

Director's Report

to the

NATIONAL ADVISORY COUNCIL ON DRUG ABUSE

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** These sections contain select information. More comprehensive information will be posted in the [February 2014 Staff Report to the Director](#).*

RESEARCH HIGHLIGHTS

Division of Basic Neuroscience and Behavioral Research (DBNBR)

C57BL/6N Mutation In Cytoplasmic FMRP Interacting Protein 2 Regulates Cocaine

Response. Kumar V, Kim K, Joseph C, Kourrich S, Yoo SH, Huang HC, Vitaterna MH, de Villena FP, Churchill G, Bonci A, Takahashi JS. *Science*. 2013 Dec 20; 342(6165): 1508-1512.

The inbred mouse C57BL/6J is the reference strain for genome sequence and for most behavioral and physiological phenotypes. However, the International Knockout Mouse Consortium uses an embryonic stem cell line derived from a related C57BL/6N substrain. The authors found that C57BL/6N has a lower acute and sensitized response to cocaine and methamphetamine. They mapped a single causative locus and identified a nonsynonymous mutation of serine to phenylalanine (S968F) in Cytoplasmic FMRP interacting protein 2 (Cyfip2) as the causative variant. The S968F mutation destabilizes CYFIP2, and deletion of the C57BL/6N mutant allele leads to acute and sensitized cocaine-response phenotypes. The authors propose that CYFIP2 is a key regulator of cocaine response in mammals and present a framework to use mouse substrains to identify previously unknown genes and alleles regulating behavior.

A Novel Model Of Chronic Sleep Restriction Reveals An Increase In The Perceived Incentive Reward Value Of Cocaine In High Drug-Taking Rats.

Puhl MD, Boisvert M, Guan Z, Fang J, Grigson PS. *Pharmacol Biochem Behav*. 2013 Aug;109: 8-15.

Substance abuse and sleep deprivation are major problems in our society. Clinical studies suggest that measures of poor sleep quality effectively predict relapse to substance abuse. Previously, the authors' laboratory has shown that acute sleep deprivation increases the rate and efficiency (i.e., the goal-directed nature of responding) of cocaine self-administration using a progressive ratio (PR) schedule of reinforcement. However, the problem of sleep deprivation in our nation is largely one of chronicity. Therefore, the current study used a rodent model of chronic sleep restriction more akin to that experienced by humans (approximately 25% reduction in baseline sleep over the course of 8 days) to assess the impact of chronic sleep deprivation on cocaine-seeking and cocaine-taking behaviors in rats early during acquisition of self-administration. While low drug-taking rats were unaffected by chronic sleep restriction, high drug-takers in the chronic sleep restriction (CSR) group exhibited enhanced fixed ratio (FR) responding by the fourth day of FR training and significantly higher PR breakpoints than their non-sleep restriction (NSR) counterparts. This study is the first to directly assess the impact of chronic sleep deprivation on drug self-administration. These results show that chronic sleep deprivation early during acquisition of self-administration has a significant effect on the perceived incentive reward value of cocaine in high drug-takers, as indicated by both increased FR responding and an increased willingness to work for drug. Thus, it is important to be mindful of such factors in clinical settings designed for treatment of addiction and relapse prevention.

Optogenetic Evidence That Pallidal Projections, Not Nigral Projections, From the Nucleus Accumbens Core are Necessary For Reinstating Cocaine Seeking.

Stefanik MT, Kupchik YM, Brown RM, Kalivas PW. *J Neurosci* (2013); 33: 13654-13662.

The core subcompartment of the nucleus accumbens (NAcore) contributes significantly to behavioral responses following motivationally relevant stimuli, including drug-induced, stress-

induced, and cue-induced reinstatement of cocaine seeking. Projections from NAcore that could carry information necessary to initiate reinstated cocaine seeking include outputs via the indirect pathway to the dorsolateral subcompartment of the ventral pallidum (dlVP) and through the direct pathway to the medial substantia nigra (SN). Here the authors used an optogenetic strategy to determine whether the dlVP or nigral projections from the NAcore are necessary for cocaine seeking initiated by a cocaine and conditioned cue combination in rats extinguished from cocaine self-administration. Rats were pretreated in the NAcore with an adeno-associated virus expressing the inhibitory opsin archaerhodopsin, and fiber-optic cannulae were implanted above the indirect pathway axon terminal field in the dlVP, or the direct pathway terminal field in the SN. Inhibiting the indirect pathway to the dlVP, but not the direct pathway to the SN, prevented cocaine-plus-cue-induced reinstatement. The authors also examined projections back to the NAcore from the ventral tegmental area (VTA) and dlVP. Inhibiting the dlVP to NAcore projection did not alter, while inhibiting VTA afferents abolished reinstated cocaine seeking. Localization of green fluorescent protein reporter expression and whole-cell patch electrophysiology were used to verify opsin expression. These data reveal a circuit involving activation of VTA inputs to the NAcore and NAcore projections through the indirect pathway to the dlVP as critical for cocaine-plus-cue-induced reinstatement of cocaine seeking.

Methamphetamine Inhibits Toll-Like Receptor 9-Mediated Anti-HIV Activity In Macrophages. Cen P, Ye L, Su QJ, Wang X, Li JL, Lin XQ, Liang H, Ho WZ. *AIDS Res Hum Retroviruses*. 2013 Aug; 29(8): 1129-1137.

Toll-like receptor 9 (TLR9) is one of the key sensors that recognize viral infection/replication in the host cells. Studies have demonstrated that methamphetamine (METH) dysregulated host cell innate immunity and facilitated HIV infection of macrophages. In this study, we present new evidence that METH suppressed TLR9-mediated anti-HIV activity in macrophages. Activation of TLR9 by its agonist CpG-ODN 2216 inhibits HIV replication, which was demonstrated by increased expression of TLR9, interferon (IFN)- α , IFN regulatory factor-7 (IRF-7), myeloid differentiation factor 88 (MyD88), and myxovirus resistance gene A (MxA) in macrophages. However, METH treatment of macrophages greatly compromised the TLR9 signaling-mediated anti-HIV effect and inhibited the expression of TLR9 downstream signaling factors. Dopamine D1 receptor (D1R) antagonists (SCH23390) could block METH-mediated inhibition of anti-HIV activity of TLR9 signaling. Investigation of the underlying mechanisms of the METH action showed that METH treatment selectively down-regulated the expression of TLR9 on macrophages, whereas it had little effect on the expression of other TLRs. Collectively, these results provide further evidence that METH suppresses host cell innate immunity against HIV infection by down-regulating TLR9 expression and its signaling-mediated antiviral effect in macrophages.

