Ca(2+) regulates spontaneous transmission is unclear. The authors found that VACCs are the major physiological triggers for spontaneous release at mouse neocortical inhibitory synapses. Moreover, despite the absence of a synchronizing action potential, they found that spontaneous fusion of a GABA-containing vesicle required the activation of multiple tightly coupled VACCs of variable type.

Williams C, Chen W, Lee CH, Yaeger D, Vyleta NP, Smith SM. Coactivation of multiple tightly coupled calcium channels triggers spontaneous release of GABA. *Nat Neurosci.* 2012 Sep; 15(9): 1195-1197. doi: 10.1038/nn.3162. Epub 2012 Jul 29.

Low Prefrontal PSA-NCAM Confers Risk For Alcoholism-Related Behavior The factors underlying vulnerability to alcoholism are largely unknown. The authors identified in rodents an innate endophenotype predicting individual risk for alcohol-related behaviors that was associated with decreased expression of the neuroplasticity-related polysialylated neural cell adhesion molecule (PSA-NCAM). Depletion of PSA-NCAM in the ventromedial prefrontal cortex was sufficient to render mice unable to extinguish alcohol seeking, indicating a causal role of naturally occurring variation. These data suggest a mechanism of aberrant prefrontal neuroplasticity that underlies enhanced propensity for inflexible addiction-related behavior. Barker JM, Torregrossa MM, Taylor JR. Low prefrontal PSA-NCAM confers risk for alcoholism-related behavior. *Nat Neurosci.* 2012 Oct; 15(10): 1356-2358. Epub 2012 Aug 26.

Withdrawal from Cocaine Self-Administration Alters NMDA Receptor-Mediated Ca²⁺ Entry in Nucleus Accumbens Dendritic Spines The authors previously showed that the time-dependent intensification (incubation) of cue-induced cocaine seeking after withdrawal from extended-access cocaine self-administration is accompanied by accumulation of Ca²⁺-permeable AMPA receptors (CP-AMPA) in the rat nucleus accumbens (NAc). These results suggest an enduring change in Ca²⁺ signaling in NAc dendritic spines. The purpose of the present study was to determine if Ca²⁺ signaling via NMDA receptors (NMDARs) is also altered after incubation. Rats self-administered cocaine or saline for 10 days (6 h/day). After 45-47 days of withdrawal, NMDAR-mediated Ca²⁺ entry elicited by glutamate uncaging was monitored in individual NAc dendritic spines. NMDAR currents were simultaneously recorded using whole cell patch clamp recordings. The authors also measured NMDAR subunit levels in a postsynaptic density (PSD) fraction prepared from the NAc of identically treated rats. NMDAR currents did not differ between groups, but a smaller percentage of spines in the cocaine group responded to glutamate uncaging with NMDAR-mediated Ca²⁺ entry. No significant group differences in NMDAR subunit protein levels were found. The decrease in the proportion of spines showing NMDAR-mediated Ca²⁺ entry suggests that NAc neurons in the cocaine group contain more spines which lack NMDARs (non-responding spines). The fact that cocaine and saline groups did not differ in NMDAR currents or NMDAR subunit levels suggests that the number of NMDARs on responding spines is not significantly altered by cocaine exposure. These findings are discussed in light of increases in dendritic spine density in the NAc observed after withdrawal from repeated cocaine exposure. Ferrario CR, Goussakov I, Stutzmann GE, Wolf ME. Withdrawal from cocaine self-administration alters NMDA receptor-mediated Ca²⁺ entry in nucleus accumbens dendritic spines. *PLoS One.* 2012; 7(8): e40898. Epub 2012 Aug 3.

Acetylcholine as a Neuromodulator: Cholinergic Signaling Shapes Nervous System Function and Behavior Acetylcholine in the brain alters neuronal excitability, influences synaptic transmission, induces synaptic plasticity, and coordinates firing of groups of neurons. As a result, it changes the state of neuronal networks throughout the brain and modifies their response to internal and external inputs: the classical role of a neuromodulator. Here, the authors identify actions of cholinergic signaling on cellular and synaptic properties of neurons in several brain areas and discuss consequences of this signaling on behaviors related to drug abuse, attention, food intake, and affect. The diverse effects of acetylcholine depend on site of release, receptor subtypes, and

target neuronal population; however, a common theme is that acetylcholine potentiates behaviors that are adaptive to environmental stimuli and decreases responses to ongoing stimuli that do not require immediate action. The ability of acetylcholine to coordinate the response of neuronal networks in many brain areas makes cholinergic modulation an essential mechanism underlying complex behaviors. Picciotto MR, Higley MJ, Mineur YS. Acetylcholine as a neuromodulator: cholinergic signaling shapes nervous system function and behavior. *Neuron*. 2012 Oct 4; 76(1): 116-129.

Modulating Neuromodulation By Receptor Membrane Traffic in the Endocytic Pathway

Cellular responsiveness to many neuromodulators is controlled by endocytosis of the transmembrane receptors that transduce their effects. Endocytic membrane trafficking of particular neuromodulator receptors exhibits remarkable diversity and specificity, determined largely by molecular sorting operations that guide receptors at trafficking branchpoints after endocytosis. In this Review, the authors discuss recent progress in elucidating mechanisms mediating the molecular sorting of neuromodulator receptors in the endocytic pathway. There is emerging evidence that endocytic trafficking of neuromodulator receptors, in addition to influencing longer-term cellular responsiveness under conditions of prolonged or repeated activation, may also affect the acute response. Physiological and pathological consequences of defined receptor trafficking events are only now being elucidated, but it is already apparent that endocytosis of neuromodulator receptors has a significant impact on the actions of therapeutic drugs. The present data also suggest, conversely, that mechanisms of receptor endocytosis and molecular sorting may themselves represent promising targets for therapeutic manipulation. von Zastrow M, Williams JT. Modulating neuromodulation by receptor membrane traffic in the endocytic pathway. *Neuron*. 2012 Oct 4; 76(1): 22-32.

Orphan GPCRs and Neuromodulation Most G protein-coupled receptors (GPCRs) started as orphan GPCRs. Matching them to known neuromodulators led to the elucidation of the broad diversity of the neuroreceptor families. Moreover, orphan GPCRs have also been used as targets to discover novel neuromodulators. These discoveries have had profound impact on our understanding of brain function. Here, the author presents an overview of how some of the novel neuropeptides have enlarged our comprehension of responses that direct sleep/wakefulness, the onset of obesity and the feeding response. The author also discusses other advances gained from orphan GPCR studies such as the concept of specificity in neuromodulation or of receptors acting as sensors instead of synaptic transmitters. Finally, the author suggests that the recently discovered neuromodulators may hold the keys to our understanding of higher brain functions and psychiatric disorders. Civelli O. Orphan GPCRs and neuromodulation. *Neuron*. 2012 Oct 4; 76(1): 12-21. doi: 10.1016/j.neuron.2012.09.009.

DAGL-Beta Inhibition Perturbs a Lipid Network Involved In Macrophage Inflammatory Responses

The endocannabinoid 2-arachidonoylglycerol (2-AG) is biosynthesized by diacylglycerol lipases DAGLalpha and DAGLbeta. Chemical probes to perturb DAGLs are needed to characterize endocannabinoid function in biological processes. Here the authors report a series of 1,2,3-triazole urea inhibitors, along with paired negative-control and activity-based probes, for the functional analysis of DAGLbeta in living systems. Optimized inhibitors showed high selectivity for DAGLbeta over other serine hydrolases, including DAGLalpha (approximately 60-fold selectivity), and the limited off-targets, such as ABHD6, were also inhibited by the negative-control probe. Using these agents and Daglb(-/-) mice, the authors show that DAGLbeta

inactivation lowers 2-AG, as well as arachidonic acid and eicosanoids, in mouse peritoneal macrophages in a manner that is distinct and complementary to disruption of cytosolic phospholipase-A2. They observed a corresponding reduction in lipopolysaccharide-induced tumor necrosis factor-alpha release. These findings indicate that AGLbeta is a key metabolic hub within a lipid network that regulates proinflammatory responses in macrophages. Hsu KL, Tsuboi K, Adibekian A, Pugh H, Masuda K, Cravatt BF. DAGL-beta inhibition perturbs a lipid network involved in macrophage inflammatory responses. *Nat Chem Biol*. 2012 Oct 28. doi: 10.1038/nchembio.1105. [Epub ahead of print].

Methamphetamine Influences On Brain And Behavior: Unsafe At Any Speed?

Methamphetamine damages monoamine-containing nerve terminals in the brains of both animals and human drug abusers, and the cellular mechanisms underlying this injury have been extensively studied. More recently, the growing evidence for methamphetamine influences on memory and executive function of human users has prompted studies of cognitive impairments in methamphetamine-exposed animals. After summarizing current knowledge about the cellular mechanisms of methamphetamine-induced brain injury, this review emphasizes research into the brain changes that underlie the cognitive deficits that accompany repeated methamphetamine exposure. Novel approaches to mitigating or reversing methamphetamine-induced brain and behavioral changes are described, and it is argued that the slow spontaneous reversibility of the injury produced by this drug may offer opportunities for novel treatment development. Marshall JF, O'Dell SJ. Methamphetamine influences on brain and behavior: unsafe at any speed? *Trends Neurosci*. 2012 Sep; 35(9): 536-545. doi: 10.1016/j.tins. 2012.05.006. Epub 2012 Jun 16.

Regulation of Endocytic Clathrin Dynamics By Cargo Ubiquitination Some endocytic cargoes control clathrin-coated pit (CCP) maturation, but it is not known how such regulation is communicated. The authors found that mu-opioid neuropeptide receptors signal to their enclosing CCPs by ubiquitination. Nonubiquitinated receptors delay CCPs at an intermediate stage of maturation, after clathrin lattice assembly is complete but before membrane scission. Receptor ubiquitination relieves this inhibition, effectively triggering CCP scission and producing a receptor-containing endocytic vesicle. The ubiquitin modification that conveys this endocytosis-promoting signal is added to the receptor's first cytoplasmic loop, catalyzed by the Smurf2 ubiquitin ligase, and coordinated with activation-dependent receptor phosphorylation and clustering through Smurf2 recruitment by the endocytic adaptor beta-arrestin. Epsin1 detects the signal at the CCP and is required for ubiquitin-promoted scission. This cargo-to-coat communication system mediates a biochemical checkpoint that ensures appropriate receptor ubiquitination for later trafficking, and it controls specific receptor loading into CCPs by sensing when a sufficient quorum is reached. Henry AG, Hislop JN, Grove J, Thorn K, Marsh M, von Zastrow M. Regulation of endocytic clathrin dynamics by cargo ubiquitination. *Dev Cell*. 2012 Sep 11; 23(3): 519-532. Epub 2012 Aug 30.

The CHRNA5-A3-B4 Gene Cluster In Nicotine Addiction Nicotine addiction (NA) is a common and devastating disease, such that the annual number of deaths (world-wide) from tobacco-related diseases will double from 5 million in the year 2000 to 10 million in 2020. Nicotine is the only substance in tobacco which animals and humans will self-administer. NA, as a lifetime diagnosis, has been assessed in various approaches, including the concept of cigarettes per day (CPD). Other assessments of NA are somewhat more comprehensive, such as the Fagerstrom Test for Nicotine Dependence or the American Psychiatric Association's Diagnostic and Statistical Manual (fourth

edition) diagnosis of nicotine dependence. These different measures have moderate agreement with one another. Twin, family and adoption studies have shown that these different assessments of NA have substantial heritability (that fraction of risk attributable to genetic factors). The heritability of NA has been estimated at 50-75%, depending on the definition and the population under study. DNA-based studies of NA have been somewhat successful in identifying a common haplotype, which increases risk for NA among European-origin populations. This haplotype explains a small amount of variance, accounting for approximately 1 CPD, and it includes the alpha5 and the alpha3 nicotinic receptor subunit genes (CHRNA5 and CHRNA3). The review will focus on this implicated region. In this risk region, there is a common (among European-origin people) mis-sense single-nucleotide polymorphism in the CHRNA5 gene (D398N), which changes a conserved amino acid from aspartic acid to asparagine. The risk allele (398N) confers decreased calcium permeability and more extensive desensitization, according to in vitro cellular studies, raising the possibility that a positive allosteric modulator of the (alpha4beta2)(2)alpha5 type of nicotinic receptor might have therapeutic potential in NA. There are other genetic influences on NA in this region, apart from the mis-sense variant, and additional biological experiments must be done to understand them. Berrettini WH, Doyle GA. The CHRNA5-A3-B4 gene cluster in nicotine addiction. *Mol Psychiatry*. 2012 Sep; 17(9): 856-866. Epub 2011 Oct 4.

Innate Immune Sensing of HIV-1 by Dendritic Cells HIV-1-specific antibodies and CD8(+) cytotoxic T cells are detected in most HIV-1-infected people, yet HIV-1 infection is not eradicated. Contributing to the failure to mount a sterilizing immune response may be the inability of antigen-presenting dendritic cells (DCs) to sense HIV-1 during acute infection, and thus the inability to effectively prime naive, HIV-1-specific T cells. Recent findings related to DC-expressed innate immune factors including SAMHD1, TREX1, and TRIM5 provide a molecular basis for understanding why DCs fail to adequately sense invasion by this deadly pathogen and suggest experimental approaches to improve T cell priming to HIV-1 in prophylactic vaccination protocols. Luban J. Innate immune sensing of HIV-1 by dendritic cells. *Cell Host Microbe*. 2012 Oct 18; 12(4): 408-418.

Discovery of Small-Molecule Inhibitors of the TLR1/TLR2 Complex An important regulator of innate immunity, the protein complex of Toll-like receptors 1 and 2 (TLR1/TLR2) provides an attractive target for the treatment of various immune disorders. The novel compound CU-CPT22 can compete with the binding of the specific lipoprotein ligand to TLR1/TLR2 with high inhibitory activity and specificity. Repression of downstream signaling from TNF-alpha and IL-1beta was also observed. Cheng K, Wang X, Zhang S, Yin H. Discovery of small-molecule inhibitors of the TLR1/TLR2 complex. *Angew Chem Int Ed Engl*. 2012 Sep 11 [Epub ahead of print].

Serotonin (2C) Receptor Regulation of Cocaine-Induced Conditioned Place Preference and Locomotor Sensitization Previous studies have identified an inhibitory regulatory role of the 5-HT(2C) receptor in serotonin and dopamine neurotransmission. As cocaine is known to enhance serotonin and dopamine transmission, the ability of 5-HT(2C) receptors to modulate cocaine-induced behaviors was investigated. Alterations in cocaine reward behavior were assessed in the conditioned place preference (CPP) paradigm. Mice were injected with a selective 5-HT(2C) receptor agonist, Ro 60-0175 (0, 1, 3, 10mg/kg, i.p.) prior to cocaine administration (10mg/kg, i.p.) on cocaine-conditioning days. Administration of Ro 60-0175(10mg/kg) prior to cocaine attenuated the development of cocaine place preference. To assess the potential of the 5-HT(2C) receptor to influence cocaine-induced behavioral sensitization, mice were pretreated with either saline or Ro

60-0175 (10mg/kg, i.p.) and 30min later, administered cocaine (20mg/kg, i.p.) or saline once daily for 5 days. Locomotor activity was measured daily following cocaine administration. After a 10-day drug-free period, locomotor activity was measured on day 16 following a challenge injection of cocaine (20mg/kg, i.p.). Pharmacological activation of 5-HT(2C) receptors with Ro 60-0175 attenuated acute cocaine-induced activity on days 1-5, as well as the development of long-term cocaine-induced locomotor sensitization. Thus, activation of 5-HT(2C) receptors attenuated the rewarding and locomotor-stimulating effects of cocaine, as well as inhibited the development of sensitization. The current study shows that 5-HT(2C) receptor activity exerts an inhibitory influence on the short-term and long-term behavioral responses to cocaine. Craig CP, Unterwald EM. Serotonin (2C) receptor regulation of cocaine-induced conditioned place preference and locomotor sensitization. *Behav Brain Res.* 2012 Oct 26. doi:pii: S0166-4328(12)00684-5. 10.1016/j.bbr.2012.10.034. [Epub ahead of print]

Increased Genetic Vulnerability To Smoking At CHRNA5 In Early-Onset Smokers Recent studies have shown an association between cigarettes per day (CPD) and a nonsynonymous single-nucleotide polymorphism in CHRNA5, rs16969968. The objective of the study was to determine whether the association between rs16969968 and smoking is modified by age at onset of regular smoking. Primary data from available genetic studies containing measures of CPD and the genotype of rs16969968 or its proxy were employed. Uniform statistical analysis scripts were run locally. Starting with 94,050 ever-smokers from 43 studies, the authors extracted the heavy smokers (CPD >20) and light smokers (CPD ≤10) with age-at-onset information, reducing the sample size to 33,348. Each study was stratified into early-onset smokers (age at onset ≤16 years) and late-onset smokers (age at onset >16 years), and a logistic regression of heavy vs light smoking with the rs16969968 genotype was computed for each stratum. Meta-analysis was performed within each age-at-onset stratum. Individuals with 1 risk allele at rs16969968 who were early-onset smokers were significantly more likely to be heavy smokers in adulthood (odds ratio [OR] = 1.45; 95% CI, 1.36-1.55; n = 13,843) than were carriers of the risk allele who were late-onset smokers (OR = 1.27; 95% CI, 1.21-1.33, n = 19,505) (P = .01). These results highlight an increased genetic vulnerability to smoking in early-onset smokers. Hartz SM, Short SE, Saccone NL, Culverhouse R, Chen L, Schwantes-An TH, Coon H, Han Y, Stephens SH, Sun J, Chen X, Ducci F, Dueker N, Franceschini N, Frank J, Geller F, Gubjartsson D, Hansel NN, Jiang C, Keskitalo-Vuokko K, Liu Z, Lyytikäinen LP, Michel M, Rawal R, Rosenberger A, Scheet P, Shaffer JR, Teumer A, Thompson JR, Vink JM, Vogelzang N, Wenzlaff AS, Wheeler W, Xiao X, Yang BZ, Aggen SH, Balmforth AJ, Baumeister SE, Beaty T, Bennett S, Bergen AW, Boyd HA, Broms U, Campbell H, Chatterjee N, Chen J, Cheng YC, Cichon S, Couper D, Cucca F, Dick DM, Foroud T, Furberg H, Giegling I, Gu F, Hall AS, Hällfors J, Han S, Hartmann AM, Hayward C, Heikkilä K, Hewitt JK, Hottenga JJ, Jensen MK, Jousilahti P, Kaakinen M, Kittner SJ, Konte B, Korhonen T, Landi MT, Laatikainen T, Leppert M, Levy SM, Mathias RA, McNeil DW, Medland SE, Montgomery GW, Muley T, Murray T, Nauck M, North K, Pergadia M, Polasek O, Ramos EM, Ripatti S, Risch A, Ruczinski I, Rudan I, Salomaa V, Schlessinger D, Styrkársdóttir U, Terracciano A, Uda M, Willemsen G, Wu X, Abecasis G, Barnes K, Bickeböller H, Boerwinkle E, Boomsma DI, Caporaso N, Duan J, Edenberg HJ, Francks C, Gejman PV, Gelernter J, Grabe HJ, Hops H, Jarvelin MR, Viikari J, Kähönen M, Kendler KS, Lehtimäki T, Levinson DF, Marazita ML, Marchini J, Melbye M, Mitchell BD, Murray JC, Nöthen MM, Penninx BW, Raitakari O, Rietschel M, Rujescu D, Samani NJ, Sanders AR, Schwartz AG, Shete S, Shi J, Spitz M, Stefansson K, Swan GE, Thorgeirsson T, Völzke H, Wei Q, Wichmann HE, Amos CI, Breslau N, Cannon DS, Ehringer M, Grucza R, Hatsukami D, Heath A, Johnson EO, Kaprio J, Madden P, Martin NG, Stevens VL, Stitzel JA, Weiss RB, Kraft P, Bierut LJ. Increased

genetic vulnerability to smoking at CHRNA5 in early-onset smokers. Arch Gen Psychiatry. 2012 Aug; 69(8): 854-860.

Increased Vulnerability To Cocaine In Mice Lacking Dopamine D3 Receptors Neuroimaging studies using positron emission tomography suggest that reduced dopamine D(2) receptor availability in the neostriatum is associated with increased vulnerability to drug addiction in humans and experimental animals. The role of D(3) receptors (D(3)Rs) in the neurobiology of addiction remains unclear, however. Here the authors report that D(3)R KO (D(3)(-/-)) mice display enhanced cocaine self-administration and enhanced motivation for cocaine-taking and cocaine-seeking behavior. This increased vulnerability to cocaine is accompanied by decreased dopamine response to cocaine secondary to increased basal levels of extracellular dopamine in the nucleus accumbens, suggesting a compensatory response to decreased cocaine reward in D(3)(-/-) mice. In addition, D(3)(-/-) mice also display up-regulation of dopamine transporters in the striatum, suggesting a neuroadaptive attempt to normalize elevated basal extracellular dopamine. These findings suggest that D(3)R deletion increases vulnerability to cocaine, and that reduced D(3)R availability in the brain may constitute a risk factor for the development of cocaine addiction. Song R, Zhang HY, Li X, Bi H, Gardner EL, Xi ZX. Increased vulnerability to cocaine in mice lacking dopamine D3 receptors. Proc Natl Acad Sci U S A. 2012 Oct 23; 109(43): 17675-17680.

DRD4 Genotype Predicts Longevity in Mouse and Human Longevity is influenced by genetic and environmental factors. The brain's dopamine system may be particularly relevant, since it modulates traits (e.g., sensitivity to reward, incentive motivation, sustained effort) that impact behavioral responses to the environment. In particular, the dopamine D4 receptor (DRD4) has been shown to moderate the impact of environments on behavior and health. The authors tested the hypothesis that the DRD4 gene influences longevity and that its impact is mediated through environmental effects. Surviving participants of a 30-year-old population-based health survey (N = 310; age range, 90-109 years; the 90+ Study) were genotyped/resequenced at the DRD4 gene and compared with a European ancestry-matched younger population (N = 2902; age range, 7-45 years). The authors found that the oldest-old population had a 66% increase in individuals carrying the DRD4 7R allele relative to the younger sample ($p = 3.5 \times 10^{-9}$), and that this genotype was strongly correlated with increased levels of physical activity. Consistent with these results, DRD4 knock-out mice, when compared with wild-type and heterozygous mice, displayed a 7-9.7% decrease in lifespan, reduced spontaneous locomotor activity, and no lifespan increase when reared in an enriched environment. These results support the hypothesis that DRD4 gene variants contribute to longevity in humans and in mice, and suggest that this effect is mediated by shaping behavioral responses to the environment. Grady DL, Thanos PK, Corrada MM, Barnett JC Jr, Ciobanu V, Shustarovich D, Napoli A, Moyzis AG, Grandy D, Rubinstein M, Wang GJ, Kawas CH, Chen C, Dong Q, Wang E, Volkow ND, Moyzis RK. DRD4 Genotype predicts longevity in mouse and human. J Neurosci. 2013 Jan 2; 33(1): 286-291.

IFITM1 is a Tight Junction Protein That Inhibits Hepatitis C Virus Entry Type 1 interferon (IFN) continues to be the foundation for the current standard of care combination therapy for chronic hepatitis C virus (HCV) infection, yet the component interferon-stimulated genes (ISGs) that mediate the antiviral actions of IFN are not fully defined. Interferon-induced transmembrane protein 1 (IFITM1) is an ISG product that suppresses early stage infection by a number of viruses through an as yet unknown mechanism of action. Moreover, the actions of IFITM1 on HCV infection are not fully elucidated. Here the authors identify IFITM1 as a hepatocyte tight junction

protein and a potent anti-HCV effector molecule. IFITM1 expression is induced early during IFN treatment of hepatocytes and accumulates at hepatic tight junctions in HCV-infected human patient liver during IFN therapy. Additionally, the authors found that IFITM1 interacts with HCV co-receptors including CD81 and occludin to disrupt the process of viral entry. Thus, IFITM1 is an anti-HCV ISG whose actions impart control of HCV infection through interruption of viral coreceptor function. This study defines IFITM1 as an ISG effector with action against HCV entry. Design of therapy regimens to enhance IFITM1 expression should improve the virologic response among HCV patients undergoing treatment with type I IFN. Wilkins C, Woodward J, Lau DT, Barnes A, Joyce M, McFarlane N, Tyrrell DL, Gale M Jr. IFITM1 is a tight junction protein that inhibits hepatitis C virus entry. *Hepatology*. 2012 Sep 19. Epub ahead of print].

A Brain On Cannabinoids: The Role Of Dopamine Release In Reward Seeking Rats emit ultrasonic vocalizations (USVs) in a variety of contexts, and it is increasingly clear that USVs reflect more complex information than mere positive and negative affect states. The authors sought to examine USVs in a common model of addiction and relapse, the self-administration/reinstatement paradigm, in order to gain insight into subjective states experienced by rats during various types of methamphetamine seeking. They measured three subtypes of 50kHz USVs [flats, trills, and non-trill frequency modulated (FM) USVs], as well as long and short duration 22kHz USVs, during self-administration and extinction training, and during reinstatement elicited by cues, a methamphetamine prime, cues+prime, or the pharmacological stressor yohimbine. During self-administration and extinction, rats emitted many flats and FMs, (and short duration 22kHz USVs on day 1 of self-administration), but few trills. In contrast, methamphetamine priming injections potently enhanced FMs and trills, and trill production was correlated with the degree of methamphetamine+cue-elicited reinstatement. Cues alone yielded increases only in flat USVs during reinstatement, though a subset of rats displaying strong cue-induced reinstatement also emitted long duration, aversion-related 22kHz USVs. Although yohimbine administration caused reinstatement, it did not induce 22kHz USVs in methamphetamine-experienced or methamphetamine-naive rats (unlike footshock stress, which did induce long duration 22kHz USVs). These findings demonstrate heterogeneity of rat USV emitted during different types of methamphetamine seeking, and highlight their potential usefulness for gaining insight into the subjective states of rats in rodent models of drug addiction and relapse. Oleson EB, Cheer JF. A brain on cannabinoids: the role of dopamine release in reward seeking. *Cold Spring Harb Perspect Med*. 2012 Aug 1; 2(8). doi:pii: a012229. 10.1101/cshperspect.a012229.

MEMS-Enabled Implantable Drug Infusion Pumps For Laboratory Animal Research, Preclinical, and Clinical Applications Innovation in implantable drug delivery devices is needed for novel pharmaceutical compounds such as certain biologics, gene therapy, and other small molecules that are not suitable for administration by oral, topical, or intravenous routes. This invasive dosing scheme seeks to directly bypass physiological barriers presented by the human body, release the appropriate drug amount at the site of treatment, and maintain the drug bioavailability for the required duration of administration to achieve drug efficacy. Advances in microtechnologies have led to novel MEMS-enabled implantable drug infusion pumps with unique performance and feature sets. In vivo demonstration of micropumps for laboratory animal research and preclinical studies include acute rapid radiolabeling, short-term delivery of nanomedicine for cancer treatment, and chronic ocular drug dosing. Investigation of MEMS actuators, valves, and other microstructures for on-demand dosing control may enable next generation implantable pumps with high performance within a miniaturized form factor for clinical applications. Meng E, Hoang

T. MEMS-enabled implantable drug infusion pumps for laboratory animal research, preclinical, and clinical applications. *Adv Drug Deliv Rev.* 2012 Nov; 64(14): 1628-1638. doi: 10.1016/j.addr.2012.08.006. Epub 2012 Aug 19.

Personalized Nanomedicine Advancements For Stem Cell Tracking Recent technological developments in biomedicine have facilitated the generation of data on the anatomical, physiological and molecular level for individual patients and thus introduces opportunity for therapy to be personalized in an unprecedented fashion. Generation of patient-specific stem cells exemplifies the efforts toward this new approach. Cell-based therapy is a highly promising treatment paradigm; however, due to the lack of consistent and unbiased data about the fate of stem cells in vivo, interpretation of therapeutic effects remains challenging hampering the progress in this field. The advent of nanotechnology with a wide palette of inorganic and organic nanostructures has expanded the arsenal of methods for tracking transplanted stem cells. The diversity of nanomaterials has revolutionized personalized nanomedicine and enables individualized tailoring of stem cell labeling materials for the specific needs of each patient. The successful implementation of stem cell tracking will likely be a significant driving force that will contribute to the further development of nanotheranostics. The purpose of this review is to emphasize the role of cell tracking using currently available nanoparticles. Janowski M, Bulte JW, Walczak P. Personalized nanomedicine advancements for stem cell tracking. *Adv Drug Deliv Rev.* 2012 Oct; 64(13): 1488-1507. doi: 10.1016/j.addr.2012.07.008. Epub 2012 Jul 20.

Membrane-Initiated Estradiol Actions Mediate Structural Plasticity and Reproduction Over the years, our ideas about estrogen signaling have greatly expanded. In addition to estradiol having direct nuclear actions that mediate transcription and translation, more recent experiments have demonstrated membrane-initiated signaling. Both direct nuclear and estradiol membrane signaling can be mediated by the classical estrogen receptors, ER-alpha and ER-beta, which are two of the numerous putative membrane estrogen receptors. Thus far, however, only ER-alpha has been shown to play a prominent role in regulating female reproduction and sexual behavior. Because ER-alpha is a ligand-gated transcription factor and not a typical membrane receptor, trafficking to the cell membrane requires post-translational modifications. Two necessary modifications are palmitoylation and association with caveolins, a family of scaffolding proteins. In addition to their role in trafficking, caveolin proteins also serve to determine ER-alpha interactions with metabotropic glutamate receptors (mGluRs). It is through these complexes that ER-alpha, which cannot by itself activate G proteins, is able to initiate intracellular signaling. Various combinations of ER-alpha-mGluR interactions have been demonstrated throughout the nervous system from hippocampus to striatum to hypothalamus to dorsal root ganglion (DRG) in both neurons and astrocytes. These combinations of ER and mGluR allow estradiol to have both facilitative and inhibitory actions in neurons. In hypothalamic astrocytes, the estradiol-mediated release of intracellular calcium stores regulating neurosteroid synthesis requires ER-alpha-mGluR1a interaction. In terms of estradiol regulation of female sexual receptivity, activation of ER-alpha-mGluR1a signaling complex leads to the release of neurotransmitters and alteration of neuronal morphology. This review examines estradiol membrane signaling (EMS) activating a limbic-hypothalamic lordosis regulating circuit, which involves ER-alpha trafficking, internalization, and modifications of neuronal morphology in a circuit that underlies female sexual receptivity. Micevych P, Christensen A. Membrane-initiated estradiol actions mediate structural plasticity and reproduction. *Front Neuroendocrinol.* 2012 Oct; 33(4): 331-341. doi: 10.1016/j.yfrne.2012.07.003. Epub 2012 Jul 22.

The Immune System and Developmental Programming Of Brain and Behavior The brain, endocrine, and immune systems are inextricably linked. Immune molecules have a powerful impact on neuroendocrine function, including hormone-behavior interactions, during health as well as sickness. Similarly, alterations in hormones, such as during stress, can powerfully impact immune function or reactivity. These functional shifts are evolved, adaptive responses that organize changes in behavior and mobilize immune resources, but can also lead to pathology or exacerbate disease if prolonged or exaggerated. The developing brain in particular is exquisitely sensitive to both endogenous and exogenous signals, and increasing evidence suggests the immune system has a critical role in brain development and associated behavioral outcomes for the life of the individual. Indeed, there are associations between many neuropsychiatric disorders and immune dysfunction, with a distinct etiology in neurodevelopment. The goal of this review is to describe the important role of the immune system during brain development, and to discuss some of the many ways in which immune activation during early brain development can affect the later-life outcomes of neural function, immune function, mood and cognition. Bilbo SD, Schwarz JM. The immune system and developmental programming of brain and behavior. *Front Neuroendocrinol.* 2012 Aug; 33(3): 267-286. doi: 10.1016/j.yfrne.2012.08.006. Epub 2012 Sep 9.

Role of Nicotinic Receptors and Acetylcholine In Mucous Cell Metaplasia, Hyperplasia, and Airway Mucus Formation In Vitro and In Vivo Airway mucus hypersecretion is a key pathophysiologic feature in a number of lung diseases. Cigarette smoke/nicotine and allergens are strong stimulators of airway mucus; however, the mechanism of mucus modulation is unclear. The authors sought to characterize the pathway by which cigarette smoke/nicotine regulates airway mucus and identify agents that decrease airway mucus. IL-13 and gamma-aminobutyric acid type A receptors (GABA(A)Rs) are implicated in airway mucus. The authors examined the role of IL-13 and GABA(A)Rs in nicotine-induced mucus formation in normal human bronchial epithelial (NHBE) and A549 cells and secondhand cigarette smoke-induced, ovalbumin-induced, or both mucus formation in vivo. Nicotine promotes mucus formation in NHBE cells; however, the nicotine-induced mucus formation is independent of IL-13 but sensitive to the GABA(A)R antagonist picrotoxin. Airway epithelial cells express alpha 7-, alpha 9-, and alpha 10-nicotinic acetylcholine receptors (nAChRs), and specific inhibition or knockdown of alpha 7- but not alpha 9/alpha 10-nAChRs abrogates mucus formation in response to nicotine and IL-13. Moreover, addition of acetylcholine or inhibition of its degradation increases mucus in NHBE cells. Nicotinic but not muscarinic receptor antagonists block allergen- or nicotine/cigarette smoke-induced airway mucus formation in NHBE cells, murine airways, or both. The authors conclude that nicotine-induced airway mucus formation is independent of IL-13, and alpha 7-nAChRs are critical in airway mucous cell metaplasia/hyperplasia and mucus production in response to various promucoid agents, including IL-13. In the absence of nicotine, acetylcholine might be the biological ligand for alpha 7-nAChRs to trigger airway mucus formation. alpha 7-nAChRs are downstream of IL-13 but upstream of GABA(A)R alpha 2 in the MUC5AC pathway. Acetylcholine and alpha 7-nAChRs might serve as therapeutic targets to control airway mucus. Gundavarapu S, Wilder JA, Mishra NC, Rir-Sima-Ah J, Langley RJ, Singh SP, Saeed AI, Jaramillo RJ, Gott KM, Pena-Philippides JC, Harrod KS, McIntosh JM, Buch S, Sopor ML. Role of nicotinic receptors and acetylcholine in mucous cell metaplasia, hyperplasia, and airway mucus formation in vitro and in vivo. *J Allergy Clin Immunol.* 2012 Sep; 130(3): 770-780.e11. doi: 10.1016/j.jaci.2012.04.002. Epub 2012 May 9.

From Antipsychotic To Anti-Schizophrenia Drugs: Role Of Animal Models Current drugs for treating schizophrenia are mostly variations on a theme that was started over 50 years ago. Sadly, clinical efficacy has not improved substantially over the years. The authors argue that both clinical and preclinical researchers have focused too much on psychosis, which is only one of the hallmarks of schizophrenia. This narrow focus has hampered the development of relevant animal models and human experimental medicine paradigms. Other fields in psychiatry, most notably in the realms of addiction and anxiety, have prospered from results obtained in parallel studies using animal models and experimental human studies. Lessons to be learned from those models and recent genetic and cognitive insights in schizophrenia can be utilized to develop better animal and human models and, potentially, novel treatment strategies. Geyer MA, Olivier B, Joels M, Kahn RS. From antipsychotic to anti-schizophrenia drugs: role of animal models. *Trends Pharmacol Sci.* 2012 Oct;33 (10): 515-521. doi: 10.1016/j.tips.2012.06.006. Epub 2012 Jul 16.

Alpha-2-Containing GABA(A) Receptors: A Target For the Development of Novel Treatment Strategies For CNS Disorders GABA(A) receptors have important physiological functions, as revealed by pharmacological studies and experiments involving gene-targeted mouse models, and are the target of widely used drugs such as the benzodiazepines. In this review, the authors summarize current knowledge about the function of alpha2-containing GABA(A) receptors, a receptor subtype representing approximately 15-20% of all GABA(A) receptors. This receptor subtype mediates anxiolytic-like, reward-enhancing, and antihyperalgesic actions of diazepam, and has antidepressant-like properties. Secondary insufficiency of alpha2-containing GABA(A) receptors has been postulated to play a role in the pathogenesis of schizophrenia, and may be involved in cognitive impairment in other disorders. Moreover, polymorphisms in the GABRA2 gene encoding the GABA(A) receptor alpha2 subunit have been found to be linked to chronic alcohol dependence and to polydrug abuse. Thus, alpha2-containing GABA(A) receptors are involved in the regulation and/or modulation of emotional behaviors and of chronic pain, and appear to be a valid target for novel therapeutic approaches for the treatment of anxiety, depression, schizophrenia and chronic pain. Engin E, Liu J, Rudolph U. alpha-2-containing GABA(A) receptors: A target for the development of novel treatment strategies for CNS disorders. *Pharmacol Ther.* 2012 Nov; 136(2): 142-152. Epub 2012 Aug 18.

Uridine Composition of the Poly-U/UC Tract Of HCV RNA Defines Non-Self Recognition By RIG-I Viral infection of mammalian cells triggers the innate immune response through non-self recognition of pathogen associated molecular patterns (PAMPs) in viral nucleic acid. Accurate PAMP discrimination is essential to avoid self recognition that can generate autoimmunity, and therefore should be facilitated by the presence of multiple motifs in a PAMP that mark it as non-self. Hepatitis C virus (HCV) RNA is recognized as non-self by RIG-I through the presence of a 5'-triphosphate (5'-ppp) on the viral RNA in association with a 3' poly-U/UC tract. Here the authors define the HCV PAMP and the criteria for RIG-I non-self discrimination of HCV by examining the RNA structure-function attributes that impart PAMP function to the poly-U/UC tract. They found that the 34 nucleotide poly-uridine core of this sequence tract was essential for RIG-I activation, and that interspersed ribocytosine nucleotides between poly-U sequences in the RNA were required to achieve optimal RIG-I signal induction. 5'-ppp poly-U/UC RNA variants that stimulated strong RIG-I activation efficiently bound purified RIG-I protein in vitro, and RNA interaction with both the repressor domain and helicase domain of RIG-I was required to activate signaling. When appended to 5'-ppp RNA that lacks PAMP activity, the poly-U/UC U-core sequence conferred non-self recognition of the RNA and innate immune signaling by RIG-I. Importantly, HCV poly-U/UC

RNA variants that strongly activated RIG-I signaling triggered potent anti-HCV responses in vitro and hepatic innate immune responses in vivo using a mouse model of PAMP signaling. These studies define a multi-motif PAMP signature of non-self recognition by RIG-I that incorporates a 5'-ppp with poly-uridine sequence composition and length. This HCV PAMP motif drives potent RIG-I signaling to induce the innate immune response to infection. These studies define a basis of non-self discrimination by RIG-I and offer insights into the antiviral therapeutic potential of targeted RIG-I signaling activation. Schnell G, Loo YM, Marcotrigiano J, Gale M Jr. Uridine composition of the poly-U/UC tract of HCV RNA defines non-self recognition by RIG-I. PLoS Pathog. 2012 Aug; 8(8): e1002839. Epub 2012 Aug 2.

Addiction-Related Gene Regulation: Risks of Exposure To Cognitive Enhancers Vs. Other Psychostimulants

The psychostimulants methylphenidate (Ritalin, Concerta), amphetamine (Adderall), and modafinil (Provigil) are widely used in the treatment of medical conditions such as attention-deficit hyperactivity disorder and narcolepsy and, increasingly, as cognitive enhancers by healthy people. The long-term neuronal effects of these drugs, however, are poorly understood. A substantial amount of research over the past two decades has investigated the effects of psychostimulants such as cocaine and amphetamines on gene regulation in the brain because these molecular changes are considered critical for psychostimulant addiction. This work has determined in some detail the neurochemical and cellular mechanisms that mediate psychostimulant-induced gene regulation and has also identified the neuronal systems altered by these drugs. Among the most affected brain systems are corticostriatal circuits, which are part of cortico-basal ganglia-cortical loops that mediate motivated behavior. The neurotransmitters critical for such gene regulation are dopamine in interaction with glutamate, while other neurotransmitters (e.g., serotonin) play modulatory roles. This review presents (1) an overview of the main findings on cocaine- and amphetamine-induced gene regulation in corticostriatal circuits in an effort to provide a cellular framework for (2) an assessment of the molecular changes produced by methylphenidate, medical amphetamine (Adderall), and modafinil. The findings lead to the conclusion that protracted exposure to these cognitive enhancers can induce gene regulation effects in corticostriatal circuits that are qualitatively similar to those of cocaine and other amphetamines. These neuronal changes may contribute to the addiction liability of the psychostimulant cognitive enhancers. Steiner H, Van Waes V. Addiction-related gene regulation: Risks of exposure to cognitive enhancers vs. other psychostimulants. Prog Neurobiol. 2012 Oct 17. doi:pii: S0301-0082(12)00153-0. 10.1016/j.pneurobio.2012.10.001. [Epub ahead of print]

Has an Angel Shown The Way? Etiological and Therapeutic Implications of the PCP/NMDA Model Of Schizophrenia

Over the last 20 years, glutamatergic models of schizophrenia have become increasingly accepted as etiopathological models of schizophrenia, based on the observation that phencyclidine (PCP) induces a schizophrenia-like psychosis by blocking neurotransmission at N-methyl-D-aspartate (NMDA)-type glutamate receptors. This article reviews developments in two key predictions of the model: first, that neurocognitive deficits in schizophrenia should follow the pattern of deficit predicted based on underlying NMDAR dysfunction and, second, that agents that stimulate NMDAR function should be therapeutically beneficial. As opposed to dopamine receptors, NMDAR are widely distributed throughout the brain, including subcortical as well as cortical brain regions, and sensory as well as association cortex. Studies over the past 20 years have documented severe sensory dysfunction in schizophrenia using behavioral, neurophysiological, and functional brain imaging approaches, including impaired generation of key sensory-related potentials such as mismatch negativity and visual P1 potentials.

Similar deficits are observed in humans following administration of NMDAR antagonists such as ketamine in either humans or animal models. Sensory dysfunction, in turn, predicts impairments in higher order cognitive functions such as auditory or visual emotion recognition. Treatment studies have been performed with compounds acting directly at the NMDAR glycine site, such as glycine, D-serine, or D-cycloserine, and, more recently, with high-affinity glycine transport inhibitors such as RG1678 (Roche). More limited studies have been performed with compounds targeting the redox site. Overall, these compounds have been found to induce significant beneficial effects on persistent symptoms, suggesting novel approaches for treatment and prevention of schizophrenia. Javitt DC, Zukin SR, Heresco-Levy U, Umbricht D. Has an angel shown the way? Etiological and therapeutic implications of the PCP/NMDA model of schizophrenia. *Schizophr Bull.* 2012 Sep; 38(5): 958-966. doi: 10.1093/schbul/sbs069.

Contributions of Nitric Oxide Synthases, Dietary Nitrite/Nitrate, and Other Sources To the Formation Of NO Signaling Products

Mice lacking all three nitric oxide synthase (NOS) genes remain viable even though deletion of the major downstream target of NO, soluble guanylyl cyclase, is associated with a dramatically shortened life expectancy. Moreover, findings of relatively normal flow responses in eNOS knockouts are generally attributed to compensatory mechanisms including upregulation of remaining NOS isoforms, but the alternative possibility that dietary nitrite/nitrate (NO_x) may contribute to basal levels of NO signaling has never been investigated. The aim of the present study was to examine how NO signaling products (nitrosated and nitrosylated proteins) and NO metabolites (nitrite, nitrate) are affected by single NOS deletions and whether dietary NO_x plays a compensatory role in any deficiency. Specifically, the authors sought to ascertain whether profound alterations of these products arise upon genetic deletion of either NOS isoform, inhibition of all NOS activity, NO_x restriction, or all of the above. The results indicate that while some significant changes do indeed occur, they are surprisingly moderate and compartmentalized to specific tissues. Unexpectedly, even after pharmacological inhibition of all NOSs and restriction of dietary NO_x intake in eNOS knockout mice significant levels of NO-related products remain. These findings suggest that a yet unidentified source of NO, unrelated to NOSs or dietary NO_x, may be sustaining basal NO signaling in tissues. Given the significance of NO for redox regulation in health and disease, it would seem to be important to identify the nature of this additional source of NO products as it may offer new therapeutic avenues for correcting NO deficiencies. Milsom AB, Fernandez BO, Garcia-Saura MF, Rodriguez J, Feelisch M. Contributions of nitric oxide synthases, dietary nitrite/nitrate, and other sources to the formation of NO signaling products. *Antioxid Redox Signal.* 2012 Aug 1; 17(3): 422-432. doi: 10.1089/ars.2011.4156. Epub 2012 Jan 18.

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 (approximately 5 years) and age-matched control animals (n = 4/group) performed cognitive tasks in morning sessions and self-administered cocaine or food in afternoon sessions. Positron emission tomography and [(18)F]-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 Nov 15; 72(10): 856-863. Epub 2012 Jun 5.

Neural Correlates Of the Formation and Retention Of Cocaine-Induced Stimulus-Reward

Associations Cocaine can elicit drug-seeking behavior for drug-predicting stimuli, even after a single stimulus-cocaine pairing. Although orbitofrontal cortex is thought to be important during encoding and maintenance of stimulus-reward value, a comprehensive model of the neural circuitry underlying this cognitive process is still lacking. The authors studied the conditioned effects of cocaine with monkey functional magnetic resonance imaging and classical conditioning by pairing a visual shape (conditioning stimulus [CS+]) with a noncontingent cocaine infusion; a control stimulus was never paired. They correlated the behavioral preference of the monkey for the CS+, as measured offline, with the activity induced by the CS+ relative to the control stimulus as function of time. They observed that during formation of stimulus-cocaine associations strong CS+-induced functional magnetic resonance imaging activations emerged in frontal cortex that correlated significantly with behavioral CS+ preference. Afterward, CS+ preference correlated only with activity in early visual cortex. Control experiments suggest that these findings cannot be explained by increased familiarity for the CS+. These findings suggest a complex interaction between frontal and occipital cortex during cocaine conditioning. Frontal cortex is important for establishing novel representations of stimulus valence when cocaine is used as reinforcer, whereas early visual cortex is involved in retaining these cocaine-stimulus associations. Nelissen K, Jarraya B, Arsenault JT, Rosen BR, Wald LL, Mandeville JB, Marota JJ, Vanduffel W. Neural correlates of the formation and retention of cocaine-induced stimulus-reward associations. *Biol Psychiatry*. 2012 Sep 1; 72(5): 422-428. doi: 10.1016/j.biopsych.2012.02.021. Epub 2012 Mar 20.

Prefrontal Cortex Modulates Desire and Dread Generated by Nucleus Accumbens Glutamate

Disruption Corticolimbic circuits, including direct projections from prefrontal cortex to nucleus accumbens (NAc), permit top-down control of intense motivations generated by subcortical circuits. In rats, localized disruptions of glutamate signaling within medial shell of NAc generate desire or dread, anatomically organized along a rostrocaudal gradient analogous to a limbic keyboard. At rostral locations in shell, these disruptions generate appetitive eating, but at caudal locations the disruptions generate progressively fearful behaviors (distress vocalizations, escape attempts, and antipredator reactions). Here, the authors asked whether medial prefrontal cortex can modulate intense motivations generated by subcortical NAc disruptions. They used simultaneous microinjections in medial prefrontal cortex regions and in NAc shell to examine whether the desire or dread generated by NAc shell disruptions is modulated by activation/inhibition of three specific

regions of prefrontal cortex: medial orbitofrontal cortex, infralimbic cortex (homologous to area 25 or subgenual anterior cingulate in the human), or prelimbic cortex (midventral anterior cingulate). The authors found that activation of medial orbitofrontal cortex biased intense bivalent motivation in an appetitive direction by amplifying generation of eating behavior by middle to caudal NAc disruptions, without altering fear. In contrast, activation of infralimbic prefrontal cortex powerfully and generally suppressed both appetitive eating and fearful behaviors generated by NAc shell disruptions. These results suggest that corticolimbic projections from discrete prefrontal regions can either bias motivational valence or generally suppress subcortically generated intense motivations of desire or fear. Richard JM, Berridge KC. Prefrontal cortex modulates desire and dread generated by nucleus accumbens glutamate disruption. *Biol Psychiatry*. 2012 Sep 12. Epub ahead of print.

Proenkephalin Mediates the Enduring Effects Of Adolescent Cannabis Exposure Associated With Adult Opiate Vulnerability

Marijuana use by teenagers often predates the use of harder drugs, but the neurobiological underpinnings of such vulnerability are unknown. Animal studies suggest enhanced heroin self-administration (SA) and dysregulation of the endogenous opioid system in the nucleus accumbens shell (NAcsh) of adults following adolescent Delta(9)-tetrahydrocannabinol (THC) exposure. However, a causal link between proenkephalin (Penk) expression and vulnerability to heroin has yet to be established. To investigate the functional significance of NAcsh Penk tone, selective viral-mediated knockdown and overexpression of Penk was performed, followed by analysis of subsequent heroin SA behavior. To determine whether adolescent THC exposure was associated with chromatin alteration, the authors analyzed levels of histone H3 methylation in the NAcsh via chromatin immunoprecipitation at five sites flanking the Penk gene transcription start site. Here they show that regulation of the Penk opioid neuropeptide gene in NAcsh directly regulates heroin SA behavior. Selective viral-mediated knockdown of Penk in striatopallidal neurons attenuates heroin SA in adolescent THC-exposed rats, whereas Penk overexpression potentiates heroin SA in THC-naive rats. Furthermore, the authors report that adolescent THC exposure mediates Penk upregulation through reduction of histone H3 lysine 9 (H3K9) methylation in the NAcsh, thereby disrupting the normal developmental pattern of H3K9 methylation. These data establish a direct association between THC-induced NAcsh Penk upregulation and heroin SA and indicate that epigenetic dysregulation of Penk underlies the long-term effects of THC. Tomaszewicz HC, Jacobs MM, Wilkinson MB, Wilson SP, Nestler EJ, Hurd YL. Proenkephalin mediates the enduring effects of adolescent cannabis exposure associated with adult opiate vulnerability. *Biol Psychiatry*. 2012 Nov 15; 72(10): 803-810. Epub 2012 Jun 8.

Psychostimulants Act Within the Prefrontal Cortex To Improve Cognitive Function

At low and clinically relevant doses, psychostimulants enhance cognitive and behavioral function dependent on the prefrontal cortex (PFC) and extended frontostriatal circuitry. These actions are observed in individuals with attention-deficit/hyperactivity disorder, as well as in normal human and animal subjects. Despite the widespread use of these drugs, the sites of action involved in their cognition-enhancing and therapeutic effects are poorly understood. Indirect and/or correlative evidence suggests the cognition-enhancing/therapeutic effects of psychostimulants may involve actions directly within the PFC or extended frontostriatal circuitry. The current studies examined the degree to which methylphenidate (MPH) (Ritalin) acts within distinct frontostriatal subfields to improve PFC-dependent cognition as measured in a delayed-response test of spatial working memory. Working memory performance was assessed following microinfusion of vehicle or varying doses of MPH (.03-8.0 mug/500 nL) directly into the dorsomedial PFC (dorsal prelimbic

and dorsal anterior cingulate cortex), the ventromedial PFC (infralimbic), and the dorsomedial striatum of rats (n = 69). Methylphenidate infusion into the dorsomedial PFC, but not ventromedial PFC, elicited an inverted U-shaped facilitation of PFC-dependent cognition as measured in this task. The magnitude of this improvement was comparable with that seen with systemic administration. Additional studies demonstrated that although the dorsomedial striatum is necessary for accurate performance in this task, MPH infusion into this region did not affect working memory performance. These observations provide the first definitive evidence that the PFC is a site of action in the cognition-enhancing and presumably therapeutic actions of low-dose psychostimulants. Spencer RC, Klein RM, Berridge CW. Psychostimulants act within the prefrontal cortex to improve cognitive function. *Biol Psychiatry*. 2012 Aug 1; 72(3): 221-227. Epub 2011 Dec 29.

R-Modafinil (Armodafinil): A Unique Dopamine Uptake Inhibitor and Potential Medication For Psychostimulant Abuse

(+/-)-Modafinil has piqued interest as a treatment for attention-deficit/hyperactivity disorder and stimulant dependence. The R-enantiomer of modafinil might have unique pharmacological properties that should be further investigated. (+/-)-Modafinil and its R-(-) and S-(+)-enantiomers were synthesized and tested for inhibition of [(3)H] dopamine (DA) uptake and [(3)H]WIN 35428 binding in human dopamine transporter (DAT) wild-type and mutants with altered conformational equilibria. Data were compared with cocaine and the atypical DA uptake inhibitor, JHW 007. R- and S-modafinil were also evaluated in microdialysis studies in the mouse nucleus accumbens shell and in a cocaine discrimination procedure. (+/-)-, R-, and S-modafinil bind to the DAT and inhibit DA uptake less potently than cocaine, with R-modafinil having approximately threefold 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 with 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 [2-(trimethylammonium) ethyl]-methanethiosulfonate reactivity on the DAT E2C I159C. Microdialysis studies demonstrated that both R- and S-modafinil produced increases in extracellular DA concentrations in the nucleus accumbens shell less efficaciously than cocaine and with a longer duration of action. Both enantiomers fully substituted in mice trained to discriminate cocaine from saline. The authors concluded that 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, Priszczano 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 Sep 1; 72(5): 405-413. Epub 2012 Apr 25.

Social Dominance In Female Monkeys: Dopamine Receptor Function and Cocaine

Reinforcement Brain imaging and behavioral studies suggest an inverse relationship between dopamine (DA) D2/D3 receptors and vulnerability to cocaine abuse, although most research has used males. For example, male monkeys that become dominant in a social group have significant elevations in D2/D3 receptor availability and are less vulnerable to cocaine reinforcement. DA D2/D3 receptor availability was assessed in female cynomolgus monkeys (n = 16) with positron emission tomography (PET) while they were individually housed, 3 months after stable social hierarchies had formed, and again when individually housed. In addition, PET was used to examine changes in dopamine transporter (DAT) availability after social hierarchy formation. After imaging studies were complete, monkeys received implantation with indwelling intravenous catheters and

self-administered cocaine (.001-.1 mg/kg/injection) under a fixed-ratio 30 schedule of reinforcement. Acquisition of cocaine reinforcement occurred when response rates were significantly higher than when saline was self-administered. Neither DAT nor D2/D3 receptor availability in the caudate nucleus and putamen was predictive of social rank, but both significantly changed after formation of social hierarchies. DA D2/D3 receptor availability significantly increased in females that became dominant, whereas DAT availability decreased in subordinate females. Dominant female monkeys acquired cocaine reinforcement at significantly lower doses than subordinate monkeys. The authors conclude that the relationship between D2/D3 receptor availability and vulnerability to cocaine reinforcement seems, on the basis of these findings, opposite in females and males. These data indicate that the social environment profoundly affects the DA system but does so in ways that have different functional consequences for females than for males. Nader MA, Nader SH, Czoty PW, Riddick NV, Gage HD, Gould RW, Blaylock BL, Kaplan JR, Garg PK, Davies HM, Morton D, Garg S, Reboussin BA. Social dominance in female monkeys: dopamine receptor function and cocaine reinforcement. *Biol Psychiatry*. 2012 Sep 1; 72(5): 414-421. Epub 2012 Apr 14.

Systems Genetics of Metabolism: The Use of the BXD Murine Reference Panel For Multiscalar Integration of Traits

Metabolic homeostasis is achieved by complex molecular and cellular networks that differ significantly among individuals and are difficult to model with genetically engineered lines of mice optimized to study single gene function. Here, the authors systematically acquired metabolic phenotypes by using the EUMODIC EMPReSS protocols across a large panel of isogenic but diverse strains of mice (BXD type) to study the genetic control of metabolism. They generated and analyzed 140 classical phenotypes and deposited these in an open-access web service for systems genetics (www.genenetwork.org). Heritability, influence of sex, and genetic modifiers of traits were examined singly and jointly by using quantitative-trait locus (QTL) and expression QTL-mapping methods. Traits and networks were linked to loci encompassing both known variants and novel candidate genes, including alkaline phosphatase (ALPL), here linked to hypophosphatasia. The assembled and curated phenotypes provide key resources and exemplars that can be used to dissect complex metabolic traits and disorders. Andreux PA, Williams EG, Koutnikova H, Houtkooper RH, Champy MF, Henry H, Schoonjans K, Williams RW, Auwerx J. Systems genetics of metabolism: the use of the BXD murine reference panel for multiscalar integration of traits. *Cell*. 2012 Sep 14; 150(6): 1287-1299. Epub 2012 Aug 30.

The Role Of Ghrelin In Reward-Based Eating The peptide hormone ghrelin acts in the central nervous system as a potent orexigenic signal. Not only is ghrelin recognized as playing an important role in feeding circuits traditionally thought of as affecting body weight homeostasis, but also an accumulating number of scientific studies have identified ghrelin as being a key regulator of reward-based, hedonic eating behaviors. In the current article, the authors review ghrelin's orexigenic actions, the evidence linking ghrelin to food reward behavior, potential mechanisms by which ghrelin mediates reward-based eating behavior, and those studies suggesting an obligatory role for ghrelin in the changed eating behaviors induced by stress. Perello M, Zigman JM. The role of ghrelin in reward-based eating. *Biol Psychiatry*. 2012 Sep 1; 72(5): 347-353. Epub 2012 Mar 28.

Acute Stress Increases Circulating Anandamide and Other N-Acylethanolamines In Healthy Humans

Stress plays an important role in psychiatric disorders, and preclinical evidence indicates that the central endocannabinoid system modulates endocrine and neuronal responses to stress. This study aimed to investigate the effect of acute stress on circulating concentrations of endocannabinoids (eCBs) in healthy humans. A total of 71 adults participated in two sessions in which they were exposed to either a standardized psychosocial stress procedure (Trier Social Stress Test) or a control task. Blood samples for eCB and cortisol assays and cardiovascular and subjective measures were obtained before and at regular intervals after the tasks. Serum concentrations of the eCBs, N-arachidonylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), as well as of the N-acylethanolamides (NAEs), N-palmitoylethanolamine (PEA) and N-oleoylethanolamine (OEA), and of the O-acylglycerol, 2-oleoylglycerol (2-OG), were determined. Compared with the control condition, stress increased serum concentrations of AEA and the other NAEs immediately after the stress period. Increases in PEA were positively correlated with increases in serum cortisol after stress. Furthermore, anxiety ratings at baseline were negatively correlated with baseline concentrations of AEA. The sex and menstrual cycle status of the subject affected the NAE responses to stress. Interestingly, subjects of Asian and African-American races exhibited different patterns of stress responses compared with the Caucasian subjects. These results indicate that stress increases circulating NAEs in healthy human volunteers. This finding supports a protective role for eCBs in anxiety. Further research is needed to elucidate the function of these lipid mediators, and to determine the mechanisms that regulate their appearance in the circulation. Dlugos A, Childs E, Stuhr KL, Hillard CJ, de Wit H. Acute stress increases circulating anandamide and other N-acylethanolamines in healthy humans. *Neuropsychopharmacology*. 2012 Oct; 37(11): 2416-2427. Epub 2012 Jul 4.

Glycine Transporter-1 Inhibition Preceding Extinction Training Inhibits Reacquisition of Cocaine Seeking

Cognitive enhancers that act by increasing glycine transmission might be useful adjuncts to cocaine-cue extinction training to deter relapse. The study investigated the effects of combining treatments of the glycine transporter-1 (GlyT-1) inhibitor, Org24598, with extinction training on the subsequent reacquisition of cocaine self-administration. Squirrel monkeys and rats were trained to self-administer cocaine under a second-order schedule of intravenous drug injection in which responding was maintained by cocaine injections and a cocaine-paired visual stimulus. During three weekly extinction sessions, saline was substituted for cocaine but responding still produced the cocaine-paired stimulus. Subjects were treated with Org24598 or vehicle, either before or after each extinction session. One week later, cocaine injections were restored, and reacquisition of cocaine self-administration was evaluated over 15 sessions. Compared with vehicle, administration of Org24598 (1.0 mg/kg in monkeys; 3.0 or 7.5 mg/kg in rats) before each extinction session significantly inhibited reacquisition of cocaine self-administration in each species. In contrast, administration of Org24598 (1.0 mg/kg in monkeys) following, rather than preceding, each extinction session did not affect reacquisition compared with vehicle. When extinction training was replaced by cocaine self-administration or abstinence control conditions, treatment with the same doses of Org24598 resulted in reacquisition that was significantly more rapid than the reacquisition observed when Org24598 was administered before extinction training sessions. The results support the potential clinical utility of GlyT-1 inhibitor pretreatments combined with cocaine-cue extinction training to inhibit relapse. Achat-Mendes C, Nic Dhonnchadha BA, Platt DM, Kantak KM, Spealman RD. Glycine transporter-1 inhibition preceding extinction training inhibits reacquisition of cocaine seeking. *Neuropsychopharmacology*. 2012 Sep 5. Epub ahead of print].

Novel Cues Reinstatement Cocaine-Seeking Behavior and Induce Fos Protein Expression As Effectively As Conditioned Cues

Cue reinstatement of extinguished cocaine-seeking behavior is a widely used model of cue-elicited craving in abstinent human addicts. This study examined Fos protein expression in response to cocaine cues or to novel cues as a control for activation produced by test novelty. Rats were trained to self-administer cocaine paired with either a light or a tone cue, or received yoked saline and cue presentations, and then underwent daily extinction training. They were then tested for reinstatement of extinguished cocaine-seeking behavior elicited by response-contingent presentations of either the cocaine-paired cue or a novel cue (that is, tone for those trained with a light or vice versa). Surprisingly, conditioned and novel cues both reinstated responding and increased Fos similarly in most brain regions. Exceptions included the anterior cingulate, which was sensitive to test cue modality in saline controls and the dorsomedial caudate-putamen, where Fos was correlated with responding in the novel, but not conditioned, cue groups. In subsequent experiments, the authors observed a similar pattern of reinstatement in rats trained and tested for sucrose-seeking behavior, whereas rats trained and tested with the cues only reinstated to a novel, and not a familiar, light or tone. The results suggest that novel cues reinstate responding to a similar extent as conditioned cues regardless of whether animals have a reinforcement history with cocaine or sucrose, and that both types of cues activate similar brain circuits. Several explanations as to why converging processes may drive drug and novel cue reinforcement and seeking behavior are discussed. Bastle RM, Kufahl PR, Turk MN, Weber SM, Pentkowski NS, Thiel KJ, Neisewander JL. Novel cues reinstate cocaine-seeking behavior and induce Fos protein expression as effectively as conditioned cues. *Neuropsychopharmacology*. 2012 Aug; 37(9): 2109-2120. Epub 2012 Apr 25.

Ceftriaxone Normalizes Nucleus Accumbens Synaptic Transmission, Glutamate Transport, and Export Following Cocaine Self-Administration and Extinction Training

Decreased basal glutamate levels are observed in the rat nucleus accumbens (NA) core following cocaine self-administration. This disruption of glutamate homeostasis arises from a reduction in the export of glutamate via system $x(C)(-)$ and is accompanied by a decrease in expression of xCT , the catalytic subunit of system $x(C)(-)$. A second hallmark of disrupted homeostasis is a decrease in expression and function of the major glutamate transporter, GLT-1. The authors have previously shown that chronic treatment with the antibiotic ceftriaxone restores xCT and GLT-1 expression following cocaine self-administration and attenuates both cue- and cocaine-primed reinstatement. Here they used a $(3)H$ -glutamate uptake assay and microdialysis to test the hypothesis that ceftriaxone restores the function of both GLT-1 and xCT (glutamate reuptake and export, respectively) in the NA core following cocaine self-administration. They also used electrophysiology to investigate the ability of ceftriaxone to normalize measures of synaptic plasticity following cocaine. They found that 5 d of ceftriaxone treatment following cocaine self-administration restores basal glutamate levels in the accumbens core, likely through an upregulation of system $x(C)(-)$ function. They also found that ceftriaxone restores glutamate reuptake and attenuates the increase in synaptically released glutamate that accompanies cocaine-primed reinstatement. Ceftriaxone also reversed the cocaine-induced synaptic potentiation in the accumbens core, evidenced by normalized spontaneous EPSC amplitude and frequency and evoked EPSC amplitude. These data indicate that ceftriaxone normalizes multiple aspects of glutamate homeostasis following cocaine self-administration and thus holds the potential to reduce relapse in human cocaine addicts. Trantham-Davidson H, LaLumiere RT, Reissner KJ, Kalivas PW, Knackstedt LA. Ceftriaxone normalizes nucleus accumbens synaptic transmission, glutamate transport, and export following cocaine self-

administration and extinction training. *J Neurosci.* 2012 Sep 5; 32(36): 12406-12410. doi: 10.1523/JNEUROSCI.1976-12.2012.

Elimination Of Dendritic Spines With Long-Term Memory Is Specific To Active Circuits

Structural changes in brain circuits active during learning are thought to be important for long-term memory storage. If these changes support long-term information storage, they might be expected to be present at distant time points after learning, as well as to be specific to the circuit activated with learning, and sensitive to the contingencies of the behavioral paradigm. Here, the authors show such changes in the hippocampus as a result of contextual fear conditioning. There were significantly fewer spines specifically on active neurons of fear-conditioned mice. This spine loss did not occur in homecage mice or in mice exposed to the training context alone. Mice exposed to unpaired shocks showed a generalized reduction in spines. These learning-related changes in spine density could reflect a direct mechanism of encoding or alternately could reflect a compensatory adaptation to previously described enhancement in transmission due to glutamate receptor insertion. Jolla, California 92093-0603, USA. Sanders J, Cowansage K, Baumgärtel K, Mayford M. Elimination of dendritic spines with long-term memory is specific to active circuits. *J Neurosci.* 2012 Sep 5; 32(36): 12570-12578.

Endocannabinoid-Mediated Long-Term Depression Of Afferent Excitatory Synapses In Hippocampal Pyramidal Cells and GABAergic Interneurons

Although endocannabinoids have emerged as essential retrograde messengers in several forms of synaptic plasticity, it remains controversial whether they mediate long-term depression (LTD) of glutamatergic synapses onto excitatory and inhibitory neurons in the hippocampus. Here, the authors show that parvalbumin- and somatostatin/metabotropic glutamate receptor 1(a) (mGlu(1a))-positive GABAergic interneurons express diacylglycerol lipase-alpha (DGL-alpha), a synthesizing enzyme of the endocannabinoid 2-arachidonoylglycerol (2-AG), albeit at lower levels than principal cells. Moreover, this lipase accumulates postsynaptically around afferent excitatory synapses in all three cell types. To address the role of retrograde 2-AG signaling in LTD, the authors investigated two forms: (1) produced by postsynaptic spiking paired with subsequent presynaptic stimulation or (2) induced by group I mGlu activation by (S)-3,5-dihydroxyphenylglycine (DHPG). Neither form of LTD was evoked in the presence of the mGlu(5) antagonist MPEP [2-methyl-6-(phenylethynyl)-pyridine], the DGL inhibitor THL [N-formyl-L-leucine (1S)-1-[[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester], or the intracellularly applied Ca(2+) chelator BAPTA in CA1 pyramidal cells, fast-spiking interneurons (representing parvalbumin-containing cells) and interneurons projecting to stratum lacunosum-moleculare (representing somatostatin/mGlu(1a)-expressing interneurons). Both forms of LTD were completely absent in CB(1) cannabinoid receptor knock-out mice, whereas pharmacological blockade of CB(1) led to inconsistent results. Notably, in accordance with their lower DGL-alpha level, a higher stimulation frequency or higher DHPG concentration was required for LTD induction in interneurons compared with pyramidal cells. These findings demonstrate that hippocampal principal cells and interneurons produce endocannabinoids to mediate LTD in a qualitatively similar, but quantitatively different manner. The shifted induction threshold implies that endocannabinoid-LTD contributes to cortical information processing during distinct network activity patterns in a cell type-specific manner. Peterfi Z, Urban GM, Papp OI, Nemeth B, Monyer H, Szabo G, Erdelyi F, Mackie K, Freund TF, Hajos N, Katona I. Endocannabinoid-mediated long-term depression of afferent excitatory synapses in hippocampal pyramidal cells and GABAergic interneurons. *J Neurosci.* 2012 Oct 10; 32(41): 14448-14463. doi: 10.1523/JNEUROSCI.1676-12.2012.

Placebo-Induced Analgesia In An Operant Pain Model In Rats Analgesia is particularly susceptible to placebo responses. Recent studies in humans have provided important insights into the neurobiology underlying placebo-induced analgesia. However, human studies provide incomplete mechanistic explanations of placebo analgesia because of limited capacity to use cellular, molecular, and genetic manipulations. To address this shortcoming, this article describes the development of a rat model of conditioned analgesia in an operant pain assay. Specifically, rats were conditioned to associate a placebo manipulation with the analgesic effect of 1 mg/kg morphine (subcutaneously) on facial thermal pain. The authors found that conditioned (placebo) responding bore 3 of the hallmarks of placebo-induced analgesia: (1) strong interanimal variability in the response, (2) suppression by the opiate antagonist naloxone (5 mg/kg subcutaneously), and (3) a positive predictive relationship between the unconditioned analgesic effect and the conditioned (placebo) effect. Because of the operant nature of the assay and the use of only a mild noxious thermal stimulus, the authors suggest that these results provide evidence of placebo-induced analgesia in a preclinical model that utilizes an affective behavioral end point. This finding may provide opportunities for invasive preclinical studies allowing greater understanding of placebo-induced analgesia, thus paving the way for avenues to harness its benefits. Nolan TA, Price DD, Caudle RM, Murphy NP, Neubert JK. Placebo-induced analgesia in an operant pain model in rats. *Pain*. 2012 Oct; 153(10): 2009-2016. Epub 2012 Aug 4.

Vpu-Deficient HIV Strains Stimulate Innate Immune Signaling Responses In Target Cells Acute virus infection induces a cell-intrinsic innate immune response comprising our first line of immunity to limit virus replication and spread, but viruses have developed strategies to overcome these defenses. HIV-1 is a major public health problem; however, the virus-host interactions that regulate innate immune defenses against HIV-1 are not fully defined. The authors have recently identified the viral protein Vpu to be a key determinant responsible for HIV-1 targeting and degradation of interferon regulatory factor 3 (IRF3), a central transcription factor driving host cell innate immunity. IRF3 plays a major role in pathogen recognition receptor (PRR) signaling of innate immunity to drive the expression of type I interferon (IFN) and interferon-stimulated genes (ISGs), including a variety of HIV restriction factors, that serve to limit viral replication directly and/or program adaptive immunity. Here the authors interrogate the cellular responses to target cell infection with Vpu-deficient HIV-1 strains. Remarkably, in the absence of Vpu, HIV-1 triggers a potent intracellular innate immune response that suppresses infection. Thus, HIV-1 can be recognized by PRRs within the host cell to trigger an innate immune response, and this response is unmasked only in the absence of Vpu. Vpu modulation of IRF3 therefore prevents virus induction of specific innate defense programs that could otherwise limit infection. These observations show that HIV-1 can indeed be recognized as a pathogen in infected cells and provide a novel and effective platform for defining the native innate immune programs of target cells of HIV-1 infection. Doehle BP, Chang K, Fleming L, McNevin J, Hladik F, McElrath MJ, Gale M Jr. Vpu-deficient HIV strains stimulate innate immune signaling responses in target cells. *J Virol*. 2012 Aug; 86(16): 8499-8506. Epub 2012 May 30.

New Neurons Generated From Running Are Broadly Recruited Into Neuronal Activation Associated With Three Different Hippocampus-Involved Tasks Running increases the formation of new neurons in the adult rodent hippocampus. However, the function of new neurons generated from running is currently unknown. One hypothesis is that new neurons from running contribute to enhanced cognitive function by increasing plasticity in the adult hippocampus. An alternative hypothesis is that new neurons generated from running incorporate into experience-

specific hippocampal networks that only become active during running. The purpose of this experiment was to determine if new neurons generated from running are selectively activated by running, or can become recruited into granule cell activity occurring during performance on other behavioral tasks that engage the hippocampus. Therefore, the activation of new 5-6 week neurons was detected using BrdU, NeuN, and Zif268 triple-label immunohistochemistry in cohorts of female running and sedentary adult C57BL/6J mice following participation in one of three different tasks: the Morris water maze, novel environment exploration, or wheel running. Results showed that running and sedentary mice displayed a nearly equivalent proportion of new neurons that expressed Zif268 following each task. Since running approximately doubled the number of new neurons, the results demonstrated that running mice had a greater number of new neurons recruited into the Zif268 induction in the granule cell layer following each task than sedentary mice. The results suggest that new neurons incorporated into hippocampal circuitry from running are not just activated by wheel running itself, but rather become broadly recruited into granule cell layer activity during distinct behavioral experiences. Clark PJ, Bhattacharya TK, Miller DS, Kohman RA, DeYoung EK, Rhodes JS. New neurons generated from running are broadly recruited into neuronal activation associated with three different hippocampus-involved tasks. *Hippocampus*. 2012 Sep; 22(9): 1860-867. doi: 10.1002/hipo.22020. Epub 2012 Mar 30.

Cannabinoid Receptors Mediate Methamphetamine Induction Of High Frequency Gamma Oscillations In the Nucleus Accumbens Patients suffering from amphetamine-induced psychosis display repetitive behaviors, partially alleviated by antipsychotics, which are reminiscent of rodent stereotypies. Due to recent evidence implicating endocannabinoid involvement in brain disorders, including psychosis, the authors studied the effects of endocannabinoid signaling on neuronal oscillations of rats exhibiting methamphetamine stereotypy. Neuronal network oscillations were recorded with multiple single electrode arrays aimed at the nucleus accumbens of freely-moving rats. During the experiments, animals were dosed intravenously with the CB1 receptor antagonist rimonabant (0.3 mg/kg) or vehicle followed by an ascending dose regimen of methamphetamine (0.01, 0.1, 1, and 3 mg/kg; cumulative dosing). The effects of drug administration on stereotypy and local gamma oscillations were evaluated. Methamphetamine treatment significantly increased high frequency gamma oscillations (approximately 80 Hz). Entrainment of a subpopulation of nucleus accumbens neurons to high frequency gamma was associated with stereotypy encoding in putative fast-spiking interneurons, but not in putative medium spiny neurons. The observed ability of methamphetamine to induce both stereotypy and high frequency gamma power was potently disrupted following CB1 receptor blockade. The present data suggest that CB1 receptor-dependent mechanisms are recruited by methamphetamine to modify striatal interneuron oscillations that accompany changes in psychomotor state, further supporting the link between endocannabinoids and schizophrenia spectrum disorders. Morra JT, Glick SD, Cheer JF. Cannabinoid receptors mediate methamphetamine induction of high frequency gamma oscillations in the nucleus accumbens. *Neuropharmacology*. 2012 Sep; 63(4): 565-574. Epub 2012 May 15.

CB2 Cannabinoid Receptors Inhibit Synaptic Transmission When Expressed In Cultured Autaptic Neurons The role of CB2 in the central nervous system, particularly in neurons, has generated much controversy. Fueling the controversy are imperfect tools, which have made conclusive identification of CB2 expressing neurons problematic. Imprecise localization of CB2 has made it difficult to determine its function in neurons. Here the authors avoid the localization controversy and directly address the question if CB2 can modulate neurotransmission. CB2 was expressed in excitatory hippocampal autaptic neurons obtained from CB1 null mice. Whole-cell

patch clamp recordings were made from these neurons to determine the effects of CB2 on short-term synaptic plasticity. CB2 expression restored depolarization induced suppression of excitation to these neurons, which was lost following genetic ablation of CBI. The endocannabinoid 2-arachidonylethanolamide (2-AG) mimicked the effects of depolarization in CB2 expressing neurons. Interestingly, ongoing basal production of 2-AG resulted in constitutive activation of CB2, causing a tonic inhibition of neurotransmission that was relieved by the CB2 antagonist AM630 or the diacylglycerol lipase inhibitor RHC80267. Through immunocytochemistry and analysis of spontaneous EPSCs, paired pulse ratios and coefficients of variation the authors determined that CB2 exerts its function at a presynaptic site of action, likely through inhibition of voltage gated calcium channels. Therefore CB2 expressed in neurons effectively mimics the actions of CB1. Thus neuronal CB2 is well suited to integrate into conventional neuronal endocannabinoid signaling processes, with its specific role determined by its unique and highly inducible expression profile. Atwood BK, Straiker A, Mackie K. CB2 cannabinoid receptors inhibit synaptic transmission when expressed in cultured autaptic neurons. *Neuropharmacology*. 2012 Sep; 63(4): 514-523. Epub 2012 May 8.

Racial Differences In The Relationship Between Tobacco Dependence and Nicotine and Carcinogen Exposure

The aims of the present study were to investigate the relationships between tobacco dependence, biomarkers of nicotine and carcinogen exposure and biomarkers of nicotine and carcinogen exposure per cigarette in black and white smokers. A total of 204 healthy black (n = 69) and white (n = 135) smokers were enrolled into two clinical studies. Nicotine equivalents (nicotine and its metabolites), 4-(methylnitrosamino)-1-(3)pyridyl-1-butanol (NNAL) and polycyclic aromatic hydrocarbon (PAH) metabolites were measured in urine. The Fagerstrom Test for Nicotine Dependence (FTND) and time to first cigarette (TFC) measured tobacco dependence. Average TFC and FTND for blacks and whites were not significantly different. Urine NNAL and nicotine equivalents increased with increasing FTND in whites but did not increase in blacks (race x FTND interaction, both $P < 0.031$). The interaction term was not significant for PAHs. An inverse relationship was seen between FTND and nicotine equivalents, NNAL and PAH metabolites per cigarette in blacks but remained flat in whites (race x FTND interaction, all $P \leq 0.039$). Regardless of dependence (low dependence, TFC >15 minutes; high dependence, TFC \leq 15 minutes), FTND and TFC were not correlated significantly with urine nicotine equivalents and carcinogen exposure in blacks. The authors found moderate correlations between FTND and TFC and nicotine equivalents and carcinogen exposure among whites of low dependence and non-significant correlations among whites of high dependence. The authors conclude that in the United States, tobacco dependence measures were related linearly to nicotine intake and carcinogen exposure in white but not in black smokers. The relationship between dependence measures and tobacco biomarkers in black smokers regardless of level of dependence resembled highly dependent white smokers. St Helen G, Dempsey D, Wilson M, Jacob P 3rd, Benowitz NL. Racial differences in the relationship between tobacco dependence and nicotine and carcinogen exposure. *Addiction*. 2012 Sep 13. doi: 10.1111/j.1360-0443.2012.04077.x. [Epub ahead of print].

Cocaine-Related Behaviors In Mice With Deficient Gliotransmission

Astrocytes play an integral role in modulating synaptic transmission and plasticity, both key mechanisms underlying addiction. However, while astrocytes are capable of releasing chemical transmitters that can modulate neuronal function, the role of these gliotransmitters in mediating behaviors associated with drugs of abuse has been largely unexplored. The objective of the present study was to utilize mice with astrocytes that lack the ability to release chemical transmitters to evaluate the behavioral

consequence of impaired gliotransmission on cocaine-related behaviors. These mice have previously been used to examine the role of gliotransmission in sleep homeostasis; however, no studies to date have utilized them in the study of addictive behaviors. Mice expressing a dominant-negative SNARE protein selectively in astrocytes (dnSNARE mice) were tested in a variety of behavioral paradigms examining cocaine-induced behavioral plasticity. These paradigms include locomotor sensitization, conditioned place preference followed by cocaine-induced reinstatement of CPP, and cocaine self-administration followed by cue-induced reinstatement of cocaine-seeking behavior. Wild-type and dnSNARE mice demonstrated no significant differences in the development or maintenance of locomotor sensitization. While there were non-significant trends for reduced CPP following a low dose of cocaine, drug-induced reinstatement of CPP is completely blocked in dnSNARE mice. Similarly, while dnSNARE mice demonstrated a non-significant trend toward reduced cocaine self-administration compared with wild-type mice, dnSNARE mice do not demonstrate cue-induced reinstatement in this paradigm. The authors conclude that gliotransmission is necessary for reinstatement of drug-seeking behaviors by cocaine or associated cues. Turner JR, Ecke LE, Briand LA, Haydon PG, Blendy JA. Cocaine-related behaviors in mice with deficient gliotransmission. *Psychopharmacology (Berl)*. 2012 Oct 27. [Epub ahead of print]

Cocaine Self-Administration Behaviors In Clock-Delta-19 Mice A key role has been identified for the circadian locomotor output cycles kaput (Clock) gene in the regulation of drug reward. Mice bearing a dominant negative mutation in the Clock gene (ClockDelta19 mice) exhibit increased cocaine-induced conditioned place preference, reduced anxiety- and depression-like behavior, increased sensitivity to intracranial self-stimulation, and increased dopaminergic cell activity in the ventral tegmental area. The authors sought to determine if this hyperhedonic phenotype extends to cocaine self-administration and measures of motivation. Two separate serial testing procedures were carried out (n = 7-10/genotype/schedule). Testing began with acquisition of sucrose pellet self-administration, implantation of intravenous catheter, acquisition of cocaine self-administration, and dose-response testing (fixed ratio or progressive ratio). To evaluate diurnal variations in acquisition behavior, these sessions occurred at Zeitgeber 2 (ZT2) or ZT14. WT and ClockDelta19 mice exhibited similar learning and readily acquired food self-administration at both ZT2 and ZT14. However, only ClockDelta19 mice acquired cocaine self-administration at ZT2. A greater percentage of ClockDelta19 mice reached acquisition criteria at ZT2 and ZT14. ClockDelta19 mice self-administered more cocaine than WT mice. Using fixed ratio and progressive ratio schedules of reinforcement dose-response paradigms, the authors found that cocaine is a more efficacious reinforcer in ClockDelta19 mice than in WT mice. These results demonstrate that the Clock gene plays an important role in cocaine reinforcement and that decreased CLOCK function increases vulnerability for cocaine use. Ozburn AR, Larson EB, Self DW, McClung CA. Cocaine self-administration behaviors in Clock-delta-19 mice. *Psychopharmacology (Berl)*. 2012 Sep; 223(2): 169-177. Epub 2012 Apr 26.

Eating High Fat Chow Enhances the Locomotor-Stimulating Effects Of Cocaine In Adolescent and Adult Female Rats Dopamine systems vary through development in a manner that can impact drugs acting on those systems. Dietary factors can also impact the effects of drugs acting on dopamine systems. This study examined whether eating high fat chow alters locomotor effects of cocaine (1-56 mg/kg) in adolescent and adult female rats. Cocaine was studied in rats (n = 6/group) with free access to standard (5.7% fat) or high fat (34.3%) chow or restricted access to high fat chow (body weight matched to rats eating standard chow). After 1 week of eating high fat chow (free or restricted access), sensitivity to cocaine was significantly increased in adolescent and

adult rats, compared with rats eating standard chow. Sensitivity to cocaine was also increased in adolescent rats with restricted, but not free, access to high fat chow for 4 weeks. When adolescent and adult rats that previously ate high fat chow ate standard chow, sensitivity to cocaine returned to normal. In adolescent and adult female rats eating high fat chow, but not those eating standard chow, sensitivity to cocaine increased progressively over once weekly tests with cocaine (i.e., sensitization) in a manner that was not statistically different between adolescents and adults. These results show that eating high fat chow alters sensitivity of female rats to acutely administered cocaine and also facilitates the development of sensitization to cocaine. That the type of food consumed can increase drug effects might have relevance to vulnerability to abuse cocaine in the female population. Baladi MG, Koek W, Aumann M, Velasco F, France CP. Eating high fat chow enhances the locomotor-stimulating effects of cocaine in adolescent and adult female rats. *Psychopharmacology (Berl)*. 2012 Aug; 222(3): 447-457. Epub 2012 Mar 15.

Effects of the Combination Of Metyrapone and Oxazepam On Intravenous Nicotine Self-Administration In Rats

Despite increased education regarding its dangers, cigarette smoking remains a significant public health concern due to serious associated health consequences such as cancer and respiratory and cardiovascular diseases. Most smokers fail in their attempts to quit smoking, and current pharmacological interventions have relatively low levels of efficacy and are associated with significant adverse events. The authors have previously reported that combinations of metyrapone and oxazepam, administered at doses that were ineffective when delivered singly, resulted in dose-related decreases in cocaine self-administration in rats while not affecting food-maintained responding during the same sessions. The current study was designed to test the effects of the administration of a metyrapone:oxazepam combination on nicotine self-administration in rats. Several dose combinations of metyrapone (12.5, 25 or 50 mg/kg) and oxazepam (5 or 10 mg/kg) were tested in rats trained to intravenously (IV) self-administer nicotine (0.03 mg/kg/infusion) during 1-h self-administration sessions using both fixed-ratio and progressive-ratio (PR) schedules of reinforcement. The administration of low doses of metyrapone and oxazepam in combination significantly decreased IV nicotine self-administration in rats. At the lowest doses of 12.5 mg/kg of metyrapone and 5 mg/kg of oxazepam, the drugs alone did not decrease IV nicotine self-administration, but the combination was effective. Varenicline was also tested using the fixed-ratio schedule, and reductions in nicotine intake were similar to those seen with the moderate dose of the combination. The results of this study suggest a potential utility of the combination of metyrapone and oxazepam for smoking cessation in humans. Goeders NE, Cohen A, Fox BS, Azar MR, George O, Koob GF. Effects of the combination of metyrapone and oxazepam on intravenous nicotine self-administration in rats. *Psychopharmacology (Berl)*. 2012 Sep; 223(1): 17-25. Epub 2012 Mar 15.

A Mutation In CLOCK Leads To Altered Dopamine Receptor Function

Mice with a mutation in the Clock gene (ClockDelta19) have a number of behavioral phenotypes that suggest alterations in dopaminergic transmission. These include hyperactivity, increased exploratory behavior, and increased reward value for drugs of abuse. However, the complex changes in dopaminergic transmission that underlie the behavioral abnormalities in these mice remain unclear. Here the authors find that a loss of CLOCK function increases dopamine release and turnover in striatum as indicated by increased levels of metabolites HVA and DOPAC, and enhances sensitivity to dopamine receptor antagonists. Interestingly, this enlarged dopaminergic tone results in downstream changes in dopamine receptor (DR) levels with a surprising augmentation of both D1- and D2-type DR protein, but a significant shift in the ratio of D1:D2 receptors in favor of D2 receptor signaling. These effects have functional consequences for both behavior and intracellular signaling, with

alterations in locomotor responses to both D1-type and D2-type specific agonists and a blunted response to cAMP activation in the ClockDelta19 mutants. Taken together, these studies further elucidate the abnormalities in dopaminergic transmission that underlie mood, activity, and addictive behaviors. Spencer S, Torres-Altoro MI, Falcon E, Arey R, Marvin M, Goldberg M, Bibb JA, McClung CA. A mutation in CLOCK leads to altered dopamine receptor function. *J Neurochem*. 2012 Oct; 123(1): 124-134. Epub 2012 Jul 27.

Disruption Of Subcellular Arc/Arg 3.1 mRNA Expression In Striatal Efferent Neurons Following Partial Monoamine Loss Induced By Methamphetamine

The immediate-early gene Arc (activity-regulated cytoskeleton-associated protein) is provocative in the context of neuroplasticity because of its experience-dependent regulation and mRNA transport to and translation at activated synapses. Normal rats have more preproenkephalin-negative (ppe-neg; presumed striatonigral) neurons with cytoplasmic Arc mRNA than ppe-positive (ppe-pos; striatopallidal) neurons, despite equivalent numbers of these neurons showing novelty-induced transcriptional activation of Arc. Furthermore, rats with partial monoamine loss induced by methamphetamine (METH) show impaired Arc mRNA expression in both ppe-neg and ppe-pos neurons relative to normal animals following response-reversal learning. In this study, Arc expression induced by exposure to a novel environment was used to assess transcriptional activation and cytoplasmic localization of Arc mRNA in striatal efferent neuron subpopulations subsequent to METH-induced neurotoxicity. Partial monoamine depletion significantly altered Arc expression. Specifically, basal Arc expression was elevated, but novelty-induced transcriptional activation was abolished. Without novelty-induced Arc transcription, METH-pre-treated rats also had fewer neurons with cytoplasmic Arc mRNA expression, with the effect being greater for ppe-neg neurons. Thus, METH-induced neurotoxicity substantially alters striatal efferent neuron function at the level of Arc transcription, suggesting a long-term shift in basal ganglia neuroplasticity processes subsequent to METH-induced neurotoxicity. Such changes potentially underlie striatally based learning deficits associated with METH-induced neurotoxicity. Barker-Haliski ML, Oldenburger K, Keefe KA. Disruption of subcellular Arc/Arg 3.1 mRNA expression in striatal efferent neurons following partial monoamine loss induced by methamphetamine. *J Neurochem*. 2012 Dec; 123(5): 845-855. doi: 10.1111/jnc.12017. Epub 2012 Oct 10.

Cocaine Produces Conditioned Place Aversion In Mice With A Cocaine Insensitive Dopamine Transporter

Cocaine is an inhibitor of the dopamine, norepinephrine, and serotonin reuptake transporters. Because its administration would therefore elevate signaling of all these three neurotransmitters, many studies have been aimed at attributing individual effects of cocaine to specific transmitter systems. Using mice with a cocaine insensitive dopamine transporter (DAT-CI mice), the authors previously showed that cocaine-induced dopamine elevations were necessary for its rewarding and stimulating effects. In this study, the authors observe that DAT-CI mice exhibit cocaine-conditioned place aversion, and that its expression depends on their genetic background. Specifically, DAT-CI mice backcrossed to the C57Bl/6J strain background did not display a preference or an aversion to cocaine, whereas DAT-CI mice that were on a mixed 129S1/SvImJ x C57Bl/6J (129B6) background had a robust conditioned place aversion to cocaine. These results indicate that while inhibition of the dopamine transporter (DAT) is necessary for cocaine reward, other cocaine targets and neurotransmitter systems may mediate the aversive properties of cocaine. Furthermore, the aversive effect of cocaine can be observed in the absence of a DAT-mediated rewarding effect, and it is affected by genomic differences between these two mouse strains. O'Neill B, Tilley MR, Gu HH. Cocaine produces conditioned place aversion in mice with a cocaine

insensitive dopamine transporter. *Genes Brain Behav.* 2012 Oct 19. doi: 10.1111/j.1601-183X.2012.00872.x. [Epub ahead of print].

A Rodent “Self-Report” Measure Of Methamphetamine Craving? Rat Ultrasonic Vocalizations During Methamphetamine Self-Administration

Rats emit ultrasonic vocalizations (USVs) in a variety of contexts, and it is increasingly clear that USVs reflect more complex information than mere positive and negative affect states. The authors sought to examine USVs in a common model of addiction and relapse, the self-administration/reinstatement paradigm, in order to gain insight into subjective states experienced by rats during various types of methamphetamine seeking. They measured three subtypes of 50kHz USVs [flats, trills, and non-trill frequency modulated (FM) USVs], as well as long and short duration 22kHz USVs, during self-administration and extinction training, and during reinstatement elicited by cues, a methamphetamine prime, cues+prime, or the pharmacological stressor yohimbine. During self-administration and extinction, rats emitted many flats and FMs, (and short duration 22kHz USVs on day 1 of self-administration), but few trills. In contrast, methamphetamine priming injections potently enhanced FMs and trills, and trill production was correlated with the degree of methamphetamine+cue-elicited reinstatement. Cues alone yielded increases only in flat USVs during reinstatement, though a subset of rats displaying strong cue-induced reinstatement also emitted long duration, aversion-related 22kHz USVs. Although yohimbine administration caused reinstatement, it did not induce 22kHz USVs in methamphetamine-experienced or methamphetamine-naive rats (unlike footshock stress, which did induce long duration 22kHz USVs). These findings demonstrate heterogeneity of rat USVs emitted during different types of methamphetamine seeking, and highlight their potential usefulness for gaining insight into the subjective states of rats in rodent models of drug addiction and relapse. Mahler SV, Moorman DE, Feltenstein MW, Cox BM, Ogburn KB, Bachar M, McGonigal JT, Ghee SM, See RE. A rodent self-report measure of methamphetamine craving? Rat ultrasonic vocalizations during methamphetamine self-administration *Behav Brain Res.* 2013 Jan 1; 236(1): 78-89. Epub 2012 Aug 24.

Homology Modeling and Molecular Dynamics Simulations Of the Active State Of the Nociceptin Receptor Reveal New Insights Into Agonist Binding and Activation

The opioid receptor-like receptor, also known as the nociceptin receptor (NOP), is a class A G protein-coupled receptor (GPCR) in the opioid receptor family. Although NOP shares a significant homology with the other opioid receptors, it does not bind known opioid ligands and has been shown to have a distinct mechanism of activation compared to the closely related opioid receptors mu, delta, and kappa. Previously reported homology models of the NOP receptor, based on the inactive-state GPCR crystal structures, give limited information on the activation and selectivity features of this fourth member of the opioid receptor family. The authors report here the first active-state homology model of the NOP receptor based on the opsin GPCR crystal structure. An inactive-state homology model of NOP was also built using a multiple template approach. Molecular dynamics simulation of the active-state NOP model and comparison to the inactive-state model suggest that NOP activation involves movements of transmembrane (TM)3 and TM6 and several activation microswitches, consistent with GPCR activation. Docking of the selective nonpeptidic NOP agonist ligand Ro 64-6198 into the active-state model reveals active-site residues in NOP that play a role in the high selectivity of this ligand for NOP over the other opioid receptors. Docking the shortest active fragment of endogenous agonist nociceptin/orphaninFQ (residues 1-13) shows that the NOP extracellular loop 2 (EL2) loop interacts with the positively charged residues (8-13) of N/OFQ. Both agonists show extensive polar interactions with residues at the extracellular end of the TM

domain and EL2 loop, suggesting agonist-induced reorganization of polar networks, during receptor activation. Daga PR, Zaveri NT. Homology modeling and molecular dynamics simulations of the active state of the nociceptin receptor reveal new insights into agonist binding and activation. *Proteins*. 2012 Aug; 80(8): 1948-1961. doi: 10.1002/prot.24077. Epub 2012 May 17.

Adolescent Exposure To Nicotine Results In Reinforcement Enhancement But Does Not Affect Adult Responding In Rats

Adolescence is a period of development associated with a peak in an organism's responsiveness to reward. Epidemiological data indicate that the initiation of smoking is high during adolescence and that earlier age of onset is associated with increased incidence of dependence as adults. In rats, nicotine is known to have primary reinforcing and reinforcement enhancing effects. Although the primary reinforcing effects of nicotine have been demonstrated in adolescent rats (self-administration), less is known about its reinforcement enhancing effects during this period. Moreover, the impact of adolescent nicotine exposure on its reinforcement enhancing effects during adulthood has not yet been examined. The objectives of this study were to assess whether (1) nicotine enhances operant responding for an unconditioned visual reinforcer (VS) in adolescent rats, and (2) exposure to nicotine during adolescence affects responsiveness to the VS in adulthood. Rats were exposed to nicotine (0.32 mg/kg, subcutaneous injection) or saline during adolescence (postnatal day 29-42) and adulthood. Nose-poking for the VS was assessed under fixed and progressive ratio schedules. Nicotine increased responding for the VS during adolescence. Adolescent nicotine exposure failed to significantly affect adult responsiveness for the VS, regardless of adult nicotine exposure, but early exposure to the VS affected responsiveness to the VS in adulthood. Nicotine exhibits reinforcement enhancing effects in adolescent rats. Long-term effects of adolescent nicotine on reinforcement enhancement are minimal, but the impact of early exposure to the VS and/or the primary reinforcing effects of nicotine requires further investigation. Weaver MT, Geier CF, Levin ME, Caggiula AR, Sved AF, Donny EC. Adolescent exposure to nicotine results in reinforcement enhancement but does not affect adult responding in rats. *Drug Alcohol Depend*. 2012 Oct 1; 125(3): 307-312. Epub 2012 Apr 7.

Deepened Extinction Of Cocaine Cues

A method for reducing the power of drug cues could help in treating drug abuse and addiction. Extinction has been used, with mixed success, in such an effort. Research with non-drug cues has shown that simultaneously presenting (compounding) those cues during extinction can enhance the effectiveness of extinction. The present study investigated whether this procedure could be used to similarly deepen the extinction of cocaine cues. Rats were first trained to self-administer cocaine during tone, click, and light stimuli. Then, these stimuli were subjected to extinction in an initial phase where they were presented individually. In a second extinction phase, one of the auditory stimuli (counterbalanced) was compounded with the light. The other auditory stimulus continued to be presented alone. Rats were then given a week of rest in their homecages prior to testing for spontaneous recovery of cocaine seeking. The cue that was compounded with the light during the second phase of extinction training occasioned less spontaneous recovery of cocaine seeking than the cue that was always presented individually during extinction. Increasing the number of compound cue extinction sessions did not produce a greater deepened extinction effect. The present study showed that simultaneously presenting already-extinguished cocaine cues during additional extinction training enhanced extinction. This extends the deepened extinction effect from non-drug cues to drug cues and further confirms predictions of error-correction learning theory. Incorporating deepened extinction into extinction-based drug abuse treatments could help to reduce the power of drug cues. (c) 2012 Elsevier Ireland Ltd. All rights

reserved. Kearns DN, Tunstall BJ, Weiss SJ. Deepened extinction of cocaine cues. *Drug Alcohol Depend.* 2012 Aug 1; 124(3): 283-287. Epub 2012 Feb 21.

Intravenous Gestational Nicotine Exposure Results In Increased Motivation For Sucrose Reward In Adult Rat Offspring

Prenatal tobacco smoke exposure is associated with alterations in motivated behavior in offspring, such as increased consumption of highly palatable foods and abused drugs. Animal models show that gestational nicotine (GN) exposure mediates changes in responding for sucrose and drug reward. A novel, intermittent low-dose intravenous (IV) exposure model was used to administer nicotine (0.05 mg/kg/injection) or saline 3 x /day to rats on gestational days 8-21. Two experiments investigated the effect of IV GN on (1) the habituation of spontaneous locomotor activity and on (2) sucrose reinforced responding in offspring. For the operant experiments, animals acquired fixed-ratio (FR-3) responding for sucrose, 26% (w/v), and were tested on varying concentrations (0, 3, 10, 30, and 56%; Latin-square) according to a FR-3, and then a progressive-ratio (PR) schedule. Male and female adult offspring were used. IV GN did not alter birth or growth weight, or the number of pups born. No between-group differences in habituation to spontaneous locomotor activity were observed. FR testing produced an inverted U-shaped response curve, and rats showed peak responding for 10% sucrose reinforcement. Neither gestation nor sex affected responding, suggesting equivalent sensitivity to varying sucrose concentrations. PR testing revealed that GN rats showed greater motivation for sucrose reinforcement relative to controls. A low-dose, IV GN exposure model resulted in increased motivation to respond for sucrose reinforcement in adult offspring. This suggests that using a low number of cigarettes throughout pregnancy will result in increased motivation for highly palatable foods in adult, and perhaps, adolescent offspring. Lacy RT, Hord LL, Morgan AJ, Harrod SB. Intravenous gestational nicotine exposure results in increased motivation for sucrose reward in adult rat offspring. *Drug Alcohol Depend.* 2012 Aug 1; 124(3): 299-306. Epub 2012 Feb 27.

Mephedrone ('Bath Salt') Elicits Conditioned Place Preference and Dopamine-Sensitive Motor Activation

Abuse of a dangerous street drug called mephedrone (4-methylmethcathinone) has become commonplace in the United States. Mephedrone is hypothesized to possess abuse liability, share pharmacological properties with psychostimulants, and display toxicity that has been linked to fatalities and non-fatal overdoses. Knowledge about the pharmacology of mephedrone has been obtained primarily from surveys of drug abusers and emergency room visits rather than experimental studies. The present study used motor activity and conditioned place preference (CPP) assays to investigate behavioral effects of mephedrone. Acute mephedrone (3, 5, 10, 30mg/kg, ip) administration increased ambulatory activity in rats. Mephedrone (5mg/kg, ip)-induced ambulation was inhibited by pretreatment with a dopamine D(1) receptor antagonist (SCH 23390) (0.5, 1, 2mg/kg, ip) and enhanced by pretreatment with a dopamine D(2) receptor antagonist (sulpiride) (2mg/kg, ip). Rats injected for 5 days with low dose mephedrone (0.5mg/kg, ip) and then challenged with mephedrone (0.5mg/kg, ip) following 10 days of abstinence displayed sensitization of ambulatory activity. In CPP experiments, mephedrone (30mg/kg, ip) conditioning elicited a preference shift in both rats and mice. The CPP and dopamine-sensitive motor activation produced by mephedrone is suggestive of abuse liability and indicates commonalities between the neuropharmacological profiles of mephedrone and established drugs of abuse. Lisek R, Xu W, Yuvashva E, Chiu YT, Reitz AB, Liu-Chen LY, Rawls SM. Mephedrone ('bath salt') elicits conditioned place preference and dopamine-sensitive motor activation. *Drug Alcohol Depend.* 2012 Nov 1; 126(1-2): 257-262. doi: 10.1016/j.drugalcdep.2012.04.021. Epub 2012 May 29.

Reduced Striatal Dopamine D1-D2 Receptor Heteromer Expression and Behavioural Subensitivity In Juvenile Rats

In adult rat striatum the dopamine D1-D2 receptor heteromer is expressed selectively in a subset of medium spiny neurons (MSNs) that coexpress the dopamine D1 and D2 receptors (D1R and D2R) as well as dynorphin (DYN) and enkephalin (ENK), with higher coexpression in nucleus accumbens (NAc) and much lower in the caudate putamen (CP). In the present study the authors showed that in neonatal striatal cultured neurons >90% exhibited the D1R/D2R-DYN/ENK phenotype. Similarly, in the striatum of juvenile rats (age 26-28days) coexpression of D1R and D2R was also coincident with the expression of both DYN and ENK. Quantification of the number of striatal MSNs exhibiting coexpression of D1R and D2R in juvenile rats revealed significantly lower coexpression in NAc shell, but not core, and CP than in adult rats. However, within MSNs that coexpressed D1R and D2R, the propensity to form the D1-D2 receptor heteromer did not differ between age groups. Consistent with reduced coexpression of the D1R and D2R, juvenile rats exhibited subsensitivity to D1-D2 receptor heteromer-induced grooming following activation by SKF 83959. Given the proposed role of D1R/D2R-coexpressing MSNs in the regulation of thalamic output, and the recent discovery that these MSNs exhibit both inhibitory and excitatory capabilities, these findings suggest that the functional regulation of neurotransmission by the dopamine D1-D2 receptor heteromer within the juvenile striatum may be significantly different than in the adult. Perreault ML, Hasbi A, Alijaniam M, O'Dowd BF, George SR. Reduced striatal dopamine D1-D2 receptor heteromer expression and behavioural subsensitivity in juvenile rats. *Neuroscience*. 2012 Dec 6; 225: 130-139. doi: 10.1016/j.neuroscience.2012.08.042. Epub 2012 Sep 15.

The Synaptic Adhesion Molecule SynCAM 1 Contributes to Cocaine Effects on Synapse Structure and Psychostimulant Behavior

Drugs of abuse have acute and persistent effects on synapse structure and addiction-related behaviors. Trans-synaptic interactions can control synapse development, and synaptic cell adhesion molecule (SynCAM) proteins (also named nectin-like molecules) are immunoglobulin adhesion proteins that span the synaptic cleft and induce excitatory synapses. The authors' studies now reveal that the loss of SynCAM 1 in knockout (KO) mice reduces excitatory synapse number in nucleus accumbens (NAc). SynCAM 1 additionally contributes to the structural remodeling of NAc synapses in response to the psychostimulant cocaine. Specifically, they find that cocaine administration increases the density of stubby spines on medium spiny neurons in NAc, and that maintaining this increase requires SynCAM 1. Furthermore, mushroom-type spines on these neurons are structurally more plastic when SynCAM 1 is absent, and challenging drug-withdrawn mice with cocaine shortens these spines in SynCAM 1 KO mice. These effects are correlated with changes on the behavioral level, where SynCAM 1 contributes to the psychostimulant effects of cocaine as measured after acute and repeated administration, and in drug-withdrawn mice. Together, these results provide evidence that the loss of a synapse-organizing adhesion molecule can modulate cocaine effects on spine structures in NAc and increases vulnerability to the behavioral actions of cocaine. SynCAM-dependent pathways may therefore represent novel points of therapeutic intervention after exposure to drugs of abuse. Giza JI, Jung Y, Jeffrey RA, Neugebauer NM, Picciotto MR, Biederer T. The synaptic adhesion molecule syncam 1 contributes to cocaine effects on synapse structure and psychostimulant behavior. *Neuropsychopharmacology*. 2012 Nov 21. doi: 10.1038/npp.2012.226. [Epub ahead of print].

Cannabinoid Exposure In Adolescent Female Rats Induces Transgenerational Effects On Morphine Conditioned Place Preference In Male Offspring

In the United States, marijuana is one of the drugs most abused by adolescents, with females representing a growing number of users. In previous studies, treatment of adolescent female rats with morphine significantly altered brain reward systems in future offspring. As both cannabinoid and opioid systems develop during adolescence, it was hypothesized that early exposure to cannabinoids would induce similar transgenerational effects. In the current study, female rats were treated with the cannabinoid receptor (CB1/CB2) agonist WIN 55,212-2 or its vehicle for three consecutive days during adolescent development (30 days of age), and were subsequently mated in adulthood (60 days of age). The adolescent and adult male offspring of these WIN 55,212-2 (WIN-F1)- or vehicle (VEH-F1)-treated females were tested for their response to morphine using the conditioned place preference (CPP) paradigm. Both adolescent and adult WIN-F1 offspring exhibited greater sensitivity to morphine CPP than their VEH-F1 counterparts. Collectively, the findings provide additional evidence of transgenerational effects of adolescent drug use. Byrnes JJ, Johnson NL, Schenk ME, Byrnes EM. Cannabinoid exposure in adolescent female rats induces transgenerational effects on morphine conditioned place preference in male offspring. *J Psychopharmacol.* 2012 Oct; 26(10): 1348-1354. Epub 2012 Apr 19.

Quantitative LC-MS/MS Analysis Of Arachidonoyl Amino Acids In Mouse Brain With Treatment Of FAAH Inhibitor

An additional class of endogenous lipid amides, N-arachidonoyl amino acids (Ara-AAs), is growing in significance in the field of endocannabinoids. The development, validation, and application of a sensitive and selective method to simultaneously monitor and quantify the level of Ara-AAs along with anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) in mouse brain has been established. The linearity of the method over the concentration ranges of 0.2-120pg/mul for the standards of N-arachidonoyl amino acids, N-arachidonoyl alanine (NAAla), serine (NASer), gamma-aminobutyric acid (NAGABA), and glycine (NAGly); 0.7-90pg/mul for AEA-d(0)/d(8); and 7.5-950pg/mul for 2-AG was determined with R(2) values of 0.99. Also the effects of the FAAH inhibitor URB 597 on the endogenous levels of these analytes were investigated. AEA and NASer brain levels exhibit a dose-dependent increase after systemic administration of URB 597, whereas NAGly and NAGABA were significantly decreased after treatment. NAAla and 2-AG were not altered after URB 597 treatment. The potential benefit of establishing this assay extends beyond the quantification of the Ara-AAs along with AEA and 2-AG in mouse brain, to reveal a variety of pharmacological effects and physiological roles of these analytes. Han B, Wright R, Kirchoff AM, Chester JA, Cooper BR, Davisson VJ, Barker E. Quantitative LC-MS/MS analysis of arachidonoyl amino acids in mouse brain with treatment of FAAH inhibitor. *Anal Biochem.* 2012 Oct 5. doi:pii: S0003-2697(12)00487-3. 10.1016/j.ab.2012.09.031. [Epub ahead of print].

Evaluation of the Endogenous Cannabinoid System In Mediating The Behavioral Effects Of Dipyrone (Metamizol) In Mice

Dipyrone is a common nonopioid analgesic and antipyretic, which, in many countries, is available over the counter and is more widely used than paracetamol or aspirin. However, the exact mechanisms by which dipyrone acts remain inconclusive. Two novel arachidonoyl-conjugated metabolites are formed in mice following the administration of dipyrone that are dependent on the activity of fatty acid amide hydrolase (FAAH), which also represents the major catabolic enzyme of the endogenous cannabinoid ligand anandamide. These arachidonoyl metabolites not only inhibit cyclooxygenase (COX-1/COX-2) but also bind to cannabinoid receptors at low micromolar concentrations. The relative contributions of cannabinoid receptors and

FAAH in the overall behavioral response to dipyrene remain untested. Accordingly, the two primary objectives of the present study were to determine whether the behavioral effects of dipyrene would (a) be blocked by cannabinoid receptor antagonists and (b) occur in FAAH(-/-) mice. Here, the authors report that thermal antinociceptive, hypothermic, and locomotor suppressive actions of dipyrene are mediated by a noncannabinoid receptor mechanism of action and occurred after acute or repeated administration irrespective of FAAH. These findings indicate that FAAH-dependent arachidonoyl metabolites and cannabinoid receptors are not requisites by which dipyrene exerts these pharmacological effects under noninflammatory conditions. Schlosburg JE, Radanova L, Di Marzo V, Imming P, Lichtman AH. Evaluation of the endogenous cannabinoid system in mediating the behavioral effects of dipyrene (metamizol) in mice. *Behav Pharmacol.* 2012 Oct; 23(7): 722-726. doi: 10.1097/FBP.0b013e3283584794.

Morphine Efficacy Is Altered In Conditional HIV-1 Tat Transgenic Mice Opiate abuse reportedly can exaggerate complications of human immunodeficiency virus type-1 (HIV-1) infection in the central nervous system (CNS), while opiate drugs are often indicated in the treatment of HIV-1-related neuropathic pain. Despite this quandary, few studies have assessed the relationship between the duration or extent of HIV-1 infection and the intrinsic neurobehavioral responsiveness to opioids. To address this problem, doxycycline (DOX)-inducible HIV-Tat(1-86) transgenic mice were used as a model for HIV-1-associated neurocognitive disorders, which permitted the regulation of Tat exposure and duration. The effects of continuous Tat induction on the activity of morphine were examined at weekly intervals using standard behavioral assays for nociception and motor function. In the spinal cord, Tat mRNA levels did not increase until the second and third weeks following induction, which corresponded to a significant loss of morphine antinociception as assessed in the tail-flick test. Alternatively, in the striatum, sustained increases in Tat mRNA expression during the second week of induction coincided with significant decreases in rotarod performance and interactions with morphine. Importantly, the behavioral effects of morphine differed depending on the timing and location of Tat expression, with increases in Tat transcript levels in the spinal cord and striatum corresponding to significant alterations in morphine-dependent nociception and rotarod performance, respectively. Assuming Tat levels contribute to the clinical manifestations of HIV-1, the results suggest that regional differences in viral load and opioid phenotype might influence the nature and degree that opiate responsiveness is altered in HIV-1-infected individuals. Fitting S, Scoggins KL, Xu R, Dever SM, Knapp PE, Dewey WL, Hauser KF. Morphine efficacy is altered in conditional HIV-1 Tat transgenic mice. *Eur J Pharmacol.* 2012 Aug 15; 689(1-3): 96-103. Epub 2012 May 30.

Structural Analogs Of Pyrazole and Sulfonamide Cannabinoids: Effects On Acute Food Intake In Mice Obesity contributes to a multitude of serious health problems. Given the demonstrated role of the endogenous cannabinoid system in appetite regulation, the purpose of the present study was to evaluate structural analogs of two cannabinoids, rimonabant (cannabinoid CB(1) receptor antagonist) and O-2050 (sulfonamide analog of Delta(8)-tetrahydrocannabinol), that showed appetite suppressant effects in previous studies. Structure-activity relationships of these two lead compounds were examined in several assays, including cannabinoid CB(1) and CB(2) receptor binding, food intake, and an in vivo test battery (locomotor activity, antinociception, ring immobility, and body temperature) in mice. Rimonabant and O-2050 reliably decreased feeding in mice; however, their analogs decreased feeding only at higher doses, even though some compounds had quite good cannabinoid CB(1) binding affinity. Results of the in vivo test battery were inconsistent, with some of the compounds producing effects characteristic of cannabinoid agonists

while other compounds were inactive or were antagonists against an active dose of Delta(9)-tetrahydrocannabinol. These results demonstrate that reduction of food intake is not a characteristic effect of pyrazole and sulfonamide cannabinoid analogs with favorable cannabinoid CB(1) binding affinity, suggesting that development of these classes of cannabinoids for the treatment of obesity will require evaluation of their effects in a broad spectrum of pharmacological assays. Wiley JL, Marusich JA, Zhang Y, Fulp A, Maitra R, Thomas BF, Mahadevan A. Structural analogs of pyrazole and sulfonamide cannabinoids: Effects on acute food intake in mice. *Eur J Pharmacol.* 2012 Nov 15; 695(1-3): 62-70. doi: 10.1016/j.ejphar.2012.08.019. Epub 2012 Sep 6.

Modulation Of Opioid Receptor Ligand Affinity and Efficacy Using Active and Inactive State Receptor Models

Mu opioid receptor (MOR) agonists are widely used for the treatment of pain; however, chronic use results in the development of tolerance and dependence. It has been demonstrated that coadministration of a MOR agonist with a delta opioid receptor (DOR) antagonist maintains the analgesia associated with MOR agonists, but with reduced negative side-effects. Using the authors' newly refined opioid receptor models for structure-based ligand design, they have synthesized several pentapeptides with tailored affinity and efficacy profiles. In particular, they have obtained pentapeptides 8, Tyr-c(S-S)[DCys-1Nal-Nle-Cys]NH₂, and 12, Tyr-c(S-S)[DCys-1Nal-Nle-Cys]OH, which demonstrates high affinity and full agonist behavior at MOR, high affinity but very low efficacy for DOR, and minimal affinity for the kappa opioid receptor (KOR). Functional properties of these peptides as MOR agonists/DOR antagonists lacking undesired KOR activity make them promising candidates for future in vivo studies of MOR/DOR interactions. Subtle structural variation of 12, by substituting D-Cys5 for L-Cys5, generated analog 13, which maintains low nanomolar MOR and DOR affinity, but which displays no efficacy at either receptor. These results demonstrate the power and utility of accurate receptor models for structure-based ligand design, as well as the profound sensitivity of ligand function on its structure. Anand JP, Purington LC, Pogozheva ID, Traynor JR, Mosberg HI. Modulation of opioid receptor ligand affinity and efficacy using active and inactive state receptor models. *Chem Biol Drug Des.* 2012 Nov; 80(5): 763-770. doi: 10.1111/cbdd.12014. Epub 2012 Sep 12.

Superior Analgesic Effect of H-Dmt-D-Arg-Phe-Lys-NH(2) ([Dmt(1)]DALDA), a Multifunctional Opioid Peptide, Compared to Morphine in a Rat Model of Neuropathic Pain

H-Dmt-D-Arg-Phe-Lys-NH(2) ([Dmt(1)]DALDA) is a synthetic tetrapeptide with extraordinary selectivity for the mu-opioid receptor and is an extremely potent analgesic. [Dmt(1)]DALDA is unusual in the way that the greater part of its analgesic potency appears to be produced by its actions in the spinal cord. Furthermore, [Dmt(1)]DALDA inhibits norepinephrine re-uptake and is a mitochondria-targeted antioxidant. Such characteristics may make [Dmt(1)]DALDA particularly effective against neuropathic pain. The present study was designed to compare the effects of [Dmt(1)]DALDA and morphine on thermal hyperalgesia in an experimental neuropathic pain model. Neuropathic pain was induced in rats by surgical ligation of the L5 spinal nerve, and thermal pain thresholds were assessed by latencies of paw withdrawal to radiant heat. The increase in paw withdrawal latency was greater after the administration of [Dmt(1)]DALDA than that of morphine in neuropathic rats at doses that were equianalgesic in naïve animals. The authors conclude that [Dmt(1)]DALDA is more effective than morphine against thermal hyperalgesia in this experimental model of neuropathic pain. Shimoyama M, Schiller PW, Shimoyama N, Toyama S, Szeto HH. Superior analgesic effect of H-Dmt-D-Arg-Phe-Lys-NH(2) ([Dmt(1)]DALDA), a multifunctional opioid peptide, compared to morphine in a rat model of neuropathic pain *Chem Biol Drug Des.* 2012 Nov; 80(5): 771-774. doi: 10.1111/cbdd.12003. Epub 2012 Sep 3.

Brain Reinforcement System Function Is Ghrelin Dependent: Studies In The Rat Using Pharmacological fMRI and Intracranial Self-Stimulation

Ghrelin (GHR) is an orexigenic gut peptide that interacts with brain ghrelin receptors (GHR-Rs) to promote food intake. Recent research suggests that GHR acts as a modulator of motivated behavior, suggesting a direct influence of GHR on brain reinforcement circuits. In the present studies, the authors investigated the role of GHR and GHR-Rs in brain reinforcement function. Pharmacological magnetic resonance imaging was used to spatially resolve the functional activation produced by systemic administration of an orexigenic GHR dose. The imaging data revealed a focal activation of a network of subcortical structures that comprise brain reinforcement circuits: ventral tegmental area, lateral hypothalamus and nucleus accumbens. The authors next analyzed whether brain reinforcement circuits require functional GHR-Rs. To this purpose, wild-type (WT) or mutant rats sustaining N-ethyl-N-nitrosourea-induced knockout of GHR-Rs (GHR-R null rats) were implanted with stimulating electrodes aimed at the lateral hypothalamus, shaped to respond for intracranial self-stimulation (ICSS) and then tested using a rate-frequency procedure to examine ICSS response patterns. WT rats were readily shaped using stimulation intensities of 75 μ A, whereas GHR-R null rats required 300 μ A for ICSS shaping. No differences in rate-frequency curves were noted for WT rats at 75 μ A and GHR-R null rats at 300 μ A. When current intensity was lowered to 100 μ A, GHR-R null rats did not respond for ICSS. Taken collectively, these data suggest that systemic GHR can activate mesolimbic dopaminergic areas, and highlight a facilitative role of GHR-Rs on the activity of brain reinforcement systems. Wellman PJ, Clifford PS, Rodriguez JA, Hughes S, Di Francesco C, Melotto S, Tessari M, Corsi M, Bifone A, Gozzi A. Brain reinforcement system function is ghrelin dependent: studies in the rat using pharmacological fMRI and intracranial self-stimulation. *Addict Biol.* 2012 Sep; 17(5): 908-919. Epub 2011 Oct 21.

Programmable Transdermal Delivery Of Nicotine In Hairless Guinea Pigs Using Carbon Nanotube Membrane Pumps

A compact switchable transdermal nicotine patch device was demonstrated to be effective in vivo in a hairless guinea pig animal model. This required the development and validation of a quantitative method for the simultaneous determination of cotinine and nicotine in hairless guinea pig plasma by liquid chromatography-mass spectrometry. Nicotine metabolism in hairless guinea pigs is rapid and cotinine was found to be the viable nicotine marker. The portable carbon nanotube membrane device, powered by a 1.5 V watch battery, was demonstrated to be a power efficient method to pump nicotine at levels six to eight times that of passive diffusion. Cotinine blood plasma levels in hairless guinea pigs were seen to increase from 6 to 12 ng/mL when the patch was turned from passive diffusion to an active pumping state. These nicotine patch devices are highly promising for potential clinical applications, with programmed delivery based on remote counseling, in order to improve smoking cessation treatments. Paudel KS, Wu J, Hinds BJ, Stinchcomb AL. Programmable transdermal delivery of nicotine in hairless guinea pigs using carbon nanotube membrane pumps. *J Pharm Sci.* 2012 Oct; 101(10): 3823-3832. doi: 10.1002/jps.23240. Epub 2012 Jul 17.

Activation of Lateral Habenula Inputs to the Ventral Midbrain Promotes Behavioral Avoidance

Lateral habenula (LHb) projections to the ventral midbrain, including the rostromedial tegmental nucleus (RMTg), convey negative reward-related information, but the behavioral ramifications of selective activation of this pathway remain unexplored. The authors found that exposure to aversive stimuli in mice increased LHb excitatory drive onto RMTg neurons. Furthermore, optogenetic activation of this pathway promoted active, passive and conditioned behavioral avoidance. Thus, activity of LHb efferents to the midbrain is aversive but can also serve

to negatively reinforce behavioral responding. Stamatakis AM, Stuber GD. Activation of lateral habenula inputs to the ventral midbrain promotes behavioral avoidance. *Nat Neurosci.* 2012 Jun 24; 15(8): 1105-1107. doi: 10.1038/nn.3145.

BDNF Is A Negative Modulator Of Morphine Action Brain-derived neurotrophic factor (BDNF) is a key positive regulator of neural plasticity, promoting, for example, the actions of stimulant drugs of abuse such as cocaine. The authors discovered a surprising opposite role for BDNF in countering responses to chronic morphine exposure. The suppression of BDNF in the ventral tegmental area (VTA) enhanced the ability of morphine to increase dopamine (DA) neuron excitability and promote reward. In contrast, optical stimulation of VTA DA terminals in nucleus accumbens (NAc) completely reversed the suppressive effect of BDNF on morphine reward. Furthermore, the authors identified numerous genes in the NAc, a major target region of VTA DA neurons, whose regulation by BDNF in the context of chronic morphine exposure mediated this counteractive function. These findings provide insight into the molecular basis of morphine-induced neuroadaptations in the brain's reward circuitry. Koo JW, Mazei-Robison MS, Chaudhury D, Juarez B, LaPlant Q, Ferguson D, Feng J, Sun H, Scobie KN, Damez-Werno D, Crumiller M, Ohnishi YN, Ohnishi YH, Mouzon E, Dietz DM, Lobo MK, Neve RL, Russo SJ, Han MH, Nestler EJ. *Science.* 2012 Oct 5; 338(6103): 124-128.

Drug Experience Epigenetically Primes FosB Gene Inducibility In Rat Nucleus Accumbens Delta-FosB, a FosB gene product, is induced in nucleus accumbens (NAc) and caudate-putamen (CPu) by repeated exposure to drugs of abuse such as cocaine. This induction contributes to aberrant patterns of gene expression and behavioral abnormalities seen with repeated drug exposure. Here, the authors assessed whether a remote history of cocaine exposure in rats might alter inducibility of the FosB gene elicited by subsequent drug exposure. They show that prior chronic cocaine administration, followed by extended withdrawal, increases inducibility of FosB in NAc, as evidenced by greater acute induction of delta-FosB mRNA and faster accumulation of delta-FosB protein after repeated cocaine reexposure. No such primed FosB induction was observed in CPu; in fact, subsequent acute induction of delta-FosB mRNA was suppressed in CPu. These abnormal patterns of FosB expression are associated with chromatin modifications at the FosB gene promoter. Prior chronic cocaine administration induces a long-lasting increase in RNA polymerase II (Pol II) binding at the FosB promoter in NAc only, suggesting that Pol II stalling primes FosB for induction in this region upon re-exposure to cocaine. A cocaine challenge then triggers the release of Pol II from the gene promoter, allowing for more rapid FosB transcription. A cocaine challenge also decreases repressive histone modifications at the FosB promoter in NAc, but increases such repressive marks and decreases activating marks in CPu. These results provide new insight into the chromatin dynamics at the FosB promoter and reveal a novel mechanism for primed FosB induction in NAc upon reexposure to cocaine. Damez-Werno D, LaPlant Q, Sun H, Scobie KN, Dietz DM, Walker IM, Koo JW, Vialou VF, Mouzon E, Russo SJ, Nestler EJ. *J Neurosci.* 2012 Jul 25; 32(30): 10267-10272.

Exaggerated Cue-Induced Reinstatement Of Cocaine Seeking But Not Incubation Of Cocaine Craving In A Developmental Rat Model Of Schizophrenia Patients with schizophrenia exhibit high comorbidity for substance abuse, but the biological underpinnings of this dual-diagnosis condition are still unclear. Previous studies have shown that rats with a neonatal ventral hippocampal lesion (NVHL), a widely used developmental animal model of schizophrenia, exhibit increased cocaine and methamphetamine self-administration and cocaine-induced reinstatement.

Here, the authors assessed whether a NVHL would also potentiate cue-induced reinstatement of cocaine seeking and the time-dependent increases in cue-induced cocaine seeking after withdrawal (incubation of cocaine craving) in adult rats. Rats were trained to self-administer cocaine (3 or 6 h/day with 0.75 mg/kg(-1) infusion(-1) paired with a tone-light cue) for 10 days, followed by extinction training (3 h/day) and cue-induced reinstatement of cocaine seeking. Other rats were tested for incubation of cocaine craving, assessed in extinction tests 1 and 30 days after the last self-administration session. Although there was no significant difference in cocaine intake between NVHL and sham controls, NVHL rats took significantly longer to reach an a priori set extinction criterion and exhibited enhanced cue-induced reinstatement. However, while cue-induced cocaine seeking was higher after 30 days than after 1 day of withdrawal (incubation of cocaine craving), the NVHL had no effect on this incubation. These data confirm previous reports on enhanced resistance to extinction after NVHL and demonstrate that NVHL rats exhibit enhanced cue-induced reinstatement of cocaine seeking after extinction, a measure of drug relapse. Karlsson RM, Kircher DM, Shaham Y, O'Donnell P. Exaggerated cue-induced reinstatement of cocaine seeking but not incubation of cocaine craving in a developmental rat model of schizophrenia. *Psychopharmacology (Berl)*. 2012 Sep 26. [Epub ahead of print].

Morphine Epigenomically Regulates Behavior through Alterations in Histone H3 Lysine 9 Dimethylation in the Nucleus Accumbens Dysregulation of histone modifying enzymes has been associated with numerous psychiatric disorders. Alterations in G9a (Ehmt2), a histone methyltransferase that catalyzes the euchromatic dimethylation of histone H3 at lysine 9 (H3K9me2), has been implicated recently in mediating neural and behavioral plasticity in response to chronic cocaine administration. Here, the authors show that chronic morphine, like cocaine, decreases G9a expression, and global levels of H3K9me2, in mouse nucleus accumbens (NAc), a key brain reward region. In contrast, levels of other histone methyltransferases or demethylases, or of other methylated histone marks, were not affected in NAc by chronic morphine. Through viral-mediated gene transfer and conditional mutagenesis, the authors found that overexpression of G9a in NAc opposes morphine reward and locomotor sensitization and concomitantly promotes analgesic tolerance and naloxone-precipitated withdrawal, whereas downregulation of G9a in NAc enhances locomotor sensitization and delays the development of analgesic tolerance. The authors identified downstream targets of G9a by providing a comprehensive chromatin immunoprecipitation followed by massively parallel sequencing analysis of H3K9me2 distribution in NAc in the absence and presence of chronic morphine. These data provide novel insight into the epigenomic regulation of H3K9me2 by chronic morphine and suggest novel chromatin-based mechanisms through which morphine-induced addictive-like behaviors arise. Sun H, Maze I, Dietz DM, Scobie KN, Kennedy PJ, Damez-Werno D, Neve RL, Zachariou V, Shen L, Nestler EJ. Morphine epigenomically regulates behavior through alterations in histone h3 lysine 9 dimethylation in the nucleus accumbens. *J Neurosci*. 2012 Nov.

Optogenetic Inhibition Of Cocaine Seeking In Rats Inhibitory optogenetics was used to examine the roles of the prelimbic cortex (PL), the nucleus accumbens core (NAcore) and the PL projections to the NAcore in the reinstatement of cocaine seeking. Rats were microinjected into the PL or NAcore with an adeno-associated virus containing halorhodopsin or archaerhodopsin. After 12 days of cocaine self-administration, followed by extinction training, animals underwent reinstatement testing along with the presence/absence of optically induced inhibition via laser light. Bilateral optical inhibition of the PL, NAcore or the PL fibers in the NAcore inhibited the reinstatement of cocaine seeking. Stefanik MT, Moussawi K, Kupchik YM, Smith KC, Miller RL, Huff ML,

Deisseroth K, Kalivas PW, Lalumiere RT. Optogenetic inhibition of cocaine seeking in rats. *Addict Biol.* 2012 Jul 24. [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 1ARs). Although alpha 1AR signaling in the prefrontal cortex (PFC) promotes mesolimbic transmission and drug-induced behaviors, the potential contribution of alpha 1ARs 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 1ARs 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, they analyzed the cellular, subcellular, and subsynaptic localization of alpha 1ARs and characterized the chemical phenotypes of alpha 1AR-containing elements within the mesocorticolimbic system using single and double immunocytochemical methods at the electron microscopic (EM) level. The authors found that alpha 1ARs are found mainly extra-synaptically in axons and axon terminals in the NAc and are enriched in glutamatergic and dopaminergic elements. alpha 1ARs 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 1ARs attenuated the increase in extracellular DA in the medial NAc shell following administration of cocaine. These data indicate that local alpha 1ARs 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, Weinschenker D. Alpha-1 adrenergic receptors are localized on presynaptic elements in the nucleus accumbens and regulate mesolimbic dopamine transmission. *Neuropsychopharmacology.* 2012 Aug; 37(9): 2161-2172. Epub 2012 May 16.

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 1 h 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, 24 h after the last binge session. Palatable rats rapidly developed binge-like eating, escalating the 1 h 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 Nov; 37(12): 2593-2604. Epub 2012 Jun 20.

Chronic Treatment With Extended Release Methylphenidate Does Not Alter Dopamine Systems Or Increase Vulnerability For Cocaine Self-Administration: A Study In Nonhuman Primates

Despite the widespread use of stimulant medications for the treatment of attention deficit hyperactivity disorder, few studies have addressed their long-term effects on the developing brain or susceptibility to drug use in adolescence. Here, the authors determined the effects of chronic methylphenidate (MPH) treatment on brain dopamine (DA) systems, developmental milestones, and later vulnerability to substance abuse in juvenile nonhuman primates. Male rhesus monkeys (approximately 30 months old) were treated daily with either a sustained release formulation of MPH or placebo (N=8 per group). Doses were titrated to achieve initial drug blood serum levels within the therapeutic range in children and adjusted throughout the study to maintain target levels. Growth, including measures of crown-rump length and weight, was assessed before and after 1 year of treatment and after 3-5 months washout. In addition, positron emission tomography scans were performed to quantify binding availability of D2/D3 receptors and dopamine transporters (DATs). Distribution volume ratios were calculated to quantify binding of [(18)F]fluoroclobopride (DA D2/D3) and [(18)F]-(+)-N-(4-fluorobenzyl)-2beta-propanoyl-3beta-(4-chlorophenyl)tropane (DAT). Chronic MPH did not differentially alter the course of weight gain or other measures of growth, nor did it influence DAT or D2/D3 receptor availability after 1 year of treatment. However, after washout, the D2/D3 receptor availability of MPH-treated animals did not continue to decline at the same rate as control animals. Acquisition of intravenous cocaine self-administration was examined by first substituting saline for food reinforcement and then cocaine doses (0.001-0.1 mg/kg per injection) in ascending order. Each dose was available for at least five consecutive sessions. The lowest dose of cocaine that maintained response rates significantly higher than saline-contingent rates was operationally defined as acquisition of cocaine reinforcement. There were no differences in rates of acquisition, overall response rates, or cocaine intake as a function of cocaine dose between groups. In an animal model that closely mimics human development; chronic treatment with therapeutic doses of sustained release MPH did not have a significant influence on the regulation of DATs or D2/D3 receptors, or on standard measures of growth. Furthermore, this treatment regimen and subsequent drug washout did not have an impact on vulnerability to cocaine abuse. Gill KE, Pierre PJ, Daunais J, Bennett AJ, Martelle S, Gage HD, Swanson JM, Nader MA, Porrino LJ. Chronic treatment with extended release methylphenidate does not alter dopamine systems or increase vulnerability for cocaine self-administration: a study in nonhuman primates. *Neuropsychopharmacology*. 2012 Nov; 37(12): 2555-2565. Epub 2012 Jul 18.

Differential Roles Of GABA(A) Receptor Subtypes In Benzodiazepine-Induced Enhancement Of Brain-Stimulation Reward

Benzodiazepines such as diazepam are widely prescribed as anxiolytics and sleep aids. Continued use of benzodiazepines, however, can lead to addiction in vulnerable individuals. Here, the authors investigate the neural mechanisms of the behavioral effects of benzodiazepines using the intracranial self-stimulation (ICSS) test, a procedure with which the reward-enhancing effects of these drugs can be measured. Benzodiazepines bind nonselectively to several different GABA(A) receptor subtypes. To elucidate the alpha subunit(s) responsible for the reward-enhancing effects of benzodiazepines, the authors examined mice carrying a histidine-to-arginine point mutation in the alpha 1, alpha 2, or alpha 3 subunit, which

renders the targeted subunit nonresponsive to diazepam, other benzodiazepines and zolpidem. In wild-type and alpha 1-point-mutated mice, diazepam caused a dose-dependent reduction in ICSS thresholds (reflecting a reward-enhancing effect) that is comparable to the reduction observed following cocaine administration. This effect was abolished in alpha 2- and alpha 3-point-mutant mice, suggesting that these subunits are necessary for the reward-enhancing action of diazepam. alpha 2 Subunits appear to be particularly important, since diazepam increased ICSS thresholds (reflecting an aversive-like effect) in alpha 2-point-mutant animals. Zolpidem, an alpha 1-preferring benzodiazepine-site agonist, had no reward-enhancing effects in any genotype. These findings implicate alpha 2 and alpha 3 subunit containing GABA(A) receptors as key mediators of the reward-related effects of benzodiazepines. This finding has important implications for the development of new medications that retain the therapeutic effects of benzodiazepines but lack abuse liability. Reynolds LM, Engin E, Tantillo G, Lau HM, Muschamp JW, Carlezon WA Jr, Rudolph U. Differential roles of GABA(A) receptor subtypes in benzodiazepine-induced enhancement of brain-stimulation reward. *Neuropsychopharmacology*. 2012 Oct; 37(11): 2531-2540. Epub 2012 Jul 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 similar to 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. Epub 2012 May 2.

BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH

Neural Responses to Infants Linked with Behavioral Interactions and Testosterone in Fathers

Few fMRI studies have investigated the brain-behavioral basis of parenting in human fathers. Ten fathers were videotaped and gave salivary testosterone samples while interacting with their 2-4 months old infants, and viewed video clips of their own infant and an unfamiliar age-, ethnicity- and sex-matched other infant during an fMRI protocol. Infant stimuli activated a network of prefrontal and subcortical brain regions. Furthermore, a subset of these regions activated significantly more to own (OWN) than other (OTHER) infants. Finally, neural responses to OWN versus OTHER were linked with paternal sensitivity, paternal reciprocity, and testosterone. In sum, these results provide a novel perspective on the links between brain, behavior, and hormones in fathers. Kuo PX, Carp J, Light KC, Grewen KM. Neural responses to infants linked with behavioral interactions and testosterone in fathers. *Biol Psychol.* 2012 Oct; 91(2): 302-306.

The Relationship Between Impulsivity, Risk-Taking Propensity and Nicotine Dependence among Older Adolescent Smokers

Impulsivity and risk-taking propensity are neurobehavioral traits that reliably distinguish between smoking and non-smoking adults. However, how these traits relate to smoking quantity and nicotine dependence among older adolescent smokers is unclear. The current study examined impulsivity and risk-taking propensity in relation to smoking behavior and nicotine dependence among current older adolescent smokers (age 16-20 years; N=107). Participants completed the Barratt Impulsiveness Scale-11 (BIS-11), the Balloon Analogue Risk Task (BART), and self-report measures of smoking behavior and nicotine dependence. Results indicated a significant positive relationship between nicotine dependence and the Attention subscale ($\beta=.20$, $t=2.07$, $p<.05$) and the Non-planning subscale ($\beta=.19$, $t=1.92$, $p<.06$) of the BIS-11. Contrary to expectation, the results also indicated a significant negative relationship between performance on the BART and nicotine dependence ($\beta=-.19$, $t=-2.18$, $p<.05$), such that greater risk-taking propensity was associated with less dependence. These data suggest that impulsivity and risk-taking propensity are related to older adolescent smoking but are separable traits with distinguishable associations with nicotine dependence among adolescents. These findings support the notion that impulsivity is related to heightened nicotine dependence, but suggest that the relationship between risk-taking propensity and nicotine dependence is more ambiguous and warrants further investigation. Ryan KK, Mackillop J, Carpenter MJ. The relationship between impulsivity, risk-taking propensity and nicotine dependence among older adolescent smokers. *Addict Behav.* 2013 Jan; 38(1): 1431-1434.

Effects of Parental Depressive Symptoms on Child Adjustment Moderated by Hypothalamic Pituitary Adrenal: Within- and Between-Family Risk

Child hypothalamic pituitary adrenal (HPA) activity was investigated as a moderator of parental depressive symptom effects on child behavior in an adoption sample (n = 210 families). Adoptive parents' depressive symptoms and child internalizing and externalizing were assessed at 18, 27, and 54 months, and child morning and evening HPA activity measured through salivary cortisol at 54 months. Children's daily cortisol levels and day-to-day variability were tested as moderators of longitudinal associations between parent and child symptoms at within- and between-family levels. Mothers' symptoms related directly to child internalizing, but child evening cortisol moderated effects of fathers' symptoms on internalizing, and of both parents' symptoms on externalizing. Different paths of within-family risk dynamics versus between-family risk synergy were found for internalizing versus externalizing outcomes. Laurent HK, Leve LD, Neiderhiser JM, Natsuaki MN, Shaw DS, Fisher PA, Marceau K,

Harold GT, Reiss D. Effects of parental depressive symptoms on child adjustment moderated by hypothalamic pituitary adrenal: Within- and between-family risk. *Child Dev.* 2012 Sep 26. [Epub ahead of print. doi: 10.1037/a0028800].

Delayed Developmental Changes in Neonatal Vocalizations Correlates with Variations in Ventral Medial Hypothalamus and Central Amygdala Development in the Rodent Infant: Effects of Prenatal Cocaine

While variations in neonatal distress vocalizations have long been shown to reflect the integrity of nervous system development following a wide range of prenatal and perinatal insults, a paucity of research has explored the neurobiological basis of these variations. To address this, virgin Sprague-Dawley rats were bred and divided into three groups: [1] untreated, [2] chronic-cocaine treated (30 mg/kg/day, gestation days (GDs) 1-20); or [3] chronic saline treated (2 mg/kg/day, GDs 1-20). Pregnant dams were injected with Bromodeoxyuridine (10 mg/kg) on GDs 13-15 to label proliferating cells in limbic regions of interest. Ultrasonic vocalizations (USVs) were recorded on postnatal days (PNDs) 1, 14, and 21, from one male and female pup per litter. Variations in acoustic properties of USVs following cocaine-exposure were age and sex-dependent including measures of total number, total duration and amplitude of USVs, and percent of USVs with at least one harmonic. Following USV testing brains were stained with standard fluorescent immunohistochemistry protocols and examined for variations in neuronal development and if variations were associated with acoustic characteristics. Limbic region developmental differences following cocaine-exposure were sex- and age-dependent with variations in the ventral medial hypothalamus and central amygdala correlating with variations in vocalizations on PND 14 and 21. Results suggest maturation of the ventral medial hypothalamus and central amygdala may provide the basis for variations in the sound and production of USVs. As vocalizations may serve as a neurobehavioral marker for nervous system integrity, understanding the neurobiological basis of neonatal vocalizations may provide the basis for early intervention strategies in high-risk infant populations. Cox ET, Hodge CW, Sheikh MJ, Abramowitz AC, Jones GF, Jamieson-Drake AW, Makam PR, Zeskind PS, Johns JM. Delayed developmental changes in neonatal vocalizations correlates with variations in ventral medial hypothalamus and central amygdala development in the rodent infant: Effects of prenatal cocaine. *Behav Brain Res.* 2012 Dec 1; 235(2): 166-175.

Δ^9 Tetrahydrocannabinol Impairs Visuo-Spatial Associative Learning and Spatial Working Memory in Rhesus Macaques

Cannabis remains the most commonly abused illicit drug and is rapidly expanding in quasi-licit use in some jurisdictions under medical marijuana laws. Effects of the psychoactive constituent Δ^9 tetrahydrocannabinol (Δ^9 THC) on cognitive function remain of pressing concern. Prior studies in monkeys have not shown consistent evidence of memory-specific effects of Δ^9 THC on recognition tasks, and it remains unclear to what extent Δ^9 THC causes sedative versus specific cognitive effects. In this study, adult male rhesus monkeys were trained on tasks which assess spatial working memory, visuo-spatial associative memory and learning as well as motivation for food reward. Subjects were subsequently challenged with 0.1-0.3 mg/kg Δ^9 THC, i.m., in randomized order and evaluated on the behavioral measures. The performance of both vsPAL and SOSS tasks was impaired by Δ^9 THC in a dose and task-difficulty dependent manner. It is concluded that Δ^9 THC disrupts cognition in a way that is consistent with a direct effect on memory. There was evidence for interference with spatial working memory, visuo-spatial associative memory and incremental learning in the latter task. These results and the lack of specific effect of Δ^9 THC in prior visual recognition studies imply a sensitivity of spatial memory processing and/or working memory to endocannabinoid perturbation. Taffe MA. Δ^9 tetrahydrocannabinol

impairs visuo-spatial associative learning and spatial working memory in rhesus macaques. *J Psychopharmacol.* 2012 Oct; 26(10): 1299-1306.

Weekend-Weekday Advances in Sleep Timing are Associated with Altered Reward-Related Brain Function in Healthy Adolescents

Sleep timing shifts later during adolescence, thus conflicting with early school start times. This can lead to irregular weekday-weekend schedules and circadian misalignment, which have been linked to depression and substance abuse, consistent with disruptions in the processing of rewards. The authors tested associations between weekend-weekday shifts in sleep timing and the neural response to monetary reward in healthy adolescents, using actigraphy and a functional magnetic resonance imaging paradigm. Region-of-interest analyses focused on the medial prefrontal cortex (mPFC) and striatum, both of which are implicated in reward function. Analyses adjusted for pubertal stage, sex, and total sleep time. Greater weekend-weekday advances in midsleep were associated with decreased mPFC and striatal reactivity to reward, which could reflect reduced regulatory response and reward sensitivity. The authors speculate that circadian misalignment associated with weekend shifts in sleep timing may contribute to reward-related problems such as depression and substance abuse. Hasler BP, Dahl RE, Holm SM, Jakubcak JL, Ryan ND, Silk JS, Phillips ML, Forbes EE. Weekend-weekday advances in sleep timing are associated with altered reward-related brain function in healthy adolescents. *Biol Psychol.* 2012 Dec; 91(3): 334-341.

Childhood and Adolescent Risk Factors for Comorbid Depression and Substance Use Disorders in Adulthood

The comorbidity of major depression and substance use disorders is well documented. However, thorough understanding of prevalence and early risk factors for comorbidity in adulthood is lacking, particularly among urban African Americans. With data from the Woodlawn Study, which follows a community cohort of urban African Americans from ages 6 to 42, the authors identify the prevalence of comorbidity and childhood and adolescent risk factors of comorbid depression and substance use disorders, depression alone, and substance use disorders alone. Prevalence of comorbid substance use disorders and major depression in adulthood is 8.3% overall. Comorbidity in cohort men is twice that for women (11.1% vs. 5.7%). Adjusted multinomial regression models found few differences in risk factors for comorbidity compared to either major depression or a substance use disorder on its own. However, results do suggest distinct risk factors for depression without a substance use disorder in adulthood compared to a substance use disorder without depression in adulthood. In particular, low socioeconomic status and family conflict was related to increased risk of developing major depression in adulthood, while dropping out of high school was a statistically significant predictor of adult-onset substance use disorders. Early onset of marijuana use differentiated those with a substance use disorder with or without depression from those with depression without a substance use disorder in adjusted models. In conclusion, comorbid substance use disorders and depression are highly prevalent among these urban African Americans. Insight into the unique childhood and adolescent risk factors for depression compared to substance use disorders is critical to intervention development in urban communities. Results suggest that these programs must consider individual behaviors, as well as the early family dynamic. Green KM, Zbrak KA, Fothergill KE, Robertson JA, Ensminger ME. Childhood and adolescent risk factors for comorbid depression and substance use disorders in adulthood. *Addict Behav.* 2012 Nov; 37(11): 1240-1247.

Brain Development During the Preschool Years The preschool years represent a time of expansive mental growth, with the initial expression of many psychological abilities that will continue to be refined into young adulthood. Likewise, brain development during this age is characterized by its "blossoming" nature, showing some of its most dynamic and elaborative anatomical and physiological changes. In this article, the authors review human brain development during the preschool years, sampling scientific evidence from a variety of sources. First, they cover neurobiological foundations of early postnatal development, explaining some of the primary mechanisms seen at a larger scale within neuroimaging studies. Next, they review evidence from both structural and functional imaging studies, which now accounts for a large portion of our current understanding of typical brain development. Within anatomical imaging, they focus on studies of developing brain morphology and tissue properties, including diffusivity of white matter fiber tracts. They also present new data on changes during the preschool years in cortical area, thickness, and volume. Physiological brain development is then reviewed, touching on influential results from several different functional imaging and recording modalities in the preschool and early school-age years, including positron emission tomography (PET), electroencephalography (EEG) and event-related potentials (ERP), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), and near-infrared spectroscopy (NIRS). Here, more space is devoted to explaining some of the key methodological factors that are required for interpretation. The authors end with a section on multimodal and multidimensional imaging approaches, which they believe will be critical for increasing our understanding of brain development and its relationship to cognitive and behavioral growth in the preschool years and beyond. Brown TT, Jernigan TL. Brain development during the preschool years. *Neuropsychol Rev.* 2012 Dec; 22(4): 313-333.

The Influence of Inhibitory Control and Episodic Memory on the Risky Sexual Behavior of Young Adult Cannabis Users Cannabis use is associated with risky sexual behavior (RSB) and sex-related negative health consequences. This investigation examined the role of inhibitory control and episodic memory in predicting RSB and sex-related negative consequences among current cannabis users. Findings indicated that the relationships among cannabis, neurocognition, and sexual-risk varied according to the dimension of neurocognition and the parameter of RSB in question. Specifically, more risk-taking was associated with more RSB. Furthermore, amount of recent cannabis use was associated with more RSB and sex-related negative consequences, but only among those with worse performances on a measure of decision-making and of risk-taking. Contrary to hypotheses, worse episodic memory also significantly predicted higher overall sexual-risk and decreased safe-sex practices. Results indicate that worse neurocognitive performance in the areas of risk-taking, decision-making, and episodic memory may influence the degree to which cannabis users engage in RSB and experience negative health consequences as a result. Schuster RM, Crane NA, Mermelstein R, Gonzalez R. The influence of inhibitory control and episodic memory on the risky sexual behavior of young adult cannabis users. *J Int Neuropsychol Soc.* 2012 Sep; 18(5): 827-833.

and Attention Processing Deficits in Preschool-Aged Children with Prenatal Methamphetamine and Tobacco Exposure The aim of this study was to examine the independent contributions of prenatal methamphetamine exposure (PME) and prenatal tobacco exposure (PTE) on brain morphology among a sample of nonalcohol-exposed 3- to 5-year-old children followed prospectively since birth. The sample included 20 children with PME (19 with PTE) and 15 comparison children (7 with PTE), matched on race, birth weight, maternal education and type of

insurance. Subcortical and cortical volumes and cortical thickness measures were derived through an automated segmentation procedure from T1-weighted structural magnetic resonance images obtained on unselected children. Attention was assessed using the computerized Conners' Kiddie Continuous Performance Test Version 5 (K-CPT™ V.5). PME effects on subcortical and cortical brain volumes and cortical thickness were tested by general linear model with type III sum of squares, adjusting for PTE, prenatal marijuana exposure, age at time of scan, gender, handedness, pulse sequence and total intracranial volume (for volumetric outcomes). A similar analysis was done for PTE effects on subcortical and cortical brain volumes and thickness, adjusting for PME and the above covariates. Children with PME had significantly reduced caudate nucleus volumes and cortical thickness increases in perisylvian and orbital-frontal cortices. In contrast, children with PTE showed cortical thinning in perisylvian and lateral occipital cortices and volumetric increases in frontal regions and decreases in anterior cingulate. PME was positively related and caudate volume was inversely related to K-CPT reaction time by inter-stimulus interval, a measure of the ability to adjust to changing task demands, suggesting that children with PME may have subtle attentional deficits mediated by caudate volume reductions. These results suggest that PME and PTE may have distinct differential cortical effects on the developing central nervous system. Additionally, PME may be associated with subtle deficits in attention mediated by caudate volume reductions. Derauf C, Lester BM, Neyzi N, Kekatpure M, Gracia L, Davis J, Kallianpur K, Efir JT, Kosofsky B. Subcortical and cortical structural central nervous system changes and attention processing deficits in preschool-aged children with prenatal methamphetamine and tobacco exposure. *Dev Neurosci.* 2012; 34(4): 327-341.

Stress Reactivity and Corticolimbic Response to Emotional Faces in Adolescents Adolescence is a critical period in the development of lifelong patterns of responding to stress. Understanding underpinnings of variations in stress reactivity in adolescents is important, as adolescents with altered stress reactivity are vulnerable to negative risk-taking behaviors including substance use, and have increased lifelong risk for psychopathology. Although both endocrinological and corticolimbic neural system mechanisms are implicated in the development of stress reactivity patterns, the roles of these systems and interactions between the systems in reactivity to social stimuli in adolescents are not clear. The authors investigated the relationship between cortisol response to a laboratory-based social stressor and regional brain responses to emotional face stimuli in adolescents. Changes in cortisol levels following the Trier Social Stress Test-Child version (TSST-C) were measured in 23 disadvantaged and chronically stressed adolescents who also participated in functional magnetic resonance imaging during processing of emotional faces and structural magnetic resonance imaging. The relationships between changes in cortisol following the TSST-C with regional brain activation during face processing, as well as with regional brain morphology, were assessed. Cortisol change on the TSST-C showed a significant inverse relationship with left hippocampus response to fearful faces ($p < .05$, corrected); significant associations with volume were not observed. Increased cortisol response to the Trier social stressor was associated with diminished response of the left hippocampus to faces depicting fear. This suggests that HPA-corticolimbic system mechanisms may underlie vulnerability to maladaptive responses to stress in adolescents that may contribute to development of stress-related disorders. Liu J, Chaplin TM, Wang F, Sinha R, Mayes LC, Blumberg HP. Stress reactivity and corticolimbic response to emotional faces in adolescents. *J Am Acad Child Adolesc Psychiatry.* 2012 Mar; 51(3): 304-312.

A Preliminary Experimental Investigation of Peer Influence on Risk-Taking among Adolescent Smokers and Non-smokers Epidemiological evidence suggests that peer influence plays a significant role in a variety of adolescent risk-taking behaviors, including tobacco use. The authors attempted to establish this relationship in a controlled laboratory setting. They modified the Balloon Analog Risk Task (BART) task to include a peer component to investigate whether peer influences alter risk-taking behaviors. Thirty-nine adolescents (22 smokers, 17 non-smokers) completed one experimental session during which the standard and peer BART were presented in counterbalanced order, with the dependent measures being adjusted mean number of pumps and explosions. The authors also examined the relationship of changes in the BART (standard-peer) to personality measures of impulsivity (BIS-11) and resistance to peer influence (RPI). A significant interaction of BART type and smoking status was present ($p=.05$); specifically smokers had a greater increase in the number of explosions by 2.27 ($SD=3.12$) compared to an increase of .29 ($SD=2.87$) by non-smokers. BIS-11 scores were related to peer-influenced BART changes: those who were more impulsive experienced greater changes in risk-taking, but no similar relationships were observed for the RPI. These results suggest that peer influences enhance risk-taking among adolescents, and that smokers may be more susceptible to these influences. Cavalca E, Kong G, Liss T, Reynolds EK, Schepis TS, Lejuez CW, Krishnan-Sarin S. A preliminary experimental investigation of peer influence on risk-taking among adolescent smokers and non-smokers. *Drug Alcohol Depend.* 2012 Nov 3. [Epub ahead of print].

Neurobehavioral Disinhibition Predicts Initiation of Substance Use in Children with Prenatal Cocaine Exposure In previous work the authors (Fisher et al., 2011) examined the emergence of neurobehavioral disinhibition (ND) in adolescents with prenatal substance exposure. They computed ND factor scores at three age points (8/9, 11 and 13/14 years) and found that both prenatal substance exposure and early adversity predicted ND. The purpose of the current study was to determine the association between these ND scores and initiation of substance use between ages 8 and 16 in this cohort as early initiation of substance use has been related to later substance use disorders. The authors' hypothesis was that prenatal cocaine exposure predisposes the child to ND, which, in turn, is associated with initiation of substance use by age 16. They studied 386 cocaine exposed and 517 unexposed children followed since birth in a longitudinal study. Five dichotomous variables were computed based on the subject's report of substance use: alcohol only; tobacco only; marijuana only; illicit substances and any substance. Cox proportional hazard regression showed that the 8/9 year ND score was related to initiation of alcohol, tobacco, illicit and any substance use but not marijuana use. The trajectory of ND across the three age periods was related to substance use initiation in all five substance use categories. Prenatal cocaine exposure, although initially related to tobacco, marijuana and illicit substance initiation, was no longer significant with ND scores in the models. Prenatal drug exposure appears to be a risk pathway to ND, which by 8/9 years portends substance use initiation. Lester BM, Lin H, Degarmo DS, Fisher PA, Lagasse LL, Levine TP, Shankaran S, Bada HS, Bauer CR, Hammond JA, Whitaker TM, Higgins RD. Neurobehavioral disinhibition predicts initiation of substance use in children with prenatal cocaine exposure. *Drug Alcohol Depend.* 2012 Nov 1; 126(1-2): 80-86.

Co-morbidity of Substance Use Disorder and Psychopathology in Women Who Use Methamphetamine during Pregnancy in the US and New Zealand Methamphetamine (MA) abuse is a worldwide problem. Little is known about the co-morbidity of substance use disorders (SUD) and other psychiatric disorders of mothers who use MA prenatally. The Infant Development, Environment and Lifestyle (IDEAL) Study is a prospective, investigation of prenatal MA use and

child outcome in the United States (US) and New Zealand (NZ). This study examined prenatal MA use and the co-morbidity of SUD and psychiatric disorders at 1-month postpartum. Mothers who used MA (US=127, NZ=97) were compared to a matched comparison group (US=193, NZ=110). The Substance Abuse Subtle Screening Inventory-3 was used to measure the probability of a SUD. The Brief Symptom Inventory (BSI) was used to measure the likelihood of a positive diagnosis of a psychiatric disorder. In the US and NZ, MA groups had lower SES, increased single parenting, delayed prenatal care, and increased polydrug use. In the US only, MA mothers had lower income than the comparison group. MA users were 10 times more likely to have a SUD and twice as likely to meet BSI criteria for a diagnosable psychiatric disorder. In NZ, but not the US, MA users were five times more likely to have co-morbidity of both. This disparity may be due to higher quantities of prenatal alcohol use associated with increased psychiatric symptoms. These findings suggest that addressing both substance abuse and psychiatric disorders in mothers who use MA may be required to effectively treat maternal MA use. Woules TA, Lagasse LL, Derauf C, Newman E, Shah R, Smith LM, Arria AM, Huestis MA, Dellagrotta S, Wilcox T, Neal CR Jr, Lester BM. Co-morbidity of substance use disorder and psychopathology in women who use methamphetamine during pregnancy in the US and New Zealand. *Drug Alcohol Depend.* 2012 Jul 10. [Epub ahead of print].

Memory Ability and Hippocampal Volume in Adolescents with Prenatal Drug Exposure The objective of the present study was to examine the influence of prenatal drug exposure (PDE) on memory performance and supporting brain structures (i.e., hippocampus) during adolescence. To achieve this goal, declarative memory ability and hippocampal volume were examined in a well-characterized sample of 138 adolescents (76 with a history of PDE and 62 from a non-exposed comparison group recruited from the same community, mean age=14 years). Analyses were adjusted for: age at time of the assessments, gender, IQ, prenatal exposure to alcohol and tobacco, and indices of early childhood environment (i.e., caregiver depression, potential for child abuse, and number of caregiver changes through 7 years of age). Results revealed that adolescents with a history of PDE performed worse on the California Verbal Learning Test-Child Version (CVLT-C), and story recall from the Children's Memory Scale (CMS), and had larger hippocampal volumes, even after covariate adjustment. Hippocampal volume was negatively correlated with memory performance on the CVLT-C, with lower memory scores associated with larger volumes. These findings provide support for long-term effects of PDE on memory function and point to neural mechanisms that may underlie these outcomes. Riggins T, Cacic K, Buckingham-Howes S, Scaletti LA, Salmeron BJ, Black MM. Memory ability and hippocampal volume in adolescents with prenatal drug exposure. *Neurotoxicol Teratol.* 2012 Jul; 34(4): 434-441.

Interrelationship of Substance Use and Psychological Distress over the Life Course among a Cohort of Urban African Americans Substance use and psychological problems are major public health issues because of their high prevalence, co-occurrence, clustering in socio-economically disadvantaged groups, and serious consequences. However, their interrelationship over time is not well understood. This study identifies and compares the developmental epidemiology from age 6 to 42 of substance use and psychological distress in a population of African American men and women. Data come from the Woodlawn study, a longitudinal study of an urban community cohort followed since 1966. The authors use structural equation modeling to examine pathways between substance use (i.e., alcohol, marijuana, and cocaine) and psychological distress over time by gender. They find significant continuity from adolescence to midlife for substance use and for psychological distress, as well as significant correlations within time periods between substance use and psychological distress, particularly among women. They also find greater adolescent substance use

predicts psychological distress in young adulthood for men, but no cross-lag associations for women. Women's adolescent psychological distress and substance use are linked uniquely to that of their mothers. Findings show additional gender differences in the developmental etiology of substance use and psychological distress. Findings demonstrate the continuity of substance use and psychological distress over time; the contemporaneous relationships between psychological distress and substance use within time periods, and minimal cross-lagged relationships. Findings also show that adolescent substance use may set boys on a pathway of long-term psychological distress, thus adding to evidence of negative consequences of frequent use. Green KM, Zebrak KA, Robertson JA, Fothergill KE, Ensminger ME. Interrelationship of substance use and psychological distress over the life course among a cohort of urban African Americans. *Drug Alcohol Depend.* 2012 Jun 1; 123(1-3): 239-248.

Childhood Abuse and Neglect and Cognitive Flexibility in Adolescents Childhood maltreatment (CM) has been associated with diminished executive functioning in children and adults; however, there is a relative paucity of study of executive function in adolescents exposed to CM. Yet, executive dysfunction in adolescence may have important adverse consequences including increased vulnerability to risky behaviors and impaired school functioning. This study investigates the relationship between self-reported CM and an executive function, cognitive flexibility, in adolescents without identified psychiatric disorders. Effects of physical and emotional, abuse and neglect, maltreatment subtypes were explored. Thirty adolescents ages 12-17 years, 50% females, completed the retrospective self-report Childhood Trauma Questionnaire (CTQ) and were administered the Wisconsin Card Sorting Test (WCST). Correlational analyses assessed the relationship between WCST perseverative error scores norm-referenced for age and education with CTQ total scores. The relationship with nonperseverative errors, as well as with physical and emotional abuse and neglect CM subscores, were explored. Total CTQ scores showed significant associations with perseverative errors on the WCST, but not with nonperseverative errors. Significant associations with perseverative errors were seen for physical abuse and physical neglect among the CTQ subscales. The results suggest both physical abuse and physical neglect are associated with diminished cognitive flexibility in adolescents. These effects were detected in adolescents without identified psychiatric diagnoses suggesting the importance of considering executive dysfunction in adolescents exposed to CM who may not meet diagnostic criteria for an Axis I disorder and that tests of perseverative errors, such as those of the WCST, may be sensitive indicators of this dysfunction. Spann MN, Mayes LC, Kalmar JH, Guiney J, Womer FY, Pittman B, Mazure CM, Sinha R, Blumberg HP. Childhood abuse and neglect and cognitive flexibility in adolescents. *Child Neuropsychol.* 2012; 18(2): 182-189.

The Relationship between Risk-taking Propensity and the COMT Val(158)Met Polymorphism among Early Adolescents as a Function of Sex Although adolescents frequently engage in a variety of risky behaviors, much remains unknown about the specific etiologies of such tendencies. Candidate genetic variants, such as the COMT Val(158)Met polymorphism, may be related to risk-taking propensity, particularly as this variant is linked to functional enzymatic differences influencing dopamine function in regions including the prefrontal cortex. The present study aimed to examine the COMT Val(158)Met variant in relation to risk-taking propensity in a community sample of youth. As part of a larger longitudinal study on adolescent risk behaviors, 223 youths (average age 11.3 years) from the metropolitan Washington D.C. area completed a measure of risk-taking propensity, the Balloon Analog Risk Task-Youth Version (BART-Y), and provided saliva samples for DNA extraction and genotyping. Results indicate that females, but not males, who are

carriers of the COMT 158Met allele had higher risk-taking propensity scores on the BART-Y compared to Val homozygotes. Analyses were also conducted in the 111 European American participants, and results were consistent with those of the full sample analyses. This study represents the first investigation of a genetic substrate of risk-taking propensity, measured by a behavioral task, in youth. Results should be taken as quite preliminary, given the small sample. Implications are discussed. Amstadter AB, Macpherson L, Wang F, Banducci AN, Reynolds EK, Potenza MN, Gelernter J, Lejuez CW. The relationship between risk-taking propensity and the COMT Val(158)Met polymorphism among early adolescents as a function of sex. *J Psychiatr Res.* 2012 Jul; 46(7): 940-945.

Association between Age at Onset of Psychosis and Age at Onset of Cannabis Use in Non-Affective Psychosis

Several studies have associated cannabis use with the development of schizophrenia. However, it has been difficult to disentangle the effects of cannabis from that of other illicit drugs, as previous studies have not evaluated pure cannabis users. To test whether the onset of cannabis use had an effect on the initiation of psychosis, the authors examined the time relationship between onset of use and onset of psychosis, restricting our analysis to a cohort of individuals who only used cannabis and no other street drugs. Fifty-seven subjects with non-affective psychoses who used cannabis prior to developing a psychosis were interviewed using the Diagnostic Interview for Genetic Studies (DIGS). The Family Interview for Genetic Studies (FIGS) was also used to interview a family informant about psychiatric illness in the patient and the entire family. Multiple linear regression techniques were used to estimate the association between variables. After adjusting for potential confounding factors such as sex, age, lifetime diagnosis of alcohol abuse or dependence, and family history of schizophrenia, the age at onset of cannabis was significantly associated with age at onset of psychosis ($\beta=0.4$, 95% CI=0.1-0.7, $p=0.004$) and age at first hospitalization ($\beta=0.4$, 95% CI=0.1-0.8, $p=0.008$). The mean time between beginning to use cannabis and onset of psychosis was 7.0 ± 4.3 . Age at onset of alcohol use was not associated with age at onset of psychosis or age at first hospitalization. Age at onset of cannabis is directly associated with age at onset of psychosis and age at first hospitalization. These associations remain significant after adjusting for potential confounding factors and are consistent with the hypothesis that cannabis could cause or precipitate the onset of psychosis after a prolonged period of time. Galvez-Buccollini JA, Proal AC, Tomaselli V, Trachtenberg M, Coconcea C, Chun J, Manschreck T, Fleming J, Delisi LE. Association between age at onset of psychosis and age at onset of cannabis use in non-affective psychosis. *Schizophr Res.* 2012 Aug; 139(1-3): 157-160.

Psychopathology and Special Education Enrollment in Children with Prenatal Cocaine

Exposure This study evaluated how enrollment in special education services in 11-year-old children relates to prenatal cocaine exposure (PCE), psychopathology, and other risk factors. Participants were 498 children enrolled in The Maternal Lifestyle Study, a prospective, longitudinal, multisite study examining outcomes of children with PCE. Logistic regression was used to examine the effect of PCE and psychopathology on enrollment in an individualized education plan (IEP; a designation specific to children with special education needs), with environmental, maternal, and infant medical variables as covariates. PCE, an interaction of PCE and oppositional defiant disorder, child attention-deficit hyperactivity disorder, parent-reported internalizing behaviors, and teacher-reported externalizing behaviors, predicted enrollment in an IEP. Other statistically significant variables in the model were male gender, low birth weight, being small for gestational age, white race, caregiver change, low socioeconomic status, low child intelligence quotient, caregiver depression, and prenatal marijuana exposure. PCE increased the likelihood of receiving

an IEP with adjustment for covariates. Psychopathology also predicted this special education outcome, in combination with and independent of prenatal cocaine exposure. Levine TP, Lester B, Lagasse L, Shankaran S, Bada HS, Bauer CR, Whitaker TM, Higgins R, Hammond J, Roberts MB. Psychopathology and special education enrollment in children with prenatal cocaine exposure. *J Dev Behav Pediatr.* 2012 Jun; 33(5): 377-386.

Educational Attainment is Not a Good Proxy for Cognitive Function in Methamphetamine Dependence

The authors sought to test the hypothesis that methamphetamine use interferes with both the quantity and quality of one's education, such that the years of education obtained by methamphetamine dependent individuals serves to underestimate general cognitive functioning and overestimate the quality of academic learning. Thirty-six methamphetamine-dependent participants and 42 healthy comparison subjects completed cognitive tests and self-report measures in Los Angeles, California. An overall cognitive battery score was used to assess general cognition, and vocabulary knowledge was used as a proxy for the quality of academic learning. Linear regression procedures were used for analyses. Supporting the hypothesis that methamphetamine use interferes with the quantity of education, the authors found that (a) earlier onset of methamphetamine use was associated with fewer years of education ($p < .01$); (b) using a normative model developed in healthy participants, methamphetamine-dependent participants had lower educational attainment than predicted from their demographics and performance on the cognitive battery score ($p < .01$); and (c) greater differences between methamphetamine-dependent participants' predicted and actual educational attainment were associated with an earlier onset of MA use ($p \leq .01$). Supporting the hypothesis that methamphetamine use interferes with the quality of education, years of education received prior to the onset of methamphetamine use was a better predictor of a proxy for academic learning, vocabulary knowledge, than was the total years of education obtained. Results support the hypothesis that methamphetamine use interferes with the quantity and quality of educational exposure, leading to under- and overestimation of cognitive function and academic learning, respectively. Dean AC, Helleman G, Sugar CA, London ED. Educational attainment is not a good proxy for cognitive function in methamphetamine dependence. *Drug Alcohol Depend.* 2012 Jun 1; 123(1-3).

Cortico-Cerebellar Abnormalities in Adolescents with Heavy Marijuana Use

There are currently no studies that have evaluated the motor network, including the cerebellum, in adolescent marijuana (MJ) smokers. The current study aimed to evaluate whether there were activation differences in Brodmann's area 4 (BA4), Brodmann's area 6 (BA6), cingulate (CG) and cerebellum between MJ-using adolescents and healthy controls (HC) on a functional magnetic resonance imaging (fMRI) bilateral finger-tapping task. Twenty-four adolescents (aged 18.2 ± 0.7 years) with heavy MJ use and 24 HC (18.0 ± 1.9) had MRI scans on a 3T Siemens scanner, including a standard bilateral fMRI finger-tapping sequence. Imaging data were analyzed using SPM5 in Matlab. As regions of interest, BA4, BA6, cingulate (CG) and cerebellum were selected, and significant clusters of activity were thresholded at $p < 0.05$, corrected. Healthy controls had significantly greater activation than MJ users for the CG and cerebellum. In addition, activation of the cerebellum and CG correlated with lifetime MJ smokes. This is one of the first studies to evaluate cortico-cerebellar circuits in adolescents with heavy MJ use. The study, which used a bilateral finger-tapping fMRI task, provides evidence for both CG and cerebellar dysfunction in MJ abuse and indicates that lifetime MJ use may impact the developing brain. Lopez-Larson MP, Rogowska J, Bogorodzki P, Bueler CE, McGlade EC, Yurgelun-Todd DA. Cortico-cerebellar abnormalities in adolescents with heavy marijuana use. *Psychiatry Res.* 2012 Jun 30; 202(3): 224-232.

Adolescents' fMRI Activation to a Response Inhibition Task Predicts Future Substance Use

Deficient behavioral regulation may be a risk factor for substance use disorders in adolescents. Abnormalities in brain regions critical to cognitive control have been linked to more intense and problematic future substance use (e.g., Durazzo, Gazdzinski, Mon, & Meyerhoff, 2010; Falk, Berkman, Whalen, & Lieberman, 2011; Paulus, Tapert, & Schuckit, 2005). The goal of this study was to examine the degree to which brain response to an inhibition task measured in mid-adolescence can predict substance use 18 months later. Adolescents aged 16-19 (N=80) performed a go/no-go response inhibition task during fMRI at project baseline, and were followed 18 months later with a detailed interview on substance use and dependence symptoms. Participants were 39 high frequency users and 41 demographically similar low frequency users (458 versus 2 average lifetime drug use occasions at baseline, respectively). Across all subjects, no-go trials produced significant increases in neural response in the ventromedial prefrontal cortex and a region including the left angular and supramarginal gyri ($p(\text{FWE}) < .01$, cluster threshold ≥ 30 voxels). Less ventromedial prefrontal activation but more left angular gyrus activation predicted higher levels of substance use and dependence symptoms in the following 18 months, particularly for those who were high frequency users in mid-adolescence ($p < .05$). These findings are consistent with studies showing that impairments in cognitive control have strong associations with substance use. The authors found a predictive relationship between atypical activation patterns at baseline and substance use behavior 18 months later, particularly among adolescents with histories of previous heavy use. Mahmood OM, Goldenberg D, Thayer R, Migliorini R, Simmons AN, Tapert SF. Adolescents' fMRI activation to a response inhibition task predicts future substance use. *Addict Behav.* 2013 Jan; 38(1): 1435-1441.

Altered Cerebral Blood Flow and Neurocognitive Correlates in Adolescent Cannabis Users

The effects of adolescent marijuana use on the developing brain remain unclear, despite its prevalence. Arterial spin labeling (ASL) is a noninvasive imaging technique that characterizes neurovascular status and cerebral blood flow (CBF), potentially revealing contributors to neuropathological alterations. No studies to date have looked at CBF in adolescent marijuana users. This study examined CBF in adolescent marijuana users and matched healthy controls at baseline and after 4 weeks of monitored abstinence. Heavy adolescent marijuana users ($n=23$, >200 lifetime marijuana use days) and demographically matched controls ($n=23$) with limited substance exposure underwent an ASL brain scan at an initial session and after 4 weeks of sequential urine toxicology to confirm abstinence. Marijuana users showed reduced CBF in four cortical regions including the left superior and middle temporal gyri, left insula, left and right medial frontal gyrus, and left supramarginal gyrus at baseline; users showed increased CBF in the right precuneus at baseline, as compared to controls (corrected p values < 0.05). No between group differences were found at follow-up. Marijuana use may influence CBF in otherwise healthy adolescents acutely; however, group differences were not observed after several weeks of abstinence. Neurovascular alterations may contribute to or underlie changes in brain activation, neuropsychological performance, and mood observed in young cannabis users with less than a month of abstinence. Jacobus J, Goldenberg D, Wierenga CE, Tolentino NJ, Liu TT, Tapert SF. Altered cerebral blood flow and neurocognitive correlates in adolescent cannabis users. *Psychopharmacology (Berl).* 2012 Aug; 222(4): 675-684.

Influence of Caffeine on the Liking of Novel-flavored Soda in Adolescents Soda manufacturers claim that caffeine is added to soda as a flavor enhancer, but many researchers have speculated that caffeine is added to increase the hedonic and reinforcing properties of the soda. Studies in adults have demonstrated that caffeine can condition flavor preferences when added to novel-flavored beverages. The purpose of this study was to test the hypothesis that caffeine added to novel-flavored drinks would increase liking and preference in adolescents. Adolescents (n=99) between the ages of 12 and 17 rated and ranked seven novel soda drinks. They were then randomly assigned to consume one of these beverages paired with either caffeine (1 or 2 mg/kg) or placebo over four consecutive days and rate liking. On the final visit, participants retasted the seven beverages and provided hedonic ratings and rankings. Participants in the 2-mg/kg caffeine group increased the liking of the beverage over the exposure period after an initial decrease, but there was no change in liking for those in the placebo group or in the 1-mg/kg group. The increase in liking in the 2-mg/kg group was accompanied by a decrease in perceived bitterness, but no change in beverage ranking or consumption during the post-test. Caffeine added to novel beverages results in a decrease in liking followed by an increase in liking with repeated exposures that may result from habituation to the bitterness of caffeine. Change in bitter perception may be the mechanism by which adolescents establish regular caffeine use. Temple JL, Ziegler AM, Graczyk A, Bendlin A, O'Leary S, Schnittker YS. Influence of caffeine on the liking of novel-flavored soda in adolescents. *Psychopharmacology (Berl)*. 2012 Sep; 223(1): 37-45.

Profiles of Reactivity in Cocaine-Exposed Children This study explored the possibility that specific, theoretically consistent profiles of reactivity could be identified in a sample of cocaine-exposed infants and whether these profiles were associated with a range of infant and/or maternal characteristics. Cluster analysis was used to identify distinct groups of infants based on physiological, behavioral and maternal reported measures of reactivity. Five replicable clusters were identified which corresponded to 1) Dysregulated/High Maternal Report Reactors, 2) Low Behavioral Reactors, 3) High Reactors, 4) Optimal Reactors and 5) Dysregulated/Low Maternal Report Reactors. These clusters were associated with differences in prenatal cocaine exposure status, birthweight, maternal depressive symptoms, and maternal negative affect during mother-infant interactions. These results support the presence of distinct reactivity profiles among high risk infants recruited on the basis of prenatal cocaine exposure and demographically similar control group infants not exposed to cocaine. Schuetze P, Molnar DS, Eiden RD. Profiles of reactivity in cocaine-exposed children. *J Appl Dev Psychol*. 2012; 33(6): 282-293.

Maternal Self Concept as a Provider and Cessation of Substance Use during Pregnancy Maternal substance use during pregnancy is a common modifiable risk factor for poor birth outcomes, and is associated with long term psychological risks to offspring. As self concept is known to affect substance use behaviors in non-pregnant women, the authors hypothesized that self concept as a provider may be particularly salient to cessation of use during pregnancy. To isolate psychological processes specific to pregnancy from those associated with the transition to parenthood, the authors examined birth mothers who made adoption placements participating in the Early Growth and Development Study. They obtained lifetime and pregnancy substance use history and psychological measures at 3 to 4months postpartum from 693 women recruited from the Northwest, Southwest, and Mid-Atlantic regions of the United States. Life history calendar and computer-assisted personal interviewing methods were used to minimize reporting bias. Using logistic regression, they assessed the association of self concept as an adequate provider with cessation of substance use during pregnancy, controlling for sociodemographic variables,

depressive symptoms experienced during pregnancy, past year antisocial behaviors, family history of substance abuse, timing of pregnancy recognition, timing of initiation of prenatal care, and emotional adjustment to the adoption decision. More positive self-concept as an adequate provider was independently associated with cessation of substance use and earlier initiation of prenatal care during pregnancy [OR=1.223; 95% C.I. (1.005-1.489); B(SE)=.201(.100)]. Familial substance abuse, depressive symptoms, and antisocial behaviors during pregnancy, were also independent predictors, and more strongly associated with cessation [OR=.531; 95% C.I. (.375-.751); B(SE)=-.634 (.178)], [OR=.940; 95% C.I. (.906-.975); B(SE)=-.062 (.019)], [OR=.961; 95% C.I. (.927-.996); B(SE)=-.040 (.018)]. Enhancing maternal identity as a provider for the fetus during pregnancy, along with treatment of depression, may improve motivation to stop substance use. Massey SH, Neiderhiser JM, Shaw DS, Leve LD, Ganiban JM, Reiss D. Maternal self concept as a provider and cessation of substance use during pregnancy. *Addict Behav.* 2012 Aug; 37. [Epub ahead of print].

Marital Hostility and Child Sleep Problems: Direct and Indirect Associations via Hostile Parenting

The current study examined two family process predictors of parent-reported child sleep problems at 4.5 years in an adoption sample: marital hostility and hostile parenting. Participants were 361 linked triads of birth parents, adoptive parents, and adopted children. The authors examined direct and indirect pathways from marital hostility to child sleep problems via hostile parenting. Mothers' marital hostility at 9 months was associated with child sleep problems at 4.5 years. Fathers' marital hostility at 9 months evidenced an indirect effect on child sleep problems at 4.5 years via fathers' hostile parenting at 27 months. Findings were significant even after controlling for genetic influences on child sleep (i.e., birth parent internalizing disorders). The findings suggest targets for prevention and intervention programs that are potentially modifiable (e.g., hostile parenting, marital hostility), and inform theory by demonstrating that relations among marital hostility, hostile parenting, and child sleep problems are significant after accounting for genetic influences. Rhoades KA, Leve LD, Harold GT, Mannering AM, Neiderhiser JM, Shaw DS, Natsuaki MN, Reiss D. Marital hostility and child sleep problems: direct and indirect associations via hostile parenting. *J Fam Psychol.* 2012 Aug; 26(4): 488-498.

CLINICAL NEUROSCIENCE RESEARCH

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, play a role in affective regulation and are 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. The authors conclude that 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, Wiley EP, Ray R, Ruparel K, Newberg A, Dubroff J, Logan J, Zubieta JK, Blendy JA, Lerman C. μ -Opioid receptor availability in the amygdala is associated with smoking for negative affect relief. *Psychopharmacology (Berl)*. 2012 Aug; 222(4): 701-708.

Decisions During Negatively Framed Messages Yield Smaller Risk Aversion-Related Brain Activation in Substance-Dependent Individuals

A sizable segment of addiction research investigates the effects of persuasive message appeals on risky and deleterious behaviors. However, to date, little research has examined how various forms of message framing and corresponding behavioral choices might be mediated by risk-related brain regions. Using event-related functional MRI, the authors investigated brain regions hypothesized to mediate the influence of message appeals on decision making in substance-dependent (SD) compared with nonsubstance-dependent (non-SD) individuals. The Iowa Gambling Task (IGT) was modified to include positively-framed, negatively-framed, and control messages about long-term deck payoffs. In the positively-framed condition, the SD and non-SD groups showed improved decision-making performance that corresponded to higher risk-aversion-related brain activity in the anterior cingulate cortex (ACC) and anterior insula (AI). In contrast, in the negatively-framed condition, the SD group showed poorer performance that corresponded to lower risk-aversion-related brain activity in the AI region. In addition, only the non-SD group showed a positive association between decision quality and greater risk-related activity in the ACC, regardless of message type. The findings suggest substance-dependent individuals may have reduced neurocognitive sensitivity in the ACC and AI regions involved in risk perception and aversion during decision-making, especially in response to framed messages that emphasize reduced prospects for long-term gains. Fukunaga, R, Bogg, T, Finn, PR, Brown, JW. Decisions during negatively-framed messages yield smaller risk-aversion-related brain activation in substance-dependent individuals. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*, 2012 Nov 12 [Epub ahead of print: DOI: 10.1037/a0030633].

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 (*CNR1*), 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 *CNR1* 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 (*CNR1*) variation and hippocampus and amygdala volumes in heavy cannabis users. *Neuropsychopharm.* 2012 Jun 12 [Epub ahead of print: DOI: 10.1038/npp.2012.92].

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 Sexual Discounting Task: HIV Risk Behavior and the Discounting of Delayed Sexual Rewards in Cocaine Dependence

Cocaine dependence is associated with high rates of sexual risk behavior and HIV infection. However, little is known about the responsible mechanism(s). Cocaine-dependent individuals (N=62) completed a novel Sexual Discounting Task assessing decisions

between immediate unprotected sex and delayed sex with a condom across four hypothetical partners: most (and least) likely to have a sexually transmitted infection (STI), and most (and least) sexually desirable; a real rewards money delay-discounting task, and self-reported sexual risk behavior using the HIV Risk-Taking Behavior Scale (HRBS). Sexual Discounting Task results were largely systematic and showed a strong effect of delay in decreasing condom use. Sexual discounting (preference for immediate unprotected sex) was significantly greater when making responses for partners judged least (compared to most) likely to have an STI, and for partners judged most (compared to least) desirable. Differences in sexual discounting were significant after controlling for differences in condom use (with no delay) between conditions. Greater discounting in 3 of the 4 Sexual Discounting Task conditions, but not in the money discounting task, was associated with greater self-reported sexual risk behavior as measured by the HRBS. Results suggest that delay is a critical variable strongly affecting HIV sexual risk behavior, and that the Sexual Discounting Task provides a clinically sensitive measure of this phenomenon that may address a variety of questions about HIV risk in future research. The wealth of behavioral and neurobiological data on delay discounting should be brought to bear on HIV education and prevention. Johnson MW, Bruner NR. The Sexual Discounting Task: HIV risk behavior and the discounting of delayed sexual rewards in cocaine dependence. *Drug Alcohol Depend.* 2012 Jun 1; 123(1-3): 15-21.

Medical Marijuana Use among Adolescents in Substance Abuse Treatment The objective of this study was to assess the prevalence and frequency of medical marijuana diversion and use among adolescents in substance abuse treatment and to identify factors related to their medical marijuana use. This study calculated the prevalence and frequency of diverted medical marijuana use among adolescents (n = 164), ages 14-18 years (mean age = 16.09, SD = 1.12), in substance abuse treatment in the Denver metropolitan area. Bivariate and multivariate analyses were completed to determine factors related to adolescents' use of medical marijuana. Approximately 74% of the adolescents had used someone else's medical marijuana, and they reported using diverted medical marijuana a median of 50 times. After adjusting for gender and race/ethnicity, adolescents who used medical marijuana had an earlier age of regular marijuana use, more marijuana abuse and dependence symptoms, and more conduct disorder symptoms compared with those who did not use medical marijuana. The authors conclude that medical marijuana use among adolescent patients in substance abuse treatment is very common, implying substantial diversion from registered users. These results support the need for policy changes that protect against diversion of medical marijuana and reduce adolescent access to diverted medical marijuana. Future studies should examine patterns of medical marijuana diversion and use in general population adolescents. Salomonsen-Sautel S, Sakai JT, Thurstone C, Corley R, Hopfer C. Medical marijuana use among adolescents in substance abuse treatment. *J Am Acad Child Adolesc Psychiatry.* 2012 Jul; 51(7): 694-702.

Persistent Cannabis Users Show Neuropsychological Decline From Childhood To Midlife

Recent reports show that fewer adolescents believe that regular cannabis use is harmful to health. Concomitantly, adolescents are initiating cannabis use at younger ages, and more adolescents are using cannabis on a daily basis. The purpose of the present study was to test the association between persistent cannabis use and neuropsychological decline and determine whether decline is concentrated among adolescent-onset cannabis users. Participants were members of the Dunedin Study, a prospective study of a birth cohort of 1,037 individuals followed from birth (1972/1973) to age 38 y. Cannabis use was ascertained in interviews at ages 18, 21, 26, 32, and 38 y.

Neuropsychological testing was conducted at age 13 y, before initiation of cannabis use, and again at age 38 y, after a pattern of persistent cannabis use had developed. Persistent cannabis use was associated with neuropsychological decline broadly across domains of functioning, even after controlling for years of education. Informants also reported noticing more cognitive problems for persistent cannabis users. Impairment was concentrated among adolescent-onset cannabis users, with more persistent use associated with greater decline. Further, cessation of cannabis use did not fully restore neuropsychological functioning among adolescent-onset cannabis users. Findings are suggestive of a neurotoxic effect of cannabis on the adolescent brain and highlight the importance of prevention and policy efforts targeting adolescents. Meier MH, Caspi A, Ambler A, Harrington H, Houts R, Keefe RS, McDonald K, Ward A, Poulton R, Moffitt TE. Persistent cannabis users show neuropsychological decline from childhood to midlife. *Proc Natl Acad Sci U S A*. 2012 Oct 2; 109(40): E2657-2664. doi: 10.1073/pnas.1206820109. Epub 2012 Aug 27.

Elevated Neurobehavioral Symptoms are Associated with Everyday Functioning Problems in Chronic Methamphetamine Users

Chronic methamphetamine (MA) use is commonly associated with neural injury and neurocognitive deficits. The authors examined the nature and correlates of self-reported neurobehavioral symptoms (e.g., apathy, disinhibition, and executive dysfunction) in 73 individuals with histories of MA dependence (MA+) and 85 comparison participants with comparable demographics and risk histories. MA+ individuals endorsed significantly more severe neurobehavioral symptoms on the Frontal Systems Behavioral Scale, especially those of disinhibition and executive dysfunction. Elevations in neurobehavioral symptoms were independent of common comorbidities, including hepatitis C infection, attention-deficit/hyperactivity disorder (ADHD), mood disorders, and other substance-use factors. Notably, the severity of neurobehavioral symptoms was uniquely associated with self-reported decrements in instrumental activities of daily living in the MA-dependent sample. Findings indicate that chronic MA users may experience elevated neurobehavioral symptoms of disinhibition and executive dysfunction, potentially increasing their risk of functional declines. Cattie JE, Woods SP, Iudicello JE, Posada C, Grant I; TMARC Group. Elevated neurobehavioral symptoms are associated with everyday functioning problems in chronic methamphetamine users. *J Neuropsychiatry Clin Neurosci*. 2012 Summer; 24(3): 331-339.

Proposed Functional Parcellation of the Striatum Based on the Type of Associations Being Encoded

It has long been recognized that the striatum is composed of distinct functional sub-units that are part of multiple cortico-striatal-thalamic circuits. Contemporary research has focused on the contribution of striatal sub-regions to three main phenomena: learning of associations between stimuli, actions and rewards; selection between competing response alternatives; and motivational modulation of motor behavior. Recent proposals have argued for a functional division of the striatum along these lines, attributing, for example, learning to one region and performance to another. Here, the authors consider empirical data from human and animal studies, as well as theoretical notions from both the psychological and computational literatures, and conclude that striatal sub-regions instead differ most clearly in terms of the associations being encoded in each region. Liljeholm M, O'Doherty JP. Contributions of the striatum to learning, motivation, and performance: an associative account. *Trends Cogn Sci*. 2012 Sep; 16(9): 467-475.[doi: 10.1016/j.tics.2012.07.007. Epub 2012 Aug 10.]

Enhanced Midbrain Response at 6-month Follow-up in Cocaine Addiction Association with Reduced Drug-related Choice

Drug addiction is characterized by dysregulated dopamine neurotransmission. Although dopamine functioning appears to partially recover with abstinence, the specific regions that recover and potential impact on drug seeking remain to be determined. Here the authors used functional magnetic resonance imaging (fMRI) to study an ecologically valid sample of 15 treatment-seeking cocaine addicted individuals at baseline and 6-month follow-up. At both study sessions, the authors collected fMRI scans during performance of a drug Stroop task, clinical self-report measures of addiction severity and behavioral measures of cocaine seeking (simulated cocaine choice); actual drug use in between the two study sessions was also monitored. At 6-month follow-up (compared with baseline), they predicted functional enhancement of dopaminergically innervated brain regions, relevant to the behavioral responsiveness toward salient stimuli. Consistent with predictions, whole-brain analyses revealed responses in the midbrain (encompassing the ventral tegmental area/substantia nigra complex) and thalamus (encompassing the mediodorsal nucleus) that were higher (and more positively correlated) at follow-up than baseline. Increased midbrain activity from baseline to follow-up correlated with reduced simulated cocaine choice, indicating that heightened midbrain activations in this context may be marking lower approach motivation for cocaine. Normalization of midbrain function at follow-up was also suggested by exploratory comparisons with active cocaine users and healthy controls (who were assessed only at baseline). Enhanced self-control at follow-up was suggested by a trend for the commonly hypoactive dorsal anterior cingulate cortex to increase response during a drug-related context. Together, these results suggest that fMRI could be useful in sensitively tracking follow-up outcomes in drug addiction. Moeller SJ, Tomasi D, Woicik PA, Maloney T, Alia-Klein N, Honorio J, Telang F, Wang G-J, Wang R, Sinha R, Carise D, Astone-Twerell J, Bolger J, Volkow ND, Goldstein RZ. Enhanced midbrain response at 6-month follow-up in cocaine addiction, association with reduced drug-related choice. *Addiction Biology*. 2012 Mar 28 [Epub ahead of print: DOI: 10.1111/j.1369-1600.2012.00440.x].

Accumbens Functional Connectivity during Reward Mediates Sensation-Seeking and Alcohol Use in High-Risk Youth

Differences in fronto-striatal connectivity in problem substance users have suggested reduced influence of cognitive regions on reward-salience regions. Youth with a family history of alcoholism (FH+) have disrupted ventral striatal processing compared with controls with no familial risk (FH-). As sensation-seeking represents an additional vulnerability factor, we hypothesized that functional connectivity during reward anticipation would differ by family history, and would mediate the relationship between sensation-seeking and drinking in high-risk subjects. Seventy 18-22 year olds (49 FH+/21 FH-) performed a monetary incentive delay task during functional magnetic resonance imaging. Group connectivity differences for incentive (reward/loss) vs. neutral conditions were evaluated with psychophysiological interaction (PPI) analysis, seeded in nucleus accumbens (NAcc). Indirect effects of sensation-seeking on drinking volume through accumbens connectivity were tested. NAcc connectivity with paracentral lobule/precuneus and sensorimotor areas was decreased for FH- vs. increased for FH+ during incentive anticipation. In FH+, task-related functional coupling between left NAcc and supplementary sensorimotor area (SSMA) and right precuneus correlated positively with sensation-seeking and drinking volume and mediated their relationship. In FH-, left NAcc-SSMA connectivity correlated negatively with sensation-seeking but was not related to drinking. These results suggest preexisting differences in accumbens reward-related functional connectivity in high-risk subjects. NAcc coupling with SSMA, involved in attention and motor networks, and precuneus, a default mode structure, appear to mediate sensation-seeking's effect on drinking in those most at-risk.

Differences in accumbens connectivity with attention/motor/default networks, rather than control systems, may influence the reward system's role in vulnerability for substance abuse. Weiland BJ, Welsh RC, Yau WY, Zucker RA, Zubieta JK, Heitzeg MM. Accumbens functional connectivity during reward mediates sensation-seeking and alcohol use in high-risk youth. *Drug Alcohol Depend.* 2012 Sep 4. [Epub ahead of print: DOI: 10.1016/j.drugalcdep.2012.08.019].

Individual Variability in the Locus of Prefrontal Craving for Nicotine: Implications for Brain Stimulation Studies and Treatments

Attenuation of cue-elicited craving with brain stimulation techniques is a growing area of attention in addiction research. This investigation aims to guide these studies by assessing individual variability in the location of peak cortical activity during cue-elicited craving. Twenty-six nicotine-dependent individuals performed a cue-elicited craving task in a 3T MRI scanner while BOLD signal data was collected. The task included epochs of smoking cues, neutral cues, and rest. The location of peak activity during smoking cues relative to neutral cues ('hot spot') was isolated for each individual. The spatial dispersion of the 26 cue-elicited hot spots (1 per participant) was quantified via hierarchical clustering. When viewing nicotine cues all 26 participants had at least one cluster of significant prefrontal cortex activity ($p < 0.05$, cluster corrected). Only 62% had peak activity in the medial prefrontal cortex cluster (including 100% of the men). In 15% of the participants peak activity was located in either the left lateral prefrontal cortex or left insula cluster. Peak activity in the remaining 23% was dispersed throughout the prefrontal cortex. There is considerable individual variability in the location of the cue-elicited 'hot spot' as measured by BOLD activity. Men appear to have a more uniform location of peak BOLD response to cues than women. Consequently, acquiring individual functional imaging data may be advantageous for either tailoring treatment to the individual or filtering participants before enrollment in treatment. Hanlon CA, Jones EM, Lia X, Hartwell KJ, Brady KT, George MS. Individual variability in the locus of prefrontal craving for nicotine: Implications for brain stimulation studies and treatments. *Drug Alc Depend.* 2012 October 1; 125(3): 239–243.

Genetic Influences on Developmental Smoking Trajectories The aims of this study were to investigate the relative contribution of genetic and environmental factors on smoking trajectory membership and to test whether individual smoking trajectories represent phenotypical thresholds of increasing genetic risk along a common genetic liability dimension. This was a prospective study of a birth cohort of female like-sex twin pairs. Female twins who had smoked ≥ 100 cigarettes lifetime ($n = 1466$ regular smokers) served as participants. Each participants completed a diagnostic interview survey four times from adolescence (average age 16) to young adulthood (average age 25). Measurements collected were number of cigarettes smoked per day during the heaviest period of smoking (two waves) or during the past 12 months (two waves). A four-trajectory class solution provided the best fit to cigarette consumption data and was characterized by low ($n = 564$, 38.47%), moderate ($n = 366$, 24.97%) and high-level smokers ($n = 197$, 13.44%), and smokers who increased their smoking from adolescence to young adulthood ($n = 339$, 23.12%). The best genetic model fit was a three-category model that comprised the low, a combined increasing + moderate and high trajectories. This trajectory categorization was heritable (72.7%), with no evidence for significant contribution from shared environmental factors. The authors concluded that the way in which smoking patterns develop in adolescence has a high level of heritability. Lessov-Schlaggar CN, Kristjansson SD, Bucholz KK, Heath AC, Madden PA. Genetic influences on developmental smoking trajectories. *Addiction.* 2012 Sep; 107(9): 1696-1704.

Reduced Dopamine D2/D3 Receptor Availability is Specific to Male Smokers In previous research, nicotine-dependent men exhibited lower putamen D2/D3 dopamine-receptor availability than non-smokers (Fehr et al. 2008), but parallel assessments were not performed in women. Women and men (19 light smokers, 18 non-smokers) were tested for differences due to sex and smoking in striatal D(2)/D(3) dopamine-receptor availability, using positron emission tomography with [(18)F]fallypride. Receptor availability was determined using a reference region method, in striatal volumes and in whole-brain, voxel-wise analysis. Significant sex \times smoking interactions were observed in the caudate nuclei and putamen. Post-hoc t tests showed that male smokers had significantly lower D(2)/D(3) dopamine-receptor availability than female smokers (-17% caudate, -21% putamen) and male non-smokers (-15% caudate, -16% putamen). Female smokers did not differ from non-smokers. Whole-brain analysis demonstrated no statistically significant voxels or clusters. These results suggest that low receptor availability may confer vulnerability to nicotine dependence or that smoking selectively affects D2/D3 receptor down-regulation in men but not women. Brown AK, Mandelkern MA, Farahi J, Robertson C, Ghahremani DG, Sumerel B, Moallem N, London ED. Sex differences in striatal dopamine D2/D3 receptor availability in smokers and non-smokers. *Int J Neuropsychopharmacol.* 2012 Aug; 15(7): 989-994.

Interactive Effects of Chronic Cigarette Smoking and Age on Brain Volumes in Controls and Alcohol-Dependent Individuals in Early Abstinence Chronic alcohol-use disorders (AUDs) have been shown to interact with normal age-related volume loss to exacerbate brain atrophy with increasing age. However, chronic cigarette smoking, a highly co-morbid condition in AUD and its influence on age-related brain atrophy have not been evaluated. The authors performed 1.5T quantitative magnetic resonance imaging in non-smoking controls [non-smoking light drinking controls (nsCONs); n=54], smoking light drinking controls (sCONs, n=34), and one-week abstinent, treatment-seeking alcohol-dependent (ALC) non-smokers (nsALCs, n=35) and smokers (sALCs, n=43), to evaluate the independent and interactive effects of alcohol dependence and chronic smoking on regional cortical and subcortical brain volumes, emphasizing the brain reward/executive oversight system (BREOS). The nsCONs and sALCs showed greater age-related volume losses than the nsALCs in the dorsal prefrontal cortex (DPFC), total cortical BREOS, superior parietal lobule and putamen. The nsALCs and sALCs demonstrated smaller volumes than the nsCONs in most cortical region of interests (ROIs). The sCONs had smaller volumes than the nsCONs in the DPFC, insula, inferior parietal lobule, temporal pole/parahippocampal region and all global cortical measures. The nsALCs and sALCs had smaller volumes than the sCONs in the DPFC, superior temporal gyrus, inferior and superior parietal lobules, precuneus and all global cortical measures. Volume differences between the nsALCs and sALCs were observed only in the putamen. Alcohol consumption measures were not related to volumes in any ROI for ALC; smoking severity measures were related to corpus callosum volume in the sCONs and sALCs. The findings indicate that consideration of smoking status is necessary for a better understanding of the factors contributing to regional brain atrophy in AUD. Durazzo TC, Mon A, Pennington D, Abé C, Gazdzinski S, Meyerhoff DJ. Interactive effects of chronic cigarette smoking and age on brain volumes in controls and alcohol-dependent individuals in early abstinence. *Addict Biol.* 2012 Sep 3.[Epub ahead of print: DOI: 10.1111/j.1369-1600.2012.00492.x.].

Response Inhibition and Psychomotor Speed during Methadone Maintenance: Impact of Treatment Duration, Dose, and Sleep Deprivation In opiate-dependent individuals, abstinence results in deficits in cognitive functioning, which may be exacerbated by medication-associated sleep disruption. To assess cognitive function and the influence of sleep deprivation (SD), 14

healthy control (HC) and 22 methadone maintained (MM) participants completed the continuous performance task (CPT) after a baseline night, a night of total SD, and two recovery sleep nights. The digit symbol substitution task (DSST) was administered at bedtime and in the morning. Secondary analyses separated MM participants into short- (< 12 months; n=8) and long-term (\geq 12 months; n=14) treatment duration groups, and into low- (< 80 mg; n=9) and high-dose (\geq 80 mg; n=13) groups. Linear mixed model ANOVAs revealed that there was no effect of SD. Across all days MM participants had more errors of omission, fewer correct responses, and slower reaction times (RTs) on the CPT, and fewer accurate substitutions on the evening and morning DSST. Short-term MM participants exhibited slower RTs on the CPT, and fewer correct substitutions on the evening DSST compared to long-term MM participants. Low-dose MM participants had slower RTs on the CPT than HCs and high-dose MM participants. These data demonstrate that methadone-maintained individuals exhibit poorer performance on tasks of psychomotor speed and selective attention/impulsivity, but with longer-term treatment, performance appears to return toward control levels. Furthermore, while one day of SD was enough to alter subjective reports of sleep quality, cognitive function may be more resilient. Bracken BK, Trksak GH, Penetar DM, Tartarini WL, Maywalt MA, Dorsey CM, Lukas SE. Response inhibition and psychomotor speed during methadone maintenance: impact of treatment duration, dose, and sleep deprivation. *Drug Alcohol Depend.* 2012 Sep 1; 125(1-2): 132-139.

Associations of Functional and Dysfunctional Impulsivity to Smoking Characteristics

Although the relation between impulsivity and smoking is well-documented, one model of impulsivity that has received little attention in the addiction literature separates impulsivity into 2 dimensions: functional impulsivity (tendency to make quick effective decisions) and dysfunctional impulsivity (tendency to make quick ineffective decisions). This cross-sectional study examined relations of functional and dysfunctional impulsivity to smoking characteristics in 212 non-treatment-seeking daily smokers (M = 15 cigarettes per day, M age = 24 years, 53% women). Dysfunctional impulsivity exhibited small- to medium-sized positive associations with difficulty refraining from smoking in forbidden places, craving, and smoking without awareness. Functional impulsivity was inversely associated with a measure of cigarette craving. Other suggestive associations were found; however, these were not statistically significant after type I error correction. Although the overall predictive validity of these impulsivity constructs for explaining variance in smoking characteristics was relatively modest, the results suggest that conceptualizing impulsivity as a unitary construct indicative of a tendency to make quick decisions may mask heterogeneity within the impulsivity-smoking relationship. These findings suggest that high-dysfunctional impulsivity smokers may perhaps require more intensive interventions to dampen motivation to smoke. They also highlight the possibility that certain manifestations of impulsivity are not related with increased smoking behavior and may actually associate with reduced drive to smoke. Pitts SR, Leventhal AM. Associations of functional and dysfunctional impulsivity to smoking characteristics. *J Addict Med.* 2012 Sep; 6(3): 226-232.

Young Adults at Risk for Stimulant Dependence Show Reward Dysfunction During Reinforcement-Based Decision Making

While stimulant-dependent individuals continue to make risky decisions, in spite of poor outcomes, much less is known about decision-making characteristics of occasional stimulant users (OSU) at risk for developing stimulant dependence. This study examines whether OSU exhibit inefficient learning and execution of reinforced decision-outcome contingencies. Occasional stimulant users (n = 161) and stimulant-naïve comparison subjects (CTL) (n = 48) performed a Paper Scissors Rock task during functional magnetic

resonance imaging. Selecting a particular option was associated with a predetermined probability of winning, which was altered repeatedly to examine neural and behavioral characteristics of reinforced contingencies. Occasional stimulant users displayed greater anterior insula, inferior frontal gyrus, and dorsal striatum activation than CTL during late trials when contingencies were familiar (as opposed to being learned) in the presence of comparable behavioral performance in both groups. Follow-up analyses demonstrated that during late trials: 1) OSU with high cannabis use displayed greater activation in these brain regions than CTL, whereas OSU with low cannabis use did not differ from the other two groups; and 2) OSU preferring cocaine exhibited greater anterior insula, inferior frontal gyrus, and dorsal striatum activation than CTL and also displayed higher activation in the former two regions than OSU who preferred prescription stimulants. Occasional stimulant users exhibit inefficient resource allocation during the execution of reinforced contingencies that may be a result of additive effects of cocaine and cannabis use. A critical next step is to establish whether this inefficiency predicts transition to stimulant dependence. J.L. Stewart, T.M. Flagan, A.C. May, M. Reske, A.N. Simmons, and M.P. Paulus. Young adults at risk for stimulant dependence show reward dysfunction during reinforcement-based decision making. *Biological Psychiatry*, 2012 September 26 [Epub ahead of print: DOI: 10.1016/j.biopsych.2012.08018].

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, Pearson, GD, Potenza, MN. Functional brain networks associated with cognitive control, cocaine dependence, and treatment outcome. *Psychology of Addictive Behaviors: Journal of the Society of Psychologists in Addictive Behaviors*, 2012 Jul 9 [Epub ahead of print: DOI: 10.1037/a0029092].

Measures of Attentional Bias and Relational Responding are Associated with Behavioral Treatment Outcome for Cocaine Dependence Psychosocial interventions for substance dependence have demonstrated efficacy. However, the mechanisms by which specific intervention strategies exert their effect have not been clearly identified. This study investigated the prospective relationships between two psychological processes, an attentional bias toward cocaine stimuli and beliefs about the consequences of cocaine use, and treatment outcome. Twenty-five cocaine-dependent participants enrolled in a 6-month outpatient treatment program that included voucher

incentives for abstinence. All participants were asked to complete two implicit assessment procedures, a Drug Stroop protocol and an Implicit Relational Assessment Procedure (IRAP), as well as explicit measures of cocaine craving and the consequences of cocaine use, prior to beginning treatment. Pearson's correlation coefficients tested the prospective relationships between treatment outcome and the implicit and explicit assessments. Stronger implicit beliefs about the positive effects of cocaine use prior to treatment were associated with poorer treatment outcome when an escalating voucher-incentive program was in place. Further, an attentional bias for cocaine-related stimuli was associated with better treatment outcome when an escalating voucher-incentive program was removed. No association between cocaine use beliefs and treatment outcome was found when beliefs were measured with self-report instruments. These findings highlight the potential utility of performance-based measures for delineating the psychological mechanisms associated with variation in response to treatment for drug dependence. Carpenter, K.M. Martinez, D. Vadhan, NP, Barnes-Holmes, D, Nunes, and EV. Measures of attentional bias and relational responding are associated with behavioral treatment outcome for cocaine dependence. *The American Journal of Drug and Alcohol Abuse*. 2012; 38(2): 146–154.