Pregnenolone Can Protect the Brain From Cannabis Intoxication. Vallée M, Vitiello S, Bellocchio L, Hébert-Chatelain E, Monlezun S, Martin-Garcia E, Kasanetz F, Baillie GL, Panin F, Cathala A, Roullot-Lacarrière V, Fabre S, Hurst DP, Lynch DL, Shore DM, Deroche-Gamonet V, Spampinato U, Revest J-M, Maldonado R, Reggio PH, Ross RA, Marsicano G, Piazza PV. *Science* 2014; 343: 94.

Pregnenolone is considered the inactive precursor of all steroid hormones, and its potential functional effects have been largely uninvestigated. The administration of the main active principle of cannabis sativa (marijuana), Δ 9-tetrahydrocannabinol (THC), substantially increases the synthesis of pregnenolone in the brain via activation of the type-1 cannabinoid (CB1) receptor.

Pregnenolone then, acting as a signaling-specific inhibitor of the CB₁ receptor, reduces several effects of THC. This negative feedback mediated by pregnenolone reveals a previously unknown paracrine/autocrine loop protecting the brain from CB₁ receptor overactivation that could open an unforeseen approach for the treatment of cannabis intoxication and addiction.

Intravenous Prenatal Nicotine Exposure Increases Orexin Expression In the Lateral Hypothalamus And Orexin Innervation Of the Ventral Tegmental Area In Adult Male Rats.

Morgan AJ, Harrod SB, Lacy RT, Stanley EM, Fadel JR. Drug Alcohol Depend. 2013; 132(3): 562-570.

Approximately 18% of pregnant women continue to smoke tobacco cigarettes throughout pregnancy. Offspring exposed to tobacco smoke in utero exhibit a higher incidence of drug use in later stages of development relative to non-exposed children. Animal models indicate that prenatal nicotine (PN) exposure alone alters the development of the mesocorticolimbic dopamine (DA) system, which, in part, organizes motivated behavior and reward. The orexin/hypocretin neuropeptide system, which originates in the lateral hypothalamus (LH), projects to key areas of the mesocorticolimbic DA pathway. Previous research suggests that orexin exerts a major influence on motivation and reward. The present experiments determined if intravenous (IV) PN exposure alters (1) the expression of orexin neurons and melanin-concentrating hormone (MCH; positive control) in the LH; and (2) orexin projections from the LH onto DA neurons in the ventral tegmental area (VTA). Dams were injected with IV nicotine (0.05 mg/kg/injection) or saline 3×/day during gestational days 8-21. Tissues from adult male offspring (~130 days) were examined using immunohistochemistry. Relative to controls, offspring of IV PN exposure showed (1) increased numbers of orexin neurons in the LH, and no changes in the expression of MCH; and (2) increased orexin appositions on DA cells in the VTA. The findings indicate that the influence of PN exposure is enduring, and suggests that the PN-induced modification of orexin expression on mesolimbic circuitry may contribute to the reported changes in motivated behaviors related to food and drug reward observed in offspring prenatally exposed to nicotine.

A Common Biological Basis Of Obesity and Nicotine Addiction. Thorgeirsson TE, Gudbjartsson DF, Sulem P, Besenbacher S, Styrkarsdottir U, Thorleifsson G, Walters GB, Furberg H, Sullivan PF, Marchini J, McCarthy MI, Steinthorsdottir V, Thorsteinsdottir U, Stefansson K. Transl Psychiatry 2013; 3: e308.

Smoking influences body weight such that smokers weigh less than non-smokers and smoking cessation often leads to weight increase. The relationship between body weight and smoking is partly explained by the effect of nicotine on appetite and metabolism. However, the brain reward system is involved in the control of the intake of both food and tobacco. The authors evaluated the effect of single-nucleotide polymorphisms (SNPs) affecting body mass index (BMI) on smoking behavior, and tested the 32 SNPs identified in a meta-analysis for association with two smoking phenotypes, smoking initiation (SI) and the number of cigarettes smoked per day (CPD) in an Icelandic sample (N=34,216 smokers). Combined according to their effect on BMI, the SNPs correlate with both SI ($r=0.019$, $P=0.00054$) and CPD ($r=0.032$, $P=8.0 \times 10^{-7}$). These findings replicate in a second large data set (N=127,274, thereof 76,242 smokers) for both SI ($P=1.2 \times 10^{-5}$) and CPD ($P=9.3 \times 10^{-5}$). Notably, the variant most strongly associated with BMI (rs1558902-A in FTO) did not associate with smoking behavior. The association with smoking behavior is not due to the effect of the SNPs on BMI. These results strongly point to a common biological basis of

the regulation of our appetite for tobacco and food, and thus the vulnerability to nicotine addiction and obesity.

Nanometre-Scale Thermometry In A Living Cell. Kucsko G, Maurer PC, Yao NY, Kubo M, Noh HJ, Lo PK, Park H, Lukin MD. Nature 2013; 500(7460): 54-58.

Sensitive probing of temperature variations on nanometre scales is an outstanding challenge in many areas of modern science and technology. In particular, a thermometer capable of subdegree temperature resolution over a large range of temperatures as well as integration within a living system could provide a powerful new tool in many areas of biological, physical and chemical research. Possibilities range from the temperature-induced control of gene expression and tumour metabolism to the cell-selective treatment of disease and the study of heat dissipation in integrated circuits. By combining local light-induced heat sources with sensitive nanoscale thermometry, it may also be possible to engineer biological processes at the subcellular level. Here the authors demonstrate a new approach to nanoscale thermometry that uses coherent manipulation of the electronic spin associated with nitrogen-vacancy colour centres in diamond. Their technique makes it possible to detect temperature variations as small as 1.8mK (a sensitivity of 9mK Hz^(-1/2)) in an ultrapure bulk diamond sample. Using nitrogen-vacancy centres in diamond nanocrystals (nanodiamonds), the authors directly measure the local thermal environment on length scales as short as 200 nanometres. Finally, by introducing both nanodiamonds and gold nanoparticles into a single human embryonic fibroblast, they demonstrate temperature-gradient control and mapping at the subcellular level, enabling unique potential applications in life sciences.