Negative Reinforcement Learning Is Affected in Substance Dependence: Drug and Alcohol Dependence

Negative reinforcement results in behavior to escape or avoid an aversive outcome. Withdrawal symptoms are purported to be negative reinforcers in perpetuating substance dependence, but little is known about negative reinforcement learning in this population. The purpose of this study was to examine reinforcement learning in substance dependent individuals (SDI), with an emphasis on assessing negative reinforcement learning. The authors modified the Iowa Gambling Task to separately assess positive and negative reinforcement. They hypothesized that SDI would show differences in negative reinforcement learning compared to controls and they investigated whether learning differed as a function of the relative magnitude or frequency of the reinforcer. Thirty subjects dependent on psychostimulants were compared with 28 community controls on a decision making task that manipulated outcome frequencies and magnitudes and required an action to avoid a negative outcome. SDI did not learn to avoid negative outcomes to the same degree as controls. This difference was driven by the magnitude, not the frequency, of negative feedback. In contrast, approach behaviors in response to positive reinforcement were similar in both groups. These findings are consistent with a specific deficit in negative reinforcement learning in SDI. SDI were relatively insensitive to the magnitude, not frequency, of loss. If this generalizes to drug-related stimuli, it suggests that repeated episodes of withdrawal may drive relapse more than the severity of a single episode. Thompson, LL, Claus, ED, Mikulich-Gilbertson, SK, Banich, MT Crowley, T, Krmpotich, T, Miller, D, Tanabe, J. Negative reinforcement learning is affected in substance dependence. *Drug and Alcohol Dependence*, 2012; 123(1-3): 84–90.

EPIDEMIOLOGY RESEARCH

Decline in Genetic Influence on the Co-Occurrence of Alcohol, Marijuana, and Nicotine Dependence Symptoms From Age 14 to 29

Cross-sectional studies have demonstrated high rates of comorbidity among substance use disorders. However, few studies have examined the developmental course of incident comorbidity and how it changes from adolescence to adulthood. The authors examine patterns of comorbidity among substance use disorders to gain insight into the effect of shared versus specific etiological influences on measures of substance abuse and dependence. The authors evaluated the pattern of correlations among nicotine, alcohol, and marijuana abuse and dependence symptom counts as well as their underlying genetic and environmental influences in a community-representative twin sample (N=3,762). Symptoms were assessed at ages 11, 14, 17, 20, 24, and 29 years. A single common factor was used to model the correlations among symptom counts at each age. The authors examined age-related changes in the influence of this general factor by testing for differences in the mean factor loading across time. Mean levels of abuse or dependence symptoms increased throughout adolescence, peaked around age 20, and declined from age 24 to age 29. The influence of the general factor was highest at ages 14 and 17, but decreased from age 17 to age 24. Genetic influences of the general factor declined considerably with age alongside an increase in nonshared environmental influences. The authors conclude that adolescent substance abuse or dependence is largely a function of shared etiology. As young people age, their symptoms are increasingly influenced by substance-specific etiological factors. Heritability analyses revealed that the generalized risk is primarily influenced by genetic factors in adolescence, but nonshared environmental influences increase in importance as substance dependence becomes more specialized in adulthood. Vrieze S, Hicks B, Iacono W, McGue M. Decline in genetic influence on the co-occurrence of alcohol, marijuana, and nicotine dependence symptoms from age 14 to 29. *Am J Psychiatry*. 2012; 1073-1081.

Comparison Of the Course Of Substance Use Disorders Among Individuals With and Without Generalized Anxiety Disorder In A Nationally Representative Sample

Generalized anxiety disorder (GAD) and substance use disorders (SUDs) are highly comorbid, and GAD-SUD comorbidity is associated with a host of poor psychosocial outcomes, including higher rates of hospitalization, disability, functional impairment, and inferior GAD and SUD treatment outcomes. Despite the noted severity of this group and clinical implications, current research is limited in a few distinct ways; studies have rarely utilized a longitudinal design and non-treatment seeking individuals to examine how GAD comorbidity impacts SUD outcomes over time. The current study utilized a nationally representative sample of individuals in the U.S. assessed in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC) at Wave 1 (2001-2002) and Wave 2 (2004-2005), comparing individuals who met criteria for both DSM-IV past year GAD and SUD (n = 286) and those who met criteria for past year SUD only without GAD (n = 5730) at Wave 1. Results indicated that GAD-SUD individuals were significantly more severe than the SUD only group across almost all outcomes assessed (with the exception of alcohol frequency); individuals with GAD-SUD had a more severe psychiatric history, worse health-related quality of life at both waves, greater incidence of new Axis I disorders, higher rates of treatment seeking, and greater self-reported drug use at the follow up. The current study is the first to compare individuals with SUD with and without comorbid GAD over time using a nationally representative sample. Findings further support the clinical severity of this group and suggest the need for GAD-SUD treatment options. Magidson J, Liu S, Lejuez C, Blanco C. Comparison of the course of substance use

disorders among individuals with and without generalized anxiety disorder in a nationally representative sample. *J Psychiatr Res.* 2012; 46 (5): 659-666.

Common Psychiatric Disorders and Caffeine Use, Tolerance, and Withdrawal: An Examination Of Shared Genetic and Environmental Effects

Previous studies examined caffeine use and caffeine dependence and risk for the symptoms, or diagnosis, of psychiatric disorders. The current study aimed to determine if generalized anxiety disorder (GAD), panic disorder, phobias, major depressive disorder (MDD), anorexia nervosa (AN), or bulimia nervosa (BN) shared common genetic or environmental factors with caffeine use, caffeine tolerance, or caffeine withdrawal. Using 2,270 women from the Virginia Adult Twin Study of Psychiatric and Substance Use Disorders, bivariate Cholesky decomposition models were used to determine if any of the psychiatric disorders shared genetic or environmental factors with caffeine use phenotypes. GAD, phobias, and MDD shared genetic factors with caffeine use, with genetic correlations estimated to be 0.48, 0.25, and 0.38, respectively. Removal of the shared genetic and environmental parameter for phobias and caffeine use resulted in a significantly worse fitting model. MDD shared unique environmental factors (environmental correlation=0.23) with caffeine tolerance; the genetic correlation between AN and caffeine tolerance and BN and caffeine tolerance were 0.64 and 0.49, respectively. Removal of the genetic and environmental correlation parameters resulted in significantly worse fitting models for GAD, phobias, MDD, AN, and BN, which suggested that there was significant shared liability between each of these phenotypes and caffeine tolerance. GAD had modest genetic correlations with caffeine tolerance, 0.24, and caffeine withdrawal, 0.35. There was suggestive evidence of shared genetic and environmental liability between psychiatric disorders and caffeine phenotypes. This might inform us about the etiology of the comorbidity between these phenotypes. Bergin J, Kendler K. Common psychiatric disorders and caffeine use, tolerance, and withdrawal: an examination of shared genetic and environmental effects. *Twin Res Hum Genet.* 2012; 15 (4): 473-482.

Risk Profiles Among Adolescent Nonmedical Opioid Users In the United States

Although prior research has provided data on nonmedical use of opioids in adolescents, studies examining the heterogeneity of risk are limited. The present study extends prior research by deepening the understanding of adolescent nonmedical opioid use by specifying empirically meaningful profiles of risk. Using data on adolescent non-medical opioid users (N=1783) from the 2008 US National Survey on Drug Use and Health (NSDUH), latent class analysis and multinomial logistic regression were employed to identify latent classes and determine the effects of covariates on class membership. Four latent classes provided the best fit to the data. Classes consisted of a low risk class (33.7%), a high delinquency/low substance use class (17.8%), a high substance use/low delinquency class (34.2%), and finally a high risk class (14.3%) characterized by high levels of both substance use and delinquent behavior. Study findings advance the understanding of adolescent nonmedical opioid use by specifying distinct latent classes. Results suggest that intervention efforts can fruitfully target a number of risk domains especially programs that enhance effective parenting and supervision. Vaughn M, Fu Q, Perron B, Wu L. Risk profiles among adolescent nonmedical opioid users in the United States. *Addict Behav.* 2012; 37 (8): 974-977.

Associations Of Alcohol, Nicotine, Cannabis, and Drug Use/Dependence With Educational Attainment: Evidence From Cotwin-Control Analyses

Although substance use is associated with reduced educational attainment, this association may be owing to common risk factors such as socioeconomic disadvantage. The authors tested whether alcohol, nicotine, and illicit drug use and

dependence were associated with lifetime educational attainment after controlling for familial background characteristics. Data were from a 1987 questionnaire and a 1992 telephone diagnostic interview of 6,242 male twins (n = 3,121 pairs; mean age = 41.9 years in 1992) who served in the U.S. military during the Vietnam era and therefore, were eligible for educational benefits after military service. Reduced educational attainment (<16 years) was examined in twin pairs discordant for substance use history. Substance use and dependence risk factors assessed were early alcohol and cannabis use, daily nicotine use, lifetime cannabis use, and alcohol, nicotine, cannabis, and any illicit drug dependence. Three significant differences were observed between at-risk twins and their cotwins: Compared to their low-risk cotwins, likelihood of completing <16 years of education was significantly increased for the following: (i) twins who used alcohol before age 18 (adjusted OR = 1.44; 95% CI: 1.02 to 2.05), (ii) twins with a lifetime alcohol dependence diagnosis (adjusted OR = 1.76; 95% CI: 1.27 to 2.44), and (iii) twins who had used nicotine daily for 30 or more days (adjusted OR = 2.54, 95% CI: 1.55 to 4.17). However, no differences in education were observed among twin pairs discordant for cannabis initiation, early cannabis use, or cannabis, nicotine, or any illicit drug dependence. Even in a veteran population with access to military educational benefits, early alcohol use, alcohol dependence, and daily nicotine use remained significantly associated with years of education after controlling for shared familial contributions to educational attainment. The association between other substances and educational attainment was explained by familial factors common to these substance use phenotypes and adult educational attainment. Grant J, Scherrer J, Lynskey M, Agrawal A, Duncan A, Haber J, Heath A, Bucholz K. Associations of alcohol, nicotine, cannabis, and drug use/dependence with educational attainment: evidence from cotwin-control analyses. *Alcohol Clin Exp Res.* 2012; 36 (8): 1412-1420.

Are the Symptoms Of Cannabis Use Disorder Best Accounted For By Dimensional, Categorical, Or Factor Mixture Models? A Comparison Of Male and Female Young Adults

Despite the consensus that criteria for cannabis abuse and dependence and symptoms of withdrawal are best explained by a single latent liability, it remains unknown whether alternative models provide a better explanation of these criteria. A series of latent factor, latent class, and hybrid factor mixture models were fitted to data from 872 recent cannabis users from the Minnesota Twin Family Study who completed Diagnostic and Statistical Manual of Mental Disorders (3rd ed., revised, and 4th ed.) diagnostic criteria for cannabis abuse, dependence, and symptoms of withdrawal. Despite theoretical appeal, results did not support latent class or factor mixture modeling. Instead, symptoms of abuse, dependence, and withdrawal were better summarized by a single latent factor Cannabis Use Disorder (CUD) for male and female young adults. An almost 2-fold sex difference in item endorsement was best explained by a single mean difference on the CUD factor, indicating that young men have a greater latent liability toward expressing CUD. Gillespie N, Neale M, Legrand L, Iacono W, McGue M. Are the symptoms of cannabis use disorder best accounted for by dimensional, categorical, or factor mixture models? A comparison of male and female young adults. *Psychol Addict Behav.* 2012; 26 (1): 68-77.

Impulsivity In the General Population: A National Study The construct of impulsivity is an important determinant of personality differences, psychiatric disorders, and associated risk-taking behaviors. Most existing knowledge about impulsivity comes from clinical samples. To date, no study has estimated the prevalence of impulsivity and examined its correlates in the general population. The authors analyzed data from a large national sample of the United States population. Face-to-face surveys of 34,653 adults aged 18 years and older residing in households were conducted during the 2004-2005 period. Diagnoses of mood, anxiety, and drug disorders as well as

personality disorders were based on the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DSM-IV Version. Impulsivity was common (17% of the sample), particularly among males and younger individuals, and associated with a broad range of axis I and II disorders, particularly drug dependence, cluster B, dependent and schizotypal personality disorders, bipolar disorder and ADHD. It was associated with behavioral disinhibition, attention deficits, and lack of planning. Individuals with impulsivity were more likely to engage in behaviors that could be dangerous to themselves or others, including driving recklessly, starting fights, shoplifting, perpetrating domestic violence and trying to hurt or kill themselves. They were exposed to higher risk of lifetime trauma and to substantial physical and psychosocial impairment. Given the association of impulsivity with psychiatric disorders and multiple adverse events, there is a need to target impulsivity in prevention and treatment efforts. Chamorro J, Bernardi S, Potenza M, Grant J, Marsh R, Wang S, Blanco C. Impulsivity in the general population: A national study. *J Psychiatr Res.* 2012; 46 (8): 994-1001.

Patterns of Prescription Drug Misuse among Young Injection Drug Users Misuse of prescription drugs and injection drug use has increased among young adults in the USA. Despite these upward trends, few studies have examined prescription drug misuse among young injection drug users (IDUs). A qualitative study was undertaken to describe current patterns of prescription drug misuse among young IDUs. Young IDUs aged 16-25 years who had misused a prescription drug, e.g., opioids, tranquilizers, or stimulants, at least three times in the past 3 months were recruited in 2008 and 2009 in Los Angeles (n = 25) and New York (n = 25). Informed by an ethno-epidemiological approach, descriptive data from a semi-structured interview guide were analyzed both quantitatively and qualitatively. Most IDUs sampled were both homeless and transient. Heroin, prescription opioids, and prescription tranquilizers were frequently misused in the past 30 days. Qualitative results indicated that young IDUs used prescription opioids and tranquilizers: as substitutes for heroin when it was unavailable; to boost a heroin high; to self-medicate for health conditions, including untreated pain and heroin withdrawal; to curb heroin use; and to reduce risks associated with injecting heroin. Polydrug use involving heroin and prescription drugs resulted in an overdose in multiple cases. Findings point to contrasting availability of heroin in North American cities while indicating broad availability of prescription opioids among street-based drug users. The results highlight a variety of unmet service needs among this sample of young IDUs, such as overdose prevention, drug treatment programs, primary care clinics, and mental health services. Lankenau S, Teti M, Silva K, Bloom J, Harocopos A, Treese M. Patterns of prescription drug misuse among young injection drug users. *J Urban Health.* 2012.

Investigating the Association Between Childhood Sexual Abuse and Alcohol Use Disorders In Women: Does It Matter How We Ask About Sexual Abuse? The purpose of this study was to determine whether the type of questions used to assess childhood sexual abuse (CSA) introduces systematic bias into estimations of the magnitude of the association between CSA and alcohol use disorders (AUDs). The Semi-Structured Assessment for the Genetics of Alcoholism was administered by telephone to 3,787 female twins ages 18-29 years (14.6% African American, 85.4% White). Interviews included questions regarding sexual abuse experiences described in behavioral terms and a standard trauma checklist (in a separate section) with the items "rape" and "sexual molestation," with definitions provided in respondent booklets. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, diagnoses of alcohol abuse and dependence, parental history of alcohol-related problems, and psychiatric conditions associated with AUDs were also assessed. The majority of women who endorsed one question type also endorsed the other type. Rates of

psychiatric risk factors for AUDs did not vary by pattern of CSA question endorsement. Separate Cox proportional hazards regression analyses using CSA variables derived from behavioral questions (hazard ratio [HR] = 1.67, 95% CI [1.27, 2.19]) and checklist items (HR = 1.41, 95% CI [1.08, 1.84]) each revealed elevated risk for AUDs associated with CSA, and HRs did not differ significantly across models. However, a Cox proportional hazards regression analysis predicting AUD from the pattern of CSA question endorsements revealed a significantly higher risk for AUDs among women who endorsed only behavioral questions (HR = 3.26, 95% CI [1.72, 6.21]) than for all other groups. Findings underscore the importance of querying CSA in studies of alcohol-related problems and highlight some of the limitations of assessment methods that can be integrated into studies covering a wide range of psychosocial domains. Sartor C, McCutcheon V, Nelson E, Duncan A, Bucholz K, Heath A. Investigating the association between childhood sexual abuse and alcohol use disorders in women: does it matter how we ask about sexual abuse? *J Stud Alcohol Drugs*. 2012; 73 (5): 740-748.

Testing Whether and When Parent Alcoholism Uniquely Affects Various Forms Of

Adolescent Substance Use The current study examined the distal, proximal, and time-varying effects of parents' alcohol-related consequences on adolescents' substance use. Previous studies show that having a parent with a lifetime diagnosis of alcoholism is a clear risk factor for adolescents' own substance use. Less clear is whether the timing of a parent's alcohol-related consequences differentially predicts the adolescent's own substance involvement. Using a multilevel modeling approach, the authors tested whether adolescents showed elevated rates of alcohol, heavy alcohol, marijuana and other illegal drug use (a) at the same time that parents showed alcohol-related consequences (time-varying effects), (b) if parents showed greater alcohol-related consequences during the child's adolescence (proximal effects), and (c) if parents had a lifetime diagnosis of alcoholism that predated the child's adolescence (distal effects). The authors tested these effects in a high-risk sample of 451 adolescents assessed over three waves beginning at ages 11-15 from 1988 to 1991 (53% male, 71% non-Hispanic Caucasian, 54% children of alcoholic parents and 46% matched controls). Strong and consistent distal effects of parent alcoholism on adolescent's substance use were found, though no additional risk was associated with proximal effects. Limited time-varying effects were also found. The importance of differentiating the timing effects of parent alcoholism in identifying underlying mechanisms of risk for adolescent substance use is discussed. Hussong A, Huang W, Serrano D, Curran P, Chassin L. Testing whether and when parent alcoholism uniquely affects various forms of adolescent substance use. *J Abnorm Child Psychol*. 2012; 40 (8): 1265-1276.

Adolescent Criminal Justice Involvement and Adulthood Sexually Transmitted Infection in a Nationally Representative US Sample

Criminal justice involvement (CJI) disrupts social and sexual networks, and sexually transmitted infections (STIs) thrive on network disruption. Adolescent CJI may be a particularly important determinant of STI because experiences during adolescence influence risk trajectories into adulthood. The authors used Wave III (2001-2002: young adulthood) of the National Longitudinal Study of Adolescent Health (N = 14,322) to estimate associations between history of adolescent (younger than 18 years) CJI and adult STI risk. Respondents who reported a history of repeat arrest in adolescence, adolescent conviction, and arrest both as an adolescent and an adult (persistent arrest) had between two to seven times the odds of STI (biologically confirmed infection with chlamydia, gonorrhea, or trichomoniasis) in adulthood and between two to three times the odds of multiple partnerships and inconsistent condom use in the past year in adulthood. In analyses adjusting for sociodemographic and behavioral factors, history

of having six or more adolescent arrests was associated with more than five times the odds of STI (adjusted odds ratio (AOR) 5.44, 95 % confidence interval (CI) 1.74-17.1). Both adolescent conviction and persistent CJI appeared to remain independent correlates of STI (conviction: AOR 1.90, 95 % CI 1.02-3.55; persistent CJI: AOR 1.60, 95 % CI 0.99-2.57). Adolescents who have repeat arrests, juvenile convictions, and persist as offenders into adulthood constitute priority populations for STI treatment and prevention. The disruptive effect of adolescent CJI may contribute to a trajectory associated with STI in adulthood. Khan M, Rosen D, Epperson M, Goldweber A, Hemberg J, Richardson J, Dyer T. Adolescent criminal justice involvement and adulthood sexually transmitted infection in a nationally representative US sample. *J Urban Health*. 2012; 89(3).

Do Substance Use Norms and Perceived Drug Availability Mediate Sexual Orientation Differences in Patterns of Substance Use? Results from the California Quality of Life Survey II

Illicit drug and heavy alcohol use is more common among sexual minorities compared with heterosexuals. This difference has sometimes been attributed to more tolerant substance use norms within the gay community, although evidence is sparse. The current study investigated the role of perceived drug availability and tolerant injunctive norms in mediating the linkage between minority sexual orientation status and higher rates of prior-year substance use. The authors used data from the second California Quality of Life Survey (Cal-QOL II), a followback telephone survey in 2008-2009 of individuals first interviewed in the population-based 2007 California Health Interview Survey. The sample comprised 2,671 individuals, oversampled for minority sexual orientation. Respondents were administered a structured interview assessing past-year alcohol and illicit drug use, perceptions of perceived illicit drug availability, and injunctive norms concerning illicit drug and heavier alcohol use. The authors used structural equation modeling methods to test a mediational model linking sexual orientation and substance use behaviors via perceptions of drug availability and social norms pertaining to substance use. Compared with heterosexual individuals, sexual minorities reported higher levels of substance use, perceived drug availability, and tolerant social norms. A successfully fitting model suggests that much of the association between minority sexual orientation and substance use is mediated by these sexual orientation-related differences in drug availability perceptions and tolerant norms for substance use. Social environmental context, including subcultural norms and perceived drug availability, is an important factor influencing substance use among sexual minorities and should be addressed in community interventions. Cochran S, Grella C, Mays V. Do substance use norms and perceived drug availability mediate sexual orientation differences in patterns of substance use? Results from the California Quality of Life Survey II. *J Stud Alcohol Drugs*. 2012; 73 (4): 675-685.

Trauma and Posttraumatic Stress Symptoms Predict Alcohol and Other Drug Consequence Trajectories in the First Year of College

College matriculation begins a period of transition into adulthood, one that is marked by new freedoms and responsibilities. This transition also is marked by an escalation in heavy drinking and other drug use as well as a variety of use-related negative consequences. Trauma and symptoms of posttraumatic stress disorder (PTSD) may affect alcohol and drug problems and, thus, may be a point of intervention. Yet, no studies have examined trauma, PTSD, and alcohol and drug problem associations during this developmental period. The present study provides such an examination. Matriculating college students (N = 997) completed surveys in September (Time 1) and at 5 subsequent time points (Time 2-Time 6) over their 1st year of college. With latent growth analysis, trajectories of alcohol- and drug-related consequences were modeled to examine how trauma (No Criterion A Trauma, Criterion A Only, No PTSD Symptoms) and PTSD

(partial or full) symptom status predicted these trajectories. Results showed substantial risk for alcohol- and other drug-related negative consequences that is conferred by the presence of PTSD at matriculation. Those with both partial and full PTSD started the year with more alcohol and drug consequences. These individuals showed a steeper decrease in consequences in the 1st semester, which leveled off as the year progressed. Both alcohol and drug consequences remained higher for those in the PTSD group throughout the academic year. Hyperarousal symptoms showed unique effects on substance consequence trajectories. Risk patterns were consistent for both partial and full PTSD symptom presentations. Trajectories did not vary by gender. The authors concluded that interventions that offer support and resources to students entering college with PTSD may help to ameliorate problem substance use and may ultimately facilitate a stronger transition into college and beyond. Read J, Colder C, Merrill J, Ouimette P, White J, Swartout A. Trauma and posttraumatic stress symptoms predict alcohol and other drug consequence trajectories in the first year of college. *J Consult Clin Psychol.* 2012; 80 (3): 426-439.

Role of Common Mental and Physical Disorders in Partial Disability around the World

Mental and physical disorders are associated with total disability, but their effects on days with partial disability (i.e. the ability to perform some, but not full-role, functioning in daily life) are not well understood. The aims of this study were to estimate individual (i.e. the consequences for an individual with a disorder) and societal effects (i.e. the avoidable partial disability in the society due to disorders) of mental and physical disorders on days with partial disability around the world. Respondents from 26 nationally representative samples (n = 61 259, age 18+) were interviewed regarding mental and physical disorders, and day-to-day functioning. The Composite International Diagnostic Interview, version 3.0 (CIDI 3.0) was used to assess mental disorders; partial disability (expressed in full day equivalents) was assessed with the World Health Organization Disability Assessment Schedule in the CIDI 3.0. Respondents with disorders reported about 1.58 additional disability days per month compared with respondents without disorders. At the individual level, mental disorders (especially post-traumatic stress disorder, depression and bipolar disorder) yielded a higher number of days with disability than physical disorders. At the societal level, the population attributable risk proportion due to physical and mental disorders was 49% and 15% respectively. Mental and physical disorders have a considerable impact on partial disability, at both the individual and at the societal level. Physical disorders yielded higher effects on partial disability than mental disorders. Bruffaerts R, Vilagut G, Demyttenaere K, Alonso J, Alhamzawi A, Andrade L, Benjet C, Bromet E, Bunting B, de Girolamo G, Florescu S, Gureje O, Haro J, He Y, Hinkov H, Hu C, Karam E, Lepine J, Levinson D, Matschinger H, Nakane Y, Ormel J, Posada-Villa J, Scott K, Varghese M, Williams D, Xavier M, Kessler R. Role of common mental and physical disorders in partial disability around the world. *Br J Psychiatry.* 2012; 200(6): 454-461.

Barriers To HIV Treatment Among People Who Use Injection Drugs: Implications For 'Treatment As Prevention'

Recent research has confirmed the efficacy of employing highly active antiretroviral therapy (HAART) to prevent the transmission of HIV. However, barriers to the use of HAART among people who use injection drugs (PWIDs) remain an international concern. The authors review recent findings regarding factors determining effective HIV treatment among PWIDs and describe their possible impact on efforts to curb HIV incidence using HAART. Internationally, HIV-seropositive PWIDs continue to experience suboptimal HIV treatment outcomes compared with other risk groups. Recent findings have better elucidated the role of ongoing illicit drug use in limiting access and adherence to HAART. However, recent research has also increasingly demonstrated the important role that social, environmental and structural factors,

resulting from the criminalization of PWIDs, have in placing barriers to optimal HAART use among this population. Treatment as prevention strategies for PWIDs will only be maximally effective if structural barriers to effective addiction and HIV treatment, which stem from the ongoing criminalization of this population, are addressed. Milloy M, Montaner J, Wood E. Barriers to HIV treatment among people who use injection drugs: implications for 'treatment as prevention'. *Curr Opin HIV AIDS*. 2012; 7(4): 332-338.

Uncommon Pathways Of Immune Escape Attenuate HIV-1 Integrase Replication Capacity

An attenuation of the HIV-1 replication capacity (RC) has been observed for immune-mediated escape mutations in Gag restricted by protective HLA alleles. However, the extent to which escape mutations affect other viral proteins during natural infection is not well understood. The authors generated recombinant viruses encoding plasma HIV-1 RNA integrase sequences from antiretroviral-naïve individuals with early (n = 88) and chronic (n = 304) infections and measured the in vitro RC of each. In contrast to data from previous studies of Gag, they authors observed little evidence that host HLA allele expression was associated with integrase RC. A modest negative correlation was observed between the number of HLA-B-associated integrase polymorphisms and RC in chronic infection (R = -0.2; P = 0.003); however, this effect was not driven by mutations restricted by protective HLA alleles. Notably, the integrase variants S119R, G163E, and I220L, which represent uncommon polymorphisms associated with HLA-C*05, -A*33, and -B*52, respectively, correlated with lower RC (all q < 0.2). The authors identified a novel C*05-restricted epitope (HTDNGSNF(114-121)) that likely contributes to the selection of the S119R variant, the polymorphism most significantly associated with lower RC in patient sequences. An NL4-3 mutant encoding the S119R polymorphism displayed a ~35%-reduced function that was rescued by a single compensatory mutation of A91E. Together, these data indicate that substantial HLA-driven attenuation of integrase is not a general phenomenon during HIV-1 adaptation to host immunity. However, uncommon polymorphisms selected by HLA alleles that are not conventionally regarded to be protective may be associated with impaired protein function. Vulnerable epitopes in integrase might therefore be considered for future vaccine strategies. Brockman M, Chopera D, Olvera A, Brumme C, Sela J, Markle T, Martin E, Carlson J, Le A, McGovern R, Cheung P, Kelleher A, Jessen H, Markowitz M, Rosenberg E, Frahm N, Sanchez J, Mallal S, John M, Harrigan P, Heckerman D, Brander C, Walker B, Brumme Z. Uncommon pathways of immune escape attenuate HIV-1 integrase replication capacity. *J Virol*. 2012; 86(12): 6913-6923.

Development Of The Perceived Risk Of HIV Scale Past studies have used various methods to assess perceived risk of HIV infection; however, few have included multiple items covering different dimensions of risk perception or have examined the characteristics of individual items. This study describes the use of Item Response Theory (IRT) to develop a short measure of perceived risk of HIV infection scale (PRHS). An item pool was administered by trained interviewers to 771 participants. Participants also completed the risk behavior assessment (RBA) which includes items measuring risky sexual behaviors, and 652 participants completed HIV testing. The final measure consisted of 8 items, including items assessing likelihood estimates, intuitive judgments and salience of risk. Higher scores on the PRHS were positively associated with a greater number of sex partners, episodes of unprotected sex and having sex while high. Participants who tested positive for HIV reported higher perceived risk. The PRHS demonstrated good reliability and concurrent criterion-related validity. Compared to single item measures of risk perception, the PRHS is more robust by examining multiple dimensions of perceived risk. Possible

uses of the measure and directions for future research are discussed. Napper L, Fisher D, Reynolds G. Development of the perceived risk of HIV scale. *AIDS Behav.* 2012; 16(4): 1075-1083.

Disparities In Receipt Of Antiretroviral Therapy Among HIV-Infected Adults (2002-2008)

Prior research has documented sociodemographic disparities in the use of antiretroviral therapy (ART). Recent therapeutic developments and changing epidemiological profiles may have altered such disparities. The authors examine the extent to which sociodemographic differences in prescribed ART have changed between 2002 and 2008. They analyzed data abstracted from medical records at 13 US sites participating in the Human Immunodeficiency Virus Research Network. Prescription of ART was assessed for each year in care for each patient. A total of 14,092 patients were followed up for 39,251 person-years. They examined ART use as a function of sex, race/ethnicity, human immunodeficiency virus risk group, age, and CD4 history (no test <500 cells/mm, one or more tests between 500 and 350 cells/mm, 1 test ≥350 cells/mm, and 2 or more tests ≥350 cells/mm). Using multiple logistic regression, they ascertained interactions between each of these variables and calendar year. The overall percentage prescribed ART increased from 60% to 80% between 2002 and 2008. Among those with 2 or more CD4 tests ≥350 cells/mm, the percentage increased from 82% to 92%. ART rates were higher for those with lower CD4 counts but increased over time for all CD4 groups and for all demographic groups. Nevertheless, sex and racial/ethnic disparities persisted. Significant interactions were obtained for CD4 history by year, age by year, and age by CD4 history. Although prescription of ART became more widespread from 2002 to 2008, patients who were female, black, or younger still had lower ART rates than male, white, or older patients. Fleishman J, Yehia B, Moore R, Gebo K, Agwu A, Agwu A. Disparities in receipt of antiretroviral therapy among HIV-infected adults (2002-2008). *Med Care.* 2012; 50(5): 419-427.

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, Hernán 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. The authors 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 1,525 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 C, Cole S, Mehta S, Kirk G. 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.

Substance Use and Sexual Behavior Among Recent Hispanic Immigrant Adolescents: Effects Of Parent-Adolescent Differential Acculturation and Communication

The objectives of this study were to ascertain the effects of parent-adolescent acculturation gaps, perceived discrimination, and perceived negative context of reception on adolescent cigarette smoking, alcohol use, sexual activity, and sexual risk taking. The authors used an expanded, multidimensional model of acculturation. A sample of 302 recently immigrated parent-adolescent dyads (152 from Miami and 150 from Los Angeles) completed measures of acculturation (Hispanic and American practices and identifications, and individualist and collectivist values) and parent-adolescent communication. Adolescents completed measures of recent cigarette smoking, alcohol use, sexual behavior, and sexual risk taking. Parent-adolescent gaps in American practices and ethnic identity, and perceptions of a negative context of reception, predicted compromised parent-adolescent communication. In Miami only, adolescent-reported communication negatively predicted odds of cigarette smoking, occasions of drunkenness, and number of sexual partners. Also in Miami only, parent-reported communication positively predicted these outcomes, as well as occasions of adolescent binge drinking, drunkenness, number of sexual partners, and odds of unprotected sex. The only significant findings in Los Angeles were protective effects of parent-reported communication on frequency of alcohol use and of binge drinking. Mediational effects emerged only in the Miami sample. Effects of parent-adolescent acculturation gaps vary across Hispanic groups and receiving contexts. The especially strong parental control in many Mexican families may account for these differences. However, other important differences between Hispanic subgroups and communities of reception could also account for these differences. Prevention efforts might encourage Hispanic youth both to retain their culture of origin and to acquire American culture. Schwartz S, Unger J, Des Rosiers S, Huang S, Baezconde-Garbanati L, Lorenzo-Blanco E, Villamar J, Soto D, Pattarroyo M, Szapocznik J. Substance use and sexual behavior among recent Hispanic immigrant adolescents: effects of parent-adolescent differential acculturation and communication. *Drug Alcohol Depend.* 2012; 125 Suppl 1: S26-S34.

Elevated Risk Of Posttraumatic Stress In Sexual Minority Youths: Mediation By Childhood Abuse and Gender Nonconformity

The authors examined whether lifetime risk of posttraumatic stress disorder (PTSD) was elevated in sexual minority versus heterosexual youths, whether childhood abuse accounted for disparities in PTSD, and whether childhood gender nonconformity explained sexual-orientation disparities in abuse and subsequent PTSD. They used data from a population-based study (n=9369, mean age=22.7 years) to estimate risk ratios for PTSD. They calculated the percentage of PTSD disparities by sexual orientation accounted for by childhood abuse and gender nonconformity, and the percentage of abuse disparities by sexual orientation accounted for by gender nonconformity. Sexual minorities had between 1.6 and 3.9 times greater risk of probable PTSD than heterosexuals. Child abuse victimization disparities accounted for one third to one half of PTSD disparities by sexual orientation. Higher prevalence of gender nonconformity before age 11 years partly accounted for higher prevalence of abuse exposure before age 11 years and PTSD by early adulthood in sexual minorities (range=5.2%-33.2%). Clinicians, teachers, and others who work with youths should consider abuse prevention and treatment measures for gender-nonconforming children and sexual minority youths. Roberts A, Rosario M, Corliss H, Koenen K, Austin S. Elevated risk of posttraumatic stress in sexual minority youths: mediation by childhood abuse and gender nonconformity. *Am J Public Health.* 2012; 102(8): 1587-1593.

The Effects Of Child Maltreatment On Early Signs Of Antisocial Behavior: Genetic Moderation By Tryptophan Hydroxylase, Serotonin Transporter, and Monoamine Oxidase A Genes

Gene-environment interaction effects in predicting antisocial behavior in late childhood were investigated among maltreated and nonmaltreated low-income children (N = 627, M age = 11.27). Variants in three genes were examined: tryptophan hydroxylase 1 (TPH1), serotonin transporter linked polymorphic region (5-HTTLPR), and monoamine oxidase A (MAOA) upstream variable number tandem repeat. In addition to child maltreatment status, the authors considered the impact of maltreatment subtypes, developmental timing of maltreatment, and chronicity. Indicators of antisocial behavior were obtained from self-, peer, and adult counselor reports. In a series of analyses of covariance, child maltreatment and its parameters demonstrated strong main effects on early antisocial behavior as assessed by all report forms. Genetic effects operated primarily in the context of gene-environment interactions, moderating the impact of child maltreatment on outcomes. Across the three genes, among nonmaltreated children no differences in antisocial behavior were found based on genetic variation. In contrast, among maltreated children specific polymorphisms of TPH1, 5-HTTLPR, and MAOA were each related to heightened self-report of antisocial behavior; the interaction of 5-HTTLPR and developmental timing of maltreatment also indicated more severe antisocial outcomes for children with early onset and recurrent maltreatment based on genotype. TPH1 and 5-HTTLPR interacted with maltreatment subtype to predict peer reports of antisocial behavior; genetic variation contributed to larger differences in antisocial behavior among abused children. The TPH1 and 5-HTTLPR polymorphisms also moderated the effects of maltreatment subtype on adult reports of antisocial behavior; again, the genetic effects were strongest for children who were abused. In addition, TPH1 moderated the effect of developmental timing of maltreatment and chronicity on adult reports of antisocial behavior. The findings elucidate how genetic variation contributes to identifying which maltreated children are most vulnerable to antisocial development. Cicchetti D, Rogosch F, Thibodeau E. The effects of child maltreatment on early signs of antisocial behavior: genetic moderation by tryptophan hydroxylase, serotonin transporter, and monoamine oxidase A genes. *Dev Psychopathol.* 2012; 24(3): 907-928.

Associations Between Selected State Laws and Teenagers' Drinking and Driving Behaviors

The authors examined the associations between selected state-level graduated driving licensing (GDL) laws and use-and-lose laws (laws that allow for the suspension of a driver's license for underage alcohol violations including purchase, possession, or consumption) with individual-level alcohol-related traffic risk behaviors among high school youth. Logistic regression models with fixed effects for state were used to examine the associations between the selected state-level laws and drinking and driving behaviors youth aged 16 to 17 years (obtained from the Youth Risk Behavior Surveillance System (YRBSS); responses dichotomized as "0 times" or "1 or more times") over an extended period of time (1999 to 2009). A total of 11.7% of students reported having driven after drinking any alcohol and 28.2% reported riding in a car with a driver who had been drinking on 1 or more occasions in the past 30 days. Restrictive GDL laws and use-and-lose laws were associated with decreased driving after drinking any alcohol and riding in a car with a driver who had been drinking alcohol. Restrictive GDL and use-and-lose laws may help to bolster societal expectations and values about the hazards of drinking and driving behaviors and are therefore partly responsible for the decline in these alcohol-related traffic risk behaviors. Cavazos-Rehg P, Krauss M, Spitznagel E, Chaloupka F, Schootman M, Gruzza R, Bierut L. Associations between selected state laws and teenagers' drinking and driving behaviors. *Alcohol Clin Exp Res.* 2012; 36(9): 1647-1652.

Brief Report: Pregnant By Age 15 Years and Substance Use Initiation Among US Adolescent Girls

The authors examined substance use onset and associations with pregnancy by age 15 years. Participants were girls ages 15 years or younger (weighted n = 8319) from the 1999-2003 Youth Risk Behavior Surveillance System (YRBS). Multivariable logistic regression examined pregnancy as a function of substance use onset (i.e., age 10 years or younger, 11-12, 13-14, and age 15 years) for alcohol, cigarettes and marijuana, controlling for race/ethnicity and metropolitan location. Of girls pregnant by age 15 years (3% of the sample, weighted n = 243), 16% had smoked marijuana by age 10 years and over 20% had smoked cigarettes and initiated alcohol use by age 10 years. In the multivariable analysis, marijuana use by age 14 years and/or cigarette smoking by age 12 years clearly distinguished girls who became pregnant by age 15 years and is perhaps due to a common underlying risk factor. Cavazos-Rehg P, Krauss M, Spitznagel E, Schootman M, Cottler L, Bierut L. Brief report: Pregnant by age 15 years and substance use initiation among US adolescent girls. *J Adolesc.* 2012; 35(5): 1393-1397.

Innovative Recruitment Using Online Networks: Lessons Learned From An Online Study Of Alcohol and Other Drug Use Utilizing A Web-Based, Respondent-Driven Sampling (WebRDS) Strategy

The authors used a web version of Respondent-Driven Sampling (webRDS) to recruit a sample of young adults (ages 18-24) and examined whether this strategy would result in alcohol and other drug (AOD) prevalence estimates comparable to national estimates (National Survey on Drug Use and Health [NSDUH]). They recruited 22 initial participants (seeds) via Facebook to complete a web survey examining AOD risk correlates. Sequential, incentivized recruitment continued until their desired sample size was achieved. After correcting for webRDS clustering effects, they contrasted our AOD prevalence estimates (past 30 days) to NSDUH estimates by comparing the 95% confidence intervals of prevalence estimates. The authors found comparable AOD prevalence estimates between their sample and NSDUH for the past 30 days for alcohol, marijuana, cocaine, Ecstasy (3,4-methylenedioxymethamphetamine, or MDMA), and hallucinogens. Cigarette use was lower than NSDUH estimates. WebRDS may be a suitable strategy to recruit young adults online. The authors discuss the unique strengths and challenges that may be encountered by public health researchers using webRDS methods. Bauermeister J, Zimmerman M, Johns M, Glowacki P, Stoddard S, Volz E. Innovative recruitment using online networks: lessons learned from an online study of alcohol and other drug use utilizing a web-based, Respondent-Driven Sampling (webRDS) strategy. *J Stud Alcohol Drugs.* 2012; 73(5): 834-838.

Alcohol Consumption and CD4 T-Cell Count Response Among Persons Initiating Antiretroviral Therapy

The authors evaluated the longitudinal association of alcohol use with immunological response to combination antiretroviral therapy (ART) among HIV infected individuals. This was a prospective cohort study of individuals initiating ART. Participants underwent an Audio Computer-Assisted Self Interview querying drug and alcohol use within 6 months of treatment. Immunological response to ART was defined by CD4 T-cell count (CD4). Primary independent variables were self-reported number of drinks consumed per drinking day (quantity) and days of alcohol consumption in a typical week (frequency). The authors used linear mixed effects models to quantify the association between CD4 T-cell count and alcohol quantity and frequency and Cox proportional hazards models to estimate the relative hazard of an increase 100, 150 and 200 CD4 cells/mm per additional drink per drinking day. Analyses were stratified by gender. Viral suppression was examined as a time-varying covariate. Between 2000-2008, 1,107 individuals were eligible for inclusion in this study. There was no statistically significant difference in CD4 T-cell count by average drinks per drinking day at any frequency of alcohol use irrespective

of gender or viral suppression. Similarly, the authors found no difference in the hazard ratio for drinks per drinking day within the categories of drinking frequency for time to CD4 T-cell count increase of 100, 150 and 200 cells/mm, respectively. The authors conclude that among individuals initiating antiretroviral therapy (ART) the benefits of therapy and viral suppression on the immune system outweigh detrimental effects of alcohol, reinforcing the importance of initiating ART and ensuring adequate adherence to therapy. Kowalski S, Colantuoni E, Lau B, Keruly J, McCaul M, Hutton H, Moore R, Chander G. Alcohol Consumption and CD4 T-cell count response among persons initiating antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2012; 61(4): 455-461.

U.S. Trends In Antiretroviral Therapy Use, HIV RNA Plasma Viral Loads, and CD4 T-Lymphocyte Cell Counts Among HIV-Infected Persons, 2000 to 2008

The U.S. National HIV/AIDS Strategy targets for 2015 include "increasing access to care and improving health outcomes for persons living with HIV in the United States" (PLWH-US). The objective of this study is to demonstrate the utility of the NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design) for monitoring trends in the HIV epidemic in the United States and to present trends in HIV treatment and related health outcomes. Trends from annual cross-sectional analyses comparing patients from pooled, multicenter, prospective, clinical HIV cohort studies with PLWH-US, as reported to national surveillance systems in 40 states were examined. The study setting comprised U.S. HIV outpatient clinics. Patients were HIV-infected adults with 1 or more HIV RNA plasma viral load (HIV VL) or CD4 T-lymphocyte (CD4) cell count measured in any calendar year from 1 January 2000 to 31 December 2008. Measurements taken were annual rates of antiretroviral therapy use, HIV VL, and CD4 cell count at death. 45,529 HIV-infected persons received care in an NA-ACCORD-participating U.S. clinical cohort from 2000 to 2008. In 2008, the 26 030 NA-ACCORD participants in care and the 655 966 PLWH-US had qualitatively similar demographic characteristics. From 2000 to 2008, the proportion of participants prescribed highly active antiretroviral therapy increased by 9 percentage points to 83% ($P < 0.001$), whereas the proportion with suppressed HIV VL ($d2.7 \log_{10}$ copies/mL) increased by 26 percentage points to 72% ($P < 0.001$). Median CD4 cell count at death more than tripled to 0.209×10^9 cells/L ($P < 0.001$). The usual limitations of observational data apply. The authors conclude that the NA-ACCORD is the largest cohort of HIV-infected adults in clinical care in the United States that is demographically similar to PLWH-US in 2008. From 2000 to 2008, increases were observed in the percentage of prescribed HAART, the percentage who achieved a suppressed HIV VL, and the median CD4 cell count at death. Althoff K, Buchacz K, Hall H, Zhang J, Hanna D, Rebeiro P, Gange S, Moore R, Kitahata M, Gebo K, Martin J, Justice A, Horberg M, Hogg R, Sterling T, Cescon A, Klein M, Thorne J, Crane H, Mugavero M, Napravnik S, Kirk G, Jacobson L, Brooks J, Brooks J. U.S. trends in antiretroviral therapy use, HIV RNA plasma viral loads, and CD4 T-lymphocyte cell counts among HIV-infected persons, 2000 to 2008. *Ann Intern Med.* 2012; 157 (5): 325-335.

Ready Access To Illicit Drugs Among Youth and Adult Users

Current drug-control strategies in Canada focus funding and resources predominantly on drug law enforcement, often at the expense of preventive, treatment, and harm reduction efforts. This study aimed to examine the availability of the most commonly used substances in Vancouver, Canada after the implementation of such strategies. Using data from two large cohorts of drug-using youth and adults in Vancouver from the calendar year 2007, the authors assessed perceived availability of heroin, crack, cocaine, crystal methamphetamine, and marijuana. Compared to youth ($n= 330$), a greater proportion of adults ($n= 1,160$) reported immediate access (ie, within 10 minutes) to heroin (81.0% vs. 55.9%, $p < .001$),

crack (90.4% vs. 69.3%, $p < .001$), and cocaine (83.7% vs. 61.1%, $p < .001$). Conversely, larger proportions of youth reported immediate access to crystal methamphetamine (62.8% vs. 39.4%, $p < .001$) and marijuana (88.4% vs. 73.2%, $p < .001$) compared to adult users. The authors conclude that regardless of differences in illicit drug availability by age, all drugs are readily accessed in Vancouver despite drug law enforcement efforts. This includes drugs that are frequently injected and place users at risk of human immunodeficiency virus (HIV) infection and transmission of other blood-borne disease. Hadland S, Marshall B, Kerr T, Lai C, Montaner J, Wood E. Ready access to illicit drugs among youth and adult users. *Am J Addict.* 2013; 21(5): 488-490.

Antiretroviral Medication Errors Remain High But Are Quickly Corrected Among Hospitalized HIV-Infected Adults

Antiretroviral therapy (ART) medication errors can lead to drug resistance, treatment failure, and death. Prior research suggests that ART medication errors are on the rise in US hospitals. This analysis provides a current estimate of inpatient antiretroviral prescribing errors. This was a retrospective review of medication orders during the first 48 hours of hospitalization for patients with human immunodeficiency virus (HIV) infection admitted to the Johns Hopkins Hospital between 1 January and 31 December 2009. Errors were classified as (1) incomplete regimen, (2) incorrect dosage, (3) incorrect schedule, and (4) nonrecommended drug-drug combinations. Multivariable regression was used to identify factors associated with errors. A total of 702 admissions occurred in 2009. Of these, 380 had ART medications prescribed on the first day and 308 on the second day of hospitalization. A total of 145 ART medication errors in 110 admissions were identified on the first day (29%), and 22 errors were identified in 21 admissions on the second day (7%). The most common errors were incomplete regimen and incorrect dosage or schedule. Protease inhibitors accounted for the majority of dosing and scheduling errors (71% - 73%). Compared with patients admitted to the HIV/AIDS service, those admitted to surgical services were at increased risk of errors (adjusted odds ratio, 3.10; 95% confidence interval, 1.18-8.18). The authors concluded that ART medication errors are common among hospitalized HIV-infected patients on the first day of admission, but most are corrected within 48 hours. Interventions are needed to safeguard patients and prevent serious complications of ART medication errors especially during the first 24 hours of hospitalization. Yehia B, Mehta J, Ciuffetelli D, Moore R, Pham P, Metlay J, Gebo K. Antiretroviral medication errors remain high but are quickly corrected among hospitalized HIV-infected adults. *Clin Infect Dis.* 2012; 55(4): 593-599.

Substance Use Patterns Among High-Risk American Indians/Alaska Natives In Los Angeles County

Substance abuse among American Indians/Alaska Natives (AI/ANs) is a significant and long-standing health problem in the U.S. Two-thirds of American AIs/ANs reside in the urban setting. However, studies analyzing substance use characteristics among urban AI/ANs are very limited. Substance use patterns among a sample of AI/ANs ($n = 77$) and other ethnic/racial groups in Los Angeles County at high risk of substance abuse were analyzed utilizing three datasets from programs targeting individuals at high risk for substance abuse and risky sexual behaviors. Compared to all other ethnic/racial groups, AI/ANs demonstrated significantly younger age of onset of alcohol, marijuana, methamphetamine, and "other" drug use, higher correlations of age of first use of amphetamine with a measure of the drug's reinforcement, and higher mean number of illicit drug injections in the 30 days before being interviewed. Results from this study highlight a critical need for furthering our understanding of substance abuse problems among urban AI/ANs. Dickerson D, Fisher D, Reynolds G, Baig S, Napper L, Anglin M. Substance use patterns among high-risk American Indians/Alaska Natives in Los Angeles County. *Am J Addict.* 2012; 21(5): 445-452.

Sexual Pleasure and Sexual Risk Among Women Who Use Methamphetamine: A Mixed Methods Study

The intersection of drug use, sexual pleasure and sexual risk behaviour is rarely explored when it comes to poor women who use drugs. This paper explores the relationship between sexual behaviour and methamphetamine use in a community-based sample of women, exploring not only risk, but also desire, pleasure and the challenges of overcoming trauma. Quantitative data were collected using standard epidemiological methods (N=322) for community-based studies. In addition, using purposive sampling, qualitative data were collected among a subset of participants (n=34). Data were integrated for mixed methods analysis. While many participants reported sexual risk behaviour (unprotected vaginal or anal intercourse) in the quantitative survey, sexual risk was not the central narrative pertaining to sexual behaviour and methamphetamine use in qualitative findings. Rather, desire, pleasure and disinhibition arose as central themes. Women described feelings of power and agency related to sexual behaviour while high on methamphetamine. Findings were mixed on whether methamphetamine use increased sexual risk behaviour. The use of mixed methods afforded important insights into the sexual behaviour and priorities of methamphetamine-using women. Efforts to reduce sexual risk should recognize and valorize the positive aspects of methamphetamine use for some women, building on positive feelings of power and agency as an approach to harm minimization. Lorvick J, Bourgois P, Wenger L, Arreola S, Lutnick A, Wechsberg W, Kral A. Sexual pleasure and sexual risk among women who use methamphetamine: A mixed methods study. *Int J Drug Policy*. 2012; 23(5): 385-392.

PREVENTION RESEARCH

Smoking Quit Success Genotype Score Predicts Quit Success and Distinct Patterns Of Developmental Involvement With Common Addictive Substances

Genotype scores that predict relevant clinical outcomes may detect other disease features and help direct prevention efforts. The authors report data that validate a previously established v1.0 smoking cessation quit success genotype score and describe striking differences in the score in individuals who display differing developmental trajectories of use of common addictive substances. In a cessation study, v1.0 genotype scores predicted ability to quit with $P=0.00056$ and area under receiver-operating characteristic curve 0.66. About 43% vs 13% quit in the upper vs lower genotype score terciles. Latent class growth analyses of a developmentally assessed sample identified three latent classes based on substance use. Higher v1.0 scores were associated with (a) higher probabilities of participant membership in a latent class that displayed low use of common addictive substances during adolescence ($P=0.0004$) and (b) lower probabilities of membership in a class that reported escalating use ($P=0.001$). These results indicate that: (a) genetic predictors of smoking cessation success have been identified, (b) genetic influences on quit success overlap with those that influence the rate at which addictive substance use is taken up during adolescence and (c) individuals at genetic risk for both escalating use of addictive substances and poor abilities to quit may provide especially urgent focus for prevention efforts. Uhl GR, Walther D, Musci R, Fisher C, Anthony JC, Storr CL, Behm FM, Eaton WW, Ialongo I, Rose JE. Smoking quit success genotype score predicts quit success and distinct patterns of developmental involvement with common addictive substances. *Molecular Psychiatry* advance online publication, 6 November 2012; doi:10.1038/mp.2012.155

How Has the Economic Downturn Affected Communities and Implementation of Science-Based Prevention in the Randomized Trial of Communities That Care?

This study examined implications of the economic downturn that began in December 2007 for the Community Youth Development Study (CYDS), a longitudinal randomized controlled trial of the Communities That Care (CTC) prevention system. The downturn had the potential to affect the internal validity of the CYDS research design and implementation of science-based prevention in study communities. The authors used archival economic indicators and community key leader reports of economic conditions to assess the extent of the economic downturn in CYDS communities and potential internal validity threats. They also examined whether stronger economic downturn effects were associated with a decline in science-based prevention implementation. Economic indicators suggested the downturn affected CYDS communities to different degrees. They found no evidence of systematic differences in downturn effects in CTC compared to control communities that would threaten internal validity of the randomized trial. The Community Economic Problems scale was a reliable measure of community economic conditions, and it showed criterion validity in relation to several objective economic indicators. CTC coalitions continued to implement science-based prevention to a significantly greater degree than control coalitions 2 years after the downturn began. However, CTC implementation levels declined to some extent as unemployment, the percentage of students qualifying for free lunch, and community economic problems worsened. Control coalition implementation levels were not related to economic conditions before or after the downturn, but mean implementation levels of science-based prevention were also relatively low in both periods. Kuklinski M, Hawkins J, Plotnick R, Abbott R, Reid C. How has the economic downturn affected communities and implementation of science-based prevention in the randomized trial of Communities That Care?. *Am J Community Psychol.* 2012.

The Efficacy Of Familias Unidas On Drug and Alcohol Outcomes For Hispanic Delinquent Youth: Main Effects and Interaction Effects By Parental Stress and Social Support

Drug and alcohol use disproportionately affect Hispanic youth. Despite these disparities, few empirically supported preventive interventions are available to ameliorate this public health concern among Hispanic youth. This study examined the effects of Familias Unidas, relative to Community Practice, in reducing past 90-day substance use, alcohol and marijuana dependence, and having sex while under the influence of alcohol or drugs. Additionally, this study explored whether Familias Unidas' effects varied by environmental context, namely parental stress and social support for parents. A total of 242 delinquent Hispanic youth aged 12-17 years and their primary caregivers were randomized to either Familias Unidas or Community Practice and assessed at three time points. Familias Unidas was efficacious in reducing past 90-day substance use, illicit drug use, and in reducing the proportion of youth with an alcohol dependence diagnosis, relative to Community Practice. Results also showed a reduction in the proportion of youth who reported having sex while under the influence of alcohol or drugs. No differences between conditions were observed in past 90-day alcohol use or marijuana dependence. Intervention effects on illicit drug use and alcohol dependence varied by environmental context. For example, Familias Unidas was most efficacious for adolescents with parents exhibiting high stress and lower levels of social support. Familias Unidas was efficacious in reducing some drug and alcohol related outcomes. The findings also support the concept of targeting family-based interventions, such as Familias Unidas, for adolescents with parents exhibiting high stress and low levels of social support. Prado G, Cordova D, Huang S, Estrada Y, Rosen A, Bacio G, Leon Jimenez G, Pantin H, Brown C, Velazquez M, Villamar J, Freitas D, Tapia M, McCollister K. The efficacy of Familias Unidas on drug and alcohol outcomes for Hispanic delinquent youth: Main effects and interaction effects by parental stress and social support. *Drug Alcohol Depend.* 2012; 125 Suppl 1: S18-S25.

Effects Of A Family Intervention In Reducing HIV Risk Behaviors Among High-Risk Hispanic Adolescents: A Randomized Controlled Trial

The objective of this study was to determine the efficacy of a family intervention in reducing human immunodeficiency virus (HIV) risks behaviors among Hispanic delinquent adolescents. The study was a randomized controlled trial conducted in the Miami-Dade County Public School System and Miami-Dade County's Department of Juvenile Services, Florida. A total of 242 Hispanic delinquent youth aged 12 to 17 years and their primary caregivers completed outcome assessments at baseline and 3 months after intervention. Participants were randomized to either Familias Unidas (120 participants), a Hispanic-specific, family intervention designed to reduce HIV risk behaviors among Hispanic youth, or a community practice control condition (122 participants). Self-reported measures included unprotected sexual behavior, engaging in sex while under the influence of alcohol and/or drugs, number of sexual partners, and incidence of sexually transmitted diseases. Family functioning (eg, parent-adolescent communication, positive parenting, and parental monitoring) was also assessed via self-report measures. Compared with community practice, Familias Unidas was efficacious in increasing condom use during vaginal and anal sex during the past 90 days, reducing the number of days adolescents were under the influence of drugs or alcohol and had sex without a condom, reducing sexual partners, and preventing unprotected anal sex at the last sexual intercourse. Familias Unidas was also efficacious, relative to community practice, in increasing family functioning and most notably in increasing parent-adolescent communication and positive parenting. These results suggest that culturally tailored, family-centered prevention interventions may be appropriate and efficacious in reducing HIV risk behaviors among Hispanic delinquent adolescents. Prado G, Pantin H, Huang S, Cordova D, Tapia M, Velazquez M, Calfee M, Malcolm

S, Arzon M, Villamar J, Jimenez G, Cano N, Brown C, Estrada Y. Effects of a family intervention in reducing HIV risk behaviors among high-risk Hispanic adolescents: a randomized controlled trial. *Arch Pediatr Adolesc Med.* 2012; 166(2): 127-133.

Effects of a Paraprofessional Home-Visiting Intervention on American Indian Teen Mothers' and Infants' Behavioral Risks: A Randomized Controlled Trial

The authors sought to examine the effectiveness of Family Spirit, a paraprofessional-delivered, home-visiting pregnancy and early childhood intervention, in improving American Indian teen mothers' parenting outcomes and mothers' and children's emotional and behavioral functioning 12 months postpartum. Pregnant American Indian teens (N=322) from four southwestern tribal reservation communities were randomly assigned in equal numbers to the Family Spirit intervention plus optimized standard care or to optimized standard care alone. Parent and child emotional and behavioral outcome data were collected at baseline and at 2, 6, and 12 months postpartum using self-reports, interviews, and observational measures. At 12 months postpartum, mothers in the intervention group had significantly greater parenting knowledge, parenting self-efficacy, and home safety attitudes and fewer externalizing behaviors, and their children had fewer externalizing problems. In a subsample of mothers with any lifetime substance use at baseline (N=285; 88.5%), children in the intervention group had fewer externalizing and dysregulation problems than those in the standard care group, and fewer scored in the clinically "at risk" range (> 10th percentile) for externalizing and internalizing problems. No between-group differences were observed for outcomes measured by the Home Observation for Measurement of the Environment scale. Outcomes 12 months postpartum suggest that the Family Spirit intervention improves parenting and infant outcomes that predict lower lifetime behavioral and drug use risk for participating teen mothers and children. Barlow A, Mullany B, Neault N, Compton S, Carter A, Hastings R, Billy T, Coho-Mescal V, Lorenzo S, Walkup JT. Effects of a paraprofessional home-visiting intervention on American Indian teen mother's and infants' behavioral risks: A randomized controlled trial. *Am J Psychiatry.* 2012; 10.1176/appi.ajp.2012.12010121.

Integrating Condom Skills into Family-Centered Prevention: Efficacy of the Strong African American Families-Teen Program

The Strong African American Families-Teen (SAAF-T) program, a family-centered preventive intervention that included an optional condom skills unit, was evaluated to determine whether it prevented unprotected intercourse and increased condom efficacy among rural African American adolescents. Ancillary analyses were conducted to identify factors that predicted youth attendance of the condom skills unit. Sixteen-year-old African American youths (N = 502) and their primary caregivers were randomly assigned to SAAF-T (n = 252) or an attention control (n = 250) intervention. SAAF-T families participated in a 5-week family skills training program that included an optional condom skills unit. All families completed in-home pretest, posttest, and long-term follow-up interviews during which adolescents reported on their sexual behavior, condom use, and condom efficacy. Because condom use was addressed only in an optional unit that required caregiver consent, the authors analyzed efficacy using complier average causal effect analyses. Attendance in both SAAF-T and the attention control intervention averaged 4 of 5 sessions; 70% of SAAF-T youth attended the condom skills unit. Complier average causal effect models indicated that SAAF-T was efficacious in reducing unprotected intercourse and increasing condom efficacy among rural African American high school students. Exploratory analyses indicated that religious caregivers were more likely than nonreligious caregivers to have their youth attend the condom skills unit. Results suggest that brief condom skills educational modules in the context of a family-centered program are feasible and reduce risk for sexually

transmitted infections and unplanned pregnancies. Kogan S, Yu T, Brody G, Chen Y, DiClemente R, Wingood G, Corso P. Integrating condom skills into family-centered prevention: Efficacy of the Strong African American Families-Teen Program. *J Adolesc Health*. 2012; 51(2): 164-170.

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 + R allele). In addition, emerging adults who reported high life stress and carried the 7 + 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 \times 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 \times DRD4 Status interaction on drug use became no significant in the presence of the risk mechanisms. This finding provides an example of "second generation" Gene \times Environment interaction research in which the interaction's effects on proximal risk mechanisms account for its effects on outcomes. Brody G, Chen Y, Yu T, Beach S, Kogan S, Simons R, Windle M, Philibert R. Life stress, the dopamine receptor gene, and emerging adult drug use trajectories: A longitudinal, multilevel, mediated moderation analysis. *Dev Psychopathology*. 2012; 24(3): 941-951.

The Impact of a Family-Centered Intervention on the Ecology of Adolescent Antisocial Behavior: Modeling Developmental Sequelae and Trajectories during Adolescence

This study used an experimental, longitudinal field trial involving random assignment to the Family Check-Up (FCU) to explore the social ecology of adolescent antisocial behavior. A sample of 998 youths and their families was followed from early to late adolescence (age 12 to 18-19). In the intervention condition, 115 families (23%) elected to receive the FCU. In general, random assignment to the FCU in middle school was associated with reductions in late adolescence antisocial behavior (age 18-19). Variable-centered analyses revealed that the effects were mediated by reductions in family conflict from early to middle adolescence (age 12-15). The link between family conflict and antisocial behavior in turn was mediated by association with deviant peers at age 17; parental monitoring at age 17 was also influential but did not attain the status of a mediator. Person-oriented analyses suggested that the FCU was associated with declining trajectories of family conflict and rising trajectories of parental monitoring but was not associated with trajectories of deviant peer association. A dual-trajectory analysis indicated that the pathways to adolescent antisocial behavior were myriad and varied, suggesting new directions for developmental and intervention research. Van Ryzin M, Dishion T. The Impact of a family-centered intervention on the ecology of adolescent antisocial behavior: Modeling developmental sequelae and trajectories during adolescence. *Dev Psychopathology*. 2012; 24(3): 1139-1155.

Sequence of Alcohol Involvement from Early Onset to Young Adult Alcohol Abuse: Differential Predictors and Moderation by Family-Focused Preventive Intervention

This study tests risk factors for four dimensions of alcohol use in the sequence from (a) early onset prior to age 13 to (b) adolescent alcohol use and (c) alcohol problems to (d) young adult alcohol abuse. It also examines whether family-focused preventive interventions buffer predictive relationships. Data

were from a randomized prevention trial extending from ages 11 to 21. Families of sixth graders enrolled in 33 rural schools in the Midwestern United States were invited to participate. Families (N = 667) were pretested and randomly assigned to a control group (n = 208) or to family interventions (n = 459). The average age of participating youth was 11.3 years when the study began (52% female). Questionnaire data were collected on alcohol dimensions during adolescence (early onset, alcohol use, alcohol problems) and young adulthood (alcohol abuse), and on risk factors in early adolescence (male gender, impulsive behaviors, aggression-hostility, peer deviance, and parent problem drinking). Impulsive behaviors predicted early onset, peer deviance predicted alcohol use, and parent problem drinking predicted alcohol problems ($p < .05$). Aggression-hostility and alcohol problems predicted alcohol abuse in the control group ($p < .05$), but not in the family interventions group ($p > .05$). Different dimensions of alcohol use and problems from before age 13 to young adulthood are predicted by different risk factors. Family-focused preventive interventions can reduce the influence of some of these risk factors, including early adolescent aggression-hostility and late adolescent alcohol problems. doi:10.1111/j.1360-0443.2012.03987.x Mason W, Spoth R. Sequence of alcohol involvement from early onset to young adult alcohol abuse: differential predictors and moderation by family-focused preventive intervention. *Addiction*. 2012.

Sustained Effects of the Communities That Care System on Prevention Service System

Transformation The authors examined whether the Communities That Care (CTC) system sustained effects 1.5 years after study funding ended on prevention system constructs expected to be important for community-level reductions in drug use and antisocial behaviors among youths. Data were from a community trial of 24 towns in the United States randomized to either the CTC intervention or control conditions. Participants were 928 community key leaders interviewed at 1 to 4 waves from 2001 to 2009. Intervention activities, including training and technical assistance, were conducted between 2003 and 2008 in the CTC communities. Leaders from CTC communities reported higher levels of adoption of a science-based approach to prevention and a higher percentage of funding desired for prevention activities in 2009 than did leaders in control communities. CTC communities showed a higher increase over time in community norms against adolescent drug use as well as adoption of a science-based approach compared with control communities. These findings indicated that CTC implementation produced enduring transformation of important prevention system constructs in intervention communities, which might, in turn, produce long-term reductions in youth problem behaviors. Rhew I, Brown E, Hawkins J, Briney J. Sustained effects of the Communities That Care System on prevention service system transformation. *Am J Public Health*. Published online ahead of print July 19, 2012: e1-e7. doi:10.2105/AJPH.2011.300567)..

Sustainability Of The Communities That Care Prevention System By Coalitions Participating In The Community Youth Development Study

Community prevention coalitions are a common strategy to mobilize stakeholders to implement tested and effective prevention programs to promote adolescent health and well-being. This article examines the sustainability of Communities That Care (CTC) coalitions approximately 20 months after study support for the intervention ended. The Community Youth Development Study is a community-randomized trial of the CTC prevention system. Using data from 2007 and 2009 coalition leader interviews, this study reports changes in coalition activities from a period of study support for CTC (2007) to 20 months following the end of study support for CTC (2009), measured by the extent to which coalitions continued to meet specific benchmarks. Twenty months after study support for CTC implementation ended, 11 of 12 CTC coalitions in the Community Youth Development Study still existed. The 11 remaining

coalitions continued to report significantly higher scores on the benchmarks of phases 2 through 5 of the CTC system than did prevention coalitions in the control communities. At the 20-month follow-up, two-thirds of the CTC coalitions reported having a paid staff person. This study found that the CTC coalitions maintained a relatively high level of implementation fidelity to the CTC system 20 months after the study support for the intervention ended. However, the downward trend in some of the measured benchmarks indicates that continued high-quality training and technical assistance may be important to ensure that CTC coalitions maintain a science-based approach to prevention, and continue to achieve public health impacts on adolescent health and behavior outcomes. Gloppen K, Arthur M, Hawkins J, Shapiro V. Sustainability of The Communities That Care Prevention System by coalitions participating in the Community Youth Development Study. *J Adolesc Health*. 2012; 51(3): 259-264.

Effects of Parenting and Deviant Peers on Early to Mid-adolescent Conduct Problems The authors investigated the influence of effective parenting behaviors (father and mother reports) and deviant peer association (adolescent reports) on subsequent young adolescent conduct problems (teacher reports) during grades 7-9, using structural equation modeling. Data were from a sample of 226 rural adolescents (n = 112 boys; n = 107 girls; n = 7 gender unknown), their parents, and teachers. Both effective parenting and association with deviant peers influenced later conduct problems; however, the pattern of influence varied across time and between fathers and mothers, with complex patterns of interactions between effective parenting and peer deviance. From seventh to eighth grade, effective parenting by both mothers and fathers buffered the effect of higher levels of peer deviance on conduct problems across adolescent gender. From eighth to ninth grade (i.e., transition into high school), fathers' effective parenting buffered the effects of deviant peer association on their daughters' conduct problems, whereas both fathers' and mothers' influence was stronger for sons when deviant peer associations were lower. Analyses also evaluated bi-directional longitudinal effects among adolescents, parents, and peers. Although varying by parent and adolescent gender or adolescent age, results generally supported the protective effects of parenting on their children's conduct problems during early to mid-adolescence. Trudeau L, Mason W, Randall G, Spoth R, Ralston E. Effects of parenting and deviant peers on early to mid-adolescent conduct problems. *J Abnorm Child Psychol*. 2012; 40(8): 1249-1264.

Do The Effects Of A Family Intervention On Alcohol and Drug Use Vary By Nativity Status? The aim of this study was to examine whether the intervention effects of Familias Unidas, compared to community practice, on Hispanic adolescent alcohol and drug use varies by nativity status (i.e., U.S.-born and foreign-born). A total of 213 eighth grade Hispanic adolescents with behavior problems and their primary caregivers were assigned randomly to one of two conditions: Familias Unidas or Community Control. Participants were assessed at baseline and at 6, 18, and 30 months post baseline. Results showed that, the effects of Familias Unidas on alcohol use were moderated by nativity status. Specifically, Familias Unidas was efficacious in preventing/reducing alcohol use for U.S.-born youth, but not foreign-born. No moderating effects were found for drug use. These findings suggest that prevention interventions may be more efficacious in preventing/reducing alcohol use among certain Hispanic adolescent subgroups. (PsycINFO Database Record (c) 2012 APA, all rights reserved). Cordova D, Huang S, Pantin H, Prado G. Do the effects of a family intervention on alcohol and drug use vary by nativity status? *Psychol Addict Behav*. 2012; 26(3): 655-660.

Community Partnership to Affect Substance Abuse among Native American Adolescents

Substance abuse is one of the nation's primary health concerns. Native American youth experience higher rates of substance abuse than other youth. There is little empirical evidence that exists concerning the use of culturally-based interventions among Native American adolescents.

This study used a community-based participatory research approach to develop and evaluate an innovative school-based cultural intervention targeting substance abuse among a Native American adolescent population. A two-condition quasi-experimental study design was used to compare the Cherokee Talking Circle (CTC) culturally-based intervention condition (n = 92) with the Be a Winner Standard Education (SE) condition (n = 87). Data were collected at pre-intervention, immediate post-intervention and 90-day post-intervention using the Cherokee Self-Reliance Questionnaire, Global Assessment of Individual Needs - Quick, and Written Stories of Stress measures. Significant improvements were found among all measurement outcomes for the CTC culturally-based intervention. The data provide evidence that a Native American adolescent culturally-based intervention was significantly more effective for the reduction of substance abuse and related problems than a noncultural-based intervention. This study suggests that cultural considerations may enhance the degree to which specific interventions address substance abuse problems among Native American adolescents. Lowe J, Liang H, Riggs C, Henson J, Elder T. Community partnership to affect substance abuse among Native American adolescents. *Am J Drug Alcohol Abuse*. 2012; 38(5): 450-455.

Interview As Intervention: The Case Of Young Adult Multidrug Users In The Club Scene

This paper reports on changes in substance use and substance dependence symptoms-without intervention-among young adult multidrug users in the club scene, ages 18-29, (N=444) who participated in a natural history study. Computer-assisted personal interviews at baseline and 6-, 12- and 18-month follow-ups included well-tested measures of substance use and dependence. Changes in substance dependence symptoms and drug use frequencies were calculated using Cohen's d statistic. Mean age was 22; 40% were female; 58% were Hispanic, 17% White, and 21% Black. At 18-month follow-up assessment, participants reported significantly fewer days of cocaine (d=-.85 at 18 months), ecstasy (d=-.93), benzodiazepine (d=-.82), and prescription opioid (d=-.81) use, as well as reduced substance dependence symptoms (d=-.42). These results, together with data from focus groups with completers, suggest that comprehensive health and social risk assessments may have quite strong intervention effects among young adult multidrug users. Kurtz S, Surratt H, Buttram M, Levi-Minzi M, Chen M. Interview as intervention: The case of young adult multidrug users in the club scene. *J Subst Abuse Treat*. 2012.

Adapting Multidimensional Treatment Foster Care for the Treatment of Co-occurring Trauma and Delinquency in Adolescent Girls

Girls in the juvenile justice system has been found to experience high rates of traumatic childhood events. Despite the well-documented coexistence of trauma and delinquency, few programs integrate the treatment of both disorders. Because of the lack of intervention studies addressing co-occurring trauma and delinquency and the lack of data about how these disorders impact each other, there is limited information about how to best treat these disorders when they co-occur. The current article provides a theoretical rationale for adapting a community-based intervention, Multidimensional Treatment Foster Care, to treat adolescent girls with co-occurring trauma and delinquency, describes the intervention approach, and presents outcomes from a small-scale pilot study. Smith DK, Chamberlain, P, Deblinger E. Adapting multidimensional treatment foster care for the treatment of co-occurring trauma and delinquency in

adolescent girls. *Journal of Child & Adolescent Trauma*. 2012; 5: 224-238.

Family and Peer Predictors Of Substance Use From Early Adolescence To Early Adulthood:

An 11-Year Prospective Analysis The focus of this study was social (i.e., family and peer) influences on substance use from early adolescence to early adulthood. A large, ethnically diverse sample of early adolescents (N=998) was followed from age 12 to age 23. The authors tested direct and indirect effects of parental monitoring, family relationship quality, and association with deviant peers on change in substance use across time. Outcomes for tobacco, alcohol, and marijuana use were analyzed as separate pathways within the same overall model. The results suggest that a significant shift in the nature of family influence occurred across adolescence and into early adulthood, but deviant peer influence was relatively consistent across this period. Specifically, parental monitoring and deviant peer association were predictive of substance use in early adolescence, but family relationship quality was a significant predictor across the transition to high school and generally continued to predict use into later adolescence, as did association with deviant peers. Deviant peers were the only significant predictor in early adulthood. These results also suggested that parental monitoring and family relationship quality indirectly predicted later substance use by way of deviant peers, implying that an important aspect of the family context is its influence on choice of friends and peer group composition. Implications for family-based prevention and intervention are discussed. Van Ryzin M, Fosco G, Dishion T. Family and peer predictors of substance use from early adolescence to early adulthood: An 11-year prospective analysis. *Addict Behav*. 2012; 37(12): 1314-1324.

Association between Adverse Life Events and Addictive Behaviors among Male and Female Adolescents

Adverse life events have been associated with gambling and substance use as they can serve as forms of escapism. Involvement in gambling and substance use can also place individuals in adversely stressful situations. The objectives of this study were to explore potential male-female differences in the association between addictive behavior and adverse life events among an urban cohort of adolescents. The study sample comprised 515 adolescent participants in a randomized prevention trial. With self-reported data, four addictive behavior groups were created: nonsubstance users and nongamblers, substance users only, gamblers only, and substance users and gamblers. Multinomial logistic regression analyses with interaction terms of sex and adverse life events were conducted. Adverse life events and engaging in at least one addictive behavior were common for both sexes. Substance users and gamblers had more than twice the likelihood of nonsubstance users and nongamblers to experience any event as well as events of various domains (i.e., relationship, violence, and instability). Neither relationship nor instability events' associations with the co-occurrence of substance use and gambling significantly differed between sexes. Conversely, females exposed to violence events were significantly more likely than similarly exposed males to report the co-occurrence of substance use and gambling. Findings from the current study prompt future studies to devote more attention to the development of effective programs that teach adaptive coping strategies to adolescents, particularly to females upon exposure to violence. Lee G, Storr C, Ialongo N, Martins S. Association between adverse life events and addictive behaviors among male and female adolescents. *Am J Addict*. 2012; 21(6): 516-523.

Family Check Up Effects on Adolescent Arrest Trajectories: Variation by Developmental Subtype

This study examines the effect of the Family Check Up intervention on the probability of arrests from ages 12 to 17 years for youth following heterogeneous developmental trajectories of antisocial behavior. Latent Growth Mixture Modeling results supported the presence of three

developmental trajectories of arrests, including a large group of youth with few police contacts, a smaller group of youth showing early onset and chronic arrests, and a group with adolescent-onset arrests. In line with hypotheses, effects of intervention were seen within the adolescent-onset group, but not in the early onset chronic arrest trajectory group, or those youth with little police contact. The trajectory groups were differentiated by peer, family, behavioral and academic risk variables at age 11. Connell A, Dishion T, Klostermann S. Family Check Up effects on adolescent arrest trajectories: Variation by developmental subtype. *J Res Adolesc.* 2012; 22(2): 367-380.

Epidemiology, Sexual Risk Behavior, and HIV Prevention Practices of Men who Have Sex with Men Using GRINDR in Los Angeles, California

Young men who have sex with men (YMSM) are at alarming risk for HIV acquisition, demonstrating the highest rates of incident infection of any age-risk group. GRINDR is a global positioning service-based social networking application popular with YMSM for sexual partnering. To assess the characteristics of YMSM who use GRINDR, the authors conducted a computer-assisted self-interview-based survey of 375 YMSM using GRINDR in metropolitan Los Angeles, recruited using the GRINDR platform. The median age was 25 (interquartile range, 22-27) years old, 42.4 % Caucasian, 6.4 % African American, 33.6 % Latino, and 14.1 % Asian/Pacific Islander. Participants reported high rates of sexual partnering and unprotected anal intercourse (UAI). The majority (70 %) of those reporting unprotected anal intercourse reported low perception of HIV-acquisition risk. Of the participants, 83.1 % reported HIV testing within the past 12 months; 4.3 % had never been HIV tested. Of the participants, 4.5 % reported HIV-positive aerostats; 51.7 % indicated that they would be interested in participating in a future HIV prevention trial. Latinos were more likely than either Caucasians or African Americans to endorse trial participation interest (odds ratio, 1.9; 95 % confidence interval [1.1-3.3]). HIV-positive test results were associated with increased number of anal sex partners in the past 3 months (adjusted odds ratio (AOR), 1.53 [0.97-2.40]), inconsistent inquiry about partners and aerostats (AOR, 3.63 [1.37-9.64]), reporting the purpose for GRINDR use including "friendship" (AOR, 0.17 [0.03-1.06], and meeting a sexual partner in a bookstore in the past 3 months (AOR, 33.84 [0.99-1152]). Men recruited via GRINDR were high risk for HIV acquisition or transmission and interested in clinical trial participation, suggesting potential for this method to be used for recruitment of YMSM to HIV prevention trials. Landovitz R, Tseng C, Weissman M, Haymer M, Mendenhall B, Rogers K, Veniegas R, Gorbach P, Reback C, Shoptaw S. Epidemiology, sexual risk behavior, and HIV prevention practices of Men who Have Sex with Men using GRINDR in Los Angeles, California. *J Urban Health.* 2012; Epub

Educational Paths and Substance Use From Adolescence Into Early Adulthood

This study examined how substance use trajectories from ages 15 to 23 in a community sample ($N = 921$) were related to educational pathways. Rates of heavy drinking converged across different paths, but starting college at a 2-year college before transferring to a 4-year college was related to later increase in drinking after high school. Higher future educational attainment was negatively associated with high school marijuana use, but marijuana use increased after high school for individuals who went to 4-year colleges compared with those who did not. Noncollege youth had the highest rates of daily cigarette smoking throughout adolescence and early adulthood, whereas college dropouts had higher rates of smoking than college students who did not drop out. The findings support the need for universal prevention for early adult heavy drinking, addressing increases in drinking and marijuana use in 4-year colleges and targeting marijuana use and cigarette smoking interventions at noncollege youth and college dropouts. Fleming CB, White HR, Haggerty

KP, Abbott RD, Catalano RF. Educational paths and substance use from adolescence into early adulthood. *J Drug Issues*. 2012; 42(2): 104-126.

Improving Elementary School Quality through the Use of a Social-Emotional and Character Development Program

School safety and quality affect student learning and success. This study examined the effects of a comprehensive elementary school-wide social-emotional and character education program, Positive Action, on teacher, parent, and student perceptions of school safety and quality utilizing a matched-pair, cluster-randomized, controlled design. The Positive Action Hawai'i trial included 20 racially/ethnically diverse schools and was conducted from 2002-2003 through 2005-2006. School-level archival data, collected by the Hawai'i Department of Education, were used to examine program effects at 1-year post-trial. Teacher, parent, and student data were analyzed to examine indicators of school quality such as student safety and well-being, involvement, and satisfaction, as well as overall school quality. Matched-paired t-tests were used for the primary analysis, and sensitivity analyses included permutation tests and random-intercept growth curve models. Analyses comparing change from baseline to 1-year post-trial revealed that intervention schools demonstrated significantly improved school quality compared to control schools, with 21%, 13%, and 16% better overall school quality scores as reported by teachers, parents, and students, respectively. Teacher, parent, and student reports on individual school-quality indicators showed improvement in student safety and well-being, involvement, satisfaction, quality student support, focused and sustained action, standards-based learning, professionalism and system capacity, and coordinated team work. Teacher reports also showed an improvement in the responsiveness of the system. School quality was substantially improved, providing evidence that a school-wide social-emotional and character education program can enhance school quality and facilitate whole-school change. Snyder FJ, Vuchinich S, Acock AA, Washburn IJ, Flay BR. Improving elementary school quality through the use of a social-emotional and character development program: A matched-pair, cluster-randomized, controlled trial in Hawai'i. *J Sch Health*. 2012; 82(1): 11-20.

Fatherhood Roles and Drug Use among Young American Indian Men

High rates of substance abuse among young American Indian (AI) fathers pose multigenerational challenges for AI families and communities. The objective of this study was to describe substance use patterns among young AI fathers and examine the intersection of substance use with men's fatherhood roles and responsibilities. As part of a home-visiting intervention trial for AI teen mothers and their children, in 2010 the authors conducted a descriptive study of fatherhood and substance use on three southwestern reservations. Substance use and parenting data were collected from n = 87 male partners of adolescent mothers using audio computer-assisted self-interviews. Male partners were on average 22.9 years old, primarily living with their children (93%), unmarried (87%), and unemployed (70%). Lifetime substance use was high: 80% reported alcohol; 78% marijuana; 34% methamphetamines; 31% crack/cocaine; and 16% reported drinking binge in the past 6 months. Substance use was associated with history of alcohol abuse among participants' fathers (but not mothers); participants' poor relationships with their own fathers; unemployment status; and low involvement in child care. The authors conclude that drug and alcohol abuse may be obstructing ideal fatherhood roles among multiple generations of AI males. Targeting drug prevention among young AI men during early fatherhood may provide special opportunity to reduce substance use and improve parenting. Intergenerational approaches may hold special promise. Neault N, Mullany B, Powers J, Coho-Mescal V, Parker S, Walkup J, Barlow A, Barlow A. Fatherhood roles and drug use among young American Indian men. *Am J Drug Alcohol Abuse*. 2012; 38(5): 395-402.

The Family Spirit Trial for American Indian Teen Mothers and Their Children: CBPR Rationale, Design, Methods and Baseline Characteristics

The purpose of this paper is to describe the rationale, design, methods and baseline results of the Family Spirit trial. The goal of the trial is to evaluate the impact of the paraprofessional-delivered "Family Spirit" home-visiting intervention to reduce health and behavioral risks for American Indian teen mothers and their children. A community based participatory research (CBPR) process shaped the design of the current randomized controlled trial of the Family Spirit intervention. Between 2006 and 2008, 322 pregnant teens were randomized to receive the Family Spirit intervention plus Optimized Standard Care, or Optimized Standard Care alone. The Family Spirit intervention is a 43-session home-visiting curriculum administered by American Indian paraprofessionals to teen mothers from 28 weeks gestation until the baby's third birthday. A mixed methods assessment administered at nine intervals measures intervention impact on parental competence, mother's and children's social, emotional and behavioral risks for drug use, and maladaptive functioning. Participants are young (mean age = 18.1 years), predominantly primiparous, unmarried, and challenged by poverty, residential instability and low educational attainment. Lifetime and pregnancy drug use were ~2-4 times higher and ~5-6 times higher, respectively, than US All Races. Baseline characteristics were evenly distributed between groups, except for higher lifetime cigarette use and depressive symptoms among intervention mothers. If study aims are achieved, the public health field will have new evidence supporting multi-generational prevention of behavioral health disparities affecting young American Indian families and the utility of indigenous paraprofessional interventionists in under-resourced communities. Mullany B, Barlow A, Neault N, Billy T, Jones T, Tortice I, Lorenzo S, Powers J, Lake K, Reid R, Walkup J. The Family Spirit Trial for American Indian teen mothers and their children: CBPR rationale, design, methods and baseline characteristics. *Prev Sci.* 2012; 13(5): 504-518.

Drinking Motives As Mediators Of the Impulsivity-Substance Use Relation: Pathways For Negative Urgency, Lack Of Premeditation, and Sensation Seeking

Trait impulsivity is a reliable, robust predictor of risky, problematic alcohol use. Mounting evidence supports a multidimensional model of impulsivity, whereby several distinct traits serve as personality pathways to rash action. Different impulsivity-related traits may predispose individuals to drink for different reasons (e.g., to enhance pleasure, to cope with distress) and these different motives may, in turn, influence drinking behavior. Previous findings support such a mediational model for two well-studied traits: sensation seeking and lack of premeditation. This study addresses other impulsivity-related traits, including negative urgency. College students (N=432) completed questionnaires assessing personality, drinking motives, and multiple indicators of problematic drinking. Negative urgency, sensation seeking, and lack of premeditation were all significantly related to problematic drinking. When drinking motives were included in the model, direct effects for sensation seeking and lack of premeditation remained significant, and indirect effects of sensation seeking and lack of premeditation on problematic drinking were observed through enhancement motives. A distinct pathway was observed for negative urgency. Negative urgency bore a significant total effect on problematic drinking through both coping and enhancement motives. This study highlights unique motivational pathways through which different impulsive traits may operate, suggesting that interventions aimed at preventing or reducing problematic drinking should be tailored to individuals' personalities. For instance, individuals high in negative urgency may benefit from learning healthier strategies for coping with distress. Adams Z, Kaiser A, Lynam D, Charnigo R, Milich R. Drinking motives as mediators of the impulsivity-substance use

relation: Pathways for negative urgency, lack of premeditation, and sensation seeking. *Addict Behav.* 2012; 37(7): 848-855.

Practitioner Review: Children In Foster Care-Vulnerabilities and Evidence-Based Interventions That Promote Resilience Processes

An increasing number of children are placed in foster care (i.e., a kin or nonkin family home other than the biological parent) due to experiences of physical, sexual, emotional, or psychological abuse, and/or neglect. Children in foster care are at increased risk for a host of negative outcomes encompassing emotional, behavioral, neurobiological, and social realms. Areas of risk and vulnerability among foster children are described, including emotional and behavioral deficits, impaired neurobiological development, and social relationship deficits. Evidence suggesting the significance of family placement changes and prenatal exposure to substances as contributing mechanisms is presented. Based on a systematic search of the PsycINFO database (to March 2012), eight efficacious evidence-based interventions for foster families are summarized. Although the development of evidence-based interventions that improve outcomes for foster children has lagged behind the delivery of interventions in other service sectors (e.g., mental health and educational sectors), several interventions across childhood and adolescence offer promise. Service system constraints offer both challenges and opportunities for more routine implementation of evidence-based interventions. Given the increased likelihood of poor outcomes for foster children, increased efforts to understand the pathways to vulnerability and to implement interventions shown to be effective in remediating risks and improving outcomes for this population are indicated. Evaluation of efficacious interventions in countries outside of the United States is also needed. Leve L, Harold G, Chamberlain P, Landsverk J, Fisher P, Vostanis P. Practitioner Review: Children in foster care - vulnerabilities and evidence-based interventions that promote resilience processes. *J Child Psychol Psychiatry.* 2012.

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 A, Milich R, Lynam D, Charnigo R. Negative Urgency, distress tolerance, and substance abuse among college students. *Addict Behav.* 2012; 37(10): 1075-1083.

Substance Use and Sexual Risk Mediated By Social Support Among Black Men

Health and social disparities are widespread among men who have sex with men (MSM). Although literature indicates that Black MSM (BMSM) are no more likely than other MSM to report sexual risk behaviors, such as unprotected anal intercourse, studies have reported that buying and trading sex

appear to be important risk factors for BMSM. Substance use generally is not significantly greater among BMSM than other MSM, studies have found that BMSM report more powder and crack cocaine use than other MSM. The lack of adequate coping skills and social support for BMSM has also been documented. This paper examines differences in substance use, sexual risk behaviors and social support among Black and non-black MSM, in a sample of 515 men participating in a randomized intervention trial. BMSM reported higher rates of substance dependence (72.2 vs. 59.5 %, $P = .015$) and buying sex (49.1 vs. 17.4 %, $P < .000$) than non-Black MSM. BMSM also reported lower levels of social support than other MSM on all measures included in the study; e.g., getting help and emotional support from others (38.0 vs. 52.8 %, $P < .006$). Mediation analyses showed that BMSM 's higher rates of substance dependence and buying sex are partially mediated by lower levels of social support. These data appear to show that lack of social support is an important influence on risk behaviors among BMSM. Qualitative data also supported these findings. Sexual risk and substance use prevention interventions should address BMSM 's capacity to build adequate and supportive relationships. Buttram M, Kurtz S, Surratt H. Substance use and sexual risk mediated by social support among Black men. *J Community Health*. 2012.

The HAWK2 Program: A Computer-Based Drug Prevention Intervention for Native American Youth American Indians and Alaska Natives (AI/ANs) have some of the highest rates of substance use compared with other ethnic groups. Native American youth start experimenting with drugs at younger ages, continue to use them after initial experimentation, and thus seem to mirror the same drug use patterns as their older peers. Despite the seriousness of the problem, there is a lack of evidence-based drug prevention interventions for AI/AN youth. This review article describes the process by which an existing evidence-based, culturally relevant drug prevention intervention was transformed into a low-cost, computerized intervention digitized in order to extend its reach to Native American youth in reservations and rural locations. The intervention, titled HAWK(2) (Honoring Ancient Wisdom and Knowledge(2): Prevention and Cessation) is aimed at young Native children in elementary school settings (grades 4 and 5) and uses engaging multimedia features such as games, animations, and video clips to impart substance abuse prevention knowledge and skills training. The development of this intervention was a collaborative process involving the participation of community experts, research scientists, school teachers, and practitioners, as well as Native youth. Specific examples are provided to illustrate the development processes. Initial feedback from practitioners and youth suggest the feasibility and acceptability of computer-based interventions by Native youth and practitioners. The authors conclude that computer-based interventions are a cost-effective way of engaging youth in prevention programming. Future studies of HAWK(2) will provide an important means of testing the long-term effectiveness of self-administered, computer-based interventions for AI/AN youth. Raghupathy S, Forth A. The HAWK2 Program: A computer-based drug prevention intervention for Native American youth. *Am J Drug Alcohol Abuse*. 2012; 38(5): 461-467.

Receipt Of Post-Rape Medical Care In A National Sample Of Female Victims It is important for rape victims to receive medical care to prevent and treat rape-related diseases and injuries, access forensic exams, and connect to needed resources. Few victims seek care, and factors associated with post-rape medical care-seeking are poorly understood. The current study examined prevalence and factors associated with post-rape medical care-seeking in a national sample of women who reported a most-recent or only incident of forcible rape, and drug- or alcohol-facilitated/incapacitated rape when they were aged ≥ 14 years. A national sample of U.S. adult women ($N=3001$) completed structured telephone interviews in 2006, and data for this study were

analyzed in 2011. Logistic regression analyses examined demographic variables, health, rape characteristics, and post-rape concerns in relation to post-rape medical care-seeking among 445 female rape victims. A minority of rape victims (21%) sought post-rape medical attention following the incident. In the final multivariate model, correlates of medical care included black race, rape-related injury, concerns about sexually transmitted diseases, pregnancy concerns, and reporting the incident to police. Women who experience rapes consistent with stereotypic scenarios, acknowledge the rape, report the rape, and harbor health concerns appear to be more likely to seek post-rape medical services. Education is needed to increase rape acknowledgment, awareness of post-rape services that do not require formal reporting, and recognition of the need to treat rape-related health problems. Zinzow H, Resnick H, Barr S, Danielson C, Kilpatrick D. Receipt of post-rape medical care in a national sample of female victims. *Am J Prev Med.* 2012; 43(2): 183-187.

The Placement History Chart: A Tool for Understanding the Longitudinal Pattern of Foster Children's Placements Despite growing concerns about foster placement instability, little information is available regarding the longitudinal patterns of placement histories among foster children. The purpose of the present study was to develop a charting system using child welfare records to facilitate a better understanding of longitudinal patterns of placement history for 117 foster children. The resulting Placement History Chart included all placements that occurred during the observed time period and accounted for various dimensions: number, length, type, and sequence of placements; timing of transitions; and total time in out-of-home care. The Placement History Chart is an effective tool for placing foster care experiences within a broader developmental context. As such, the Placement History Chart can be a valuable research tool for understanding various dimensions and variations of placement transitions among foster children by capturing sequences and cumulative risks over time. Furthermore, this chart can facilitate the development of intervention programs that are developmentally sensitive and effectively address particularly vulnerable subpopulations of foster children. Kim H, Pears K, Fisher P. The Placement History Chart: A tool for understanding the longitudinal pattern of foster children's placements. *Child Youth Serv Rev.* 2012; 34(8): 1459-1464.

Introducing the At-Risk Average Causal Effect With Application To Health Wise South Africa Researchers often hypothesize that a causal variable, whether randomly assigned or not, has an effect on an outcome behavior and that this effect may vary across levels of initial risk of engaging in the outcome behavior. In this paper, the authors propose a method for quantifying initial risk status. They then illustrate the use of this risk-status variable as a moderator of the causal effect of leisure boredom, a non-randomized continuous variable, on cigarette smoking initiation. The data come from the Health Wise South Africa study. The authors define the causal effects using marginal structural models and estimate the causal effects using inverse propensity weights. Indeed, they found leisure boredom had a differential causal effect on smoking initiation across different risk statuses. The proposed method may be useful for prevention scientists evaluating causal effects that may vary across levels of initial risk. Coffman D, Caldwell L, Smith E. Introducing the at-risk average causal effect with application to health Wise South Africa. *Prev Sci.* 2012; 13(4): 437-447.

Too Little, Too Late Or Too Much, Too Early? Differential Hemodynamics Of Response Inhibition In High and Low Sensation Seekers High sensation seeking is associated with strong approach behaviors and weak avoidance responses. The present study used functional magnetic resonance imaging (fMRI) to further characterize the neurobiological underpinnings of this behavioral profile using a Go/No-go task. Analysis of brain activation associated with response

inhibition (No-go) versus response initiation and execution (Go) revealed the commonly reported right lateral prefrontal, insula, cingulate, and supplementary motor area network. However, right lateral activation was associated with greater No-go than Go responses only in low sensation seekers. High sensation seekers showed no differential activation in these regions but a more pronounced Go compared to No-go response in several other regions that are involved in salience detection (insula), motor initiation (anterior cingulate) and attention (inferior parietal cortex). Temporal analysis of the hemodynamic response for Go and No-go conditions revealed that the stronger response to Go than No-go trials in high sensation seekers occurred in the earliest time window in the right middle frontal gyrus, right mid-cingulate and right precuneus. In contrast, the greater No-go than Go response in low sensation seekers occurred in the later time window in these same regions. These findings indicate that high sensation seekers more strongly attend to or process Go trials and show delayed or minimal inhibitory responses on No-go trials in regions that low sensation seekers use for response inhibition. Failure to engage such regions for response inhibition may underlie some of the risky and impulsive behaviors observed in high sensation seekers. Collins H, Corbly C, Liu X, Kelly T, Lynam D, Joseph J. Too little, too late or too much, too early? Differential hemodynamics of response inhibition in high and low sensation seekers. *Brain Res.* 2012; 1481: 1-12.

Identifying the HIV Transmission Bridge: Which Men Are Having Unsafe Sex With Female Sex Workers and With Their Own Wives Or Steady Partners? The aim 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 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 sexually transmitted infection or HIV was 16.5% among bridgers and 2.3% among nonbridgers. Compared with 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 as follows: 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 TL, Volkmann T, Gallardo M, Goldenberg S, Lozada R, Semple SJ, Anderson CM, Strathdee SA. 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; 60(4): 414-420.

Prevalence and Correlates of Female Condom Use and Interest among Injection Drug-Using Female Sex Workers in Two Mexico-US Border Cities Little is known about female condom use among female sex workers who inject drugs (FSW-IDUs) in Northern Mexico, where HIV/STI prevalence is high. The authors examined the prevalence and correlates of female condom use and interest in female condom use among FSW-IDUs aged >18 years in Tijuana and Ciudad Juárez, Mexico enrolled in a behavioral intervention designed to reduce high-risk sexual and injection

behaviors. Of 621 FSW-IDUs, 8 % reported ever using female condoms, and 67.2 % expressed interest in trying female condoms. Factors independently associated with female condom use were having had a client become angry at the suggestion of using condoms and having engaged in unprotected vaginal sex with non-regular clients. Factors independently associated with interest in using female condoms were lifetime physical abuse and lifetime sexual abuse. Increasing the availability of female condoms and providing education on their use in the context of drug use and violence is recommended. Stockman J, Morris M, Martinez G, Lozada R, Patterson T, Ulibarri M, Vera A, Strathdee S. Prevalence and correlates of female condom use and interest among injection drug-using female sex workers in two Mexico-US border cities. *AIDS Behav.* 2012; 16(7): 1877-1886.

Resilience, Syndemic Factors, and Serosorting Behaviors among HIV-Positive and HIV-Negative Substance-Using MSM

Serosorting is commonly employed by MSM to reduce HIV risk. The authors hypothesize that MSM perceive serosorting to be effective, and that serosorting is predicted by resilience and inversely related to syndemic characteristics. Surveys included 504 substance-using MSM. Logistic regression models examined syndemic and resilience predictors of serosorting, separately by serostatus. For HIV-positive men, positive coping behaviors ($P = .015$) and coping self-efficacy ($P = .014$) predicted higher odds, and cognitive escape behaviors ($P = .003$) lower odds, of serosorting. For HIV-negative men, social engagement ($P = .03$) and coping self-efficacy ($P = .01$) predicted higher odds, and severe mental distress ($P = .001$), victimization history ($P = .007$) and cognitive escape behaviors ($P = .006$) lower odds, of serosorting. HIV-negative serosorters reported lower perceptions of risk for infection than non-serosorters ($P < .000$). Although high risk HIV-negative men may perceive serosorting to be effective, their high rates of UAI and partner change render this an ineffective risk reduction approach. Relevant public health messages are urgently needed. Kurtz SP, Buttram ME, Surratt HL, Stall RD. Resilience, Syndemic factors, and serosorting behaviors among HIV-positive and HIV-negative substance-using MSM. *AIDS Educ Prev.* 2012. Epub.

Psychosocial Problems Among Truant Youths: A Multi-Group, Exploratory Structural Equation Modeling Analysis

Truant youths represent a critical group needing problem-oriented research and involvement in effective services. The limited number of studies on the psychosocial functioning of truant youths have focused on one or a few problem areas, rather than examining comorbid problem behaviors. The present study addresses the need to examine the interrelationships of multiple domains of psychosocial functioning, including substance involvement, mental health, and delinquency, among truant youths. Exploratory structural equation modeling on baseline data collected on 219 truant youths identified two major factors reflecting psychosocial functioning and found that the factor structure was similar across major sociodemographic subgroups. Further analyses supported the validity of the factor structure. The research and service delivery implications of the findings are discussed. Dembo R, Briones-Robinson R, Barrett K, Winters KC, Ungaro R, Karas L, Wareham J, Belenko S. Psychosocial problems among truant youths: A multi-group, exploratory structural equation modeling analysis. *Journal of Child & Adolescent Substance Abuse.* 2012; 21: 440-465.

Girls Tobacco and Alcohol Use during Early Adolescence: Prediction from Trajectories of Depressive Symptoms across Two Studies

Associations between trajectories of depressive symptoms and subsequent tobacco and alcohol use were examined in two samples of girls assessed at age 11.5 (T1), 12.5 (T2), and 13.5 (T3). Two samples were examined to ascertain if there was

generalizability of processes across risk levels and cultures. Study 1 comprised a United States-based sample of 100 girls in foster care; Study 2 comprised 264 girls in a United Kingdom community-based sample. Controlling for T1 aggression and T1 substance use, individual variation in intercept and slope of depressive symptoms was associated with tobacco use at T3 in both samples: greater intercept and increases in depressive symptoms increased the risk for T3 tobacco use. A similar pattern of associations was found for alcohol use in Study 1. The replicability of findings for the prediction of tobacco use from trajectories of depressive symptoms suggests potential benefit in identifying girls with elevated depressive symptoms for tobacco use prevention programs, prior to the transition to secondary school. D. Leve LD, Harold GT, Van Ryzin MJ, Elam K, Chamberlain P. Girls tobacco and alcohol use during early adolescence: Prediction from trajectories of depressive symptoms across two studies. *J Child Adolesc Subst Abuse*. 2012; 21: 254-272.

Sensation Seeking Predicts Brain Responses In The Old-New Task: Converging Multimodal Neuroimaging Evidence Novel images and message content enhance visual attention and memory for high sensation seekers, but the neural mechanisms associated with this effect are unclear. To investigate the individual differences in brain responses to new and old (studied) visual stimuli, the authors utilized event-related potentials (ERP) and functional Magnetic Resonance Imaging (fMRI) measures to examine brain reactivity among high and low sensation seekers during a classic old-new memory recognition task. Twenty low and 20 high sensation seekers completed separate, but parallel, ERP and fMRI sessions. For each session, participants initially studied drawings of common images, and then performed an old-new recognition task during scanning. High sensation seekers showed greater ERP responses to new objects at the frontal N2 ERP component, compared to low sensation seekers. The ERP Novelty-N2 responses were correlated with fMRI responses in the orbitofrontal gyrus. Sensation seeking status also modulated the FN400 ERP component indexing familiarity and conceptual learning, along with fMRI responses in the caudate nucleus, which correlated with FN400 activity. No group differences were found in the late ERP positive components indexing classic old-new amplitude effects. These combined ERP and fMRI results suggest that sensation-seeking personality affects the early brain responses to visual processing, but not the later stage of memory recognition. Lawson A, Liu X, Joseph J, Vagnini V, Kelly T, Jiang Y. Sensation seeking predicts brain responses in the old-new task: Converging multimodal neuroimaging evidence. *Int J Psychophysiol*. 2012; 84(3): 260-269.

Life Goal Appraisal and Marijuana Use Among College Students The current study was designed to examine the motivational context of marijuana use among college students using idiographic and nomothetic goal assessment approaches. One hundred and ninety-eight introductory psychology students completed a questionnaire that included measures of life goals and marijuana use behavior. Forty-three percent of students surveyed reported the use of marijuana in the past 90 days. Students rated a set of five personally salient, self-generated and five normative life goals on a series of dimensions using the personal projects methodology (Little, 1983). Goal meaning and goal efficacy ratings for each type of assessment were studied in relation to the likelihood of marijuana use and the frequency of use among current users. Logistic regression analyses showed that levels of meaning for self-generated life goals and normative academic life goals were independent predictors of whether students used marijuana in the past 90 days. Students who reported high levels of meaning were less likely to have used marijuana in the past 90 days. For students who used marijuana, higher meaning ratings related to involvement in groups/organizations and fitness were correlated with decreased frequency of use. Moreover, ratings of efficacy related to self-

generated goals were associated with less frequent use among smokers. These results suggest that meaning related to life goal pursuit may be associated with students' decisions to use marijuana. Potential implications for interventions are discussed. Wright L, Palfai T. Life goal appraisal and marijuana use among college students. *Addict Behav.* 2012; 37(7): 797-802.

Associations Between Community Attachments and Adolescent Substance Use In Nationally Representative Samples

Social capital and social attachment theories of substance use argue that positive bonds to society and the conventional values they promote deter adolescents from substance use. Using nationally representative samples of U.S. high school seniors, the authors hypothesized that adolescents' community attachments, measured by social trust, social responsibility, and religiosity, would be negatively associated with lifetime and 30-day substance use. The authors used repeated cross-sectional nationally representative high school senior data from 1976 to 2008 Monitoring the Future Study cohorts (weighted N = 64,246; 51.6% female). Participation rate ranged from 77% to 86% across years. A series of multiple linear and logistic regressions examined unique associations of adolescents' social trust, social responsibility, and religiosity with lifetime and 30-day use of cigarettes, alcohol, marijuana, hallucinogens, cocaine, amphetamines, barbiturates, tranquilizers, and narcotics. Models controlled for gender, race, college aspirations, high school grades, parents' education, and survey year. Social trust, social responsibility, and religiosity showed independent negative associations with use of cigarettes, alcohol, marijuana, and six other types of drugs. After accounting for controls, community attachments related to lower lifetime and past 30-day use. Associations were consistent across measures, except social responsibility was not associated with binge drinking or lifetime illicit drugs besides marijuana. Study strengths included nationally representative samples, diverse substance use measures, and inclusion of controls. The authors extend the theory by suggesting that distinct aspects of adolescents' community attachments uniquely relate to lower substance use. Results suggest potential public health benefits of integrating promotion of community attachments with substance use prevention. Wray-Lake L, Maggs J, Johnston L, Bachman J, O'Malley P, Schulenberg J. Associations between community attachments and adolescent substance use in nationally representative samples. *J Adolesc Health.* 2012; 51(4): 325-331.

Translational Research in South Africa: Evaluating Implementation Quality Using a Factorial Design

HealthWise South Africa: Life Skills for Adolescents (HW) is an evidence-based substance use and sexual risk prevention program that emphasizes the positive use of leisure time. Since 2000, this program has evolved from pilot testing through an efficacy trial involving over 7,000 youth in the Cape Town area. Beginning in 2011, through 2015, the authors are undertaking a new study that expands HW to all schools in the Metro South Education District. This paper describes a research study designed in partnership with their South African collaborators that examines three factors hypothesized to affect the quality and fidelity of HW implementation: enhanced teacher training; teacher support, structure and supervision; and enhanced school environment. Teachers and students from 56 schools in the Cape Town area will participate in this study. Teacher observations are the primary means of collecting data on factors affecting implementation quality. These factors address the practical concerns of teachers and schools related to likelihood of use and cost-effectiveness, and are hypothesized to be "active ingredients" related to high-quality program implementation in real-world settings. An innovative factorial experimental design was chosen to enable estimation of the individual effect of each of the three factors. Because this paper describes the conceptualization of this study, results are not yet available. The results of this study may have both substantive and methodological implications for advancing Type 2 translational research. Caldwell L, Smith E,

Collins L, Graham J, Lai M, Wegner L, Vergnani T, Matthews C, Jacobs J. Translational research in South Africa: Evaluating implementation quality using a factorial design. *Child Youth Care Forum*. 2012; 41(2): 119-136.

Prevention of Smoking in Middle School Students: Psychometric Assessment of the Temptations to Try Smoking Scale

Establishment of psychometrically sound measures is critical to the development of effective interventions. The current study examined the psychometric properties, including factorial invariance, of a six item Temptations to Try Smoking Scale on a sample of middle school students. The sample of 6th grade students (N=3527) was from 20 Rhode Island middle schools and was 52% male and 84% white. The Temptations to Try Smoking Scale consisted of two correlated subscales: Positive Social and Curiosity/Stress. Structural equation modeling was implemented to evaluate the factorial invariance across four different subgroups defined by gender (male/female), race (white/black), ethnicity (Hispanic/Non-Hispanic), and school size (<200/ >200 6th graders). A model is factorially invariant when the measurement model is the same in each of the subgroups. Three levels of invariance were examined in sequential order: 1) Configural Invariance (unconstrained nonzero factor loadings); 2) Pattern Identity Invariance (equal factor loadings); and 3) Strong Factorial Invariance (equal factor loadings and measurement errors). Strong Factorial Invariance provided a good fit to the model across gender (CFI=.96), race (CFI=.96), ethnicity (CFI=.94), and school size (CFI=.97). Coefficient Alphas for the two subscales, Positive Social and Curiosity/Stress, were .87 and .86, respectively. These findings provide empirical support for the construct validity of the Temptations to Try Smoking Scale in middle school students. McGee H, Babbin S, Redding C, Paiva A, Oatley K, Meier K, Harrington M, Velicer W. Prevention of smoking in middle school students: Psychometric assessment of the Temptations to Try Smoking Scale. *Addict Behav*. 2012; 37(4): 521-523.

Drinking To Distraction: Does Alcohol Increase Attentional Bias In Adults With ADHD?

Previous research has shown that social drinkers continue to show attentional bias toward alcohol-related stimuli even after consuming a moderate dose of alcohol. In contrast, little is known about how alcohol acutely affects attentional bias in groups at risk to develop alcohol-related problems, such as adults with attention-deficit/hyperactivity disorder (ADHD). Such individuals may show increased attentional bias following alcohol relative to nonclinical controls. The present study tested this hypothesis by examining acute alcohol effects on attentional bias in 20 social drinkers with ADHD and 20 social drinkers with no history of ADHD. Participants performed a visual-probe task after receiving the following doses of alcohol: 0.64 g/kg, 0.32 g/kg, and 0.0 g/kg (placebo). Those in the ADHD group showed increased attentional bias under active alcohol doses, whereas attentional bias was similar across doses in the control group. Attentional bias predicted ad libitum alcohol consumption during a taste-rating session. This relation was observed only in the ADHD group. These findings indicate that an acute alcohol dose increases attentional bias in adults with ADHD. Further, attentional bias appears to be a predictor of ad libitum consumption in this group. Roberts W, Fillmore M, Milich R. Drinking to distraction: Does alcohol increase attentional bias in adults with ADHD?. *Exp Clin Psychopharmacol*. 2012; 20(2): 107-117

Correlates of Reasons for Not Reporting Rape to Police: Results from a National Telephone Household Probability Sample of Women With Forcible or Drug-or-Alcohol

Facilitated/Incapacitated Rape Rape tactics, rape incident characteristics, and mental health problems (lifetime depression, PTSD, and substance abuse) were investigated as correlates of eight different reasons for not reporting a rape to police among women who had experienced but did not report a rape to police (n = 441) within a national telephone household probability sample. Rape tactics (nonmutually exclusive) included drug or alcohol-facilitated or incapacitated rape (DAFR/IR; n = 119) and forcible rape (FR; n = 376). Principal Components Analysis (PCA) was conducted to extract a dominant set of patterns among the eight reasons for not reporting, and to reduce the set of dependent variables. PCA results indicated three unique factors: Not Wanting Others to Know, Nonacknowledgment of Rape, and Criminal Justice Concerns. Hierarchical regression analyses showed DAFR/IR and FR were both positively and significantly associated with Criminal Justice Concerns, whereas DAFR/IR, but not FR, was associated with Nonacknowledgment as a reason for not reporting to police. Neither DAFR/IR nor FR emerged as significant predictors of Others Knowing after controlling for fear of death or injury at the time of the incident. Correlations among variables showed that the Criminal Justice Concerns factor was positively related to lifetime depression and PTSD and the Nonacknowledgment factor was negatively related to lifetime PTSD. Findings suggest prevention programs should educate women about the definition of rape, which may include incapacitation due to alcohol or drugs, to increase acknowledgement and decrease barriers to police reporting. Cohn A, Zinzow H, Resnick H, Kilpatrick D. Correlates of reasons for not reporting rape to police: Results from a national telephone household probability sample of women with forcible or drug-or-alcohol facilitated/incapacitated rape. *J Interpers Violence*. 2012.

The What and the How of Dispositional Mindfulness: Using Interactions among Subscales of the Five-Facet Mindfulness Questionnaire to Understand Its Relation To Substance Use

Although self-report measures of dispositional mindfulness have good psychometric properties, a few studies have shown unexpected positive correlations between substance use and mindfulness scales measuring observation of present-moment experience. The current study tested the hypothesis that the relationship between present-moment observation and substance use is moderated by the tendency to be nonjudgmental and nonreactive toward the observed stimuli. Two hundred and ninety-six undergraduates completed the five-facet mindfulness questionnaire (FFMQ), a calendar measuring periods of substance use, and a measure of the five-factor model of personality. Controlling for FFMQ and personality subscales, significant interactions between the observing and nonreactivity subscales indicated that the observing subscale was negatively associated with substance use at higher levels of nonreactivity but positively associated with periods of substance use at lower levels of nonreactivity. Results support the use of statistical interactions among FFMQ subscales to test for the presence of interactive effects of different aspects of mindfulness. Eisenlohr-Moul T, Walsh E, Charnigo R, Lynam D, Baer R. The what and the how of dispositional mindfulness: Using interactions among subscales of the five-facet mindfulness questionnaire to understand its relation to substance use. *assessment*. 2012; 19(3): 276-286.

Psychiatric Disorders and Treatment Among Newly Homeless Young Adults With Histories Of Foster Care

Although foster care placement is often preceded by stressful events such as child abuse, foster care itself often exposes children to additional severe stressors. A history of foster care, as well as the childhood abuse that often precedes it, is common among homeless young adults. This study examined whether a history of foster care was associated with psychiatric

disorders, prior psychiatric counseling, prescription of psychiatric medications, and prior psychiatric hospitalization among newly homeless young adults. A consecutive sample of 423 adults aged 18 to 21 years who sought emergency shelter for the first time between October 1, 2007, and February 29, 2008, were assessed at intake. Logistic regression analyses determined the associations between foster care and any psychiatric disorder (affective, anxiety, personality, and psychotic) and psychiatric treatment. The analyses adjusted for demographic characteristics, childhood abuse, substance use, prior arrest, unemployment, lack of high school diploma, and histories of psychiatric disorders and drug abuse among biological relatives. Homeless young adults with histories of foster care were 70% more likely than those without such histories to report any psychiatric disorder. They were more than twice as likely to have received mental health counseling for a psychiatric disorder, to have been prescribed psychiatric medication, and to have been hospitalized for psychiatric problems. Histories of foster care among homeless young adults should trigger screening for psychiatric disorders to aid in the provision of treatment (counseling, medication, and hospitalization) tailored to the psychiatric needs of this highly vulnerable population. Thompson R, Hasin D. Psychiatric disorders and treatment among newly homeless young adults with histories of foster care. *Psychiatr Serv.* 2012; 63(9): 906-912.

BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH

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.

Tobacco Dependence Treatment for Korean Americans: Preliminary Findings The study was conducted to examine the relative effectiveness of cognitive behavior therapy with a cultural tailoring intervention compared to brief medication management. The study used a two-arm randomized controlled trial in which participant assignment was stratified by gender. The intervention condition received eight weekly 40-min individualized counseling sessions of culturally tailored cognitive behavior therapy, while the control condition received eight weekly 10-min individualized counseling sessions of medication management. Both conditions received nicotine patches for 8 weeks. Data were collected at baseline and at four follow-up points (one and 4 weeks, and three and 6 months post-quit). Treatment outcomes were presented as an intention-to-treat analysis. Thirty Korean immigrants participated in the study. At 6-month follow-up, 57.1% of participants in the intervention and 18.8% of participants in the control had 7-day point prevalence abstinence (odds ratio = 5.8, 95% confidence interval = 1.12-26.04, $P = 0.04$). Participants' self-reported abstinence was biochemically verified with exhaled carbon monoxide and salivary cotinine levels. A combination of the culturally tailored cognitive behavior therapy and nicotine replacement therapy had a better treatment outcome compared to brief medication management. The promising result suggests a need to further test the intervention in larger samples and longer follow-up assessments before it can be adapted in clinical settings. Kim SS, Kim SH, Ziedonis D. Tobacco dependence treatment for Korean Americans: Preliminary findings. *J Immigr Minor Health.* 2012 Jun; 14(3): 395-404.

Correlates of Tobacco Dependence and Motivation to Quit Among Young People Receiving Mental Health Treatment Young people with mental health concerns are at high-risk for initiation and continuation of tobacco use. To inform treatment needs, the current study sought to describe tobacco dependence, motivations to quit and associated sociodemographic factors among young people seen in mental health settings. Sixty adolescent and young adult smokers (age mean=19.5 years, range 13-25) receiving outpatient mental health treatment completed measures of tobacco dependence, motivation to quit smoking, mental health, and social environmental factors. Participants averaged 8.0 cigarettes per day ($SD=6.6$) and moderate nicotine dependence (mFTQ

M=4.8, SD=1.6). Participants' mean rating (10-point scales) of perceived difficulty with avoiding relapse during a quit attempt was significantly higher (M=6.7, SD=2.6), than ratings of desire (M=5.1, SD=2.6) and perceived success (M=4.6, SD=2.6) with quitting. Over half (52%) did not intend to quit smoking in the next 6 months, and few (11%) were prepared to quit in the next 30 days. Mental health treatment and symptomatology measures were unrelated to level of dependence or motivation to quit. Among the social environmental factors, having close friends who smoke was associated with greater perceived difficulty with avoiding relapse during a quit attempt ($r=0.25$, $p<0.01$). In this sample of adolescent and young adult smokers in mental health treatment, moderate levels of tobacco dependence and motivation to quit were observed and found to be unrelated to mental health measures. Over half of the sample was not intending to quit smoking in the near future, supporting the need for treatment strategies aimed at increasing motivation. Grana RA, Ramo DE, Fromont SC, Hall SM, Prochaska JJ. Correlates of tobacco dependence and motivation to quit among young people receiving mental health treatment. *Drug Alcohol Depend.* 2012 Sep 1; 125(1-2): 127-131.

Assessing the Role of Attention-Deficit/Hyperactivity Disorder Symptoms in Smokers with and without Posttraumatic Stress Disorder Smoking prevalence among individuals with posttraumatic stress disorder (PTSD) is elevated relative to non-PTSD smokers, and there is evidence to suggest that affect regulation may be a motivation for smoking among those with this disorder. Previous studies have also indicated that (a) PTSD is frequently comorbid with attention-deficit/hyperactivity disorder (ADHD), (b) individuals with ADHD smoke at significantly higher rates than the general population, (c) subclinical ADHD symptoms are a risk factor for smoking, and (d) affect regulation is a motivation for smoking in ADHD. The goal of this study was to assess the degree to which ADHD symptoms were uniquely associated with smoking-related affective functioning (SRAF) variables above and beyond the variance already explained by PTSD symptoms. Smokers with ($n = 55$) and without PTSD ($n = 68$) completed measures assessing PTSD symptoms, ADHD symptoms, and SRAF. The PTSD group endorsed significantly more severe levels of DSM-IV inattentive and hyperactive-impulsive ADHD symptoms. A series of hierarchical regressions among the entire sample indicated that, after accounting for PTSD symptoms, ADHD symptoms were associated with lower positive affect, higher negative affect, higher emotion dysregulation, higher anxiety sensitivity, and higher urges to smoke to increase positive affect. Taken together, these findings suggest that ADHD symptoms may increase affective dysregulation difficulties already faced by smokers, particularly those with PTSD, which may, in turn, confer increased risk for smoking relapse in those with higher levels of symptomatology of both disorders. Mitchell JT, Van Voorhees EE, Dennis MF, McClernon FJ, Calhoun PS, Kollins SH, Beckham JC. Assessing the role of attention-deficit/hyperactivity disorder symptoms in smokers with and without posttraumatic stress disorder. *Nicotine Tob Res.* 2012 Aug; 14(8): 986-992.

Combining Cognitive Behavioral Therapy and Contingency Management to Enhance Their Effects in Treating Cannabis Dependence: Less Can be More, More or Less The aim of this study was to evaluate reciprocal enhancement (combining treatments to offset their relative weaknesses) as a strategy to improve cannabis treatment outcomes. Contingency management (CM) with reinforcement for homework completion and session attendance was used as a strategy to enhance cognitive-behavioral therapy (CBT) via greater exposure to skills training; CBT was used as a strategy to enhance durability of CM with rewards for abstinence. The study setting was a community-based out-patient treatment program in New Haven, Connecticut, USA. The study design was a twelve-week randomized clinical trial of four treatment conditions: CM for abstinence

alone or combined with CBT, CBT alone or combined with CM with rewards for CBT session attendance and homework completion. A total of 127 treatment-seeking young adults (84.3% male, 81.1% minority, 93.7% referred by criminal justice system, average age 25.7 years) served as participants. Measures taken were weekly urine specimens testing positive for cannabis, days of cannabis use via the time-line follow-back method. Findings indicated that within treatment, reinforcing homework and attendance did not significantly improve CBT outcomes, and the addition of CBT worsened outcomes when added to CM for abstinence (75.5 versus 57.1% cannabis-free urine specimens, $F = 2.25$, $P = 0.02$). The CM for abstinence condition had the lowest percentage of cannabis-negative urine specimens and the highest mean number of consecutive cannabis-free urine specimens (3.3, $F = 2.33$, $P = 0.02$). Attrition was higher in the CBT alone condition, but random effect regression analyses indicated this condition was associated with the greatest rate of change overall. Cannabis use during the 1-year follow-up increased most rapidly for the two enhanced groups. The authors conclude that combining contingency management and cognitive-behavioural therapy does not appear to improve success rates of treatment for cannabis dependence in clients involved with the criminal justice system. Carroll KM, Nich C, Lapaglia DM, Peters EN, Easton CJ, Petry NM. Combining cognitive behavioral therapy and contingency management to enhance their effects in treating cannabis dependence: less can be more, more or less. *Addiction*. 2012 Sep; 107(9): 1650-1659.

Efficacy of Disulfiram and Twelve Step Facilitation in Cocaine-Dependent Individuals Maintained on Methadone: A Randomized Placebo-Controlled Trial

Cocaine use remains a major problem within methadone maintenance programs. Disulfiram's efficacy in reducing cocaine use has been demonstrated in several trials, but its relative efficacy among individuals who use versus abstain from alcohol remains unclear. Treatment approaches which seek to enhance substance users' involvement in self-help activities (Twelve Step Facilitation, TSF) have been associated with better outcomes among alcohol and cocaine users, but have rarely been evaluated among methadone-maintained cocaine-opioid users. The authors conducted a randomized, placebo-controlled, double blind (for medication condition), factorial (2x2) trial with 4 treatment conditions: Disulfiram plus TSF, disulfiram plus standard counseling only, placebo plus TSF, and placebo plus standard counseling in the context of a community-based methadone maintenance program. Participants (N=112) received either disulfiram (250mg/d) or placebo in conjunction with daily methadone maintenance. Assignment to TSF was associated with less cocaine use throughout treatment and a higher number of cocaine-negative urines. While there were no significant main effects of disulfiram versus placebo, individuals without an alcohol use disorder demonstrated greater reductions in cocaine use over time when assigned to disulfiram. The authors conclude that TSF appears feasible in this methadone maintenance program and was associated with modest reductions in cocaine use, an often intractable problem in this setting. Support for the efficacy of disulfiram was weaker, as it appeared effective only for those without a current alcohol use disorder for this sample. Carroll KM, Nich C, Shi JM, Eagan D, Ball SA. Efficacy of disulfiram and Twelve Step Facilitation in cocaine-dependent individuals maintained on methadone: A randomized placebo-controlled trial. *Drug Alcohol Depend*. 2012 Nov 1; 126(1-2): 224-231.

Moderating Effects of Race in Clinical Trial Participation and Outcomes among Marijuana-Dependent Young Adults

Few studies have examined clinical trial participation rates and treatment outcomes among underserved young adults who are dependent on marijuana, the most commonly abused illicit drug. The present study was a secondary analysis of a trial of court-referred marijuana-dependent young adults (ages 18-25) randomized to one of four treatment

conditions: Motivational Enhancement Therapy/Cognitive Behavioral Therapy (MET/CBT), MET/CBT+Contingency Management (CM), Drug Counseling (DC) or DC+CM. African American (N=81) participants were compared to White (N=31) participants with respect to rates of participation in phases of treatment and substance use outcomes. In addition, the interaction of race and treatment condition was examined to ascertain if the interventions yielded different effects based on race. Among those who started treatment, African American young adults were significantly less likely to complete the treatment and posttreatment phases of the clinical trial than their White counterparts. Irrespective of treatment type, substance use outcomes (i.e., percentage of marijuana-negative specimens and longest duration of continuous abstinence) did not vary by race. However, there was a significant interaction effect between treatment type and race; African American young adults did not benefit differentially from any specific type of treatment, but CM was effective in reducing proportion of marijuana positive samples among White young adults. Findings suggest that clinical trial treatment and posttreatment completion rates vary by race in this population, as does response to specific treatment types. More treatment research focusing specifically on African American marijuana-dependent young adults is warranted. Montgomery L, Petry NM, Carroll KM. Moderating effects of race in clinical trial participation and outcomes among marijuana-dependent young adults. *Drug Alcohol Depend.* 2012 Jun 26. [Epub ahead of print].

A Randomized Controlled Trial of a Tailored Group Smoking Cessation Intervention for HIV-Infected Smokers More than half of the persons living with human immunodeficiency virus (HIV; PLWH) in the US smoke cigarettes, and tobacco use is responsible for considerable morbidity and mortality in this group. Little is known about the efficacy of tobacco treatment strategies in PLWH. This was a randomized controlled trial comparing Positively Smoke Free (PSF), an intensive group-therapy intervention targeting HIV-infected smokers, to standard care. A cohort of 145 PLWH smokers, recruited from an HIV-care center in the Bronx, New York, were randomized 1:1 into the PSF program or standard care. All were offered a 3-month supply of nicotine replacement therapy. PSF is an 8-session program tailored to address the needs and concerns of HIV-infected smokers. The sessions were cofacilitated by a graduate student and an HIV-infected peer. The primary outcome was biochemically confirmed, 7-day point-prevalence abstinence at 3 months. In the intention-to-treat analysis, PSF condition subjects had nearly double the quit rate of controls (19.2% vs. 9.7%, $P = 0.11$). In the complete case, as-treated analysis, assignment to PSF was associated with increased odds of quitting (odds ratio(adj) 3.55, 95% confidence interval 1.04 to 12.0). Latino ethnicity and lower loneliness score were predictive of abstinence. The subjects in the PSF condition exhibited significant decreases in daily cigarette consumption and significant increases in self-efficacy and in motivation to quit. Attendance of ≥ 7 sessions was associated with higher quit rates. These findings suggest a positive effect of PSF on cessation rates in PLWH smokers. Loneliness and self-efficacy are influential factors in the smoking behaviors of PLWH. Moadel AB, Bernstein SL, Mermelstein RJ, Arnsten JH, Dolce EH, Shuter J. A randomized controlled trial of a tailored group smoking cessation intervention for HIV-infected smokers. *J Acquir Immune Defic Syndr.* 2012 Oct 1; 61(2): 208-215.

YMCA Commit to Quit: Randomized Trial Outcomes Vigorous-intensity exercise has been shown to aid in smoking cessation, especially among women. In a previous trial, cognitive behavioral therapy (CBT) for smoking cessation plus regular vigorous aerobic exercise enhanced cessation rates, improved exercise capacity, and reduced weight gain compared to CBT plus equal contact time. This study examined the effectiveness of this program adapted for and implemented

in the YMCAs. The study design was an RCT comparing CBT + Exercise (Exercise) to CBT + Contact Control (Control). Participants were apparently healthy female smokers recruited to four local YMCAs. YMCA staff members were trained to lead the manualized CBT smoking-cessation intervention and a standardized YMCA exercise program. Main outcome measures were seven-day point prevalence and continuous abstinence. Participants (330 women, mean age=44 years) were randomized to the Exercise (n=166) or Control (n=164) group. Results revealed no differences in 7-day point prevalence (29.5% vs 29.9%) nor continuous abstinence (13.9% vs 14.0%) between the Exercise and Control groups, respectively, at end of treatment or at the 3-, 6-and 12-month follow-up. An examination of the relationship between exercise dose and quit status at end of treatment revealed that over 12 weeks, the odds of being quit (7-day point prevalence) grew by 4.5% for each additional aerobic exercise session (OR=1.05, 95% CI=1.01, 1.08) and by 7.7% for each additional resistance training session (OR=1.08, 95% CI=1.02, 1.14). Analyses were conducted between August 19, 2010, and December 16, 2011. No differences were seen between groups in smoking outcomes. The association between greater exercise participation and higher odds of quitting within the exercise condition suggests that the lack of between-group differences might be a result of poor compliance with the exercise program. Whiteley JA, Williams DM, Dunsiger S, Jennings EG, Ciccolo JT, Bock BC, Albrecht A, Parisi A, Linke SE, Marcus BH. YMCA commit to quit: randomized trial outcomes. *Am J Prev Med.* 2012 Sep; 43(3): 256-262.

Factors Associated with Mental Health Clinicians' Referrals to 12-Step Groups As substance use and mental illness services are increasingly integrated, mental health professionals are presented with opportunities to refer greater numbers of dually diagnosed clients to 12-Step groups. This study examined the relationships among clinicians' 12-Step experiences, attitudes, and referral practices in 6 mental health clinics in New York, New York. A path analysis model showed that greater interest in learning about 12-Step groups directly predicted 12-Step referral practices and that 12-Step interest was predicted by clinicians' perception of the helpfulness of 12-Step groups and the severity of their patients' problems with substance abuse. Clinicians' responses to open-ended questions supported this model. Didactic and experiential education for clinicians in substance abuse and mutual aid would likely increase patient referrals to 12-Step groups. Matusow H, Rosenblum A, Fong C, Laudet A, Uttaro T, Magura S. Factors associated with mental health clinicians' referrals to 12-Step groups. *J Addict Dis.* 2012; 31(3): 303-312.

Integration of Parenting Skills Education and Interventions in Addiction Treatment Children of parents with substance use disorders are at risk for various adverse outcomes, and maladaptive parenting behaviors seem to be an important mediator of this risk. Although numerous research studies have highlighted the promise of parenting interventions in modifying parenting behavior, very little is known about the integration of parenting skills education and interventions into addiction treatment programs. In this study, a convenience sample of 125 addiction treatment programs in the United States was drawn. A key staff member was interviewed to gather basic information about the extent and nature of parenting skills education and interventions offered at their program. In addition, respondents were asked to rate the importance of parenting skills relative to other addiction treatment priorities. Descriptive analyses revealed that 43% reported some form of parenting classes, but few used a structured curriculum. Given the known beneficial influence of effective parenting practices on reducing adverse childhood outcomes, it is surprising that relatively few substance abuse treatment programs have adopted structured parenting skills interventions as part of their standard service offerings. More research is warranted on the extent to which parenting skills interventions are integrated into the continuum of services available to parents with a

substance use disorder. Arria AM, Mericle AA, Rallo D, Moe J, White WL, Winters KC, O'Connor G. Integration of parenting skills education and interventions in addiction treatment. *J Addict Med.* 2012 Oct 17. [Epub ahead of print].

Initiation of Abstinence in Adolescents Treated for Marijuana Use Disorders This study assessed the time to initiation of marijuana abstinence in an adolescent treatment-seeking sample, and identified variables that were predictive of abstinence. Adolescents (N=69), ages 14 to 18 were randomly assigned to one of two 14-week behavioral treatments. Abstinence was measured with twice weekly urine toxicology plus teen and parent reports. Discrete-time survival and hazard functions were conducted. The majority of adolescents achieved at least 1 week of abstinence, and 51% achieved 6 weeks of abstinence. Initiation of abstinence occurred by the sixth treatment week for 94% of teens with any abstinence suggesting that alternative, clinical approaches should be considered for those not responding by week 6. Teens with a drug negative urinalysis at intake, and teens that had two parents participating in treatment were more likely to achieve at least 6 weeks of abstinence. These findings, if replicated, can be used to inform clinical and research strategies that might lead to enhanced treatment efficacy and cost effectiveness for substance abuse treatment programming. Brown PC, Budney AJ, Thostenson JD, Stanger C. Initiation of abstinence in adolescents treated for marijuana use disorders. *J Subst Abuse Treat.* 2012 Oct 19. pii: S0740-5472(12)00376-5.

Clinical Correlates of Co-occurring Cannabis and Tobacco Use: A Systematic Review

A growing literature has documented the substantial prevalence of and putative mechanisms underlying co-occurring (i.e. concurrent or simultaneous) cannabis and tobacco use. Greater understanding of the clinical correlates of co-occurring cannabis and tobacco use may suggest how intervention strategies may be refined to improve cessation outcomes and decrease the public health burden associated with cannabis and tobacco use. A systematic review of the literature on clinical diagnoses, psychosocial problems and outcomes associated with co-occurring cannabis and tobacco use was performed. Twenty-eight studies compared clinical correlates in co-occurring cannabis and tobacco users versus cannabis- or tobacco-only users. These included studies of treatment-seekers in clinical trials and non-treatment-seekers in cross-sectional or longitudinal epidemiological or non-population-based surveys. Sixteen studies examined clinical diagnoses, four studies examined psychosocial problems and 11 studies examined cessation outcomes in co-occurring cannabis and tobacco users (several studies examined multiple clinical correlates). Relative to cannabis use only, co-occurring cannabis and tobacco use was associated with a greater likelihood of cannabis use disorders, more psychosocial problems and poorer cannabis cessation outcomes. Relative to tobacco use only, co-occurring use did not appear to be associated consistently with a greater likelihood of tobacco use disorders, more psychosocial problems or poorer tobacco cessation outcomes. Cannabis users who also smoke tobacco are more dependent on cannabis, have more psychosocial problems and have poorer cessation outcomes than those who use cannabis but not tobacco. The converse does not appear to be the case. Peters EN, Budney AJ, Carroll KM. Clinical correlates of co-occurring cannabis and tobacco use: a systematic review. *Addiction.* 2012 Aug; 107(8): 1404-1417.

The Co-occurring Use and Misuse of Cannabis and Tobacco: A Review Cannabis and tobacco use and misuse frequently co-occur. This review examines the epidemiological evidence supporting the life-time co-occurrence of cannabis and tobacco use and outlines the mechanisms that link these drugs to each other. Mechanisms include (i) shared genetic factors; (ii) shared environmental influences, including (iii) route of administration (via smoking), (iv) co-administration and (v)

models of co-use. Respiratory harms associated with co-use of cannabis and tobacco, overlapping withdrawal syndromes and outline treatment implications for co-occurring use were also discussed. Both cannabis and tobacco use and misuse are influenced by genetic factors, and a proportion of these genetic factors influence both cannabis and tobacco use and misuse. Environmental factors such as availability play an important role, with economic models suggesting a complementary relationship where increases in price of one drug decrease the use of the other. Route of administration and smoking cues may contribute to their sustained use. Similar withdrawal syndromes, with many symptoms in common, may have important treatment implications. Emerging evidence suggests that dual abstinence may predict better cessation outcomes, yet empirically researched treatments tailored for co-occurring use are lacking. There is accumulating evidence that some mechanisms linking cannabis and tobacco use are distinct from those contributing to co-occurring use of drugs in general. There is an urgent need for research to identify the underlying mechanisms and harness their potential etiological implications to tailor treatment options for this serious public health challenge. Agrawal A, Budney AJ, Lynskey MT. The co-occurring use and misuse of cannabis and tobacco: a review. *Addiction*. 2012 Jul; 107(7): 1221-1233.

Treatment Desires and Symptomatology among Substance-Abusing Homeless Mothers: What I Want Versus What I Need

The current study sought to identify information that may inform treatment providers regarding services for, and engagement of, substance-abusing homeless mothers. Shelter-recruited, substance-abusing homeless mothers' desires for treatment in several commonly reported problem areas including substance use, parenting, depressive symptoms/mood, physical health, and childhood abuse history were assessed. The correspondence between mother's desire for treatment and self-reported problem severity was also examined. The majority of mothers reported at least some desire (versus no desire at all) for assistance with substance use, depressive symptoms/mood, and parenting. A series of independent-sample t tests and chi-square tests showed that mothers indicating any treatment desire in the areas of substance use, depressive symptoms/mood, health problems, and sexual abuse also reported higher levels of severity in the corresponding problem areas. The findings imply that psychosocial treatment should be available to all homeless mothers entering the shelter system, especially given that problem severity appears to be a fair indicator of interest in treatment. Slesnick N, Guo X. Treatment desires and symptomatology among substance-abusing homeless mothers: What I want versus what I need. *J Behav Health Serv Res*. 2012 Oct 18. [Epub ahead of print].

Perceptions of Chronicity and Recovery among Youth in Treatment for Substance Use Problems

The aim of this study was to explore how youth contextualize substance use problems and recovery, in general and for themselves, in relation to the commonly accepted chronicity framework. Fourteen focus groups were conducted with 118 youth in substance abuse treatment settings (aged 12-24 years; 78.3% male; 66.1% Latino) located throughout diverse areas of Los Angeles County. Transcribed qualitative focus group data were analyzed for major substance use and recovery themes. Most (80%) youth do not accept a chronicity framework that conceptualizes substance use problems as recurring and constituting a lifelong illness. Most (65%) view substance use problems as a function of poor behavioral choices or a developmental/social lifestyle phase. Youth perceptions of recovery tend to parallel this view, as most define recovery to mean having an improved or changed lifestyle that is achieved through making better behavioral choices (67%) and exerting personal control over one's behavior (57%) through willpower, confidence, or discipline. Other recovery themes identified by youth were substance use related (47%), wellness or well-being

related (43%), and therapeutic or treatment related (14%). Findings highlight the importance of considering youth perceptions about substance use chronicity and recovery in making improvements and promoting new developments in clinical and recovery support approaches to better meet the needs of youth with substance use problems. Findings are discussed under a theoretical context of behavior change to provide insights for the treatment and recovery communities. Gonzales R, Anglin MD, Beattie R, Ong CA, Glik DC. Perceptions of chronicity and recovery among youth in treatment for substance use problems. *J Adolesc Health*. 2012 Aug; 51(2): 144-149.

Understanding Recovery Barriers: Youth Perceptions about Substance Use Relapse The aim of this study was to qualitatively explore how treatment-involved youth retrospectively contextualize relapse from substance use. Fourteen focus groups were conducted with 118 youth (78.3% male; 66.1% Latino) enrolled in participating substance abuse treatment programs (4 young adult and 10 adolescent) throughout Los Angeles County. Transcripts were analyzed for relapse perception themes. Dominant relapse themes include emotional reasons (90%), life stressors (85%), cognitive factors (75%), socialization processes (65%), and environmental issues (55%). Youth perceptions about relapse during treatment should be used to better inform clinical approaches and shape early-intervention recovery agendas for substance-abusing youth. Gonzales R, Anglin MD, Beattie R, Ong CA, Glik DC. Understanding recovery barriers: youth perceptions about substance use relapse. *Am J Health Behav*. 2012 Sep; 36(5): 602-614.

Maintenance of Reinforcement to Address the Chronic Nature of Drug Addiction Drug addiction can be a chronic problem. Abstinence reinforcement can initiate drug abstinence, but as with other treatments many patients relapse after the intervention ends. Abstinence reinforcement can be maintained to promote long-term drug abstinence, but practical means of implementing long-term abstinence reinforcement are needed. Eight clinical trials were conducted in Baltimore, MD from 1996 through 2010 that evaluated the therapeutic workplace as a vehicle for maintaining reinforcement for the treatment of drug addiction. The therapeutic workplace uses employment-based reinforcement in which employees must provide objective evidence of drug abstinence or medication adherence to work and earn wages. Employment-based reinforcement can initiate (3 of 4 studies) and maintain (2 studies) cocaine abstinence in methadone patients, although relapse can occur even after long-term exposure to abstinence reinforcement (1 study). Employment-based reinforcement can also promote abstinence from alcohol in homeless alcohol dependent adults (1 study), and maintain adherence to extended-release naltrexone in opioid dependent adults (2 studies). Treatments should seek to promote life-long effects in patients. Therapeutic reinforcement may need to be maintained indefinitely to prevent relapse. Workplaces could be effective vehicles for the maintenance of therapeutic reinforcement contingencies for drug abstinence and adherence to addiction medications. Silverman K, DeFulio A, Sigurdsson SO. Maintenance of reinforcement to address the chronic nature of drug addiction. *Prev Med*. 2012 Nov; 55 Suppl: S46-53.

The Use of Incentives to Reinforce Medication Adherence Poor medication adherence is a longstanding problem, and is especially pertinent for individuals with chronic conditions or diseases. Adherence to medications can improve patient outcomes and greatly reduce the cost of care. The purpose of the present review is to describe the literature on the use of incentives as applied to the problem of medication adherence. A systematic review was conducted of peer-reviewed empirical evaluations of incentives provided to patients contingent upon medication adherence. This review suggests that incentive-based medication adherence interventions can be

very effective, but there are few controlled studies. The studies on incentive-based medication adherence interventions most commonly feature patients taking medication for drug or alcohol dependence, HIV, or latent tuberculosis. Across studies that reported percent adherence comparisons, incentives increased adherence by a mean of 20 percentage points, but effects varied widely. Cross-study comparisons indicate a positive relationship between the value of the incentive and the impact of the intervention. Post-intervention evaluations were rare, but tended to find that adherence effects diminish after the interventions are discontinued. Incentive-based medication adherence interventions are promising but understudied. A significant challenge for research in this area is the development of sustainable and cost-effective long-term interventions. DeFulio A, Silverman K. The use of incentives to reinforce medication adherence. *Prev Med.* 2012 Nov; 55 Suppl: S86-94.

Fathers Entering Substance Abuse Treatment: An Examination of Substance Abuse, Trauma Symptoms and Parenting Behaviors

The relationship between fatherhood and both psychiatric distress and severity of substance abuse (SA) among men entering SA treatment has not been well explored. This study was designed to (a) examine differences in symptoms of men presenting for SA assessment based on fatherhood status and (b) determine how posttraumatic stress disorder (PTSD) symptoms and severity of SA were associated with parenting for men who were fathers. PTSD symptoms, severity of SA, and parenting data reported on structured questionnaires were collected from 126 men presenting for an SA evaluation at a forensic drug diversion clinic. There were no differences in severity of alcohol or drug use between fathers and nonfathers; however, fathers with more PTSD symptoms reported greater severity of alcohol and drug use. Among the fathers, PTSD symptoms correlated significantly and positively with negative parenting behaviors, whereas SA did not. Fathers with more significant PTSD symptoms were more likely to want help with parenting. Further exploration of the impact of trauma-related symptoms on the parenting behaviors of substance-abusing men is warranted. Stover CS, Hall C, McMahon TJ, Easton CJ. Fathers entering substance abuse treatment: An examination of substance abuse, trauma symptoms and parenting behaviors. *J Subst Abuse Treat.* 2012 Oct; 43(3): 335-343.

Attachment-based Intervention for Substance-using Mothers: A Preliminary Test of the Proposed Mechanisms of Change

Although randomized controlled trials examining the efficacy of attachment-based interventions have been increasing in recent years, adequate measurement of treatment integrity, integrity-outcome associations, and mechanisms of change has been rare. The aim of this investigation was to conduct a rigorous test of proposed mechanisms of change in the Mothers and Toddlers Program (MTP) treatment model, a 12-session, attachment-based individual therapy for substance-using mothers of children birth to 3 years of age. The MTP aims to improve maternal reflective functioning (RF) and representation quality (RQ) to bring about second-order change in maternal caregiving behavior. Following guidelines from M.K. Nock (2007), it was hypothesized that (a) therapist adherence to unique MTP treatment components would uniquely predict improvement in RF and RQ and that (b) improvement in RF and RQ would function as unique mechanisms of change (when compared with other potential mechanisms-reduction in depression and increase in abstinence from drug use) in the improvement of caregiving behavior. Findings supported each hypothesis, confirming the proposed mechanisms of the treatment model. However, improvement in maternal depression also uniquely predicted improvement in caregiving behavior. Results underscore the potential value of attachment-based parenting interventions for improving mother-child relations and the importance of providing these interventions in clinic settings where mothers have access to comprehensive care (e.g., psychiatric services). Suchman NE,

Decoste C, Rosenberger P, McMahon TJ. Attachment-based intervention for substance-using mothers: a preliminary test of the proposed mechanisms of change. *Infant Ment Health J.* 2012 Jul 1; 33(4): 360-371.

A Randomized Study of Contingency Management in Cocaine-Dependent Patients with Severe and Persistent Mental Health Disorders

Contingency management (CM) is efficacious for reducing drug use, but it has rarely been applied to patients with severe and persistent mental health problems. This study evaluated the efficacy of CM for reducing cocaine use in psychiatric patients treated at a community mental health center. Nineteen cocaine-dependent patients with extensive histories of mental health problems and hospitalizations were randomized to twice weekly urine sample testing with or without CM for 8 weeks. In the CM condition, patients earned the chance to win prizes for each cocaine-negative urine sample. Patients also completed an instrument assessing severity of psychiatric symptoms pre- and post-treatment. Patients assigned to CM achieved a mean (standard deviation) of 2.9 (1.7) weeks of continuous cocaine abstinence versus 0.6 (1.7) weeks for patients in the testing only condition, $p=.008$, Cohen's effect size $d=1.35$. Of the 16 expected samples, 46.2% (27.5) were cocaine negative in the CM condition versus 13.8% (27.9) in the testing only condition, $p=.02$, $d=1.17$, but proportions of negative samples submitted did not differ between groups. Reductions in psychiatric symptoms were noted over time in CM, but not the testing only, condition, $p=.02$. CM yielded benefits for enhancing durations of abstinence in dual diagnosis patients, and it also was associated with reduced psychiatric symptoms. These findings call for larger-scale and longer-term evaluations of CM in psychiatric populations. Petry NM, Alessi SM, Rash CJ. A randomized study of contingency management in cocaine-dependent patients with severe and persistent mental health disorders. *Drug Alcohol Depend.* 2012 Nov 19. [Epub ahead of print].

A Randomized Trial of Contingency Management Delivered by Community Therapists

Contingency management (CM) is an evidence-based treatment, but few clinicians deliver this intervention in community-based settings. Twenty-three clinicians from 3 methadone maintenance clinics received training in CM. Following a didactics seminar and a training and supervision period in which clinicians delivered CM to pilot patients, a randomized trial evaluated the efficacy of CM when delivered entirely by clinicians. Sixteen clinicians treated 130 patients randomized to CM or standard care. In both conditions, urine and breath samples were collected twice weekly for 12 weeks. In the CM condition, patients earned the opportunity to win prizes ranging in value from \$1 to \$100 for submitting samples negative for cocaine and alcohol. Primary treatment outcomes were retention, longest continuous period of abstinence, and proportion of negative samples submitted. Patients randomized to CM remained in the study longer (9.5 ± 3.6 vs. 6.7 ± 5.0 weeks), achieved greater durations of abstinence (4.7 ± 4.7 vs. 1.7 ± 2.7 weeks), and submitted a higher proportion of negative samples ($57.7\% \pm 40.0\%$ vs. $29.4\% \pm 33.3\%$) than those assigned to standard care. These data indicate that, with appropriate training, community-based clinicians can effectively administer CM. This study suggests that resources ought to be directed toward training and supervising community-based providers in delivering CM, as patient outcomes can be significantly improved by integrating CM in methadone clinics. Petry NM, Alessi SM, Ledgerwood DM. A randomized trial of contingency management delivered by community therapists. *J Consult Clin Psychol.* 2012 Apr; 80(2): 286-298.

A Randomized Trial Adapting Contingency Management Targets Based on Initial Abstinence Status of Cocaine-Dependent Patients

Contingency management (CM) reduces drug use, but questions remain regarding optimal targets and magnitudes of reinforcement. The authors evaluated the efficacy of CM reinforcing attendance in patients who initiated treatment with cocaine-negative samples, and of higher magnitude abstinence-based CM in patients who began treatment positive. Initially cocaine-negative patients (n = 333) were randomized to standard care (SC), SC + CM reinforcing submission of negative samples with \$250 in prizes (\$250Abs), or SC + CM reinforcing attendance (\$250Att). Initially cocaine-positive patients (n = 109) were randomized to SC, \$250Abs, or higher magnitude CM (\$560Abs). For initially cocaine-negative patients, \$250Abs and \$250Att were equally efficacious to SC in enhancing longest duration of abstinence (LDA); \$250Att patients submitted lower proportions of negative samples when missing samples were considered missing, but these patients also attended more study sessions, provided more samples, and submitted a higher proportion of negative samples than SC patients when expected samples were analyzed, $ps < .05$. In initially cocaine-positive patients, both CM conditions increased proportions of negative samples relative to SC when missing samples were excluded from analyses, but only \$560Abs was efficacious in increasing LDA and proportion of negative samples when expected samples were analyzed, $ps < .05$. Follow-ups revealed no differences among groups, but LDA was consistently associated with abstinence during follow-up, $p < .05$. High magnitude abstinence-based reinforcement improved all abstinence outcomes in patients who began treatment while using cocaine. For patients initiating treatment abstinent, both attendance- and abstinence-based CM resulted in improvements on some measures. Petry NM, Barry D, Alessi SM, Rounsaville BJ, Carroll KM. A randomized trial adapting contingency management targets based on initial abstinence status of cocaine-dependent patients. *J Consult Clin Psychol.* 2012 Apr; 80(2): 276-285.

Delay Discounting Decreases in those Completing Treatment for Opioid Dependence

Several studies examining both control and substance-dependent populations have found delay discounting to remain stable over time. In this report, the authors examine whether delay discounting changes in opioid-dependent individuals who complete a 12-week treatment. The 159 subjects who completed discounting assessments at baseline and treatment-end come from two separate clinical trials: 56 from Chopra et al. (2009) and 103 from Christensen et al. (2012). Mean discounting at 12 weeks significantly decreased to less than half (44.8%) of the baseline level (95% CIs (27.5, 73.2)). Analyzing each subject's discounting data individually, over 3 times (95% CIs (1.9, 5.5)) as many subjects statistically decreased their discounting from their own baseline levels than those who exhibited a statistical increase. Though the authors failed to find any relationship among discounting measures and abstinence outcomes, the results from this large study suggest that treatment for substance dependence promotes decreases in delay discounting. Landes RD, Christensen DR, Bickel WK. Delay discounting decreases in those completing treatment for opioid dependence. *Exp Clin Psychopharmacol.* 2012 Aug; 20(4): 302-309.

Employment-Based Reinforcement of Adherence to Oral Naltrexone Treatment in Unemployed Injection Drug Users

Oral naltrexone has high potential for use as a relapse prevention pharmacotherapy for opiate dependence yet suffers from notoriously poor adherence. This study evaluated whether entry to a therapeutic workplace could reinforce adherence with oral naltrexone. Opiate-dependent and cocaine-using injection drug users were detoxified, inducted onto oral naltrexone, and randomly assigned to a contingency (n = 35) or prescription (n = 32) group for a 26-week period. Contingency participants were required to ingest naltrexone under staff

observation to gain access to the therapeutic workplace. Prescription participants received a take-home supply of naltrexone and could access the workplace independent of naltrexone ingestion. Primary outcome measures were percent of urine samples positive for naltrexone at 30-day assessments and negative for opiates and cocaine at 30-day assessments. Contingency participants provided significantly more urine samples that were positive for naltrexone compared with prescription participants (72% vs. 21%, $p < .01$); however, no effect of experimental group was observed on percent opiate-negative (71% vs. 60%, $p = .19$.) or cocaine-negative (56% vs. 53%, $p = .82$) samples in the contingency and prescription groups, respectively. Opiate-positive samples were significantly more likely to occur in conjunction with cocaine ($p < .001$) and when not protected by naltrexone ($p < .02$), independent of experimental group. Overall, these results show that contingent access to a therapeutic workplace significantly promoted adherence to oral naltrexone, and that the majority of opiate use occurred in conjunction with cocaine use, suggesting that untreated cocaine use may limit the effectiveness of oral naltrexone in promoting opiate abstinence. Dunn KE, Defulio A, Everly JJ, Donlin WD, Aklin WM, Nuzzo PA, Leoutsakos JM, Umbricht A, Fingerhood M, Bigelow GE, Silverman K. Employment-based reinforcement of adherence to oral naltrexone treatment in unemployed injection drug users. *Exp Clin Psychopharmacol*. 2012 Dec 3. [Epub ahead of print].

Risk-Taking Propensity as a Predictor of Induction onto Naltrexone Treatment for Opioid Dependence

Heroin addiction is a chronic relapsing disorder that has devastating social, medical, and economic consequences. Naltrexone is an antagonist that blocks opioid effects and could be an effective medication for the treatment of opioid dependence. However, its clinical utility has been limited partly because of poor adherence and acceptability. Given the importance of compliance to naltrexone treatment for opioid dependence, the goal of the current study was to examine predictors involved in successful induction onto naltrexone treatment. Parametric and nonparametric statistical tests were performed on data from a sample of 64 individuals entering treatment who met DSM-IV criteria for opioid dependence. The relationship between naltrexone induction (i.e., inducted vs. not inducted onto naltrexone) and risk-taking propensity, as indexed by riskiness on the Balloon Analogue Risk Task (BART), was examined. Participants were recruited from local detoxification programs, inpatient drug treatment, and other Baltimore programs that provided services to opioid-dependent adults (e.g., Baltimore Needle Exchange Program) during the period from August 2007 to September 2008. A positive association was shown between risk-taking propensity and odds of naltrexone induction. Specifically, each 5-point increase in the total BART score was associated with a 25% decrease in odds of naltrexone induction (OR = 0.76; 95% CI, 0.58-0.99; $P = .041$). This association remained statistically significant, even after adjusting for potential confounds, including injection drug use and cocaine positive urine results ($P = .05$). After adjusting for the covariates, each 5-point increase in BART score was associated with 28% decrease in the odds of achieving the maintenance dose (adjusted OR = 0.73; 95% CI, 0.54-0.99; $P = .046$). Risk-taking propensity was predictive of induction onto naltrexone treatment, above and beyond injection drug use and cocaine-positive urine samples. Aklin WM, Severtson SG, Umbricht A, Fingerhood M, Bigelow GE, Lejuez CW, Silverman K. Risk-taking propensity as a predictor of induction onto naltrexone treatment for opioid dependence. *J Clin Psychiatry*. 2012 Aug; 73(8): e1056-1061.

Counseling and Directly Observed Medication for Primary Care Buprenorphine

Maintenance: A Pilot Study

Counseling and medication adherence can affect opioid agonist treatment outcomes. The authors investigated the impact of 2 counseling intensities and 2 medication-dispensing methods in patients receiving buprenorphine in primary care. In a 12-week trial, patients were assigned to physician management (PM) with weekly buprenorphine dispensing (n = 28) versus PM and directly observed, thrice-weekly buprenorphine (DOT) and cognitive-behavioral therapy (CBT) (PM+DOT/CBT; n = 27) based on therapist availability. Fifteen-minute PM visits were provided at entry, after induction, and then monthly. Cognitive-behavioral therapy was weekly 45-minute sessions provided by trained therapists. Treatment groups differed on baseline characteristics of years of opioid use, history of detoxification from opioids, and opioid negative urines during induction. Analyses adjusting for baseline characteristics showed no significant differences between groups on retention or drug use based on self-report or urines. Patient satisfaction was high across conditions, indicating acceptability of CBT counseling with observed medication. The number of CBT sessions attended was significantly associated with improved outcome, and session attendance was associated with a greater abstinence the following week. Although the current findings were nonsignificant, DOT and individual CBT sessions were feasible and acceptable to patients. Additional research evaluating the independent effect of directly observed medication and CBT counseling is needed. Moore BA, Barry DT, Sullivan LE, O'Connor PG, Cutter CJ, Schottenfeld RS, Fiellin DA. Counseling and directly observed medication for primary care buprenorphine maintenance: a pilot study. *J Addict Med.* 2012 Sep; 6(3): 205-211.

Technology-Based Extension of Motivational Interviewing to Reduce Non-injection Drug Use in HIV Primary Care Patients - A Pilot Study

To reduce non-injection drug use (NIDU) among HIV primary care patients, more than a single brief intervention may be needed, but clinic resources are often too limited for extended interventions. To extend brief motivational interviewing (MI) to reduce NIDU, the authors designed and conducted a pilot study of "HealthCall," consisting of brief (1-3 minutes) daily patient calls reporting NIDU and health behaviors to a telephone-based interactive voice response (IVR) system, which provided data for subsequent personalized feedback. Urban HIV adult clinic patients reporting ≥ 4 days of NIDU in the previous month were randomized to two groups: MI-only (n=20) and MI+HealthCall (n=20). At 30 and 60 days, patients were assessed and briefly discussed their NIDU behaviors with their counselors. The outcome was the number of days patients used their primary drug in the prior 30 days. Medical marijuana issues precluded HealthCall with patients whose primary substance was marijuana (n=7); excluding these, 33 remained, of whom 28 patients (MI-only n=17; MI+HealthCall n=11) provided post-treatment data for analysis. Time significantly predicted reduction in "days used" in both groups (p<0.0001). At 60 days, between-group differences approached trend level, with an effect size of 0.62 favoring the MI+HealthCall arm. This pilot study suggests that HealthCall is feasible and acceptable to patients in resource-limited HIV primary care settings and can extend patient involvement in brief intervention with little additional staff time. A larger efficacy trial of HealthCall for NIDU-reduction in such settings is warranted. Aharonovich E, Greenstein E, O'Leary A, Johnston B, Seol SG, Hasin DS. HealthCall: Technology-based extension of motivational interviewing to reduce non-injection drug use in HIV primary care patients - a pilot study. *AIDS Care.* 2012 Dec; 24(12): 1461-1469.

Developing and Implementing a Multispecialty Graduate Medical Education Curriculum on Screening, Brief Intervention, and Referral to Treatment (SBIRT)

The authors sought to evaluate the feasibility and acceptability of initiating a Screening, Brief Intervention, and Referral to Treatment (SBIRT) for alcohol and other drug use curriculum across multiple residency programs. SBIRT project faculty in the internal medicine (traditional, primary care internal medicine, medicine/pediatrics), psychiatry, obstetrics and gynecology, emergency medicine, and pediatrics programs were trained in performing and teaching SBIRT. The SBIRT project faculty trained the residents in their respective disciplines, accommodating discipline-specific implementation issues and developed a SBIRT training Web site. Post-training, residents were observed performing SBIRT with a standardized patient. Measurements included number of residents trained, performance of SBIRT in clinical practice, and training satisfaction. One hundred and ninety-nine residents were trained in SBIRT: 98 internal medicine, 35 psychiatry, 18 obstetrics and gynecology, 21 emergency medicine, and 27 pediatrics residents. To date, 338 self-reported SBIRT clinical encounters have occurred. Of the 196 satisfaction surveys completed, the mean satisfaction score for the training was 1.60 (1 = very satisfied to 5 = very dissatisfied). Standardized patient sessions with SBIRT project faculty supervision were the most positive aspect of the training and length of training was a noted weakness. Implementation of a graduate medical education SBIRT curriculum in a multispecialty format is feasible and acceptable. Future efforts focusing on evaluation of resident SBIRT performance and sustainability of SBIRT are needed. Tetrault JM, Green ML, Martino S, Thung SF, Degutis LC, Ryan SA, Martel S, Pantaloni MV, Bernstein SL, O'Connor PG, Fiellin DA, D'Onofrio G. Developing and implementing a multispecialty graduate medical education curriculum on Screening, Brief Intervention, and Referral to Treatment (SBIRT). *Subst Abus.* 2012; 33(2): 168-181.

A Pilot Trial of Integrated Behavioral Activation and Sexual Risk Reduction Counseling for HIV-Uninfected Men Who Have Sex with Men Abusing Crystal Methamphetamine

Crystal methamphetamine use is a major driver behind high-risk sexual behavior among men who have sex with men (MSM). Prior work suggests a cycle of continued crystal methamphetamine use and high-risk sex due to loss of the ability to enjoy other activities, which appears to be a side effect of this drug. Behavioral activation (BA) is a treatment for depression that involves learning to reengage in life's activities. The authors evaluated a novel intervention for crystal methamphetamine abuse and high-risk sex in MSM, incorporating 10 sessions of BA with integrated HIV risk reduction counseling (RR). Forty-four subjects were screened, of whom 21 met initial entry criteria. A total of 19 participants enrolled; 16 completed an open-phase study of the intervention. Behavioral assessments were conducted at baseline, 3 months post-baseline, and 6 months post-baseline. Linear mixed effects regression models were fit to assess change over time. Mean unprotected anal intercourse (UAI) episodes decreased significantly from baseline to acute post-intervention ($\beta=-4.86$; 95% confidence interval [CI]=-7.48, -2.24; $p=0.0015$) and from baseline to 6 months post-baseline ($\beta=-5.07$; 95% CI=-7.85, -2.29; $p=0.0017$; test of fixed effects $\chi(2)=16.59$; $df=2,13$; $p=0.0002$). On average, there was a significant decrease over time in the number of crystal methamphetamine episodes in the past 3 months ($\chi(2)=22.43$; $df=2,15$; $p<0.0001$), and the number of days of crystal methamphetamine use in the past 30 days ($\chi(2)=9.21$; $df=2,15$; $p=0.010$). Statistically significant reductions in depressive symptoms and poly-substance use were also maintained. Adding behavioral activation to risk reduction counseling for MSM with problematic crystal methamphetamine use may augment the potency of a risk reduction intervention for this population. Due to the small sample size and time intensive intervention, future testing in a randomized design is necessary to determine efficacy, with subsequent effectiveness testing.

Mimiaga MJ, Reisner SL, Pantalone DW, O'Cleirigh C, Mayer KH, Safren SA. A pilot trial of integrated behavioral activation and sexual risk Reduction Counseling for HIV-uninfected men who have sex with men abusing crystal methamphetamine. *AIDS Patient Care STDS*. 2012 Nov; 26(11): 681-693.

RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE

Extended-Release Mixed Amphetamine Salts and Topiramate For Cocaine Dependence: A Randomized Controlled Trial

Cocaine dependence is a substantial public health problem, yet there are no clearly effective medication treatments. Amphetamine and topiramate have both shown promise for the treatment of cocaine dependence in preclinical and early-stage clinical studies. Eighty-one cocaine-dependent adults were randomized to receive a combination of extended-release mixed amphetamine salts (MAS-ER) and topiramate or placebo for 12 weeks under double-blind conditions. MAS-ER doses were titrated over 2 weeks to a maximum dose of 60 mg daily, and topiramate doses were titrated over 6 weeks to a maximum dose of 150 mg twice daily. All participants received a supportive behavioral intervention. The primary outcome was the proportion of individuals who achieved 3 consecutive weeks of abstinence as measured by urine toxicology confirmed self-report. The overall proportion of participants who achieved 3 consecutive weeks of abstinence was larger in the extended-release mixed amphetamine salts and topiramate group (33.3%) than in placebo group (16.7%). There was a significant moderating effect of baseline total number of cocaine use days (Wald $\chi(2) = 3.75$, $df = 1$, $p = .05$) on outcome, suggesting that the combination treatment was most effective for participants with a high baseline frequency of cocaine use. The results of this study supported the authors' hypothesis that the combination of MAS-ER and topiramate would be superior to placebo in achieving 3 weeks of consecutive abstinence. These findings provide evidence that the combination of MAS-ER and topiramate is efficacious in promoting abstinence in cocaine-dependent individuals. Mariani JJ, Pavlicova M, Bisaga A, Nunes EV, Brooks DJ, Levin FR. Extended-release mixed amphetamine salts and topiramate for cocaine dependence: a randomized controlled trial. *Biol Psychiatry*. 2012 Dec 1; 72(11): 950-956. doi: 10.1016/j.biopsych.2012.05.032. Epub 2012 Jul 12.

Predictors of Marijuana Relapse in the Human Laboratory: Robust Impact of Tobacco

Cigarette Smoking Status

Few marijuana smokers in treatment achieve sustained abstinence yet factors contributing to high relapse rates are unknown. Study 1: data from five inpatient laboratory studies assessing marijuana intoxication withdrawal and relapse were combined to assess factors predicting the likelihood and severity of relapse. Daily nontreatment-seeking marijuana smokers ($n = 51$, 10 ± 5 marijuana cigarettes/day) were enrolled. Study 2: to isolate the effects of cigarette smoking marijuana intoxication withdrawal and relapse were assessed in daily marijuana and cigarette smokers ($n = 15$) under two within-subject counter-balanced conditions: while smoking tobacco cigarettes as usual (SAU) and after at least 5 days without cigarettes (Quit). Study 1: 49% of participants relapsed the first day active marijuana became available. Tobacco cigarette smokers (75%) who were not abstaining from cigarettes were far more likely to relapse than non-cigarette smokers (odds ratio: 19 $p < .01$). Individuals experiencing more positive subjective effects (i.e. feeling "high") after marijuana administration and those with more negative affect and sleep disruption during marijuana withdrawal were more likely to have severe relapse episodes ($p < .05$). Study 2: most participants (>87%) relapsed to marijuana whether in the SAU or Quit phase. Tobacco cigarette smoking did not significantly influence relapse nor did it affect marijuana intoxication or most symptoms of withdrawal relative to tobacco cessation. Daily marijuana smokers who also smoke cigarettes have high rates of marijuana relapse and cigarette smoking versus recent abstinence does not directly influence this association. These data indicate that current cigarette smoking is a clinically important marker for increased risk of marijuana relapse. Haney M, Bedi G, Cooper ZD, Glass A, Vosburg SK, Comer SD, Foltin RW. Predictors of marijuana relapse

in the human laboratory: robust impact of tobacco cigarette smoking status. *Biol Psychiatry* 2012 Aug, [Epub ahead of print].

Randomized Trial of Long-Acting Sustained-Release Naltrexone Implant Vs Oral Naltrexone or Placebo for Preventing Relapse to Opioid Dependence

Sustained-release naltrexone implants may improve outcomes of nonagonist treatment of opioid addiction. The objective of this study was to compare outcomes of naltrexone implants oral naltrexone hydrochloride and nonmedication treatment. This was a six-month double-blind double-dummy randomized trial conducted in addiction treatment programs in St Petersburg Russia. Participants were 306 opioid-addicted patients recently undergoing detoxification. Interventions comprised biweekly counseling and 1 of the following 3 treatments for 24 weeks: (1) 1000-mg naltrexone implant and oral placebo (NI+OP group, 102 patients), (2) placebo implant and 50-mg oral naltrexone hydrochloride (PI+ON group, 102 patients), or (3) placebo implant and oral placebo (PI+OP group, 102 patients). Main outcome measures were percentage of patients retained in treatment without relapse. By month 6, 54 of 102 patients in the NI+OP group (52.9%) remained in treatment without relapse compared with 16 of 102 patients in the PI+ON group (15.7%) (survival analysis log-rank test $P < .001$) and 11 of 102 patients in the PI+OP group (10.8%) ($P < .001$). The PI+ON vs PI+OP comparison showed a nonsignificant trend favoring the PI+ON group ($P = .07$). Counting missing test results as positive the proportion of urine screening tests yielding negative results for opiates was 63.6% (95% CI 60%-66%) for the NI+OP group, 42.7% (40%-45%) for the PI+ON group, and 34.1% (32%-37%) for the PI+OP group ($P < .001$ Fisher exact test compared with the NI+OP group). Twelve wound infections occurred among 244 implantations (4.9%) in the NI+OP group 2 among 181 (1.1%) in the PI+ON group and 1 among 148 (0.7%) in the PI+OP group ($P = .02$). All events were in the first 2 weeks after implantation and resolved with antibiotic therapy. Four local-site reactions (redness and swelling) occurred in the second month after implantation in the NI+OP group ($P = .12$) and all resolved with antiallergy medication treatment. Other nonlocal-site adverse effects were reported in 8 of 886 visits (0.9%) in the NI+OP group 4 of 522 visits (0.8%) in the PI+ON group and 3 of 394 visits (0.8%) in the PI+OP group, all resolved and none were serious. No evidence of increased deaths from overdose after naltrexone treatment ended was found. The authors concluded that the implant is more effective than oral naltrexone or placebo. More patients in the NI+OP than in the other groups develop wound infections or local irritation but none are serious and all resolve with treatment. Krupitsky E, Zvartau E, Blokhina E, Verbitskaya E, Wahlgren V, Tsoy-Podosenin M, Bushara N, Burakov A, Masalov D, Romanova T, Tyurina A, Palatkin V, Slavina T, Pecoraro A, Woody GE. Randomized trial of long-acting sustained-release naltrexone implant vs oral naltrexone or placebo for preventing relapse to opioid dependence. *Arch Gen Psychiatry* 2012 Sep, (9): 973-981.

Pharmacogenetic Randomized Trial for Cocaine Abuse: Disulfiram and Dopamine β -Hydroxylase

Disulfiram has been an effective cocaine addiction pharmacotherapy, and one of its possible mechanisms of efficacy is through copper chelation and inhibition of an enzyme involved in catecholamine metabolism, dopamine β -hydroxylase (D β H), which converts dopamine to norepinephrine. A variant in the gene encoding D β H leads to reduced D β H activity, and as such, disulfiram might not be an effective treatment of cocaine dependence for individuals with this variant. This study explored that potential matching. Seventy-four cocaine- and opioid-codependent (DSM-V) subjects were stabilized on methadone for 2 weeks and subsequently randomized into disulfiram (250 mg/day, $n = 34$) and placebo groups ($n = 40$) for 10 weeks. The authors genotyped the DBH gene polymorphism, -1021C/T (rs1611115), that reduces D β H enzyme levels and

evaluated its role for increasing cocaine free urines with disulfiram. With repeated measures analysis of variance, corrected for population structure, disulfiram pharmacotherapy reduced cocaine-positive urines from 80% to 62% ($p = .0001$), and this disulfiram efficacy differed by DBH genotype group. Patients with the normal D β H level genotype dropped from 84% to 56% on disulfiram ($p = .0001$), whereas those with the low DBH level genotype showed no disulfiram effect. This study indicates that the DBH genotype of a patient could be used to identify a subset of individuals for which disulfiram treatment might be an effective pharmacotherapy for cocaine dependence. Kosten TR, Wu G, Huang W, Harding MJ, Hamon SC, Lappalainen J, Nielsen DA. Pharmacogenetic randomized trial for cocaine abuse: disulfiram and dopamine β -hydroxylase. *Biol Psychiatry* 2012 Aug 17. [Epub ahead of print].

Combination of Modafinil and D-Amphetamine for the Treatment of Cocaine Dependence: A Preliminary Investigation Two stimulant medications modafinil and d-amphetamine when tested individually have shown safety and efficacy for treatment of cocaine addiction. The authors hypothesized that the combination of modafinil and d-amphetamine at low doses would show equivalent or greater benefit in reducing cocaine use compared to higher doses of each individual medication or placebo. The method used was a sixteen week randomized parallel-group design with four treatment arms comparing placebo to modafinil 400mg, d-amphetamine 60mg, modafinil 200mg plus d-amphetamine 30mg. Primary outcome variables retention and cocaine use were analyzed on the sample of 73 participants who received the first dose of the study medication. Retention rates did not differ between groups and were generally low with 40% remaining in treatment at week 12 and 20% at week 16. Participants receiving the combination of modafinil and d-amphetamine showed a trend of increased cocaine use over time with a corresponding low Bayesian probability of benefit (33%). Relatively better cocaine outcomes were observed in the placebo and d-amphetamine only groups. The study medications were generally well-tolerated with few adverse effects yet rates of adherence were suboptimal ($\leq 80\%$). Data from this preliminary investigation fail to provide evidential support for conducting a larger study of this dual-agonist medication combination for treatment of cocaine dependence. Schmitz JM, Rathnayaka N, Green CE, Moeller FG, Dougherty AE, Grabowski J. Combination of modafinil and d-amphetamine for the treatment of cocaine dependence: a preliminary investigation. *Front Psychiatry* 2012, [Epub ahead of print].

Effects of Chronic Buspirone Treatment on Cocaine Self-Administration Cocaine abuse and dependence is a major public health problem that continues to challenge medication-based treatment. Buspirone (Buspar) is a clinically available, non-benzodiazepine anxiolytic medication that acts on both serotonin and dopamine systems. In recent preclinical studies, acute buspirone treatment reduced cocaine self-administration at doses that did not also decrease food-reinforced behavior in rhesus monkeys (Bergman et al, 2012). The present study evaluated the effectiveness of chronic buspirone treatment on self-administration of cocaine and food. Five adult rhesus monkeys (*Macaca mulatta*) were trained to self-administer cocaine and food during four 1-h daily sessions under a second-order schedule of reinforcement (FR2 [VR 16:S]). Buspirone (0.32 and 0.56 mg/kg/h) was administered intravenously through one lumen of a double-lumen catheter every 20 min for 23 h each day for 7-10 consecutive days. Each buspirone treatment period was followed by saline control treatment until drug- and food-maintained responding returned to baseline levels. Buspirone significantly reduced responding maintained by cocaine, and shifted the dose-effect curve downwards. Buspirone had minimal effects on food-maintained responding. In cocaine discrimination studies, buspirone (0.1-0.32 mg/kg, IM) did not antagonize the discriminative

stimulus and rate-altering effects of cocaine in four of six monkeys. These findings indicate that buspirone selectively attenuates the reinforcing effects of cocaine in a nonhuman primate model of cocaine self-administration, and has variable effects on cocaine discrimination. Mello NK, Fivel PA, Kohut SJ, Bergman J. Effects of chronic buspirone treatment on cocaine self-administration. *Neuropsychopharmacology* advance online publication, 17 October 2012.

Assessment of Riboflavin as a Tracer Substance: Comparison of a Qualitative to a Quantitative Method of Riboflavin Measurement Noncompliance with medications may have major impacts on outcomes measured in research potentially distorting the validity of controlled clinical trials. Riboflavin is frequently used in trials as a marker of adherence. It can be combined with study medication and is excreted in urine where it fluoresces under UV light. This study compares qualitative visual inspection of fluorescence to quantitative fluorometric analysis of riboflavin concentration in its ability to detect the presence of riboflavin in urine. Twenty-four volunteers received 0mg 25mg and 50mg doses of riboflavin under single-blind conditions with 20 also receiving a 100mg dose. Five serial urine samples were collected over the following 36h. Quantitative measurement of riboflavin by fluorometric analysis and qualitative assessment of each sample using visual inspection were performed. The overall false positive rate for qualitative assessment was 53%. for quantitative assessment a riboflavin concentration of 900ng/mL was established to classify positive samples. More than 80% of samples were positive 2-24h following ingestion of 25mg and 50mg and less than 80% were positive at 36h. At least 95% of observations for the 100mg dose were above 900ng/mL at all timepoints. Quantitative fluorometric assessment is superior to qualitative visual inspection alone in determining medication adherence. The combination of 25-50mg of daily riboflavin and a cut-off level of 900ng/mL allows for the acceptable sensitivity of missing detection of non-compliant participants while preserving a high level of power to detect all cases of medication compliance. Herron AJ, Mariani JJ, Pavlicova M, Parrinello CM, Bold KW, Levin FR, Nunes EV, Sullivan MA, Raby WN, Bisaga A. Assessment of riboflavin as a tracer substance: comparison of a qualitative to a quantitative method of riboflavin measurement. *Drug Alcohol Depend* 2012 Aug, [Epub ahead of print].

Placebo-group Responders in Methamphetamine Pharmacotherapy Trials: The Role of Immediate Establishment of Abstinence Treatment responses of placebo groups in addiction medicine trials have important implications for research methodology and clinical practice, however studies examining placebo group responses in addiction medicine are scarce. Extant data suggest the importance of early treatment responsiveness for long-term outcomes. Among methamphetamine- (MA) dependent individuals randomized to placebo pill plus behavioral support conditions in pharmacotherapy development trials, the authors hypothesized that immediate abstinence would be a necessary but insufficient predictor for end-of-trial (EOT) abstinence. The study is a secondary analysis of participants (n = 184; 36% female) in the placebo condition of three randomized, placebo-controlled methamphetamine dependence pharmacotherapy trials. Receiver operating characteristic (ROC) curve analyses assessed the predictive power of initial abstinence, assessed by thrice weekly urine samples, for EOT abstinence. Sixty percent of individuals with complete abstinence in the first two weeks of treatment were abstinent at EOT, while 18% of people who failed to meet this standard were abstinent at EOT. Early response was related to retention at EOT and 12-month follow-up. Findings suggest that the inability to achieve at least three MA negative screenings in the first two weeks is associated with greater than 90% likelihood of treatment failure. A third week of screening added minimally to the prediction of EOT outcomes. The prediction of treatment failure was more precise than the prediction of treatment success. The

absence of a clinical response in the first two weeks of treatment among participants in the placebo group signals high risk of treatment failure. The majority of information regarding response in the placebo group from a 12-week trial is obtained early in the trial. Brensilver M, Heinzerling KG, Swanson AN, Shoptaw SJ. Placebo-group responders in methamphetamine pharmacotherapy trials: The role of immediate establishment of abstinence. *Exp Clin Psychopharmacol*. 2012 Oct; 20(5): 430-435. doi: 10.1037/a0029210. Epub 2012 Aug 6.

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, the authors 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, (7): 958-972.

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 Sep; 223(2): 179-190.

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 Dec; (3): 413-420.

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 [¹¹C]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. μ -Opioid receptor availability in the amygdala is associated with smoking for negative affect relief. *Psychopharmacology (Berl)* 2012 Aug; (4): 701-708.

DRD1 Associations with Smoking Abstinence Across Slow and Normal Nicotine Metabolizers

Nicotine metabolism and genetic variation have an impact on nicotine addiction and smoking abstinence, however further research is required. The nicotine metabolite ratio (NMR) is a robust biomarker of nicotine metabolism used to categorize slow and normal nicotine metabolizers (lower 25th quartile cut off). In two randomized clinical trials of smoking abstinence treatments the authors conducted NMR-stratified analyses on smoking abstinence across 13 regions coding for nicotinic acetylcholine receptors and proteins involved in the dopamine reward system. Gene \times NMR interaction P-values were adjusted for multiple correlated tests and we used a Bonferroni-corrected α -level of 0.004 to determine system-wide significance. Three single-nucleotide polymorphisms in DRD1 (rs11746641 rs2168631 and rs11749035) had significant interactions ($0.001 \leq$ adjusted P-values ≤ 0.004) with increased odds of abstinence within slow metabolizers (odds ratios=3.1-3.5 95% confidence interval 1.7-6.7). These findings support the role of DRD1 in nicotine dependence and identify genetic and nicotine metabolism profiles that may interact to impact nicotine dependence. Lee W, Ray R, Bergen AW, Swan GE, Thomas P, Tyndale RF, Benowitz NL, Lerman C, Conti DV. DRD1 associations with smoking abstinence across slow and normal nicotine metabolizers. *Pharmacogenet Genomics* 2012 Jul; (7): 551-554.

S-Adenosyl-L-Methionine (SAME) for Smoking Abstinence: A Randomized Clinical Trial

S-Adenosyl-L-methionine (SAME) is a dietary supplement commonly used to treat depression. SAME facilitates dopamine and norepinephrine synthesis in the central nervous system. This study investigated the efficacy of SAME for increasing tobacco abstinence among cigarette smokers. A randomized blinded placebo-controlled three-arm dose-ranging clinical trial was conducted. Subjects were randomly allocated to receive SAME 1600 mg or 800 mg by mouth every day or a matching placebo for 8 weeks. All subjects received a behavioral smoking cessation intervention. Self-reported smoking abstinence was biochemically confirmed with exhaled-air carbon monoxide. Subjects in the study comprised 120 adults. One hundred and twenty (120) subjects with a mean age of 40.0 ± 14.0 (SD) years were enrolled. Participants smoked an average of 19.6 ± 8.6 cigarettes per day for 21 ± 13.2 years. The study dropout rate was high (42.5%). By intention-to-treat analysis no significant differences were observed in abstinence rates at 8 and 24 weeks between SAME dose groups and placebo. SAME did not attenuate withdrawal symptoms among abstinent subjects. Rates of gastrointestinal side-effects were higher with SAME 1600 mg/d compared to placebo. SAME did not increase smoking abstinence rates. Abstinence and tobacco withdrawal data from this clinical trial suggest that SAME holds little promise for the treatment of tobacco dependence. Sood A, Prasad K, Croghan IT, Schroeder DR, Ehlers SL, Ebbert JO. S-Adenosyl-L-methionine (SAME) for smoking abstinence: A randomized clinical trial. *J Altern Complement Med* 2012 Sep; (9): 854-859.

Developing and Validating a Human Laboratory Model to Screen Medications for Smoking

Cessation To facilitate translational work in medications development for smoking cessation the authors have developed a human laboratory analogue of smoking lapse behavior. Their paradigm models 2 critical features of smoking lapse: the ability to resist the first cigarette and subsequent ad libitum smoking. In this paper the authors present the results of 2 studies designed to develop and validate the effect of nicotine deprivation on smoking lapse behavior. Study 1 (n = 30) was designed to develop the model parameters by examining varying levels of nicotine deprivation (1 6 and 18 hr, within-subject) and identifying optimum levels of monetary reinforcement to provide while modeling the ability to resist smoking. Study 2 was designed to validate the model by screening smoking cessation medications with known clinical efficacy. Subjects (n = 62) were randomized to

either varenicline 2 mg/day, bupropion 300 mg/day, or placebo and the authors then modeled their ability to resist smoking and subsequent ad libitum smoking. In Study 1 increasing levels of nicotine deprivation and decreasing levels of monetary reinforcement decreased the ability to resist smoking. In Study 2 the lapse model was found to be sensitive to medication effects among smokers who demonstrated a pattern of heavy uninterrupted and automated smoking (i.e. smoked within 5 min of waking). Ratings of craving mood withdrawal and subjective cigarette effects are presented as secondary outcomes with results mirroring clinical findings. This smoking lapse model demonstrates promise as a translational tool to screen novel smoking cessation medications. Next steps in this line of research will focus on evaluating predictive validity. McKee SA, Weinberger AH, Shi J, Tetrault J, Coppola S. Developing and validating a human laboratory model to screen medications for smoking cessation. *Nicotine Tob Res* 2012 Nov; (11): 1362-1371.

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, and 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 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 Aug; (4): 310-317.

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 Oct; (4): 427-438.

Alcohol-Induced Serotonergic Modulation: The Role of Histone Deacetylases Previous studies have demonstrated that alcohol use disorders (AUDs) are regulated by multiple mechanisms such as neurotransmitters and enzymes. The neurotransmitter, serotonin (5-hydroxytryptamine, 5-HT) may contribute to alcohol effects and serotonin receptors, including 5-HT₃, play an important role in AUDs. Recent studies have also implicated histone deacetylases (HDACs) and acetyltransferases (HATS) in regulation of drug addiction, and HDAC inhibitors (HDACi) have been reported as transcriptional modulators of monoaminergic neurotransmission. Therefore, the authors hypothesize that HDACs may play a role in ethanol-induced serotonergic modulation. The effects of ethanol on serotonin and 5-HT₃, and the role HDACs, HDAC activity and the HDACi, trichostatin A (TSA), play in alcohol-induced serotonergic effects were studied. Human SK-N-MC and neurons, were treated with ethanol (0.05, 0.1 and 0.2%), and/or TSA (50 nM), and 5-HT₃ levels were assessed at 24-72 h. Gene expression was evaluated by qRT-PCR and protein by western blot and flow cytometry. Serotonin release was assessed by ELISA and HDAC activity by fluorometric assay. These results show an increase in 5-HT₃ gene after ethanol treatment. Further, ethanol significantly increased HDACs 1 and 3 genes accompanied by an increased in HDAC activity while TSA significantly inhibited HDACs. Studies with TSA show a significant upregulation of ethanol effects on 5-HT₃, while surprisingly TSA inhibited ethanol-induced serotonin production. These results suggest that ethanol affects 5-HT₃ and serotonin through mechanisms involving HDACs and HATs. In summary, these studies demonstrate some of the novel properties of HDAC inhibitors and contribute to the understanding of the mechanisms involve in alcohol-serotonergic modulation in the CNS. Agudelo M, Yoo C, Nair MP. Alcohol-induced serotonergic modulation: the role of histone deacetylases. *Alcohol*. 2012 Nov; 46(7): 635-642. doi: 10.1016/j.alcohol.2012.03.005. Epub 2012 Jul 12.

P-glycoprotein is a Major Determinant of Norbuprenorphine Brain Exposure and Antinociception Norbuprenorphine is a major metabolite of buprenorphine and potent agonist of μ , δ , and κ opioid receptors. Compared with buprenorphine, norbuprenorphine causes minimal antinociception but greater respiratory depression. It is unknown whether the limited antinociception is caused by low efficacy or limited brain exposure. Norbuprenorphine is an in vitro substrate of the efflux transporter P-glycoprotein (Mdr1), but the role of P-glycoprotein in norbuprenorphine transport in vivo is unknown. This investigation tested the hypothesis that limited norbuprenorphine antinociception results from P-glycoprotein-mediated efflux and limited brain access. Human P-glycoprotein-mediated transport in vitro of buprenorphine, norbuprenorphine, and their respective glucuronide conjugates was assessed by using transfected cells. P-glycoprotein-mediated norbuprenorphine transport and consequences in vivo were assessed by using *mdr1a*(+/+) and *mdr1a*(-/-) mice. Antinociception was determined by hot-water tail-flick assay, and respiratory effects were determined by unrestrained whole-body plethysmography. Brain and plasma norbuprenorphine and norbuprenorphine-3-glucuronide were quantified by mass spectrometry. In vitro, the net P-glycoprotein-mediated efflux ratio for norbuprenorphine was nine, indicating significant efflux. In contrast, the efflux ratio for buprenorphine and the two glucuronide conjugates

was unity, indicating absent transport. The norbuprenorphine brain/plasma concentration ratio was significantly greater in *mdr1a(-/-)* than *mdr1a(+/+)* mice. The magnitude and duration of norbuprenorphine antinociception were significantly increased in *mdr1a(-/-)* compared with *mdr1a(+/+)* mice, whereas the reduction in respiratory rate was similar. Results show that norbuprenorphine is an *in vitro* and *in vivo* substrate of P-glycoprotein. P-glycoprotein-mediated efflux influences brain access and antinociceptive, but not the respiratory, effects of norbuprenorphine. Brown SM, Campbell SD, Crafford A, Regina KJ, Holtzman MJ, Kharasch ED. P-glycoprotein is a major determinant of norbuprenorphine brain exposure and antinociception. *J Pharmacol Exp Ther.* 2012 Oct; 343(1): 53-61. doi: 10.1124/jpet.112.193433. Epub 2012 Jun 27.

High Immunogenicity of Nicotine Vaccines Obtained by Intradermal Delivery with Safe Adjuvants

Immunotherapy for tobacco addiction may offer a safe, alternative treatment if the immunogenicity of the current nicotine vaccines can be improved. The authors show here that intradermal (ID) immunization induces the production of antibody directed against nicotine (NicAb) at a much higher level than conventional intramuscular (IM) immunization. The magnitude and duration of NicAb production was further increased robustly by non-inflammatory laser vaccine adjuvant (LVA), slightly inflammatory monophosphoryl lipid A (MPL) or a combination of MPL and CpG adjuvants. Consequently, significantly fewer vaccination doses were required to attain a high level of NicAb production for an extended period of time and reduce nicotine entry into the brain in the presence of LVA, MPL or MPL/CpG adjuvant, respectively. Yet, the potency of these adjuvants to augment ID nicotine vaccine immunogenicity came at the expense of local skin reactogenicity, with LVA causing little skin reaction and MPL/CpG stimulating overt skin irritation. These observations underscore a necessity of a balance between optimal adjuvant potency and undesired local reactogenicity. In summary, this study presents a novel approach to significantly improve nicotine vaccine immunogenicity by a combination of safe cutaneous vaccine adjuvants with ID immunization. Chen X, Pravetoni M, Bhayana B, Pentel PR, Wu MX. High immunogenicity of nicotine vaccines obtained by intradermal delivery with safe adjuvants vaccine. 2012 Oct 30. S0264-410X(12) 01529-0

Anti-Cocaine Antibody and Butyrylcholinesterase-Derived Cocaine Hydrolase Exert Cooperative Effects on Cocaine Pharmacokinetics and Cocaine-Induced Locomotor Activity in Mice

The authors are investigating treatments for cocaine abuse based on viral gene transfer of a cocaine hydrolase (CocH) derived from human butyrylcholinesterase, which can reduce cocaine-stimulated locomotion and cocaine-primed reinstatement of drug-seeking behavior in rats for many months. Here, in mice, they explored the possibility that anti-cocaine antibodies can complement the actions of CocH to reduce cocaine uptake in brain and block centrally-evoked locomotor stimulation. Direct injections of test proteins showed that CocH (0.3 or 1mg/kg) was effective by itself in reducing drug levels in plasma and brain of mice given cocaine (10mg/kg, s.c., or 20mg/kg, i.p.). Administration of cocaine antibody per se at a low dose (8mg/kg, i.p.) exerted little effect on cocaine distribution. However, a higher dose of antibody (12mg/kg) caused peripheral trapping (increased plasma drug levels), which led to increased cocaine metabolism by CocH, as evidenced by a 6-fold rise in plasma benzoic acid. Behavioral tests with small doses of CocH and antibody (1 and 8mg/kg, respectively) showed that neither agent alone reduced mouse locomotor activity triggered by a very large cocaine dose (100mg/kg, i.p.). However, dual treatment completely suppressed the locomotor stimulation. Altogether, the authors found cooperative and possibly synergistic actions that warrant further exploration of dual therapies for treatment of cocaine abuse. Brimijoin S, Orson F, Kosten TR, Kinsey B, Shen XY, White SJ, Gao Y. Anti-cocaine antibody

and butyrylcholinesterase-derived cocaine hydrolase exert cooperative effects on cocaine pharmacokinetics and cocaine-induced locomotor activity in mice. *Chem Biol Interact.* 2012 Aug 31. pii: S0009-2797(12)00153-6. [Epub ahead of print].

Combined Cocaine Hydrolase Gene Transfer and Anti-Cocaine Vaccine Synergistically Block

Cocaine-Induced Locomotion

Mice and rats were tested for reduced sensitivity to cocaine-induced hyper-locomotion after pretreatment with anti-cocaine antibody or cocaine hydrolase (CocH) derived from human butyrylcholinesterase (BChE). In Balb/c mice, direct i.p. injection of CocH protein (1 mg/kg) had no effect on spontaneous locomotion, but it suppressed responses to i.p. cocaine up to 80 mg/kg. When CocH was injected i.p. along with a murine cocaine antiserum that also did not affect spontaneous locomotion, there was no response to any cocaine dose. This suppression of locomotor activity required active enzyme, as it was lost after pretreatment with iso-OMPA, a selective BChE inhibitor. Comparable results were obtained in rats that developed high levels of CocH by gene transfer with helper-dependent adenoviral vector, and/or high levels of anti-cocaine antibody by vaccination with norcocaine hapten conjugated to keyhole limpet hemocyanin (KLH). After these treatments, rats were subjected to a locomotor sensitization paradigm involving a "training phase" with an initial i.p. saline injection on day 1 followed by 8 days of repeated cocaine injections (10 mg/kg, i.p.). A 15-day rest period then ensued, followed by a final "challenge" cocaine injection. As in mice, the individual treatment interventions reduced cocaine-stimulated hyperactivity to a modest extent, while combined treatment produced a greater reduction during all phases of testing compared to control rats (with only saline pretreatment). Overall, the present results strongly support the view that anti-cocaine vaccine and cocaine hydrolase vector treatments together provide enhanced protection against the stimulatory actions of cocaine in rodents. A similar combination therapy in human cocaine users might provide a robust therapy to help maintain abstinence. Carroll ME, Zlebnik NE, Anker JJ, Kosten TR, Orson FM, Shen X, Kinsey B, Parks RJ, Gao Y, Brimijoin S. Combined cocaine hydrolase gene transfer and anti-cocaine vaccine synergistically block cocaine-induced locomotion. *PLoS One.* 2012; 7(8): e43536. doi: 10.1371/journal.pone.0043536. Epub 2012 Aug 17.

Effects of Anti-Cocaine Vaccine and Viral Gene Transfer of Cocaine Hydrolase in Mice on

Cocaine Toxicity Including Motor Strength and Liver Damage

In developing an *in vivo* drug-interception therapy to treat cocaine abuse and hinder relapse into drug seeking provoked by re-encounter with cocaine, two promising agents are: (1) a cocaine hydrolase enzyme (CocH) derived from human butyrylcholinesterase and delivered by gene transfer; (2) an anti-cocaine antibody elicited by vaccination. Recent behavioral experiments showed that antibody and enzyme work in a complementary fashion to reduce cocaine-stimulated locomotor activity in rats and mice. The authors' present goal was to test protection against liver damage and muscle weakness in mice challenged with massive doses of cocaine at or near the LD50 level (100-120mg/kg, i.p.). They found that, when the interceptor proteins were combined at doses that were only modestly protective in isolation (enzyme, 1mg/kg; antibody, 8mg/kg), they provided complete protection of liver tissue and motor function. When the enzyme levels were ~400-fold higher, after *in vivo* transduction by adeno-associated viral vector, similar protection was observed from CocH alone. Gao Y, Geng L, Orson F, Kinsey B, Kosten TR, Shen X, Brimijoin S. Effects of anti-cocaine vaccine and viral gene transfer of cocaine hydrolase in mice on cocaine toxicity including motor strength and liver damage. *Chem Biol Interact.* 2012 Aug 23. pii: S0009-2797(12)00137-8. [Epub ahead of print].

Co-Administration of Morphine and Oxycodone Vaccines Reduces the Distribution Of 6-Monoacetylmorphine and Oxycodone to Brain in Rats

Opioid conjugate vaccines have shown promise in animal models as a potential treatment for opioid addiction. Individual vaccines are quite specific and each targets only a limited number of structurally similar opioids. Since opioid users can switch or transition between opioids, the authors studied a bivalent immunization strategy of combining 2 vaccines that could target several of the most commonly abused opioids; heroin, oxycodone and their active metabolites. Morphine (M) and oxycodone (OXY) haptens were conjugated to keyhole limpet hemocyanin (KLH) through tetraglycine (Gly)(4) linkers at the C6 position. Immunization of rats with M-KLH alone produced high titers of antibodies directed against heroin, 6-monoacetylmorphine (6-MAM) and morphine. Immunization with OXY-KLH produced high titers of antibodies against oxycodone and oxymorphone. Immunization with the bivalent vaccine produced consistently high antibody titers against both immunogens. Bivalent vaccine antibody titers against the individual immunogens were higher than with the monovalent vaccines alone owing, at least in part, to cross-reactivity of the antibodies. Administration of a single concurrent intravenous dose of 6-MAM and oxycodone to rats immunized with the bivalent vaccine increased 6-MAM, morphine and oxycodone retention in serum and reduced the distribution of 6-MAM and oxycodone to brain. Vaccine efficacy correlated with serum antibody titers for both monovalent vaccines, alone or in combination. Efficacy of the individual vaccines was not compromised by their combined use. Consistent with the enhanced titers in the bivalent group, a trend toward enhanced pharmacokinetic efficacy with the bivalent vaccine was observed. These data support the possibility of co-administering two or more opioid vaccines concurrently to target multiple abusable opioids without compromising the immunogenicity or efficacy of the individual components. Pravetoni M, Raleigh MD, Le Naour M, Tucker AM, Harmon TM, Jones JM, Birnbaum AK, Portoghese PS, Pentel PR. Co-administration of morphine and oxycodone vaccines reduces the distribution of 6-monoacetylmorphine and oxycodone to brain in rats. *Vaccine*. 2012 Jun 29; 30(31): 4617-4624.

A Methamphetamine Vaccine Attenuates Methamphetamine-Induced Disruptions in Thermoregulation and Activity in Rats

There are no approved pharmacotherapies for d-methamphetamine (METH) addiction and existing therapies have limited efficacy. Advances in using immunotherapeutic approaches for cocaine and nicotine addiction have stimulated interest in creating a similar approach for METH addiction. This study investigated whether active vaccination against METH could potentially attenuate responses to METH in vivo. Male Sprague Dawley rats (n = 32) received a four-boost series with one of three candidate anti-METH vaccines (MH2[R], MH6, and MH7) or a control keyhole limpet hemocyanin conjugate vaccine. Effects of METH on rectal temperature and wheel activity at 27°C ambient temperature were determined. The most efficacious vaccine, MH6, was then contrasted with keyhole limpet hemocyanin conjugate vaccine in a subsequent experiment (n = 16), wherein radiotelemetry determined home cage locomotor activity and body temperature at 23°C ambient temperature. The MH6 vaccine produced high antibody titers with nanomolar affinity for METH and sequestered METH in the periphery of rats. In experiment 1, the thermoregulatory and psychomotor responses produced by METH at 27°C were blocked in the MH6 group. In experiment 2, METH-induced decreases in body temperature and locomotor activity at 23°C were also attenuated in the MH6 group. A pharmacokinetic study in experiment 2 showed that MH6-vaccinated rats had higher METH serum concentrations, yet lower brain METH concentrations, than control rats, and METH concentrations correlated with individual antibody titer. These data demonstrate that active immunopharmacotherapy provides functional protection against physiological and behavioral disruptions induced by METH. Miller ML, Moreno

AY, Aarde SM, Creehan KM, Vandewater SA, Vaillancourt BD, Wright MJ Jr, Janda KD, Taffe MA. A methamphetamine vaccine attenuates methamphetamine-induced disruptions in thermoregulation and activity in rats. *Biol Psychiatry*. 2012 Oct 22. pii: S0006-3223(12)00803-7. doi: 10.1016/j.biopsych.2012.09.010. [Epub ahead of print]

A Vaccine Against Methamphetamine Attenuates its Behavioral Effects in Mice Vaccines have treatment potential for methamphetamine (MA) addiction. The authors tested whether a conjugate vaccine against MA (succinyl-methamphetamine-keyhole limpet hemocyanin carrier protein; SMA-KLH) would generate MA antibodies and alter MA-induced behaviors. Mice were injected with SMA-KLH and received booster administrations 3 and 20 weeks later. Serum antibody titers reached peak levels by 4-6 weeks, remained at a modest level through 18 weeks, peaked again at 22 weeks after the second boost, and were still elevated at 35 weeks. At 7 weeks, groups of vaccinated and non-vaccinated mice were administered one of three MA doses (1, 2 or 3mg/kg) to assess locomotor activity. Non-vaccinated mice showed dose-dependent effects of MA with hypolocomotion at the lowest dose and elevated activity levels at the highest dose. Both dose effects were reduced in SMA-KLH groups, particularly low dose-induced hypolocomotion at later times post MA administration. Separate groups of vaccinated and non-vaccinated mice were trained in MA place conditioning at 30 weeks with either 0 (vehicle) or 0.5mg/kg MA. Although times spent in the MA-paired side did not differ between groups on test vs. baseline sessions, SMA-KLH mice conditioned with MA showed reduced conditioned approach behaviors and decreased conditioned activity levels compared to control groups. These data suggest SMA-KLH attenuates the ability of MA to support place conditioning and reduces or delays its locomotor effects. Overall, results support SMA-KLH as a candidate MA vaccine. Shen XY, Kosten TA, Lopez AY, Kinsey BM, Kosten TR, Orson FM. A vaccine against methamphetamine attenuates its behavioral effects in mice. *Drug Alcohol Depend*. 2012 Sep 27. pii: S0376-8716(12)00371-7. doi: 10.1016/j.drugalcdep.2012.09.007. [Epub ahead of print].

Therapeutic Anti-Methamphetamine Antibody Fragment-Nanoparticle Conjugates:

Synthesis and In Vitro Characterization Treatments specific to the medical problems caused by methamphetamine (METH) abuse are greatly needed. Toward this goal, the authors are developing new multivalent anti-METH antibody fragment-nanoparticle conjugates with customizable pharmacokinetic properties. They have designed a novel anti-METH single chain antibody fragment with an engineered terminal cysteine (scFv6H4Cys). Generation 3 (G3) polyamidoamine dendrimer nanoparticles were chosen for conjugation due to their monodisperse properties and multiple amine functional groups. ScFv6H4Cys was conjugated to G3 dendrimers via a heterobifunctional PEG cross-linker that is reactive to a free amine on one end and a thiol group on the other. PEG modified dendrimers were synthesized by reacting the PEG cross-linker with dendrimers in a stoichiometric ratio of 11:1, which were further reacted with 3-fold molar excess of anti-METH scFv6H4Cys. This reaction resulted in a heterogeneous mix of G3-PEG-scFv6H4Cys conjugates (dendribodies) with three to six scFv6H4Cys conjugated to each dendrimer. The dendribodies were separated from the unreacted PEG modified dendrimers and scFv6H4Cys using affinity chromatography. A detailed in vitro characterization of the PEG modified dendrimers and the dendribodies was performed to determine size, purity, and METH binding function. The dendribodies were found to have affinity for METH identical to that of the unconjugated scFv6H4Cys in saturation binding assays, whereas the PEG modified dendrimers had no affinity for METH. These data suggest that an anti-METH scFv can be successfully conjugated to a PEG modified dendrimer nanoparticle with no adverse effects on METH binding properties. This study

is a critical step toward preclinical characterization and development of a novel nanomedicine for the treatment of METH abuse. Nanaware-Kharade N, Gonzalez GA 3rd, Lay JO Jr, Hendrickson HP, Peterson EC. Therapeutic anti-methamphetamine antibody fragment-nanoparticle conjugates: synthesis and in vitro characterization. *Bioconjug Chem.* 2012 Sep 19; 23(9): 1864-1872. Epub 2012 Aug 28.

Orally Active Metabotropic Glutamate Subtype 2 Receptor Positive Allosteric Modulators: Structure-Activity Relationships and Assessment in a Rat Model of Nicotine Dependence

Compounds that modulate metabotropic glutamate subtype 2 (mGlu(2)) receptors have the potential to treat several disorders of the central nervous system (CNS) including drug dependence. Herein the authors describe the synthesis and structure-activity relationship (SAR) studies around a series of mGlu(2) receptor positive allosteric modulators (PAMs). The effects of N-substitution (R(1)) and substitutions on the aryl ring (R(2)) were identified as key areas for SAR exploration (Figure 3). Investigation of the effects of varying substituents in both the isoindolinone (2) and benzisothiazolone (3) series led to compounds with improved in vitro potency and/or efficacy. In addition, several analogues exhibited promising pharmacokinetic (PK) properties. Furthermore, compound 2 was shown to dose-dependently decrease nicotine self-administration in rats following oral administration. These data, showing for the first time efficacy of an mGlu(2) receptor PAM in this in vivo model, suggest potential utility for the treatment of nicotine dependence in humans. Sidique S, Dhanya RP, Sheffler DJ, Nickols HH, Yang L, Dahl R, Mangravita-Novo A, Smith LH, D'Souza MS, Semenova S, Conn PJ, Markou A, Cosford ND. Orally active metabotropic glutamate subtype 2 receptor positive allosteric modulators: structure-activity relationships and assessment in a rat model of nicotine dependence. *J Med Chem.* 2012 Nov 26; 55(22): 9434-9445.

Interaction Between Behavioral and Pharmacological Treatment Strategies to Decrease Cocaine Choice in Rhesus Monkeys

Behavioral and pharmacotherapeutic approaches constitute two prominent strategies for treating cocaine dependence. This study investigated interactions between behavioral and pharmacological strategies in a preclinical model of cocaine vs food choice. Six rhesus monkeys, implanted with a chronic indwelling double-lumen venous catheter, initially responded under a concurrent schedule of food delivery (1-g pellets, fixed-ratio (FR) 100 schedule) and cocaine injections (0-0.1mg/kg/injection, FR 10 schedule) during continuous 7-day treatment periods with saline or the agonist medication phenmetrazine (0.032-0.1 mg/kg/h). Subsequently, the FR response requirement for cocaine or food was varied (food, FR 100; cocaine, FR 1-100; cocaine, FR 10; food, FR 10-300), and effects of phenmetrazine on cocaine vs food choice were redetermined. Decreases in the cocaine FR or increases in the food FR resulted in leftward shifts in the cocaine choice dose-effect curve, whereas increases in the cocaine FR or decreases in the food FR resulted in rightward shifts in the cocaine choice dose-effect curve. The efficacy of phenmetrazine to decrease cocaine choice varied systematically as a function of the prevailing response requirements, such that phenmetrazine efficacy was greatest when cocaine choice was maintained by relatively low unit cocaine doses. These results suggest that efficacy of pharmacotherapies to modulate cocaine use can be influenced by behavioral contingencies of cocaine availability. Agonist medications may be most effective under contingencies that engender choice of relatively low cocaine doses. Banks ML, Blough BE, Stevens Negus S. Interaction between behavioral and pharmacological treatment strategies to decrease cocaine choice in rhesus monkeys. *Neuropsychopharmacology.* 2012 Sep 12. doi: 10.1038/npp.2012.193.