Prolonged Dopamine Signalling In Striatum Signals Proximity and Value Of Distant Rewards. Howe MW, Tierney PL, Sandberg SG, Phillips PEM, Graybiel AM. Nature 2013; 500(7464): 575-579.

Predictions about future rewarding events have a powerful influence on behaviour. The phasic spike activity of dopamine-containing neurons, and corresponding dopamine transients in the striatum, are thought to underlie these predictions, encoding positive and negative reward prediction errors. However, many behaviours are directed towards distant goals, for which transient signals may fail to provide sustained drive. Here the authors report an extended mode of reward-predictive dopamine signalling in the striatum that emerged as rats moved towards distant goals. These dopamine signals, which were detected with fast-scan cyclic voltammetry (FSCV), gradually increased or--in rare instances--decreased as the animals navigated mazes to reach remote rewards, rather than having phasic or steady tonic profiles. These dopamine increases (ramps) scaled flexibly with both the distance and size of the rewards. During learning, these dopamine signals showed spatial preferences for goals in different locations and readily changed in magnitude to reflect changing values of the distant rewards. Such prolonged dopamine signalling could provide with class III PI3K complex components and Bcl-2. However, Beclin 2, but not Beclin 1, functions in an additional lysosomal degradation pathway. Beclin 2 is required for ligand-induced endolysosomal degradation of several G protein-coupled receptors (GPCRs) through its interaction with GASP1. Beclin 2 homozygous knockout mice have decreased embryonic viability, and heterozygous knockout mice have defective autophagy, increased levels of brain cannabinoid 1 receptor, elevated food intake, and obesity and insulin resistance. The authors' findings identify Beclin 2 as a converging regulator of autophagy and GPCR turnover and highlight the functional and mechanistic diversity of Beclin family members in autophagy, endolysosomal trafficking, and metabolism.

The Inhibitory Circuit Architecture Of the Lateral Hypothalamus Orchestrates Feeding.

Jennings JH, Rizzi G, Stamatakis AM, Ung RL, Stuber GD. *Science* 2013; 341(6153): 1517-1521. The growing prevalence of overeating disorders is a key contributor to the worldwide obesity epidemic. Dysfunction of particular neural circuits may trigger deviations from adaptive feeding behaviors. The lateral hypothalamus (LH) is a crucial neural substrate for motivated behavior, including feeding, but the precise functional neurocircuitry that controls LH neuronal activity to engage feeding has not been defined. The authors observed that inhibitory synaptic inputs from the extended amygdala preferentially innervate and suppress the activity of LH glutamatergic neurons to control food intake. These findings help explain how dysregulated activity at a number of unique nodes can result in a cascading failure within a defined brain network to produce maladaptive feeding.

Maturation Of Silent Synapses In Amygdala-Accumbens Projection Contributes To

Incubation Of Cocaine Craving. Lee BR, Ma YY, Huang YH, Wang X, Otaka M, Ishikawa M, Neumann PA, Graziane NM, Brown TE, Suska A, Guo C, Lobo MK, Sesack SR, Wolf ME, Nestler EJ, Shaham Y, Schluter OM, Dong Y. *Nat Neurosci* 2013; 16(11): 1644-1651.

In rat models of drug relapse and craving, cue-induced cocaine seeking progressively increases after withdrawal from the drug. This 'incubation of cocaine craving' is partially mediated by time-dependent adaptations at glutamatergic synapses in nucleus accumbens (NAc). However, the circuit-level adaptations mediating this plasticity remain elusive. The authors studied silent synapses, often regarded as immature synapses that express stable NMDA receptors with AMPA receptors being either absent or labile, in the projection from the basolateral amygdala to the NAc in incubation of cocaine craving. Silent synapses were detected in this projection during early withdrawal from cocaine. As the withdrawal period progressed, these silent synapses became unsilenced, a process that involved synaptic insertion of calcium-permeable AMPA receptors (CP-AMPA receptors). In vivo optogenetic stimulation-induced downregulation of CP-AMPA receptors at amygdala-to-NAc synapses, which re-silenced some of the previously silent synapses after prolonged withdrawal, decreased incubation of cocaine craving. These findings indicate that silent synapse-based reorganization of the amygdala-to-NAc projection is critical for persistent cocaine craving and relapse after withdrawal.

Cortical Activation Of Accumbens Hyperpolarization-Active NMDARS Mediates Aversion-Resistant Alcohol Intake.

Seif T, Chang SJ, Simms JA, Gibb SL, Dadgar J, Chen BT, Harvey BK, Ron D, Messing RO, Bonci A, Hopf FW. *Nat Neurosci* 2013; 16(8): 1094-1100.

Compulsive drinking despite serious adverse medical, social and economic consequences is a characteristic of alcohol use disorders in humans. Although frontal cortical areas have been implicated in alcohol use disorders, little is known about the molecular mechanisms and pathways that sustain aversion-resistant intake. Here, the authors show that nucleus accumbens core (NAcore) NMDA-type glutamate receptors and medial prefrontal (mPFC) and insula glutamatergic inputs to the NAcore are necessary for aversion-resistant alcohol consumption in rats. Aversion-resistant intake was associated with a new type of NMDA receptor adaptation, in which hyperpolarization-active NMDA receptors were present at mPFC and insula but not amygdalar inputs in the NAcore. Accordingly, inhibition of Grin2c NMDA receptor subunits in the NAcore reduced aversion-resistant alcohol intake. None of these manipulations altered intake when alcohol was not paired with an aversive consequence. These results identify a mechanism by which hyperpolarization-

active NMDA receptors under mPFC- and insula-to-NAcore inputs sustain aversion-resistant alcohol intake.

DNA Methylation Regulates Associative Reward Learning. Day JJ, Childs D, Guzman-Karlsson MC, Kibe M, Moulden J, Song E, Tahir A, Sweatt JD. Nat Neurosci 2013; 16(10): 1445-1452. Reward-related memories are essential for adaptive behavior and evolutionary fitness, but they are also a core component of maladaptive brain diseases such as addiction. Reward learning requires dopamine neurons located in the ventral tegmental area (VTA), which encode relationships between predictive cues and future rewards. Recent evidence suggests that epigenetic mechanisms, including DNA methylation, are essential regulators of neuronal plasticity and experience-driven behavioral change. However, the role of epigenetic mechanisms in reward learning is poorly understood. Here the authors show that the formation of reward-related associative memories in rats upregulates key plasticity genes in the VTA, which are correlated with memory strength and associated with gene-specific changes in DNA methylation. Moreover, DNA methylation in the VTA is required for the formation of stimulus-reward associations. These results provide the first evidence that activity-dependent methylation and demethylation of DNA is an essential substrate for the behavioral and neuronal plasticity driven by reward-related experiences.

ReaChR: A Red-Shifted Variant Of Channelrhodopsin Enables Deep Transcranial Optogenetic Excitation. Lin JY, Knutsen PM, Muller A, Kleinfeld D, Tsien RY. Nat Neurosci 2013; 16(10): 1499-1508.

Channelrhodopsins (ChRs) are used to optogenetically depolarize neurons. The authors engineered a variant of ChR, denoted red-activatable ChR (ReaChR), that is optimally excited with orange to red light ($\lambda \sim 590\text{-}630$ nm) and offers improved membrane trafficking, higher photocurrents and faster kinetics compared to existing red-shifted ChRs. Red light is less scattered by tissue and is absorbed less by blood than the blue to green wavelengths that are required by other ChR variants. The authors used ReaChR expressed in the vibrissa motor cortex to drive spiking and vibrissa motion in awake mice when excited with red light through intact skull. Precise vibrissa movements were evoked by expressing ReaChR in the facial motor nucleus in the brainstem and illumination with red light through the external auditory canal. Thus, ReaChR enables transcranial optical activation of neurons in deep brain structures without the need to surgically thin the skull, form a transcranial window or implant optical fibers.

A Unique Population Of Ventral Tegmental Area Neurons Inhibits The Lateral Habenula To Promote Reward. Stamatakis AM, Jennings JH, Ung RL, Blair GA, Weinberg RJ, Neve RL, Boyce F, Mattis J, Ramakrishnan C, Deisseroth K, Stuber GD. Neuron 2013; 80(4): 1039-1053. Lateral habenula (LHb) neurons convey aversive and negative reward conditions through potent indirect inhibition of ventral tegmental area (VTA) dopaminergic neurons. Although VTA dopaminergic neurons reciprocally project to the LHb, the electrophysiological properties and the behavioral consequences associated with selective manipulations of this circuit are unknown. Here, the authors identify an inhibitory input to the LHb arising from a unique population of VTA neurons expressing dopaminergic markers. Optogenetic activation of this circuit resulted in no detectable dopamine release in LHb brain slices. Instead, stimulation produced GABA-mediated inhibitory synaptic transmission, which suppressed the firing of postsynaptic LHb neurons in brain slices and increased the spontaneous firing rate of VTA dopaminergic neurons in vivo. Furthermore, in vivo activation of this pathway produced reward-related phenotypes that were dependent on

intra-LHb GABAA receptor signaling. These results suggest that noncanonical inhibitory signaling by these hybrid dopaminergic-GABAergic neurons act to suppress LHb output under rewarding conditions.

Nicotine Decreases Ethanol-Induced Dopamine Signaling And Increases Self-Administration Via Stress Hormones. Doyon WM, Dong Y, Ostroumov A, Thomas AM, Zhang TA, Dani JA. *Neuron* 2013; 79(3): 530-540.

Tobacco smoking is a well-known risk factor for subsequent alcohol abuse, but the neural events underlying this risk remain largely unknown. Alcohol and nicotine reinforcement involve common neural circuitry, including the mesolimbic dopamine system. The authors demonstrate in rodents that pre-exposure to nicotine increases alcohol self-administration and decreases alcohol-induced dopamine responses. The blunted dopamine response was due to increased inhibitory synaptic transmission onto dopamine neurons. Blocking stress hormone receptors prior to nicotine exposure prevented all interactions with alcohol that we measured, including the increased inhibition onto dopamine neurons, the decreased dopamine responses, and the increased alcohol self-administration. These results indicate that nicotine recruits neuroendocrine systems to influence neurotransmission and behavior associated with alcohol reinforcement.

Increasing Dopamine D2 Receptor Expression In the Adult Nucleus Accumbens Enhances Motivation. Trifilieff P, Feng B, Urizar E, Winiger V, Ward RD, Taylor KM, Martinez D, Moore H, Balsam PD, Simpson EH, Javitch JA. *Mol Psychiatry* 2013; 18(9): 1025-1033.

A decrease in dopamine D2 receptor (D2R) binding in the striatum is one of the most common findings in disorders that involve a dysregulation of motivation, including obesity, addiction and attention deficit hyperactivity disorder. As disruption of D2R signaling in the ventral striatum--including the nucleus accumbens (NAc)--impairs motivation, the authors sought to determine whether potentiating postsynaptic D2R-dependent signaling in the NAc would improve motivation. In this study, they used a viral vector strategy to overexpress postsynaptic D2Rs in either the NAc or the dorsal striatum. They investigated the effects of D2R overexpression on instrumental learning, willingness to work, use of reward value representations and modulation of motivation by reward associated cues. Overexpression of postsynaptic D2R in the NAc selectively increased motivation without altering consummatory behavior, the representation of the value of the reinforcer, or the capacity to use reward associated cues in flexible ways. In contrast, D2R overexpression in the dorsal striatum did not alter performance on any of the tasks. Thus, consistent with numerous studies showing that reduced D2R signaling impairs motivated behavior, these data show that postsynaptic D2R overexpression in the NAc specifically increases an animal's willingness to expend effort to obtain a goal. Taken together, these results provide insight into the potential impact of future therapeutic strategies that enhance D2R signaling in the NAc.

Impaired Periamygdaloid-Cortex Prodynorphin Is Characteristic Of Opiate Addiction and Depression. Anderson SAR, Michaelides M, Zarnegar P, Ren Y, Fagergren P, Thanos PK, Wang GJ, Bannon M, Neumaier JF, Keller E, Volkow ND, Hurd YL. *J Clin Invest* 2013.