High-Affinity and Selective Dopamine D3 Receptor Full Agonists The authors have designed, synthesized and evaluated a series of new compounds with the goal to identify potent and selective D(3) ligands. The two most potent and selective new D(3) ligands are compounds 38 and 52, which bind to the D(3) receptors with a $K(i)$ value of $<nM$ and display a selectivity of 450-494 times over the D(2) receptors and $>10,000$ times over the D(1) receptors. Both 38 and 52 are full agonists with high potency at the D(3) receptor in a D(3) functional assay. Chen J, Levant B, Wang S. High-affinity and selective dopamine D₃ receptor full agonists. *Bioorg Med Chem Lett*. 2012 Sep 1; 22(17): 5612-5617.

RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS

Methamphetamine Activates Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B Cells (NF- κ B) And Induces Human Immunodeficiency Virus (HIV) Transcription In Human Microglial Cells

Human immunodeficiency virus (HIV) primarily infects glial cells in the central nervous system (CNS). Recent evidence suggests that HIV-infected individuals who abuse drugs such as methamphetamine (METH) have higher viral loads and experience more severe neurological complications than HIV-infected individuals who do not abuse drugs. The aim of this study was to determine the effect of METH on HIV expression from the HIV long terminal repeat (LTR) promoter and on an HIV integrated provirus in microglial cells, the primary host cells for HIV in the CNS. Primary human microglial cells immortalized with SV40 T antigen (CHME-5 cells) were cotransfected with an HIV LTR reporter and the HIV Tat gene, a key regulator of viral replication and gene expression, and exposed to METH. These results demonstrate that METH treatment induced LTR activation, an effect potentiated in the presence of Tat. The authors also found that METH increased the nuclear translocation of the nuclear factor kappa B (NF- κ B), a key cellular transcriptional regulator of the LTR promoter, and the activity of an NF- κ B-specific reporter plasmid in CHME-5 cells. The presence of a dominant-negative regulator of NF- κ B blocked METH-related activation of the HIV LTR. Furthermore, treatment of HIV-latently infected CHME-5 (CHME-5/HIV) cells with METH induced HIV expression and nuclear translocation of the p65 subunit of NF- κ B. These results suggest that METH can stimulate HIV gene expression in microglia cells through activation of the NF- κ B signaling pathway. This mechanism may outline the initial biochemical events leading to the observed increased neurodegeneration in HIV-positive individuals who use METH. Wires ES, Alvarez D, Dobrowolski C, Wang Y, Morales M, Karn J, Harvey BK. Methamphetamine activates nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and induces human immunodeficiency virus (HIV) transcription in human microglial cells. *J Neurovirol.* 2012 Oct; 18(5): 400-410. doi: 10.1007/s13365-012-0103-4. Epub 2012 May 22.

Exosome-Mediated Shuttling Of MicroRNA-29 Regulates HIV Tat and Morphine-Mediated Neuronal Dysfunction

Neuronal damage is a hallmark feature of HIV-associated neurological disorders (HANDs). Opiate drug abuse accelerates the incidence and progression of HAND; however, the mechanisms underlying the potentiation of neuropathogenesis by these drugs remain elusive. Opiates such as morphine have been shown to enhance HIV transactivation protein Tat-mediated toxicity in both human neurons and neuroblastoma cells. In the present study, the authors demonstrate reduced expression of the tropic factor platelet-derived growth factor (PDGF)-B with a concomitant increase in miR-29b in the basal ganglia region of the brains of morphine-dependent simian immunodeficiency virus (SIV)-infected macaques compared with the SIV-infected controls. In vitro relevance of these findings was corroborated in cultures of astrocytes exposed to morphine and HIV Tat that led to increased release of miR-29b in exosomes. Subsequent treatment of neuronal SH-SY5Y cell line with exosomes from treated astrocytes resulted in decreased expression of PDGF-B, with a concomitant decrease in viability of neurons. Furthermore, it was shown that PDGF-B was a target for miR-29b as evidenced by the fact that binding of miR-29 to the 3'-untranslated region of PDGF-B mRNA resulted in its translational repression in SH-SY5Y cells. Understanding the regulation of PDGF-B expression may provide insights into the development of potential therapeutic targets for neuronal loss in HIV-1-infected opiate abusers. Hu G, Yao H, Chaudhuri AD, Duan M, Yelamanchili SV, Wen H, Cheney PD, Fox HS, Buch S. Exosome-

mediated shuttling of microRNA-29 regulates HIV Tat and morphine-mediated neuronal dysfunction. *Cell Death Dis.* 2012 August; 3(8): e381.

Changes In Sexual and Drug-Related Risk Behavior Following Antiretroviral Therapy

Initiation Among HIV-Infected Injection Drug User

The objective of this study was to evaluate whether HAART is associated with subsequent sexual and drug-related risk behavior compensation among injection drug users (IDUs). A community-based cohort study of 362 HIV-infected IDUs initiating HAART in Baltimore, Maryland was employed. HAART use and risk behavior was assessed at 8316 biannual study visits (median 23). Using logistic regression with generalized estimating equations (GEE), the authors examined the effect of HAART initiation on changes in risk behavior while adjusting for sociodemographics, alcohol use, CD4 cell count, year of initiation and consistency of HAART use. At HAART initiation, participants were a median of 44.4 years old, 71.3% men and 95.3% African-American. In multivariable analysis, HAART initiation was associated with a 75% reduction in the likelihood of unprotected sex [adjusted odds ratio (aOR) 0.25; 95% confidence interval (CI), 0.19-0.32] despite no change in overall sexual activity (aOR 0.95; 0.80-1.12). Odds of any injecting decreased by 38% (aOR 0.62; 0.51-0.75) after HAART initiation. Among the subset of persistent injectors, needle-sharing increased nearly two-fold (aOR 1.99; 1.57-2.52). Behavioral changes were sustained for more than 5 years after HAART initiation and did not differ by consistency of HAART use. Reporting specific high-risk behaviors in the year prior to initiation was a robust predictor of engaging in those behaviors subsequent to HAART. Overall, substantial declines in sexual risk-taking and active injecting argue against significant behavioral compensation among IDUs following HAART initiation. These data also provide evidence to support identifying persons with risky pre-HAART behavior for targeted behavioral intervention. Fu TC, Westergaard RP, Lau B, Celentano DD, Vlahov D, Mehta SH, Kirk GD. Changes in sexual and drug-related risk behavior following antiretroviral therapy initiation among HIV-infected injection drug users. *AIDS.* 2012 Nov 28; 26(18): 2383-2391. doi: 10.1097/QAD.0b013e32835ad438.

Racial/Ethnic Differences In Spontaneous HCV Clearance In HIV Infected and Uninfected

Women

Among individuals without human immunodeficiency virus (HIV), African Americans have lower spontaneous clearance of hepatitis C virus (HCV) than Caucasians, and women have higher clearance than men. Few studies report racial/ethnic differences in acute HCV in HIV infected, or Hispanic women. The authors examined racial/ethnic differences in spontaneous HCV clearance in a population of HCV mono- and co-infected women. They conducted a cross sectional study of HCV seropositive women (897 HIV infected and 168 HIV uninfected) followed in the US multicenter, NIH-funded Women's Interagency HIV Study (WIHS), to determine the association of race/ethnicity with spontaneous HCV clearance, as defined by undetectable HCV RNA at study entry. Among HIV and HCV seropositive women, 18.7 % were HCV RNA negative, 60.9 % were African American, 19.3 % Hispanic and 17.7 % Caucasian. HIV infected African American women were less likely to spontaneously clear HCV than Hispanic (OR 0.59, 95 % CI 0.38-0.93, $p = 0.022$) or Caucasian women (OR 0.57, 95 % CI 0.36-0.93, $p = 0.023$). Among HIV uninfected women, African Americans had less HCV clearance than Hispanics (OR 0.18, 95 % CI 0.07-0.48, $p = 0.001$) or Caucasians (OR 0.26, 95 % CI 0.09-0.79, $p = 0.017$). There were no significant differences in HCV clearance between Hispanics and Caucasians, among either HIV infected (OR 0.97, 95 % CI 0.57-1.66, $p = 0.91$) or uninfected (OR 1.45, 95 % CI 0.56-3.8, $p = 0.45$) women. African Americans were less likely to spontaneously clear HCV than Hispanics or Caucasians, regardless of HIV status. No significant differences in spontaneous HCV clearance were observed between

Caucasian and Hispanic women. Future studies incorporating IL28B genotype may further explain these observed racial/ethnic differences in spontaneous HCV clearance. Sarkar M, Bacchetti P, Tien P, Mileti E, French AL, Edlin BR, Keller M, Seaberg E, Nowicki MJ, Young M, Peters MG. Racial/ethnic differences in spontaneous HCV clearance in HIV infected and uninfected women. *Dig Dis Sci*. 2012 Nov 24. [Epub ahead of print].

Cocaine and HIV-1 Interplay in CNS: Cellular and Molecular Mechanisms Although antiretrovirals are the mainstay of therapy against HIV infection, neurological complications associated with the virus continue to hamper quality of life of the infected individuals. Drugs of abuse in the infected individuals further fuel the epidemic. Epidemiological studies have demonstrated that abuse of cocaine resulted in acceleration of HIV infection and the progression of NeuroAIDS. Cocaine has not only been shown to play a crucial role in promoting virus replication, but also has diverse but often deleterious effects on various cell types of the CNS. In the neuronal system, cocaine exposure results in neuronal toxicity and also potentiates gp120-induced neurotoxicity. In the astroglia and microglia, cocaine exposure leads to up-regulation of pro-inflammatory mediators such as cytokines and chemokines. These in turn, can lead to neuroinflammation and transmission of toxic responses to the neurons. Additionally, cocaine exposure can also lead to leakiness of the blood-brain barrier that manifests as enhanced transmigration of leukocytes/monocytes into the CNS. Both *in vitro* and *in vivo* studies have provided valuable tools in exploring the role of cocaine in mediating HIV-associated neuropathogenesis. This review summarizes previous studies on the mechanism(s) underlying the interplay of cocaine and HIV as it relates to the CNS. Buch S, Yao H, Guo M, Mori T, Mathias-Costa B, Singh V, Seth P, Wang J, Su TP. Cocaine and HIV-1 interplay in CNS: Cellular and molecular mechanisms. *Curr HIV Res*. 2012 Jul; 10(5): 425-428.

Enhanced Pulmonary Arteriopathy in Simian Immunodeficiency Virus-Infected Macaques Exposed to Morphine HIV-associated pulmonary arterial hypertension (PAH) is likely a more prevalent noninfectious complication of AIDS than previously recognized. Furthermore, the majority of HIV-PAH cases occur in individuals with a history of intravenous drug use. In this study the authors used a simian immunodeficiency (SIV) macaque model and a primary cell-culture system to investigate the association between drug abuse and HIV infection in HIV-PAH development. The archival lung tissues from macaques previously used to study the effect of morphine on SIV infection-associated neuropathogenesis were analyzed for pulmonary vascular changes. The direct effect of HIV proteins and illicit drugs was investigated on oxidative stress, survival, and proliferation of human pulmonary microvascular endothelial cells. SIVmacR71/17E-infected rhesus macaques treated with morphine (VM group) demonstrated significant pulmonary vascular remodeling, including the presence of early and advanced complex (plexiform) lesions, when compared with either the SIV-infected (V group) or morphine-treated uninfected (M group) macaques. However, both the V (two of five) and VM (two of six) groups included some animals with *Pneumocystis jirovecii* pneumonia. The endothelial cells lining the vessels with medial hypertrophy or initial-stage intimal lesions in lung sections from VM macaques demonstrated an increase in positivity for both terminal dUTP nick-end labeling and Ki67. Oxidative stress-mediated enhanced apoptosis followed by enhanced proliferation of endothelial cells was observed on simultaneous treatment with viral proteins and drugs of abuse compared with either treatment alone. These findings suggest that SIV/HIV protein(s) and morphine interact to cause the proliferation of apoptosis-resistant endothelial cells leading to angio-obliteration. Spikes L, Dalvi P, Tawfik O, Gu H, Voelkel NF, Cheney P, O'Brien-Ladner A, Dhillon NK. Enhanced pulmonary arteriopathy in

simian immunodeficiency virus-infected macaques exposed to morphine. *Am J Respir Crit Care Med.* 2012 Jun 1; 185(11): 1235-1243. Epub 2012 Mar 23.

HIV-Associated Nephropathy Patients With and Without Apolipoprotein L1 Gene Variants Have Similar Clinical and Pathological Characteristics

Recently, an association was found between nondiabetic kidney disease in African Americans and two independent sequence variants in the APOL1 gene, encoding apolipoprotein L1. In this study the authors determined the frequency of APOL1 risk variants in patients with biopsy-proven HIV-associated nephropathy (HIVAN) and distinctive pathological characteristics potentially driven by those risk variants. Among 76 patients with HIVAN, 60 were successfully genotyped for APOL1 G1 and G2 polymorphisms. In this cohort, 37 had two risk alleles, 18 were heterozygous, and 5 had neither risk variant. There were no differences in the pathological findings of HIVAN and the number of APOL1 risk alleles. Further, the progression to end-stage kidney disease or death did not differ by the number of risk alleles. Median renal survival was 9.3 months in patients with zero or one risk allele compared to 11.7 months in patients with two APOL1 risk alleles. Thus, this study suggests that although the majority of African-American patients with HIVAN have two APOL1 risk alleles other as yet unknown factors in the host, including genetic risk variants and environmental or viral factors, may influence the development of this disorder in those with zero or one APOL1 risk allele. Atta MG, Estrella MM, Kuperman M, Foy MC, Fine DM, Racusen LC, Lucas GM, Nelson GW, Warner AC, Winkler CA, Kopp JB. HIV-associated nephropathy patients with and without apolipoprotein L1 gene variants have similar clinical and pathological characteristics. *Kidney Int.* 2012 Aug; 82(3): 338-343. doi: 10.1038/ki.2012.111. Epub 2012 Apr 11.

Modulation of HIV Pathogenesis and T-Cell Signaling by HIV-1 Nef

HIV-1 Nef protein is an approximately 27-kDa myristoylated protein that is a virulence factor essential for efficient viral replication and infection in CD4(+) T cells. The functions of CD4(+) T cells are directly impeded after HIV infection. HIV-1 Nef plays a crucial role in manipulating host cellular machinery and in HIV pathogenesis by reducing the ability of infected lymphocytes to form immunological synapses by promoting virological synapses with APCs, and by affecting T-cell stimulation. This article reviews the current status of the efficient Nef-mediated spread of virus in the unreceptive environment of the immune system by altering CD4(+) T-lymphocyte signaling, intracellular trafficking, cell migration and apoptotic pathways. Saxena SK, Shrivastava G, Tiwari S, Swamy MA, Nair MP. Modulation of HIV pathogenesis and T-cell signaling by HIV-1 Nef. *Future Virol.* 2012 Jun 1; 7(6): 609-620.

Untreated HIV Infection is Associated with Higher Blood Alcohol Levels

Alcohol abuse has been associated with HIV/AIDS progression, but the effects of HIV infection and treatment on alcohol exposure have not been explored to date. This pilot study examines the relationship of untreated HIV infection to blood alcohol concentrations (BAC) relative to BAC after initiation of antiretroviral therapy (ART). Fifteen volunteers with untreated HIV/AIDS participated in 2 sets of alcohol or alcohol placebo administration studies before and after initiation of ART. Oral alcohol (1 g/kg) or alcohol placebo was administered, participants were followed for pharmacokinetics, subjective responses, and cognitive effects over 8 hours. After initial alcohol studies, the ART regimen selected by participant clinicians was instituted. Observed ART dosing took place for at least 2 weeks. Participants then returned for a second set of alcohol/placebo administration studies while on ART. Participants had significantly higher BAC ($P < 0.001$) before ART than after ART administration. Alcohol area under the curve was significantly higher in untreated HIV disease ($P =$

0.011) with significantly higher C(max) (P = 0.015) and C(min) (P = 0.05). The elimination rate was not different between pre-ART and post-ART conditions. Despite declines in BAC after ART initiation, no differences in subjective responses were observed with alcohol administration. Untreated HIV infection is associated with risk for higher BAC than that observed after ART. These findings indicate that patients with untreated HIV disease who ingest alcohol are at greater risk for alcohol associated adverse events and toxicities and underscores the need for simultaneous treatment of alcohol use disorders and HIV in patients with co-occurring conditions. McCance-Katz EF, Lum PJ, Beatty G, Gruber VA, Peters M, Rainey PM. Untreated HIV infection is associated with higher blood alcohol levels. *J Acquir Immune Defic Syndr.* 2012 Jul 1; 60(3): 282-288.

Impact of Protective Killer Inhibitory Receptor/Human Leukocyte Antigen Genotypes on Natural Killer Cell and T-Cell Function in HIV-1-Infected Controllers

Both protective T-cell genotypes and natural killer (NK) cell genotypes have been associated with delayed progression to AIDS and shown to be co-inherited in HIV-1-infected individuals who limit viral replication in absence of antiretroviral therapy ('controllers'). However, a comparative analysis of the genotype and function of the innate and adaptive immune compartments in HIV-1-infected controller individuals has been understudied to date. Here, the authors simultaneously tested NK and T-cell function in controllers to investigate the mechanism(s) that might account for host immune control over viral replication. They measured CD8 T-cell responses against HIV-1 utilizing overlapping 15-mer peptides spanning the HIV-1 consensus clade B Gag protein and tested NK cell degranulation and cytokine secretion against tumor target cells following interferon- α (IFN α) stimulation. Among a cohort of 37 controllers, the presence of protective major histocompatibility complex class I human leukocyte antigen (HLA) alleles (such as HLA-B*57) was not correlated with HIV-specific CD8 responses. In contrast, the inheritance of a protective killer inhibitory receptor KIR3DL1*h/*y receptor genotype along with the corresponding HLA-Bw4*80I ligand was associated with significantly heightened target cell-induced NK degranulation and cytokine secretion following IFN α stimulation (P = 0.0201, n = 13). Interestingly, the authors observed a significant inverse association between the IFN α stimulated NK response to K562 cells and the HIV-specific CD8 T-cell response to Gag among elite controllers (rho=-0.8321, P = 0.0010, n = 12). Together, these results suggest that heightened NK responses can be evidenced independently of HIV-specific T-cell responses in HIV-1-infected elite controllers. Tomescu C, Duh FM, Hoh R, Viviani A, Harvill K, Martin MP, Carrington M, Deeks SG, Montaner LJ. Impact of protective killer inhibitory receptor/human leukocyte antigen genotypes on natural killer cell and T-cell function in HIV-1-infected controllers. *AIDS.* 2012 Sep 24; 26(15): 1869-1878.

Inhibition of Nuclear Factor Erythroid 2-Related Factor 2 Exacerbates HIV-1 gp120-Induced Oxidative and Inflammatory Response: Role in HIV Associated Neurocognitive Disorder

The HIV epidemic continues to be the most severe public health problem and concern within USA and across the globe. In spite of the highly active antiretroviral therapy, HIV infected subjects experience major neurological complications that range from HIV associated dementia to moderate neurocognitive and motor impairments collectively termed as HIV associated neurocognitive disorders (HAND). Astrocytes play an important role in the neuropathogenesis of HAND. Further, in recent years it has been shown that oxidative stress plays a major role in the neuropathogenesis of HAND. Nuclear factor erythroid 2-related factor 2 (Nrf2), a leucine zipper redox-sensitive transcription factor, is an important regulator of cell survival and adaptive mechanisms and has been shown to possess a protective role in a variety of neurological and inflammatory disorders. Earlier

the authors have shown that Nrf2 is upregulated in response to HIV-1 gp120 and such upregulation of Nrf2 may be a protective mechanism against the HIV-induced oxidative stress. They hypothesize that Nrf2-mediated antioxidant pathways are important in regulating the HIV-induced oxidative stress and that the disruption of Nrf2 makes the cells more susceptible to HIV gp120-induced deleterious effects. Their results indicate that when astrocytes are exposed to gp120 there is an increase in the expression of NOX2, a subunit of NADPH oxidase, and also an upregulated expression of nuclear factor kappa B, tumor necrosis factor- α (TNF- α) and matrix metalloproteinase-9 (MMP-9). However, the degree of expression was significantly higher in those cells where Nrf2 was silenced by siRNA. Taken together, these results suggest a possible protective role of Nrf2 in regulating the levels of pro-oxidative and pro-inflammatory molecules in HAND. Reddy PV, Agudelo M, Atluri VS, Nair MP. Inhibition of nuclear factor erythroid 2-related factor 2 exacerbates HIV-1 gp120-induced oxidative and inflammatory response: role in HIV associated neurocognitive disorder. *Neurochem Res.* 2012 Aug; 37(8): 1697-1706. doi: 10.1007/s11064-012-0779-0. Epub 2012 Apr 25.

Relationship of Liver Disease Stage and Antiviral Therapy with Liver-Related Events and Death in Adults Coinfected with HIV/HCV

Human immunodeficiency virus (HIV) accelerates hepatitis C virus (HCV) disease progression; however, the effect of liver disease stage and antiviral therapy on the risk of clinical outcomes is incompletely understood. The objective of this study was to determine the incidence of end-stage liver disease (ESLD), hepatocellular carcinoma (HCC), or death according to baseline hepatic fibrosis and antiviral treatment for HIV/HCV coinfecting individuals. This was a prospective cohort study of 638 coinfecting adults (80% black, 66% men) receiving care at the Johns Hopkins HIV clinic and receiving a liver biopsy and who were prospectively monitored for clinical events between July 1993 and August 2011 (median follow-up, 5.82 years; interquartile range, 3.42-8.85 years). Histological specimens were scored for hepatic fibrosis stage according to the METAVIR scoring system. Main outcome measures were incidence of composite outcome of ESLD, HCC, or death. Patients experienced a graded increased risk in incidence of clinical outcomes based on baseline hepatic fibrosis stage (classification range, F0-F4): F0, 23.63 (95% CI, 16.80-33.24); F1, 36.33 (95% CI, 28.03-47.10); F2, 53.40 (95% CI, 33.65-84.76); F3, 56.14 (95% CI, 31.09-101.38); and F4, 79.43 (95% CI, 55.86-112.95) per 1000 person-years ($P < .001$). In multivariable negative binomial regression, fibrosis stages F2 through F4 and antiretroviral therapy were independently associated with composite ESLD, HCC, or all-cause mortality after adjustment for demographic characteristics, injection drug use, and CD4 cell count. Compared with F0, the incidence rate ratio (RR) for F2 was 2.31 (95% CI, 1.23-4.34; $P = .009$); F3, 3.18 (95% CI, 1.47-6.88; $P = .003$); and F4, 3.57 (95% CI, 2.06-6.19; $P < .001$). Human immunodeficiency virus treatment was associated with fewer clinical events (incidence RR, 0.27; 95% CI, 0.19-0.38; $P < .001$). For the 226 patients who underwent HCV treatment, the incidence of clinical events did not significantly differ between treatment nonresponders and untreated patients (incidence RR, 1.27; 95% CI, 0.86-1.86; $P = .23$). In contrast, no events were observed in the 51 patients with sustained virologic response ($n = 36$) and relapse ($n = 15$), including 19 with significant fibrosis. In this cohort of patients with HIV/HCV coinfection, hepatic fibrosis stage was independently associated with a composite outcome of ESLD, HCC, or death. Limketkai BN, Mehta SH, Sutcliffe CG, Higgins YM, Torbenson MS, Brinkley SC, Moore RD, Thomas DL, Sulkowski MS. Relationship of liver disease stage and antiviral therapy with liver-related events and death in adults coinfecting with HIV/HCV. *JAMA.* 2012 Jul 25; 308(4): 370-378.

Stability of Liver Fibrosis Among HCV-Infected Injection Drug Users There are few published data characterizing patterns of liver stiffness measurements (LSMs) among HCV-infected persons and their potential impact on clinical decisions (for example, deferring treatment and hepatocellular carcinoma surveillance). A total of 591 HCV-infected injection drug users in a community-based cohort had four LSMs. The authors used semi-parametric latent class growth modelling to identify patterns, which then became a gold standard against which they characterized validity of information from the initial measurements. Median age was 49, 68% were male, 92% African-American and 33% HIV-coinfected. The median LSM at visit 1 was 6.7 kPa (IQR 5.3-8.8). Over a median 1.75 years, LSM measures were stable; median change between visits was 0 kPa (IQR -1.4-1.7). Only 3% had evidence of fibrosis progression. Other groups included stable patterns of no fibrosis (59%), moderate fibrosis (21%), severe fibrosis (7%) and cirrhosis (9%). Individuals with fibrosis progression were more likely to be HIV-infected than those with stable low fibrosis ($P<0.001$). The diagnostic accuracy of the first LSM for identification of need for cancer surveillance (cirrhosis ≥ 12.3 kPa) was high (positive predictive value =97%). Although no single low LSM had high negative predictive value for significant fibrosis (metavir <2), individuals with two or more low results rarely had progression. These data underscore the stability of liver fibrosis in a cohort of predominantly African-American HCV-infected persons over 1.75 years, support using LSMs to monitor untreated persons at risk for progression and assess need for hepatocellular carcinoma surveillance. Mehta SH, Kirk GD, Astemborski J, Sulkowski MS, Afdhal NH, Thomas DL. Stability of liver fibrosis among HCV-infected injection drug users. *Antivir Ther.* 2012; 17(5): 813-821. doi: 10.3851/IMP2085. Epub 2012 Mar 15.

Virological Responses During Treatment for Recent Hepatitis C Virus: Potential Benefit for Ribavirin Use in HCV/HIV Co-Infection The role of ribavirin (RBV) in the treatment of recent hepatitis C virus (HCV) (acute/early chronic) is unclear, particularly in HIV-infected individuals. This study evaluated early virological decline during recent HCV therapy in HIV-uninfected individuals receiving pegylated interferon (PEG-IFN) monotherapy and HIV-infected individuals receiving PEG-IFN/RBV. The Australian Trial in Acute Hepatitis C was a nonrandomized prospective study of patients with recent HCV. All participants received PEG-IFN (24 weeks); HCV/HIV participants also received RBV. Early HCV RNA decline was assessed among adherent participants ($\geq 80\%$ PEG-IFN, $\geq 80\%$ treatment). Logistic regression identified predictors of rapid virological response (RVR) (<10 IU/ml). Of 109 treated, 82% were adherent (HCV, $n=57$; HCV/HIV, $n=32$). Overall, RVR was 51% (HCV: 55% vs. HCV/HIV: 43%; $P=0.323$). Factors independently associated with RVR included duration of infection less than 26 weeks, HCV RNA below 5.6 log(10) IU/ml at baseline and HCV genotype 2/3 infection. Between baseline and week 12, mean decline in HCV RNA was greater in HCV/HIV participants (PEG-IFN/RBV) compared to HCV participants (PEG-IFN) (4.19 vs. 3.32 log(10) IU/ml; $P=0.029$). Greater HCV RNA decline was observed in those treated with RBV, particularly amongst those with an estimated duration of infection at least 26 weeks and those with unfavourable IL28B genotypes. Adherent HIV-uninfected and infected participants had similar early virological response (76 vs. 90%; $P=0.102$) and sustained virological response (63 vs. 75%; $P=0.253$), respectively. RVR was highly predictive of sustained virological response (adjusted odds ratio 4.09; 1.49, 11.25). The results of this study suggest a potential benefit for PEG-IFN and RBV combination therapy in maximizing virological responses in HCV/HIV participants with recent HCV, particularly those with a longer duration of HCV infection and unfavourable IL28B genotypes. Grebely J, Hellard M, Applegate T, Petoumenos K, Yeung B, Feld JJ, Rawlinson W, Lloyd AR, George J, Kaldor JM, Dore GJ, Matthews GV;

ATAHC Study Group. Virological responses during treatment for recent hepatitis C virus: potential benefit for ribavirin use in HCV/HIV co-infection. *AIDS*. 2012 Aug 24; 26(13): 1653-1661.

Cohort Profile: The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC3) Study

The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC(3)) Study is an international multi-cohort project of pooled biological and behavioural data from nine prospective cohorts of people who inject drugs (PWID). InC(3) brings together researchers from Australia, Canada, USA and the Netherlands with expertise in epidemiology, biostatistics, clinical and behavioural sciences, virology and immunology to investigate research questions relevant to hepatitis C virus (HCV) and HIV outcomes. InC(3) was established to: (i) create a merged multi-cohort study of pooled data from well-characterized cohorts of PWID with prospective data on HIV and HCV infections, with a particular focus on HCV; (ii) facilitate new studies not possible within individual cohorts; and (iii) bring together researchers across disciplines to answer a broad range of research questions. Study cohorts identify acute HCV cases through follow-up of high-risk HCV antibody-negative PWID or through clinical referral networks. To date, data from 1986 to 2010 have been received from all contributing cohorts, with 821 HCV-infected and 1216 HCV-uninfected participants (overall, n = 2037). Data collected include demographics, host genetics, HCV ribonucleic acid testing, alanine aminotransferase testing, HIV/hepatitis B virus testing, HCV therapy, loss to follow-up and mortality. Grebely J, Morris MD, Rice TM, Bruneau J, Cox AL, Kim AY, McGovern BH, Shoukry NH, Lauer G, Maher L, Lloyd AR, Hellard M, Prins M, Dore GJ, Page K; on behalf of the InC Study Group. Cohort profile: The international collaboration of incident HIV and Hepatitis C in injecting cohorts (InC3) study. *Int J Epidemiol*. 2012 Nov 30. [Epub ahead of print] PMID: 23203695

Detection of Microbial Translocation in HIV and SIV Infection Using the Limulus Amebocyte Lysate Assay is Masked by Serum and Plasma

Microbial translocation (MT) is thought to be a major contributor to the pathogenesis of HIV-related immune activation, and circulating lipopolysaccharide (LPS) from gram-negative bacteria is the principle measurement of this process. However, related research has been impeded by inconsistent LPS test results. Specimens were obtained from HIV-infected adults enrolled in the PEARLS study (ACTG A5175) and HIV-HCV co-infected participants enrolled in a study of liver disease staging using MRI elastography. Pig-tailed macaque specimens were obtained from SIV-infected and -uninfected animals. Samples were tested for LPS using the LAL assay with diazo-coupling modifications to improve sensitive detection. When exogenous LPS was added to macaque plasma, >25% inhibition of LPS detection was found in 10/10 (100%) samples at 20% plasma concentration compared to control; in contrast 5/10 (50%) samples at 2% plasma concentration (p=0.07) and 0/10 (0%) at 0.1% plasma concentration (p=0.004) showed >25% inhibition of LPS detection. Similarly, when LPS was added to human serum, >25% inhibition of LPS detection was found in 5/12 (42%) of samples at 2% serum concentration compared to control, while 0/12 (0%) of samples in 0.1% serum showed >25% inhibition of LPS detection (p=0.07). Likewise, LPS detection in human sera without exogenous LPS was improved by dilution: LPS was detected in 2/12 (17%) human samples in 2% serum, ranging from 3,436-4,736 pg/mL, compared to 9/12 (75%) samples in 0.1% serum, ranging from 123 pg/mL -60,131 pg/mL (p=0.016). In a separate validation cohort of HIV-HCV co-infected participants sampled at two different times on the same day, LPS measured in 0.2% plasma and with diazo-coupling was closely correlated between the first and second samples (R=0.66, p<0.05). Undiluted serum and plasma mask LPS detection. The extent of MT may be substantially underestimated. Balagopal A, Gama L, Franco V, Russell JN, Quinn J, Higgins Y, Smeaton LM,

Clements JE, Thomas DL, Gupta A. Detection of microbial translocation in HIV and SIV infection using the Limulus amoebocyte lysate assay is masked by serum and plasma. *PLoS One*. 2012; 7(8): e41258. Epub 2012 Aug 1.

Discordance Between CD4+ T-lymphocyte Counts and Percentages in HIV-infected Persons with Liver Fibrosis

Cirrhosis of the liver can induce splenic sequestration of peripheral blood cells, recently suggested to reduce the number but not percentage of circulating CD4(+) T cells in persons uninfected with human immunodeficiency virus (HIV). The authors investigated whether earlier stages of liver fibrosis prior to cirrhosis were associated with discordance between CD4 count (CD4N) and CD4 percentage (CD4%) in HIV-infected patients. In cross-sectional analysis of 287 HIV-infected participants of the AIDS Linked to the Intravenous Experience cohort, the authors evaluated CD4N, CD4%, and transient elastography staging of liver fibrosis. High CD4(+) lymphocyte discordance was defined as higher CD4% relative to CD4N based on accepted clinical cutoffs; multivariable logistic regression was used to determine covariates associated with discordance. Of 287 participants, 99 (34.4%) had high CD4(+) discordance, which increased to 76% of 114 participants with marked lymphopenia (total lymphocyte count [TLC] ≤ 1200 cells/ μ L). In multivariable analysis, the odds of having high CD4(+) discordance was increased in persons with significant liver fibrosis compared to those without fibrosis (odds ratio, 1.69; 95% confidence interval [CI], .95-2.96); the odds ratio of discordance increased to 2.66 (95% CI, 1.11-6.40) among the subset of participants with TLC ≤ 1200 cells/ μ L. The odds for discordance associated with cirrhosis were of similar magnitude as those observed with significant fibrosis. In HIV-infected persons, liver fibrosis is associated with discordant peripheral CD4(+) lymphocyte results, especially in the setting of marked lymphopenia. Clinicians should also consider CD4% when interpreting absolute CD4(+) counts of HIV-infected persons with known or suspected liver disease, particularly if TLC is < 1200 cells/ μ L. Claassen CW, Diener-West M, Mehta SH, Thomas DL, Kirk GD. Discordance between CD4+ T-lymphocyte counts and percentages in HIV-infected persons with liver fibrosis. *Clin Infect Dis*. 2012 Jun; 54(12): 1806-1813. Epub 2012 Mar 28.

Buprenorphine for Human Immunodeficiency Virus/Hepatitis C Virus-Coinfected Patients: Does it Serve as a Bridge to Hepatitis C Virus Therapy?

Buprenorphine is associated with enhanced human immunodeficiency virus (HIV) treatment outcomes including increased antiretroviral therapy initiation rates, adherence, and CD4 cell counts among HIV-infected opioid-dependent individuals. Buprenorphine facilitates hepatitis C virus (HCV) treatment in opioid-dependent patients with HCV mono-infection. Less is known about buprenorphine's role in HIV/HCV coinfection. The authors conducted a retrospective chart review to evaluate HCV care for HIV-infected buprenorphine patients in the first 4 years of buprenorphine's integration into a Rhode Island HIV clinic. Sixty-one patients initiated buprenorphine. All had HCV antibody testing; 57 (93%) were antibody-positive. All antibody-positive patients underwent HCV RNA testing; 48 (84%) were RNA-positive. Of these, 15 (31%) were not referred to HCV care. Among chronically infected patients, 3 received HCV treatment after buprenorphine; all had cirrhosis and none achieved viral eradication. At buprenorphine induction, most patients had inadequately controlled HIV infection, with detectable HIV RNA (59%) or CD4 cell count less than or equal to 350/ μ L (38%). Buprenorphine has shown limited success to date as a bridge to HCV treatment within an HIV clinic. Buprenorphine's stabilization of opioid dependence and HIV disease may permit the use of HCV therapy over time. Taylor LE, Maynard MA, Friedmann PD, Macleod CJ, Rich JD, Flanagan TP, Sylvestre DL. Buprenorphine for human immunodeficiency virus/hepatitis C virus-

coinfecting patients: Does it serve as a bridge to hepatitis C virus therapy? *J Addict Med.* 2012 Sep; 6(3): 179-185. doi: 10.1097/ADM.0b013e318257377f.

Mortality in Hepatitis C Virus-Infected Patients with a Diagnosis of AIDS in the Era of Combination Antiretroviral Therapy

Before the introduction of combination antiretroviral therapy (cART), patients infected with the human immunodeficiency virus (HIV) rarely died of liver disease. In resource-rich countries, cART dramatically increased longevity. As patients survived longer, hepatitis C virus (HCV) infection became a leading cause of death; however, because patients with AIDS continue to have 5-fold greater mortality than non-AIDS patients, it is unclear whether HCV infection increases mortality in them. In this investigation, which is part of the Longitudinal Studies of the Ocular Complications of AIDS, plasma banked at enrollment from 2025 patients with AIDS as defined by the Centers for Disease Control and Prevention were tested for HCV RNA and antibodies. Three hundred thirty-seven patients had HCV RNA (chronic infection), 91 had HCV antibodies and no HCV RNA (cleared infection), and 1597 had no HCV markers. Median CD4(+) T-cell counts/ μ L were 200 (chronic), 193 (cleared), and 175 (no markers). There were 558 deaths. At a median follow-up of 6.1 years, patients with chronic HCV had a 50% increased risk of mortality compared with patients with no HCV markers (relative risk [RR], 1.5; 95% confidence interval [CI], 1.2-1.9; $P = .001$) in an adjusted model that included known risk factors. Mortality was not increased in patients with cleared infection (RR, 0.9; 95% CI, .6-1.5; $P = .82$). In patients with chronic HCV, 20.4% of deaths were liver related compared with 3.8% in patients without HCV. Chronic HCV infection is independently associated with a 50% increase in mortality among patients with a diagnosis of AIDS, despite competing risks. Effective HCV treatment may benefit HIV/HCV-coinfecting patients with AIDS. Branch AD, Van Natta ML, Vachon ML, Dieterich DT, Meinert CL, Jabs DA Mortality in hepatitis C virus-infected patients with a diagnosis of AIDS in the era of combination antiretroviral therapy. *Clin Infect Dis.* 2012 Jul; 55(1): 137-144. Epub 2012 Apr 24.

Acute Toxicant Exposure and Cardiac Autonomic Dysfunction from Smoking a Single Narghile Waterpipe with Tobacco and with a "Healthy" Tobacco-Free Alternative

Tobacco smoking using a waterpipe (narghile, hookah, shisha) has become a global epidemic. Unlike cigarette smoking, little is known about the health effects of waterpipe use. One acute effect of cigarette smoke inhalation is dysfunction in autonomic regulation of the cardiac cycle, as indicated by reduction in heart rate variability (HRV). Reduced HRV is implicated in adverse cardiovascular health outcomes, and is associated with inhalation exposure-induced oxidative stress. Using a 32 participant cross-over study design, the authors investigated toxicant exposure and effects of waterpipe smoking on heart rate variability when, under controlled conditions, participants smoked a tobacco-based and a tobacco-free waterpipe product promoted as an alternative for "health-conscious" users. Outcome measures included HRV, exhaled breath carbon monoxide (CO), plasma nicotine, and puff topography, which were measured at times prior to, during, and after smoking. The authors found that waterpipe use acutely decreased HRV ($p < 0.01$ for all measures), independent of product smoked. Plasma nicotine, blood pressure, and heart rate increased only with the tobacco-based product ($p < 0.01$), while CO increased with both products ($p < 0.01$). More smoke was inhaled during tobacco-free product use, potentially reflecting attempted regulation of nicotine intake. The data thus indicate that waterpipe smoking acutely compromises cardiac autonomic function, and does so through exposure to smoke constituents other than nicotine. Cobb CO, Sahmarani K, Eissenberg T, Shihadeh A. Acute toxicant exposure and cardiac autonomic dysfunction from smoking a single narghile waterpipe with tobacco and with a "healthy" tobacco-

free alternative. *Toxicol Lett.* 2012 Nov 23; 215(1): 70-75. doi: 10.1016/j.toxlet.2012.09.026. Epub 2012 Oct 8.

A Multiyear Survey of Waterpipe and Cigarette Smoking on a US University Campus

The objectives of this study were to examine the prevalence and characteristics of dual users of cigarettes and waterpipes by comparing them with individuals who use either product exclusively. Participants were cross-sections of undergraduate students at a public university recruited each spring semester from 2006 to 2011 (total N = 2,998). Participants completed an Internet survey that assessed demographics, tobacco use, perceptions, and norms concerning various tobacco products. Individuals who reported exclusive cigarette, exclusive waterpipe, and dual (waterpipe + cigarette) use were examined. Across years, 22% reported exclusive cigarette, 6.1% exclusive waterpipe, and 9.3% dual cigarette and waterpipe use. Dual users differed in demographics and social influences from their exclusive counterparts. Findings suggest that dual waterpipe and cigarette use was more prevalent than exclusive waterpipe use, and dual users may differ from individuals who use either product alone. These results warrant the inclusion of waterpipe-specific content in state and national surveys as well as tobacco prevention and intervention efforts. Cobb CO, Khader Y, Nasim A, Eissenberg T. A multiyear survey of waterpipe and cigarette smoking on a US university campus. *J Am Coll Health.* 2012; 60(7): 521-527.

An LC-MS/MS Method for Concurrent Determination of Nicotine Metabolites and the Role of CYP2A6 in Nicotine Metabolite-Mediated Oxidative Stress in SVGA Astrocytes

Nicotine is known to generate oxidative stress through cytochrome P450 2A6 (CYP2A6)-mediated metabolism in the liver and other organs, including macrophages. This study has been designed to examine the role of CYP2A6 in nicotine metabolism and oxidative stress in SVGA cells, an immortalized human astrocyte cell line. SVGA astrocytes were treated with 1 μ M nicotine, followed by determination of mRNA and protein levels of several CYPs using quantitative RT-PCR and western blot analyses, respectively. Quantitation of nicotine and the nicotine metabolites, cotinine and nicotine-derived nitrosamine ketones (NNK), was performed using an LC-MS/MS method. The generation of reactive oxygen species (ROS) was measured using flow cytometry. Nicotine significantly upregulated mRNA and protein expression of the most abundantly expressed CYPs in SVGA astrocytes, CYP2A6 and CYP1A1. To characterize the metabolism of nicotine in astrocytes, a highly sensitive LC-MS/MS method was developed which is capable of quantifying very low concentrations of nicotine (0.3 ng/mL), cotinine and NNK (0.11 ng/mL). The LC-MS/MS results showed that nicotine is steadily metabolized to cotinine and NNK from 0.5 to 4h. Finally, the authors showed that nicotine initially causes an increase in ROS formation which is then gradually decreased, perhaps due to the increase in superoxide dismutase level. Nicotine metabolism and ROS formation by CYP2A6 were further confirmed by using tryptamine, a selective inhibitor of CYP2A6, which significantly lowered the levels of cotinine and NNK and inhibited ROS formation. CYP2A6 plays a key role in nicotine metabolism and oxidative stress in astrocytes, and this has implications in nicotine-associated brain toxicity. Ande A, Earla R, Jin M, Silverstein PS, Mitra AK, Kumar A, Kumar S. An LC-MS/MS method for concurrent determination of nicotine metabolites and the role of CYP2A6 in nicotine metabolite-mediated oxidative stress in SVGA astrocytes. *Drug Alcohol Depend.* 2012 Sep 1; 125(1-2): 49-59. Epub 2012 Apr 11.

SERVICES RESEARCH

Interplay of Genetic Risk Factors (Chrna5-Chrna3-Chrnb4) and Cessation Treatments in Smoking Cessation Success

Smoking is highly intractable, and the genetic influences on cessation are unclear. Identifying the genetic factors affecting smoking cessation could elucidate the nature of tobacco dependence, enhance risk assessment, and support development of treatment algorithms. This study tested whether variants in the nicotinic receptor gene cluster CHRNA5-CHRNA3-CHRN4 predict age at smoking cessation and relapse after an attempt to quit smoking. In a community-based, cross-sectional study (N=5,216) and a randomized comparative effectiveness smoking cessation trial (N=1,073), the authors used Cox proportional hazard models and logistic regression to model the relationships of smoking cessation (self-reported quit age in the community study and point-prevalence abstinence at the end of treatment in the clinical trial) to three common haplotypes in the CHRNA5-CHRNA3-CHRN4 region defined by rs16969968 and rs680244. The genetic variants in the CHRNA5-CHRNA3-CHRN4 region that predict nicotine dependence also predicted a later age at smoking cessation in the community sample. In the smoking cessation trial, haplotype predicted abstinence at end of treatment in individuals receiving placebo but not among individuals receiving active medication. Haplotype interacted with treatment in affecting cessation success. Smokers with the high-risk haplotype were three times as likely to respond to pharmacologic cessation treatments as were smokers with the low-risk haplotype. The high-risk haplotype increased the risk of cessation failure, and this increased risk was ameliorated by cessation pharmacotherapy. By identifying a high-risk genetic group with heightened response to smoking cessation pharmacotherapy, this work may support the development of personalized cessation treatments. Chen L, Baker T, Piper M, Breslau N, Cannon D, Doheny K, Gogarten S, Johnson E, Saccone N, Wang J, Weiss R, Goate A, Bierut L. Interplay of genetic risk factors (CHRNA5-CHRNA3-CHRN4) and cessation treatments in smoking cessation success. *Am J Psychiatry*. 2012; 169 (7): 735-742.

Evaluating Brief Screeners to Discriminate Between Drug Use Disorders in a Sample Of Treatment-Seeking Adults

The objective of this study was to identify a potential core set of brief screeners for the detection of individuals with a substance use disorder (SUD) in medical settings. Data were from two multisite studies that evaluated stimulant use outcomes of an abstinence-based contingency management intervention as an addition to usual care (National Drug Abuse Treatment Clinical Trials Network trials 006:007). The sample comprised 847 substance-using adults who were recruited from 12 outpatient substance abuse treatment settings across the United States. Alcohol and drug use disorders were assessed by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Checklist. Data were analyzed by factor analysis, item response theory (IRT), sensitivity, and specificity procedures. Comparatively prevalent symptoms of dependence, especially inability to cut down for all substances, showed high sensitivity for detecting an SUD (low rate of false negative). IRT-defined severe (infrequent) and low discriminative items, especially withdrawal for alcohol, cannabis and cocaine, had low sensitivity in identifying cases of an SUD. IRT-defined less severe (frequent) and high discriminative items, including inability to cut down or taking larger amounts than intended for all substances and withdrawal for amphetamines and opioids, showed good-to-high values of area under the receiver operating characteristic curve in classifying cases and noncases of an SUD. Findings suggest the feasibility of identifying psychometrically reliable substance dependence symptoms to develop a two-item screen for alcohol and drug disorders. Wu L, Swartz MS, Pan J, Burchett B, Mannelli P, Yang C, Blazer DG.

Evaluating brief screeners to discriminate between drug use disorders in a sample of treatment-seeking adults. *Gen Hosp Psychiatry*. 2012; epub ahead of print.

A Pilot Cohort Study of the Determinants of Longitudinal Opioid Use After Surgery

Determinants of the duration of opioid use after surgery have not been reported. The authors hypothesized that both preoperative psychological distress and substance abuse would predict more prolonged opioid use after surgery. Between January 2007 and April 2009, a prospective, longitudinal inception cohort study enrolled 109 of 134 consecutively approached patients undergoing mastectomy, lumpectomy, thoracotomy, total knee replacement, or total hip replacement. The authors measured preoperative psychological distress and substance use, and then measured the daily use of opioids until patients reported the cessation of both opioid consumption and pain. The primary end point was time to opioid cessation. All analyses were controlled for the type of surgery done. Overall, 6% of patients continued on new opioids 150 days after surgery. Preoperative prescribed opioid use, depressive symptoms, and increased self-perceived risk of addiction were each independently associated with more prolonged opioid use. Preoperative prescribed opioid use was associated with a 73% (95% confidence interval [CI] 0.51%-87%) reduction in the rate of opioid cessation after surgery ($P = 0.0009$). Additionally, each 1-point increase (on a 4-point scale) of self-perceived risk of addiction was associated with a 53% (95% CI 23%-71%) reduction in the rate of opioid cessation ($P = 0.003$). Independent of preoperative opioid use and self-perceived risk of addiction, each 10-point increase on a preoperative Beck Depression Inventory II was associated with a 42% (95% CI 18%-58%) reduction in the rate of opioid cessation ($P = 0.002$). The variance in the duration of postoperative opioid use was better predicted by preoperative prescribed opioid use, self-perceived risk of addiction, and depressive symptoms than postoperative pain duration or severity. Preoperative factors, including legitimate prescribed opioid use, self-perceived risk of addiction, and depressive symptoms each independently predicted more prolonged opioid use after surgery. Each of these factors was a better predictor of prolonged opioid use than postoperative pain duration or severity. Carroll I, Barelka P, Wang C, Wang B, Gillespie M, McCue R, Younger J, Trafton J, Humphreys K, Goodman S, Dirbas F, Whyte R, Donington J, Cannon W, Mackey S. A Pilot cohort study of the determinants of longitudinal opioid use after surgery. *Anesth Analg*. 2012; 115 (3): 694-702.

HIV Rapid Testing with Information Only in Substance Abuse Treatment Programs Is Cost Effective Compared with Off-Site Referral

The President's National HIV/AIDS Strategy calls for coupling HIV screening and prevention services with substance abuse treatment programs. Fewer than half of US community-based substance abuse treatment programs make HIV testing available on-site or through referral. The authors measured the cost-effectiveness of three HIV testing strategies evaluated in a randomized trial conducted in 12 community-based substance abuse treatment programs in 2009: off-site testing referral, on-site rapid testing with information only, on-site rapid testing with risk-reduction counseling. Data from the trial included patient demographics, prior testing history, test acceptance and receipt of results, undiagnosed HIV prevalence (0.4%) and program costs. The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) computer simulation model was used to project life expectancy, lifetime costs, and quality-adjusted life years (QALYs) for HIV-infected individuals. Incremental cost-effectiveness ratios (2009 US \$/QALY) were calculated after adding costs of testing HIV-uninfected individuals; costs and QALYs were discounted at 3% annually. Referral for off-site testing is less efficient (dominated) compared to offering on-site testing with information only. The cost-effectiveness ratio for on-site testing with information is \$60,300/QALY in the base case, or \$76,300/QALY with 0.1% undiagnosed HIV

prevalence. HIV risk-reduction counseling costs \$36 per person more without additional benefit. A strategy of on-site rapid HIV testing offer with information only in substance abuse treatment programs increases life expectancy at a cost-effectiveness ratio <\$100,000/QALY. Policymakers and substance abuse treatment leaders should seek funding to implement on-site rapid HIV testing in substance abuse treatment programs for those not recently tested. Schackman B, Metsch L, Colfax G, Leff J, Wong A, Scott C, Feaster D, Gooden L, Matheson T, Haynes L, Paltiel A, Walensky R. The cost-effectiveness of rapid HIV testing in substance abuse treatment: Results of a randomized trial. *Drug Alcohol Depend.* 2012.

Depression and Prescription Opioid Misuse Among Chronic Opioid Therapy Recipients with No History of Substance Abuse Opioid misuse in the context of chronic opioid therapy (COT) is a growing concern. Depression may be a risk factor for opioid misuse, but it has been difficult to tease out the contribution of co-occurring substance abuse. This study aims to examine whether there is an association between depression and opioid misuse in patients receiving COT who have no history of substance abuse. A telephone survey was conducted at Group Health Cooperative and Kaiser Permanente of Northern California. The authors interviewed 1,334 patients on COT for non-cancer pain who had no history of substance abuse. Patients were asked about 3 forms of opioid misuse: (1) self-medicating for symptoms other than pain, (2) self-increasing doses, and (3) giving to or getting opioids from others. Depression was evaluated by the 8-item Patient Health Questionnaire (PHQ-8). Compared with patients who were not depressed (PHQ-8 score 0 to 4), patients with moderate depression (PHQ-8 score 10 to 14) and severe depression (PHQ-8 score 15 or higher) were 1.8 and 2.4 times more likely, respectively, to misuse their opioid medications for non-pain symptoms. Patients with mild (PHQ-8 score 5 to 9), moderate, and severe depression were 1.9, 2.9, and 3.1 times more likely, respectively, to misuse their opioid medications by self-increasing their dose. There was no statistically significant association between depression and giving opioids to or getting them from others. In patients with no substance abuse history, depressive symptoms are associated with increased rates of some forms of self-reported opioid misuse. Clinicians should be alert to the risk of patients with depressive symptoms using opioids to relieve these symptoms and thereby using more opioids than prescribed. Grattan A, Sullivan M, Saunders K, Campbell C, Von Korff M. Depression and prescription opioid misuse among chronic opioid therapy recipients with no history of substance abuse. *Ann Fam Med.* 2012; 10 (4): 304-311

Psychiatric Diagnoses Among Quitters Versus Continuing Smokers 3 Years After Their Quit Day People with psychiatric disorders are more likely to smoke and smoke more heavily than the general population, and they suffer disproportionately from smoking-related illnesses. However, little is known about how quitting versus continuing to smoke affects mental health and the likelihood of developing a psychiatric diagnosis. This study used data from a large prospective clinical trial to examine the relations of smoking cessation success with psychiatric diagnoses 1 and 3 years after the target quit day. This study enrolled 1,504 smokers (83.9% white; 58.2% female) in a cessation trial that involved the completion of the Composite International Diagnostic Interview to assess psychiatric diagnoses and biochemical confirmation of point-prevalence abstinence at Baseline and Years 1 and 3. Regression analyses showed that, after controlling for pre-quit (past-year) diagnoses, participants who were smoking at the Year 3 follow-up were more likely to have developed and maintained a substance use or major depressive disorder by that time than were individuals who were abstinent at Year 3. Quitting smoking does not appear to negatively influence mental health in the long-term and may be protective with respect to depression and substance use diagnoses; this should encourage smokers to make quit attempts and encourage clinicians to provide cessation

treatment. Piper M, Rodock M, Cook J, Schlam T, Fiore M, Baker T. Psychiatric diagnoses among quitters versus continuing smokers 3 years after their quit day. *Drug Alcohol Depend.* 2012.

Risk Adjustment and Reinsurance Can Mitigate the Effects of Adverse Selection of Individuals with Mental Health Conditions into Insurance Plans

In 2014, an estimated 15 million individuals who currently do not have health insurance, including many with chronic mental illness, are expected to obtain coverage through state insurance exchanges. The authors examined how two mechanisms in the Affordable Care Act (ACA), namely, risk adjustment and reinsurance, might perform to ensure the financial solvency of health plans that have a disproportionate share of enrollees with mental health conditions. Risk adjustment is an ACA provision requiring that a federal or state exchange move funds from insurance plans with healthier enrollees to plans with sicker enrollees. Reinsurance is a provision in which all plans in the state contribute to an overall pool of money that is used to reimburse costs to individual market plans for expenditures of any individual enrollee that exceed a high predetermined level. Using 2006--2007 claims data from a sample of private and public health plans, the authors compared expected health plan compensation under diagnosis-based risk adjustment with actual health care expenditures, under different assumptions for chronic mental health and medical conditions. Analyses were conducted with and without the addition of \$100,000 reinsurance. Risk adjustment performed well for most plans. For some plans with a high share of enrollees with mental health conditions, underpayment was substantial enough to raise concern. Reinsurance appeared to be helpful in addressing the most serious underpayment problems remaining after risk adjustment. Risk adjustment performed similarly for health plan cohorts that had a disproportionate share of enrollees with chronic mental health and medical conditions. Cost models indicate that the regulatory provisions in the ACA requiring risk adjustment and reinsurance can help protect health plans covering treatment for mentally ill individuals against risk selection. This model analysis may be useful for advocates for individuals with mental illness in considering their own state's insurance exchange. Barry C, Weiner J, Lemke K, Busch S. Risk Adjustment in health insurance exchanges for individuals with mental illness. *Am J Psychiatry.* 2012; 169 (7): 704-709.

Developmental Timing of First Drug Treatment and 10-Year Patterns of Drug Use

To examine the developmental timing of first drug treatment and its associations with 10-year drug use patterns, pooled data (N=1318) from four longitudinal studies conducted in California was used to compare individuals first treated during young adulthood (26%) to those first treated at an older age. Treatment timing was associated with particular participant characteristics and experiences. Matched data showed that most people in both age groups exhibited a low level of drug use after first treatment, albeit fewer who were first treated during young adulthood maintained a low drug use level over time. Receipt of more drug treatment over 10 years was associated with maintenance of low drug use levels among those first treated as young adults, but not among those first treated as older adults. Developmental timing of first drug treatment interacts with subsequent treatment experiences in ways that impact the course of drug use. Evans E, Li L, Grella C, Brecht M, Hser Y. Developmental Timing Of First Drug Treatment And 10-Year Patterns Of Drug Use. *J Subst Abuse Treat.* 2012.

Methadone Dose, Take Home Status, and Hospital Admission Among Methadone Maintenance Patients

Among patients receiving methadone maintenance treatment (MMT) for opioid dependence, receipt of unobserved dosing privileges (take homes) and adequate doses (ie, e80 mg) are each associated with improved addiction treatment outcomes, but the association with

acute care hospitalization is unknown. The authors studied whether take-home dosing and adequate doses (ie, ≥ 80 mg) were associated with decreased hospital admission among patients in an MMT. They reviewed daily electronic medical records of patients enrolled in one MMT program to determine receipt of take-home doses, methadone dose ≥ 80 mg or more, and hospital admission date. Nonlinear mixed-effects logistic regression models were used to evaluate whether take-home doses or dose ≥ 80 mg or more on a given day were associated with hospital admission on the subsequent day. Covariates in adjusted models included age, sex, race/ethnicity, human immunodeficiency virus status, medical illness, mental illness, and polysubstance use at program admission. Subjects ($n = 138$) had the following characteristics: mean age 43 years; 52% female; 17% human immunodeficiency virus-infected; 32% medical illness; 40% mental illness; and 52% polysubstance use. During a mean follow-up of 20 months, 42 patients (30%) accounted for 80 hospitalizations. Receipt of take homes was associated with significantly lower odds of a hospital admission (adjusted odds ratio [AOR] = 0.26; 95% confidence interval [CI], 0.11-0.62), whereas methadone dose ≥ 80 mg or more was not (AOR = 1.01; 95% CI, 0.56-1.83). Among MMT patients, receipt of take homes, but not dose of methadone, was associated with decreased hospital admission. Take-home status may reflect not only patients' improved addiction outcomes but also reduced health care utilization. Walley A, Cheng D, Pierce C, Chen C, Filippelli T, Samet J, Alford D. Methadone dose, take home status, and hospital admission among methadone maintenance patients. *J Addict Med*. 2012 Sep; 6(3): 186-190.

A Longitudinal Investigation of The Role of Self-Medication in The Development of Comorbid Mood and Drug Use Disorders: Findings From The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) To examine whether self-medication with drugs confers risk of comorbid mood and drug use disorders. A longitudinal, nationally representative survey was conducted by the National Institute on Alcohol Abuse and Alcoholism. The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) assessed DSM-IV-TR psychiatric disorders, self-medication, and sociodemographic variables at 2 time points. A total of 34,653 adult, US participants completed both waves of the survey. Wave 1 was conducted between 2001 and 2002, and Wave 2 interviews took place 3 years later (2004-2005). Logistic regression and population attributable fractions were calculated to obtain estimates of the association between self-medication and incident disorders. Logistic regression analyses revealed that self-medication with drugs conferred a heightened risk of new-onset drug dependence among those with baseline mood disorders (adjusted odds ratio [AOR] = 7.65; 95% CI, 3.70-15.82; $P < .001$) and accounted for over 25% of incident drug dependence disorders among people with mood disorders. Among those with comorbid mood and drug use disorders at baseline, self-medication with drugs was associated with the persistence of drug abuse (AOR = 2.47; 95% CI, 1.34-4.56; $P < .01$), accounting for over one-fifth of the persistence of drug use disorders at 3-year follow-up. Self-medication with drugs among individuals with mood disorders confers substantial risk of developing incident drug dependence and is associated with the persistence of comorbid mood and drug use disorders. These results clarify a pathway that may lead to the development of mood and drug use disorder comorbidity and indicate an at-risk population, with potential points of intervention for prevention of comorbidity. Lazareck S, Robinson JA, Crum RM, Mojtabai R, Sareen J, Bolton JM. A longitudinal investigation of the role of self-medication in the development of comorbid mood and drug use disorders: Findings from the NESARC. *J Clin Psychiatry*. 2012; 73 e588-e593.

Unhealthy Alcohol and Illicit Drug Use Are Associated With Decreased Quality of HIV Care

HIV-infected patients with substance use experience suboptimal health outcomes, possibly because of variations in care. To assess the association between substance use and the quality of HIV care (QOC) received. Retrospective cohort study. HIV-infected patients enrolled in the Veterans Aging Cohort Study. The authors collected self-report substance use data and abstracted 9 HIV quality indicators (QIs) from medical records. Independent variables were unhealthy alcohol use (AUDIT-C score ≥ 4) and illicit drug use (self-report of stimulants, opioids, or injection drug use in past year). Main outcome was the percentage of QIs received, if eligible. They estimated associations between substance use and QOC using multivariable linear regression. The majority of the 3,410 patients were male (97.4%) and black (67.0%) with a mean age of 49.1 years (SD = 8.8). Overall, 25.8% reported unhealthy alcohol use, 22% illicit drug use, and participants received 81.5% (SD = 18.9) of QIs. The mean percentage of QIs received was lower for those with unhealthy alcohol use versus not (59.3% vs. 70.0%, $P < 0.001$) and those using illicit drugs vs. not (57.8% vs. 70.7%, $P < 0.001$). In multivariable models, unhealthy alcohol use (adjusted β -2.74; 95% confidence interval: -4.23 to -1.25) and illicit drug use (adjusted β -3.51; 95% CI: -4.99 to -2.02) remained inversely associated with the percentage of QIs received. Although the overall QOC for these HIV-infected Veteran patients was high, gaps persist for those with unhealthy alcohol and illicit drug use. Interventions that address substance use in HIV-infected patients may improve the QOC received. Korthuis P, Fiellin D, McGinnis K, Skanderson M, Justice A, Gordon A, Doebler D, Asch S, Fiellin L, Bryant K, Gibert C, Crystal S, Goetz M, Rimland D, Rodriguez-Barradas M, Kraemer K. Unhealthy alcohol and illicit drug use are associated with decreased quality of HIV Care. *J Acquir Immune Defic Syndr.* 2012; 61(2): 171-178.

Pharmacy Staff Characteristics Associated with Support for Pharmacy-Based HIV Testing

The aim of this study was to determine support of in-pharmacy human immunodeficiency virus (HIV) testing among pharmacy staff and the individual-level characteristics associated with in-pharmacy HIV testing support. This was a descriptive, non-experimental, cross-sectional study conducted in New York City (NYC) from January 2008 to March 2009 involving 480 pharmacy staff, including pharmacists, owners/managers, and technicians/clerks. 131 pharmacies registered in the Expanded Syringe Access Program (ESAP) completed a survey. Support of in-pharmacy HIV testing is high among pharmacy staff (79.4%). Pharmacy staff who supported in-pharmacy vaccinations were significantly more likely to support in-pharmacy HIV testing. Pharmacy staff who thought that selling syringes to injection drug users (IDUs) caused the community to be littered with dirty syringes were significantly less likely to support in-pharmacy HIV testing. Support for in-pharmacy HIV testing was high among this sample of ESAP pharmacy staff actively involved in nonprescription syringe sales. These findings suggest that active ESAP pharmacy staff may be amenable to providing HIV counseling and testing to IDUs and warrants further investigation. Amesty S, Blaney S, Crawford N, Rivera A, Fuller C. Pharmacy staff characteristics associated with support for pharmacy-based HIV testing. *J Am Pharm Assoc (2003).* 2012; 52(4): 472-479.

Hepatitis C Viremia and Genotype Distribution Among a Sample of Nonmedical Prescription Drug Users Exposed to HCV in Rural Appalachia

Research has demonstrated that hepatitis C (HCV) genotype distribution varies geographically and demographically. This exploratory study examines HCV viremia, viral concentration, and genotype distribution among anti-HCV positive, rural Appalachian nonmedical prescription drug users. The study population was randomly selected from a pool of 200 anti-HCV positive participants in a longitudinal study. Those randomly chosen were representative of the overall pool in terms of demographics, drug use, and other risk behaviors.

Participants were tested serologically for HCV RNA, viral concentration, and genotype, and interview-administered questionnaires examined behavioral and demographic characteristics. Of the 81 participants, 69% tested RNA positive, 59% of which had viral loads exceeding 800,000 IU/ml. Approximately 66% of the RNA positive sample had genotype 1a; types 2b (16%) and 3a (13%) were less common. RNA positive participants were not significantly different than RNA negative participants demographically or behaviorally. Likewise, with the exception of education, genotype 1 participants were not significantly different than those with genotype 2 or 3. The prevalence of active HCV infection highlights a need for prevention and treatment in this population. However, the predominance of genotype 1 may present challenges due to its association with decreased responsiveness to drug treatment, although the novel class of direct-acting antivirals such as telaprevir and boceprevir offer new hope in this regard. The prevalence of genotype 1 may also foreshadow heightened burden of hepatocellular carcinoma and elevated healthcare expenditures. More research is needed to characterize HCV infection and genotype in this population. Young A, Crosby R, Oser C, Leukefeld C, Stephens D, Havens J. Hepatitis C viremia and genotype distribution among a sample of nonmedical prescription drug users exposed to HCV in rural Appalachia. *J Med Virol.* 2012; 84(9): 1376-1387.

Risky Relationships: Targeting HIV Prevention for Women Offenders HIV is a health issue for women offenders who are at particularly high risk. Women's prisons can be opportune settings for HIV prevention interventions. How women perceive partner relationships could be central to targeting HIV interventions. Consequently, this study examines changes in women offenders' risky relationships. Baseline and follow-up data are presented from 344 women offenders. Intent-to-treat analysis is used as well as analysis of covariance to control for baseline values. Findings indicate that women released to the community from prison who were randomized into the prevention intervention were significantly more likely to report changes in five of seven risky relationship thinking myths. Findings suggest that a relationship theory-based prevention intervention for reducing HIV risk could be promising for women offenders reentering the community after prison. Additional research is suggested. Leukefeld C, Havens J, Tindall M, Oser C, Mooney J, Hall M, Knudsen H. Risky relationships: Targeting HIV prevention for women offenders. *AIDS Educ Prev.* 2012; 24(4): 339-349.

Dual HIV Risk and Vulnerabilities Among Women Who Use or Inject Drugs: No Single Prevention Strategy is the Answer This article examines the dual HIV and sexually transmitted infection (STI) risk behaviors engaged in by women who use or inject drugs; the individual, social, and structural drivers of HIV and STI risk; prevention strategies; and the implications for multilevel, combined, sex-specific HIV prevention strategies. Women who use or inject drugs, especially female sex workers, are at dual risk for HIV, the hepatitis C virus (HCV), and other STIs. In countries with HIV prevalence higher than 20% among injecting drug users (IDUs), female IDUs have slightly higher HIV prevalence than male IDUs. Women who use or inject drugs face multilevel drivers that increase their vulnerabilities to HIV, HCV, and STIs. Despite advances in behavioral HIV prevention strategies for this population, most prevention studies have not sufficiently targeted dyadic, social, and structural levels. Few recent advances in biomedical HIV prevention have focused on women who use drugs and their unique needs. HIV prevention strategies and services need to address the unique and multilevel drivers that increase the vulnerabilities to HIV, HCV, and STIs among women who use drugs including those who engage in sex work. Scaling-up and improving access to multilevel and combined HIV prevention strategies for these women is central to combating the HIV epidemic. El-Bassel N, Wechsberg W, Shaw S.

Dual HIV risk and vulnerabilities among women who use or inject drugs: No single prevention strategy is the answer. *Curr Opin HIV AIDS*. 2012; 7(4): 326-331.

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 regressions 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 ≥ 500 cells per cubic millimeter. These data highlight the need to improve establishment and retention in HIV care. Fleishman J, Yehia B, Moore R, Korthuis P, Gebo K, Gebo K. Establishment, retention, and loss to follow-up in outpatient HIV care. *J Acquir Immune Defic Syndr*. 2012; 60(3): 249-259.

A Mixed Methods Approach to Identifying Factors Related to Voluntary HIV Testing Among Injection Drug Users in Shanghai, China Injection drug use is a major route of HIV transmission in China, yet relatively little is known about why so few injection drug users utilize free HIV testing services. This study aimed to examine barriers to HIV testing and voluntary counseling and testing (VCT) service utilization among injection drug users in Shanghai, China. Utilizing mixed methods, the authors analyzed data from a survey of 540 compulsory drug abuse treatment patients and data from focus groups with 70 service providers and patients. Only 24.4% of patients expressed willingness to be tested for HIV. Willingness to be tested was associated with younger age and more positive attitudes towards condom use. Patients reported several barriers to utilization of voluntary HIV testing services, including lack of information about these services, perceptions of no risk or low-risk for HIV infection, fear of positive results, and the stigma or discrimination that may be experienced by the patient or their family. Having limited skills related to HIV counseling was reported by service providers as the primary barrier to encouraging patients to utilize HIV testing/VCT services. Special intervention programs targeting injection drug users, their family members, and service providers may increase HIV testing in China. Du J, Lombardi C, Evans E, Jiang H, Zhao M, Meng Y. A Mixed methods approach to identifying factors related to voluntary HIV testing among injection drug users in Shanghai, China. *Int J Infect Dis*. 2012; 16(7): 498-503.

Effects of Laboratory Data Exchange in The Care of Patients with HIV Electronic health record (EHR) systems are often modified through the addition of new features over time. Few studies have examined the specific effects of such changes. The authors examined whether implementation of a bidirectional laboratory interface for order entry and data reporting within an existing ambulatory EHR would result in more prompt responses to laboratory indications for antiretroviral therapy (ART) changes or in improved communication with HIV+ patients about

relevant laboratory results. They conducted a single-arm intervention study comparing the timeliness of ART regimen changes, HIV viral load (VL) outcomes and patient-reported assessments of care before and after implementation of a laboratory data exchange interface within an existing EHR, without changing the EHR ordering or results reporting user interface. Patient data was extracted from the EHR covering the period from 1 year before to 2 years after the intervention for a cohort of 1181 patients who had received care during the baseline year. The timeliness of ART changes was represented by the days from a laboratory-result "signal" (CD4 dropping below 350 or 200 or VL increasing by a half-log or to a value over 100,000) to an ART-change "response". Patient assessments of care were collected by interviewing 100 anonymous patients at baseline and another 125 at 2 years post-intervention. A total of 171 laboratory "signal" events were followed within 80 days by a change in ART therapy. The mean time from signal to therapy change (adjusted for clustering by patient) initially increased, from 37.7 days during the pre-intervention year to 48.2 days during the quarter immediately following activation of the lab intervention. It then declined to a mean of 31.4 days over the remaining 21 months of observation ($P=0.03$ for the 6-day improvement from the pre-period). A majority of patients (65%) achieved undetectable VL values by the end of the observation period; faster signal-response times were not associated with greater achievement of undetectable VL. Patients rated communication about laboratory tests more highly after implementation of the interface (91 vs. 83 on a 100-point scale, $P=0.01$); ratings were not higher for other aspects of care. Adding laboratory data exchange interfaces within existing EHRs holds promise for improving HIV care, both in the timeliness of responses to important laboratory results and in the quality of provider communication about lab tests. However, the benefits from this incremental change may be modest unless more extensive redesign of laboratory follow-up workflows is undertaken, with support from enhanced user interfaces that take advantage of the laboratory information delivered. Providers should also consider increased staffing to compensate for dips in follow-up performance during the initial post-implementation months. Bell D, Cima L, Seiden D, Nakazono T, Alcouloumre M, Cunningham W. Effects of laboratory data exchange in the care of patients with HIV. *Int J Med Inform.* 2012; 81(10): 74-82.

Developing an Evidence-Based, Multimedia Group Counseling Curriculum Toolkit Training community-based addiction counselors in empirically supported treatments (ESTs) far exceeds the ever-decreasing resources of publicly funded treatment agencies. This feasibility study describes the development and pilot testing of a group counseling toolkit (an approach adapted from the education field) focused on relapse prevention (RP). When counselors ($N = 17$) used the RP toolkit after 3 hours of training, their content adherence scores on coping with craving and drug refusal skills showed significant improvement, as indicated by very large effect sizes (Cohen's $d = 1.49$ and 1.34 , respectively). Counselor skillfulness, in the adequate-to-average range at baseline, did not change. Although this feasibility study indicates some benefit to counselor EST acquisition, it is important to note that the impact of the curriculum on client outcomes is unknown. Because a majority of addiction treatment is delivered in group format, a multimedia curriculum approach may assist counselors in applying ESTs in the context of actual service delivery. Brooks AC, DiGuseppi G, Laudet A, Rosenwasser B. Developing an evidence-based, multimedia group counseling curriculum toolkit. *J Subst Abuse Treat.* 2012; 43: 178-189.

Impact of Intensive Case Management on Child Welfare System Involvement for Substance Dependent Parenting Women This study examined the impact of intensive case management (ICM) on decreasing child welfare system involvement in a sample of substance-dependent parenting women who participated in a welfare demonstration study comparing ICM to usual

screen-and-refer models employed in welfare settings. Previous research established the effectiveness of ICM in both increasing engagement in substance abuse treatment and in promoting abstinence, and the current study tested whether ICM had downstream impacts on child welfare outcomes not directly targeted by the intervention. The sample included 302 mothers recruited from welfare offices and their 888 minor children. Child welfare outcomes were available from administrative records for 4 years following study entry and included incident reports and out-of-home child placements. An initial positive effect of ICM was found on child placements, but its impact lessened over time and was likely due to the increased contact with case managers that occurred early in the study. Overall, minimal benefits of ICM were found, suggesting that while ICM was effective in the areas of treatment engagement and abstinence, there were no downstream benefits for child welfare outcomes. Implications of findings in terms of increased need for cross-system collaboration are discussed. Dauber S, Neighbors C, Dasaro C, Riordan A, Morgenstern J. Impact of intensive case management on child welfare system involvement for substance-dependent parenting women on public assistance. *Child Youth Serv Rev.* 2012; 34: 1359-1366.

The Role of Culture in Substance Abuse Treatment Programs for AI/AN Communities

Culture figures prominently in discussions regarding the etiology of alcohol and substance abuse in American Indian and Alaska Native (AI/AN) communities, and a substantial body of literature suggests that it is critical to developing meaningful treatment interventions. However, no study has characterized how programs integrate culture into their services. Furthermore, reports regarding the associated challenges are limited. Twenty key informant interviews with administrators and 15 focus groups with clinicians were conducted in 18 alcohol and substance abuse treatment programs serving AI/AN communities. Transcripts were coded to identify relevant themes. Substance abuse treatment programs for AI/AN communities are integrating culture into their services in two discrete ways: by implementing specific cultural practices and by adapting Western treatment models. More important, however, are the fundamental principles that shape these programs and their interactions with the people and communities they serve. These foundational beliefs and values, defined in this study as the core cultural constructs that validate and incorporate AI/AN experience and world view, include an emphasis on community and family, meaningful relationships with and respect for clients, a homelike atmosphere within the program setting, and an open door policy for clients. The primary challenges for integrating these cultural practices include AI/AN communities, cultural diversity and limited socioeconomic resources to design and implement these practices. The prominence of foundational beliefs and values is striking and suggests a broader definition of culture when designing services. This definition of foundational beliefs and values should help other diverse communities culturally adapt their substance abuse interventions in more meaningful ways. Legha RK, Novins D. The role of culture in substance abuse treatment programs for American Indian and Alaska Native communities. *Psychiatr Serv.* 2012; 63: 686-692.

Alcohol and Drug Use Disorders Among Adults in Emergency Department Settings in The US

Improving identification and treatment for substance use disorders is a national priority, but data about various drug use disorders encountered in emergency departments (EDs) are lacking. The authors examine past-year substance use and substance use disorders (alcohol, 9 drug classes) among adult ED users. Prevalences of substance use and substance use disorders among ED nonusers are calculated for reference purposes. Using data from the 2007 to 2009 National Surveys on Drug Use and Health, the authors assessed substance use disorders among non-institutionalized adults aged 18 years or older who responded to standardized survey questions administered by

audio computer-assisted self-interviewing methods. Of all adults (N=113,672), 27.8% used the ED in the past year. ED users had higher prevalence's than ED nonusers of coexisting alcohol and drug use (15.2% versus 12.1%), drug use (any drug, 16.9% versus 13.0%; marijuana, 12.1% versus 9.7%; opioids, 6.6% versus 4.1%), and alcohol or drug disorders (11.0% versus 8.5%). Among substance users, the ED group on average spent more days using drugs than the non-ED group; ED users manifested higher conditional rates of substance use disorders than ED nonusers (alcohol or drugs, 15.9% versus 11.7%; marijuana, 16.6% versus 13.2%; cocaine, 33.2% versus 22.3%; opioids, 20.6% versus 10.0%; stimulants, 18.6% versus 9.2%; sedatives, 35.0% versus 4.4%; tranquilizers, 12.4% versus 5.2%). Regardless of ED use status, substance-using young adults, men, and less-educated adults showed increased odds of having a substance use disorder. Drug use is prevalent and combined with high rates of drug use disorders among drug users treated in the ED. Wu L, Swartz MS, Wu Z, Mannelli P, Yang C, Blazer D. Alcohol and drug use disorders among adults in emegrence department settings in the United States. *Ann Emerg Med.* 2012 Aug; 60(2): 172-180.e5. doi: 10.1016/j.annemergmed.2012.02.003. Epub 2012 Mar 15.

The Role of Continuing Care in 9-Year Cost Trajectories of Patients with Intakes Into an Outpatient Alcohol and Drug Treatment Program

The importance of a continuing care approach for substance use disorders (SUDs) is increasingly being recognized. The authors' prior research found that a Continuing Care model for SUDs that incorporates 3 components (regular primary care, and specialty SUD and psychiatric treatment as needed) is beneficial to long-term remission. The study builds on this work to examine the cost implications of this model and to examine associations between receiving Continuing Care and subsequent health care costs over 9 years among adults entering outpatient SUD treatment in a private nonprofit, integrated managed care health plan. The authors also compare the results to a similar analysis of a demographically matched control group without SUDs. This was a longitudinal observational study. Measures collected over 9 years include demographic characteristics, self-reported alcohol and drug use and Addiction Severity Index, and health care utilization and cost data from health plan databases. Within the treatment sample, SUD patients receiving all components of Continuing Care had lower costs than those receiving fewer components. Compared with the demographically matched non-SUD controls, those not receiving Continuing Care had significantly higher inpatient costs (excess cost = \$65.79/member-month; $P < 0.01$) over 9 years, whereas no difference was found between those receiving Continuing Care and controls. Although a causal link cannot be established between receiving Continuing Care and reduced long-term costs in this observational study, the findings reinforce the importance of access to health care and development of interventions that optimize patients receiving those services and that may reduce costs to health systems. Parthasarathy S, Chi F, Mertens J, Weisner C. The role of continuing care in 9-year cost trajectories of patients with intakes into an outpatient alcohol and drug treatment program. *Med Care.* 2012; 50(6): 540-546

The Economic Cost of Substance Abuse Treatment in the State Of Florida

Public and private stakeholders of substance abuse treatment services require economic cost data to guide program evaluations and funding decisions. Rigorous cost assessments have been conducted for several treatment programs across the United States, but a systematic and comprehensive evaluation of programs in a particular state has never been attempted. The present study recruited all publicly funded treatment programs in the State of Florida and administered the Brief Drug Abuse Treatment Cost Analysis Program. A total of 175 programs participated in the study, representing a 71% response rate. Annual, weekly, and episode costs are estimated by modality. The study procedures and empirical findings from this research can be used by program evaluators and government

officials in Florida and other states as they develop service reimbursement algorithms and initiate more extensive evaluations of publicly funded substance abuse treatment programs. Alexandre P, Beulaygue I, French M, McCollister K, Popovici I, Sayed B. The economic cost of substance abuse treatment in the state of Florida. *Eval Rev.* 2012; 36(3): 167-185. 2012; 60: 172-180.

The Effect of Comprehensive Behavioral Health Parity on Choice of Provider Parity laws remove treatment limitations for mental health and substance-abuse services covered by commercial health plans. A number of studies of parity implementations have suggested that parity does not lead to large increases in utilization or expenditures for behavioral health services. However, less is known about how parity might affect changes in patients' choice of providers for behavioral health treatment. The authors compared initiation and provider choice among 46,470 Oregonians who were affected by Oregon's 2007 parity law. Oregon is the only state to have enacted a parity law that places restrictions on how plans manage behavioral health services. This approach has been adopted federally in the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act. In 1 set of analyses, the authors assess initiation and provider choice using a difference-in-difference approach, with a matched group of commercially insured Oregonians who were exempt from parity. In a second set of analyses, they assess the impact of distance on provider choice. Overall, parity in Oregon was associated with a slight increase (0.5% to 0.8%) in initiations with masters-level specialists, and relatively little changes for generalist physicians, psychiatrists, and psychologists. Patients are particularly sensitive to distance for nonphysician specialists. These results suggest that the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act may lead to a shift in the use of nonphysician specialists and away from generalist physicians. The extent to which these changes occur is likely to be contingent on the ease and accessibility of nonphysician specialists. McConnell K, Gast S, McFarland B. The effect of comprehensive behavioral health parity on choice of provider. *Med Care.* 2012; 50 (6): 527-533.

The Relationship between Substance Abuse Performance Measures and Mutual Help Group Participation after Treatment The authors examined the relationship between treatment quality, using during-treatment process measures, and mutual help group (e.g., Alcoholics Anonymous) attendance after outpatient substance use disorder (SUD) treatment for 739 clients in the Alcohol and Drug Services Study. Logistic regression models estimated any and regular mutual help attendance after treatment. Clients referred to mutual help groups were significantly more likely to attend any mutual help after treatment. Results were mixed for facility offered mutual help groups; treatment engagement and retention were not significant. These findings offer treatment providers further evidence of the importance of referring clients to post-treatment mutual help groups, an effective, low-cost option. Strickler G, Reif S, Horgan C, Acevedo A. The relationship between substance abuse performance measures and mutual help group participation after treatment. *Alcohol Treat Q.* 2012; 30(2): 190-210.

Assessing the Sensitivity of Treatment Effect Estimates to Differential Follow-Up Rates: Implications for Translational Research The authors developed a new tool for assessing the sensitivity of findings on treatment effectiveness to differential follow-up rates in the two treatment conditions being compared. The method censors the group with the higher response rate to create a synthetic respondent group that is then compared with the observed cases in the other condition to estimate a treatment effect. Censoring is done under various assumptions about the strength of the relationship between follow-up and outcomes to determine how informative differential dropout can alter inferences relative to estimates from models that assume the data are missing at random. The

method provides an intuitive measure for understanding the strength of the association between outcomes and dropout that would be required to alter inferences about treatment effects. The authors' approach is motivated by translational research in which treatments found to be effective under experimental conditions are tested in standard treatment conditions. In such applications, follow-up rates in the experimental setting are likely to be substantially higher than in the standard setting, especially when observational data are used in the evaluation. The authors test the method on a case study evaluation of the effectiveness of an evidence-supported adolescent substance abuse treatment program (Motivational Enhancement Therapy/Cognitive Behavioral Therapy-5 [MET/CBT-5]) delivered by community-based treatment providers relative to its performance in a controlled research trial. In this case study, follow-up rates in the community based settings were extremely low (54%) compared to the experimental setting (95%) giving raise to concerns about non-ignorable drop-out. Griffin B, McCaffrey D, Ramchand R, Hunter S, Suttorp M. Assessing the sensitivity of treatment effect estimates to differential follow-up rates: Implications for translational research. *Health Serv Outcomes Res Methodol.* 2012; 12(2-3): 84-103.

Racial and Ethnic Differences in Substance Abuse Treatment Initiation and Engagement This study examined variations by race and ethnicity in initiation and engagement, two performance measures of treatment for substance use disorders that focus on the timely receipt of services during the early stage of substance abuse treatment. Administrative data from the Oklahoma Department of Mental Health and Substance Abuse Services were linked with facility-level information from the National Survey of Substance Abuse Treatment Services. The authors found that Black clients were least likely to initiate treatment, but no race or ethnic differences in treatment engagement were found when compared by race or ethnicity. Most client and facility characteristics' association with initiation or engagement did not differ across racial or ethnic groups. Increased attention is needed to understand what may contribute to the differences and how to address them. This study also offers an approach that state agencies may implement for monitoring treatment quality and examining racial and ethnic disparities in substance abuse treatment services. Acevedo A, Garnick D, Lee M, Horgan C, Ritter G, Panas L, Davis S, Leeper T, Moore R, Reynolds M. Racial and ethnic differences in substance abuse treatment initiation and engagement. *J Ethn Subst Abuse.* 2012; 11(1): 1-21.

Course of Comorbid Anxiety Disorders Among Adults with Bipolar Disorder in The U.S.

Population The purpose of this study was to examine the prevalence and correlates of comorbid anxiety disorders among individuals with bipolar disorders (BP) and their association with prospectively ascertained comorbidities, treatment, and psychosocial functioning. As part of the National Epidemiologic Survey on Alcohol and Related Conditions, 1600 adults who met lifetime DSM-IV criteria for BP-I (n = 1172) and BP-II (n = 428) were included. Individuals were evaluated using the Alcohol Use Disorder and Associated Disabilities Interview Schedule-DMS-IV Version and data was analyzed from Waves 1 and 2, approximately 3 years apart. Sixty percent of individuals with BP had at least one lifetime comorbid anxiety disorder. Individuals with BP and anxiety disorders shared lifetime risk factors for major depressive disorder and had prospectively more depressive and manic/hypomanic episodes, suicidal ideation, suicide attempts, and more treatment seeking than those without anxiety. During the follow-up, higher incidence of panic disorder, drug use disorders, and lower psychosocial functioning were found in individuals with BP with versus without anxiety disorders. Anxiety disorders are prospectively associated with elevated BP severity and BP-related mental health service use. Early identification and treatment of anxiety disorders are warranted to improve the course and outcome of individuals with BP. Sala R,

Goldstein B, Morcillo C, Liu S, Castellanos M, Blanco C. Course of comorbid anxiety disorders among adults with bipolar disorder in the U.S. population. *J Psychiatr Res.* 2012; 46(7): 865-872.

Providing Support to Patients in Emotional Encounters: A New Perspective on Missed Empathic Opportunities

Studies have repeatedly found that providers miss 70-90% of opportunities to express empathy. This study sought to characterize provider responses to patients' emotions, with the overall goal of better understanding reasons for lack of empathic response. The authors analyzed 47 visits between patients and their providers. They defined empathic opportunities as instances where patients expressed a strong negative emotion. They then developed thematic categories to describe provider response. They found a total of 29 empathic opportunities within 21 visits. Provider responses were categorized as ignore, dismiss, elicit information, problem-solve, or empathize. An empathic statement occurred at some point in the response sequence in 13/29 opportunities (45%). When problem-solving was the initial response, empathic statements rarely occurred in subsequent dialogue. Among the 16 instances with no empathic statements, providers engaged in problem-solving in 8 (50%). Similar to other studies, the authors found providers missed most opportunities to respond empathically to patient emotion. Yet contrary to common understanding, providers often addressed the problem underlying the emotion, especially when the problem involved logistical or biomedical issues, as opposed to grief. With enhanced awareness, providers may better recognize situations where they can offer empathy in addition to problem-solving. Hsu I, Saha S, Korthuis P, Sharp V, Cohn J, Moore R, Beach M. Providing support to patients in emotional encounters: A new perspective on missed empathic opportunities. *Patient Educ Couns.* 2012; 88(3): 436-442.

Exercise and Mental Illness: Results from The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)

Regular exercise is thought to be associated with low rates of mental illness, but this association has been inadequately studied. The purpose of this study was to test the hypotheses that the recommended amount of self-reported vigorous exercise would be cross-sectionally associated with reduced prevalence and incidence of various DSM-IV psychiatric disorders, as well as increased rates of remission. Data were collected from 2001 to 2005 as part of the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC), a 2-wave face-to-face survey conducted by the National Institute on Alcohol Abuse and Alcoholism. For this study, the sample consisted of 23,505 nondisabled adults aged between 18 and 65 years. Individuals who engaged in vigorous exercise at Wave 2 were significantly more likely than were nonexercisers to be diagnosed with a current psychiatric disorder (adjusted odds ratio [AOR] = 1.22, 95% CI, 1.12-1.34 for the nationally recommended amount vs. no exercise), significantly less likely to attain remission from a psychiatric disorder between waves (AOR = 0.77, 95% CI, 0.65-0.91), and significantly more likely to relapse or be newly diagnosed with a psychiatric disorder between waves (AOR = 1.15, 95% CI, 1.02-1.30). Alcohol dependence and bipolar II disorder were the disorders most strongly associated with exercise. This investigation suggests that the pursuit of vigorous exercise is associated with a vulnerability to mental illness. This surprising finding may be due to reward-related factors that influence both exercise engagement and the expression of certain psychiatric disorders. Prospective trials will be helpful in further clarifying the associations between exercise and mental illness, as the relationships between the 2 are more complex than previously believed. Dakwar E, Blanco C, Lin K, Liu S, Warden D, Trivedi M, Nunes E. Exercise and mental illness: Results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry.* 2012; 73(7): 960-966.

Isoniazid Preventive Therapy in Correctional Facilities: A Systematic Review Tuberculosis (TB) remains a major cause of morbidity and mortality worldwide and the main cause of death in correctional facilities in middle- and low-income countries. Due to the closed environment and the concentration of individuals with TB-related risk factors, effective measures are required to control TB in such settings. Isoniazid preventive therapy (IPT) represents an effective and cost-effective measure. Despite international recommendations that IPT be integral to TB control, it is seldom deployed. A systematic review of interventions used to assess IPT initiation and completion in correctional facilities was conducted using published studies from two biomedical databases and relevant keywords. Additional references were reviewed, resulting in 18 eligible studies. Most (72%) studies were conducted in the United States and in jail settings (60%), with the main objective of improving completion rates inside the facility or after release. Studies that provided data about initiation and completion rates showed poor success in correctional facilities. Adverse consequences and treatment interruption ranged from 1% to 55% (median 5%) in reported studies; hepatotoxicity was the most prevalent adverse reaction. Despite its accelerating effect on the development of active TB, information on human immunodeficiency virus (HIV) status was provided in only half of the studies. Among the four studies where IPT effectiveness was assessed, the results mirror those described in community settings. Future studies require thorough assessments of IPT initiation and completion rates and adverse effects, particularly in low- and middle-income countries and where comorbid viral hepatitis may contribute significantly to outcomes and in settings where TB and HIV are more endemic. Al-Darraji H, Kamarulzaman A, Altice F. Isoniazid preventive therapy in correctional facilities: A systematic review. *Int J Tuberc Lung Dis.* 2012; 16(7): 871-879.

Child Physical Abuse and Adult Mental Health: A National Study This study characterizes adults who report being physically abused during childhood, and examines associations of reported type and frequency of abuse with adult mental health. Data were derived from the 2000-2001 and 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions, a large cross-sectional survey of a representative sample (N = 43,093) of the U.S. population. Weighted means, frequencies, and odds ratios of socio-demographic correlates and prevalence of psychiatric disorders were computed. Logistic regression models were used to examine the strength of associations between child physical abuse and adult psychiatric disorders adjusted for socio-demographic characteristics, other childhood adversities, and comorbid psychiatric disorders. Child physical abuse was reported by 8% of the sample and was frequently accompanied by other childhood adversities. Child physical abuse was associated with significantly increased adjusted odds ratios (AORs) of a broad range of DSM-IV psychiatric disorders (AOR = 1.16-2.28), especially attention-deficit hyperactivity disorder, posttraumatic stress disorder, and bipolar disorder. A dose-response relationship was observed between frequency of abuse and several adult psychiatric disorder groups; higher frequencies of assault were significantly associated with increasing adjusted odds. The long-lasting deleterious effects of child physical abuse underscore the urgency of developing public health policies aimed at early recognition and prevention. Sugaya L, Hasin D, Olfson M, Lin K, Grant B, Blanco C. Child physical abuse and adult mental health: A national study. *J Trauma Stress.* 2012; 25(4): 384-392.

E-Cigarette Awareness, Use, and Harm Perceptions in US Adults The authors estimated e-cigarette (electronic nicotine delivery system) awareness, use, and harm perceptions among US adults. They drew data from 2 surveys conducted in 2010: a national online study (n = 2649) and the Legacy Longitudinal Smoker Cohort (n = 3658). They used multivariable models to examine e-

cigarette awareness, use, and harm perceptions. In the online survey, 40.2% (95% confidence interval [CI] = 37.3, 43.1) had heard of e-cigarettes, with awareness highest among current smokers. Utilization was higher among current smokers (11.4%; 95% CI = 9.3, 14.0) than in the total population (3.4%; 95% CI = 2.6, 4.2), with 2.0% (95% CI = 1.0, 3.8) of former smokers and 0.8% (95% CI = 0.35, 1.7) of never-smokers ever using e-cigarettes. In both surveys, non-Hispanic Whites, current smokers, young adults, and those with at least a high-school diploma were most likely to perceive e-cigarettes as less harmful than regular cigarettes. Awareness of e-cigarettes is high, and use among current and former smokers is evident. The authors recommend product regulation and careful surveillance to monitor public health impact and emerging utilization patterns, and to ascertain why, how, and under what conditions e-cigarettes are being used. Pearson J, Richardson A, Niaura R, Vallone D, Abrams D. e-Cigarette awareness, use, and harm perceptions in US Adults. *Am J Public Health*. 2012; 102(9): 1758-1766.

Substance Abuse Among Individuals with Intellectual Disabilities Individuals with disabilities are a growing population that confronts multiple disadvantages from social and environmental determinants of health. In particular, the 78 million people in the U.S. with an intellectual disability (ID) suffer disproportionately from substance use problems, largely because of a lack of empirical evidence to inform prevention and treatment efforts for them. Although available research could inform future research efforts, studies are scattered across disciplines with the last review synthesizing findings written more than five years ago. To consider more recent findings with earlier works, PubMed, PsychINFO, and Google Scholar were searched and produced 37 peer-reviewed texts across multiple disciplines, 15 from 2006 or later. While the prevalence of alcohol and illicit drug use in this population are low, the risk of having a substance-related problem among ID substance users is comparatively high. Gaps in the research and population subgroups that warrant special attention are identified, such as individuals with borderline and mild ID, individuals with co-occurring mental illness, and individuals who are incarcerated. Compared with substance abusers without ID, ID substance abusers are less likely to receive substance abuse treatment or remain in treatment. Research is needed to better gauge the magnitude of substance use problems, identify prevention strategies, and specify treatment components that meet the unique needs of individuals with ID. Chapman SL, Wu L. Substance abuse among individuals with intellectual disabilities. *Research in Developmental Disabilities*. 2012; 33: 1147-1156.

Recovering Substance-Impaired Pharmacists' Views Regarding Occupational Risks for Addiction The objective of this study was to better understand the occupational risks for substance use disorders among pharmacists and possibilities for improved prevention. This was a descriptive, nonexperimental, cross-sectional study conducted in a southeastern state from December 2008 to April 2009. 32 participants (72.7% men) from the impaired professionals monitoring groups in the geographic regions within the state that had the greatest number of physicians, pharmacists, and allied health professionals currently under monitoring contracts for substance use disorders engaged in guided group discussions regarding substance use among health care providers. Persistent occupational risks for development of a substance use disorder among pharmacists were found. Several occupational hazards unique to the pharmacy profession might contribute to the problem of substance use disorders among some members of this population, including increased access to potent drugs of abuse, a stressful/unpleasant working environment, a culture that unofficially condones medication diversion, lack of education related to addiction, and lack of support for individuals seeking treatment. These results have important implications for the education of student pharmacists, the continuing education of licensed pharmacists, and the management of

pharmacies in which these individuals work. Given the potential occupational risks for substance abuse associated with the pharmacy profession, additional training, monitoring, changes to the work environment and increased confidential access to treatment may be needed to safeguard pharmacy professionals and the communities they serve. Merlo L, Cummings S, Cottler L. Recovering substance-impaired pharmacists' views regarding occupational risks for addiction. *J Am Pharm Assoc* (2003). 2012; 52(4): 480-491.

CTN-RELATED RESEARCH

Buprenorphine/Naloxone and Methadone Effects On Laboratory Indices Of Liver Health: A Randomized Trial

Buprenorphine/naloxone (BUP) and methadone (MET) are efficacious treatments for opioid dependence, although concerns about a link between BUP and drug-induced hepatitis have been raised. This study compares the effects of BUP and MET on liver health in opioid-dependent participants. This was a randomized controlled trial of 1269 opioid-dependent participants seeking treatment at 8 federally licensed opioid treatment programs and followed for up to 32 weeks between May 2006 and August 2010; 731 participants met "evaluable" criteria defined as completing 24 weeks of medication and providing at least 4 blood samples for transaminase testing. Participants were randomly assigned to receive BUP or MET for 24 weeks. Shift table analysis determined how many evaluable participants moved between categories of low and elevated transaminase levels. Predictors of moving from low to high transaminase levels were identified. Changes in transaminase levels did not differ by medication condition. Baseline infection with hepatitis C or B was the only significant predictor of moving from low to elevated transaminase levels; 9 BUP and 15 MET participants showed extreme liver test elevations and were more likely than those without extreme elevations to have seroconverted to both hepatitis B and C during the study, or to use illicit drugs during the first 8 weeks of treatment. MET participants were retained longer in treatment than BUP participants. This study demonstrated no evidence of liver damage during the initial 6 months of treatment in either condition. Physicians can prescribe either medication without major concern for liver injury. Saxon AJ, Ling W, Hillhouse M, Thomas C, Hasson A, Ang A, Doraimani G, Tasissa G, Lokhnygina Y, Leimberger J, Bruce RD, McCarthy J, Wiest K, McLaughlin P, Bilangi R, Cohen A, Woody G, Jacobs P. Buprenorphine/Naloxone and methadone effects on laboratory indices of liver health: A randomized trial. *Drug Alcohol Depend.* 2012 Aug 22. [Epub ahead of print].

The Cost-Effectiveness Of Rapid HIV Testing In Substance Abuse Treatment: Results Of A Randomized Trial

The President's National HIV/AIDS Strategy calls for coupling HIV screening and prevention services with substance abuse treatment programs. Fewer than half of US community-based substance abuse treatment programs make HIV testing available on-site or through referral. The authors measured the cost-effectiveness of three HIV testing strategies evaluated in a randomized trial conducted in 12 community-based substance abuse treatment programs in 2009: off-site testing referral, on-site rapid testing with information only, on-site rapid testing with risk-reduction counseling. Data from the trial included patient demographics, prior testing history, test acceptance and receipt of results, undiagnosed HIV prevalence (0.4%) and program costs. The Cost-Effectiveness of Preventing AIDS Complications (CEPAC) computer simulation model was used to project life expectancy, lifetime costs, and quality-adjusted life years (QALYs) for HIV-infected individuals. Incremental cost-effectiveness ratios (2009 US \$/QALY) were calculated after adding costs of testing HIV-uninfected individuals; costs and QALYs were discounted at 3% annually. Referral for off-site testing is less efficient (dominated) compared to offering on-site testing with information only. The cost-effectiveness ratio for on-site testing with information is \$60,300/QALY in the base case, or \$76,300/QALY with 0.1% undiagnosed HIV prevalence. HIV risk-reduction counseling costs \$36 per person more without additional benefit. A strategy of on-site rapid HIV testing offer with information only in substance abuse treatment programs increases life expectancy at a cost-effectiveness ratio <\$100,000/QALY. Policymakers and substance abuse treatment leaders should seek funding to implement on-site rapid HIV testing in substance abuse treatment programs for those not recently tested. Schackman BR, Metsch LR,

Colfax GN, Leff JA, Wong A, Scott CA, Feaster DJ, Gooden L, Matheson T, Haynes LF, Paltiel AD, Walensky RP. The cost-effectiveness of rapid HIV testing in substance abuse treatment: Results of a randomized trial. *Drug Alcohol Depend.* 2012 Sep 6. [Epub ahead of print].

A Comparison Of Buprenorphine Taper Outcomes Between Prescription Opioid and Heroin Users

Dependence on prescription opioids (PO) is a growing problem. Although most research with buprenorphine has focused on heroin-dependent populations, the authors hypothesize that individuals dependent on PO display characteristics that may predict different outcomes in treatment, particularly in short-term taper procedures in which comorbidities such as pain conditions may complicate taper. This secondary data analysis examined differences in outcomes between PO users (n = 90) and heroin users (n = 426) after a buprenorphine taper. Data were collected in a multisite randomized clinical trial conducted by the National Drug Abuse Treatment Clinical Trials Network at 11 study sites across the United States. After a 4-week buprenorphine induction/stabilization phase, 516 opioid-dependent individuals were randomized into 1 of 2 taper lengths (7 vs 28 days) to assess the association between taper length and outcome. The primary outcome was measured by urine drug test for opioids at the end of the taper period. Craving, withdrawal, and buprenorphine dose were also examined. After controlling for baseline demographic and drug use differences between the opioid use groups, results indicate that a higher percentage of the PO group (49%) provided an opioid-free urine drug specimen at the end of taper compared with the heroin group (36%; $\chi^2 = 6.592$, $P < 0.010$). Short-term taper is not recommended as a stand-alone treatment; however, patients may taper from buprenorphine as part of a treatment plan. Despite greater comorbidity, PO users seem to have favorable taper outcomes compared with heroin users. Further studies are required to examine longer-term treatment outcomes. Nielsen S, Hillhouse M, Thomas C, Hasson A, Ling W. A comparison of buprenorphine taper outcomes between prescription opioid and heroin users. *J Addict Med.* 2012 Dec 6. [Epub ahead of print].