Negative affect is critical for conferring vulnerability to opiate addiction as reflected by the high comorbidity of opiate abuse with major depressive disorder (MDD). Rodent models implicate amygdala prodynorphin (Pdyn) as a mediator of negative affect; however, evidence of PDYN involvement in human negative affect is limited. Here, the authors found reduced PDYN mRNA expression in the postmortem human amygdala nucleus of the periamygdaloid cortex (PAC) in both

heroin abusers and MDD subjects. Similar to humans, rats that chronically self-administered heroin had reduced Pdyn mRNA expression in the PAC at a time point associated with a negative affective state. Using the in vivo functional imaging technology DREAMM (DREADD-assisted metabolic mapping, where DREADD indicates designer receptors exclusively activated by designer drugs), they found that selective inhibition of Pdyn-expressing neurons in the rat PAC increased metabolic activity in the extended amygdala, which is a key substrate of the extrahypothalamic brain stress system. In parallel, PAC-specific Pdyn inhibition provoked negative affect-related physiological and behavioral changes. Altogether, this translational study supports a functional role for impaired Pdyn in the PAC in opiate abuse through activation of the stress and negative affect neurocircuitry implicated in addiction vulnerability.

Bispecific Antibodies Directed to CD4 Domain 2 and HIV Envelope Exhibit Exceptional Breadth and Picomolar Potency Against HIV-1. Pace CS, Song R, Ochsenbauer C, Andrews CD, Franco D, Yu J, Oren DA, Seaman MS, Ho DD. Proc Natl Acad Sci U S A 2013; 110(33): 13540-13545.

In the absence of an effective HIV-1 vaccine, passive immunization using broadly neutralizing Abs or Ab-like molecules could provide an alternative to the daily administration of oral antiretroviral agents that has recently shown promise as preexposure prophylaxis. Currently, no single broadly neutralizing Ab (bNAb) or combination of bNAbs neutralizes all HIV-1 strains at practically achievable concentrations in vivo. To address this problem, the authors created bispecific Abs that combine the HIV-1 inhibitory activity of ibalizumab (iMab), a humanized mAb directed to domain 2 of human CD4, with that of anti-gp120 bNAbs. These bispecific bNAbs (BibNAbs) exploit iMab's potent anti-HIV-1 activity and demonstrated clinical efficacy and safety to anchor and thereby concentrate a second broadly neutralizing agent at the site of viral entry. Two BibNAbs, PG9-iMab and PG16-iMab, exhibit exceptional breadth and potency, neutralizing 100% of the 118 viruses tested at low picomolar concentrations, including viruses resistant to both parental mAbs. The enhanced potency of these BibNAbs was entirely dependent on CD4 anchoring, not on membrane anchoring per se, and required optimal Ab geometry and linker length. The authors propose that iMab-based BibNAbs, such as PG9-iMab and PG16-iMab, are promising candidates for passive immunization to prevent HIV-1 infection.

NR2B Subunit Of the NMDA Glutamate Receptor Regulates Appetite In the Parabrachial Nucleus. Wu Q, Zheng R, Srisai D, McKnight GS, Palmiter RD. Proc Natl Acad Sci U S A 2013; 110(36): 14765-14770.

Diphtheria toxin-mediated, acute ablation of hypothalamic neurons expressing agouti-related protein (AgRP) in adult mice leads to anorexia and starvation within 7 d that is caused by hyperactivity of neurons within the parabrachial nucleus (PBN). Because NMDA glutamate receptors are involved in various synaptic plasticity-based behavioral modifications, the authors hypothesized that modulation of the NR2A and NR2B subunits of the NMDA receptor in PBN neurons could contribute to the anorexia phenotype. They observed by Western blot analyses that ablation of AgRP neurons results in enhanced expression of NR2B along with a modest suppression of NR2A. Interestingly, systemic administration of LiCl in a critical time window before AgRP neuron ablation abolished the anorectic response. LiCl treatment suppressed NR2B levels in the PBN and ameliorated the local Fos induction that is associated with anorexia. This protective role of LiCl on feeding was blunted in vagotomized mice. Chronic infusion of RO25-6981, a selective NR2B inhibitor, into the PBN recapitulated the role of LiCl in maintaining feeding after AgRP

neuron ablation. The authors suggest that the accumulation of NR2B subunits in the PBN contributes to aphagia in response to AgRP neuron ablation and may be involved in other forms of anorexia.

Division of Clinical Neuroscience and Behavioral Research (DCNBR)

Web-Based Behavioral Treatment for Substance Use Disorders as a Partial Replacement of Standard Methadone Maintenance Treatment. Marsch LA, Guarino H, Acosta M, Aponte-Melendez Y, Cleland C, Grabinski M, Brady R, Edwards J. *J Subst Abuse Treat.* 2014 Jan; 46(1): 43-51.

This study is the first experimental trial to evaluate the effectiveness of a Web-based behavioral intervention when deployed in a model where it partially substituted for standard counseling in a community-based specialty addiction treatment program. New opioid-dependent intakes in methadone maintenance treatment (n=160) were randomly assigned for 12 months to either: (1) standard treatment or (2) reduced standard treatment plus a Web-based psychosocial intervention, the Therapeutic Education System (TES). Results demonstrated that replacing a portion of standard treatment with TES resulted in significantly greater rates of objectively measured opioid abstinence (48% vs. 37% abstinence across all study weeks; $F(1, 158)=5.90$, $p<.05$ and 59% vs. 43% abstinence on weeks participants provided urine samples for testing; $F(1, 158)=8.81$, $p<.01$). This result was robust and was evident despite how opioid abstinence was operationally defined and evaluated. The potential implications for service delivery models within substance abuse treatment programs and other healthcare entities are discussed.

CYP2B6 SNPs are Associated with Methadone Dose Required for Effective Treatment of Opioid Addiction. Levrán O, Peles E, Hamon S, Randesi M, Adelson M, Kreek MJ. *Addiction Biology* 2013; 18: 709–716.

Adequate methadone dosing in methadone maintenance treatment (MMT) for opioid addiction is critical for therapeutic success. One of the challenges in dose determination is the inter-individual variability in dose-response. Methadone metabolism is attributed primarily to cytochrome P450 enzymes CYP3A4, CYP2B6 and CYP2D6. The CYP2B6*6 allele [single nucleotide polymorphisms (SNPs) 785A>G (rs2279343) and 516G>T (rs3745274)] was associated with slow methadone metabolism. To explore the effects of CYP2B6*6 allele on methadone dose requirement, it was genotyped in a well-characterized sample of 74 Israeli former heroin addicts in MMT. The sample is primarily of Middle Eastern/European ancestry, based on ancestry informative markers (AIMs). Only patients with no major co-medication that may affect methadone metabolism were included. The stabilizing daily methadone dose in this sample ranges between 13 and 260 mg (mean 140.52 mg). The mean methadone doses required by subjects homozygous for the variant alleles of the CYP2B6 SNPs 785A>G and 516G>T (88, 96 mg, respectively) were significantly lower than those of the heterozygotes (133, 129 mg, respectively) and the non-carriers (150, 151 mg, respectively) (nominal $P = 0.012$, 0.048 , respectively). The results remain significant after controlling for age, sex and the ABCB1 SNP 1236C>T (rs1128503), which was previously shown to be associated with high methadone dose requirement in this population ($P = 0.006$, 0.030 , respectively). An additional 77 CYP2B6, CYP3A4 and CYP2D6 SNPs were genotyped. Of these, 24 SNPs were polymorphic and none showed significant association with methadone dose. Further studies are necessary to replicate these preliminary findings in additional subjects and other populations.

Association between Nicotine Dependence Severity, BOLD Response to Smoking Cues, and Functional Connectivity.

Claus ED, Blaine SK, Filbey FM, Mayer AR, Hutchison KE. *Neuropsychopharmacology* 2013 Nov; 38(12): 2363-2372.

Enhanced motivational salience towards smoking cues is a consequence of chronic nicotine use, but the degree to which this value increases beyond that of other appetitive cues is unknown. In addition, it is unclear how connectivity between brain regions influences cue reactivity and how cue reactivity and functional connectivity are related to nicotine dependence severity. This study examined neural responses during the presentation of smoking cues and appetitive control cues, as well as functional connectivity in 116 smokers with a range of nicotine dependence severity. Smoking cues elicited greater response above baseline than food cues in orbitofrontal cortex (OFC) and supplementary motor area (SMA) and less deactivation below baseline in middle frontal gyrus, inferior parietal lobe, and middle temporal gyrus. Psychophysiological interaction (PPI) analysis using right OFC as a seed revealed increased connectivity with somatosensory cortex and lateral inferior parietal lobe during smoking cues compared with food cues. Similarly, a PPI analysis using left insula as a seed showed stronger connectivity with somatosensory cortex, right insula, OFC, and striatum. Finally, relationships with nicotine dependence scores showed enhanced response in insula and dorsal anterior cingulate cortex in the smoking vs. food comparison, and increased connectivity between insula and circuits involved in motivated behavior. Combined, these results suggest that smokers engage attentional networks and default mode networks involved in self-referential processing to a greater degree during smoking cues. In addition, individuals with greater nicotine dependence severity show increased engagement of sensorimotor and motor preparation circuits, suggesting increased reliance on habitual behavior.

White Matter Characterization of Adolescent Binge Drinking with and without Co-occurring Marijuana Use: A 3-year Investigation.

Jacobus J, Squeglia LM, Bava S, Tapert SF. *Psychiatry Res.* 2013 Dec 30; 214(3):374-381.

The aims of this study were to investigate the consequences of prolonged patterns of alcohol and marijuana use on white matter integrity and neurocognitive functioning in late adolescence, and examine neurodevelopmental trajectories over three years of regular follow-up visits. Three groups of demographically similar teens received assessments every 1.5 years (controls with consistently minimal substance use, n=16; teens who gradually increase their heavy episodic drinking n=17, and continuous binge drinkers with heavy marijuana use, n=21), including comprehensive neuropsychological evaluations, diffusion tensor imaging, and detailed substance use interviews. One-way ANOVA identified fifteen white matter clusters that significantly differed between groups at 3-year follow-up, ages 19-22; controls consistently demonstrated higher values of tissue integrity across fiber tracts. Repeated measures ANOVA revealed significant declines in white matter integrity from baseline to 3-year follow-up in the subsample of substance users, along with poorer global neurocognitive performance in alcohol users with heavy marijuana use by the 18-month follow-up. Findings suggest healthier brain white matter microstructure and better neurocognitive performance for teens free from heavy alcohol and marijuana use. Long-term engagement in these substances may adversely influence white matter and increase vulnerability for development of neuropathology purported to underlie future risk-taking and addictive behaviors.

Analyse Study of Peer Influence on Risk-Taking Behavior in Older Adolescents. Reynolds EK, Macpherson L, Schwartz S, Fox NA, Lejuez CW. Prev Sci. 2013 Oct 11. [Epub ahead of print]. This experimental study aimed to examine whether adolescents act in a riskier manner in the presence of peers and whether peer presence alone influences risk behavior or if a direct influence process is necessary. Utilizing a behavioral task assessing risk-taking, 183 older adolescents (18-20 year olds) came to the laboratory alone once and then were randomized to one of three conditions as follows: alone, peers present, and peers encouraging. An interaction was found such that at baseline, there were no significant differences between the three conditions, but at the experimental session, there was a significant increase in risk task scores particularly for the encouraging condition. These findings challenge proposed models of the interaction between peer influence and risk taking by providing evidence that adolescents take more risks when being encouraged by peers, but that the presence of peers on its own does not lead to more risks than when completing the task alone.

Robust Changes in Reward Circuitry during Reward Loss in Current and Former Cocaine Users during Performance of a Monetary Incentive Delay Task. Patel KT, Stevens MC, Meda SA, Muska C, Thomas AD, Potenza MN, Pearlson GD. Biol Psychiat. 2013 Oct 1; 74(7): 529-537. Abnormal function in reward circuitry in cocaine addiction could predate drug use as a risk factor, follow drug use as a consequence of substance-induced alterations, or both. The authors used a functional magnetic resonance imaging monetary incentive delay task (MIDT) to investigate reward-loss neural response differences among 42 current cocaine users, 35 former cocaine users, and 47 healthy subjects who also completed psychological measures and tasks related to impulsivity and reward. They found various reward processing-related group differences in several MIDT phases. Across task phases the authors found a control > current user > former user activation pattern, except for loss outcome, where former compared with current cocaine users activated ventral tegmental area more robustly. They also found regional prefrontal activation differences during loss anticipation between cocaine-using groups. Both groups of cocaine users scored higher than control subjects on impulsivity, compulsivity and reward-punishment sensitivity factors. In addition, impulsivity-related factors correlated positively with activation in amygdala and negatively with anterior cingulate activation during loss anticipation. Compared with healthy subjects, both former and current users displayed abnormal brain activation patterns during MIDT performance. Both cocaine groups differed similarly from healthy subjects, but differences between former and current users were localized to the ventral tegmental area during loss outcome and to prefrontal regions during loss anticipation, suggesting that long-term cocaine abstinence does not normalize most reward circuit abnormalities. Elevated impulsivity-related factors that relate to loss processing in current and former users suggest that these tendencies and relationships may pre-exist cocaine addiction.