Characteristics Of Northern Plains American Indians Seeking Substance Abuse Treatment In An Urban, Non-Tribal Clinic: A Descriptive Study

Because few data exist on substance abuse rates in American Indian (AI) communities, the Methamphetamine and Other Drug project was developed and implemented by five nodes within the National Institute on Drug Abuse Clinical Trials Network (NIDA CTN). This article presents findings from AI clients in a Northern Plains urban non-Native substance abuse treatment setting. Alcohol and marijuana were used earlier, longer, and by more clients, followed by stimulants and prescription opioids. Most regularly smoked tobacco. Differences in substance use patterns were associated with age of onset and victimization. Age of onset was correlated with victimization, gender, cognitive impairment, and suicidal behavior. Despite considerable health and economic disparities, most clients found support for recovery in relationships and elements of Native culture. Kropp F, Somoza E, Lilleskov M, Moccasin MG, Moore M, Lewis D, Boetel B, Smith C, Winhusen T. Characteristics of Northern Plains American Indians seeking substance abuse treatment in an urban, non-tribal clinic: A descriptive study. *Community Ment Health J.* 2012 Jul 28. [Epub ahead of print].

Common Data Elements For Substance Use Disorders In Electronic Health Records: The NIDA Clinical Trials Network Experience

Electronic health records (EHRs) are essential in improving quality and enhancing efficiency of health-care delivery. By 2015, medical care receiving service reimbursement from US Centers for Medicare and Medicaid Services (CMS) must show 'meaningful use' of EHRs. Substance use disorders (SUD) are grossly under-detected and under-treated in current US medical care settings. Hence, an urgent need exists for improved

identification of and clinical intervention for SUD in medical settings. The National Institute on Drug Abuse Clinical Trials Network (NIDA CTN) has leveraged its infrastructure and expertise and brought relevant stakeholders together to develop consensus on brief screening and initial assessment tools for SUD in general medical settings, with the objective of incorporation into US EHRs. Stakeholders were identified and queried for input and consensus on validated screening and assessment for SUD in general medical settings to develop common data elements to serve as shared resources for EHRs on screening, brief intervention and referral to treatment (SBIRT), with the intent of supporting interoperability and data exchange in a developing Nationwide Health Information Network. Through consensus of input from stakeholders, a validated screening and brief assessment instrument, supported by Clinical Decision Support tools, was chosen to be used at out-patient general medical settings. The creation and adoption of a core set of validated common data elements and the inclusion of such consensus-based data elements for general medical settings will enable the integration of SUD treatment within mainstream health care, and support the adoption and 'meaningful use' of the US Office of the National Coordinator for Health Information Technology (ONC)-certified EHRs, as well as CMS reimbursement. Ghitza UE, Gore-Langton RE, Lindblad R, Shide D, Subramaniam G, Tai B. Common data elements for substance use disorders in electronic health records: the NIDA Clinical Trials Network experience. *Addiction*. 2013 Jan; 108(1): 3-8. Epub 2012 May 8.

Evaluating Brief Screeners To Discriminate Between Drug Use Disorders In A Sample Of Treatment-Seeking Adults The objective of this study was to identify a potential core set of brief screeners for the detection of individuals with a substance use disorder (SUD) in medical settings. Data were from two multisite studies that evaluated stimulant use outcomes of an abstinence-based contingency management intervention as an addition to usual care (National Drug Abuse Treatment Clinical Trials Network trials 006-007). The sample comprised 847 substance-using adults who were recruited from 12 outpatient substance abuse treatment settings across the United States. Alcohol and drug use disorders were assessed by the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Checklist. Data were analyzed by factor analysis, item response theory (IRT), sensitivity and specificity procedures. Comparatively prevalent symptoms of dependence, especially inability to cut down for all substances, showed high sensitivity for detecting an SUD (low rate of false negative). IRT-defined severe (infrequent) and low discriminative items, especially withdrawal for alcohol, cannabis and cocaine, had low sensitivity in identifying cases of an SUD. IRT-defined less severe (frequent) and high discriminative items, including inability to cut down or taking larger amounts than intended for all substances and withdrawal for amphetamines and opioids, showed good-to-high values of area under the receiver operating characteristic curve in classifying cases and noncases of an SUD. Findings suggest the feasibility of identifying psychometrically reliable substance dependence symptoms to develop a two-item screen for alcohol and drug disorders. Wu LT, Swartz MS, Pan JJ, Burchett B, Mannelli P, Yang C, Blazer DG. Evaluating brief screeners to discriminate between drug use disorders in a sample of treatment-seeking adults. *Gen Hosp Psychiatry*. 2012 Jul 20. [Epub ahead of print].

Study Design To Examine the Potential Role Of Assessment Reactivity In The Screening, Motivational Assessment, Referral, and Treatment In Emergency Departments (SMART-ED) Protocol Screening, brief intervention, and referral to treatment (SBIRT) approaches to reducing hazardous alcohol and illicit drug use have been assessed in a variety of health care settings, including primary care, trauma centers, and emergency departments. A major methodological concern in these trials, however, is "assessment reactivity," the hypothesized impact of intensive

research assessments to reduce alcohol and drug use and thus mask the purported efficacy of the interventions under scrutiny. Thus, it has been recommended that prospective research designs take assessment reactivity into account. The present article describes the design of the National Institute on Drug Abuse Clinical Trials Network protocol, Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED), which addresses the potential bias of assessment reactivity. The protocol employs a 3-arm design. Following an initial brief screening, individuals identified as positive cases are consented, asked to provide demographic and locator information, and randomly assigned to one of the three conditions: minimal screening only, screening + assessment, or screening + assessment + brief intervention. In a two-stage process, the randomization procedure first reveals whether or not the participant will be in the minimal-screening-only condition. Participants in the other two groups receive a more extensive baseline assessment before it is revealed whether they have been randomized to also receive a brief intervention. Comparing the screening only and screening + assessment conditions will allow determination of the incremental effect of assessment reactivity. Assessment reactivity is a potential source of bias that may reduce and/or lead to an underestimation of the purported effectiveness of brief interventions. From a methodological perspective, it needs to be accounted for in research designs. The SMART-ED design offers an approach to minimize assessment reactivity as a potential source of bias. Elucidating the role of assessment reactivity may offer insights into the mechanisms underlying SBIRT as well as suggest clinical options incorporating assessment reactivity as a treatment adjunct. Donovan DM, Bogenschutz MP, Perl H, Forcehimes A, Adinoff B, Mandler R, Oden N, Walker R. Study design to examine the potential role of assessment reactivity in the Screening, Motivational Assessment, Referral, and Treatment in Emergency Departments (SMART-ED) protocol. *Addict Sci Clin Pract.* 2012 Aug 28; 7(1): 16. [Epub ahead of print].

Preliminary Evidence That Adherence To Counseling Mediates The Effects Of Pretreatment Self-Efficacy and Motivation On Outcome Of A Cessation Attempt In Smokers With ADHD

Few studies have evaluated predictors of smoking cessation outcomes in smokers with attention-deficit/hyperactivity disorder (ADHD), which could help to improve suboptimal treatment outcomes in this population. The purpose of this study was to examine pretreatment thoughts about smoking abstinence (i.e., desire to quit, perceived difficulty quitting, and expected success in quitting) as predictors of smoking cessation outcomes in smokers with ADHD and to determine the extent to which treatment adherence mediates these relationships. Participants were adult smokers with ADHD (n = 255), who were enrolled in a multisite smoking cessation study and received either osmotic-release oral system methylphenidate (OROS-MPH) or placebo in combination with transdermal nicotine replacement and brief cessation counseling. Bootstrapped logistic regression models were generated to test main effects of thoughts about abstinence on smoking cessation outcomes and to examine treatment adherence as a mediator of these relationships. Desire to quit and expected success in quitting, but not perceived difficulty quitting, predicted smoking cessation outcomes, as did all of the treatment adherence variables (i.e., percent sessions attended, counselor ratings of counseling adherence, and percent patch adherence). Counseling adherence partially mediated the relationship between smoking cessation outcomes and both pretreatment desire to quit and expected success. Smokers with ADHD who have higher self-efficacy (i.e., expected success) and motivation (i.e., desire) to quit are more adherent to smoking cessation counseling and have better smoking cessation outcomes. Additional research is needed to determine whether treatment-seeking smokers with ADHD would benefit from an intervention designed to increase self-efficacy and motivation to quit. Heffner JL, Lewis DF, Winhusen TM. Preliminary Evidence that adherence

to counseling mediates the effects of pretreatment self-efficacy and motivation on outcome of a cessation attempt in smokers with ADHD. *Nicotine Tob Res.* 2012 Sep 4. [Epub ahead of print].

Possible Barriers To Enrollment In Substance Abuse Treatment Among A Diverse Sample Of Asian Americans and Pacific Islanders: Opinions Of Treatment Clients

This mixed methods study examined motivations and barriers to substance abuse treatment entry and treatment continuation among Asian American and Pacific Islander (AAPI) substance users. AAPI substance users (N=61) were recruited from substance abuse treatment programs in California and Hawaii. Semi-structured interviews and interviewer-administered surveys assessed barriers and facilitators to entering substance abuse treatment. Barriers included peer pressure, family influences, and face loss concerns. Facilitators included peer support, involvement in the criminal justice system, a perceived need for treatment, and culturally competent substance abuse treatment services. Family and peer influences may act as both facilitators and impediments. AAPI substance using populations face many of the same individual-level and structural and systems barriers to entry to treatment as other substance using populations. However, similar to other racial/ethnic minority groups, it is important to address cultural differences and develop culturally competent substance abuse treatments for the AAPI population. Masson CL, Shopshire MS, Sen S, Hoffman KA, Hengl NS, Bartolome J, McCarty D, Sorensen JL, Iguchi MY. Possible barriers to enrollment in substance abuse treatment among a diverse sample of Asian Americans and Pacific Islanders: Opinions of treatment clients. *J Subst Abuse Treat.* 2012 Sep 14. [Epub ahead of print].

American Indians With Substance Use Disorders: Treatment Needs and Comorbid

Conditions American Indians and Alaska Natives (AI/ANs) experience significant disparities in health status and access to care. Furthermore, only limited data are available on substance use, mental health disorders, and treatment needs for this population. Addressing such disparities and developing culturally relevant, effective interventions for AI/AN communities require participatory research. The Western States Node of the National Institute on Drug Abuse Clinical Trials Network partnered with two American Indian substance abuse treatment programs: an urban health center and a reservation-based program to assess client characteristics, drug use patterns, and treatment needs. Data collected by staff members at the respective programs from urban (n = 74) and reservation (n = 121) clients were compared. Additional sub-analysis examined patients reporting regular opioid use and mood disorders. Findings indicate that urban clients were more likely to report employment problems, polysubstance use, and a history of abuse. Reservation-based clients reported having more severe medical problems and a greater prevalence of psychiatric problems. Clients who were regular opioid users were more likely to report having a chronic medical condition, suicidal thoughts, suicide attempts, polysubstance abuse, and IV drug use. Clients who reported a history of depression had twice as many lifetime hospitalizations and more than five times as many days with medical problems. Findings from this project provide information about the patterns of substance abuse and the importance of comprehensive assessments of trauma and comorbid conditions. Results point to the need for integrative coordinated care and auxiliary services for AI/AN clients seeking treatment for substance use disorders. Rieckmann T, McCarty D, Kovas A, Spicer P, Bray J, Gilbert S, Mercer J. American Indians with substance use disorders: treatment needs and comorbid conditions. *Am J Drug Alcohol Abuse.* 2012 Sep; 38(5): 498-504.

Substance Use, Treatment Admissions, and Recovery Trends In Diverse Washington State Tribal Communities

Qualitative and quantitative data and participatory research approaches might be most valid and effective for assessing substance use/abuse and related trends in American Indian and Alaska Native (AIAN) communities. Twenty-nine federally recognized AIAN tribes in Washington (WA) State were invited to participate in Health Directors (HD) interviews and State treatment admissions data analyses. Ten Tribal HD (or designees) from across WA participated in 30-60-minute qualitative interviews. State treatment admissions data from 2002 to 2008 were analyzed for those who identified with one of 11 participating AIAN communities to explore admission rates by primary drug compared to non-AIANs. Those who entered treatment and belonged to one of the 11 participating tribes (n = 4851) represented 16% of admissions for those who reported a tribal affiliation. Interviewees reported that prescription drugs, alcohol, and marijuana are primary community concerns, each presenting similar and distinct challenges. Additionally, community health is tied to access to resources, services, and culturally appropriate and effective interventions. Treatment data results were consistent with interviewee-reported substance use/abuse trends, with alcohol as the primary drug for 56% of AIAN adults compared to 46% of non-AIAN, and other opiates as second most common for AIAN adults in 2008 with 15% of admissions. Findings are limited to those tribal communities/community members who agreed to participate. Analyses suggest that some diverse AIAN communities in WA State share similar substance use/abuse, treatment, and recovery trends and continuing needs. Appropriate and effective research with AIAN communities requires respectful and flexible approaches. Radin SM, Banta-Green CJ, Thomas LR, Kutz SH, Donovan DM. Substance use, treatment admissions, and recovery trends in diverse Washington state tribal communities. *Am J Drug Alcohol Abuse*. 2012 Sep; 38(5): 511-517.

Osmotic Release Oral System Methylphenidate Prevents Weight Gain During A Smoking-Cessation Attempt In Adults With ADHD

Adults with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for both cigarette smoking and being overweight or obese. Although smoking cessation tends to result in weight increase, potentially initiating or exacerbating weight problems, adults with ADHD who are treated with osmotic release oral system methylphenidate (OROS-MPH) tend to lose weight. It is unclear how the use of OROS-MPH during a smoking-cessation attempt might affect the typical weight gain that accompanies cessation. The authors examined changes in weight and hunger during a smoking-cessation attempt in 215 adults with ADHD who completed a multisite, randomized, controlled trial and were randomized to either OROS-MPH (n = 107) or placebo (n = 108) (NCT #00253747). Both groups also received open-label transdermal nicotine replacement and counseling. Participants who received OROS-MPH lost an average of 1.6% of their body weight during the 11-week study, whereas those who received placebo gained an average of 1.3% of their weight (p < .001). Hunger ratings were lower in the OROS-MPH group (M = 1.1, SD = 0.8) than in the placebo group (M = 1.6, SD = 0.9; p < .001). The use of OROS-MPH during a smoking-cessation attempt prevents weight gain in adults with ADHD who substantially reduce or quit smoking. The potential utility of OROS-MPH in individuals with ADHD who are attempting to quit smoking and for whom weight gain would be problematic warrants further research. Heffner JL, Lewis DF, Winhusen TM. Osmotic release oral system methylphenidate prevents weight gain during a smoking-cessation attempt in adults with ADHD. *Nicotine Tob Res*. 2012 Sep 6. [Epub ahead of print].

Therapist Effects In A NIDA CTN Intervention Trial With Pregnant Substance Abusing Women: Findings From A RCT With MET and TAU Conditions

The authors investigated whether therapist effects may account for treatment outcomes among pregnant substance users in controlled and naturalistic treatments. Therapists randomized to Motivational Enhancement Therapy (MET) and treatment as usual (TAU) conditions and assigned at least five clients were included. Client self-reported substance use and urine toxicology at posttreatment, 1- and 3-month follow-ups were obtained. A therapist main effect was found across therapy conditions and within MET (five therapists) but not within TAU (five therapists). When substance use was treated as a dichotomous measure (abstinence/nonabstinence) corroborated with urine toxicology screening, no therapist effect was found. Clients perceived therapists to vary in their supportiveness and listening skills, for example, but these impressions were not associated with therapist effectiveness to reduce substance use. The authors found support for a limited therapist effect, but only within the MET condition and only with a continuous outcome variable. Secondary analyses identified differences in client impressions of their therapist, but these impressions did not predict therapist effectiveness in reducing substance use. Although these findings warrant replication, they suggest that client substance use outcomes among pregnant women may be rather homogeneous regardless of the type of intervention or therapist. Erickson SJ, Tonigan JS, Winhusen, T. Therapist effects in a NIDA CTN intervention trial with pregnant substance abusing women: findings from a RCT with MET and TAU conditions. *Alcoholism Treatment Quarterly* 2012; 30(2): 224-237.

Early Data From Project Engage: A Program To Identify and Transition Medically Hospitalized Patients Into Addictions Treatment

Patients with untreated substance use disorders (SUDs) are at risk for frequent emergency department visits and repeated hospitalizations. Project Engage, a US pilot program at Wilmington Hospital in Delaware, was conducted to facilitate entry of these patients to SUD treatment after discharge. Patients identified as having hazardous or harmful alcohol consumption based on results of the Alcohol Use Disorders Identification Test-Primary Care (AUDIT-PC), administered to all patients at admission, received bedside assessment with motivational interviewing and facilitated referral to treatment by a patient engagement specialist (PES). This program evaluation provides descriptive information on self-reported rates of SUD treatment initiation of all patients and health-care utilization and costs for a subset of patients. Program-level data on treatment entry after discharge were examined retrospectively. Insurance claims data for two small cohorts who entered treatment after discharge (2009, n=18, and 2010, n=25) were reviewed over a six-month period in 2009 (three months pre- and post-Project Engage), or over a 12-month period in 2010 (six months pre- and post-Project Engage). These data provided descriptive information on health-care utilization and costs. (Data on those who participated in Project Engage but did not enter treatment were unavailable). Between September 1, 2008, and December 30, 2010, 415 patients participated in Project Engage, and 180 (43%) were admitted for SUD treatment. For a small cohort who participated between June 1, 2009, and November 30, 2009 (n=18), insurance claims demonstrated a 33% (\$35,938) decrease in inpatient medical admissions, a 38% (\$4,248) decrease in emergency department visits, a 42% (\$1,579) increase in behavioral health/substance abuse (BH/SA) inpatient admissions, and a 33% (\$847) increase in outpatient BH/SA admissions, for an overall decrease of \$37,760. For a small cohort who participated between June 1, 2010, and November 30, 2010 (n=25), claims demonstrated a 58% (\$68,422) decrease in inpatient medical admissions; a 13% (\$3,308) decrease in emergency department visits; a 32% (\$18,119) decrease in BH/SA inpatient admissions, and a 32% (\$963) increase in outpatient BH/SA admissions, for an overall decrease of \$88,886.

These findings demonstrate that a large percentage of patients entered SUD treatment after participating in Project Engage, a novel intervention with facilitated referral to treatment. Although the findings are limited by the retrospective nature of the data and the small sample sizes, they do suggest a potentially cost-effective addition to existing hospital services if replicated in prospective studies with larger samples and controls. Pecoraro A, Horton T, Ewen E, Becher J, Wright PA, Silverman B, McGraw P, Woody GE. Early data from project engage: a program to identify and transition medically hospitalized patients into addictions treatment. *Addict Sci Clin Pract.* 2012 Sep 25; 7(1): 20.

Predictors Of Outcome After Short-Term Stabilization With Buprenorphine Using buprenorphine as a medication to treat opioid dependence is becoming more prevalent as illicit opiate use increases. Identifying the characteristics of opiate dependent individuals best suited to benefit from buprenorphine would improve guidelines for its administration. This study evaluates baseline and treatment participation variables for predicting positive response to short-term stabilization with buprenorphine. Data include demographic, drug use, and other variables collected from participants undergoing stabilization over a 4-week period before being tapered off buprenorphine in a short-term detoxification process. Outcome variables include opioid use and retention. Logistic regression results indicate several characteristics associated with opioid use at the end of the stabilization period. These include being older, having no criminal history, and less opiate use. Criminal activity and opioid use in the last 30 days were significantly associated with shorter treatment stays. The benefits of identifying individual characteristics that may predict treatment response are discussed. Hillhouse M, Canamar CP, Ling W. Predictors of outcome after short-term stabilization with buprenorphine. *J Subst Abuse Treat.* 2012 Sep 25. [Epub ahead of print].

HIV Rapid Testing In Drug Treatment: Comparison Across Treatment Modalities Despite high rates of risky behavior among patients, many drug abuse treatment programs do not provide on-site HIV testing. This secondary analysis examined differences in outcome by program modality from a multi-site trial in which 1281 HIV-negative patients in three methadone programs, seven non-methadone outpatient programs, and three residential programs were randomly assigned to: (1) off-site referral for HIV risk reduction counseling and testing; or on-site rapid testing (2) with or (3) without risk reduction counseling. The parent study using generalized estimating equations with site as a cluster variable found significantly higher rates of HIV testing and feedback of results by 1 month post-enrollment for the combined on-site conditions compared to the offsite condition [RR=4.52, 97.5% CI (3.57, 5.72)]. Utilizing the same statistical approach, the authors found neither significant treatment modality nor significant treatment modality by testing condition interaction effects either for receipt of HIV test results at 1 month or for sexual or drug use HIV-risk behaviors at 6-month follow-up. On-site HIV testing is effective across treatment modalities for achieving high rates of testing and results feedback. All programs should be encouraged to adopt or expand this service. Schwartz RP, Stitzer ML, Feaster DJ, Korthuis PT, Alvanzo AA, Winhusen TM, Donnard L, Snead N, Metsch LR. HIV rapid testing in drug treatment: comparison across treatment modalities. *J Subst Abuse Treat.* 2012 Sep 26. [Epub ahead of print].

Clinician Attitudes, Social Norms and Intentions To Use A Computer-Assisted Intervention The National Drug Abuse Treatment Clinical Trials Network (CTN) works to bridge the gap between research and practice and tested a Web-delivered psychosocial intervention (the Therapeutic Education System, TES) in 10 community treatment centers. Computer-assisted

therapies, such as Web-delivered interventions, may improve the consistency and efficiency of treatment for alcohol and drug use disorders. Prior to the start of the study, the authors surveyed counselors (N=96) in participating treatment centers and assessed counselor attitudes, perceived social norms and intentions to use a Web-delivered intervention. Analysis of the intention to adopt a Web-delivered intervention assessed the influence of attitudes and perceived social norms. Perceived social norms were a significant contributor to clinician intention to adopt Web-based interventions while attitude was not. To promote successful implementation, it may be helpful to create social norms supportive of computer-assisted therapies. Buti AL, Eakins D, Fussell H, Kunkel LE, Kudura A, McCarty D. Clinician attitudes, social norms and intentions to use a computer-assisted intervention. *J Subst Abuse Treat.* 2012 Sep 26. [Epub ahead of print].

Sex Differences In Disinhibition and Its Relationship To Physical Abuse In A Sample Of Stimulant-Dependent Patients

Research suggests that impulsivity is a vulnerability factor for developing stimulant dependence, that women develop dependence more quickly than men, and that physical abuse can increase impulsivity and may have greater adverse health consequences in women. This study sought to tie these findings together by evaluating: (1) sex differences in disinhibition prior to lifetime initiation of stimulant abuse and (2) the relationship between physical abuse and disinhibition in stimulant-dependent patients. The Frontal Systems Behavior Scale (FrSBe) is 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 pre-morbid functioning and has a specific cutoff for defining clinically significant abnormalities. Six sites evaluating 12-step facilitation for stimulant abusers obtained the FrSBe from 118 methamphetamine- and/or cocaine-dependent participants. Lifetime physical abuse was measured by the Addiction Severity Index (ASI). The proportion reporting clinically significant disinhibition was significantly higher in women (64.9%) than in men (45.0%, $p=0.04$), with no significant difference on the other FrSBe scales. Physical abuse in women, but not men, was associated with worse functioning, with physically abused, relative to non-abused, women having a significantly greater proportion with clinically significant disinhibition ($p<0.01$) and total neurobehavioral abnormalities ($p<0.01$). These findings suggest that women may have significantly greater disinhibition than men prior to lifetime initiation of stimulant abuse and that physical abuse in women is associated with greater disinhibition. Winhusen T, Lewis D. Sex differences in disinhibition and its relationship to physical abuse in a sample of stimulant-dependent patients. *Drug Alcohol Depend.* 2012 Oct 10. [Epub ahead of print].

Utilization Of Communication Technology By Patients Enrolled In Substance Abuse Treatment

Technology-based applications represent a promising method for providing efficacious, widely available interventions to substance abuse treatment patients. However, limited access to communication technology (i.e., mobile phones, computers, internet, and e-mail) could significantly impact the feasibility of these efforts, and little is known regarding technology utilization in substance abusing populations. A survey was conducted to characterize utilization of communication technology in 266 urban, substance abuse treatment patients enrolled at eight drug-free, psychosocial or opioid-replacement therapy clinics. Survey participants averaged 41 years of age and 57% had a yearly household income of less than \$15,000. The vast majority reported access to a mobile phone (91%), and to SMS text messaging (79%). Keeping a consistent mobile phone number and yearly mobile contract was higher for White participants, and also for those with higher education, and enrolled in drug-free, psychosocial treatment. Internet, e-mail, and computer use was much lower (39-45%), with younger age, higher education and income predicting greater use. No

such differences existed for the use of mobile phones however. Concern regarding the digital divide for marginalized populations appears to be disappearing with respect to mobile phones, but still exists for computer, internet, and e-mail access and use. Results suggest that mobile phone and texting applications may be feasibly applied for use in program-client interactions in substance abuse treatment. Careful consideration should be given to frequent phone number changes, access to technology, and motivation to engage with communication technology for treatment purposes. McClure EA, Acquavita SP, Harding E, Stitzer ML. Utilization of communication technology by patients enrolled in substance abuse treatment. *Drug Alcohol Depend.* 2012 Oct 26. [Epub ahead of print].

Cocaine Use Reduction With Buprenorphine (CURB): Rationale, Design, and Methodology

Effective medications to treat cocaine dependence have not been identified. Recent pharmacotherapy trials demonstrate the potential efficacy of buprenorphine (BUP) (alone or with naltrexone) for reducing cocaine use. The National Institute on Drug Abuse Clinical Trials Network (CTN) launched the Cocaine Use Reduction with Buprenorphine (CURB) investigation to examine the safety and efficacy of sublingual BUP (as Suboxone®) in the presence of extended-release injectable naltrexone (XR-NTX) for the treatment of cocaine dependence. This paper describes the design and rationale for this study. This multi-site, double-blind, placebo-controlled study will randomize 300 participants across 11 sites. Participants must meet the DSM-IV criteria for cocaine dependence and past or current opioid dependence or abuse. Participants are inducted onto XR-NTX after self-reporting at least 7 days of abstinence from opioids and tolerating a naloxone challenge followed by oral naltrexone and are then randomly assigned to one of three medication conditions (4mg BUP, 16mg BUP, or placebo) for 8 weeks. Participants receive a second injection of XR-NTX 4 weeks after the initial injection, and follow-up visits are scheduled at 1 and 3 months post-treatment. Participants receive weekly cognitive behavioral therapy (CBT). Recruitment commenced in September, 2011. Enrollment, active medication, and follow-up phases are ongoing, and recruitment is exceeding targeted enrollment rates. This research using 2 medications will demonstrate whether BUP, administered in the presence of XR-NTX, reduces cocaine use in adults with cocaine dependence and opioid use disorders and will demonstrate if XR-NTX prevents development of physiologic dependence on BUP. Mooney LJ, Nielsen S, Saxon A, Hillhouse M, Thomas C, Hasson A, Stablein D, McCormack J, Lindblad R, Ling W. Cocaine Use Reduction with Buprenorphine (CURB): rationale, design, and methodology. *Contemp Clin Trials.* 2012 Nov 16; 34(2): 196-204. [Epub ahead of print].

Predictors Of Treatment Response In Adolescents With Comorbid Substance Use Disorder and Attention-Deficit/Hyperactivity Disorder

Attention-Deficit/Hyperactivity Disorder (ADHD) frequently co-occurs with substance use disorder (SUD) and is associated with poor substance-use treatment outcomes. A trial evaluating osmotic-release oral system methylphenidate (OROS-MPH) for adolescents with ADHD and SUD, concurrently receiving behavioral therapy, revealed inconsistent medication effects on ADHD or SUD. Clinical care for this population would be advanced by knowledge of treatment outcome predictors. Data from the randomized placebo-controlled trial (n = 299) were analyzed. Significant treatment predictors included: 1) Substance use severity, associated with poorer ADHD and SUD outcomes, 2) ADHD severity, associated with better ADHD and SUD outcomes, 3) comorbid conduct disorder, associated with poorer ADHD outcomes, and 4) court-mandated status, associated with better SUD outcomes but poorer treatment completion. An interaction effect showed that OROS-MPH improved SUD outcomes in adolescents with comorbid conduct disorder compared to placebo. While severe SUD may require more

intensive psychosocial treatment, OROS-MPH may improve substance treatment outcomes in adolescents with co-morbid attention and conduct problems. Tamm L, Trello-Rishel K, Riggs P, Nakonezny PA, Acosta M, Bailey G, Winhusen T. Predictors of treatment response in adolescents with comorbid substance use disorder and attention-deficit/hyperactivity disorder. *J Subst Abuse Treat.* 2013 Feb; 44(2): 224-230. Epub 2012 Aug 11.

Assessing Fidelity Of Treatment Delivery In Group and Individual 12-Step Facilitation

Twelve step facilitation (TSF) is an emerging, empirically supported treatment, the study of which will be strengthened by rigorous fidelity assessment. This report describes the development, reliability and concurrent validity of the Twelve Step Facilitation Adherence Competence Empathy Scale (TSF ACES), a comprehensive fidelity rating scale for group and individual TSF treatment developed for the National Drug Abuse Treatment Clinical Trials Network study, Stimulant Abuser Groups to Engage in 12-Step. Independent raters used TSF ACES to rate treatment delivery fidelity of 966 (97% of total) TSF group and individual sessions. TSF ACES summary measures assessed therapist treatment adherence, competence, proscribed behaviors, empathy and overall session performance. TSF ACES showed fair to good overall reliability; weighted kappa coefficients for 59 co-rated sessions ranged from .31 to 1.00, with a mean of .69. Reliability ratings for session summary measures were good to excellent (.69-.91). Internal consistency for the instrument was variable (.47-.71). Relationships of the TSF ACES summary measures with each other, as well as relationships of the summary measures with a measure of therapeutic alliance provided support for concurrent and convergent validity. Implications and future directions for the use of TSF ACES in clinical trials and community treatment implementation are discussed. Campbell BK, Manuel JK, Manser ST, Peavy KM, Stelmokas J, McCarty D, Guydish JR. Assessing fidelity of treatment delivery in group and individual 12-step facilitation. *J Subst Abuse Treat.* 2013 Feb; 44(2): 169-176. Epub 2012 Sep 1.

INTRAMURAL RESEARCH

Synaptic Plasticity Section

Synaptic and Behavioral Profile Of Multiple Glutamatergic Inputs To the Nucleus

Accumbens Excitatory afferents to the nucleus accumbens (NAc) are thought to facilitate reward seeking by encoding reward-associated cues. Selective activation of different glutamatergic inputs to the NAc can produce divergent physiological and behavioral responses, but mechanistic explanations for these pathway-specific effects are lacking. Here, IRP scientists compared the innervation patterns and synaptic properties of ventral hippocampus, basolateral amygdala, and prefrontal cortex input to the NAc. Ventral hippocampal input was found to be uniquely localized to the medial NAc shell, where it was predominant and selectively potentiated after cocaine exposure. In vivo, bidirectional optogenetic manipulations of this pathway attenuated and enhanced cocaine-induced locomotion. Challenging the idea that any of these inputs encode motivationally neutral information, activation of each discrete pathway reinforced instrumental behaviors. Finally, direct optical activation of medium spiny neurons proved to be capable of supporting self-stimulation, demonstrating that behavioral reinforcement is an explicit consequence of strong excitatory drive to the NAc. Britt JP, Benaliouad F, McDevitt RA, Stuber GD, Wise RA, Bonci A. Synaptic and behavioral profile of multiple glutamatergic inputs to the nucleus accumbens. *Neuron* 2012; 31(11): 790-803.

The Dual Orexin/Hypocretin Receptor Antagonist, Almorexant, In the Ventral Tegmental Area Attenuates Ethanol Self-Administration

Recent studies have implicated the hypocretin/orexinergic system in reward-seeking behavior. Almorexant, a dual orexin/hypocretin R(1) and R(2) receptor antagonist, has proven effective in preclinical studies in promoting sleep in animal models and was in Phase III clinical trials for sleep disorders. The present study combines behavioral assays with in vitro biochemical and electrophysiological techniques to elucidate the role of almorexant in ethanol and sucrose intake. Using an operant self-administration paradigm, IRP researchers demonstrate that systemic administration of almorexant decreased operant self-administration of both 20% ethanol and 5% sucrose. They further demonstrate that intra-ventral tegmental area (VTA) infusions, but not intra-substantia nigra infusions, of almorexant reduced ethanol self-administration. Extracellular recordings performed in VTA neurons revealed that orexin-A increased firing and this enhancement of firing was blocked by almorexant. The results demonstrate that orexin/hypocretin receptors in distinct brain regions regulate ethanol and sucrose mediated behaviors. Srinivasan S, Simms JA, Nielsen CK, Lieske SP, Bito-Onon JJ, Yi H, Hopf FW, Bonci A, Barlett SE. The dual orexin/hypocretin receptor antagonist, Almorexant, in the ventral tegmental area attenuates ethanol self-administration. *PloS One* 2012; 7(9): e44726.

Transient Stimulation Of Distinct Subpopulations Of Striatal Neurons Mimics Changes In Action Value

In changing environments, animals must adaptively select actions to achieve their goals. In tasks involving goal-directed action selection, striatal neural activity has been shown to represent the value of competing actions. Striatal representations of action value could potentially bias responses toward actions of higher value. However, no study to date has demonstrated the direct effect of distinct striatal pathways in goal-directed action selection. IRP scientists found that transient optogenetic stimulation of dorsal striatal dopamine D1 and D2 receptor-expressing neurons during decision-making in mice introduced opposing biases in the distribution of choices. The effect of stimulation on choice was dependent on recent reward history and mimicked an

additive change in the action value. Although stimulation before and during movement initiation produced a robust bias in choice behavior, this bias was substantially diminished when stimulation was delayed after response initiation. Together, these data suggest that striatal activity is involved in goal-directed action selection. Tai LH, Lee AM, Benavidez N, Bonci A, Wilbrecht L. Transient stimulation of distinct subpopulations of striatal neurons mimics changes in action value. *Nat Neurosci.* 2012; 15(9): 1281-1289.

Neuronal Networks Section

Heterogeneous Composition Of Dopamine Neurons Of the Rat A10 Region: Molecular Evidence For Diverse Signaling Properties

The A10 region contains different neurons: dopamine (expressing tyrosine hydroxylase; TH), GABA, glutamate-only (expressing the vesicular glutamate transporter 2; VGluT2), and TH-VGluT2 (coexpressing TH and VGluT2). IRP scientists used three methods to investigate proteins necessary for the synthesis (aromatic L: -amino acid decarboxylase, AADC) or transport (vesicular monoamine transporter; VMAT2 or dopamine transporter; DAT) of dopamine within TH neurons in the A10 region. By in situ hybridization-immunohistochemistry, they found that all TH neurons in the A10 region had AADC, but not all had VMAT2, DAT or D2 receptors (D(2)R). To determine whether TH-VGluT2 neurons account for TH neurons lacking these dopamine markers, the authors implemented an anatomical "mirror technique", and found that not all TH-VGluT2 neurons lacked VMAT2, DAT or D(2)R. Next, by quantitative RT-PCR of individual micro-dissected TH neurons, the authors discovered two classes of TH-VGluT2 and three classes of TH-only neurons with different latero-medial distribution. Some of the TH-VGluT2 neurons had both VMAT2 and DAT (TH-VGluT2 Class 1); others lacked detectable levels of both transporters (TH-VGluT2 Class 2). Most of the TH-only neurons contained VMAT2 and DAT (TH-only Class 1), a few had DAT without detectable VMAT2 (TH-only Class 2), and others lacked detectable levels of both transporters (TH-only Class 3). The authors concluded that (a) the majority of TH neurons lacking DAT are TH-VGluT2 neurons, (b) very few TH-only neurons express DAT without VMAT2, and (c) TH-VGluT2 neurons lacking DAT also lack VMAT2. Thus, the A10 region contains dopamine neurons with differential compartmentalization and unique signaling properties. Li X, Qi J, Yamaguchi T, Wang HL, Morales M. Heterogeneous composition of dopamine neurons of the rat A10 region: molecular evidence for diverse signaling properties. *Brain Struct Funct.* 2012 Aug 29. [Epub ahead of print].

Electrophysiology Research Section, Cellular Neurobiology Research Branch

Synaptic Targets Of Δ^9 -Tetrahydrocannabinol In the Central Nervous System The availability of potent synthetic agonists for cannabinoid receptors has facilitated our understanding of cannabinoid actions on synaptic transmission in the central nervous system. Moreover, the ability of these compounds to inhibit neurotransmitter release at many central synapses is thought to underlie most of the behavioral effects of cannabinoid agonists. However, despite the widespread use and misuse of marijuana, and recognition of its potential adverse psychological effects in humans, comparatively few studies have examined the actions of its primary psychoactive constituent, Δ^9 -tetrahydrocannabinol (THC), at well-defined synaptic pathways. Here IRP investigators examine the recent literature describing the effects of acute and repeated THC exposure on synaptic function

in several brain regions and explore the importance of these neurobiological actions of THC in drug addiction. Synaptic targets of Δ^9 -tetrahydrocannabinol in the central nervous system. Hoffman AF, Lupica CR. Cold Spring Harbor Perspectives in Medicine. 2012 Dec 3. doi:pii: cshperspect.a012237v1. 10.1101/cshperspect.a012237. [Epub ahead of print]

Silent Synapses In Selectively Activated Nucleus Accumbens Neurons Following Cocaine

Sensitization Cocaine-induced alterations in synaptic glutamate function in nucleus accumbens are thought to mediate drug-related behaviors such as psychomotor sensitization. However, previous studies have examined global alterations in randomly selected accumbens neurons regardless of their activation state during cocaine-induced behavior. IRP scientists recently found that a minority of strongly activated Fos-expressing accumbens neurons are necessary for cocaine-induced psychomotor sensitization, whereas the majority of accumbens neurons are less directly involved. They assessed synaptic alterations in these strongly activated accumbens neurons in Fos-GFP mice, which express a fusion protein of Fos and GFP in strongly activated neurons, and compared these alterations with those in surrounding non-activated neurons. Cocaine sensitization produced higher levels of 'silent synapses', which contained functional NMDA receptors and nonfunctional AMPA receptors only in GFP-positive neurons, 6-11 d after sensitization. Thus, distinct synaptic alterations are induced in the most strongly activated accumbens neurons that mediate psychomotor sensitization. Koya E, Cruz FC, Ator R, Golden SA, Hoffman AF, Lupica CR, Hope BT. Silent synapses in selectively activated nucleus accumbens neurons following cocaine sensitization. Nature Neuroscience. 2012 Nov; 15(11): 1556-1562. doi: 10.1038/nn.3232. Epub 2012 Sep 30.

PTEN Deletion Enhances Survival, Neurite Outgrowth, and Function Of Dopamine Neuron Grafts To Mito Park Mice

Clinical trials in Parkinson's disease have shown that transplants of embryonic mesencephalic dopamine neurons form new functional connections within the host striatum, but the therapeutic benefits have been highly variable. One obstacle has been poor survival and integration of grafted dopamine neurons. Activation of Akt, a serine/threonine kinase that promotes cell survival and growth, increases the ability of neurons to survive after injury and to regenerate lost neuronal connections. Because the lipid phosphatase, phosphatase and tensin homolog (PTEN) inhibits Akt, the authors generated a mouse with conditional knock-out of PTEN in dopamine neurons, leading to constitutive expression of Akt in these neurons. Ventral mesencephalic tissue from dopamine phosphatase and tensin homologue knock-out or control animals was then transplanted bilaterally into the dopamine depleted striata of MitoPark mice that express a parkinsonian phenotype because of severe respiratory chain dysfunction in dopamine neurons. After transplantation into MitoPark mice, PTEN-deficient dopamine neurons were less susceptible to cell death, and exhibited a more extensive pattern of fibre outgrowth compared to control grafts. Voltammetric measurements demonstrated that dopamine release and reuptake were significantly increased in the striata of animals receiving dopamine PTEN knock-out transplants. These animals also displayed enhanced spontaneous and drug-induced locomotor activity, relative to control transplanted MitoPark mice. These results suggest that disinhibition of the Akt-signalling pathway may provide a valuable strategy to enhance survival, function and integration of grafted dopamine neurons within the host striatum and, more generally, to improve survival and integration of different forms of neural grafts. Zhang Y, Granholm AC, Huh K, Shan L, Diaz-Ruiz O, Malik N, Olson L, Hoffer BJ, Lupica CR, Hoffman AF, Bäckman CM. PTEN deletion enhances survival, neurite outgrowth and function of dopamine neuron grafts to Mito Park mice. Brain. 2012 Sep; 135(Pt 9): 2736-2749. doi: 10.1093/brain/aws196.

Attenuated Response To Methamphetamine Sensitization and Deficits In Motor Learning and Memory After Selective Deletion Of B-Catenin In Dopamine Neurons

In the present study, IRP investigators analyzed mice with a targeted deletion of β -catenin in DA neurons (DA- β cat KO mice) to address the functional significance of this molecule in the shaping of synaptic responses associated with motor learning and following exposure to drugs of abuse. Relative to controls, DA- β cat KO mice showed significant deficits in their ability to form long-term memories and displayed reduced expression of methamphetamine-induced behavioral sensitization after subsequent challenge doses with this drug, suggesting that motor learning and drug-induced learning plasticity are altered in these mice. Morphological analyses showed no changes in the number or distribution of tyrosine hydroxylase-labeled neurons in the ventral midbrain. While electrochemical measurements in the striatum determined no changes in acute DA release and uptake, a small but significant decrease in DA release was detected in mutant animals after prolonged repetitive stimulation, suggesting a possible deficit in the DA neurotransmitter vesicle reserve pool. However, electron microscopy analyses did not reveal significant differences in the content of synaptic vesicles per terminal, and striatal DA levels were unchanged in DA- β cat KO animals. In contrast, striatal mRNA levels for several markers known to regulate synaptic plasticity and DA neurotransmission were altered in DA- β cat KO mice. This study demonstrates that ablation of β -catenin in DA neurons leads to alterations of motor and reward-associated memories and to adaptations of the DA neurotransmitter system and suggests that β -catenin signaling in DA neurons is required to facilitate the synaptic remodeling underlying the consolidation of long-term memories. Diaz-Ruiz O, Zhang Y, Shan L, Malik N, Hoffman AF, Ladenheim B, Cadet JL, Lupica CR, Tagliaferro A, Brusco A, Bäckman CM. Attenuated response to methamphetamine sensitization and deficits in motor learning and memory after selective deletion of β -catenin in dopamine neurons. *Learn Mem.* 2012 Jul 20; 19(8): 341-350. doi: 10.1101/lm.026716.112.

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 researchers 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 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 noncontingent 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 nonactivated GFP-negative mPFC neurons following yohimbine-induced reinstatement of food seeking. This reinstatement was associated with reduced AMPA receptor/NMDA receptor current ratios and increased paired-pulse facilitation in activated GFP-positive but not GFP-negative neurons. While ovarian hormones do not appear to play a role in stress-induced relapse of food seeking in the authors' 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 QR, 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. *J Neurosci*. 2012 Jun 20; 32(25): 8480-8490. doi: 10.1523/JNEUROSCI.5895-11.2012.

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 scientists 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. doi: 10.1016/j.bbrc.2012.05.042. Epub 2012 May 15.

Altered Dendritic Distribution Of Dopamine D2 Receptors and Reduction In Mitochondrial Number In Parvalbumin-Containing Interneurons In the Medial Prefrontal Cortex Of Cannabinoid-1 (CB1) Receptor Knockout Mice

The prelimbic prefrontal cortex (PL) is a brain region integral to complex behaviors that are highly influenced by cannabinoids and by dopamine D2 receptor (D2R)-mediated regulation of fast-firing parvalbumin-containing interneurons. IRP scientists have recently shown that constitutive deletion of the cannabinoid-1 receptor (CB1R) greatly reduces parvalbumin levels in these neurons. The effects of CB1R deletion on PL parvalbumin interneurons may be ascribed to loss of CB1R-mediated retrograde signaling on mesocortical dopamine transmission, and, in turn, altered expression and/or subcellular distribution of D2R in the PL. Furthermore, diminished parvalbumin expression could indicate metabolic changes in fast-firing interneurons that may be reflected in changes in mitochondrial density in this population. The authors therefore comparatively examined electron microscopic dual labeling of D2R and parvalbumin in CB1 (-/-) and CB1 (+/+) mice to test the hypothesis that absence of CB1R produces changes in D2R localization and mitochondrial distribution in parvalbumin-containing interneurons of the PL. CB1 (-/-) mice had a significantly lower density of cytoplasmic D2R-immunogold particles in medium parvalbumin-labeled dendrites and a concomitant increase in the density of these particles in small dendrites. These dendrites received both excitatory and inhibitory-type synapses from unlabeled terminals and contained many mitochondria, whose numbers were significantly reduced in CB1 (-/-) mice. Non-parvalbumin dendrites showed no between-group differences in either D2R distribution or mitochondrial number. These results suggest that cannabinoid signaling provides an important determinant of dendritic D2 receptor distribution and mitochondrial availability in fast-spiking interneurons. Fitzgerald ML, Chan J, Mackie K, Lupica CR, Pickel VM. Altered dendritic distribution of dopamine D2 receptors and

reduction in mitochondrial number in parvalbumin-containing interneurons in the medial prefrontal cortex of cannabinoid-1 (CB1) receptor knockout mice. *J Comp Neurol.* 2012 Dec 1; 520(17): 4013-4031. doi: 10.1002/cne.23141.

Altered Dopamine Metabolism and Increased Vulnerability To MPTP In Mice With Partial Deficiency Of Mitochondrial Complex I In Dopamine Neurons

A variety of observations support the hypothesis that deficiency of complex I [reduced nicotinamide-adenine dinucleotide (NADH):ubiquinone oxidoreductase] of the mitochondrial respiratory chain plays a role in the pathophysiology of Parkinson's disease (PD). However, recent data from a study using mice with knockout of the complex I subunit NADH:ubiquinone oxidoreductase iron-sulfur protein 4 (Ndufs4) has challenged this concept as these mice show degeneration of non-dopamine neurons. In addition, primary dopamine (DA) neurons derived from such mice, reported to lack complex I activity, remain sensitive to toxins believed to act through inhibition of complex I. The authors tissue-specifically disrupted the Ndufs4 gene in mouse heart and found an apparent severe deficiency of complex I activity in disrupted mitochondria, whereas oxidation of substrates that result in entry of electrons at the level of complex I was only mildly reduced in intact isolated heart mitochondria. Further analyses of detergent-solubilized mitochondria showed the mutant complex I to be unstable but capable of forming supercomplexes with complex I enzyme activity. The loss of Ndufs4 thus causes only a mild complex I deficiency in vivo. The authors proceeded to disrupt Ndufs4 in midbrain DA neurons and found no overt neurodegeneration, no loss of striatal innervation and no symptoms of Parkinsonism in tissue-specific knockout animals. However, DA homeostasis was abnormal with impaired DA release and increased levels of DA metabolites. Furthermore, Ndufs4 DA neuron knockouts were more vulnerable to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Taken together, these findings lend in vivo support to the hypothesis that complex I deficiency can contribute to the pathophysiology of PD. Sterky FH, Hoffman AF, Milenkovic D, Bao B, Paganelli A, Edgar D, Wibom R, Lupica CR, Olson L, Larsson NG. Altered dopamine metabolism and increased vulnerability to MPTP in mice with partial deficiency of mitochondrial complex I in dopamine neurons. *Hum Mol Genet.* 2012 Mar 1; 21(5): 1078-1089. doi: 10.1093/hmg/ddr537. Epub 2011 Nov 16.

Linking Context With Reward: A Functional Circuit From Hippocampal CA3 To Ventral Tegmental Area

Reward-motivated behavior is strongly influenced by the learned significance of contextual stimuli in the environment. However, the neural pathways that mediate context-reward relations are not well understood. IRP investigators have identified a circuit from area CA3 of dorsal hippocampus to ventral tegmental area (VTA) that uses lateral septum (LS) as a relay. Theta frequency stimulation of CA3 excited VTA dopamine (DA) neurons and inhibited non-DA neurons. DA neuron excitation was likely mediated by disinhibition because local antagonism of γ -aminobutyric acid receptors blocked responses to CA3 stimulation. Inactivating components of the CA3-LS-VTA pathway blocked evoked responses in VTA and also reinstatement of cocaine-seeking by contextual stimuli. This transsynaptic link between hippocampus and VTA appears to be an important substrate by which environmental context regulates goal-directed behavior. Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR, Aston-Jones G. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. *Science.* 2011 Jul 15; 333(6040): 353-357. doi: 10.1126/science.1204622.

Decreased Parvalbumin Immunoreactivity In the Cortex and Striatum Of Mice Lacking the CB1 Receptor Cortical and striatal regions of the brain contain high levels of the cannabinoid-1 (CB1) receptor, the central neuronal mediator of activity-dependent synaptic plasticity evoked by endocannabinoids. The expression levels of parvalbumin, a calcium-binding protein found in fast-spiking interneurons of both regions, may be controlled in part by synaptic activity during critical periods of development. However, there is currently no evidence that CB1 receptor expression affects parvalbumin levels in either cortical or striatal interneurons. To assess this possibility, the authors examined parvalbumin immunoreactivity in the dorsolateral striatum, primary motor cortex (M1), and prefrontal cortex (PFC) of CB1 knockout and wild-type C57/BL6 mice. Quantitative densitometry showed a significant decrease in parvalbumin immunoreactivity within individual neurons in each of these regions of CB1 knockout mice relative to controls. A significantly lower density (number of cells per unit area) of parvalbumin-labeled neurons was observed in the striatum, but not the cortical regions of CB1 knockout mice. These findings suggest that CB1 receptor deletion may elicit a compensatory mechanism for network homeostasis affecting parvalbumin-containing cortical and striatal interneurons. Fitzgerald ML, Lupica CR, Pickel VM. Decreased parvalbumin immunoreactivity in the cortex and striatum of mice lacking the CB1 receptor. *Synapse*. 2011 Aug; 65(8): 827-831. doi: 10.1002/syn.20911. Epub 2011 Mar 28.

Impaired Nigrostriatal Function Precedes Behavioral Deficits In A Genetic Mitochondrial Model Of Parkinson's Disease Parkinson's disease (PD) involves progressive loss of nigrostriatal dopamine (DA) neurons over an extended period of time. Mitochondrial damage may lead to PD, and neurotoxins affecting mitochondria are widely used to produce degeneration of the nigrostriatal circuitry. Deletion of the mitochondrial transcription factor A gene (Tfam) in C57BL6 mouse DA neurons leads to a slowly progressing parkinsonian phenotype in which motor impairment is first observed at ~12 wk of age. L-DOPA treatment improves motor dysfunction in these "MitoPark" mice, but this declines when DA neuron loss is more complete. To investigate early neurobiological events potentially contributing to PD, the authors compared the neurochemical and electrophysiological properties of the nigrostriatal circuit in behaviorally asymptomatic 6- to 8-wk-old MitoPark mice and age-matched control littermates. Release, but not uptake of DA, was impaired in MitoPark mouse striatal brain slices, and nigral DA neurons lacked characteristic pacemaker activity compared with control mice. Also, hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channel function was reduced in MitoPark DA neurons, although HCN messenger RNA was unchanged. This study demonstrates altered nigrostriatal function that precedes behavioral parkinsonian symptoms in this genetic PD model. A full understanding of these presymptomatic cellular properties may lead to more effective early treatments of PD. Good CH, Hoffman AF, Hoffer BJ, Chefer VI, Shippenberg TS, Bäckman CM, Larsson NG, Olson L, Gellhaar S, Galter D, Lupica CR. Impaired nigrostriatal function precedes behavioral deficits in a genetic mitochondrial model of Parkinson's disease. *FASEB J*. 2011 Apr; 25(4): 1333-1344. doi: 10.1096/fj.10-173625. Epub 2011 Jan 13.

Neuronal Ensembles in Addiction Unit, Behavioral Neuroscience Branch

Unique Gene Alterations Are Induced In FACS-Purified Fos-Positive Neurons Activated During Cue-Induced Relapse To Heroin Seeking Cue-induced heroin seeking after prolonged withdrawal is associated with neuronal activation and altered gene expression in prefrontal cortex (PFC). However, these previous studies assessed gene expression in all neurons regardless of their

activity state during heroin seeking. Using Fos as a marker of neural activity, IRP scientists describe distinct molecular alterations induced in activated versus non-activated neurons during cue-induced heroin seeking after prolonged withdrawal. The authors trained rats to self-administer heroin for 10 days (6 h/day) and assessed cue-induced heroin seeking in extinction tests after 14 or 30 days. They used fluorescent-activated cell sorting (FACS) to purify Fos-positive and Fos-negative neurons from PFC 90 min after extinction testing. Flow cytometry showed that Fos-immunoreactivity was increased in less than 10% of sparsely distributed PFC neurons. mRNA levels of the immediate early genes fosB, arc, egr1, and egr2, as well as npy and map2k6, were increased in Fos-positive, but not Fos-negative, neurons. In support of these findings, double-label immunohistochemistry indicated substantial coexpression of neuropeptide Y (NPY)- and Arc-immunoreactivity in Fos-positive neurons. These data indicate that cue-induced relapse to heroin seeking after prolonged withdrawal induces unique molecular alterations within activated PFC neurons that are distinct from those observed in the surrounding majority of non-activated neurons. Fanous S, Guez-Barber DH, Goldart EM, Schrama R, Theberge FR, Shaham Y, Hope BT. Unique gene alterations are induced in FACS-purified Fos-positive neurons activated during cue-induced relapse to heroin seeking. *J Neurochem.* 2013 Jan; 124(1): 100-108.

Role Of Orbitofrontal Cortex Neuronal Ensembles In The Expression Of Incubation Of

Heroin Craving In humans, exposure to cues previously associated with heroin use often provokes relapse after prolonged withdrawal periods. In rats, cue-induced heroin seeking progressively increases after withdrawal (incubation of heroin craving). Here, IRP researchers examined the role of orbitofrontal cortex (OFC) neuronal ensembles in the enhanced response to heroin cues after prolonged withdrawal or the expression of incubation of heroin craving. They trained rats to self-administer heroin (6 h/d for 10 d) and assessed cue-induced heroin seeking in extinction tests after 1 or 14 withdrawal days. Cue-induced heroin seeking increased from 1 to 14 d and was accompanied by increased Fos expression in 12% of OFC neurons. Nonselective inactivation of OFC neurons with the GABA agonists baclofen + muscimol decreased cue-induced heroin seeking on withdrawal day 14 but not day 1. The authors then used the Daun02 inactivation procedure to assess a causal role of the minority of selectively activated Fos-expressing OFC neurons (that presumably form cue-encoding neuronal ensembles) in cue-induced heroin seeking after 14 withdrawal days. They trained c-fos-lacZ transgenic rats to self-administer heroin and 11 d later reexposed them to heroin-associated cues or novel cues for 15 min (induction day), followed by OFC Daun02 or vehicle injections 90 min later; they then tested the rats in extinction tests 3 d later. Daun02 selectively decreased cue-induced heroin seeking in rats previously reexposed to the heroin-associated cues on induction day but not in rats exposed previously to novel cues. Results suggest that heroin-cue-activated OFC neuronal ensembles contribute to the expression of incubation of heroin craving. Fanous S, Goldart EM, Theberge FR, Bossert JM, Shaham Y, Hope BT. Role of orbitofrontal cortex neuronal ensembles in the expression of incubation of heroin craving. *J Neurosci.* 2012 Aug 22; 32(34): 11600-11609.

FACS Purification Of Immunolabeled Cell Types From Adult Rat Brain Molecular analysis of brain tissue is greatly complicated by having many different classes of neurons and glia interspersed throughout the brain. Fluorescence-activated cell sorting (FACS) has been used to purify selected cell types from brain tissue. However, its use has been limited to brain tissue from embryos or transgenic mice with promoter-driven reporter genes. To overcome these limitations, IRP scientists developed a FACS procedure for dissociating intact cell bodies from adult wild-type rat brains and sorting them using commercially available antibodies against intracellular and extracellular proteins.

As an example, the authors isolated neurons using a NeuN antibody and confirmed their identity using microarray and real time PCR of mRNA from the sorted cells. Their FACS procedure allows rapid, high-throughput, quantitative assays of molecular alterations in identified cell types with widespread applications in neuroscience. Guez-Barber D, Fanous S, Harvey BK, Zhang Y, Lehrmann E, Becker KG, Picciotto MR, Hope BT. FACS purification of immunolabeled cell types from adult rat brain. *J Neurosci Methods*. 2012 Jan 15; 203(1): 10-18.

Drug Design and Synthesis Section, Chemical Biology Research Branch

In Vivo Effects Of Abused 'Bath Salt' Constituent 3,4-Methylenedioxypropylamphetamine (MDPV)

In Mice: Drug Discrimination, Thermoregulation, and Locomotor Activity In recent years, synthetic analogues of naturally occurring cathinone have emerged as psychostimulant-like drugs of abuse in commercial 'bath salt' preparations. 3,4-Methylenedioxypropylamphetamine (MDPV) is a common constituent of these illicit products, and its structural similarities to the more well-known drugs of abuse 3,4-methylenedioxymethamphetamine (MDMA), and methamphetamine (METH) suggest that it may have similar in vivo effects to these substances. In these studies, adult male NIH Swiss mice were trained to discriminate 0.3 mg/kg MDPV from saline, and the interoceptive effects of a range of substitution doses of MDPV, MDMA, and METH were then assessed. In separate groups of mice, surgically implanted radiotelemetry probes simultaneously monitored thermoregulatory and locomotor responses to various doses of MDPV and MDMA, as a function of ambient temperature. The authors found that mice reliably discriminated the MDPV training dose from saline and that cumulative doses of MDPV, MDMA, and METH fully substituted for the MDPV training stimulus. All three drugs had similar ED(50) values in this procedure. Stimulation of motor activity was observed following administration of a wide range of MDPV doses (1-30 mg/kg), and the warm ambient temperature potentiated motor activity and elicited profound stereotypy and self-injurious behavior at 30 mg/kg. In contrast, MDPV-induced hyperthermic effects were observed in only the warm ambient environment. This pattern of effects is in sharp contrast to MDMA, where ambient temperature interacts with thermoregulation, but not locomotor activity. These studies suggest that although the interoceptive effects of MDPV are similar to those of MDMA and METH, direct effects on thermoregulatory processes and locomotor activity are likely mediated by different mechanisms than those of MDMA. Fantegrossi WE, Gannon BM, Zimmerman SM, Rice KC. In vivo Effects of Abused 'Bath Salt' Constituent 3,4-methylenedioxypropylamphetamine (MDPV) in Mice: Drug Discrimination, Thermoregulation, and Locomotor Activity. *Neuropsychopharmacology*. 2012 Dec 5. [Epub ahead of print].

Neuropeptide Deficient Mice Have Attenuated Nociceptive, Vascular, and Inflammatory Changes In A Tibia Fracture Model Of Complex Regional Pain Syndrome

Distal limb fracture in man can induce a complex regional pain syndrome (CRPS) with pain, warmth, edema, and cutaneous inflammation. In the present study substance P (SP, Tac1^{-/-}) and CGRP receptor (RAMP1^{-/-}) deficient mice were used to investigate the contribution of neuropeptide signaling to CRPS-like changes in a tibia fracture mouse model. Wildtype, Tac1^{-/-}, and RAMP1^{-/-} mice underwent tibia fracture and casting for 3 weeks, then the cast was removed and hindpaw mechanical allodynia, unweighting, warmth, and edema were tested over time. Hindpaw skin was collected at 3 weeks post-fracture for immunoassay and femurs were collected for micro-CT analysis. Wildtype mice developed hindpaw allodynia, unweighting, warmth, and edema at 3

weeks post-fracture, but in the *Tac1*^{-/-} fracture mice allodynia and unweighting were attenuated and there was no warmth and edema. *RAMP1*^{-/-} fracture mice had a similar presentation, except there was no reduction in hindpaw edema. Hindpaw skin TNF α , IL-1 β , IL-6 and NGF levels were up-regulated in wildtype fracture mice at 3 weeks post-fracture, but in the *Tac1*^{-/-} and *RAMP1*^{-/-} fracture mice only IL-6 was increased. The epidermal keratinocytes were the cellular source for these inflammatory mediators. An IL-6 receptor antagonist partially reversed post-fracture pain behaviors in wildtype mice. In conclusion, both SP and CGRP are critical neuropeptide mediators for the pain behaviors, vascular abnormalities, and up-regulated innate immune responses observed in the fracture hindlimb. The authors postulate that the residual pain behaviors observed in the *Tac1*^{-/-} and *RAMP1*^{-/-} fracture mice are attributable to the increased IL-6 levels observed in the hindpaw skin after fracture. Guo TZ, Wei T, Shi X, Li WW, Hou S, Wang L, Tsujikawa K, Rice KC, Cheng K, Clark DJ, Kingery WS. Neuropeptide deficient mice have attenuated nociceptive, vascular, and inflammatory changes in a tibia fracture model of complex regional pain syndrome. *Mol Pain*. 2012 Nov 28; 8(1): 85. [Epub ahead of print]

Probes For Narcotic Receptor Mediated Phenomena. 46. N-Substituted-2,3,4,9,10,10a-Hexahydro-1H-1,4a-(Epiminoethano)Phenanthren-6- And 8-Ols - Carbocyclic Relatives Of F-Oxide-Bridged Phenylmorphans

Oxide-bridged phenylmorphans were conceptualized as topologically distinct, structurally rigid ligands with 3-dimensional shapes that could not be appreciably modified on interaction with opioid receptors. An enantiomer of the N-phenethyl-substituted ortho-f isomer was found to have high affinity for the μ -receptor ($K(i) = 7$ nM) and was about four times more potent than naloxone as an antagonist. In order to examine the effect of introduction of a small amount of flexibility into these molecules, the authors have replaced the rigid 5-membered oxide ring with a more flexible 6-membered carbon ring. Synthesis of the new N-phenethyl-substituted tricyclic N-substituted-2,3,4,9,10,10a-hexahydro-1H-1,4a-(epiminoethano) phenanthren-6- and 8-ols resulted in a two carbon-bridged relative of the f-isomers, the dihydrofuran ring was replaced by a cyclohexene ring. The carbocyclic compounds had much higher affinity and greater selectivity for the μ -receptor than the f-oxide-bridged phenylmorphans. They were also much more potent μ -antagonists, with activities comparable to naltrexone in the [(35)S]GTP- γ -S assay. Li F, Deck JA, Dersch CM, Rothman RB, Deschamps JR, Jacobson AE, Rice KC. Probes for narcotic receptor mediated phenomena. 46. N-substituted-2,3,4,9,10,10a-hexahydro-1H-1,4a-(epiminoethano)phenanthren-6- and 8-ols - carbocyclic relatives of f-oxide-bridged phenylmorphans. *Eur J Med Chem*. 2012 Dec; 58: 557-567. Epub 2012 Oct 30.

Pharmacological Characterization Of The 20% Alcohol Intermittent Access Model In Sardinian Alcohol-Preferring Rats: A Model Of Binge-Like Drinking

Binge drinking is defined as a pattern of alcohol drinking that brings blood alcohol levels to 80 mg/dl or above. In this study, IRP scientists pharmacologically characterized the intermittent access to 20% ethanol (EtOH) model (Wise, *Psychopharmacologia* 1973;29:203) in Sardinian alcohol-preferring (sP) rats to determine to which of the compounds known to reduce drinking in specific animal models this binge-like drinking was sensitive to. Adult male sP rats were divided into 2 groups and allowed to drink either 20% v/v alcohol or water for 24 hours on alternate days (Monday, Wednesday, and Friday) or 10% v/v alcohol and water for 24 hours every day. After stabilization of their intake, both groups were administered 3 pharmacological agents with different mechanisms of action, naltrexone-an opioid receptor antagonist, SCH 39166-a dopamine D1 receptor antagonist, and R121919-a Corticotropin-Releasing Factor 1 (CRF(1)) receptor antagonist, and their effects on alcohol and water intake were determined. Intermittent 20% alcohol ("Wise") procedure in sP rats

led to binge-like drinking. Alcohol drinking was suppressed by naltrexone and by SCH 39166, but not by R121919. Finally, naltrexone was more potent in reducing alcohol drinking in the intermittent 20% binge-drinking group than in the 10% continuous access drinking group. The Wise procedure in sP rats induces binge-like drinking, which appears opioid- and dopamine-receptor mediated; the CRF(1) system, on the other hand, does not appear to be involved. In addition, these results suggest that naltrexone is particularly effective in reducing binge drinking. Such different pharmacological responses may apply to subtypes of alcoholic patients who differ in their motivation to drink, and may eventually contribute to treatment response. Sabino V, Kwak J, Rice KC, Cottone P. Pharmacological characterization of the 20% alcohol intermittent access model in Sardinian alcohol-preferring rats: A model of binge-like drinking. *Alcohol Clin Exp Res.* 2012 Nov 5 [Epub ahead of print].

Clinically Employed Opioid Analgesics Produce Antinociception Via μ - δ Opioid Receptor Heteromers In Rhesus Monkeys

Morphine and related drugs are widely employed as analgesics despite the side effects associated with their use. Although morphine is thought to mediate analgesia through μ opioid receptors, delta opioid receptors have been implicated in mediating some side effects such as tolerance and dependence. Here the authors present evidence in rhesus monkeys that morphine, fentanyl, and possibly methadone selectively activate μ -delta heteromers to produce antinociception that is potently antagonized by the delta opioid receptor antagonist, naltrindole (NTI). Studies with HEK293 cells expressing μ -delta heteromeric opioid receptors exhibit a similar antagonism profile of receptor activation in the presence of NTI. In mice, morphine was potently inhibited by naltrindole when administered intrathecally, but not intracerebroventricularly, suggesting the possible involvement of μ -delta heteromers in the spinal cord of rodents. Taken together, these results strongly suggest that, in primates, μ -delta heteromers are allosterically coupled and mediate the antinociceptive effects of three clinically employed opioid analgesics that have been traditionally viewed as μ -selective. Given the known involvement of delta receptors in morphine tolerance and dependence, these results implicate μ -delta heteromers in mediating both antinociception and these side effects in primates. These results open the door for further investigation in humans. Yekkirala AS, Banks ML, Lunzer MM, Negus SS, Rice KC, Portoghese PS. Clinically employed opioid analgesics produce antinociception via μ - δ opioid receptor heteromers in rhesus monkeys. *ACS Chem Neurosci.* 2012 Sep 19; 3(9): 720-727. Epub 2012 Jul 5.

Modification Of The Behavioral Effects Of Morphine In Rats By Serotonin (5-HT)(1A) and 5-HT (2A) Receptor Agonists: Antinociception, Drug Discrimination, and Locomotor Activity

Indirect-acting serotonin (5-HT) receptor agonists can enhance the antinociceptive effects of morphine; however, the specific 5-HT receptor subtype(s) mediating this enhancement is not established. This study examined interactions between morphine and both 5-HT(1A) and 5-HT(2A) receptor agonists in rats using measures of antinociception (radiant heat tail flick and warm water tail withdrawal), drug discrimination (3.2 mg/kg morphine versus saline), and locomotion.

Male Sprague-Dawley rats (n=7-8 per group) were used to examine the effects of morphine alone and in combination with DOM (5-HT(2A) agonist) and 8-OH-DPAT (5-HT(1A) agonist). DOM did not modify antinociceptive or discriminative stimulus effects while modestly attenuating locomotor-stimulating effects of morphine; the effect of DOM (0.32 mg/kg) on morphine-induced locomotion was prevented by the 5-HT(2A) receptor-selective antagonist MDL 100907. In contrast, 8-OH-DPAT (0.032-0.32 mg/kg) fully attenuated the antinociceptive effects (both procedures), did not modify the discriminative stimulus effects, and enhanced (0.32 mg/kg) the locomotor-stimulating effects of morphine. These effects of 8-OH-DPAT were prevented by the 5-HT(1A) receptor-

selective antagonist WAY100635. Agonists acting at 5-HT(1A) or 5-HT(2A) receptors do not modify all effects of mu opioid receptor agonists in a similar manner. Moreover, interactions between 5-HT and opioid receptor agonists vary significantly between rats and nonhuman primates, underscoring the value of comparing drug interactions across a broad range of conditions and in multiple species. Li JX, Shah AP, Patel SK, Rice KC, France CP. Modification of the behavioral effects of morphine in rats by serotonin (5-HT)(1A) and 5-HT (2A) receptor agonists: antinociception, drug discrimination, and locomotor activity. *Psychopharmacology (Berl)*. 2012 Sep 20. [Epub ahead of print].

Opioid Activation Of Toll-Like Receptor 4 Contributes To Drug Reinforcement Opioid action was thought to exert reinforcing effects solely via the initial agonism of opioid receptors. Here, the authors present evidence for an additional novel contributor to opioid reward: the innate immune pattern-recognition receptor, toll-like receptor 4 (TLR4), and its MyD88-dependent signaling. Blockade of TLR4/MD2 by administration of the nonopioid, unnatural isomer of naloxone, (+)-naloxone (rats), or two independent genetic knock-outs of MyD88-TLR4-dependent signaling (mice), suppressed opioid-induced conditioned place preference. (+)-Naloxone also reduced opioid (remifentanyl) self-administration (rats), another commonly used behavioral measure of drug reward. Moreover, pharmacological blockade of morphine-TLR4/MD2 activity potently reduced morphine-induced elevations of extracellular dopamine in rat nucleus accumbens, a region critical for opioid reinforcement. Importantly, opioid-TLR4 actions are not a unidirectional influence on opioid pharmacodynamics, since TLR4(-/-) mice had reduced oxycodone-induced p38 and JNK phosphorylation, while displaying potentiated analgesia. Similar to the authors' recent reports of morphine-TLR4/MD2 binding, here they provide a combination of in silico and biophysical data to support (+)-naloxone and remifentanyl binding to TLR4/MD2. Collectively, these data indicate that the actions of opioids at classical opioid receptors, together with their newly identified TLR4/MD2 actions, affect the mesolimbic dopamine system that amplifies opioid-induced elevations in extracellular dopamine levels, therefore possibly explaining altered opioid reward behaviors. Thus, the discovery of TLR4/MD2 recognition of opioids as foreign xenobiotic substances adds to the existing hypothesized neuronal reinforcement mechanisms, identifies a new drug target in TLR4/MD2 for the treatment of addictions, and provides further evidence supporting a role for central proinflammatory immune signaling in drug reward. Hutchinson MR, Northcutt AL, Hiranita T, Wang X, Lewis SS, Thomas J, van Steeg K, Kopajtic TA, Loram LC, Sfregola C, Galer E, Miles NE, Bland ST, Amat J, Rozeske RR, Maslanik T, Chapman TR, Strand KA, Fleshner M, Bachtell RK, Somogyi AA, Yin H, Katz JL, Rice KC, Maier SF, Watkins LR. Opioid activation of toll-like receptor 4 contributes to drug reinforcement. *J Neurosci*. 2012 Aug 15; 32(33): 11187-11200.

Peripheral Cannabinoid-1 Receptor Inverse Agonism Reduces Obesity By Reversing Leptin Resistance Obesity-related leptin resistance manifests in loss of leptin's ability to reduce appetite and increase energy expenditure. Obesity is also associated with increased activity of the endocannabinoid system, and CB(1) receptor (CB(1)R) inverse agonists reduce body weight and the associated metabolic complications, although adverse neuropsychiatric effects halted their therapeutic development. Here IRP investigators show that in mice with diet-induced obesity (DIO), the peripherally restricted CB(1)R inverse agonist JD5037 is equieffective with its brain-penetrant parent compound in reducing appetite, body weight, hepatic steatosis, and insulin resistance, even though it does not occupy central CB(1)R or induce related behaviors. Appetite and weight reduction by JD5037 are mediated by resensitizing DIO mice to endogenous leptin through reversing the hyperleptinemia by decreasing leptin expression and secretion by adipocytes and

increasing leptin clearance via the kidney. Thus, inverse agonism at peripheral CB(1)R not only improves cardiometabolic risk in obesity but has antiobesity effects by reversing leptin resistance. Tam J, Cinar R, Liu J, Godlewski G, Wesley D, Jourdan T, Szanda G, Mukhopadhyay B, Chedester L, Liow JS, Innis RB, Cheng K, Rice KC, Deschamps JR, Chorvat RJ, McElroy JF, Kunos G. Peripheral cannabinoid-1 receptor inverse agonism reduces obesity by reversing leptin resistance. *Cell Metab.* 2012 Aug 8; 16(2): 167-179. Epub 2012 Jul 26.

Self-Administration Of Agonists Selective For Dopamine D2, D3, and D4 Receptors By

Rhesus Monkeys Dopamine receptor mechanisms are believed to play a role in the reinforcing effects of cocaine and other drugs of abuse. The lack of receptor-selective agonists has made it difficult to determine the role of the individual dopamine receptors in mediating these reinforcing effects. In this study, rhesus monkeys with a history of intravenous cocaine self-administration were tested for the reinforcing effects of several D(3)-preferring agonists, a D(2)-preferring agonist, and a D(4) agonist. The D(2)-preferring agonist did not maintain responding in any monkeys, and the D(4) agonist was self-administered at low rates, just above those maintained by saline, in one monkey. The D(3)-preferring agonists were self-administered by approximately half of the animals, although at lower rates than cocaine. These results indicate that the apparent limited reinforcing effectiveness of D(2)-like agonists requires activity at D(3) receptors. Previous data from this laboratory and others also suggest that these drugs may not serve as reinforcers directly; the behavior may be maintained by response-contingent delivery of stimuli previously paired with cocaine. The ability of drug-related stimuli to maintain responding apparently differs among monkeys and other organisms, and may be related to individual differences in drug-taking behavior in humans. Koffarnus MN, Collins GT, Rice KC, Chen J, Woods JH, Winger G. Self-administration of agonists selective for dopamine D2, D3, and D4 receptors by rhesus monkeys. *Behav Pharmacol.* 2012 Aug; 23(4): 331-338.

Effects Of CB1 and CRF1 Receptor Antagonists On Binge-Like Eating In Rats With Limited Access To A Sweet Fat Diet: Lack Of Withdrawal-Like Responses

Positive reinforcement (e.g., appetitive, rewarding properties) has often been hypothesized to maintain excessive intake of palatable foods. Recently, rats receiving intermittent access to high sucrose diets showed binge-like intake with withdrawal-like signs upon cessation of access, suggesting negative reinforcement mechanisms contribute as well. Whether intermittent access to high fat diets also produces withdrawal-like syndromes is controversial. The present study therefore tested the hypothesis that binge-like eating and withdrawal-like anxiety would arise in a novel model of binge eating based on daily 10-min access to a sweet fat diet (35% fat kcal, 31% sucrose kcal). Within 2-3 weeks, female Wistar rats developed binge-like intake comparable to levels seen previously for high sucrose diets (~40% of daily caloric intake within 10 min) plus excess weight gain and adiposity, but absent increased anxiety-like behavior during elevated plus-maze or defensive withdrawal tests after diet withdrawal. Binge-like intake was unaffected by pretreatment with the corticotropin-releasing factor type 1 (CRF(1)) receptor antagonist R121919, and corticosterone responses to restraint stress did not differ between sweet-fat binge rats and chow-fed controls. In contrast, pretreatment with the cannabinoid type 1 (CB(1)) receptor antagonist SR147778 dose-dependently reduced binge-like intake, albeit less effectively than in ad lib chow or sweet fat controls. A priming dose of the sweet fat diet did not precipitate increased anxiety-like behavior, but rather increased plus-maze locomotor activity. The results suggest that CB(1)-dependent positive reinforcement rather than CRF(1)-dependent negative reinforcement mechanisms predominantly maintain excessive intake in this limited access model of sweet-fat diet binges. Parylak SL, Cottone P, Sabino V, Rice KC,

Zorrilla EP. Effects of CB1 and CRF1 receptor antagonists on binge-like eating in rats with limited access to a sweet fat diet: lack of withdrawal-like responses. *Physiol Behav.* 2012 Sep 10; 107(2): 231-242 Epub 2012 Jul 6.

Synergism Between A Serotonin 5-HT_{2A} Receptor (5-HT_{2A}R) Antagonist and 5-HT_{2C}R Agonist Suggests New Pharmacotherapeutics For Cocaine Addiction

Relapse to cocaine dependence, even after extended abstinence, involves a number of liability factors including impulsivity (predisposition toward rapid, unplanned reactions to stimuli without regard to negative consequences) and cue reactivity (sensitivity to cues associated with cocaine-taking which can promote cocaine-seeking). These factors have been mechanistically linked to serotonin (5-hydroxytryptamine, 5-HT) signaling through the 5-HT_{2A} receptor (5-HT_{2A}R) and 5-HT_{2C}R; either a selective 5-HT_{2A}R antagonist or a 5-HT_{2C}R agonist suppresses impulsivity and cocaine-seeking in preclinical models. IRP scientists conducted proof-of-concept analyses to evaluate whether a combination of 5-HT_{2A}R antagonist plus 5-HT_{2C}R agonist would have synergistic effects over these liability factors for relapse as measured in a 1-choice serial reaction time task and cocaine self-administration/reinstatement assay. Combined administration of a dose of the selective 5-HT_{2A}R antagonist M100907 plus the 5-HT_{2C}R agonist WAY163909, each ineffective alone, synergistically suppressed cocaine-induced hyperactivity, inherent and cocaine-evoked impulsive action, as well as cue- and cocaine-primed reinstatement of cocaine-seeking behavior. The identification of synergism between a 5-HT_{2A}R antagonist plus a 5-HT_{2C}R agonist to attenuate these factors important in relapse indicates the promise of a bifunctional ligand as an anti-addiction pharmacotherapeutic, setting the stage to develop new ligands with improved efficacy, potency, selectivity, and *in vivo* profiles over the individual molecules. Cunningham KA, Anastasio NC, Fox RG, Stutz SJ, Bubar MJ, Swinford SE, Watson CS, Gilbertson SR, Rice KC, Rosenzweig-Lipson S, Moeller FG. Synergism between a serotonin 5-HT_{2A} receptor (5-HT_{2A}R) Antagonist and 5-HT_{2C}R agonist suggests new pharmacotherapeutics for cocaine addiction. *ACS Chem. Neurosci.*, Articles ASAP, August 11, 2012.

A Common Molecular Basis For Exogenous and Endogenous Cannabinoid Potentiation Of Glycine Receptors

Both exogenous and endogenous cannabinoids can allosterically modulate glycine receptors (GlyRs). However, little is known about the molecular basis of cannabinoid-GlyR interactions. Here the authors report that sustained incubation with the endocannabinoid anandamide (AEA) substantially increased the amplitude of glycine-activated current in both rat cultured spinal neurons and in HEK-293 cells expressing human α 1, rat α 2 and α 3 GlyRs. While the α 1 and α 3 subunits were highly sensitive to AEA-induced potentiation, the α 2 subunit was relatively insensitive to AEA. Switching a serine at 296 and 307 in the TM3 (transmembrane domain 3) of the α 1 and α 3 subunits with an alanine (A) at the equivalent position in the α 2 subunit converted the α 1/ α 3 AEA-sensitive receptors to sensitivity resembling that of α 2. The S296 residue is also critical for exogenous cannabinoid-induced potentiation of I(Gly). The magnitude of AEA potentiation decreased with removal of either the hydroxyl or oxygen groups on AEA. While desoxy-AEA was significantly less efficacious in potentiating I(Gly), desoxy-AEA inhibited potentiation produced by both Δ (9)-tetrahydrocannabinol (THC), a major psychoactive component of marijuana, and AEA. Similarly, didesoxy-THC, a modified THC with removal of both hydroxyl/oxygen groups, did not affect I(Gly) when applied alone but inhibited the potentiation of I(Gly) induced by AEA and THC. These findings suggest that exogenous and endogenous cannabinoids potentiate GlyRs via a hydrogen bonding-like interaction. Such a specific interaction likely stems from a common molecular basis involving the S296 residue in the TM3 of the α 1 and

$\alpha 3$ subunits. Xiong W, Wu X, Li F, Cheng K, Rice KC, Lovinger DM, Zhang L. A common molecular basis for exogenous and endogenous cannabinoid potentiation of glycine receptors. *J Neurosci.* 2012 Apr 11; 32(15): 5200-5208.

Cannabinoids Suppress Inflammatory and Neuropathic Pain By Targeting $\alpha 3$ Glycine Receptors

Certain types of nonpsychoactive cannabinoids can potentiate glycine receptors (GlyRs), an important target for nociceptive regulation at the spinal level. However, little is known about the potential and mechanism of glycinergic cannabinoids for chronic pain treatment. IRP scientists report that systemic and intrathecal administration of cannabidiol (CBD), a major nonpsychoactive component of marijuana, and its modified derivatives significantly suppress chronic inflammatory and neuropathic pain without causing apparent analgesic tolerance in rodents. The cannabinoids significantly potentiate glycine currents in dorsal horn neurons in rat spinal cord slices. The analgesic potency of 11 structurally similar cannabinoids is positively correlated with cannabinoid potentiation of the $\alpha 3$ GlyRs. In contrast, the cannabinoid analgesia is neither correlated with their binding affinity for CB1 and CB2 receptors nor with their psychoactive side effects. NMR analysis reveals a direct interaction between CBD and S296 in the third transmembrane domain of purified $\alpha 3$ GlyR. The cannabinoid-induced analgesic effect is absent in mice lacking the $\alpha 3$ GlyRs. These findings suggest that the $\alpha 3$ GlyRs mediate glycinergic cannabinoid-induced suppression of chronic pain. These cannabinoids may represent a novel class of therapeutic agents for the treatment of chronic pain and other diseases involving GlyR dysfunction. Xiong W, Cui T, Cheng K, Yang F, Chen SR, Willenbring D, Guan Y, Pan HL, Ren K, Xu Y, Zhang L. Cannabinoids suppress inflammatory and neuropathic pain by targeting $\alpha 3$ glycine receptors. *Exp Med.* 2012 Jun 4; 209(6): 1121-1134. Epub 2012 May 14.

Behavioral Neurophysiology Science Section, Cellular Neurobiology Research Branch

The Orbitofrontal Cortex Is Fundamental For Accessing Model-Based Representations Of the Environment To Compute Value Rather Than For Signaling Value Per Se

Computational and learning theory models propose that behavioral control reflects value that is both cached (computed and stored during previous experience) and inferred (estimated on the fly on the basis of knowledge of the causal structure of the environment). The latter is thought to depend on the orbitofrontal cortex. Yet some accounts propose that the orbitofrontal cortex contributes to behavior by signaling "economic" value, regardless of the associative basis of the information. The authors found that the orbitofrontal cortex is critical for both value-based behavior and learning when value must be inferred but not when a cached value is sufficient. The orbitofrontal cortex is thus fundamental for accessing model-based representations of the environment to compute value rather than for signaling value per se. Jones JL, Esber GR, McDannald MA, Gruber AJ, Hernandez A, Mirenzi A, Schoenbaum G. *Science* 2012; 338(6109): 953-956.

Normal Aging Alters Learning and Attention-Related Teaching Signals In Basolateral Amygdale

Normal aging has been associated with an increased propensity to wait for rewards. When this is tested experimentally, rewards are typically offered at increasing delays. In this setting, persistent responding for delayed rewards in aged rats could reflect either changes in the evaluation of delayed rewards or diminished learning, perhaps due to the loss of subcortical teaching signals induced by changes in reward; the loss or diminution of such teaching signals would result in slower learning with progressive delay of reward, which would appear as persistent responding.

Such teaching signals have commonly been reported in phasic firing of midbrain dopamine neurons; however, similar signals have also been found in reward-responsive neurons in the basolateral amygdala (ABL). Unlike dopaminergic teaching signals, those in ABL seem to reflect surprise, increasing when reward is either better or worse than expected. Accordingly, activity is correlated with attentional responses and with the speed of learning after surprising increases or decreases in reward. Here the authors examined whether these attention-related teaching signals might be altered in normal aging. Young (3-6 months) and aged (22-26 months) male Long-Evans rats were trained on a discounting task used previously to demonstrate these signals. As expected, aged rats were less sensitive to delays, and this change was associated with a loss of attentional changes in orienting behavior and neural activity. These results indicate that normal aging alters teaching signals in the ABL. Changes in these teaching signals may contribute to a host of age-related cognitive changes. Roesch MR, Esber GR, Bryden DW, Cerri DH, Haney ZR, Schoenbaum G. Normal aging alters learning and attention-related teaching signals in basolateral amygdala. *J Neurosci.* 2012, 32(38): 13137-13144.

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, IRP researchers 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; 2(12): 1012-1019.

Reward Prediction Error Signaling In Posterior Dorsomedial Striatum Is Action Specific

Neural correlates of reward prediction errors (RPEs) have been found in dorsal striatum. Such signals may be important for updating associative action representations within striatum. In order that the appropriate representations can be updated, it might be important for the RPE signal to be specific for the action that led to that error. However, RPEs signaled by midbrain dopamine neurons, which project heavily to striatum, are not action-specific. Here the authors tested whether RPE-like activity in dorsal striatum is action-specific; they recorded single-unit activity in posterior dorsomedial and dorsolateral striatum as rats performed a task in which the reward predictions associated with two different actions were repeatedly violated, thereby eliciting RPEs. They separately analyzed fast firing neurons (FFNs) and phasically firing neurons (total n = 1076). Only among FFNs recorded in posterior dorsomedial striatum did they find a population with RPE-like

characteristics (19 of all 196 FFNs, 10%). This population showed a phasic increase in activity during unexpected rewards, a phasic decrease in activity during unexpected omission of rewards, and a phasic increase in activity during cues when they predicted high-value reward. However, unlike a classical RPE signal, this signal was linked to the action that elicited the prediction error, in that neurons tended to signal RPEs only after their anti-preferred action. This action-specific RPE-like signal could provide a mechanism for updating specific associative action representations in posterior dorsomedial striatum. Stalnaker TA, Calhoun GG, Ogawa M, Roesch MR, Schoenbaum G. Reward prediction error signaling in posterior dorsomedial striatum is action specific. *J Neurosci.* 2012; 32(30): 10296-10305.

Cellular Pathobiology Section, Integrative Neuroscience Branch

Sigma-1 Receptor Chaperones Regulate the Secretion Of Brain-Derived Neurotrophic Factor

The sigma-1 receptor (Sig-1R) is a novel endoplasmic reticulum (ER) molecular chaperone that regulates protein folding and degradation. The Sig-1R activation by agonists is known to improve memory, promote cell survival, and exert an antidepressant-like action in animals. Cutamesine (SA4503), a selective Sig-1R ligand, was shown to increase BDNF in the hippocampus of rats. How exactly the intracellular chaperone Sig-1R or associated ligand causes the increase of BDNF or any other neurotrophins is unknown. IRP scientists examined here whether the action of Sig-1Rs may relate to the post-translational processing and release of BDNF in neuroblastoma cell lines. They used in vitro assays and confirmed that cutamesine possesses the bona fide Sig-1R agonist property by causing the dissociation of BiP from Sig-1Rs. The C-terminus of Sig-1Rs exerted robust chaperone activity by completely blocking the aggregation of BDNF and GDNF in vitro. Chronic treatment with cutamesine in rat B104 neuroblastoma caused a time- and dose-dependent potentiation of the secretion of BDNF without affecting the mRNA level of BDNF. Cutamesine decreased the intracellular level of pro-BDNF and mature BDNF whereas increased the extracellular level of mature BDNF. The pulse-chase experiment indicated that the knockdown of Sig-1Rs decreased the secreted mature BDNF in B104 cells without affecting the synthesis of BDNF. These findings indicate that, in contrast to clinically used antidepressants that promote the transcriptional upregulation of BDNF, the Sig-1R agonist cutamesine potentiates the post-translational processing of neurotrophins. This unique pharmacological profile may provide a novel therapeutic opportunity for the treatment of neuropsychiatric disorders. Fujimoto M, Hayashi T, Urfer R, Mita S, Su TP Sigma-1 receptor chaperones regulate the secretion of brain-derived neurotrophic factor. *Synapse* 2012; 66(7): 630-639.

Compromising Sigma-1 Receptors At the ER Renders Cytotoxicity To Physiologically Relevant Concentrations Of Dopamine In A NF- κ B/Bcl-2-Dependent Mechanism: Potential

Relevance To Parkinson's Disease The endoplasmic reticulum (ER) chaperone σ -1 receptor (Sig-1R) is cytoprotective against ER stress-induced apoptosis. The level of Sig-1Rs in the brain was reported to be lower in early parkinsonian patients. Because dopamine (DA) toxicity is well known to be involved in the etiology of Parkinson's disease, the authors tested in this study whether a relationship might exist between Sig-1Rs and DA-induced cytotoxicity in a cellular model by using Chinese hamster ovary (CHO) cells. DA in physiological concentrations (e.g., lower than 10 μ M) does not cause apoptosis. However, the same concentrations of DA cause apoptosis in Sig-1R knockdown CHO cells. In search of a mechanistic explanation, the authors found that unfolded protein response is not involved. Rather, the level of protective protein Bcl-2 is critically involved

in this DA/Sig-1R knockdown-induced apoptosis. Specifically, the DA/Sig-1R knockdown causes a synergistic proteasomal conversion of nuclear factor κ B (NF- κ B) p105 to the active form of p50, which is known to down-regulate the transcription of Bcl-2. It is noteworthy that the DA/Sig-1R knockdown-induced apoptosis is blocked by the overexpression of Bcl-2. These results therefore indicate that DA is involved in the activation of NF- κ B and suggest that endogenous Sig-1Rs are tonically inhibiting the proteasomal conversion/activation of NF- κ B caused by physiologically relevant concentrations of DA that would otherwise cause apoptosis. Thus, Sig-1Rs and associated ligands may represent new therapeutic targets for the treatment of parkinsonism. Mori T, Hayashi T, Su TP Compromising sigma-1 receptors at the ER renders cytotoxicity to physiologically relevant concentrations of dopamine in a NF- κ B/Bcl-2-dependent mechanism: Potential relevance to Parkinson's disease. *J Pharmacol Exp Ther* 2012; 341(3): 663-671.

Cocaine and HIV Interplay In CNS: Cellular and Molecular Mechanism Although antiretrovirals are the mainstay of therapy against HIV infection, neurological complications associated with the virus continue to hamper quality of life of the infected individuals. Drugs of abuse in the infected individuals further fuel the epidemic. Epidemiological studies have demonstrated that abuse of cocaine resulted in acceleration of HIV infection and the progression of NeuroAIDS. Cocaine has not only been shown to play a crucial role in promoting virus replication, but also has diverse but often deleterious effects on various cell types of the CNS. In the neuronal system, cocaine exposure results in neuronal toxicity and also potentiates gp120-induced neurotoxicity. In the astroglia and microglia, cocaine exposure leads to up-regulation of pro-inflammatory mediators such as cytokines and chemokines. These in turn, can lead to neuroinflammation and transmission of toxic responses to the neurons. Additionally, cocaine exposure can also lead to leakiness of the blood-brain barrier that manifests as enhanced transmigration of leukocytes/monocytes into the CNS. Both in vitro and in vivo studies have provided valuable tools in exploring the role of cocaine in mediating HIV-associated neuropathogenesis. This review summarizes previous studies on the mechanism(s) underlying the interplay of cocaine and HIV as it relates to the CNS. Buch S, Yao H, Guo M, Mori T, Seth P, Su TP, Wang J. Cocaine and HIV interplay in CNS: Cellular and molecular mechanism. *Curr HIV Res* 2012; 10(5): 425-428.

The Sigma-1 Receptor: Roles In Neuronal Plasticity and Disease Sigma-1 receptors (Sig-1Rs) have been implicated in many neurological and psychiatric conditions. Sig-1Rs are intracellular chaperones that reside specifically at the endoplasmic reticulum (ER)-mitochondrion interface, referred to as the mitochondrion-associated ER membrane (MAM). Here, Sig-1Rs regulate ER-mitochondrion Ca(2+) signaling. In this review, IRP scientists discuss the current understanding of Sig-1R functions. Based on this, they suggest that the key cellular mechanisms linking Sig-1Rs to neurological disorders involve the translocation of Sig-1Rs from the MAM to other parts of the cell, whereby Sig-1Rs bind and modulate the activities of various ion channels, receptors, or kinases. Thus, Sig-1Rs and their associated ligands may represent new avenues for treating aspects of neurological and psychiatric diseases. Kourrich S, Su TP, Fujimoto M, Bonci A. The sigma-1 receptor: roles in neuronal plasticity and disease. *Trends in Neurosci* 2012; 35(12): 762-771.

Combination Treatment Of Hypothermia and Mesenchymal Stromal Cells Amplifies Neuroprotection In Primary Rat Neurons Exposed To Hypoxic-Ischemic-Like Injury In Vitro: Role Of the Opioid System

This study was designed to reveal the therapeutic regimen and mechanism of action underlying hypothermia treatment in combination with stem cell transplantation for ameliorating neonatal hypoxic-ischemic-like injury. Primary rat neurons were exposed to oxygen-glucose deprivation (OGD), which produced hypoxic-ischemic-like injury in vitro, then incubated at 25°C (severe hypothermia), 34°C (moderate hypothermia), and 37°C (normothermia) with or without subsequent co-culture with mesenchymal stromal cells (MSCs). Combination treatment of moderate hypothermia and MSCs significantly improved cell survival and mitochondrial activity after OGD exposure. The exposure of delta opioid human embryonic kidney cells (HEK293) to moderate hypothermia attenuated OGD-mediated cell alterations, which were much more pronounced in HEK293 cells overexpressing the delta opioid receptor. Further, the addition of delta opioid peptide to 34°C hypothermia and stem cell treatment in primary rat neurons showed synergistic neuroprotective effects against OGD which were significantly more robust than the dual combination of moderate hypothermia and MSCs, and were significantly reduced, but not completely abolished, by the opioid receptor antagonist naltrexone altogether implicating a ligand-receptor mechanism of neuroprotection. Further investigations into non-opioid therapeutic signaling pathways revealed growth factor mediation and anti-apoptotic function accompanying the observed therapeutic benefits. These results support combination therapy of hypothermia and stem cells for hypoxic-ischemic-like injury in vitro, which may have a direct impact on current clinical trials using stand-alone hypothermia or stem cells for treating neonatal encephalopathy. Kaneko Y, Tajiri N, Su TP, Wang Y, Borlongan C Combination treatment of hypothermia and mesenchymal stromal cells amplifies neuroprotection in primary rat neurons exposed to hypoxic-ischemic-like injury in vitro: role of the opioid system. *PLoS One* 2012; 7(10): e47583. e-Pub Oct 15, 2012.

The Lifetime Of UDP-Galactose:Ceramide Galactosyltransferase Is Controlled By A Distinct Endoplasmic Reticulum-Associated Degradation (ERAD) Regulated By Sigma-1 Receptor Chaperones

The glycosphingolipid biosynthesis is initiated by monoglycosylation of ceramides, the action of which is catalyzed either by UDP-glucose:ceramide glucosyltransferase or by UDP-galactose:ceramide galactosyltransferase (CGalT). CGalT is expressed predominantly at the endoplasmic reticulum (ER) of oligodendrocytes and is responsible for synthesizing galactosylceramides (GalCer) that play an important role in regulation of axon conductance. However, despite the importance of ceramide monoglycosylation enzymes in a spectrum of cellular functions, the mechanism that fine-tunes activities of those enzymes is largely unknown. In the present study, IRP investigators demonstrated that the sigma-1 receptor chaperone (Sig-1R), the mammalian homologue of a yeast C8-C7 sterol isomerase, controls the protein level and activity of the CGalT enzyme via a distinct ER-associated degradation (ERAD) system involving Insig. The Sig-1R forms a complex with Insig via its transmembrane domain partly in a sterol-dependent manner and associates with CGalT at the ER. The knockdown of Sig-1Rs dramatically prolonged the lifetime of CGalT without affecting the trimming of N-linked oligosaccharides at CGalT. The increased lifetime leads to the upregulation of CGalT protein as well as elevated enzymatic activity in CHO cells stably expressing CGalT. Knockdown of Sig-1Rs also decreased CGalT degradation endogenously expressed in D6P2T-schwanoma cells. These data suggest that Sig-1Rs negatively regulate the activity of GalCer synthesis under physiological conditions by enhancing the degradation of CGalT through regulation of the dynamics of Insig in the lipid-activated ERAD system. The GalCer synthesis may thus be influenced by sterols at the ER. Hayashi T, Hayashi E, Fujimoto M, Sprong H, Su TP The lifetime of UDP-galactose:ceramide galactosyltransferase is

controlled by a distinct endoplasmic reticulum-associated degradation (ERAD) regulated by sigma-1 receptor chaperones. J Biol Chem 2012; e-Pub Oct 26, 2012.

Medicinal Chemistry Section, Molecular Targets and Medications Discovery Branch

The Allosteric Binding Site For Antidepressants In the Serotonin Transporter Is Located To the Conserved Extracellular Vestibule The serotonin transporter (SERT) controls synaptic serotonin levels and is the primary target for antidepressants including selective serotonin reuptake inhibitors (e.g. S-citalopram) and tricyclic antidepressants (e.g. clomipramine). In addition to a high-affinity binding site, SERT possesses a low-affinity allosteric site for antidepressants. Binding to the allosteric site impedes dissociation of antidepressants from the high affinity site, which may enhance antidepressant efficacy. Here the authors employ an induced-fit docking/molecular dynamics protocol to locate the allosteric binding site to the extracellular vestibule above the central substrate binding site (S1) and corresponding to the S2 site in the neurotransmitter: sodium symporter (NSS) homologue LeuT. Mutagenesis of selected residues in the vestibule decreases the allosteric potency of S-CIT and CMI suggesting that the binding site is in the vestibule. The authors' conclusion is further substantiated by a Zn²⁺ binding site engineered in the vestibule, and by modification of a cysteine inserted there by the benzocainemethanethiosulfonate reagent. The data provide a mechanistic explanation for the allosteric action of antidepressants at SERT and suggest that the role of the vestibule evolutionarily conserved among NSS proteins as a binding pocket for small-molecule ligands. Plenge P, Shi L, Beuming T, Newman AH, Weinstein H, Gether U, Loland CJ The allosteric binding site for antidepressants in the serotonin transporter is located to the conserved extracellular vestibule. J Biol Chem 2012, e-pub Sept. 24, 2012.

The Dopamine D₃ Receptor Is Not Necessary For Cocaine Self-Administration: Studies In D₃ Knockout Mice The dopamine D₃ receptor has received attention over the last two decades as a target for medications development for substance abuse disorders. Results have remained mixed. Despite emergence of more D₃-selective ligands, possible attribution of observed effects to D₂ receptors remains a concern. Knockout mice may help shed light on mechanisms. Here IRP scientists evaluated the effect of constitutive D₃ receptor inactivation (“knockout”) on the reinforcing effects of cocaine. They tested D₃ wild-type (WT), heterozygous (D₃^{+/-}), and knockout (D₃^{-/-}), mice in acquisition and maintenance of IV self-administration across a broad range of cocaine doses, using a fixed ratio (FR) 1 and a progressive ratio (PR) schedule of reinforcement, along with parallel food-reinforced studies. Generally, D₃^{-/-} mice showed cocaine self-administration comparable to wild-type controls across assays. Moderate and nonsignificant trends toward lesser reinforcing effects of a low cocaine dose (0.32 mg/kg) were apparent in acquisition and PR studies, consistent with the idea that the D₃ receptor may play a subtle role in the reinforcing effects of low cocaine doses under low FR conditions. However, those effects with cocaine self-administration were more subtle than the lower responding of D₃ knockout mice observed with food-maintained behavior. In addition, the D₃ antagonist PG01037 failed to affect cocaine self-administration under an FR 1 schedule in WT mice. The present data do not support a necessary role for the D₃ receptor in the direct reinforcing effects of cocaine. Caine SB, Thomsen M, Barrett A, Collins GT, Grundt P, Newman AH, Butler P, Xu M. The dopamine D₃ receptor is not necessary for cocaine self-administration: studies in D₃ knockout mice. Exp. Clin. Psychopharmacol. 2012; 20(5): 352-363.

Medication Discovery For Addiction: Translating The Dopamine D3 Receptor Hypothesis

The dopamine D3 receptor (D3R) has been investigated as a potential target for medication development to treat substance use disorders (SUDs) with a particular focus on cocaine and methamphetamine. Currently, there are no approved medications to treat cocaine and methamphetamine addiction and thus developing pharmacotherapeutics to complement existing behavioral strategies is a fundamental goal. Novel compounds with high affinity and D3R selectivity have been evaluated in numerous animal models of drug abuse and favorable outcomes in nonhuman primate models of self-administration and relapse have provided compelling evidence to advance these agents into the clinic. One approach is to repurpose drugs that share the D3R mechanism and already have clinical utility, and to this end buspirone has been identified as a viable candidate for clinical trials. A second, but substantially more resource intensive and risky approach involves the development of compounds that exclusively target D3R, such as GSK598809 and PG 619. Clinical investigation of these drugs or other novel D3R-selective agents will provide a better understanding of the role D3R plays in addiction and whether or not antagonists or partial agonists that are D3R selective are effective in achieving abstinence in this patient population. Newman AH, Blaylock BL, Nader MA, Bergman J, Sibley DR, Skolnick P. *Biochem Pharmacol.* 2012 Oct 1; 84(7): 882-890.