Alterations in Endogenous Opioid Functional Measures in Chronic Back Pain. Martikainen IK, Peciña M, Love TM, Nuechterlein EB, Cummiford CM, Green CR, Harris RE, Stohler CS, Zubieta JK. J Neurosci. 2013 Sep 11;33(37): 14729-14737.

The absence of consistent end organ abnormalities in many chronic pain syndromes has led to a search for maladaptive CNS mechanisms that may explain their clinical presentations and course. Here, the authors addressed the role of brain regional μ -opioid receptor-mediated neurotransmission, one of the best recognized mechanisms of pain regulation, in chronic back pain in human subjects. They compared μ -opioid receptor availability in vivo at baseline, during pain expectation, and with moderate levels of sustained pain in 16 patients with chronic nonspecific back

pain (CNBP) and in 16 age- and gender-matched healthy control subjects, using the μ -opioid receptor-selective radioligand [(11)C]carfentanil and positron emission tomography. The authors found that CNBP patients showed baseline increases in thalamic μ -opioid receptor availability, contrary to a previously studied sample of patients diagnosed with fibromyalgia. During both pain expectation and sustained pain challenges, CNBP patients showed regional reductions in the capacity to activate this neurotransmitter system compared with their control sample, further associated with clinical pain and affective state ratings. These results demonstrate heterogeneity in endogenous opioid system functional measures across pain conditions, and alterations in both receptor availability and endogenous opioid function in CNBP that are relevant to the clinical presentation of these patients and the effects of opioid analgesics on μ -opioid receptors.

MDMA Decreases the Effects of Simulated Social Rejection. Frye CG, Wardle MC, Norman GJ, de Wit H. *Pharmacol Biochem Behav.* 2013 Dec 3. [Epub ahead of print]
3-4-Methylenedioxymethamphetamine (MDMA) increases self-reported positive social feelings and decreases the ability to detect social threat in faces, but its effects on experiences of social acceptance and rejection have not been determined. The authors examined how an acute dose of MDMA affects subjective and autonomic responses to simulated social acceptance and rejection. They predicted that MDMA would decrease subjective responses to rejection. On an exploratory basis, they also examined the effect of MDMA on respiratory sinus arrhythmia (RSA), a measure of parasympathetic cardiac control often thought to index social engagement and emotional regulation. Over three sessions, healthy adult volunteers with previous MDMA experience (N=36) received capsules containing placebo, 0.75 or 1.5mg/kg of MDMA under counter-balanced double-blind conditions. During expected peak drug effect, participants played two rounds of a virtual social simulation task called "Cyberball" during which they experienced acceptance in one round and rejection in the other. During the task we also obtained electrocardiograms (ECGs), from which we calculated RSA. After each round, participants answered questionnaires about their mood and self-esteem. As predicted, MDMA decreased the effect of simulated social rejection on self-reported mood and self-esteem and decreased perceived intensity of rejection, measured as the percent of ball tosses participants reported receiving. Consistent with its sympathomimetic properties, MDMA decreased RSA as compared to placebo. This finding that MDMA decreases perceptions of rejection in simulated social situations extends previous results indicating that MDMA reduces perception of social threat in faces. Together these findings suggest a cognitive mechanism by which MDMA might produce pro-social behavior and feelings and how the drug might function as an adjunct to psychotherapy. These phenomena merit further study in non-simulated social environments.

Endogenous Opioid Function Mediates the Association Between Laboratory-evoked Pain Sensitivity and Morphine Analgesic Responses. Bruehl S, Burns JW, Gupta R, Buvanendran A, Chont M, Kinner E, Schuster E, Passik S, France CR. *Pain.* 2013 Sep; 154(9): 1856-1864.

Predictors of responsiveness to opioid analgesic medications are not well understood. This study tested whether individual differences in endogenous opioid (EO) function are associated with analgesic responsiveness to morphine. In randomized, counterbalanced order over 3 sessions, 45 chronic low back pain participants and 31 healthy controls received an opioid antagonist (8 mg naloxone), morphine (0.08 mg/kg), or placebo. Participants then engaged in 2 laboratory-evoked pain tasks (ischemic and thermal). Outcomes included pain threshold, pain tolerance, and pain

ratings. Indexes of EO function and morphine analgesic responsiveness were derived for each measure as the difference in pain responses between the placebo condition and naloxone or morphine condition, respectively. For all 7 pain measures across the 2 laboratory pain tasks, greater EO function was associated with significantly lower morphine analgesic responsiveness ($P < 0.001$ - $P = 0.02$). Morphine reduced pain responses of low EO individuals to levels similar to those of high EO individuals receiving placebo. Higher placebo condition-evoked pain sensitivity was associated with significantly greater morphine analgesic responsiveness for 5 of 7 pain measures ($P < 0.001$ - $P = 0.02$). These latter associations were significantly mediated by EO function for 4 of these 5 pain outcomes (all P values < 0.05). In the laboratory-evoked pain context, opioid analgesic medications may supplement inadequate EO analgesia, with little incremental benefit in those with preexisting high EO function. Implications for personalized medicine are discussed.

Real-Time fMRI Links Subjective Experience with Brain Activity during Focused Attention.

Garrison KA, Scheinost D, Worhunsky PD, Elwafi HM, Thornhill TA 4th, Thompson E, Saron C, Desbordes G, Kober H, Hampson M, Gray JR, Constable RT, Papademetris X, Brewer JA. *Neuroimage*. 2013 Nov 1; 81: 110-118.