Psychoactive "Bath Salts": Not So Soothing Recently there has been a dramatic rise in the abuse of so-called "bath salts" products that are purchased as legal alternatives to illicit drugs like cocaine and 3,4-methylenedioxymethamphetamine (MDMA). Bath salts contain one or more synthetic derivatives of the naturally-occurring stimulant cathinone. Low doses of bath salts produce euphoria and increase alertness, but high doses or chronic use can cause serious adverse effects such as hallucinations, delirium, hyperthermia and tachycardia. Owing to the risks posed by bath salts, the governments of many countries have made certain cathinones illegal, namely: 4-methylmethcathinone (mephedrone), 3,4-methylenedioxymethcathinone (methyldrone) and 3,4-methylenedioxy-pyrovalerone (MDPV). Similar to other psychomotor stimulants, synthetic cathinones target plasma membrane transporters for dopamine (i.e., DAT), norepinephrine (i.e., NET) and serotonin (i.e., SERT). Mephedrone and methyldrone act as non-selective transporter substrates, thereby stimulating non-exocytotic release of dopamine, norepinephrine and serotonin. By contrast, MDPV acts as a potent blocker at DAT and NET, with little effect at SERT. Administration of mephedrone or methyldrone to rats increases extracellular concentrations of dopamine and serotonin in the brain, analogous to the effects of MDMA. Not surprisingly, synthetic cathinones elicit locomotor activation in rodents. Stimulation of dopamine transmission by synthetic cathinones predicts a high potential for addiction and may underlie clinical adverse effects. As popular synthetic cathinones are rendered illegal, new replacement cathinones are appearing in the marketplace. More research on the pharmacology and toxicology of abused cathinones is needed to inform public health policy and develop strategies for treating medical consequence of bath salts abuse. Baumann MH, Partilla JS, Lehner KR. *Psychoactive "bath salts": not so soothing.* *European Journal of Pharmacology* 2012, e-pub Nov. 23, 2012.

Psychobiology Section, Molecular Targets and Medications Discovery Branch

Self-Administration Of Cocaine Induces Dopamine-Independent Self-Administration Of Sigma Agonists

Sigma₁ receptors (σ_1 Rs) are intracellularly-mobile chaperone proteins implicated in several disease processes, as well as psychiatric disorders and substance abuse. Here IRP researchers report that although selective σ_1 R agonists (PRE-084, (+)-pentazocine) lacked reinforcing effects in drug-naive rats; over the course of 28 experimental sessions, which was more than sufficient for acquisition of cocaine self-administration, responding was not maintained by either σ_1 R agonist. In contrast, after subjects self-administered cocaine σ_1 R agonists were readily self-administered. The induced reinforcing effects were long lasting; a response for which subjects had no history of reinforcement was newly conditioned with both σ_1 R agonists, extinguished when injections were discontinued, and reconditioned when σ_1 R agonists again followed responses. Experience with food reinforcement was ineffective as an inducer of σ_1 R agonist reinforcement. While a variety of dopamine-receptor antagonists blocked cocaine self-administration, consistent with its dopaminergic mechanism, PRE-084 self-administration was entirely insensitive to these drugs. Conversely, the σ R antagonist, BD1063, blocked PRE-084 self-administration but was inactive against cocaine. In microdialysis studies i.v. PRE-084 did not significantly stimulate dopamine at doses that were self-administered in rats either with or without a cocaine self-administration experience. The results indicate that cocaine experience induces reinforcing effects of previously inactive σ_1 R agonists, and that the mechanism underlying these reinforcing effects is dopamine-independent. It is further suggested that induced σ_1 R mechanisms may play an essential role in treatment-resistant stimulant abuse, suggesting new approaches for the development of effective medications for stimulant abuse. Hiranita, T, Mereu, M, Soto, PL, Tanda, G, Katz, JL. Self-administration of cocaine induces dopamine-independent self-administration of sigma agonists. *Neuropsychopharmacology*, (doi:10.1038/npp.2012.224)

The Stereotypy-Inducing Effects Of N-Substituted Benztropine Analogs Alone and In Combination With Cocaine Do Not Account For Their Blockade Of Cocaine Self-

Administration Previous studies have demonstrated that several N-substituted 4',4''-diF-benzotropine (BZT) analogs with high dopamine transporter affinity selectively decreased cocaine self-administration without affecting food-maintained behavior in rats. The present study examined if the decreases in cocaine self-administration are due to competition from excess behavioral activity (hyperlocomotion or stereotypy) induced by the BZT analogs alone or in combination with cocaine. Pretreatments with the typical dopamine uptake inhibitor methylphenidate (1.0, 3.2 and 10 mg/kg, i.p.) dose-dependently shifted the cocaine self-administration dose-effect curve (0, 0.032, 0.1, 0.32 1.0 mg/kg/injection) leftward. The shift in the dose-effect curve was obtained at doses of methylphenidate that, when administered alone, also decreased food-maintained behavior and increased locomotor activity and stereotypy. In contrast, the N-substituted BZT analogs, JHW 007 (1.0, 3.2 and 10 mg/kg, i.p.), AHN 1-055 (10 mg/kg), and, AHN 2-005 (10 mg/kg), as previously reported, decreased the maximum for the cocaine self-administration dose-effect curve, and did so at doses that were virtually without effects on food-maintained behavior. Further, the BZT analogs alone had minimal effects on locomotor activity and stereotypies and did not appreciably change the effects of cocaine on these measures when administered in combination with cocaine. The present results suggest that the decrease in cocaine self-administration produced by the N-substituted BZT analogs is due to an antagonism of the reinforcing effects of cocaine rather than due to interference from competing behavioral overstimulation, and further supports the development of N-substituted BZT analogs as medications to treat cocaine abuse. Li L, Hiranita T, Hayashi S, Newman AH, Katz

JL. The stereotypy-inducing effects of N-substituted benztropine analogs alone and in combination with cocaine do not account for their blockade of cocaine self-administration. *Psychopharmacology*, (DOI 10.1007/s00213-012-2862-2).

Interactions Of Cocaine With Dopamine D2-Like Antagonists In Squirrel Monkeys Studies investigating dopamine D2 receptor antagonism of cocaine's discriminative-stimulus effects have resulted in varied effects possibly due to the use of different antagonists, species, and procedures. The present study sought to further investigate D2 antagonism of cocaine's discriminative-stimulus effects using a variety of D2 antagonists and multiple doses of the antagonists in combination with cocaine. The benzamide D2 antagonists, eticlopride, raclopride, and sulpiride, and the butyrophenone D2 antagonists haloperidol and spiperone were administered alone and in combination with cocaine in squirrel monkeys trained to discriminate cocaine from saline under a fixed-ratio food reinforcement procedure. All the D2 antagonists, except haloperidol, antagonized the discriminative-stimulus effects of the cocaine training dose. However, only the benzamide D2 antagonists produced significant rightward shifts in the cocaine discriminative-stimulus dose-effect curve and they only did so within a narrow dose range and time after administration. In contrast, the D2 antagonists failed to antagonize the rate-suppressant effects of cocaine and in some cases, cocaine appeared to antagonize the rate-suppressant effects of the antagonists. The present results suggest 1) that D2 antagonism of cocaine's discriminative stimulus effects depends critically on the selected antagonist, antagonist dose, and time of administration, as well as how antagonism is assessed (i.e., in terms of effects on training dose or on the cocaine dose-effect curve), 2) that the maximal shift in cocaine's discriminative stimulus dose-effect curve possible with D2 antagonists is ~2- to 3-fold, and 3) that different effects of cocaine are differentially sensitive to dopamine receptor antagonism. Soto PL, Katz JL. Interactions of cocaine with dopamine D2-like antagonists in squirrel monkeys. *Psychopharmacology*, (DOI: 10.1007/s00213-012-2914-7).

Chemistry and Drug Metabolism Section, Clinical Pharmacology and Therapeutics Research Branch

The Dose Effects Of Short-Term Dronabinol (Oral THC) Maintenance In Daily Cannabis Users Prior studies have separately examined the effects of dronabinol (oral THC) on cannabis withdrawal, cognitive performance, and the acute effects of smoked cannabis. A single study examining these clinically relevant domains would benefit the continued evaluation of dronabinol as a potential medication for the treatment of cannabis use disorders. Thirteen daily cannabis smokers completed a within-subject crossover study and received 0, 30, 60 and 120mg dronabinol per day for 5 consecutive days. Vital signs and subjective ratings of cannabis withdrawal, craving and sleep were obtained daily; outcomes under active dose conditions were compared to those obtained under placebo dosing. On the 5th day of medication maintenance, participants completed a comprehensive cognitive performance battery and then smoked five puffs of cannabis for subjective effects evaluation. Each dronabinol maintenance period occurred in a counterbalanced order and was separated by 9 days of ad libitum cannabis use. Dronabinol dose-dependently attenuated cannabis withdrawal and resulted in few adverse side effects or decrements in cognitive performance. Surprisingly, dronabinol did not alter the subjective effects of smoked cannabis, but cannabis-induced increases in heart rate were attenuated by the 60 and 120mg doses. Dronabinol's ability to dose-dependently suppress cannabis withdrawal may be therapeutically beneficial to individuals trying to stop cannabis use. The absence of gross cognitive impairment or side effects in

this study supports safety of doses up to 120mg/day. Continued evaluation of dronabinol in targeted clinical studies of cannabis treatment, using an expanded range of doses, is warranted. Vandrey R, Stitzer ML, Mintzer MZ, Huestis MA, Murray JA, Lee D. The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users. *Drug Alcohol Dependence*. 2012 Aug 22.

Simultaneous Quantification Of Free and Glucuronidated Cannabinoids In Human Urine By Liquid Chromatography-Tandem Mass Spectrometry

Cannabis is the most commonly abused drug of abuse and is commonly quantified during urine drug testing. IRP scientists are conducting controlled drug administration studies investigating efficacy of urinary cannabinoid glucuronide metabolites for documenting recency of cannabis intake and for determining stability of urinary cannabinoids. A liquid chromatography tandem mass spectrometry method was developed and validated quantifying Δ^9 -tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), 11-nor-9-carboxy-THC (THCCOOH), cannabidiol, cannabinol, THC-glucuronide and THCCOOH-glucuronide in 0.5 mL human urine via supported-liquid extraction. Chromatography was performed on an Ultra Biphenyl column with a gradient of 10mM ammonium acetate, pH 6.15 and 15% methanol in acetonitrile at 0.4mL/min. Analytes were monitored by positive and negative mode electrospray ionization and multiple reaction monitoring mass spectrometry. Linear ranges were 0.5-50ng/mL for THC-glucuronide, 1-100ng/mL for THCCOOH, 11-OH-THC and cannabidiol, 2-100ng/mL for THC and cannabinol, and 5-500ng/mL for THCCOOH-glucuronide ($R^2 > 0.99$). Mean extraction efficiencies were 34-73% with analytical recovery (bias) 80.5-118.0% and total imprecision 3.0-10.2% coefficient of variation. This is the first analytical method that simultaneously quantifies urinary cannabinoids and phase II glucuronide metabolites, and enables evaluation of urinary cannabinoid glucuronides for documenting recency of cannabis intake and cannabinoid stability. The assay is applicable for routine urine cannabinoid testing. Scheidweiler KB, Desrosiers N, Huestis MA. Simultaneous quantification of free and glucuronidated cannabinoids in human urine by liquid chromatography-tandem mass spectrometry. *Clinica Chimica Acta*. 2012 Nov 20; 413(23-24): 1839-18347.

On-Site Test For Cannabinoids In Oral Fluid

Oral fluid (OF) testing offers noninvasive sample collection for on-site drug testing; however, to date, test performance for Δ^9 (9)-tetrahydrocannabinol (THC) detection has had unacceptable diagnostic sensitivity. On-site tests must accurately identify cannabis exposure because this drug accounts for the highest prevalence in workplace drug testing and driving under the influence of drugs (DUID) programs. Ten cannabis smokers (9 males, 1 female) provided written informed consent to participate in this institutional review board-approved study and smoked 1 6.8%-THC cigarette ad libitum. OF was collected with the Draeger DrugTest(®) 5000 test cassette and Quantisal™ device 0.5 h before and up to 22 h after smoking. Test cassettes were analyzed within 15 min (n = 66), and Quantisal GC-MS THC results obtained within 24 h. Final THC detection times and test performances were assessed at different cannabinoid cutoffs. Diagnostic sensitivity, diagnostic specificity, and efficiency at DrugTest 5000's 5 µg/L screening cutoff and various THC confirmation cutoffs were 86.2-90.7, 75.0-77.8, and 84.8-87.9%, respectively. Last detection times were >22 h, longer than previously suggested. Confirmation of 11-nor-9-carboxy-THC, absent in THC smoke, minimized the potential for passive OF contamination and still provided 22-h windows of detection, appropriate for workplace drug testing, whereas confirmation of cannabidiol, and/or cannabinol yielded shorter 6-h windows of detection, appropriate for DUID OF testing. The DrugTest 5000 on-site device provided high diagnostic sensitivity for detection of cannabinoid exposure, and the selection of OF confirmation analytes and cutoffs provided appropriate windows of detection to meet the goals of different drug

testing programs. Desrosiers NA, Lee D, Schwoppe DM, Milman G, Barnes AJ, Gorelick DA, Huestis MA. On-Site test for cannabinoids in oral fluid. *Clinical Chemistry*. 2012 Oct; 58(10): 1418-1425.

Predictive Model Accuracy In Estimating Last $\Delta(9)$ -Tetrahydrocannabinol (THC) Intake From Plasma and Whole Blood Cannabinoid Concentrations In Chronic, Daily Cannabis Smokers Administered Subchronic Oral THC

Determining time since last cannabis/ $\Delta(9)$ -tetrahydrocannabinol (THC) exposure is important in clinical, workplace, and forensic settings. Mathematical models calculating time of last exposure from whole blood concentrations typically employ a theoretical 0.5 whole blood-to-plasma (WB/P) ratio. No studies previously evaluated predictive models utilizing empirically derived WB/P ratios, or whole blood cannabinoid pharmacokinetics after subchronic THC dosing. Ten male chronic, daily cannabis smokers received escalating around-the-clock oral THC (40-120 mg daily) for 8 days. Cannabinoids were quantified in whole blood and plasma by two-dimensional gas chromatography-mass spectrometry. Maximum whole blood THC occurred 3.0 h after the first oral THC dose and 103.5h (4.3 days) during multiple THC dosing. Median WB/P ratios were THC 0.63 (n=196), 11-hydroxy-THC 0.60 (n=189), and 11-nor-9-carboxy-THC (THCCOOH) 0.55 (n=200). Predictive models utilizing these WB/P ratios accurately estimated last cannabis exposure in 96% and 100% of specimens collected within 1-5h after a single oral THC dose and throughout multiple dosing, respectively. Models were only 60% and 12.5% accurate 12.5 and 22.5h after the last THC dose, respectively. Predictive models estimating time since last cannabis intake from whole blood and plasma cannabinoid concentrations were inaccurate during abstinence, but highly accurate during active THC dosing. THC redistribution from large cannabinoid body stores and high circulating THCCOOH concentrations create different pharmacokinetic profiles than those in less than daily cannabis smokers that were used to derive the models. Thus, the models do not accurately predict time of last THC intake in individuals consuming THC daily. Karschner EL, Schwoppe DM, Schwilke EW, Goodwin RS, Kelly DL, Gorelick DA, Huestis MA. Predictive model accuracy in estimating last $\Delta(9)$ -tetrahydrocannabinol (THC) intake from plasma and whole blood cannabinoid concentrations in chronic, daily cannabis smokers administered subchronic oral THC. *Drug and Alcohol Dependence*. 2012 Oct 1; 125(3): 313-319.

Altering the Landscape For Women In Clinical Chemistry: Perspectives From Multigenerational Leaders

Representation and progression among women with advanced degrees in science and medicine have significantly improved over the past 50 years. A recent report from the Association of American Medical Colleges indicates that despite women being in the minority, the number of female division/section chiefs, department chairs, and deans has increased overall by more than 50% in the past 10 years (<https://www.aamc.org/members/gwims/statistics/>; accessed April 2, 2012). This information and the election of 3 consecutive female AACC presidents and a new female AACC executive vice president caused us to reflect on the increasing global presence of female leaders in clinical chemistry and laboratory medicine. As female laboratory directors, mothers, and members of AACC's Society for Young Clinical Laboratorians group, we have the perception that our profession is a supportive environment and a well-suited career for young women today, but we wondered if it has always been that way. The authors posed a series of questions to a multigenerational panel of female clinical chemists, who relate their experiences as women in clinical chemistry and laboratory medicine over the past several decades. Haymond S, Saenger AK, Free HM, Hicks JM, Huestis MA, Horvath R, Fantz CR. Altering the landscape for

women in clinical chemistry: Perspectives from multigenerational leaders. *Clinical Chemistry*. 2012 Jul; 58(7): 1082-1085. Epub 2012 May 23.

Psychomotor Performance, Subjective and Physiological Effects and Whole Blood D9-Tetrahydrocannabinol Concentrations In Heavy, Chronic Cannabis Smokers Following Acute Smoked Cannabis

Δ^9 -Tetrahydrocannabinol (THC) is the illicit drug most frequently observed in accident and driving under the influence of drugs investigations. Whole blood is often the only available specimen collected during such investigations, yet few studies have examined relationships between cannabis effects and whole blood concentrations following cannabis smoking. Nine male and one female heavy, chronic cannabis smokers resided on a closed research unit and smoked ad libitum one 6.8% THC cannabis cigarette. THC, 11-hydroxy-THC and 11-nor-9-carboxy-THC were quantified in whole blood and plasma. Assessments were performed before and up to 6 h after smoking, including subjective [visual analog scales (VAS) and Likert scales], physiological (heart rate, blood pressure and respirations) and psychomotor (critical-tracking and divided-attention tasks) measures. THC significantly increased VAS responses and heart rate, with concentration-effect curves demonstrating counter-clockwise hysteresis. No significant differences were observed for critical-tracking or divided-attention task performance in this cohort of heavy, chronic cannabis smokers. The cannabis influence factor was not suitable for quantifying psychomotor impairment following cannabis consumption and was not precise enough to determine recent cannabis use with accuracy. These data inform our understanding of impairment and subjective effects following acute smoked cannabis and interpretation of whole blood cannabinoid concentrations in forensic investigations. Schwoppe DM, Bosker WM, Ramaekers JG, Gorelick DA, Huestis MA. Psychomotor performance, subjective and physiological effects and whole blood D9-tetrahydrocannabinol concentrations in heavy, chronic cannabis smokers following acute smoked cannabis. *Journal of Analytical Toxicology*. 2012 Jul; 36(6): 405-412.

Cannabinoid Stability In Authentic Oral Fluid After Controlled Cannabis Smoking

Defining cannabinoid stability in authentic oral fluid (OF) is critically important for result interpretation. There are few published OF stability data, and of those available, all employed fortified synthetic OF solutions or elution buffers; none included authentic OF following controlled cannabis smoking. An expectorated OF pool and a pool of OF collected with Quantisal™ devices were prepared for each of 10 participants. Δ^9 -tetrahydrocannabinol (THC), 11-nor-9-carboxy-THC (THCCOOH), cannabidiol (CBD), and cannabinol (CBN) stability in each of 10 authentic expectorated and Quantisal-collected OF pools were determined after storage at 4 °C for 1 and 4 weeks and at -20 °C for 4 and 24 weeks. Results within $\pm 20\%$ of baseline concentrations analyzed within 24 h of collection were considered stable. All Quantisal OF cannabinoid concentrations were stable for 1 week at 4 °C. After 4 weeks at 4 °C, as well as 4 and 24 weeks at -20 °C, THC was stable in 90%, 80%, and 80% and THCCOOH in 89%, 40%, and 50% of Quantisal samples, respectively. Cannabinoids in expectorated OF were less stable than in Quantisal samples when refrigerated or frozen. After 4 weeks at 4 and -20 °C, CBD and CBN were stable in 33%-100% of Quantisal and expectorated samples; by 24 weeks at -20 °C, CBD and CBN were stable in $\leq 44\%$. Cannabinoid OF stability varied by analyte, collection method, and storage duration and temperature, and across participants. OF collection with a device containing an elution/stabilization buffer, sample storage at 4 °C, and analysis within 4 weeks is preferred to maximize result accuracy. Lee D, Milman G, Schwoppe DM, Barnes AJ, Gorelick DA, Huestis MA. Cannabinoid stability in authentic oral fluid after controlled cannabis smoking. *Clinical Chemistry*. 2012 Jul; 58(7): 1101-1109.

Methadone and Metabolites In Hair Of Methadone-Assisted Pregnant Women and Their Infants

Methadone is the recommended pharmacotherapy for opioid-dependent pregnant women. The primary aims of this study were to determine whether a dose-concentration relationship exists between cumulative maternal methadone dose, methadone and metabolite concentrations in maternal hair during pregnancy and whether maternal hair methadone and metabolite concentrations predict neonatal outcomes. Hair specimens were collected monthly from opioid-dependent mothers enrolled in methadone treatment and 4 of their infants. Hair specimens were segmented (3 cm), washed (maternal hair only), and analyzed for methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), and 2-ethyl-5-methyl-3,3-diphenylpyrroline by liquid chromatography tandem mass spectrometry. There was large intersubject variability and no dose-concentration relationship for cumulative methadone dose and methadone, EDDP, 2-ethyl-5-methyl-3,3-diphenylpyrroline, or total concentrations in hair. For individual women, a positive trend was noted for cumulative methadone dose and methadone and EDDP concentrations in hair. There was a positive linear trend for cumulative methadone dose and EDDP/methadone ratio in maternal hair, perhaps reflecting methadone's induction of its own metabolism. Maternal methadone concentrations were higher than those in infant hair, and infant EDDP hair concentrations were higher than those in maternal hair. Maternal methadone dose, and methadone and EDDP hair concentrations were not correlated with peak infant neonatal abstinence syndrome (NAS) scores, days to peak NAS, duration of NAS, time to NAS onset, birth length, head circumference, or amount of neonatal morphine pharmacotherapy. Maternal cumulative third trimester methadone dose was positively correlated with infant birth weight. Methadone and EDDP in pregnant women's hair are markers of methadone exposure and do not predict total methadone dose, nor neonatal outcomes from in utero methadone exposure. Himes SK, Goodwin RS, Rock CM, Jones HE, Johnson RE, Wilkins DG, Huestis MA. Methadone and metabolites in hair of methadone-assisted pregnant women and their infants. *Therapeutic Drug Monitoring*. 2012 Jun; 34(3): 337-344.

Reversible and Regionally Selective Downregulation Of Brain Cannabinoid CB1 Receptors In Chronic Daily Cannabis Smokers

Chronic cannabis (marijuana, hashish) smoking can result in dependence. Rodent studies show reversible downregulation of brain cannabinoid CB(1) (cannabinoid receptor type 1) receptors after chronic exposure to cannabis. However, whether downregulation occurs in humans who chronically smoke cannabis is unknown. Here IRP researchers show, using positron emission tomography imaging, reversible and regionally selective downregulation of brain cannabinoid CB(1) receptors in human subjects who chronically smoke cannabis. Downregulation correlated with years of cannabis smoking and was selective to cortical brain regions. After 4 weeks of continuously monitored abstinence from cannabis on a secure research unit, CB(1) receptor density returned to normal levels. This is the first direct demonstration of cortical cannabinoid CB(1) receptor downregulation as a neuroadaptation that may promote cannabis dependence in human brain. Hirvonen J, Goodwin RS, Li CT, Terry GE, Zoghbi SS, Morse C, Pike VW, Volkow ND, Huestis MA, Innis RB. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. *Molecular Psychiatry*. 2012 Jun; 17(6): 642-649.

Simultaneous Quantification Of Nicotine, Cotinine, Trans-3'-Hydroxycotinine, Norcotinine and Mecamylamine In Human Urine By Liquid Chromatography-Tandem Mass Spectrometry

Mecamylamine is a nicotine antagonist under investigation in combination with nicotine replacement for smoking treatment. A simple, rapid and reliable liquid chromatography tandem mass spectrometry (LCMSMS) method was developed and validated for quantifying

nicotine, cotinine, *trans*-3'-hydroxycotinine, norcotinine and mecamlamine in human urine. Chromatography was performed on a Synergi PolarRP column with a gradient of 0.1% formic acid and 0.1% formic acid in acetonitrile at 0.25mL/min with an 8-min total runtime. Analytes were monitored by positive mode electrospray ionization and multiple reaction monitoring mass spectrometry. Linear dynamic ranges were 1-500ng/mL for nicotine and norcotinine, 0.5-500ng/mL for *trans*-3'-hydroxycotinine, 0.2-500ng/mL for cotinine, and 0.1-100ng/mL for mecamlamine; correlation coefficients were consistently greater than 0.99, and all calibrator concentrations were within 20% of target. Extensive endogenous and exogenous interferences were evaluated. At three concentrations spanning the linear dynamic range of the assay, mean extraction efficiencies from urine were 55.1-109.1% with analytical recovery (bias) 82.0-118.7% and total imprecision 0.7-9.1% relative standard deviation. Analytes were stable for 24h at room temperature, 72h at 4°C, 72h in autosampler at 15°C and after three freeze/thaw cycles. This method is useful for monitoring mecamlamine, nicotine and nicotine metabolites in smoking cessation and other clinical nicotine research. Scheidweiler KB, Shakleya DM, Huestis MA. Simultaneous quantification of nicotine, cotinine, *trans*-3'-hydroxycotinine, norcotinine and mecamlamine in human urine by liquid chromatography-tandem mass spectrometry. *Clinica Chimica Acta*, 2012 Jun 14; 413(11-12): 978-984.

Incorporation Of Methamphetamine and Amphetamine In Human Hair Following Controlled Oral Methamphetamine Administration

Although hair testing is well established for the assessment of past drug exposure, uncertainties persist about mechanisms of drug incorporation into hair and interpretation of results. The aim of this study was to administer methamphetamine (MAMP) under controlled conditions as a model drug to investigate drug incorporation into human hair. Seven volunteers with a history of stimulant use received 4×10 mg (low) doses of sustained release S-(+)-MAMP HCl within 1 week, with weekly head hair samples collected by shaving. 3 weeks later, 4 of them received 4×20 mg (high) doses. After extensive isopropanol/phosphate buffer washing of the hair, MAMP and its metabolite amphetamine (AMP) concentrations were determined in all weekly hair samples by LC-MS-MS in selected reaction monitoring mode with the undeca- and deca-deuterated drugs, respectively, as internal standards (LLOQ, 0.005 ng mg(-1)). MAMP T(max) occurred from 1 to 2 weeks after both doses, with C(max) ranging from 0.6 to 3.5 ng mg(-1) after the low and 1.2 to 5.3 ng mg(-1) after the high MAMP doses. AMP C(max) in hair was 0.1-0.3 ng mg(-1) and 0.2-0.5 ng mg(-1), respectively, for low and high doses. Highly dose-related concentrations within subjects, but large variability between subjects were observed. MAMP concentrations were above the 0.2 ng mg(-1) cut-off for at least 2 weeks following administration of both low and high doses. The overall AMP/MAMP ratio ranged from 0.07 to 0.37 with a mean value of 0.15 ± 0.07, and a median of 0.13. The percentage of MAMP and AMP removed with the washing procedure decreased with time after administration. A strong correlation was found between area under the curve of MAMP ($r(2)=0.90$, $p=0.00$) and AMP ($r(2)=0.94$, $p=0.00$) concentrations calculated for the 3-week period following administration and the total melanin concentration in hair. Significant correlations were observed also between C(max) and melanin. This study demonstrated that despite large inter-individual differences, the incorporation of MAMP and AMP into hair is dose-related with much of the observed scatter of MAMP and AMP concentrations explained by melanin concentration in hair. Polletini AE, Cone EJ, Gorelick DA, Huestis MA. Incorporation of methamphetamine and amphetamine in human hair following controlled oral methamphetamine administration. *Analytica Chimica Acta*. 2012 May 13; 726: 35-43.

Cannabinoid Disposition In Oral Fluid Following Controlled Smoked Cannabis The authors measured $\Delta(9)$ -tetrahydrocannabinol (THC), 11-nor-9-carboxy-THC (THCCOOH), cannabidiol (CBD), and cannabinol (CBN) disposition in oral fluid (OF) following controlled cannabis smoking to evaluate whether monitoring multiple cannabinoids in OF improved OF test interpretation. Cannabis smokers provided written informed consent for this institutional review board-approved study. OF was collected with the Quantisal™ device following ad libitum smoking of one 6.8% THC cigarette. Cannabinoids were quantified by 2-dimensional GC-MS. The authors evaluated 8 alternative cutoffs based on different drug testing program needs. 10 participants provided 86 OF samples -0.5 h before and 0.25, 0.5, 1, 2, 3, 4, 6, and 22 h after initiation of smoking. Before smoking, OF samples of 4 and 9 participants were positive for THC and THCCOOH, respectively, but none were positive for CBD and CBN. Maximum THC, CBD, and CBN concentrations occurred within 0.5 h, with medians of 644, 30.4, and 49.0 $\mu\text{g/L}$, respectively. All samples were THC positive at 6 h (2.1-44.4 $\mu\text{g/L}$), and 4 of 6 were positive at 22 h. CBD and CBN were positive only up to 6 h in 3 (0.6-2.1 $\mu\text{g/L}$) and 4 (1.0-4.4 $\mu\text{g/L}$) participants, respectively. The median maximum THCCOOH OF concentration was 115 ng/L, with all samples positive to 6 h (14.8-263 ng/L) and 5 of 6 positive at 22 h. By quantifying multiple cannabinoids and evaluating different analytical cutoffs after controlled cannabis smoking, the authors determined windows of drug detection, found suggested markers of recent smoking, and minimized the potential for passive contamination. Lee D, Schwoppe DM, Milman G, Barnes AJ, Gorelick DA, Huestis MA. Cannabinoid disposition in oral fluid following controlled smoked cannabis. *Clinical Chemistry*. 2012 Apr; 58(4): 748-756.

Cannabinoids and Metabolites In Expectorated Oral Fluid Following Controlled Smoked Cannabis $\Delta(9)$ -Tetrahydrocannabinol (THC) in oral fluid (OF) implies cannabis intake, but eliminating passive exposure and improving interpretation of test results requires additional research. Ten adult cannabis users smoked ad libitum one 6.8% THC cigarette. Expectorated OF was collected for up to 22 h, and analyzed within 24h of collection. THC, 11-nor-9-carboxy-THC (THCCOOH), cannabidiol, and cannabinol were quantified by 2-dimensional-GCMS. Eighty specimens were analyzed; 6 could not be collected due to dry mouth. THC was quantifiable in 95.2%, cannabidiol in 69.3%, cannabinol in 62.3%, and THCCOOH in 94.7% of specimens. Highest THC, cannabidiol, and cannabinol concentrations were 22370, 1000, and 1964 $\mu\text{g/l}$, respectively, 0.25 h after the start of smoking; THCCOOH peaked within 2h (up to 560 ng/l). Concentrations 6h after smoking were THC (0.9-90.4 $\mu\text{g/l}$) and THCCOOH (17.0-151 ng/l) (8 of 9 positive for both); only 4 were positive for cannabidiol (0.5-2.4 $\mu\text{g/l}$) and cannabinol (1.0-3.0 $\mu\text{g/l}$). By 22 h, there were 4 THC (0.4-10.3 $\mu\text{g/l}$), 5 THCCOOH (6.0-24.0 ng/l), 1 cannabidiol (0.3 $\mu\text{g/l}$), and no cannabinol positive specimens. THCCOOH in OF suggests no passive contamination, and CBD and CBN suggest recent cannabis smoking. Seventeen alternative cutoffs were evaluated to meet the needs of different drug testing programs. Milman G, Schwoppe DM, Gorelick DA, and Huestis MA. Cannabinoids and metabolites in expectorated oral fluid following controlled smoked cannabis, *Clinica Chimica Acta*. 2012 Apr 11; 413(7-8): 765-770.

Rimonabant For Neurocognition In Schizophrenia: A 16-Week Double Blind Randomized Placebo Controlled Trial The objective of this study was to examine the effect of rimonabant on neurocognitive impairments in people with schizophrenia. Participants entered a 16-week double-blind, placebo-controlled, randomized clinical trial. A neurocognitive battery was administered at baseline and end of study. In comparison to rimonabant (20mg/day), placebo-treated participants exhibited a significant improvement on the Repeatable Battery for the Assessment of

Neuropsychological Status total score. In contrast, rimonabant was associated with significant improvement on a probabilistic learning task. There were no other significant treatment effects. Rimonabant did not improve global cognitive functioning, but did improve a specific learning deficit based on response to positive feedback. Boggs DL, Kelly DL, McMahon RP, Gold JM, Gorelick DA, Linthicum J, Conley RR, Liu F, Waltz J, Huestis MA, Buchanan RW. Rimonabant for neurocognition in schizophrenia: A 16-week double blind randomized placebo controlled trial. *Schizophrenia Research*. 2012 Feb; 134(2-3): 207-210.

Stereoselective Urinary MDMA (Ecstasy) and Metabolites Excretion Kinetics Following Controlled MDMA Administration To Humans

The R- and S-enantiomers of racemic 3,4-methylenedioxymethamphetamine (MDMA) exhibit different dose-concentration curves. In plasma, S-MDMA was eliminated at a higher rate, most likely due to stereoselective metabolism. Similar data were shown in various in vitro experiments. The aim of the present study was the in vivo investigation of stereoselective elimination of MDMA's phase I and phase II metabolites in human urine following controlled oral MDMA administration. Urine samples from 10 participants receiving 1.0 and 1.6 mg/kg MDMA separated by at least one week were analyzed blind by liquid chromatography-high resolution-mass spectrometry and gas chromatography-mass spectrometry after chiral derivatization with S-heptafluorobutylpropyl chloride. R/S ratios at C(max) were comparable after low and high doses with ratios >1 for MDMA, free DHMA, and HMMA sulfate, and with ratios <1 for MDA, free HMMA, DHMA sulfate and HMMA glucuronide. In the five days after the high MDMA dose, a median of 21% of all evaluated compounds were excreted as R-stereoisomers and 17% as S-stereoisomers. Significantly greater MDMA, DHMA, and HMMA sulfate R-enantiomers and HMMA and HMMA glucuronide S-stereoisomers were excreted. No significant differences were observed for MDA and DHMA sulfate stereoisomers. Changes in R/S ratios could be observed over time for all analytes, with steady increases in the first 48 h. R/S ratios could help to roughly estimate time of MDMA ingestion and therefore, improve interpretation of MDMA and metabolite urinary concentrations in clinical and forensic toxicology. Schwaninger AE, Meyer MR, Barnes AJ, Kolbrich-Spargo EA, Gorelick DA, Goodwin RS, Huestis MA, Maurer HH. Stereoselective urinary MDMA (ecstasy) and metabolites excretion kinetics following controlled MDMA administration to humans. *Biochemical Pharmacology*. 2012 Jan 1; 83(1): 131-138.

Cannabis Withdrawal In Chronic Cannabis Users With Schizophrenia

Chronic users of cannabis often report withdrawal symptoms after abstinence from use, but little is known about cannabis withdrawal in people with schizophrenia. Cannabis use patterns and withdrawal symptoms in adults with schizophrenia who had at least weekly cannabis use before attempting to quit without formal treatment were assessed with the Marijuana Quit Questionnaire (MJQQ), a 176-item, semi-structured questionnaire. 120 participants, predominantly African-American (62.5%) and male (76.7%), met inclusion criteria. 20.1% reported that their first regular cannabis use (median age 15 years [range 8-48]) preceded their age at first psychotic symptoms (20 [4-50] years). Twenty (16.7%) participants met lifetime criteria for cannabis abuse; 98 (81.7%) met surrogate criteria for lifetime cannabis dependence. Withdrawal symptoms were reported by 113 (94.2%) participants, with 74.2% reporting ≥ 4 symptoms. The most frequently reported withdrawal symptoms were craving for cannabis (59.2%), feeling anxious (52.57%), feeling bored (47.5%), feeling sad or depressed (45.8%), feeling irritable or jumpy (45.0%), feeling restless (43.3%), and trouble falling asleep (33.3%). One hundred-and-four (92.0%) participants took some action to relieve at least one of their withdrawal symptoms during their index-quit attempt, including 26 (23.0%) participants who reported resuming cannabis use. Cannabis withdrawal is a clinically significant feature of

cannabis use among people with schizophrenia, may serve as a negative reinforcer for relapse, and deserves greater attention in treatment and research. Boggs DL, Kelly DL, Liu F, Linthicum JA, Turner H, Schroeder JR, McMahon RP, Gorelick DA. Cannabis withdrawal in chronic cannabis users with schizophrenia J Psychiatr Res 2012 Nov 9.

CB1-Cannabinoid Receptor Antagonist Effects On Cortisol In Cannabis-Dependent Men The endocannabinoid system modulates the hypothalamic-pituitary-adrenal (HPA) axis, but the effect of cannabinoid type 1 (CB1) receptor antagonism following chronic CB1 receptor stimulation in humans is unknown. The objective of this study was to evaluate effects of the CB1 receptor antagonist rimonabant on the HPA axis in cannabis-dependent individuals. Fourteen daily cannabis smokers received increasingly frequent 20 mg oral Δ^9 -tetrahydrocannabinol (THC) doses (60-120 mg/day) over 8 days to standardize cannabis tolerance. Concurrent with the last THC dose, double-blind placebo or rimonabant (20 or 40 mg) was administered. Cannabinoid, rimonabant, and cortisol plasma concentrations were measured 1.5 hours prior to rimonabant administration and 2.0, 5.5, and 12.5 hours post-dose. Ten participants completed before premature study termination due to rimonabant's withdrawal from development. Five participants received 20 mg, three received 40 mg, and two placebo. There was a significant positive association between rimonabant concentration and change in cortisol concentration from baseline ($r = .53, p < .01$). There also was a borderline significant association between rimonabant dose and cortisol concentrations when the dose-by-time interaction was included. Four of eight participants receiving rimonabant (none of two receiving placebo) had greater cortisol concentrations 2 hours after dosing (at 11:30) than at 08:00, while normal diurnal variation should have peak concentrations at 08:00. Rimonabant 20 or 40 mg did not significantly increase plasma cortisol concentrations, consistent with an absence of antagonist-elicited cannabis withdrawal. Rimonabant doses >40 mg might elicit cortisol changes, confirming a role for CB1 receptors in modulating the HPA axis in humans. Goodwin RS, Gorelick DA, Schwilke E, Schwoppe DM, Darwin WD, Kelly DL, Schroeder JR, Ortemann-Renon C, Bonnet D, Huestis MA. CB1-cannabinoid receptor antagonist effects on cortisol in cannabis-dependent men. American Journal of Drug Alcohol Abuse. 2012 Jan; 38(1): 114-119.

State Of the Art Treatments For Cannabis Dependence The treatment of cannabis dependence can be viewed as a cup half empty or half full. On the one hand, few people who might benefit from treatment actually receive it. Among those who undergo treatment in randomized trials, long-term abstinence is achieved by fewer than 20%. Moderate use goals have been associated with decreases in consequences, but the differential impact of such goals on the long-term course of cannabis dependence is unknown. Optimal duration of treatment is unclear, and certain populations, particularly patients with co-occurring disorders, have not been studied adequately. Twelve-step programs are low cost, effective for other substance use disorders, and readily available in most regions of the world. However, their role and efficacy in cannabis dependence has not been examined. Finally, effective pharmacologic treatments are under development, but none have yet been firmly established. On the other hand, psychotherapeutic strategies used to treat other substance use disorders can be effective for cannabis dependence. A recent meta-analysis of psychosocial interventions for illicit substance use disorders found that treatments for cannabis dependence had comparatively larger effect sizes than treatments for other substance use disorders. Combination therapies have proven most effective, particularly those that begin with a motivational intervention, utilize incentives to enhance the commitment to change, and teach behavioral and cognitive coping skills to prevent relapse. Among adolescents, family engagement and collaboration with community stakeholders adds substantial value. Although only 9% of cannabis

users develop cannabis dependence, the volume of people who smoke cannabis ensures that the total number of people in need of help is larger than the capacity of substance abuse specialty services. Thus, although efforts to refine and improve the efficacy of treatment interventions continue, innovations that increase the availability and accessibility of treatment are also needed. Computer- and phone-based interventions, social media, and brief interventions that can be implemented in primary care settings are areas that may hold promise for reaching at-risk populations. Adolescents and persons with co-occurring mental illness are at particularly high risk of cannabis dependence, and may suffer disproportionately from cannabis's adverse effects. As in the treatment of other substance use disorders, there is a need for a continuing care model with long-term follow-up that extends past the periods typically evaluated in treatment studies. Additionally, there is a need for further investigation of genetic underpinnings and endophenotypes underlying cannabis dependence to identify neurobiological mechanisms for targeted intervention. One benefit of the societal focus on cannabis has been a prominent increase in research covering everything from the basic science to public health impact of cannabis. Over the next decade, physicians who provide treatment for individuals with cannabis dependence are likely to see their armamentarium of effective interventions expand, to the ultimate betterment of patients, their families, and society at large. Danovitch I, Gorelick DA. State of the art treatments for cannabis dependence. *Psychiatr Clin North Am* 2012 Jun; 35(2): 309-326.

Use Of A 'Microecological Technique' To Study Crime Incidents Around Methadone Maintenance Treatment Centers Concern about crime is a significant barrier to the establishment of methadone treatment centers (MTCs). Methadone maintenance reduces crime among those treated, but the relationship between MTCs and neighborhood crime is unknown. The authors evaluated crime around MTCs. The study setting was Baltimore City, MD, USA. The authors evaluated crime around 13 MTCs and three types of control locations: 13 convenience stores (stores), 13 residential points and 10 general medical hospitals. They collected reports of Part 1 crimes from 1 January 1999 to 31 December 2001 from the Baltimore City Police Department. Crimes and residential point locations were mapped electronically by street address (geocoded), and MTCs, hospitals and stores were mapped by visiting the sites with a global positioning satellite (GPS) locator. Concentric circular 'buffers' were drawn at 25-m intervals up to 300 m around each site. The authors used Poisson regression to assess the relationship between crime counts (incidents per unit area) and distance from the site. There was no significant geographic relationship between crime counts and MTCs or hospitals. A significant negative relationship (parameter estimate - 0.3127, $P < 0.04$) existed around stores in the daytime (7 am-7 pm), indicating higher crime counts closer to the stores. The authors found a significant positive relationship around residential points during daytime (0.5180, $P < 0.0001$) and at night (0.3303, $P < 0.0001$), indicating higher crime counts further away. Methadone treatment centers, in contrast to convenience stores, are not associated geographically with crime. Boyd SJ, Fang LJ, Medoff DR, Dixon LB, Gorelick DA. Use of a 'microecological technique' to study crime incidents around methadone maintenance treatment centers. *Addiction* 2012 Sep; 107(9): 1632-1638.

Pharmacokinetic Strategies For Treatment Of Drug Overdose and Addiction The pharmacokinetic treatment strategy targets the drug molecule itself, aiming to reduce drug concentration at the site of action, thereby minimizing any pharmacodynamic effect. This approach might be useful in the treatment of acute drug toxicity/overdose and in the long-term treatment of addiction. Phase IIa controlled clinical trials with anticocaine and antinicotine vaccines have shown good tolerability and some efficacy, but Phase IIb and III trials have been disappointing because of

the failure to generate adequate antibody titers in most participants. Monoclonal antibodies against cocaine, methamphetamine and phencyclidine have shown promise in animal studies, as has enhancing cocaine metabolism with genetic variants of human butyrylcholinesterase, with a bacterial esterase, and with catalytic monoclonal antibodies. Pharmacokinetic treatments offer potential advantages in terms of patient adherence, absence of medication interactions and benefit for patients who cannot take standard medications. Gorelick, DA. Pharmacokinetic strategies for treatment of drug overdose and addiction. *Future Med Chem* 2012 Feb; 4(2): 227-243.

Diagnostic Criteria For Cannabis Withdrawal Syndrome Cannabis withdrawal occurs in frequent users who quit, but there are no accepted diagnostic criteria for a cannabis withdrawal syndrome (CWS). This study evaluated diagnostic criteria for CWS proposed in DSM-V and two earlier proposals. A convenience sample of 384 adult, non-treatment-seeking lifetime cannabis smokers provided retrospective self-report data on their "most difficult" quit attempt without formal treatment, which was used in this secondary analysis. Prevalence, time of onset, and peak intensity (5-point Likert scale) for 39 withdrawal symptoms (drawn from the literature) were assessed via computer-administered questionnaire. Subject groups were compared using chi-square or ANOVA. Symptom clustering was evaluated with principal components analysis. 40.9% of subjects met the DSM-V criterion of ≥ 3 symptoms from a list of 7. There were no associations with sex, race, or type of cannabis preparation used. There were significant positive associations between duration or frequency of cannabis use prior to the quit attempt and experiencing CWS. Subjects with CWS had a significantly shorter duration of abstinence. Alternative syndromal criteria (dropping physical symptoms from DSM-V list; requiring ≥ 2 or ≥ 4 symptoms from a list of 11) yielded a similar prevalence of CWS and similar associations with prior cannabis use and relapse. The PCA yielded 12 factors, including some symptom clusters not included in DSM-V. Findings support the concurrent and predictive validity of the proposed DSM-V CWS, but suggest that the list of withdrawal symptoms and number required for diagnosis warrant further evaluation. Gorelick DA, Levin KH, Copersino ML, Heishman SJ, Liu F, Boggs DL, Kelly DL. Diagnostic criteria for cannabis withdrawal syndrome. *Drug Alcohol Depend* 2012 Jun 1; 123(1-3): 141-147.

MR Imaging and Spectroscopy Section, Neuroimaging Research Branch

Intrinsic Resting-State Activity Predicts Working Memory Brain Activation and Behavioral Performance Although resting-state brain activity has been demonstrated to correspond with task-evoked brain activation, the relationship between intrinsic and evoked brain activity has not been fully characterized. For example, it is unclear whether intrinsic activity can also predict task-evoked deactivation and whether the rest-task relationship is dependent on task load. In this study, IRP investigators addressed these issues on 40 healthy control subjects using resting-state and task-driven [N-back working memory (WM) task] functional magnetic resonance imaging data collected in the same session. Using amplitude of low-frequency fluctuation (ALFF) as an index of intrinsic resting-state activity, they found that ALFF in the middle frontal gyrus and inferior/superior parietal lobules was positively correlated with WM task-evoked activation, while ALFF in the medial prefrontal cortex, posterior cingulate cortex, superior frontal gyrus, superior temporal gyrus, and fusiform gyrus was negatively correlated with WM task-evoked deactivation. Further, the relationship between the intrinsic resting-state activity and task-evoked activation in lateral/superior frontal gyri, inferior/superior parietal lobules, superior temporal gyrus, and midline regions was stronger at higher WM task loads. In addition, both resting-state activity and the task-evoked

activation in the superior parietal lobule/precuneus were significantly correlated with the WM task behavioral performance, explaining similar portions of intersubject performance variance. Together, these findings suggest that intrinsic resting-state activity facilitates or is permissive of specific brain circuit engagement to perform a cognitive task, and that resting activity can predict subsequent task-evoked brain responses and behavioral performance. Zou Q, Ross TJ, Gu H, Geng X, Zuo XN, Hong LE, Gao JH, Stein EA, Zang YF, Yang Y. Intrinsic resting-state activity predicts working memory brain activation and behavioral performance. *Hum Brain Mapp.* e-pub 2012 June 19.

Mechanisms Of White Matter Changes Induced By Meditation Using diffusion tensor imaging, several recent studies have shown that training results in changes in white matter efficiency as measured by fractional anisotropy (FA). In their work, IRP scientists found that a form of mindfulness meditation, integrative body-mind training (IBMT), improved FA in areas surrounding the anterior cingulate cortex after 4-wk training more than controls given relaxation training. Reductions in radial diffusivity (RD) have been interpreted as improved myelin but reductions in axial diffusivity (AD) involve other mechanisms, such as axonal density. They now report that after 4-wk training with IBMT, both RD and AD decrease accompanied by increased FA, indicating improved efficiency of white matter involves increased myelin as well as other axonal changes. However, 2-wk IBMT reduced AD, but not RD or FA, and improved moods. These results demonstrate the time-course of white matter neuroplasticity in short-term meditation. This dynamic pattern of white matter change involving the anterior cingulate cortex, a part of the brain network related to self-regulation, could provide a means for intervention to improve or prevent mental disorders. Tang YY, Lu Q, Fan M, Yang Y, Posner MI. Mechanisms of white matter changes induced by meditation. *Proc Natl Acad Sci U S A.* 2012 Jun 26; 109(26): 10570-10574.

In Vivo High-Resolution Localized (1) H MR Spectroscopy In the Awake Rat Brain At 7 T

In vivo localized high-resolution (1) H MR spectroscopy was performed in multiple brain regions without the use of anesthetic or paralytic agents in awake head-restrained rats that were previously trained in a simulated MRI environment using a 7T MR system. Spectra were obtained using a short echo time single-voxel point-resolved spectroscopy technique with voxel size ranging from 27 to 32.4 mm³ in the regions of anterior cingulate cortex, somatosensory cortex, hippocampus, and thalamus. Quantifiable spectra, without the need for any additional postprocessing to correct for possible motion, were reliably detected including the metabolites of interest such as γ -aminobutyric acid, glutamine, glutamate, myo-inositol, N-acetylaspartate, taurine, glycerophosphorylcholine/phosphorylcholine, creatine/phosphocreatine, and N-acetylaspartate/N-acetylaspartylglutamate. The spectral quality was comparable to spectra from anesthetized animals with sufficient spectral dispersion to separate metabolites such as glutamine and glutamate. Results from this study suggest that reliable information on major metabolites can be obtained without the confounding effects of anesthesia or paralytic agents in rodents. Xu S, Ji Y, Chen X, Yang Y, Gullapalli RP, Masri R. In vivo high-resolution localized (1) H MR spectroscopy in the awake rat brain at 7 T. *Magn Reson Med.* e-pub 2012 May 8.

Nicotine Psychopharmacology Section/Clinical Pharmacology and Therapeutics Branch

Drug Use In Smokers With and Without Schizophrenia The prevalence of cigarette smoking among people with schizophrenia is greater than that of the general population. Because smoking and use of other drugs covary, the authors examined illicit drug use in current smokers not trying to

quit or reduce their tobacco use. They recruited outpatient participants who had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder (schizophrenia, n=70) and a control group who had no Axis I psychiatric disorders (control, n=97). During a 2-3 hour session, participants completed demographic and research questionnaires, including the Drug Use Survey (DUS). Participants with schizophrenia were older than controls ($p < 0.001$) and smoked more cigarettes per day ($p = 0.01$), but did not differ in degree of nicotine dependence. Ever using a drug was similar between the groups, except that significantly more participants with schizophrenia reported ever using hallucinogens ($p < 0.001$) and inhalants ($p = 0.001$). For alcohol, cocaine, and marijuana, fewer participants with schizophrenia were current users, but more participants with schizophrenia were past users (p 's < 0.0001). Heavy smokers from the general population continued to use illicit drugs throughout their lives, while schizophrenia participants had the highest period of illicit drug use in their 20's. These data suggest that illicit drug use tends to be high in heavy cigarette smokers, regardless of a schizophrenia diagnosis. However, while illicit drug use is high across the lifespan of heavy smokers in the general population, heavy smokers with schizophrenia use illicit drugs mostly in the first decade of their illness. Mackowick KM, Heishman SJ, Wehring HJ, Liu F, McMahon RP, Kelly DL. Illicit drug use in heavy smokers with and without schizophrenia. *Schizophr Res* 2012; 139: 194-200.

Dose-Response Effects Of Spectrum Research Cigarettes Experimental cigarettes are needed to conduct studies examining the effects of varying doses of nicotine content on smoking behavior. The National Institute on Drug Abuse contracted with Research Triangle Institute to make such cigarettes available to researchers. The goal of this study was to determine whether cigarettes that vary in nicotine content produce an expected dose-response effect. Two studies were conducted. The first study recruited subjects from three sites and consisted of a single, within-subject laboratory session. Subjects first smoked 4 puffs on their usual-brand cigarette and then in double-blind, random order, smoked 4 puffs on each experimental cigarette that contained either low nicotine (LN, 0.4 mg/g), intermediate nicotine (IN, 5.7-5.8 mg/g), or high nicotine (HN, 11.4-12.8 mg/g). Each puffing bout was separated by a 30-minute interval. Subjects completed questionnaires and were assessed for vital signs after each cigarette. The second study involved one site and used a between-subject design in which subjects were assigned to one of the 3 experimental cigarettes for one week. Subjective responses and biomarkers of exposure were assessed. In the first study, significant dose response effects were observed, particularly between the LN and HN cigarettes. The second study showed decreases in cigarette smoking and exposure biomarkers predominantly in the LN group, with no changes in the HN cigarette group. These results are similar to those observed in prior literature, confirming that these experimental cigarettes can be used safely and with the expected pharmacological effects. Hatsukami DK, Heishman SJ, Isaksson-Vogel R, Denlinger RL, Roper-Batker AN, Mackowick KM, Jensen J, Murphy SE, Thomas BF, Donny E. Dose response effects of Spectrum research cigarettes. *Nicotine Tob Res* 2012, e-pub Nov. 22, 2012.

Neurocircuitry of Motivation Section, Behavioral Neuroscience Branch

Rewarding and Incentive Motivational Effects Of Excitatory Amino Acid Receptor Antagonists Into the Median Raphe and Adjacent Regions Of The Rat The motivational process that regulates approach behavior toward salient distal stimuli (i.e., incentive motivation) plays a key role in voluntary behavior and motivational disorders such as addiction. This process

may be mediated by many neurotransmitter systems and a network of many brain structures, including the median and dorsal raphe regions (MR and DR, respectively). The authors sought to examine whether the blockade of excitatory amino acid receptors in the MR and DR is rewarding, using intracranial self-administration, and whether the self-administration effect can be explained by drug's effectiveness to enhance incentive motivation, using a visual sensation seeking procedure. Rats learned to self-administer the AMPA receptor antagonist ZK 200775 into the vicinity of the MR, DR, or medial oral pontine reticular regions, but not the ventral tegmental area. The NMDA receptor antagonist AP5 was also self-administered into the MR, while it was not readily self-administered into other regions. When ZK 200775 was noncontingently administered into the MR, rats markedly increased approach responses rewarded by brief illumination of a light stimulus. In addition, contingent administration of ZK 200775 into the MR induced a conditioning effect on approach responses. Rats self-administer excitatory amino acid receptor antagonists into the MR and adjacent regions. Self-administration effect of AMPA receptor antagonists into the MR can be largely explained by the manipulation's properties to invigorate ongoing approach behavior and induces conditioned approach. Glutamatergic afferents to the median raphe and adjacent regions appear to tonically suppress incentive-motivational processes. Webb SM, Vollrath-Smith FR, Shin R, Zhou TC, Xu S, Ikemoto S. *Psychopharmacology (Berl)*. 2012 Dec; 224(3): 401-412. doi:10.1007/s00213-012-2759-0. Epub 2012 Jun 30.

Mapping Of Reinforcing and Analgesic Effects Of the Mu Opioid Agonist Endomorphin-1 In the Ventral Midbrain Of the Rat

Agonists at the mu opioid receptor (MOR) are widely recognized for their effects on reward and pain. Although prior studies have attributed some of these effects to MORs on GABA neurons in the ventral tegmental area (VTA), recent studies have identified a region of particularly strong MOR immunostaining residing caudal to the VTA, in a region denoted the rostromedial tegmental nucleus (RMTg). Hence, the authors examined whether rats would self-administer small doses (50-250 pmol) of the selective MOR agonist endomorphin-1 (EM1) into the RMTg and adjacent sites. EM1 was chosen due to its short half-life, thus limiting drug spread, and due to its presence endogenously in brain neurons, including some afferents to the RMTg. The highest rates of EM1 self-administration occurred within 0.5 mm of the RMTg center, in a region roughly 0.8-1.6 mm caudal to the majority of VTA DA neurons. In contrast, self-administration rates were much lower in the adjacent VTA, interpeduncular nucleus, central linear nucleus, or median raphe nucleus. Furthermore, EM1 infusions into the RMTg, but not surrounding regions, produced conditioned place preference, while EM1 infusions into the RMTg but not anterior VTA markedly reduced formalin-induced pain behaviors. EM1 effects were mimicked by infusions of the GABA agonist muscimol into the same region, consistent with EM1 having inhibitory actions on its target neurons. These results implicate a novel brain region in modulating MOR influences on both appetitive and aversive behavior. Zhou TC, Xu SP, Lee MR, Gallen CL, Ikemoto S. *Psychopharmacology (Berl)*. 2012 Nov; 224(2): 303-312. doi:10.1007/s00213-012-2753-6. Epub 2012 Jun 6.

Synergistic Interaction Between Baclofen Administration Into The Median Raphe Nucleus and Inconsequential Visual Stimuli On Investigatory Behavior Of Rats

Noncontingent administration of amphetamine into the ventral striatum or systemic nicotine increases responses rewarded by inconsequential visual stimuli. When these drugs are contingently administered, rats learn to self-administer them. IRP scientists recently found that rats self-administer the GABA(B) receptor agonist baclofen into the median (MR) or dorsal (DR) raphe nuclei. They examined whether noncontingent administration of baclofen into the MR or DR increases rats' investigatory

behavior rewarded by a flash of light. Contingent presentations of a flash of light slightly increased lever presses. Whereas noncontingent administration of baclofen into the MR or DR did not reliably increase lever presses in the absence of visual stimulus reward, the same manipulation markedly increased lever presses rewarded by the visual stimulus. Heightened locomotor activity induced by intraperitoneal injections of amphetamine (3 mg/kg) failed to concur with increased lever pressing for the visual stimulus. These results indicate that the observed enhancement of visual stimulus seeking is distinct from an enhancement of general locomotor activity. Visual stimulus seeking decreased when baclofen was co-administered with the GABA(B) receptor antagonist, SCH 50911, confirming the involvement of local GABA(B) receptors. Seeking for visual stimulus also abated when baclofen administration was preceded by intraperitoneal injections of the dopamine antagonist, SCH 23390 (0.025 mg/kg), suggesting enhanced visual stimulus seeking depends on intact dopamine signals. Baclofen administration into the MR or DR increased investigatory behavior induced by visual stimuli. Stimulation of GABA(B) receptors in the MR and DR appears to disinhibit the motivational process involving stimulus-approach responses. Vollrath-Smith FR, Shin R, Ikemoto S. *Psychopharmacology (Berl)*. 2012 Mar; 220(1): 15-25. Epub 2011 Sep 9.

Neurobiology of Relapse Section, Behavioral Neuroscience Branch

Context-Induced Relapse To Alcohol Seeking After Punishment In A Rat Model Rat studies have demonstrated that exposure to environments associated with alcohol intake reinstates alcohol seeking after extinction of alcohol-reinforced responding in a different context. However, extinction is limited as an abstinence model because humans typically abstain because of negative consequences associated with excessive drinking. It is currently unknown whether alcohol-associated contexts can provoke relapse to alcohol seeking after alcohol-taking behavior is suppressed by adverse consequences in a different context. Alcohol-preferring P rats were first given home-cage access to 20% ethanol. Next, they were trained to self-administer 20% ethanol in one context (context A). Subsequently, all rats continued to self-administer alcohol in a different context (context B). For one group, 50% of alcohol-reinforced responses were punished by mild footshock; two other groups either received non-contingent shocks or no shock. A fourth group was given extinction training in context B. All rats were then tested for relapse to alcohol seeking under extinction conditions in contexts A and B. In Context B, alcohol-taking behavior was suppressed by contingent shock (punishment) and extinction training but not by non-contingent shock. In Context A, relapse to alcohol seeking was reliably observed in the punished and extinction groups; a context switch had no effect on alcohol seeking in the no-shock or non-contingent shock groups. These data indicate that punishment-induced suppression of alcohol-taking behavior is context-dependent. The authors propose that their procedure can be used to explore mechanisms of context-induced relapse to alcohol seeking after alcohol-taking behavior is suppressed by adverse consequences. Marchant NJ, Khuc TN, Pickens CL, Bonci A, Shaham Y. Context-induced relapse to alcohol seeking after punishment in a rat model. *Biological Psychiatry* 2012, e-pub August 7, 2012.

In-Vivo Electrophysiology Unit, Behavioral Neuroscience Branch

Rapid Fluctuations In Extracellular Brain Glucose Levels Induced By Natural Arousing Stimuli and Intravenous Cocaine: Fueling the Brain During Neural Activation Glucose, a primary energetic substrate for neural activity, is continuously influenced by two opposite forces,

which tend to either decrease its extracellular levels due to enhanced utilization in neural cells or increase its levels due to entry from peripheral circulation via enhanced cerebral blood flow. How this balance is maintained under physiological conditions and how it is changed during neural activation remain unclear. To clarify this issue, enzyme-based glucose sensors coupled with high-speed amperometry were used in freely moving rats to evaluate fluctuations in extracellular levels of glucose induced by a brief audio stimulus, tail-pinch (TP), social interaction with another rat (SI), and intravenous (iv) cocaine (1 mg/kg). The authors' measurements were performed in the *nucleus accumbens* (NAcc) and *substantia nigra pars reticulata* (SNr), which drastically differ in their neuronal activity. In the NAcc, where most cells are powerfully excited following salient stimulation, glucose levels rapidly (latency 2-6 s) increased (30-70 μ M or 6-14% over baseline) by all stimuli; the increase differed in its magnitude and duration for each stimulus. In the SNr, where most cells are transiently inhibited by salient stimuli, TP, SI and cocaine induced a biphasic glucose response, with the initial decrease (-20-40 μ M or 5-10% below baseline) followed by a rebound-like increase. The critical role of neuronal activity in mediating the initial glucose response was confirmed by monitoring glucose currents following local microinjections of either glutamate (GLU) or procaine (PRO). While intra-NAcc injection of GLU transiently increased glucose levels in this structure, intra-SNr PRO injection resulted in rapid, transient decreases in SNr glucose. Therefore, extracellular glucose levels in the brain change very rapidly following physiological and pharmacological stimulation, the response is structure-specific, and the pattern of neuronal activity appears to be a critical factor determining the direction and magnitude of physiological fluctuations in glucose levels. Kiyatkin EA, Lenoir M. Rapid fluctuations in extracellular brain glucose levels induced by natural arousing stimuli and intravenous cocaine: Fueling the brain during neural activation. *J Neurophys* 2012; 108: 1669-1684.

Preclinical Pharmacology Section, Behavioral Neuroscience Research Branch

Modification Of Pharmacokinetic and Abuse-Related Effects Of Cocaine By Human-Derived Cocaine Hydrolase In Monkeys

Although substantial research effort has focused on developing pharmacological treatments for cocaine abuse, no effective medications have been developed. Recent studies show that enzymes that metabolize cocaine in the periphery, forestalling its entry into the brain, can prevent cocaine toxicity and its behavioral effects in rodents. Here the authors report on effects of one such enzyme (Albu-CocH) on the pharmacokinetic and behavioral effects of cocaine in squirrel monkeys. Albu-CocH was developed from successive mutations of human butyrylcholinesterase (BChE) and has 1000-fold greater catalytic activity against cocaine than naturally occurring BChE. Pharmacokinetic studies showed mg/kg) had a half-life of 56.6 hours in squirrel monkeys. In that Albu-CocH (5 mg/kg cocaine were these studies, plasma levels of cocaine following i.v. 1 reduced 2 hours after administration of Albu-CocH, whereas plasma levels of the cocaine metabolite ecgonine methyl ester were increased. These effects were still evident 72 hours following Albu-CocH administration. In behavioral mg/kg Albu-CocH dramatically experiments in monkeys, pre-treatment with 5 decreased self-administration of a reinforcing dose of i.v. cocaine mg/kg Albu-CocHug/kg/injection) for over 24 hours. Pre-treatment with 5 (30 also attenuated the reinstatement of extinguished cocaine self-administration by mg/kg) and, in separate an i.v. priming injection of cocaine (0.1 or 0.3 studies, attenuated the discriminative-stimulus effects of cocaine. The ability of Albu-CocH to attenuate the abuse-related effects of cocaine in squirrel monkeys indicates that further investigation of BChE mutants as potential treatment for cocaine abuse and toxicity is warranted. Schindler CW, Justinova Z, Lafleur D, Woods D, Roschke V, Hallak H,

Sklair-Tavron L, Redhi GH, Yasar S, Bergman J, Goldberg SR. Modification of pharmacokinetic and abuse-related effects of cocaine by human-derived cocaine hydrolase in monkeys. *Addiction Biology* 2012, e-pub Jan 20, 2012.

Pharmacological Modulation Of the Endocannabinoid Signalling Alters Binge-Type Eating Behaviour In Female Rats

Binge eating disorder (BED) is characterized by excessive food intake during short periods of time. Recent evidence suggests that alterations in the endocannabinoid signalling could be involved in the pathophysiology of BED. In this study IRP scientists investigated whether the pharmacological manipulation of the endocannabinoid transmission may be effective in modulating the aberrant eating behaviour present in a validated rat model of BED. Binge-type eating was induced in female rats by providing limited access to an optional source of fat dietary (margarine). Rats were divided into three groups, all with ad libitum access to chow and water: Control (C), with no access to margarine; Low-restriction (LR), with 2h margarine access 7 days/week; High-restriction (HR), with 2h margarine access 3 days/week. As compared to LR group, HR group displayed higher consumption of margarine accompanied by an increasing in body weight. The cannabinoid CB1/CB2 receptor (CB1R/CBR2) agonist $\Delta(9)$ -tetrahydrocannabinol (THC) significantly increased margarine intake selectively in LR rats, while the fatty acid amide hydrolase inhibitor URB597 showed no effect. The CB1R inverse agonist/antagonist rimonabant dose-dependently reduced margarine intake in HR rats. Notably, in HR rats, chronic treatment with a low dose of rimonabant induced a selective long-lasting effect on margarine intake that did not develop tolerance, and produced a significant and persistence reduction of body weight. Chronic pharmacological blockade of CB1Rs reduces binge eating behaviour in female rats and may prove effective in treating BED, with an associated significant reduction in the body weight. Scherma M, Fattore L, Satta V, Businco F, Pigliacampo B, Goldberg S, Dessy C, Fratta W, Fadda P. Pharmacological modulation of the endocannabinoid signalling alters binge-type eating behaviour in female rats. *Br J Pharm*, epub Oct 16, 2012.

Powerful Cocaine-Like Actions Of 3,4-Methylenedioxypropylamphetamine (MDPV), A Principal Constituent Of Psychoactive 'Bath Salts' Product

The abuse of psychoactive 'bath salts' containing cathinones such as 3,4-methylenedioxypropylamphetamine (MDPV) is a growing public health concern, yet little is known about their pharmacology. Here, the authors evaluated the effects of MDPV and related drugs using molecular, cellular, and whole-animal methods. In vitro transporter assays were performed in rat brain synaptosomes and in cells expressing human transporters, while clearance of endogenous dopamine was measured by fast-scan cyclic voltammetry in mouse striatal slices. Assessments of in vivo neurochemistry, locomotor activity, and cardiovascular parameters were carried out in rats. The authors found that MDPV blocks uptake of [(3)H]dopamine ($IC_{50}=4.1nM$) and [(3)H]norepinephrine ($IC_{50}=26nM$) with high potency but has weak effects on uptake of [(3)H]serotonin ($IC_{50}=3349nM$). In contrast to other psychoactive cathinones (eg, mephedrone), MDPV is not a transporter substrate. The clearance of endogenous dopamine is inhibited by MDPV and cocaine in a similar manner, but MDPV displays greater potency and efficacy. Consistent with in vitro findings, MDPV (0.1-0.3mg/kg, intravenous) increases extracellular concentrations of dopamine in the nucleus accumbens. Additionally, MDPV (0.1-3.0mg/kg, subcutaneous) is at least 10 times more potent than cocaine at producing locomotor activation, tachycardia, and hypertension in rats. These data show that MDPV is a monoamine transporter blocker with increased potency and selectivity for catecholamines when compared with cocaine. The robust stimulation of dopamine transmission by MDPV predicts serious potential for abuse and may provide a mechanism to explain the adverse effects observed in humans taking high

doses of 'bath salts' preparations *Neuropsychopharmacology* advance online publication, Baumann MH, Partilla JS, Lehner KR, Thorndike EB, Hoffman AF, Holy M, Rothman RB, Goldberg SR, Lupica CR, Sitte HH, Brandt SD, Tella SR, Cozzi NV, Schindler CW Powerful cocaine-like actions of 3,4-methylenedioxypyrovalerone (MDPV), a principal constituent of psychoactive 'bath salts' products. *Neuropsychopharmacology*, epub Oct 17, 2012.

Modeling of Pharmacokinetics of Cocaine in Human Reveals the Feasibility for Development of Enzyme Therapies for Drugs of Abuse

A promising strategy for drug abuse treatment is to accelerate the drug metabolism by administration of a drug-metabolizing enzyme. The question is how effectively an enzyme can actually prevent the drug from entering brain and producing physiological effects. In the present study, the authors have developed a pharmacokinetic model through a combined use of in vitro kinetic parameters and positron emission tomography data in human to examine the effects of a cocaine-metabolizing enzyme in plasma on the time course of cocaine in plasma and brain of human. Without an exogenous enzyme, cocaine half-lives in both brain and plasma are almost linearly dependent on the initial cocaine concentration in plasma. The threshold concentration of cocaine in brain required to produce physiological effects has been estimated to be $0.22 \pm 0.07 \mu\text{M}$, and the threshold area under the cocaine concentration versus time curve (AUC) value in brain (denoted by $\text{AUC}_{2(\infty)}$) required to produce physiological effects has been estimated to be $7.9 \pm 2.7 \mu\text{M} \cdot \text{min}$. It has been demonstrated that administration of a cocaine hydrolase/esterase (CocH/CocE) can considerably decrease the cocaine half-lives in both brain and plasma, the peak cocaine concentration in brain, and the $\text{AUC}_{2(\infty)}$. The estimated maximum cocaine plasma concentration which a given concentration of drug-metabolizing enzyme can effectively prevent from entering brain and producing physiological effects can be used to guide future preclinical/clinical studies on cocaine-metabolizing enzymes. Understanding of drug-metabolizing enzymes is key to the science of pharmacokinetics. The general insights into the effects of a drug-metabolizing enzyme on drug kinetics in human should be valuable also in future development of enzyme therapies for other drugs of abuse. Zheng F, Zhan CG. Modeling of pharmacokinetics of cocaine in human reveals the feasibility for development of enzyme therapies for drugs of abuse. *PLoS Comput Biol*. 2012 Jul; 8(7): e1002610.

Sigma Receptor Antagonists Attenuate Acute Methamphetamine-Induced Hyperthermia by A Mechanism Independent of IL-1 β mRNA Expression in the Hypothalamus

Methamphetamine is currently one of the most widely abused drugs worldwide, with hyperthermia being a leading cause of death in methamphetamine overdose situations. Methamphetamine-induced hyperthermia involves a variety of cellular mechanisms, including increases in hypothalamic interleukin-1 beta (IL-1 β) expression. Methamphetamine also interacts with sigma receptors and previous studies have shown that sigma receptor antagonists mitigate many of the behavioral and physiological effects of methamphetamine, including hyperthermia. The purpose of the current study was to determine if the attenuation of methamphetamine-induced hyperthermia by the sigma receptor antagonists, AZ66 and SN79, is associated with a concomitant attenuation of IL-1 β mRNA expression, particularly in the hypothalamus. Methamphetamine produced dose- and time-dependent increases in core body temperature and IL-1 β mRNA expression in the hypothalamus, striatum, and cortex in male, Swiss Webster mice. Pretreatment with the sigma receptor antagonists, AZ66 and SN79, significantly attenuated methamphetamine-induced hyperthermia, but further potentiated IL-1 β mRNA in the mouse hypothalamus when compared to animals treated with methamphetamine alone. These findings suggest sigma receptor antagonists attenuate methamphetamine-induced hyperthermia through a different mechanism from that involved in the modulation of hypothalamic IL-1 β mRNA

expression. Seminerio MJ, Robson MJ, McCurdy CR, Matsumoto RR. Sigma receptor antagonists attenuate acute methamphetamine-induced hyperthermia by a mechanism independent of IL-1 β Mrna expression in the hypothalamus. *Eur J Pharmacol.* 2012 Sep 15; 691(1-3): 103-109.

Self-Administration of Agonists Selective for Dopamine D2, D3, and D4 Receptors by Rhesus Monkeys

Dopamine receptor mechanisms are believed to play a role in the reinforcing effects of cocaine and other drugs of abuse. The lack of receptor-selective agonists has made it difficult to determine the role of the individual dopamine receptors in mediating these reinforcing effects. In this study, rhesus monkeys with a history of intravenous cocaine self-administration were tested for the reinforcing effects of several D(3)-preferring agonists, a D(2)-preferring agonist, and a D(4) agonist. The D(2)-preferring agonist did not maintain responding in any monkeys, and the D(4) agonist was self-administered at low rates, just above those maintained by saline, in one monkey. The D(3)-preferring agonists were self-administered by approximately half of the animals, although at lower rates than cocaine. These results indicate that the apparent limited reinforcing effectiveness of D(2)-like agonists requires activity at D(3) receptors. Previous data from this laboratory and others also suggest that these drugs may not serve as reinforcers directly; the behavior may be maintained by response-contingent delivery of stimuli previously paired with cocaine. The ability of drug-related stimuli to maintain responding apparently differs among monkeys and other organisms, and may be related to individual differences in drug-taking behavior in humans. Koffarnus MN, Collins GT, Rice KC, Chen J, Woods JH, Winger G. Self-administration of agonists selective for dopamine D2, D3, and D4 receptors by rhesus monkeys. *Behav Pharmacol.* 2012 Aug; 23(4): 331-338.

Synthesis and Nicotinic Acetylcholine Receptor In Vitro and In Vivo Pharmacological Properties of 2'-Fluoro-3'-(Substituted Phenyl)Deschloroepibatidine Analogues of 2'-Fluoro-3'-(4-Nitrophenyl)Deschloroepibatidine

Herein, the authors report the synthesis and nicotinic acetylcholine receptor (nAChR) in vitro and in vivo pharmacological properties of 2'-fluoro-3'-(substituted phenyl)deschloroepibatidines 5b-g, analogues of 3'-(4-nitrophenyl) compound 5a. All compounds had high affinity for $\alpha 4\beta 2$ -nAChR and low affinity for $\alpha 7$ -nAChR. Initial electrophysiological studies showed that all analogues were antagonists at $\alpha 4\beta 2$ -, $\alpha 3\beta 4$ -, and $\alpha 7$ -nAChRs. The 4-carbamoylphenyl analogue 5g was highly selective for $\alpha 4\beta 2$ -nAChR over $\alpha 3\beta 4$ - and $\alpha 7$ -nAChRs. All the analogues were antagonists of nicotine-induced antinociception in the tail-flick test. Molecular modeling docking studies using the agonist-bound form of the X-ray crystal structure of the acetylcholine binding protein suggested several different binding modes for epibatidine, varenicline, and 5a-g. In particular, a unique binding mode for 5g was suggested by these docking simulations. The high binding affinity, in vitro efficacy, and selectivity of 5g for $\alpha 4\beta 2$ -nAChR combined with its nAChR functional antagonist properties suggest that 5g will be a valuable pharmacological tool for studying the nAChR and may have potential as a pharmacotherapy for addiction and other central nervous system disorders. Ondachi P, Castro A, Luetje CW, Damaj MI, Mascarella SW, Navarro HA, Carroll FI. Synthesis and nicotinic acetylcholine receptor in vitro and in vivo pharmacological properties of 2'-fluoro-3'-(substituted phenyl) deschloroepibatidine analogues of 2'-fluoro-3'-(4-nitrophenyl)deschloroepibatidine. *J Med Chem.* 2012 Jul 26; 55(14): 6512-6522.

The Antinociceptive Effects of Nicotinic Partial Agonists Varenicline and Sazetidine-A in Murine Acute and Tonic Pain Models

Nicotinic agonists display a wide-range profile of antinociceptive activity in acute, tonic, and chronic pain models. However, their effectiveness is limited by their unacceptable side effects. The authors investigated the antinociceptive effects of two new $\alpha 4\beta 2^*$ nicotinic partial agonists, varenicline and sazetidine-A, in acute thermal and tonic pain mouse models. Both drugs failed to induce significant effects in the tail-flick and hot-plate tests after subcutaneous administration. However, they blocked nicotine's effects in these tests at very low doses. In contrast to acute pain tests, varenicline and sazetidine-A dose-dependently induced an analgesic effect in the mouse formalin test after systemic administration. Their antinociceptive effects were mediated, however, by different nicotinic acetylcholine receptor (nAChR) subtypes. Sazetidine-A effects were mediated by $\beta 2^*$ nAChR subtypes, whereas varenicline actions were attributed to $\alpha 3\beta 4$ nAChRs. Moreover, low inactive doses of varenicline blocked nicotine's actions in phase II of the formalin test. Overall, these results suggest that the antagonistic actions of varenicline at low doses are mediated by $\beta 2^*$ -nAChRs and at higher doses as an agonist by $\alpha 3\beta 4^*$ -nAChRs. In contrast, both actions of sazetidine-A are mediated by $\beta 2^*$ -nAChR subtypes. These results suggest that nicotinic partial agonists possess analgesic effects in a rodent tonic pain model and may provide a potential treatment for the treatment of chronic pain disorders. AlSharari SD, Carroll FI, McIntosh JM, Damaj MI. The antinociceptive effects of nicotinic partial agonists varenicline and sazetidine-a in murine acute and tonic pain models. *J Pharmacol Exp Ther.* 2012 Sep; 342(3): 742-749.

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, the authors 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 Aug 9; 55(15): 6689-6699.

Modification of Cocaine Self-Administration by Buspirone (buspar®): Potential Involvement of D3 and D4 Dopamine Receptors

Converging lines of evidence indicate that elevations in synaptic dopamine levels play a pivotal role in the reinforcing effects of cocaine, which are associated with its abuse liability. This evidence has led to the exploration of dopamine receptor blockers as pharmacotherapy for cocaine addiction. While neither D1 nor D2 receptor antagonists have proven effective, medications acting at two other potential targets, D3 and D4 receptors, have yet to be explored for this indication in the clinic. Buspirone, a 5-HT_{1A} partial agonist approved for the treatment of anxiety, has been reported to also bind with high affinity to D3 and D4 receptors. In view of this biochemical profile, the present research was conducted to examine both the functional effects of buspirone on these receptors and, in non-human primates, its ability to modify the

reinforcing effects of i.v. cocaine in a behaviourally selective manner. Radioligand binding studies confirmed that buspirone binds with high affinity to recombinant human D3 and D4 receptors (~98 and ~29 nm respectively). Live cell functional assays also revealed that buspirone, and its metabolites, function as antagonists at both D3 and D4 receptors. In behavioural studies, doses of buspirone that had inconsistent effects on food-maintained responding (0.1 or 0.3 mg/kg i.m.) produced a marked downward shift in the dose-effect function for cocaine-maintained behaviour, reflecting substantial decreases in self-administration of one or more unit doses of i.v. cocaine in each subject. These results support the further evaluation of buspirone as a candidate medication for the management of cocaine addiction. Bergman J, Roof RA, Furman CA, Conroy JL, Mello NK, Sibley DR, Skolnick P. Modification of cocaine self-administration by buspirone (buspar®): potential involvement of D3 and D4 dopamine receptors. *Int J Neuropsychopharmacol*. 2012 Jul 25: 1-14. [Epub ahead of print].

Cocaine Self-Administration in Dopamine D3 Receptor Knockout Mice The dopamine D3 receptor has received attention over the last two decades as a target for medications development for substance abuse disorders. Results have remained mixed. Despite emergence of more D3-selective ligands, possible attribution of observed effects to D2 receptors remains a concern. Knockout mice may help shed light on mechanisms. Here the authors evaluated the effect of constitutive D3 receptor inactivation (“knockout”) on the reinforcing effects of cocaine. They tested D3 wild-type (WT), heterozygous (D3+/-), and knockout (D3-/-), mice in acquisition and maintenance of intravenous self-administration across a broad range of cocaine doses, using a fixed ratio (FR) 1 and a progressive ratio (PR) schedule of reinforcement, along with parallel food-reinforced studies. Generally, D3-/- mice showed cocaine self-administration comparable to WT controls across assays. Moderate and nonsignificant trends toward lesser reinforcing effects of a low cocaine dose (0.32 mg/kg) were apparent in acquisition and PR studies, consistent with the idea that the D3 receptor may play a subtle role in the reinforcing effects of low cocaine doses under low FR conditions. However, those effects with cocaine self-administration were more subtle than the lower responding of D3 knockout mice observed with food-maintained behavior. In addition, the D3 antagonist PG01037 failed to affect cocaine self-administration under an FR 1 schedule in WT mice. The present data do not support a necessary role for the D3 receptor in the direct reinforcing effects of cocaine. Caine, S. Barak; Thomsen, Morgane; Barrett, Andrew C.; Collins, Gregory T.; Grundt, Peter; Newman, Amy Hauck; Butler, Paul; Xu, Ming Cocaine self-administration in dopamine D3 receptor knockout mice. *Experimental and Clinical Psychopharmacology*, Vol 20(5), Oct 2012, 352-363.

Effects of Dopamine D2/D3 Receptor Ligands on Food-Cocaine Choice in Socially Housed Male Cynomolgus Monkeys Dopamine D2/D3 receptor partial agonists have been suggested as medications for cocaine dependence. These experiments examined the effect of acute and repeated administration of drugs with varying intrinsic efficacy at D2/D3 receptors on the relative reinforcing strength of cocaine. Use of socially housed cynomolgus monkeys permitted the assessment of the whether social status, known to influence D2/D3 receptor availability, influenced the behavioral effects of D2/D3 receptor compounds. The high-efficacy agonist R(-)-norpropylapomorphine ((-)-NPA), low-efficacy agonist aripiprazole (ARI) and antagonist eticlopride (ETIC) were administered acutely to monkeys self-administering cocaine under a food-cocaine choice procedure in which a cocaine self-administration dose-effect curve was determined daily. The effects of 5-day treatment with ARI and (-)-NPA were characterized under conditions in which monkeys did (ARI) or did not (ARI and (-)-NPA) self-administer cocaine during treatment. When administered acutely, ARI and

ETIC increased choice of low cocaine doses and only (-)-NPA decreased choice of higher cocaine doses and cocaine intake; effects were similar across social ranks. When administered repeatedly while self-administration occurred only on days 1 and 5 of treatment, ARI, but not (-)-NPA, decreased cocaine choice in dominant monkeys, whereas (-)-NPA but not ARI did so in subordinates. When dominant monkeys self-administered cocaine all five days of ARI treatment, however, these effects were not observed. The results indicate that the behavioral effects of D2/D3 receptor agonists can differ according to intrinsic efficacy and subject characteristics. Moreover, these results suggest that exposure to cocaine during treatment can counteract treatment-induced reductions in the reinforcing effects of cocaine. Czoty PW, Nader MA Effects of dopamine D2/D3 receptor ligands on food-cocaine choice in socially housed male cynomolgus monkeys. *J Pharmacol Exp Ther.* 2012 Dec 4. [Epub ahead of print].

Potent Rewarding and Reinforcing Effects Of the Synthetic Cathinone 3,4-Methylenedioxy-Pyrovalerone (MDPV) Reports of abuse and toxic effects of synthetic cathinones, frequently sold as 'bath salts' or 'legal highs', have increased dramatically in recent years. One of the most widely used synthetic cathinones is 3,4-methylenedioxy-pyrovalerone (MDPV). The current study evaluated the abuse potential of MDPV by assessing its ability to support intravenous self-administration and to lower thresholds for intracranial self-stimulation (ICSS) in rats. In the first experiment, the rats were trained to intravenously self-administer MDPV in daily 2-hour sessions for 10 days at doses of 0.05, 0.1 or 0.2mg/kg per infusion. The rats were then allowed to self-administer MDPV under a progressive ratio (PR) schedule of reinforcement. Next, the rats self-administered MDPV for an additional 10 days under short access (ShA; 2hours/day) or long access (LgA; 6hours/day) conditions to assess escalation of intake. A separate group of rats underwent the same procedures, with the exception of self-administering methamphetamine (0.05mg/kg per infusion) instead of MDPV. In the second experiment, the effects of MDPV on ICSS thresholds following acute administration (0.1, 0.5, 1 and 2mg/kg, i.p.) were assessed. MDPV maintained self-administration across all doses tested. A positive relationship between MDPV dose and breakpoints for reinforcement under PR conditions was observed. LgA conditions led to escalation of drug intake at 0.1 and 0.2mg/kg doses, and rats self-administering methamphetamine showed similar patterns of escalation. Finally, MDPV significantly lowered ICSS thresholds at all doses tested. Together, these findings indicate that MDPV has reinforcing properties and activates brain reward circuitry, suggesting a potential for abuse and addiction in humans. Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Grabenauer M, Thomas BF, Marusich JA, Wegner S, Olive MF. Potent rewarding and reinforcing effects of the synthetic cathinone 3,4-methylenedioxy-pyrovalerone (MDPV). *Addict Biol.* 2012 Jul 11. doi: 10.1111/j.1369-1600.2012.00474.x. [Epub ahead of print].

Attenuation of Reinstatement of Methamphetamine-, Sucrose-, and Food-Seeking Behavior in Rats by Fenobam, a Metabotropic Glutamate Receptor 5 Negative Allosteric Modulator

Methamphetamine (METH) is a highly potent and addictive psychostimulant with severe detrimental effects to the health of users. Currently, METH addiction is treated with a combination of cognitive and behavioral therapies, but these traditional approaches suffer from high relapse rates. Furthermore, there are currently no pharmacological treatment interventions approved by the FDA specifically for the treatment of METH addiction. Metabotropic glutamate receptor 5 (mGluR5) negative allosteric modulators (NAMs) have shown promise in significantly attenuating drug self-administration and drug-seeking in reinstatement paradigms. However, studies assessing the potential efficacy of mGluR5 NAMs that have been tested in human subjects are lacking. The current study sought to assess the effect of the mGluR5 NAM fenobam on METH-seeking behavior.

Rats were trained to self-administer METH (0.05 mg/kg i.v.), and following extinction, tested for effects of fenobam (5, 10, or 15 mg/kg intraperitoneal) on cue- and drug-induced reinstatement of METH-seeking. To determine if fenobam also alters reinstatement of seeking of natural reinforcers, separate groups of rats were trained to self-administer sucrose or food pellets and were tested for the effects of fenobam on cue-induced reinstatement of sucrose- and food-seeking. Fenobam attenuated drug- and cue-induced reinstatement of METH-seeking behavior at doses of 10 and 15 mg/kg. Fenobam also attenuated cue-induced reinstatement of sucrose- and food-seeking at all doses tested. The mGluR5 NAM fenobam attenuates the reinstatement of METH-seeking behavior, but these effects may be due to nonspecific suppression of general appetitive behaviors. Attenuation of reinstatement of methamphetamine-, sucrose-, and food-seeking behavior in rats by fenobam, a metabotropic glutamate receptor 5 negative allosteric modulator. Watterson LR, Kufahl PR, Nemirovsky NE, Sewalia K, Hood LE, Olive MF. Attenuation of reinstatement of methamphetamine-, sucrose-, and food-seeking behavior in rats by fenobam, a metabotropic glutamate receptor 5 negative allosteric modulator. *Psychopharmacology (Berl)*. 2012 Jul 21. [Epub ahead of print].

Positive Allosteric Modulation of mGluR5 Accelerates Extinction Learning but Not Relearning Following Methamphetamine Self-Administration

Recent studies have implicated glutamate neurotransmission as an important substrate for the extinction of conditioned behaviors, including responding for drug reinforcement. Positive allosteric modulation of the type-5 metabotropic glutamate receptor (mGluR5) in particular has emerged as a treatment strategy for the enhancement of extinction of drug-motivated behaviors. Here, the authors investigated the effects of the mGluR5 positive allosteric modulator CDPPB, a compound known for its cognitive enhancing effects in rodents, on extinction learning in rats with different histories of methamphetamine (METH) training. Rats were trained to self-administer METH under two conditions: 16 daily sessions of short access (90min/day, ShA), or eight daily sessions of short access followed by eight sessions of long access (6h/day, LgA). Control rats self-administered sucrose pellets in daily 30min sessions. Next, rats were administered vehicle or 30mg/kg CDPPB prior to seven consecutive daily extinction sessions, subjected to additional extinction sessions to re-establish a post-treatment baseline, and then tested for reinstatement of behavior in the presence of METH- or sucrose-paired cues. Rats were then subjected to a second series of extinction sessions, preceded by vehicle or 30mg/kg CDPPB, and an additional test for cue-triggered reinstatement. CDPPB treatment resulted in a more rapid extinction of responding on the active lever, especially in the early sessions of the first extinction sequence. However, treatment effects were minimal during subsequent cue reinstatement tests and non-existent during the second series of extinction sessions. Rats with histories of ShA, LgA, and sucrose training expressed similar behavioral sensitivities to CDPPB, with LgA rats demonstrating a modestly higher treatment effect. Positive allosteric modulation of mGluR5 may therefore have some beneficial effects on efforts to facilitate extinction learning and reduce methamphetamine seeking. Positive Allosteric modulation of mglur5 accelerates extinction learning but not relearning following methamphetamine self-administration. Kufahl PR, Hood LE, Nemirovsky NE, Barabas P, Halstengard C, Villa A, Moore E, Watterson LR, Olive MF. Positive allosteric modulation of mGluR5 accelerates extinction learning but not relearning following methamphetamine self-administration. *Front Pharmacol*. 2012;3:194. doi: 10.3389/fphar.2012.00194. Epub 2012 Nov 26.

Exposure to Variable Prenatal Stress in Rats: Effects on Anxiety-Related Behaviors, Innate and Contextual Fear, and Fear Extinction

Rats repeatedly exposed to variable prenatal stress (PNS) exhibit behavioral features often observed in neuropsychiatric disorders including elevated sensitivity to stimulants and impairments of attention, inhibitory control and memory-related task performance. However, to date there have been relatively few studies designed to assess the effects of PNS on anxiety, stress and fear responses, or the function of the hypothalamic-pituitary-adrenal (HPA) axis (a system clearly linked to stress and fear-related responses as well as neuropsychiatric disorders). In the current study, rats exposed to variable PNS were evaluated for anxiety-related behaviors in open field, elevated plus maze, and light/dark preference tasks. Innate fear responses were assessed using a predatory odor task and learned fear and extinction were assessed with a contextual fear conditioning task. As an indicator of HPA axis function, serum corticosterone levels were determined by enzyme immunoassay at various time points. The results indicated that PNS resulted in several behavioral anomalies including decreased innate fear responses to predator odor, impaired fear extinction, increased locomotor activity and stereotypic-like behaviors. Baseline levels of corticosterone in PNS subjects were similar to non-stressed controls; however, when exposed to acute stress, they exhibited an increase in corticosterone that was greater in magnitude. PNS was not associated with increased anxiety-like behaviors or deficits in learning or retention during contextual fear conditioning. Collectively, these data support the argument that variable PNS in rats is a valid model system for studying some behavioral components of neuropsychiatric disorders as well as the influence of stress hormones. Exposure to variable prenatal stress in rats: Effects on anxiety-related behaviors, innate and contextual fear, and fear extinction. Wilson CA, Vazdarjanova A, Terry AV Jr. Exposure to variable prenatal stress in rats: Effects on anxiety-related behaviors, innate and contextual fear, and fear extinction. Behav Brain Res. 2013 Feb 1; 238: 279-288. doi: 10.1016/j.bbr.2012.10.003. Epub 2012 Oct 13.

Quantitation Of Cotinine and Its Metabolites In Rat Plasma and Brain Tissue By Hydrophilic Interaction Chromatography Tandem Mass Spectrometry (HILIC-MS/MS)

In this work, the authors developed a sensitive method to quantify cotinine (COT), norcotinine (NCOT), trans-3'-hydroxycotinine (OHCOT) and cotinine-N-oxide (COTNO) in rat plasma and brain tissue, using solid phase extraction (SPE), hydrophilic interaction liquid chromatography (HILIC) and tandem mass spectrometry (MS/MS). The linear range was 1-100 ng/mL for each analyte in rat plasma and brain homogenate (3-300 ng/g brain tissue). The method was validated with precision within 15% relative standard deviation (RSD) and accuracy within 15% relative error (RE). Stable isotope-labeled internal standards (IS) were used for all the analytes to achieve good reproducibility, minimizing the influence of recovery and matrix effects. This method can be used in future studies to simultaneously determine the concentrations of COT and three major metabolites in rat plasma and brain tissue. Quantitation of cotinine and its metabolites in rat plasma and brain tissue by hydrophilic interaction chromatography tandem mass spectrometry (HILIC-MS/MS). Li P, Beck WD, Callahan PM, Terry AV Jr, Bartlett MG. Quantitation of cotinine and its metabolites in rat plasma and brain tissue by hydrophilic interaction chromatography tandem mass spectrometry (HILIC-MS/MS). J Chromatogr B Analyt Technol Biomed Life Sci. 2012 Oct 15;907:117-25. doi: 10.1016/j.jchromb.2012.09.018. Epub 2012 Sep 15.

PROGRAM ACTIVITIES

New NIDA RFAs

No new NIDA RFAs to report.

New NIDA Program Announcements

On September 10, 2012, NIDA issued a PA entitled **AIDS-Science Track Award for Research Transition (R03)** [PA-12-282](#). This PA seeks to facilitate the entry of both newly independent and early career investigators to the area of drug abuse research on HIV/AIDS. This FOA, AIDS--Science Track Award for Research Transition (A-START), encourages Small Research Grant (R03) applications to support research projects on drug abuse and HIV/AIDS that can be carried out in a short period of time with limited resources. Open date: August 7, 2013. Application due date(s): Not applicable. AIDS application due date(s): September 7, 2013, September 7, 2014, September 7, 2015, by 5:00 PM local time of applicant organization.

On September 10, 2012, NIDA issued a PA entitled **HIV/AIDS, Drug Use, and Vulnerable Populations in the US (R21)** [PA-12-280](#) **(R01)** [PA-12-281](#). This PA encourages research to identify the role(s) that drug abuse plays in fueling the epidemic in vulnerable groups (racial/ethnic minorities, men who have sex with men (MSM), youth) in the United States and to develop effective interventions to prevent new infections and to improve the health and well-being of those living with HIV/AIDS. Open date: December 7, 2012. Application due date(s): Not applicable. AIDS application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On September 25, 2012, NIDA issued a PA entitled **Drug Abuse Aspects of HIV/AIDS (R01)** [PA-12-293](#) **(R03)** [PA-12-294](#) **(R21)** [PA-12-295](#). This PA encourages Exploratory/Developmental Research Grant (R21) applications to examine the drug abuse aspects of HIV/AIDS, including research on drug-related risk behaviors, addiction and HIV disease, and drug use/HIV-related comorbidities and consequences. Open date: April 7, 2013. Application due date(s): Not applicable. AIDS application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization.

On September 26, 2012, NIDA issued a PAR entitled **Mechanism for Time-Sensitive Drug Abuse Research (R21)** [PAR-12-297](#). This PAR is intended to support pilot, feasibility or exploratory research for up to 2 years in 4 priority areas, including: 1) responses to unexpected and time-sensitive medical system issues (e.g. opportunities to understand addiction services in the evolving health care system); 2) responses to emerging drug abuse-related HIV trends and topics (e.g. rapidly evolving drug abuse-related epidemics, time-sensitive policy or environmental changes); 3) responses to unexpected and time-sensitive criminal justice opportunities (e.g. new system and/or structural level changes) that relate to drug abuse and access and provision of health care service; and 4) responses to unexpected and time-sensitive prescription drug abuse opportunities (e.g., new state or local efforts). Open date: February 6, 2013. Application due date(s): March 6, 2013, June 4, 2013, September 9, 2013, December 9, 2013; March 6, 2014, June 4, 2014, September 9, 2014,

December 9, 2014; March 6, 2015, June 4, 2015, September 9, 2015, December 9, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On November 2, 2012, NIDA issued a PA entitled **Prescription Drug Abuse (R01) [PA-13-015](#) (R21) [PA-13-016](#)**. This PA is intended to encourage development of innovative research applications on prescription drug abuse, including research to examine the factors contributing to prescription drug abuse; to characterize the adverse medical, mental health and social consequences associated with prescription drug abuse; and to develop effective prevention and service delivery approaches and behavioral and pharmacological treatments. Open date: January 5, 2013 (R01) or January 16, 2013 (R21). Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 9, 2013, NIDA issued a PAR entitled **Accelerating the Pace of Drug Abuse Research Using Existing Data (R01) [PAR-13-080](#)**. The purpose of this PAR is to invite applications proposing the innovative analysis of existing social science, behavioral, administrative, and neuroimaging data to study the etiology and epidemiology of drug using behaviors (defined as alcohol, tobacco, prescription and other drug) and related disorders, associated HIV risk behaviors, prevention of drug use and HIV, and health service utilization. Open date: January 9, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 9, 2013, NIDA issued a PA entitled **Behavioral & Integrative Treatment Development Program (R01) [PA-13-077](#)**. The purpose of this PA is to encourage behavioral intervention development research to test efficacy, conduct clinical trials, examine mechanisms of behavior change, determine dose-response, optimize combinations, and/or ascertain best sequencing of behavioral, combined, sequential, or integrated behavioral and pharmacological (1) drug abuse treatment interventions, including interventions for patients with comorbidities, in diverse settings; (2) drug abuse treatment and adherence interventions for use in primary care; (3) drug abuse treatment and adherence interventions that utilize technologies to boost effects and increase implementability; (4) interventions to prevent the acquisition or transmission of HIV infection among individuals in drug abuse treatment; (5) interventions to promote adherence to drug abuse treatment, HIV and addiction medications; and (6) interventions to treat chronic pain. Open date: January 9, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 9, 2013, NIDA issued a PA entitled **Behavioral & Integrative Treatment Development Program (R34) [PA-13-078](#) (R03) [PA-13-079](#)**. The purpose of this PA is to encourage investigators to propose discrete well-defined projects that can be completed within three years for R34s and two years for R03s. Projects of interest fall within the research domain of behavioral or integrated (e.g., behavioral and pharmacological) interventions targeting: (a) substance abuse (including comorbidities); (b) prevention of acquisition or transmission of HIV infection among individuals in substance abuse treatment; (c) promotion of adherence to substance abuse treatment, HIV and addiction medications; and (d) chronic pain. Open date: January 16, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant

organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 10, 2013, NIDA issued a PAR entitled **NIDA Research Education Program for Clinical Researchers and Clinicians (R25)** [PAR-13-084](#). The purpose of this PAR is to support research education for those in clinically focused careers, in a topic area related to substance use/abuse/addiction. Participants (those receiving the research education) should be training for careers as clinical researchers, clinicians/service providers, or optimally, a combination of the two. Open date: April 22, 2013. Application due date(s): May 22, 2013, May 22, 2014, May 22, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): September 9, 2013, September 8, 2014, September 7, 2015, by 5:00 PM local time of applicant organization.

New FOAs Issued by the NIH Roadmap

On November 16, 2012, the NIH Common Fund issued a Roadmap RFA entitled **Enhancing GTEEx with molecular analyses of stored biospecimens (U01)** [RFA-RM-12-009](#). The purpose of this RFA is to support molecular analyses of stored biospecimens from the Genotype-Tissue Expression (GTEEx) project. Open date: February 28, 2013. Application due date(s): March 28, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

On November 21, 2012, the NIH Common Fund issued a Roadmap RFA entitled **Determinants and Consequences of Personalized Health Care and Prevention (U01)** [RFA-RM-12-024](#). The purpose of this FOA is to expand generalizable understanding of the determinants and consequences of personalization in health care and prevention; it is not primarily intended to support evaluation of specific interventions or strategies for addressing particular health conditions. Open date: January 28, 2013. Application due date(s): February 28, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not applicable.

New Administrative Supplement Program Announcements Issued by NIH

No new Administrative Supplement Program Announcements.

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

On December 7, 2012, NIDA, in collaboration with numerous other NIH components, issued an RFA entitled **Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) for Neuroscience and Disorders of the Nervous System (R01)** [RFA-NS-13-007](#). This RFA solicits Research Project Grant (R01) applications addressing exceptionally novel hypotheses and/or remarkably difficult problems in neuroscience and disorders of the nervous system. This announcement is for support of new rather than ongoing projects, and is not intended for pilot research. Open date: February 21, 2013. Application due date(s): March 21, 2013, by 5:00 PM local time of applicant organization. AIDS application due date(s): March 21, 2013.

New PAs Issued with Other NIH/HHS Components in which NIDA is a participant

On September 11, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Exploratory/Developmental Bioengineering Research Grants (EBRG) [R21] [PA-12-284](#)**. The purpose of this PA is to encourage Exploratory/Developmental Bioengineering Research Grants (EBRG) applications which establish the feasibility of technologies, techniques or methods that: 1) explore a unique multidisciplinary approach to a biomedical challenge; 2) are high-risk but have a considerable pay-off; and 3) develop data which can lead to significant future research. Open date(s): January 16, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard dates](#) apply.

On November 28, 2012, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Opportunities for Collaborative Research at the NIH Clinical Center (U01) [PAR-13-029](#)**. The purpose of this PAR is to support collaborative translational research projects aligned with NIH efforts to enhance the translation of basic biological discoveries into clinical applications that improve health. Open date(s): February 20, 2013. Application due date(s): March 20, 2013, March 20, 2014, March 20, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): March 20, 2013, March 20, 2014, March 20, 2015, by 5:00 PM local time of applicant organization.

On December 18, 2012, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Drug Discovery for Nervous System Disorders (R01) [PAR-13-048](#) (R21) [PAR-13-049](#)**. This PAR encourages research grant applications directed toward the discovery and preclinical testing of novel compounds for the prevention and treatment of nervous system disorders. Open date(s): January 5, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On December 20, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **Pain in Aging (R01) [PA-13-058](#)**. This PA encourages Research Project Grant (R01) applications from institutions/organizations that propose to study pain from an aging perspective, including studies of older populations, studies of age differences and age-related changes in pain processes and experiences, and studies of pain treatment and management in older adults. Open date(s): January 5, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 9, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **Dissemination and Implementation Research in Health (R21) [PAR-13-054](#) (R01) [PAR-13-055](#) (R03) [PAR-13-056](#)**. This PAR encourages investigators to submit research grant applications that will identify, develop, evaluate and refine effective and efficient methods, systems, infrastructures, and strategies to disseminate and implement research-tested health behavior change interventions, evidence-based prevention, early detection, diagnostic, treatment and management, and quality of life improvement services, and data monitoring and surveillance reporting tools into public health and clinical practice settings that focus on patient outcomes. Open date(s): January 16, 2013 (R21) and (R03) or January 9, 2013 (R01). Application due date(s): [Standard dates](#) apply,

by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 11, 2013, NIDA, in collaboration with numerous other NIH components, issued a PAR entitled **National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of Mental Disorders, Drug or Alcohol Addiction (U19)** [PAR-13-086](#) (UM1) [PAR-13-087](#). The purpose of the National Cooperative Drug Discovery/Development Group (NCDDG) Program is to create multidisciplinary research groups or partnerships for the discovery of pharmacological agents to treat and to study mental illness, drug or alcohol addiction. This PAR encourages applications to advance the discovery, preclinical development, and proof of concept testing of new, rationally based candidate agents to treat mental disorders or drug or alcohol addiction, and to develop novel ligands as tools to further characterize existing or to validate new drug targets. Open date(s): January 22, 2013. Application due date(s): February 22, 2013; June 24, 2013; October 24, 2013; February 24, 2014; June 22, 2014; October 22, 2014; February 22, 2015; June 22, 2015; October 22, 2015, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On January 24, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **PHS 2013-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant Applications (Parent STTR [R41/R42])** [PA-13-089](#). This PA invites eligible United States small business concerns (SBCs) to submit Small Business Technology Transfer (STTR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH awarding components identified in this FOA are encouraged to submit STTR grant applications in response to identified topics (see [PHS 2013-2 SBIR/STTR Program Descriptions and Research Topics for NIH](#)). Open date(s): March 5, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On January 24, 2012, NIDA, in collaboration with numerous other NIH components, issued a PA entitled **PHS 2013-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44])** [PA-13-088](#). This PA invites eligible United States small business concerns (SBCs) to submit Small Business Innovation Research (SBIR) grant applications. United States SBCs that have the research capabilities and technological expertise to contribute to the R&D mission(s) of the NIH, CDC, FDA or ACF awarding components identified in this FOA are encouraged to submit SBIR grant applications in response to identified topics (see [PHS 2013-2 SBIR/STTR Program Descriptions and Research Topics for NIH, CDC, FDA and ACF](#)). Open date(s): March 5, 2013. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

New NIH FOAs Issued in Collaboration with the FDA Center for Tobacco Products

On December 18, 2012, NIDA, in collaboration with numerous other NIH components and with the FDA Center for Tobacco Products, issued a Request for Application entitled **NIH Revision Applications for Research Relevant to the Family Smoking Prevention and Tobacco Control Act (P30) [RFA-OD-12-007](#)**. This Funding Opportunity Announcement (FOA) invites revision applications from investigators and institutions/organizations with active National Institutes of Health (NIH)-supported P30 project awards to support an expansion of the scope of approved and funded scientific research programs involving smoking and tobacco-related products and/or their constituents. Application due date(s): March 26, 2012. Start date: December 1, 2013.

NIDA is participating in a Request for Applications (RFA) issued by the National Institutes of Health (NIH) in collaboration with the Russian Foundation for Basic Research (RFBR) to establish Collaborative Research Partnerships (CRP) to study prevention and treatment of HIV/AIDS and comorbidities. NIH expects that \$3 million USD will be available in fiscal year 2014 to fund up to 10 R21 exploratory/developmental grants. U.S. research institutions working with a Russian institutional partner could apply for up to \$275,000 in direct costs over 2 years. The applications, which were due January 15, 2013, were to describe a single research plan for the partner institutions to investigate topics such as HIV genomics, HIV-associated coinfections, and HIV-associated comorbidities. For more information, see [RFA-DA-14-001](#).

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. Over 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>

CONGRESSIONAL AFFAIRS SECTION
(Prepared January 23, 2013)

APPROPRIATIONS

The President's Fiscal Year 2013 budget request included \$1.054 billion for NIDA, essentially the same as the appropriated FY 2012 level. NIH is currently operating under a Continuing Resolution (at FY 2012 levels) that will expire on March 27. This could be affected by the current "sequestration" discussion in the Congress.

113th CONGRESS

The most relevant committee-related information for NIDA is listed below.

Senate: In the Senate, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, and Education; Financial Services; and Commerce, Justice, Science;
- Committee on Health, Education, Labor, and Pensions (HELP);
- Committee on the Judiciary; and the
- Caucus on International Narcotics Control (this is an officially recognized Caucus, established by law in 1985).

House: In the House, primary focus is on the

- Committee on Appropriations (Subcommittee on Labor, Health and Human Services, Education, and Related Agencies; Financial Services; and Commerce, Justice, Science and Related Agencies);
- Committee on Energy and Commerce (Subcommittee on Health); and the
- Committee on Oversight and Government Reform (Subcommittee on Domestic Policy).

In both the House and Senate, committee and subcommittee rosters are still being finalized. To present a complete picture, details will be provided in the May 2013 Report to Council.

EXTRAMURAL POLICY AND REVIEW ACTIVITIES

Receipt, Referral, and Review

NIDA received 1,299 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 880 applications.

OEA arranged and managed 20 grant review meetings in which 168 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 4 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 19 Special Emphasis Panels to review grant applications for a variety of reasons:

- Imaging Science Track Award for Research Transition (I/START)
- Cutting-Edge Basic Research Awards (CEBRA) (R21)
- Conference Grants (R13)
- NIH Summer Research Experience Programs (R25)
- Diversity-Promoting Institutions Drug Abuse Research Program (DIDARP) (R24)
- NIDA Research Education Program for Clinical Researchers and Clinicians (R25)
- Science Education Drug Abuse Partnership Award (R25)
- Research Education Grants for Statistical and Computational Training in The Genetics Of Addiction (R25)
- Grand Opportunity In Medications Development for Substance-Related Disorders (U01)
- Requests for Applications (RFAs)

OEA managed the following RFA reviews:

- DA13-001 Phased Services Research Studies of Drug Use Prevention, Addiction Treatment, and HIV in an Era of Health Care Reform (R21/R33)
- DA13-004 Synthesis and Preclinical Evaluation of Medications to Treat Substance Use Disorders (SUDS) (R01)
- DA 13-007 Identifying Health Outcomes Associated with Changes in Use of Illicit Drugs (R01)

Completed contract-related review activity since the last Council includes:

Contract Reviews (R&D and non-R&D)

- NO1DA-13-8908 Rodent Testing to Identify Pharmacotherapies for Substance Dependence
- NO1DA-13-2230 Clinical Trials Research Coordination Center

Concept Reviews

- N43DA-13-7786 Development of Predictive *in vivo* Screening Systems for Phenotypic Drug Discovery
- N01DA-13-8910 Analytical Services Center for Medications Development Program

Certificates of Confidentiality

Between July 16 and December 10, 2012 OEA processed 104 Certificate of Confidentiality applications, including 20 amendments for either extension of expiration date or protocol change.

Other Review Activities

The CTN Data and Safety Monitoring Board(s) met:

- September 10, 2012, to discuss progress of protocol CTN 0048, Cocaine Use Reduction with Buprenorphine (CURB)
- November 5, 2012, to review protocol CTN 0055, Comparing Treatments for HIV-Positive Opioid Users in an Integrated Care Effectiveness Study (CHOICES)
- November 29, 2012, to discuss final study results of the Project AWARE: HIV Rapid Testing & Counseling in STD Clinics in the U.S.
- December 14, 2012, to review the final study report of protocol CTN 0046, Smoking-Cessation and Stimulant Treatment (S-CAST): Evaluation of the Impact of Concurrent Outpatient Smoking-Cessation and Stimulant Treatment on Stimulant-Dependence Outcomes

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 NIDA's programs for Small Business Innovation Research (SBIR) by Dr. Elena Koustova, NIDA, the use of administrative tools (NEPS) for tracking and monitoring grants, by Mr. James Dellosa, and the use of Special Emphasis Panels (SEPs) by CSR, by Dr. Jonathan Arias, CSR.

INTERNATIONAL ACTIVITIES

Binational Agreements

NIDA, Russian Officials Discuss Research Programs

NIDA Director Nora D. Volkow, M.D., Victor Ivanov, Director of the Federal Drug Control Service of Russia, and their colleagues met December 14, 2012 to review the Institute's research priorities and programs. The group discussed a wide range of topics, including developments in addiction medications and possible options for continued collaboration. After Dr. Volkow's presentation, the following NIDA staff made brief presentations about research programs in their respective divisions: Dionne Jones, Ph.D., DESPR, Phil Skolnick, Ph.D., DPMCDA, Jack Stein, Ph.D., OSPC, Joni Rutter, Ph.D., DBNBR, Joseph Frascella, Ph.D., DCNBR, and Betty Tai, Ph.D., CCTN. Other NIDA staff who participated in the discussions included: Deputy Director David Shurtleff, Ph.D., Associate Director for Scientific Affairs Susan Weiss, Ph.D., IP Director Steve Gust, Ph.D. and Associate Director Dale Weiss, Elena Koustova, Ph.D., OTIPI, and Cecelia Spitznas, Ph.D., DCNBR.

NIDA, Italian Researchers Plan Collaborative Clinical Studies

As part of the ongoing collaboration under the binational agreement between NIDA and the Italian Department for Antidrug Policies, the NIDA IRP and researchers at the Catholic University of Rome will conduct joint clinical studies on reducing alcohol consumption. The Italian principal investigator is Giovanni Addolorato, M.D. The research plan was agreed upon during meetings that were held November 6-14, 2012, in Rome and Verona, where NIDA Director Nora D. Volkow, M.D., and IRP Scientific Director Antonello Bonci, M.D., discussed the role of drugs in the disruption of self-control and strategies to prevent and treat addiction.

Research Results

HIV Prevention Programs Should Include Female Partners of IDUs

Researchers investigating the status of HIV and hepatitis C (HCV) infection among injection drug users (IDUs) in the Republic of Georgia have concluded that prevention programs should include the partners of IDUs, even if the female partners do not abuse drugs themselves, in order to reduce the risk of HIV and HCV spreading from the subpopulation of male IDUs into the general population. Conducting a secondary data analysis, the team found that only 10 percent of the IDUs' partners reported using condoms most of the time; 3 percent reported they were HIV-positive and 8 percent reported they were HCV-positive. Nearly half (48 percent) reported feeling unsafe in their current relationships, and 42 percent reported being physically abused by their partners during the past year. The research team included former NIDA Hubert H. Humphrey Fellow David Otiashvili and former WHO/NIDA/CPDD International Traveling Fellow Irma Kirtadze, both of Georgia, as well as Ingunn O. Lund of Norway and Kevin E. O'Grady and Hendrée Jones of the United States. The secondary data analysis was funded through an international supplement to the parent randomized clinical trial, *Treating the Partners of Drug Using Pregnant Women: Stage II (HOPE)*. The article, Female partners of opioid-injecting men in the Republic of Georgia: an initial characterization, appears in *Substance Abuse Treatment and Prevention Policy*, 2012 Nov 16;7(1):46.

Review Finds Response to Eastern European HIV Epidemic Among IDUs “Insufficient”

A systematic review to identify and synthesize prevalence estimates and risk factors for HIV among injection drug users (IDUs) in Central and Eastern Europe and Central Asia suggests that the current response to HIV among IDUs is “insufficient” and “hindered by multiple environmental barriers, including restricted access to services and unsupportive policy or social environments.” The authors found HIV prevalence varies widely in the region, with some studies suggesting that as many as 50 percent of IDUs in parts of Estonia, Russia and Ukraine are HIV-positive. Gender, socioeconomic position, and contact with law enforcement agencies were associated with HIV prevalence. The authors found that availability of the recommended integrated interventions to prevent HIV among IDUs (which include needle exchange programs, opiate substitution therapy, and antiretroviral therapy) ranges from “low to non-existent,” and call for policy changes and additional resources to contain the epidemic. Former NIDA Hubert H. Humphrey Drug Abuse Research Fellow Alisher Latypov, Tajikistan, is a co-author, along with Emma Jolley, Tim Rhodes, Lucy Platt, and Vivian Hope of the United Kingdom; Martin Donoghoe of the World Health Organization; and David Wilson of the World Bank. The article, HIV among people who inject drugs in Central and Eastern Europe and Central Asia: a systematic review with implications for policy, appears in *BMJ Open*, 2012 Oct 18;2(5); pii: e001465; doi: 10.1136/bmjopen-2012-001465.

Chinese Study Explores Biological and Environmental Factors in Drug Use

A jointly funded study of 450 heroin-dependent Chinese patients provides new insights into the complex relationship between biological and environmental factors in the development of drug use. Genetic variations in the Catechol-O-methyltransferase (COMT) gene, childhood trauma, and impulsive personality traits were all associated with development of drug use. Using a structural equation model, the authors found that childhood trauma and impulsive personality traits were more influential on the age of onset for heroin use than were the COMT genetic variations. The study was supported by grants from the National Nature Science Foundation of China and a NIDA/Fogarty International Center grant (R01TW007279) to former NIDA INVEST Drug Abuse Research Fellow Min Zhao, M.D., Ph.D., Shanghai Mental Health Center. Dr. Zhao’s coauthors included two other former INVEST Fellows, Jiang Du, Ph.D., and Hanhui Chen, M.D., also of the Shanghai Mental Health Center. The article, Pathways to Age of Onset of Heroin Use: A Structural Model Approach Exploring the Relationship of the COMT Gene, Impulsivity and Childhood Trauma, appears in *PLoS One*. 2012;7(11):e48735. doi: 10.1371/journal.pone.0048735.

NIDA-Supported Meetings

NIDA, INSERM Explore Potential Collaboration

NIDA and Institut national de la santé et de la recherche médicale (INSERM) co-hosted a workshop during the Society for Neuroscience annual conference to explore opportunities to enhance collaborative research and research training activities between the United States and France. NIDA Director Nora Volkow, M.D., and Etienne Hirsch, Ph.D., INSERM, co-chaired the October 15, 2012 workshop. After speakers described the research priorities and capabilities of the two organizations, the invited U.S. and French scientists suggested areas for future cooperation: animal research in drug discovery; clinical research in medications development and brain imaging; and generating new strategies for analyzing large imaging, genetic/epigenetic, and clinical data sets. Several mechanisms were proposed to support the collaboration, including: research training and

exchange programs, such as the NIDA INVEST Drug Abuse Research Fellowship; funding support through research supplement awards; clinical trials; and web-based communications.

ISAM Meeting Focuses on the Future of Drug Treatment Systems

Several NIDA staff members played a role at the International Society of Addiction Medicine annual conference, which was held October 14-18, 2012 in Geneva, Switzerland. DESPR Director Wilson Compton, M.D., M.P.E., and Jag Khalsa, Ph.D., DPMCDA, spoke during the meeting, which focused on the future of drug treatment systems. In addition, DPMCDA Associate Director Ivan Montoya, M.P.H., M.D., and Dr. Khalsa both chaired sessions.

International AIDS Meeting Satellite Focuses on AIDS Research at NIH

During the XIX International AIDS Conference, which was held July 22- 27, 2012 in Washington, DC, NIDA Director Nora D. Volkow, M.D., joined other National Institutes of Health (NIH) leaders in presenting advances and challenges in AIDS research. Dr. Volkow focused on seek-test-treat-and retain strategies that NIDA-funded research has recently shown to prevent HIV infection, particularly among injection drug users, and on a second NIDA study that found primary care physicians may defer antiretroviral treatment for their patients who inject drugs, despite evidence that treating both HIV and substance use disorders can reduce or eliminate HIV transmission. She described NIDA priorities for developing a heroin vaccine and opiate addiction treatment medications, especially those that are not based on opiate agonists. The satellite was chaired by Jack Whitescarver, Ph.D., NIH Office of AIDS Research, and featured NIH Director Francis S. Collins; Anthony Fauci, M.D., and Carl Dieffenbach, Ph.D., National Institute of Allergy and Infectious Diseases; Avi Nath, M.D., National Institute of Neurological Disorders and Stroke; and Robert Yarchoan, M.D., National Cancer Institute. A recording of the session and a transcript are available on the [Kaiser Family Foundation website](#).

Mexico City Meeting Spurs Local, International Action on Inhalant Abuse

A September 2012 international meeting in Mexico City that focused on inhalant abuse featured presentations by members of the NIDA IP Inhalant Working Group (IWG) and has already begun yielding results. El Instituto para la Atención y Prevención de las Adicciones en la Ciudad de México (IAPA) hosted the meeting, which attracted more than 200 policy makers, researchers, service providers, and industry representatives. Former NIDA INVEST Fellow and IWG member Silvia Cruz, Ph.D., Cinvestav, chaired the scientific program. NIDA Acting Deputy Director David A. Shurtleff, Ph.D., provided a video introduction to the meeting. Speakers included IAPA Director Rafael Camacho Solís, M.D.; María Elena Medina-Mora Icaza, Ph.D., Instituto Nacional de Psiquiatría Ramón de la Fuente; representatives of other Mexican addiction and research organizations; and five IWG experts:

- Ms. Debra Dell, Canadian Youth Solvent Addiction Committee, described the culture-based structure and effectiveness of Canada's residential inhalant abuse treatment programs.
- Colleen Anne Dell, Ph.D., University of Saskatchewan, Canada, reviewed the global inhalants situation and the need for qualitative and quantitative data collection.
- Robert L. Balster, Ph.D., Virginia Commonwealth University, discussed the international research agenda needs and suggested a framework for a countrywide harm reduction approach to inhalant abuse in Mexico.
- Mr. Harvey Weiss, National Inhalant Prevention Coalition, reported on successful prevention programs, including the Texas media/community action model and U.S. Awareness Week.

- Dr. Cruz introduced the neuroscience of inhalant abuse to the non-scientific audience.

During the IAPA meeting, the IWG experts met with Dr. Medina-Mora to discuss how the group can support the work of the developing strategy in Mexico and further the IWG work internationally. As a result of that meeting, IWG members are developing binational research proposals with Mexican scientists, and the *Canadian Journal of Public Health* has accepted a letter to the editor by IWG members calling for increased qualitative and quantitative research on inhalant abuse. IWG also has created an online networking group on LinkedIn to provide inhalant abuse researchers with additional opportunities for sharing research findings, best practices, and ideas for future investigations with colleagues around the world. In late October, Dr. Camacho Solís presented Mexico City Mayor Marcelo Ebard with the IAPA plan to address inhalant abuse, developed with input from meeting participants, recommending that the city adopt integrated, evidence-based, harm-, supply-, and demand-reduction activities in the areas of policy, research, training, treatment, prevention, and community outreach. Dr. Camacho Solís also met with representatives of an industry group to discuss recommendations controlling the importation, manufacturing, and sale of consumer and industrial products that can be abused by inhaling their vapors or gases.

Online Initiatives

NIDA International Program Launches LinkedIn Networking Group

To help the international drug abuse research community find colleagues, share information, and join discussions about research issues, the NIDA IP has established a networking group on LinkedIn, a social networking website for people in professional positions. The IP chose LinkedIn after reviewing social networking research and talking with members of the international drug abuse research community. Pew Research Center found that LinkedIn has more than twice as many users with graduate degrees than other social networking sites, and about 60 percent of the participants at the 2012 NIDA International Forum reported that they used LinkedIn either weekly or monthly. The NIDA IP Inhalant Working Group is already using the LinkedIn group to coordinate its activities.

Fellowships

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, 13 scientists have completed their fellowships and have successfully continued their research in their countries; two are currently working on their projects and one will start in the spring 2013.

NIDA Selects INVEST Fellow

Jan Klimas, Ph.D., Ireland, has been selected as a NIDA INVEST Drug Abuse Research Fellow. He will spend his fellowship working with Dennis McCarty, Ph.D., Oregon Health & Science

University. A research assistant at University College Dublin and Cochrane Research Fellow at University of Limerick, Dr. Klimas will extend his research on screening and brief intervention for alcohol use disorders among methadone patients in primary care settings, compare Irish systems of primary care screening and methadone treatment with methods for screening and brief intervention in U.S. primary care settings, and contrast buprenorphine services in the United States with primary care methadone services in Ireland.

Humphrey Fellows Meet NIDA During Campus Visits and Global Leadership Forum

Twenty-five Hubert H. Humphrey fellows from 20 countries met with NIDA IP Associate Director Dale S. Weiss on Monday, October 22, 2012, during the Humphrey Fellowship Program Global Leadership Forum. Ms. Weiss described NIDA activities and research priorities; discussed the broad health, social, economic, and criminal justice impacts of drug use around the world; and reviewed NIDA opportunities available to the Humphrey Fellows. A 4-day event sponsored by the U.S. Department of State and the Institute of International Education (IIE), the Global Leadership Forum brought nearly 200 Hubert H. Humphrey fellows representing 93 countries to Washington, DC to learn more about U.S. institutions, Federal agencies, and international organizations. The Humphrey Program brings young and mid-career professionals from eligible countries to the United States for a year of non-degree, graduate-level study at one of 18 universities. The fellowship also includes leadership development and professional collaboration with U.S. counterparts. Earlier, Ms. Weiss and fellowships administrator Ms. Lisa Jordre met with the Hubert H. Humphrey Fellows from Virginia Commonwealth University (VCU) and Johns Hopkins University (JHU) to discuss their professional affiliations with drug abuse researchers.

The NIDA-supported Humphrey Fellows at VCU include:

- **Sossinou Awoussi, (Togo)** An ophthalmologist, Dr. Awoussi wants to improve his skills in public health policy and management and develop partnerships with American sight organizations.
- **Suzan Ben Ezra, M.S.W. (Israel)** Ms. Ben Ezra will focus on: special populations such as women, youth, and families; community-based alcohol prevention programs; new treatment and rehabilitation methods; the use of cannabis for medicinal purposes; and the development of coherent drug and alcohol policies.
- **Jezelle Charles, M.S. (Trinidad and Tobago)** Ms. Charles wants to enhance her knowledge of drug pharmacology and qualitative and quantitative analytical methods so that she can improve procedures in her toxicology laboratory and help create a national clinical toxicology laboratory.
- **Bola Ola, F.M.C. Psych. (Nigeria)** Dr. Ola is interested in drafting and promoting drug abuse policies and programs for primary health care settings.
- **Rosie Myint (Burma [Myanmar])** Ms. Myint would like to improve her monitoring and evaluation skills as they relate to early drug prevention, relapse prevention, and behavioral change communication programs. She will also focus on enhancing community involvement in demand-reduction activities.
- **Kouame Sedaminou, M.A.S. (Togo)** Mr. Sedaminou seeks to enhance his knowledge of drug abuse prevention programs for youth in order to train other teachers as substance abuse advisors.
- **Claudemir Dos Santos (Brazil)** Mr. Dos Santos would like to develop culturally appropriate prevention programs for children and adolescents and to improve his skills in evaluating prevention programs.

The 2012-2013 Humphrey Fellows at JHU include:

- **Basat Iter, M.B.A. (Turkey)** Mr. Iter intends to focus on occupational safety and health policy and training programs for employers and employees that promote workers' safety and health.
- **George Leveridge, MBBS, DM, M.P.H. (Jamaica)** A psychiatrist, Dr. Leveridge is interested in public health policy development and its application to violence prevention.
- **Nang Mo Kham, M.B., M.P.H. (Burma [Myanmar])** Dr. Kham aims to enhance her knowledge and skills in public health policy and management.
- **Poongothai Balaji, MBBS, MRCOG (India)** An obstetrician and gynecologist, Dr. Poongothai is interested in prevention programs for both communicable and non-communicable diseases.
- **Mariana Salamoun, M.A. (Lebanon)** A psychologist, Ms. Salamoun is interested in promoting mental health through evidence-based research and community services, particularly in developing programs to protect youth.
- **Pavla Dolezalova, Ph.D., Mgr. (Czech Republic)** Dr. Dolezalova wants to learn about evidenced-based research and cost-effective tools to improve the quality of life of drug-addicted people, particularly interventions based on attachment theory.
- **Heather Susan Ruturi, M.S. (Kenya)** Ms. Ruturi will focus on substance abuse prevention and treatment programs, particularly different concepts of client enrolment to care and the chemical and psychosocial management of patients.
- **Arnold Simpreux, M.D. (Haiti)** Dr. Simpreux will emphasize HIV/AIDS policy and prevention programs for remote communities in low-income countries and health information systems focusing on HIV/AIDS prevention and education.

Travel Support

NIDA Supports Student at FENS-IBRO Training Course

The NIDA IP supported a student in the Advanced Course in Computational Neuroscience, which was held July 30–August 24, 2012 at the Institute of Mathematics of the Polish Academy of Sciences in Będlewo, Poland. Matt Lewis, a graduate student at Cornell University, participated in the course, which is sponsored by the Federation of European Neurosciences (FENS) and the International Brain Research Organization. The course combines lectures on experimental and computational neuroscience topics with practical training in neural modeling. Each student pursues an individual research project and presents the results to students and faculty at the end of the course.

NIDA Supports Participants at NHSN Conference

The NIDA IP supported nine researchers who participated in the 2012 National Hispanic Science Network (NHSN) 12th Annual International Conference. The conference was held September 26-29 in San Diego, California. The meeting focused on the integration of translational research and ways to health needs among subpopulations with a variety of comorbid diseases and differing genetic and environmental backgrounds. Panel discussions addressed the impact of comorbidities among drug- and alcohol-dependent populations; delivery, evaluation, and improvement of treatment; development of pharmacotherapies; and evidence-based psychosocial and social cognitive therapies. The conference honored retiring NIDA Senior Advisor on Special Populations Ana Anders, L.I.C.S.W., for her commitment and guidance to NHSN since the Network's inception in 2001. The NIDA-supported participants included:

- *Chile*: Luis Caris
- *Mexico*: Tania Gonzalez, Maria de Lourdes Gutierrez Lopez, Octavio Campollo, Miguel Angel Lopez Brambilla, Miguel Angel Mendoza Melendez, and Gayle Rosio Valdez Gonzalez
- *Spain*: Javier Gonzalez Riera and Francisco Jose Montero Bancalero.

Other International Activities

A group from the Zhejiang, China Drug Relief Reformatory visited NIDA on December 14, 2012. The purpose of the visit was to learn more about NIDA's research and in particular evidenced based treatments and the interaction of drug abuse and HIV/AIDS. Meeting with the group were NIDA staff Yu (Woody) Lin, Ph.D, DCNBR, Lao Guifang, Ph.D., DPMC and Dale Weiss, IP.

Dr. John Satterlee, DBNBR, in his role as co-coordinator of the NIH Roadmap Epigenomics Program gave a presentation entitled "The International Human Epigenome Consortium" at the International Human Epigenome Consortium meeting in Seoul, South Korea September 6-7, 2012.

Dr. Wilson M. Compton, Director, DESPR, presented a plenary on *Mainstreaming Addictions in Medicine* and presented an *Update on DSM-5* at the International Society of Addiction Medicine, Geneva, Switzerland, October 15-17, 2012.

Dr. Jag Khalsa, DPMCD, delivered an invited plenary talk on Nanotechnology/Nanomedicine for Treating Addiction and Infections, at the Annual Meeting of the International Society of Addiction Medicine (ISAM), October 13-18, 2012, Geneva, Switzerland, and participated in various ISAM programmatic activities.

Dr. Jag Khalsa delivered an invited talk on Biotechnology in Medicine and co-chaired with NIH staff from NIMH and NCI a symposium on "NeuroAIDS and Drug Abuse" at the 2012 World Congress on Biotechnology in Hyderabad, India, September 13-15, 2012.

Dr. Ivan Montoya, DPMCD, was invited to give the Javier Escobar Lecture at the School of Medicine of the University of Antioquia, in Medellin, Colombia, on June 24, 2012.

Dr. Ivan Montoya was invited to give the lecture titled "Advances in the Research of Medications to Treat Addiction" at the Crime Reduction Initiatives Conference, in Manchester, England, on September 5th, 2012.

Dr. Ivan Montoya attended, chaired a symposium, and presented at the annual meeting of the International Society of Addiction Medicine (ISAM) in Geneva, Switzerland, on October 14-18, 2012.

In August 2012, NIDA Scientific Director, Dr. Antonello Bonci co-chaired the Cold Spring Harbor course on the cell biology of addiction in Barcelona, Spain.

In November 2012, Dr. Bonci was invited to be the keynote speaker at the Karolinska Institute in Stockholm at the Swedish dopamine meeting. While there, he met with Dr. Arvid Carlsson to discuss collaborations between NIDA and the department of psychiatry at the Karolinska Institute.

In November 2012, Dr. Bonci gave a lecture in Verona, Italy, at an international meeting where Dr. Nora Volkow was also present.

Dr. Marisela Morales, IRP, gave an invited lecture at the UNAM, Queretaro, Mexico.

Dr. Carl Lupica, IRP, gave a presentation on his research at the University of Montreal, Department of Neuroscience, and served as an external committee member for a doctoral thesis in this department in March of 2012.

Dr. Bruce Hope, IRP, gave invited lectures at the conference *Plasticity in the Basal Ganglia: Dopamine and Beyond* in Beijing, China.

Dr. Tsung-Ping Su was invited to give a seminar at the Pharmacology Department at the *National Cheng Kong University* at Tainan, Taiwan in May 2012.

Dr. Tsung-Ping Su was invited to give a seminar at the Institute of BioMedical Sciences of the *Taipei Medical University* at Taipei, Taiwan in May 2012.

Drs. Tsung-Ping Su and Dr. Antonello Bonci, IRP, visited the National Research Council (NSC) of Taiwan in May and have thus placed NIDA IRP as an U.S. institute to train the Taiwanese postdoctoral fellows with full financial support by the Taiwanese NSC in the future.

Dr. Marilyn Huestis, IRP, was invited to present her research on oral fluid drug testing at the Nordic Association of Clinical Chemists in Reykjavik, Iceland.

Dr. Marilyn Huestis was invited to Cordoba, Salta and Jujuy, Argentina to discuss the problem of *in utero* drug exposure to pesticide-treated cocaine by the indigenous population living in the high Andes mountains. A series of lectures were given on behalf of the Argentinian Public Health Departments and clinicians in these towns.

Dr. Amy Newman, IRP, gave an invited lecture at the 5th SFB35 Transporter Symposium at the Medical University of Vienna in September 2012.

Dr. Amy Newman gave an invited lecture at the University of Copenhagen, Department of Neuroscience and Pharmacology in September 2012.

Dr. Marilyn Huestis gave two invited plenary lectures at the Australian Association of Clinical Biochemists meeting in Sydney, Australia.

Dr. David Gorelick, IRP, gave two invited plenary lectures on the topics of “Perspectives on Research in the Pharmacological Treatment of Addiction,” and “Pharmacotherapy in the Treatment of Addiction” at the IV Congress of the Latin American Association for Addictionology, Cuenca, Ecuador.

Dr. Marilyn Huestis was invited to present her research on *in utero* drug exposure at the University of Zurich in Zurich, Switzerland.

Dr. Marilyn Huestis presented plenary lectures on “Synthetic Cannabinoids” and the Pharmacology and Toxicology of Cannabinoids” at the Department of Forensic Medicine in Istanbul, Turkey and taught in the Turkish course on Addiction in Izmir, Turkey.

Dr. Yang, IRP, was invited as a keynote speaker to give a lecture in the Symposium on Functional Connectivity of the Brain in Taipei, Taiwan in June 2012.

Dr. David Gorelick, IRP, gave three invited plenary lectures on the topics of “Pharmacology of Stimulants and their Treatment,” “Transcranial Magnetic Stimulation (TMS) as a New Treatment for Addiction,” and “Management of Intoxication and Withdrawal from Stimulants, Hallucinogens, Marijuana, Phencyclidine, and ‘Club Drugs’” at the XVI International Congress of Neuropsychopharmacology, Bogota, Colombia.

Dr. Stephen Heishman, IRP, presented his research on the enhancing effects of nicotine on attention in a symposium, Attention Deficit-Hyperactivity Disorder and Tobacco Smoking, at the Society for Research on Nicotine and Tobacco conference in Helsinki, Finland in September.

Dr. Elliot Stein, IRP, was an invited speaker at the 3rd Biennial Resting State Conference in Magdeburg, Germany in September 2012 where he spoke on ‘Can Functional Connectivity Serve as a Biomarker for Drug Use and Addiction?’

Dr. Yavin Shaham, IRP, gave an invited lecture at Concordia University, Montreal.

Dr. Yavin Shaham, IRP, gave an invited lecture at the University of Rome.

Dr. Kiyatkin, IRP, gave an invited presentation at the 14th International Conference “Monitoring Molecules in Neuroscience”, Imperial College, London, UK where both post-doctoral fellows, Dr. Lenoir and Dr. Wakabayashi also presented posters. Dr. Kiyatkin and colleagues’ data (four posters) were also presented at the Annual Meeting of the Society for Neuroscience (New Orleans, October). Dr. Lenoir made poster a presentation at the NIDA/INSERM Workshop on U.S.-France Collaboration on Drug Abuse and Addiction Research in New Orleans, LA.

Dr. Yavin Shaham, IRP, gave an invited lecture at the EBPS workshop, Lecce, Italy.

MEETINGS/CONFERENCES

NIDA's DCNBR hosted the Translational **Research on Child Neglect Consortium: Final Meeting** on September 20-21, 2012 at the NIH Neuroscience Center in Rockville, MD. An evening poster session highlighting early investigators and travel awardees was held on September 20, 2012. A special community videocast co-chaired by Dr. Jacqueline Lloyd (DESPR) and Dr. Cheryl Anne Boyce on "Home Visitation and Child Neglect" on September 21, 2012 highlighted recent research on home visitation to reduce child neglect featured introductory remarks by Agnes Leshner, Director, Child Welfare Services, Montgomery County. Presenters included Dr. David Olds, Ph.D., University of Colorado, Dr. Anne Duggan, Johns Hopkins University, and Dr. Brenda Jones Harden, University of Maryland, College Park.

The Special Populations Office held the **16th Annual Summer Research with NIDA** program, which commenced on June 1, 2012. Sixty seven high school and undergraduate students engaged in drug abuse research at various NIDA-supported institutions for 8-10 weeks during the summer. Participants received certificates of participation signed by Dr. Nora Volkow and the site principal investigator. This program was coordinated by Flair Lindsey, Program Analyst, Special Populations Office.

The Special Populations Office convened a two-day "**Diversity Supplements Workshop**" at the National Institute on Drug Abuse (NIDA) headquarters in Bethesda, Maryland, October 4-5, 2012. Twenty-two current recipients of postdoctoral and early investigator-level diversity supplements from NIDA and NIAAA attended. Participants met and interacted with NIDA and NIAAA program staff and with funded NIDA investigators, many of whom were past recipients of diversity supplement awards through NIDA. In addition, they were presented overviews of NIDA's research program priorities, the NIH research grant application and peer review processes, and shared posters of their own NIDA and NIAAA-supported research. This workshop was coordinated by Pamela Goodlow, Public Health Analyst, Special Populations Office.

The African American Researchers and Scholars Workgroup (AARSWG) presented two posters at the NIDA mini-convention satellite meeting at the Society for Neuroscience Annual Meeting held in New Orleans, Louisiana, October 12, 2012 entitled **Increasing Diversity in Substance Abuse and Related Conditions: The NIDA African American Researchers and Scholars Workgroup's Mission, Goals and Activities** (Authors: AARSWG) and "Hypothesized Pathways of Methamphetamine Use/Abuse to Cardiovascular Disease" (Authors: D.F. Sarpong and C. Patrick)

The Special Populations Office convened the "**NIDA SPO Translational Research Speaker Series: Promoting Diversity and Moving Toward Health Equity**" in conjunction with the Division of Epidemiology Services and Prevention Research Services (DESPR) at NIDA headquarters in Bethesda, Maryland, on Wednesday October 24, 2012. Featured speaker C. Hendricks Brown, Ph.D. of University of Miami – Miller School of Medicine presented "Towards a Scientific and Methodological Prevention Agenda for Health Equity." This ongoing bi-monthly series is coordinated by Flair Lindsey, Special Populations Office.

The Special Populations Office and Kathy Etz, Ph.D., Prevention Research Branch, DESPR, convened a 2-day meeting of the **American Indian/Alaska Native (AI/AN) Researchers and Scholars Workgroup** at the NIDA headquarters in Bethesda, Maryland, December 3-4, 2012. In attendance were 20 scholars and select NIDA staff members. This workgroup was brought together to discuss and identify critical issues in the research and research development needs of the AI/AN community and to provide guidance to the NIDA Director and staff.

The Special Populations Office convened the “**NIDA SPO Translational Research Speaker Series: Promoting Diversity and Moving Toward Health Equity**” in conjunction with the DESPR HIV/AIDS Workgroup at NIDA headquarters in Bethesda, Maryland, on Thursday, December 11, 2012. Featured Speaker Steffanie Strathdee, Ph.D. of University of California – San Diego, presented on “Integrating Training and HIV Prevention Research among Substance Using Populations: A Binational Model.” This bi-monthly series is coordinated by Flair Lindsey, Special Populations Office.

On December 14-15, 2012, NIDA’s **African American Researchers and Scholars Workgroup (AARSWG)** held a two-day “*Booster Session*” a grant writing workshop intended for underrepresented early career investigators applying for research grant funding through the NIH. The workshop is a follow-up to the annual week-long *Addiction Research Training Institute (ARTI)* sponsored by the AARSWG workgroup, and limited in attendance. One-on-one interaction between invited early career scholars and assigned faculty mentors resulted in fine tuning research grant proposals. Six scholars and six faculty mentors participated in this workshop, held in Baltimore, Maryland.

Dr. Jack Stein, Director, OSPC, facilitated a performance of the Addiction Performance Project held in Philadelphia at the American Academy of Family Physicians in October 2012.

Dr. Gaya Dowling, Chief, Science Policy Branch, OSPC, participated in a Town Hall Meeting sponsored by the Arlington Ready Coalition entitled “Marijuana in Arlington—What’s the Big Deal?” on November 29, 2012.

Dr. Ruben Baler, Science Policy Branch, OSPC, gave a lecture entitled “Where Do Addictions Come From?” to the freshman Drug Awareness class at the School of Public Health, George Washington University, on September 19, 2012.

Dr. Cheryl Anne Boyce participated in the Center for Disease Policy and Control (CDC) Expert Meeting for Perinatal Illicit for Drug Abuse at their headquarters in Atlanta, GA on September 12-14, 2012.

Dr. Cheryl Anne Boyce participated in the Meeting on the Next Generation of Study on Child Well-Being hosted by Zero to Three on September 24, 2012 in Washington, DC.

Dr. Cheryl Anne Boyce participated in the Center for Disease Policy and Control (CDC) Expert Meeting for Perinatal Illicit for Drug Abuse at their headquarters in Atlanta, GA on September 12-14, 2012.

On October 5, 2012, Dr. Cheryl Anne Boyce presented at the Sisters of the Academy (SOTA) Institute's Intensive Grantsmanship Workshop in Baltimore, MD. The meeting was co-sponsored by NIH's Office of Women's Health.

Along with other NIDA and federal colleagues, Dr. Cheryl Anne Boyce attended the Interagency Meeting on Prescription Drug Abuse at the headquarters of the Office of National Drug Control Policy, Washington on October 18, 2012.

At the 59th Annual Meeting of the American Academy of Child and Adolescent Psychiatry, in San Francisco, October 23 – 27th, 2012, Dr. Cheryl Anne Boyce and Dr. Karen Sirocco organized workshop and symposium sessions with support from NIDA OSPC. Drs. Karen Sirocco and Cheryl Anne Boyce co-chaired a session entitled, "Peers, Adolescent Decision-Making, and Risk for Substance Abuse: A Look Inside the Teen Brain." Dr. Cheryl Boyce chaired and presented at the workshop "NIH Research Priorities and Competitive Grant Writing for Success" along with Dr. Geetha Subramaniam (CCTN), Dr. Karen Sirocco (DCNBR) and Dr. Julia Zehr (NIMH) who presented on current research priorities. Dr. Bennett Leventhal (Nathan Kline Institute for Psychiatric Research) and Dr. Neal Ryan (University of Pittsburgh) conducted a mock grant review for early career research investigators at the session. Recent data was highlighted in a session co-chaired by Cheryl Anne Boyce and James Swanson (University of California at Irvine) entitled, "Substance Use Determinants and ADHD: Findings from the Multimodal Treatment Study of ADHD (MTA) Children" with presenters Dr. Brooke Molina (University of Pittsburgh), Dr. Scott Kollins (Duke University), Dr. Peter Jensen (The REACH Institute) and Dr. F. Xavier Castellanos (New York University).

As part of the Robert Wood Johnson Foundation's (RWJF) New Connections: Increasing Diversity of RWJF Programming Sixth Annual Research and Coaching Clinic, Dr. Cheryl Anne Boyce presented in the workshop on "Obtaining Funding and Getting Published" on November 3, 2012 at the National Harbor, Maryland.

Dr. Cheryl Anne Boyce, Dr. Karen Sirocco and Dr. James Bjork participated via webinar for the N-CANDA Grantees Meeting on November 5 – 6, 2012 from the NIAAA RFA-AA-12-006 (U01), Longitudinal Studies on the Impact of Adolescent Drinking on the Adolescent Brain (Phase II) co-funded by NIDA, NIMH, and NICHD.

Dr. Cheryl Anne Boyce participated along with Dr. Mariela Shirley (NIAAA) and other NIH colleagues in the "speed mentoring" session at NIH's Office of Women's Health meeting entitled Building Interdisciplinary Research Careers in Women's Health (BIRCWH, K12) Scholars on November 14th, 2012 in Rockville, MD.

On December 10, 2012, Dr. Cheryl Anne Boyce attended the meeting Strengthening APA's and Psychology's Role and Collaborations in Reducing Tobacco Use in Health Disparity Populations held in Washington, DC.

Dr. Cheryl Anne Boyce participated in the open session and communications session of the Institute of Medicine's (IOM) Committee on Child Maltreatment, Research, Policy and Practice for the Next Decade Workshop held in Washington, DC on December 10, 2012.

Dr. Cheryl Anne Boyce and Dr. Samia Noursi (DESPR) are participating in the planning meetings for World Health Organization (WHO) Guidelines on the Identification and Management of Substance Use in Pregnancy.

Dr. David Thomas, DBNBR, made a presentation titled “NIH Centers of Excellence in Pain Education Program” at the Second Meeting of the Interagency Pain Research Coordinating Committee Meeting, October 22, 2012, Bethesda, Maryland.

Dr. Susan Volman, DBNBR, organized the Early Career Investigators Poster Session for the NIDA “Frontiers in Addiction Research” mini-convention, a satellite meeting of the Society for Neuroscience annual meeting in New Orleans, LA, October 12, 2012.

Dr. Cora Lee Wetherington, DBNBR, and the Women and Sex/Gender Differences Research Program, gave an invited talk, “Sex Differences in Pain: Progress & Promise,” in the session, “Beyond the Fig Leaf: The Science of Sex and Gender Differences,” at the annual NIH Research Festival held October 9, 2012, NIH main campus, Natcher Building. The session was organized by the NIH Office of Research on Women’s Health.

Dr. Cora Lee Wetherington participated in the NIH Office of Research on Women’s Health annual meeting of the PIs of the ORWH-led program, “Building Interdisciplinary Research Careers in Women’s Health (BIRCWH),” held November 14, 2012. She also participated in the ORWH annual meeting of the PIs of the ORWH-led program, “Specialized Centers of Research (SCOR) on Sex Differences,” held November 16, 2012. NIDA has grantees in each of these signature programs of the ORWH.

Dr. Cora Lee Wetherington was invited by the NIH Office of Research on Women’s Health to serve as a session moderator in their Ninth Annual Interdisciplinary Women’s Health Research Symposium held November 15, 2012, in Natcher Auditorium. Dr. Wetherington moderated Session I: Sex and Gender Differences in Substance Use/Behavioral and Mental Health. The session included NIDA-supported researchers, Dr. Kathleen Brady (Medical University of South Carolina) and Dr. Elise DeVito (Yale University School of Medicine).

Dr. Samia Noursi, DBNBR, and the Women and Sex/Gender Differences Research Program participated in a panel entitled “Federal Initiatives, Funding & Priorities,” at the 17th International Conference on Violence, Abuse and Trauma, September 9-12, 2012, San Diego, CA. Other presenters were Ms. Rebecca Odor from the Administration for Children and Families and Dr. Howard Spivak from Centers for Disease Control and Prevention.

Dr. Samia Noursi led a breakout session entitled “Gender Differences in Substance Abuse: are Females Less Vulnerable to Drug Abuse than Males?” at the 17th International Conference on Violence, Abuse and Trauma, September 9-12, 2012, San Diego, CA.

Dr. Samia Noursi and Dr. Cora Lee Wetherington organized and hosted a NIDA seminar entitled “New Developments in the Study of Sex Differences and Drug Abuse,” on September 26, 2012. The seminar featured two NIDA grantees: Dr. Marilyn Carroll (University of Minnesota) and Dr. Wendy Lynch (University of Virginia). Dr. Carroll’s talk was entitled “Sex Differences and Hormonal Influences in Drug Abuse and its Treatment” and Dr. Lynch’s was entitled “Sex and

Hormonal Influences on Motivation for Cocaine at Different Stages of Addiction: Neurobiological Mechanisms.”

Dr. Samia Noursi was invited to join the Federal working group to address the intersection of HIV/AIDS, violence against women, and gender-related health disparities. The working group was established following a presidential memorandum issued in March 2012 and its first meeting was convened on November 16, 2012 by the White House Office of National AIDS Policy and was co-chaired by CDC and the Office on Women’s Health at HHS.

Dr. Jonathan D. Pollock, DBNBR, organized and chair the session entitled, “Role of Phagocytes in Synaptic Plasticity and Remodeling of Tissues in the Nervous System” at the NIDA Mini-convention, New Orleans, LA, Sheraton Hotel, October 12, 2012.

Dr. John Satterlee, DBNBR, co-organized the NIH Roadmap Epigenomics Program-sponsored meeting “Epigenomic Surrogates for Difficult to Access Tissues” which took place in Building 45, Bethesda, MD on September 28, 2012.

Dr. Satterlee gave a presentation entitled “Common Fund Epigenomics Program Outreach: Overview and Lessons Learned” at the Common Fund All Hands meeting in Wilson Hall, October 9, 2012.

Dr. Satterlee is a member of the Common Fund Extracellular RNA Communication Workgroup, and oversees the RFA-RM-12-010 Data Management and Coordinating Center (U54) for the Extracellular RNA Communication Program.

Dr. Albert Avila, DBNBR, organized an early career workshop at NIDA for the Special Populations Office (SPO/LPC meeting).

Dr. Roger Sorensen, DBNBR, gave a grant writing tips webinar; Grant Writing for Success: Your Funded NIH Application; to the University of Tennessee Health Sciences Center on September 10, 2012.

Dr. Roger Sorensen gave a grant writing tips presentation; Grant Writing for Success: Your Funded NIH Application; and led a Specific Aims analysis workshop during the NIH New Innovator Awardees Meeting held in Bethesda, MD, on September 12, 2012.

Drs. Roger Sorensen and David Thomas, DBNBR, co-chaired the session; Central Nervous System Immune Signaling and Addiction, during the 2012 NIDA Mini-Convention: Frontiers in Addiction Research, held on October 12, 2012 in conjunction with the annual meeting of the Society for Neuroscience.

Dr. Roger Sorensen organized and hosted the Sixth Annual Julius Axelrod Symposium held on November 14, 2012 in New Orleans, LA as a satellite meeting of the annual meeting of the Society for Neuroscience. NIDA, NINDS, and NIMH provided support for this event.

Drs. Nancy Pilotte, Roger Sorensen and Albert Avila, DBNBR, and Dr. Harold Gordon, DCNBR, held a satellite event, NIH Grants Workshop for Early Career Investigators, on November 16, 2012 in Washington, DC during the annual meeting of the Society for Neuroscience to provide a forum through which early career investigators could learn about the NIH and the NIH grants process.

Drs. Roger Sorensen, Mary Abood, Temple University, and Nephi Stella, University of Washington, are co-editors of the volume; *EndoCannabinoids: Actions at non-CB1/CB2 Cannabinoid Receptors*, part of *The Receptors* series, Springer, NY, 2012.

Dr. Roger Sorensen participated in a panel discussion on establishing scientific collaborations, developing scientific careers and establishing an independent research program at the NIH Early Independence Award (EIA) meeting held in Bethesda, MD, on 14 December 2012.

Drs. José Ruiz from the Office of Extramural Affairs and Joe Frascella, DCNBR, organized and presented at a workshop entitled “Grant Application Peer Review” at the annual meeting of the National Hispanic Science Network to provide junior investigators insights into the peer review process and the value of participating in peer review. This workshop was held on September 27, 2012 in San Diego, CA.

Dr. Lisa Onken, DCNBR, in collaboration with the NIH Science of Behavior Change Work Group, led a meeting on October 9-10, 2012, *Revisiting Pasteur’s Quadrant: Fostering Use-Inspired Basic Research*. This meeting, held in Washington D.C., explored 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 examined 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.

Dr. Yu (Woody) Lin organized a training session entitled “Funding Opportunities for Enhancing Diversity in Addiction Research” at the NIDA Exhibition Booth at the Society for Neuroscience Annual Conference held on October 14 and 15, 2012, in New Orleans, LA. The activity was co-sponsored by NIDA Asian-American Pacific Islander Scholar and Researcher Workgroup and Special Populations Office.

Dr. James Bjork, DCNBR, and Dr. David Van Essen of Washington University co-chaired “The Human Connectome Project,” a symposium presented at the Society for Neuroscience Annual Meeting, held on October 16, 2012 in New Orleans, LA.

Dr. Harold Gordon, DCNBR, together with Albert Avila and Roger Sorenson of DBNBR presented a Workshop for Young Investigators at the Society for Neuroscience Annual Meeting, held on October 16, 2012 in New Orleans, LA.

Dr. Steven Grant, DCNBR, participated in the meeting of the ACNP Liaison committee and was a Travel Awardee Mentor at the American College of Neuropsychopharmacology Annual Meeting on December 1-6, 2012 in Hollywood, Florida.

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 Epidemiology of Drug Abuse as part of a panel on Sex Differences in Drug Abuse at the Winter Brain Conference, Colorado, January 29, 2013.

Dr. Wilson M. Compton chaired a panel on Reward/Motivation Deficits in Attention Deficit Hyperactivity Disorder (ADHD) and the Effects of Medication at the American College of Neuropsychopharmacology meeting, Florida, December 5, 2012. Presenters were: Dr. Elliot Stein on Functional Connectivity of Reward Circuits in the Rat and Human Brain, Dr. Francisco Xavier Castellanos on Reward Circuitry, Risky Behaviors, and ADHD, Dr. Nora Volkow on Dopamine Reward Circuitry in Attention Deficit Disorder, and Dr. Scott Kollins on Altered Sensitivity to Reinforcement in Individuals with ADHD: Implications for the Development of Aberrant Health Behaviors. The discussant was Dr. James Swanson.

Dr. Wilson M. Compton presented at the Columbia University Department of Psychiatry Grand Rounds on Mainstreaming Addictions in Medicine, New York, New York, September 21, 2012.

Dr. Wilson M. Compton presented a plenary on *The Science of Drug Abuse Prevention* at the National Prevention Network meeting, Pittsburgh, Pennsylvania, September 20, 2012.

Dr. Harold Perl, DESPR, participated on the faculty for the “NIH Day” technical assistance workshop at the 54th Annual Meeting of the National Council of University Research Administrators and taught the session entitled, “Grant Writing for Success: Coach Your PIs to a Winning Score” on November 8, 2012 in Washington, DC.

Dr. Harold Perl presented a keynote address entitled, “Keeping the Kids Out of the River: The Current State of Prevention Science in Drug Abuse”, a Regional Summit sponsored by Long Island Jewish Hospital, the Alcoholism and Substance Abuse Providers of New York State, the New York Chapter of the Society of Addiction Medicine, and Friends for Recovery (NY) on October 2, 2012 in Melville, NY.

Dr. Harold Perl presented a plenary address entitled, “Research Findings from the National Institute on Drug Abuse (NIDA): The Science Behind Effective Interventions for Treating and Preventing Drug Problems”, at the 36th Annual Educational Conference of the International Nurses Society on Addictions on September 7, 2012 in Washington, DC.

Drs. Jacqueline Lloyd, DESPR, and Cheryl Anne Boyce, DCNBR, presented and participated as co-chairs of a Special Community Lecture Webinar on “Home Visitation and Child Neglect”, which was part of a meeting titled “Translational Research on Child Neglect Consortium: Research on Child Neglect, Progress Over a Decade”, that took place September 20, 2012 in Bethesda, Maryland.

Drs. Elizabeth Robertson, Belinda Sims, and Jacqueline Lloyd, DESPR, participated in a Working Meeting on Advancing Prevention in Communities through Evidence-Based Programs on September 13, 2012, in Washington, DC. The meeting was sponsored by the Academic Centers of Excellence in Youth Violence Prevention, in partnership with the Society for Prevention Research (SPR), the Coalition for Evidence-Based Policy and Blueprints for Violence Prevention.

Dr. Augusto Diana, DESPR, organized and chaired a session titled, “How to Use Existing Datasets for Your Community Planning Process,” at the National Prevention Network conference in Pittsburgh, PA on September 19, 2012.

Dr. Aria Crump, DESPR, participated in a federal panel at the US Department of Education’s Higher Education Center Training Institute on Prescription Drug Abuse Prevention among College Students in Washington D.C. on October 10, 2012.

Dr. Richard A. Jenkins, DESPR, presented at an invited presentation on NIDA HIV/AIDS research priorities at the Columbia University HIV Center on September 21, 2012.

Dr. Belinda Sims participated in a CDC sponsored Federal Partner Panel, September 11-12, 2012, in Atlanta, GA. The panel focused on implementation and adaptation, including information that would be useful to gather from the research and practice fields, and input on how to improve existing guidance on adaptation.

Dr. Peter Hartsock, DESPR, represented NIH at the APHA national conference, where he organized and co-chaired an invited session, San Francisco, October 30, 2012. The session was a first-time for NIH presentation on the entire NIH grants process--from application development, through review and post-review scenarios--and included both NIH program and review staff.

Dr. Ivan Montoya participated in the Abuse Liability Evaluation for Research, Treatment, and Training (ALERTT) Meeting organized by the FDA, in Washington DC, on November 29, 2012.

The 2012 Annual National Conference of the Association for Medical Education and Research in Substance Abuse (AMERSA) was held November 1-3, 2012 in Bethesda, Maryland. NIDA CCTN staff presented the following: Dr. Udi Ghitza chaired a workshop entitled “Electronic health record systems for substance use disorders (SUD): Where we stand and future directions” and Dr. David Liu chaired a workshop entitled “Medication-assisted treatments for substance use disorders.”

Dr. Nadine Rogers served as a facilitator during a discussion of *The Righteous Mind: Why Good People Are Divided by Politics and Religion* with the author Jonathan Haidt, Professor of Psychology at New York University, while attending the Public Responsibility in Medicine & Research (PRIM&R) meeting in San Diego, CA from December 4 – 6, 2012.

Dr. Scott Chen, OEA, co-organized and co-hosted, a NIH-wide Staff Training in Extramural Programs (STEP) talk entitled, "Change is Inevitable: How to Lead It". Speakers included Dr. M. Susan Taylor (University of Maryland - College Park, School of Business), Dr. Thomas Hajduk (Georgetown University School of Business), and Dr. John J. McGowan (NIAID, NIH) in Rockville, Maryland on October 18, 2012.

Dr. Scott Chen co-organized the "NIDA SBIR Coordinating Committee's SBIR Contract Topic Writing Workshop." The workshop was designed to help Program Officers generate and prepare SBIR contract concept proposals, and was held in Rockville, MD on November 27, 2012.

In September 2012, NIDA Scientific Director, Dr. Antonello Bonci co-chaired the Catecholamines and Drug Abuse Theme and gave a lecture in the Catecholamine Targets for Addiction Medication Discovery session at the 10th International Catecholamine Symposium, Asilomar, CA.

Dr. Bonci was the co-organizer and co-chair of the 125th NIH Festival held in October 2012 at NIH.

On October 17, 2012, Dr. Bonci was given the honor of presenting a special lecture at the Society for Neuroscience meeting in New Orleans.

In November 2012, Dr. Bonci gave an invited lecture as a keynote speaker at the Johns Hopkins University Medical School MD-PhD program retreat.

In December 2012, Dr. Bonci participated in a symposium at the ACNP 51st Annual Meeting held in Hollywood, Florida.

Dr. Marisela Morales, IRP, gave invited lectures at the ACNP 51st Annual Meeting, Hollywood, Florida, and at The Scripps Research Institute, La Jolla, CA

Dr. Carl Lupica, IRP, gave the keynote lecture at the Carolina Cannabinoid Collaborative conference at the Brody School of Medicine in Greenville North Carolina in September 2012.

Dr. Bruce Hope, IRP, gave an invited address for the Psychology Department at Hunter College in New York.

Dr. Bruce Hope, IRP, gave an invited address for the Neuroscience Department at Brown University.

Dr. Tsung-Ping Su was invited to give a seminar at the Neuroscience Department of Temple University in March 2012.

Dr. Tsung-Ping Su was invited to give a seminar at the Neuroscience Department of the University of Florida School of Medicine in August 2012.

Dr. Tsung-Ping Su was invited to give a seminar at the Neuroscience Department of the University of North Texas in September 2012.

Drs. Amy Newman and Antonello Bonci, IRP, co-chaired the Catecholamines and Drug Abuse Theme and Dr. Newman chaired and gave a lecture in the Catecholamine Targets for Addiction Medication Discovery session at the 10th International Catecholamine Symposium, Asilomar, CA, in September.

Dr. Amy Newman chaired and presented her research on fluorescent monoamine transporter ligands at the Molecular Tools: Using Chemistry to See, Wrestle, Unravel, and Trap Biology Symposium at the NIH Research Festival in Bethesda in October. This symposium was highlighted in the NIH Catalyst.

In October 2012, Dr. Amy Newman gave invited lectures to the Geriatrics Research Branch, National Institute on Mental Health, NIH, in Bethesda MD and to the Johns Hopkins University Medical School, Brain Science Institute, in Baltimore MD.

Dr. Baumann was invited to give a seminar for the Department of Physiology at Virginia Commonwealth University (VCU) on November 8, 2012; the title of his talk was “Pharmacology of ‘Bath Salts’ Cathinones and Related Drugs”.

Dr. Katz, IRP, presented an invited address to the 15th Annual Meeting of the Maryland Association for Behavior Analysis on November 30, 2012, entitled What is the Place of Behavior Analysis with Neuroscience in Ascendancy?

Dayong Lee, M.S., IRP, a doctoral student performing her research in CDM, gave an invited presentation on her research on the disposition of cannabinoids in oral fluid to the 2012 Eastern Analytical Symposium.

Rebecca Hartman, BS (a CDM doctoral student) and Dr. Marilyn Huestis were invited to record a podcast to further highlight their manuscript entitled “Cannabis Effects on Driving Skills” recently published in *Clinical Chemistry*, the highest impact journal in this field. The podcast also was highlighted and broadcast to a national audience on public radio.

Nathalie Desrosiers, MS (a CDM doctoral student) and Dr. Marilyn Huestis also were invited to record a podcast to further highlight their manuscript entitled “On-Site Test for Cannabinoids in Oral Fluid” recently published in *Clinical Chemistry*. The article was considered of such importance that an Editorial was commissioned and accompanied the original article. A podcast also was recorded to highlight the publication and also was selected for national distribution by public radio.

The Motivational Incentives Implementation Software (MIIS) was developed by BIS under a collaboration between NIDA HQ and IRP in order to enhance community substance abuse treatment providers in delivering evidence-based behavioral interventions at no cost. The development effort was led by Drs. Vahabzadeh and Preston. As a new dissemination channel,

potential users of the software were trained in a three hour setting during the Road to Recovery conference hosted by the Johns Hopkins University, Baltimore, MD, in September 2012.

Dr. Stephen Heishman, IRP, was invited to speak about research internships to the Biology Council of Majors at the University of Maryland, Baltimore County in October.

In September 2012, Dr. Stephen Goldberg, IRP, was invited to speak at Northeastern University and gave a talk entitled “Endocannabinoid System Modulation of Nicotine Reward”.

Dr. Elliot Stein, IRP, was an invited speaker at the University of Pennsylvania Neuroscience of Behavior Program in October 2012 where he spoke on ‘Neuroimaging Genetic Biomarkers of Addiction.’

Dr. Elliot Stein was an invited speaker at the Maryland Neuroimaging Retreat in Baltimore in November 2012 on ‘Can Resting State fMRI Serve as a Biomarker for Addiction?’

Dr. Yavin Shaham, IRP, gave an invited lecture at Hunter College, NY.

Dr. Yavin Shaham gave an invited lecture at Columbia University

Dr. Yavin Shaham gave an invited lecture at Cornell University

Dr. Yavin Shaham gave an invited lecture at Mount Sinai School of Medicine.

Dr. Yavin Shaham gave an invited lecture at the Behavior, Biology, and Chemistry meeting San Antonio, (symposium organizer).

Dr. Yavin Shaham, IRP, gave an invited lecture at the NIDA mini symposium at the SFN meeting, New Orleans.

Dr. Yavin Shaham, IRP, gave an invited lecture at the NIH Research Festival (symposium organizer).

Dr. Bossert, IRP, gave an invited lecture at the University of North Carolina.

MEDIA AND EDUCATION ACTIVITIES

MEDIA SUPPORT OF EVENTS AND MEETINGS

International AIDS Society Conference

NIDA participated in a Twitter Chat with ABC's Dr. Richard Besser surrounding the July International AIDS Society conference in Washington, D.C. NIDA also provided on-site media support at a joint NIH press conference, conducted its own press event to announce the 2012 Avant Garde Awards for Medications Development, and assisted staff with the NIH exhibit booth during the conference.

The Medicine Abuse Project

NIDA helped promote the launch of The Partnership at Drug Free.org's Medicine Abuse Project (MAP) via Facebook and Twitter posts. NIDA also participated in the MAP's partner teleconference and attended the launch event in September which encouraged parents to talk to their children about the dangers of prescription drug abuse.

Society for Neuroscience Meeting

NIDA hosted its annual satellite Society for Neuroscience (SfN) mini-convention "Frontiers in Addiction Research" in October in New Orleans. NIDA promoted the event via traditional and social media outreach efforts. @NIDAnews twitter followers were kept up-to-date throughout the mini-convention by three NIDA staffers who tweeted conference highlights. NIDA shared 44 tweets and gained 88 retweets from the conference.

Addiction Performance Project

NIDA conducted traditional and social media outreach efforts surrounding the October Addiction Performance Project held in Philadelphia at the American Academy of Family Physicians, resulting in several interviews.

PRESS RELEASES

July 23, 2012

Prevention of HIV spread focus of NIDA's 2012 Avant-Garde Awards

The National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, today announced the recipients of the 2012 Avant-Garde Award for HIV/AIDS Research. The three scientists, Drs. David Smith, Samuel Friedman and Jeremy Luban, will each receive \$500,000 per year for five years to support their research. NIDA's annual Avant-Garde award competition, now in its fifth year, is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug abusers.

Awardees are:

David Smith, M.D., University of California, San Diego School of Medicine

Project: Molecular epidemiology for HIV prevention for drug users and other risk groups

Dr. Smith's group will develop a novel system that integrates information regarding patient demographics, geographic location, drug use, and HIV viral strain in order to map patterns of new HIV infections as they occur in real time. A successful system would allow for the quick delivery of tailored prevention resources to affected communities based on their unique characteristics (e.g., injection drug use or methamphetamine use and sexual transmission). The ultimate goal is to stop HIV clusters from developing or expanding, particularly among substance using populations.

"Identifying and targeting HIV transmission clusters will allow us to make the most of HIV prevention resources," said Smith. "We believe this could be the key to ending HIV transmission in some of the most at-risk populations in San Diego and, in turn, other communities."

Samuel Friedman, Ph.D., National Development and Research Institutes, New York City

Project: Preventing HIV transmission by recently-infected drug users Dr. Friedman's research team plans to identify people newly infected with HIV and link them to care, since the first few months of infection represent a period of high infectivity and risk behavior. Novel interventions that include community alerts and education within affected drug using and other social networks and venues, and efforts to prevent stigmatization of the newly-infected, will be developed and tested to prevent further spread within the community.

"Unlike many other HIV prevention and treatment methods, this technique will follow the virus to where it is likely to be transmitted," said Friedman. "We will start with drug users, but the network and community aspects of the project mean that we will also prevent transmissions among other high-risk persons if the infection chains lead us to them."

Jeremy Luban, M.D., University of Massachusetts Medical School, Worcester

Project: Human genes that influence HIV-1 replication, pathogenesis, and immunity in intravenous drug users Dr. Luban's group plans to develop new methods for studying the ways in which human genes can influence whether an exposed person will become infected with HIV or, if infected, how the disease will progress. These studies will guide future strategies aimed at preventing and treating HIV among drug abusers.

"Despite 30 years of AIDS research, there is still no experimental system for studying how genes actually function in humans to regulate HIV replication, pathogenesis, and immunity," Luban said. "Now that the number of human genes suspected of influencing HIV is skyrocketing, the need for such technology has never been greater."

"This year's award recipients proposed especially exciting research aimed at reducing HIV transmission and progression," said NIDA Director Nora D. Volkow, M.D. "We expect that this innovative research will provide new leads in the fight against HIV/AIDS in drug abusing populations."

These awardees were among the many applicants whose proposals reflect diverse scientific disciplines and approaches to HIV/AIDS research. The Avant-Garde Awards are modeled after the NIH Pioneer Awards and are granted to scientists of exceptional creativity who propose high-impact research that could open new avenues for prevention and treatment of HIV/AIDS among drug abusers.

According to the most recent estimates provided by the Centers for Disease Control and Prevention, approximately 1.2 million people in the United States live with HIV, with about 50,000 new cases diagnosed each year, an incidence rate that has held relatively steady since the late 1990s. Drug abuse and its related behaviors, such as sharing drug injection equipment and/or engaging in risky sexual behavior while intoxicated, have been central to the spread of HIV/AIDS since the pandemic began 30 years ago. NIDA's AIDS Research Program supports a multidisciplinary portfolio that investigates the role of drug use and its related behaviors in the evolving dynamics of HIV/AIDS epidemiology, natural history, etiology, pathogenesis, treatment, and prevention.

For information about NIDA's AIDS Research Program, including the Avant-Garde Award Program for HIV/AIDS Research and the International AIDS Society-NIDA Joint Fellowship Program, go to www.drugabuse.gov/AIDS.

Smith, Friedman and Luban are funded under grant numbers DA034978, DA034989, and DA034990.

July 25, 2012

NIDA supports development of combined anti-heroin and HIV vaccine

Dr. Gary R. Matyas has been selected the 2012 recipient of the NIDA Avant-Garde Award for Medications Development.

Matyas proposes to develop an effective, safe and easily manufactured combination anti-heroin/HIV vaccine that could treat heroin addiction while at the same time prevent HIV infection in those receiving the vaccine. Matyas will receive \$1,000,000 per year for five years to support his research. He works at the Walter Reed Army Institute of Research (WRAIR) in Silver Spring, MD.

The National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, announced the award today. "This highly innovative dual-vaccine model would simultaneously address the intertwined epidemics of heroin abuse and HIV," said NIDA Director Dr. Nora D. Volkow. "This is precisely the type of ground-breaking research NIDA's Avant-Garde program was designed to support. The implications for public health are enormous."

The proposal stems from an existing research collaboration between NIDA and the U.S. Military HIV Research Program, part of the WRAIR. In 2010, the two organizations entered into an agreement to create a combination anti-heroin/HIV vaccine. The goal was to build upon previous preclinical research indicating that hapten-based anti-drug vaccines—in which a small molecule chemically similar to a drug of abuse (hapten) is bound to a protein carrier to induce an immune response—showed promise against a variety of abused drugs, including heroin. As a result of this collaboration, the heroin component of a combination anti-heroin/HIV vaccine has now been created and is ready for optimization and advanced preclinical testing. This current grant award will support this next phase of research and development.

The award will be administered through the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc. and work done in collaboration with the U.S. Military HIV Research Program and NIDA.

“Heroin use is strongly associated with a high risk of HIV infection and represents an increasingly important worldwide health problem,” stated Matyas. “The possibility of creating a combination heroin-HIV vaccine provides an important opportunity to address both a unique treatment for heroin abuse as well as continuing the quest to develop an effective preventive HIV vaccine.”

This research competition is an extension of NIDA’s [Avant-Garde Award for Innovative HIV/AIDS Research](#), now in its fifth year. Both competitions are intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of drug abuse. For further information about NIDA’s Avant-Garde Award for Medications Development, please visit <http://grants.nih.gov/grants/guide/rfa-files/RFA-DA-12-010.html>.

Also statement from the NIDA Director on NIDA’s commitment to vaccine development can be found at www.drugabuse.gov/about-nida/directors-page/messages-director/2011/05/vaccines. Matyas is funded under grant number: DA034787.

August 8, 2012

New dates. National Drug Facts Week begins Jan. 28, 2013

The third annual National Drug Facts Week will be held Jan. 28 through Feb. 3, 2013, the [National Institute on Drug Abuse](#) (NIDA), part of the National Institutes of Health, announced today. This week-long observance will bring together teens and scientific experts in community events across the country to discuss scientific facts about drug abuse. National Drug Facts Week is a NIDA initiative.

National Drug Facts Week encourages community-based events where teens ask questions of addiction scientists or educators familiar with NIDA’s scientific materials. Events can be sponsored by a variety of organizations, including schools, community groups, sports clubs, book clubs, and local hospitals.

With events often held at schools, the observance has been moved to late January to give teachers and counselors more time to plan drug information activities. "This week is designed to counteract the myths teens have about drug abuse, often reinforced by their peers, the Internet, and the entertainment industry," said NIDA Director Dr. Nora D. Volkow. "When given the facts from people they trust, teens are in a better position to make good decisions about drug use."

NIDA provides an [online toolkit](#) that advises teens and their sponsoring organizations on to how create an event, publicize it, find an expert, and obtain scientific information on drugs. NIDA will support event holders by offering its popular teen booklet, [Drugs: Shatter the Myths](#), free of charge as well as a new online [National Drug IQ Challenge](#), a 10-question multiple choice quiz that teens and adults can take to test their knowledge about drugs.

National Drug Facts Week is being supported by many federal agencies, including the [White House Office of National Drug Control Policy \(ONDCP\)](#); the [National Institute on Alcohol Abuse and Alcoholism](#) at NIH; the [Office of Safe and Healthy Students](#) in the U.S. Department of Education;

the [Substance Abuse and Mental Health Services Administration](#); and the [Drug Enforcement Administration](#) (DEA) in the U.S. Department of Justice. Each agency will post National Drug Facts Week information on its website and will encourage the development of special events linking experts to teens. "America's success in the 21st century depends on our ability to educate our children and help them make decisions that will keep them healthy and safe," said ONDCP Director Gil Kerlikowske. "This administration is committed to using science to educate young people and inform policy in order to help raise a new generation of healthy and safe young people."

The Office of Safe and Healthy Students in the Department of Education will reach out to schools across America to encourage activities during National Drug Facts Week. "In too many cases youth don't understand the harm caused by illicit drugs or misuse of prescription medications," said David Esquith, director of the Office of Safe and Healthy Students. "They want and need accurate and clear information. That's what National Drug Facts Week is all about."

DEA will again share in efforts to promote the week. "Asking questions and getting honest answers are essential to making good choices, particularly when it comes to drug use," said DEA Administrator Michele M. Leonhart. "National Drug Facts Week is a great opportunity for teens and young adults to learn the facts and develop healthy habits they will keep for the rest of their lives." Also during National Drug Facts Week, NIDA scientists will hold their annual Web chat with teens around the country. Drug Facts Chat Day will be held Jan. 31st from 8 a.m. to 6 p.m. EST. Schools can register by going to <http://drugfactsweek.drugabuse.gov/chat>. Registration is offered on a first come first serve basis, and the website offers information on the popular annual chat.

Organizations wishing to hold events during National Drug Facts Week can now register at: <http://drugfactsweek.drugabuse.gov> or email: drugfacts@nida.nih.gov. Organizations that register can receive free teen booklets and other advice and information about holding successful events.

**October 1, 2012 (ONDCP press release posted by NIDA)
White House Drug Policy Office and National Institute on Drug Abuse Unveil New Training Materials to Combat National Prescription Drug Abuse Epidemic**

Today, the Office of National Drug Control Policy (ONDCP) and the National Institute on Drug Abuse (NIDA) launched a new online learning tool which will provide training for healthcare providers on proper prescribing and patient management practices for patients on opioid analgesics (painkillers). The launch of the tool builds upon previously announced Administration efforts to address the nation's prescription drug abuse epidemic through a balanced public health and safety approach and support the Administration's goal of reducing the misuse of prescription drug abuse by 15 percent by 2015.

The new training materials, which include video vignettes modeling doctor patient conversations on the safe and effective use of opioid pain medications, are part of NIDA's [NIDAMED](#) initiative, created to help physicians, medical interns and residents, and other clinicians understand and address the complex problem of prescription drug abuse. In addition to providing more accessible and self-guided information for healthcare providers, the training modules will also provide an opportunity for healthcare professionals to earn continuing medical education (CME) credits.

“It’s no coincidence that our strategy to address our nation’s prescription drug abuse epidemic begins with education,” said Gil Kerlikowske, Director of National Drug Control Policy. “All of us – parents, patients, and prescribers - have a shared responsibility to learn more about this challenge and act to save lives. Prescribers in particular play a critical role in this national effort and I strongly encourage them to take advantage of this training to ensure the safe and appropriate use of painkillers.”

“Physicians can be the first line of defense against prescription drug abuse by knowing how to prescribe opioid pain medications safely and effectively,” said NIDA Director Nora D. Volkow, M.D. “These CME courses provide practical guidance for clinicians in screening their pain patients for risk factors before prescribing. They also help medical professionals identify when patients are abusing their medications, using videos that model effective communication about sensitive issues, without losing sight of addressing pain.”

The training materials, funded by ONDCP, will include two online CME modules employing a “test-and-teach” model of instruction. During the first year, the training modules will reside on the [Medscape Website](#) for CME credit. The modules are also available on the [NIDA Website](#) where they can be adapted for use in the syllabi of academic medical schools.

According to data from the National Survey on Drug Use and Health (NSDUH) released last week, the number of young adults (people aged 18 to 25) who used prescription drugs for non-medical purposes in the past month declined 14 percent -- from 2 million in 2010 to 1.7 million in 2011. However, the Centers for Disease Control and Prevention (CDC) still classifies prescription drug abuse as an epidemic, with roughly 100 people dying each day from drug overdoses, driven primarily by prescription drugs.

The number of prescriptions filled for opioid pain relievers has increased dramatically in recent years. From 1997 to 2007, the milligram per person use of prescription opioids in the U.S. increased from 74 milligrams to 369 milligrams, an increase of 402 percent. In 2000, retail pharmacies dispensed 174 million prescriptions for opioids; by 2009, 257 million prescriptions were dispensed, an increase of 48 percent. Further, opiate overdoses, once almost always due to heroin use, are now increasingly due to abuse of prescription painkillers.

To address the threat of prescription drug abuse and diversion while also protecting legitimate access to these drugs for those suffering from chronic pain, the Administration released *Epidemic: Responding to America's Prescription Drug Abuse Crisis* ([PDF, 350Kb](#)) in 2011. The action plan provides a national framework for reducing prescription drug diversion and abuse by supporting education for patients and healthcare providers, recommending more convenient and environmentally responsible disposal methods to remove unused medications from the home, supporting the expansion of state-based prescription drug monitoring programs, and reducing the prevalence of pill mills and doctor shopping through enforcement efforts.

More information about **NIDAMED**. To access the training materials for CME credit visit the links below: [Safe Prescribing for Pain CME/CE](#); [Managing Pain Patients Who Abuse Rx Drugs CME/CE](#). A full copy of the *Epidemic: Responding to America's Prescription Drug Abuse Crisis* ([PDF, 350Kb](#)) is available. To learn more about Administration efforts to reduce drug use and its consequences visit www.WhiteHouse.gov/ONDCP

SCIENCE SPOTLIGHTS AND ANNOUNCEMENTS

August 8, 2012 -- NIDA-funded research in rats showed that using a combination of buprenorphine and naltrexone can reduce cocaine intake without producing opioid dependence -- a promising step toward an effective medical treatment for cocaine addiction in humans, for which there are no current FDA-approved medications. For a copy of the study by Wee et al., go to <http://stm.sciencemag.org/content/current>.

September 10, 2012 -- NIH-funded research showed that long-term marijuana is associated with impaired intellectual functioning, especially if usage starts during the teen years. This is the first long-term prospective study to test young people *before* their first use of marijuana and again *after* 20+ years of use. For a copy of the study, go to www.pnas.org/content/early/2012/08/22/1206820109.abstract?sid=aaccd18b-26ef-4497-8da0-fa55c5ad15fe

October 4, 2012 -- A NIDA-funded study examined amphetamine-induced dopamine release in patients with comorbid schizophrenia and substance dependence. The results suggest that comorbid patients suffer from a combined dysfunction: a) increased dopamine sensitivity in the part of the striatum responsible for the psychotic symptoms *and*, based on prior research, b) reduced sensitivity to dopamine in the area of the striatum associated with reward. Such a set of alterations in dopamine release could set up a vicious cycle of using drugs to self-medicate, which in turn may cause or further worsen psychosis. For a copy of the article abstract, go to: www.nature.com/mp/journal/vaop/ncurrent/abs/mp2012109a.html

October 9, 2012 -- NIDA sent out an announcement seeking to develop and test a prototype mobile/tablet technology-based application to provide a low-cost, highly personalized, interactive patient-centric medication adherence tool that improves upon currently available mobile technology-based medication adherence applications. The full announcement can be found at <http://grants.nih.gov/grants/funding/sbir.htm>

October 9, 2012 -- An NIH-funded study showed that on-site rapid HIV testing has the potential to increase life expectancy for substance abuse treatment patients newly diagnosed with HIV in a cost effective way. For a copy of the study abstract, go to www.ncbi.nlm.nih.gov/pubmed/22971593.

October 10, 2012 -- As part of National Substance Abuse Prevention Month, NIDA launched [*Family Checkup*](#), an online resource that equips parents with research-based skills to help keep their children drug-free.

October 11, 2012 -- The American Journal of Drug and Alcohol Abuse recently published a special edition devoted to NIH-funded research in American Indian/Alaska Native (AI/AN) communities. The special edition can be found in its entirety at <http://informahealthcare.com/toc/ada/38/5>.

October 16, 2012 -- The American Institutes for Research in Washington, DC, is the 2012 Mentor International Best Practice in Prevention Award winner for the Good Behavior Game, an evidence-based substance abuse prevention program funded by NIDA and NIMH. The Mentor Foundation, founded in 1994 by Her Majesty Queen Silvia of Sweden in collaboration with the World Health Organization, identifies and develops best practices and effective policies in drug abuse prevention.

October 17, 2012 -- NIDA research published in *Neuropsychopharmacology* showed that MDPV, a synthetic chemical commonly found in the drugs referred to as “bath salts,” is potentially more dangerous than cocaine when tested in rodents. For a copy of the study abstract, go to www.nature.com/npp/journal/vaop/ncurrent/abs/npp2012204a.html.

October 31, 2012 -- [New training materials](#) for health providers who prescribe or counsel patients about opioids for pain relief, are available on NIDA’s website. The two courses, entitled “Safe Prescribing for Pain” and “Managing Patients Who Abuse Prescription Drugs”, include video vignettes modeling doctor patient conversations on the safe and effective use of opioid pain medications. The materials are part of the NIDAMED initiative, designed to help physicians, medical interns and residents, and other clinicians understand and address the complex problem of prescription drug abuse.

November 1, 2012 NIDA awarded grants to Yale University, the Medical University of South Carolina, and the University of Minnesota to explore sex differences in drug addiction. These three grants are part of the Specialized Centers of Research (SCOR) on Sex Differences program, developed and coordinated by NIH’s Office of Research on Women’s Health, which has recently awarded a total of 11 SCORs among NIH Institutes. The RFA can be viewed at <http://grants1.nih.gov/grants/guide/rfa-files/RFA-OD-11-003.html>.

MEDIA ADVISORIES

June 28, 2012

NIDA Director Nora Volkow to speak at Aspen Ideas Festival July 2

NIDA’s Dr. Nora D. Volkow spoke at 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.

July 18, 2012

NIDA Announces 2012 Avant-Garde Award for Medications Development

NIDA’s Dr. Nora D. Volkow announced the winner of the 2012 Avant-Garde Award for Medications Development during the XIX International AIDS Conference in Washington, DC. This research competition, now in its third year, is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of drug abuse. This year’s winner will receive \$1,000,000 per year for five years in research support.

September 27, 2012

NIDA/ONDCP to launch online physician training tools

NIDA Director Dr. Nora D. Volkow joined White House Drug Policy Director R. Gil Kerlikowske at a media briefing to announce the launch of two new continuing medical education courses on safe prescribing practices for pain and managing pain patients who abuse prescription drugs. Using a “test and teach” approach, the online modules, which reside on the Medscape Web site, include several video vignettes modeling doctor-patient conversations on the safe and effective use of opioid pain medications.

October 16, 2012

Actors Elizabeth Marvel and Reed Birney to raise the curtain in NIDA's Addiction Performance Project

Elizabeth Marvel and Reed Birney led an impressive cast in the Addiction Performance Project, an innovative continuing medical education (CME) program for doctors and other health providers, on October 20 in Philadelphia. The performance is a project of NIDA, part of NIH, 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: July 2012 – November 2012

PBS — Dr. Nora Volkow was interviewed for a profile piece.

Associated Press — Dr. Nora Volkow was interviewed about marijuana.

Christian Science Monitor — Dr. David Shurtleff was interviewed about bath salts.

Time — Dr. Nora Volkow was interviewed about cocaine.

Milwaukee Journal Sentinel — Dr. Nora Volkow was interviewed about opioids.

Univision — Dr. Nora Volkow was interviewed for a profile piece.

Andrea Mitchell Reports/MSNBC — Dr. Nora Volkow was interviewed about addiction.

WebMD — Dr. Marilyn Huestis was interviewed about K2/Spice.

Huffington Post — Dr. David Shurtleff was interviewed about bath salts.

Marie Claire — Dr. Nora Volkow was interviewed about prescription drug abuse.

The New York Times — Dr. Nora Volkow was interviewed about adderall abuse.

The Washington Post — Dr. Wilson Compton was interviewed about prescription drug abuse.

ABC.com — Dr. Gaya Dowling was interviewed about prescription drug abuse.

BBC Radio — Dr. Wilson Compton was interviewed about prescription drug abuse.

Newsweek — Dr. Nora Volkow was interviewed about food addiction.

NPR Talk of the Nation Science Friday — Dr. Nora Volkow was interviewed about tobacco/nicotine.

The Wall Street Journal — Dr. Nora Volkow was interviewed about vaccine addiction.

Parade Magazine — Dr. David Shurtleff was interviewed about OTC drug abuse.

Reuters Television — Dr. Ruben Baler was interviewed about prescription drug abuse.

The Miami Herald — Dr. Gaya Dowling was interviewed about drug abuse among the elderly.

New Scientist -- Dr. Steven Grant was interviewed for an article on the presentation by NIDA grantee Dr. Cherie Marvel at the 2012 Society for Neuroscience Annual Meeting demonstrating working memory deficits and associated heightened activity in the frontal lobe of methadone-maintained heroin abusers relative to healthy controls.

RECENT AND UPCOMING CONFERENCES/EXHIBITS

2012 U.S. Conference on AIDS -- Las Vegas, NV -- September 30-October 3, 2012

2012 Society for Neuroscience -- New Orleans, LA -- October 13-17, 2012

American Academy of Child & Adolescent Psychiatry Annual Meeting -- San Francisco, CA
October 23-28, 2012

Association for Middle Level Education National Conference – Portland, OR -- November 8-10,
2012

Community Anti-Drug Coalitions of America National Leadership Forum XXII -- National Harbor,
MD -- February 4-6, 2013

PLANNED MEETINGS

Drs. Lisa Onken, DCNBR, NIDA, Wilson Compton, DESPR, NIDA, and Varda Shoham, NIMH, are planning a meeting, **Improving Smoking Cessation Treatment for People with Schizophrenia**. The meeting will be co-sponsored by NIMH and NCI and is planned to be held sometime in the spring in the Washington D.C. area.

The next **National CTN Steering Committee Meetings** will be held March 12-15, 2013 in Bethesda, Maryland.

PUBLICATIONS

NIDA PUBLICATIONS/VIDEOS

Principles of Effective Treatment for Adolescents

NIH Pub. No.: 12-7953

This publication is intended to provide parents, referring clinicians, treatment practitioners, youth, and others with an evidence-based guide to the principles of effective substance abuse treatment for youth. It includes FAQs, description of multiple treatment modalities and settings, and a listing of other resources.

Mentoring: A Guide for Drug Abuse Researchers (Revised)

NIH Pub. No.: 12-5770

This NIDA guide offers valued approaches for enhancing the mentoring process in the field of drug abuse and addiction health services, epidemiology, treatment, and prevention. It is intended for both mentors and mentees.

Mind Over Matter: Inhalants (Revised)

NIH Pub. No.: 13-4038

This pamphlet describes how inhalants can wear away at the myelin sheath that protects the brain's nerve cells.

Mind Over Matter: Nicotine (Revised)

NIH Pub. No.: 13-4248

This pamphlet explains scientifically how nicotine affects the entire body. Describes how the drug acts directly on the heart to change heart rate and blood pressure. It discusses dependency, treatment, and effects of long-term nicotine use.

Commonly Abused Prescription Drugs (Revised)

This chart lists prescription drugs with potential drug abuse, their commercial or street names, routes of administration, intoxication effects, and potential health consequences.

Spanish Language Videos

NIDA produced three Spanish language videos which have been posted on the NIDA website (<http://www.drugabuse.gov/es/temas-relacionados/el-abuso-de-drogas-y-la-drogadiccion/que-sabemos-de-la-adiccion>). The videos cover 1) Addiction & Adolescents; 2) Dopamine & Pleasure Sensors; and 3) Multiple Factors Affecting Addiction. The videos are part of an online “speakers kit” package created to equip Spanish-speaking community educators to give a talk about drugs and teens. In addition to the videos, the kit includes:

- A glossary of terms specific to the presentation
- Tips for giving a presentation
- Questions and answers

INTERNATIONAL PROGRAM-RELATED PUBLICATIONS

NIDA International Program E-News

- *September 2012* – This issue reports on an NIH satellite to the XIX International AIDS Conference and the 2012 NIDA International Forum. New awards were announced for the INVEST, INVEST/CTN, and NIDA/International AIDS Society fellowship programs, as well as the Distinguished International Scientist Collaboration Award. Other features focused on binational activities between NIDA and Italy, new funding opportunities for international research, and a regional grant-writing seminar held in Latin America.
- *December 2012* – This issue features a meeting to explore potential collaboration between NIDA and France. Other stories report on an inhalant abuse meeting organized in Mexico City and the 2012 NIH Director’s Award presented to a team of NIH program officers including IP Director Steven W. Gust, Ph.D. Stories also introduced a new INVEST fellow and the 2012-2013 Hubert H. Humphrey Fellows.

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>. Nearly, 1,800 data sets have been downloaded by researchers from 34 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.

OTHER PUBLICATIONS

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STAFF HIGHLIGHTS

Staff Honors and Awards

Dr. Rao Rapaka, DBNBR, has been elected as the AAAS Fellow for outstanding service as an innovative and creative research administrator at the NIH and for distinguished scholarship in drug abuse research. Dr. Rapaka will be presented the honor in February 2013.

Dr. Roger Sorensen, DBNBR, received the OD Honor Award, NIH, for his participation in developing the new annual NIH grant progress report form, Research Performance Progress Report (RPPR), which will replace current Form PHS 2590.

Drs. Kevin Conway and **Augusto Diana**, DESPR, were granted the Contracting Officer's Representative of the Year Award on October 23, 2012, in recognition of outstanding service overseeing NIDA contracts.

Dr. Harold Perl, DESPR, was honored with the "Best Workshop of 2011 Award" for the workshop entitled, "Unlock the Mysteries of NIH Research Funding: Improve Your Grant Application and Improve Your Chance at Success", at the 36th Annual National Conference of the Association for Medical Education and Research in Substance Abuse on November 3, 2012 in Bethesda, MD.

Dr. Nadine Rogers, OEA, earned certification as a Project Management Professional (PMP) from the Project Management Institute on October 10, 2012.

Dr. Meena Hiremath, OEA, earned certification as a Project Management Professional (PMP) from the Project Management Institute on December 17, 2012.

Dr. Scott Chen, OEA, earned certification as a Project Management Professional (PMP) from the Project Management Institute on July 18, 2012.

Dr. Scott Chen graduated from the NIH Mid-Level Leadership Program Series 2 Cohort, certified by Dr. Francis Collins, NIH Director, and Colleen Barros, NIH Deputy Director for Management on, on November 1, 2012.

Dr. Scott Chen was elected Vice President of Programs, Project Management Institute Montgomery County Maryland Chapter on November 7, 2012.

Steven W. Gust, Ph.D., NIDA IP Director, was a member of the team of NIH program officers who received the 2012 NIH Director's Award for their work on the Fogarty International Center (FIC) program Brain Disorders in the Developing World: Research Across the Lifespan. The Brain Disorders Program Director Kathleen Michels, Ph.D., and her colleagues from eight NIH Institutes and Centers were honored in recognition of an "exceedingly successful, decade-long, multi-Institute/Center partnership to address the major global impact of brain disorders across the lifespan." The Brain Disorders Program develops innovative, collaborative research and sustainable research capacity building projects in developing countries on a broad range of brain and nervous system disorders.

Dr. Carl Lupica, IRP, was elected to the board of advisors for the Winter Conference on Brain Research and served as a program committee member for this conference. He also serves as an Associate Editor at the Journal of Neuroscience.

Dr. Karl Scheidweiler, IRP, received the Patsalos Prize for the best manuscript published in Therapeutic Drug Monitoring during the previous 2 years at the meeting of the International Association of Therapeutic Drug Monitoring – Clinical Toxicology in Stuttgart, Germany for his manuscript entitled “Pharmacokinetics of Cocaine and Metabolites in Human Oral Fluid and Correlation with Plasma Concentrations following Controlled Administration.”

Dr. Teresa Gray, IRP, received the prestigious Irving Sunshine Award from the American Academy of Forensic Sciences in February, 2012 for her research on *in utero* drug exposure conducted at CDM that recently completed her doctoral degree requirements.

Dr. David Schwope, IRP, also a recent doctoral student in CDM, received the Society of Forensic Toxicology (SOFT) EDIT award for the best manuscript in the Journal of Analytical Toxicology. Dr. Schwope’s paper was entitled “Psychomotor Performance, Subjective and Physiological Effects and Whole Blood D9-Tetrahydrocannabinol Concentrations in Heavy, Chronic Cannabis Smokers Following Acute Smoked Cannabis.” The research was performed as part of CDM’s clinical research program and also fulfilled his doctoral degree requirements.

Dr. Marilyn Huestis, IRP, received the University of Mississippi’s 2012 Coy W. Waller Distinguished Lecture award in Oxford, MS and presented a public lecture on “Chronic Daily Cannabis Use, Neuroadaptation and Psychomotor Impairment.”

Dr. Marilyn Huestis was the Scientific Chair of the world’s largest forensic toxicology meeting conducted by the Society of Forensic Toxicology’s and The International Association of Forensic Toxicologists’ (TIAFT) in San Francisco, CA.

Staff Changes

New Employees

Drs. Brandon Selfridge and **Joshua Antoline** have joined the IRP’s Chemical Biology Research Branch, Section on Drug Design and Synthesis as IRTA Postdoctoral Fellows.

Ellie Johnson joined the NIDA Office of the Director as a Supervisory Staff Assistant and provides executive support to Glenda Conroy, Susan Weiss (Associate Director for Scientific Affairs) and Helio Chaves (Deputy Executive Officer) as well as oversight to OD office operations. Ellie was previously the Executive Assistant to the Director, National Institute of Nursing Research at NIH and has a wealth of experience in administrative and executive support in the public and private settings.

Maggie Stevenson joined the NIDA Office of the Director as a Staff Assistant and provides support to the NIDA OD and NIDA Executive Secretariat. Maggie was previously a Program Coordinator in the NIMH Office of Science Policy, Planning and Communications and has a wealth of experience in administrative and executive support in public and private settings. She has a Bachelor of Arts degree from the University of Maryland and Certifications from George Washington University and HHS University.

Josie Anderson, B.A. joined NIDA in November as an Audio Visual Production Specialist in the Public Information Liaison Branch, OSPC. Josie served in the United States Air Force (USAF) for more than ten years, as part of their broadcast journalist team. She pioneered the first USAF media outreach team in Iraq, and served as the on-location correspondent during combat, training and humanitarian missions in over 15 countries. She was the lead videographer for the USAF premier air demonstration team for the Air Combat Command and was an aerial videographer for the USAF Thunderbirds. In addition, Josie has provided media training to over one hundred military and civilian leaders to ensure accuracy and consistency of communications themes and messages.

Dr. Mariela Shirley (NIAAA) has renewed her part time detail assignment for 2013 to serve as a science officer to BBDB, DCNBR and NIDA's Child and Adolescent Workgroup.

Dr. Masaki Suzuki has joined the IRP's Chemical Biology Research Branch, Section on Drug Design and Synthesis as a Special Volunteer, on a two year sabbatical from Otsuka Pharmaceutical Co., Ltd., Japan.

Zoe Shieh joined the Information and Resource Management Branch (IRMB) in the NIDA Office of Management as an Information Technology Specialist (Information Security.) He will be supporting NIDA's IT systems and enhancing security programs, policies, procedures, and tools. Zoe was previously a Computer Analyst/Team Leader with Terrapin Systems and provided technical IT support to NIDA. Zoe has a Bachelor of Arts degree from the University of Maryland and Certifications in IT Security, Network Administration, and an A+ Certification in network hardware, installation, and troubleshooting.

New Appointments

Gaya Dowling, Ph.D. has been named Chief, Science Policy Branch, OSPC.

Glenda Conroy will be assuming the role of Acting NIDA Chief Information Officer (CIO) and was appointed as the NIDA Deputy Ethics Counselor.

Helio Chaves will serve as the Acting Chief, Information and Resource Management Branch (IRMB.)

Dr. Jag Khalsa, DPMCD, was on a detail to the Office of Assistant Secretary for Health (OASH), DHHS, to work on issues of viral hepatitis in IDUs. Currently, he is leading an effort to plan and present, in collaboration with other Federal partners (NIH [NIAID, NIDA, NIDDK], HRSA, SAMHSA, and CDC), an HHS-sponsored Technical Consultation on HCV infection in young IDUs.

Jennifer Cooke Katt, M.A. (formerly Jennifer Elcano) has been promoted to the role of Deputy Branch Chief, Science Policy Branch, OSPC.

Departures

Dr. Cecelia Spitznas of the Behavioral & Integrative Treatment Branch left NIDA December 15, 2013 and has accepted a new a position in the Office of Research & Data at the Office of National Drug Control Policy.

Garlin Hallas left her position of Management Analyst within the Management Analysis Branch, Office of Management at NIDA to start a new role at the FDA Center on Tobacco Products. She will be responsible for setting up the Risk Management program as well as writing policies and procedures for the Center.

Jennifer Bidle is leaving her position as the Branch Chief of the Management Analysis Branch, Office of Management, NIDA to start her new role as the Chief of the Management Analysis Section (MAS) within the Office of Administrative Management at the National Heart, Lung, and Blood Institute. As the Section Chief, Jennifer will be responsible for managing the formal management analysis functions for the IC.

Susan Cook has accepted a position as the Director, Division of Amenities and Transportation Services, Office of Research Services (ORS), NIH. Over the last seven years, Susan has been involved in several initiatives touching various programs at NIDA. She was instrumental in establishing the GMB Telework Program which included the NIDA hoteling suites. Also, she developed the NIDA Onboarding Program. While serving as the Acting CIO and Branch Chief for IRMB, as well as the Acting Branch Chief of MAB, she implemented NIH IT directives and the NIDA Risk Management program. She continued to serve as the NIDA Emergency Coordinator, A-76 Coordinator and Mandatory Training Coordinator. In 2010, Susan was appointed the NIDA Deputy Ethics Counselor by Dr. Raynard Kington and has strived to strengthen the NIDA ethics program.

Susan Nsangou, Chief of the Station Support/Simplified Acquisitions Branch in the NIDA COAC, has accepted the position of Acquisition Director of the Clinical Center where she will oversee all of the purchasing and contracts for NIH's clinical research hospital. Susan has worked at NIDA in the Branch Chief role since the COAC's inception in 2005 and has done an exceptional job supporting COAC customers and member Institutes. Under her leadership, the branch consistently achieved high customer satisfaction ratings for acquisitions support. Susan has also succeeded in training and mentoring junior staff members, assisting them in achieving individual goals.

Retirements

Ana Anders, previously Special Advisor in NIDA's Special Populations Office, retired in January after 51 years of federal service. Ana came to NIDA to help promote Hispanic researchers in drug abuse and helped establish National Hispanic Science Network, whose core mission is to improve the health equity of Hispanics through increasing research and fostering the development and advancement of Hispanic scientists. One of the NHSN's founding members, Dr. Hortensia Amaro, said of Ana, "Ana's contribution to the formation, development and success of the NHSN can't be overstated."

Jan Lipkin retired on December 31, 2012 after 15 years as the Deputy Branch Chief of the Public Information and Liaison Branch, OSPC. While at NIDA, Jan played a key role in coordinating all aspects of NIDA publications development, press activities, health campaigns, and development and growth of NIDA's Web site. She created and managed the NIDA Teen Web site, which has seen more than ten million visitors since 2005. She led the teams that built the HIV/AIDS "Learn the Link" campaign and most recently was the manager and creative force behind NIDA's Rx campaign for teens, "PEERx." She was also the PILB lead behind the HBO Addiction Special. Jan plans to spend her retirement years working at her beloved National Zoo, where she has been a volunteer for 20 years, working mostly with the reptiles and Great Apes.

Joan Nolan retired on January 3, 2013 from her role as NIDA's Publications, Graphics, and Exhibits Manager, a position she has held since 1980. As Publications Manager, she developed and executed NIDA's comprehensive long-range publications plan. She was responsible for all phases of publication development and execution, including maintaining standards, integrity, and continuity throughout NIDA's publication and graphic programs. As Exhibits Manager, she developed and implemented strategies for reaching NIDA's principal target audiences. Joan had been with NIDA since 1972, starting her career as an editorial assistant.

Sharan Jayne, Special Assistant to the Director for Media, retired on September 30, 2012. Sharan had a long and illustrious 33 year federal career in media management for high profile government directors. She joined the FDA in 1979 where she was a broadcast media advisor to six FDA Commissioners. She handled media appearances for Commissioner David Kessler during FDA's emerging years addressing tobacco. Sharan was also responsible for all aspects of the FDA's media strategy for 17 years until she moved to the Office of the Director at NIH. For the last seven years, Sharan was responsible for coordinating a number of articles highlighting NIDA science in publications including Time, Newsweek, AP, CNN, Bloomberg, and The New York Times.

Dr. Mark Green, Deputy Director, OEA, retired January 3, 2013 after a long and distinguished career in the Public Health Service and at the National Institutes of Health. Dr. Green was responsible for a variety of activities, including managing the processing of applications for Certificates of Confidentiality, serving as the Privacy Act Coordinator and managing clinicaltrials.com activities for the Institute as well as being the point of contact for R13 conference grant applications. Furthermore, he developed and administered a number of tracking procedures and data bases used not only by OEA but also by other parts of NIDA. Mark was recognized throughout the Institute as a resource on matters of extramural policies, procedures and practices and he served on many NIDA and NIH committees.

GRANTEE HONORS

The American Institutes for Research (AIR) was awarded the **2012 Mentor International Best Practice Award**, September 20, 2012. This Award bestowed by the Mentor Foundation recognizes AIR's *Good Behavior Game* program and model of training and support, as an example of evaluated best practice for preventing substance abuse. **Drs. Jeanne Poduska**, AIR, and **Sheppard Kellam**, Johns Hopkins University, accepted the award. The Mentor Foundation was founded in 1994 by Her Majesty Queen Silvia of Sweden in collaboration with the World Health Organization (WHO) as an independent, non-governmental, not for profit, working in the field of drug abuse prevention at a global level.

CTN -- New England Consortium

Dr. Roger Weiss, Principal Investigator of the New England Consortium, is the recipient of the 2012 Jack H. Mendelson Memorial Research Award from McLean Hospital. The late Dr. Mendelson was the Co-Director of the Alcohol and Drug Abuse Research Center at McLean Hospital and the first Chief of the National Center for Prevention and Control of Alcoholism at the National Institutes of Health. McLean Hospital established the annual research award for excellence in behavioral and biological research on substance abuse.

CTN-- Southern Consortium Node

Bob Hiott, Executive Director of Behavioral Health Services of Pickens County, was recently awarded the *Addiction Professional of the Year* by the South Carolina Association of Alcohol and Drug Abuse Counselors for his contribution to addiction services in the state. The Southern Consortium is incredibly grateful for the opportunity to work with their dedicated and talented community providers like Bob Hiott, who has been an integral part of their Node since they first joined the CTN. Beginning January 1, 2013, Bob will assume the role of Community Treatment Representative for the Southern Consortium Node and will work with Louise Haynes to promote collaboration with our community providers.