Recent advances in brain imaging have improved the measure of neural processes related to perceptual, cognitive and affective functions, yet the relation between brain activity and subjective experience remains poorly characterized. In part, it is a challenge to obtain reliable accounts of participant's experience in such studies. Here the authors addressed this limitation by utilizing experienced meditators who are expert in introspection. They tested a novel method to link objective and subjective data, using real-time fMRI (rt-fMRI) to provide participants with feedback of their own brain activity during an ongoing task. They provided real-time feedback during a focused attention task from the posterior cingulate cortex, a hub of the default mode network shown to be activated during mind-wandering and deactivated during meditation. In a first experiment, both meditators and non-meditators reported significant correspondence between the feedback graph and their subjective experience of focused attention and mind-wandering. When instructed to volitionally decrease the feedback graph, meditators, but not non-meditators, showed significant deactivation of the posterior cingulate cortex. The authors were able to replicate these results in a separate group of meditators using a novel step-wise rt-fMRI discovery protocol in which participants were not provided with prior knowledge of the expected relationship between their experience and the feedback graph (i.e., focused attention versus mind-wandering). These findings support the feasibility of using rt-fMRI to link objective measures of brain activity with reports of ongoing subjective experience in cognitive neuroscience research, and demonstrate the generalization of expertise in introspective awareness to novel contexts.

Division of Epidemiology, Services and Prevention Research (DESPR)

Genetic and Environmental Influences On The Familial Transmission Of Externalizing Disorders In Adoptive And Twin Offspring. Hicks BM, Foster KT; Iacono WG, McGue M. *JAMA Psychiatry*. 2013; 70 (10):1076-83.

Twin-family studies have shown that parent-child resemblance on substance use disorders and antisocial behavior can be accounted for by the transmission of a general liability to a spectrum of externalizing disorders. Most studies, however, include only biological parents and offspring, which confound genetic and environmental transmission effects. The objective of this study was to

examine the familial transmission of externalizing disorders among both adoptive (genetically unrelated) and biological relatives to better distinguish genetic and environmental mechanisms of transmission. This was a family study design wherein each family included the mother, father, and 2 offspring, including monozygotic twin, dizygotic twin, nontwin biological, and adoptive offspring. Structural equation modeling was used to estimate familial transmission effects and their genetic and environmental influences. Participants were recruited from the community and assessed at a university laboratory. Participants comprised a total of 1,590 families with biological offspring and 409 families with adoptive offspring. Offspring participants were young adults (mean age, 26.2 years). Main outcomes measures were symptom counts of conduct disorder, adult antisocial behavior, and alcohol, nicotine, and drug dependence. Results indicated that there was a medium effect for the transmission of the general externalizing liability for biological parents ($r=0.27-0.30$) but not for adoptive parents ($r=0.03-0.07$). In contrast, adoptive siblings exhibited significant similarity on the general externalizing liability ($r=0.21$). Biometric analyses revealed that the general externalizing liability was highly heritable ($a^2=0.61$) but also exhibited significant shared environmental influences ($c^2=0.20$). The authors conclude that parent-child resemblance for substance use disorders and antisocial behavior is primarily due to the genetic transmission of a general liability to a spectrum of externalizing disorders. Including adoptive siblings revealed a greater role of shared environmental influences on the general externalizing liability than previously detected in twin studies and indicates that sibling rather than parent-child similarity indexes important environmental risk factors for externalizing disorders.

[Opening The "Black Box": Family Check-Up Intervention Effects On Self-Regulation That Prevents Growth In Problem Behavior and Substance Use.](#) Fosco GM, Frank JL, Stormshak EA, Dishion T. *J Sch Psychol.* 2013; 51 (4): 455-468.

Family-school interventions are a well-established method for preventing and remediating behavior problems in at-risk youth, yet the mechanisms of change underlying their effectiveness are often overlooked or poorly understood. The Family Check-Up (FCU), a school-based, family-centered intervention, has been consistently associated with reductions in youth antisocial behavior, deviant peer group affiliation, and substance use. The purpose of this study was to explore proximal changes in student-level behavior that accounts for links between implementation of the FCU and changes in youth problem behavior. Data were drawn from a randomized controlled trial study of the efficacy of the FCU among 593 ethnically diverse middle school students followed longitudinally from 6th through 8th grades. Latent growth curve analyses revealed that random assignment to the FCU intervention condition was related to increased mean levels of students' self-regulation from 6th to 7th grades, which in turn reduced the risk for growth in antisocial behavior, involvement with deviant peers, and alcohol, tobacco, and marijuana use through the 8th grade. Overall, these findings highlight the robust implications of self-regulation as a proximal target for family-centered interventions.

[The Predictive Utility Of A Brief Kindergarten Screening Measure Of Child Behavior Problems.](#) Racz SJ, King KM, Wu J, Witkiewitz K, McMahon RJ. *J Consult Clin Psychol.* 2013; 81 (4): 588-599.

Kindergarten teacher ratings, such as those from the Teacher Observation of Classroom Adaptation-Revised (TOCA-R), are a promising cost- and time-effective screening method to identify children at risk for later problems. Previous research with the TOCA-R has been mainly limited to outcomes in a single domain measured during elementary school. The goal of the current study was to

examine the ability of TOCA-R sum scores to predict outcomes in multiple domains across distinct developmental periods (i.e., late childhood, middle adolescence, late adolescence). The authors used data from the Fast Track Project, a large multisite study with children at risk for conduct problems (n = 752; M age at start of study = 6.55 years; 57.7% male; 49.9% Caucasian, 46.3% African American). Kindergarten TOCA-R sum scores were used as the predictor in regression analyses; outcomes included school difficulties, externalizing diagnoses and symptom counts, and substance use. TOCA-R sum scores predicted school outcomes at all time points, diagnosis of ADHD in 9th grade, several externalizing disorder symptom counts, and cigarette use in 12th grade. The findings demonstrate the predictive utility of the TOCA-R when examining outcomes within the school setting. Therefore, these results suggest the 10-item TOCA-R may provide a quick and accurate screening of children at risk for later problems. Implications for prevention and intervention programs are discussed.

[A Randomized Trial Of A Hepatitis Care Coordination Model In Methadone Maintenance Treatment.](#) Masson CL, Delucchi KL, McKnight C, Hetteema J, Khalili M, Min A, Jordan AE et al., *Am J Public Health.* 2013; 103 (10):e81-e88.

The authors evaluated the efficacy of a hepatitis care coordination intervention to improve linkage to hepatitis A virus (HAV) and hepatitis B virus (HBV) vaccination and clinical evaluation of hepatitis C virus (HCV) infection among methadone maintenance patients. The authors conducted a randomized controlled trial of 489 participants from methadone maintenance treatment programs in San Francisco, California, and New York City from February 2008 through June 2011. They randomized participants to a control arm (n = 245) and an intervention arm (n = 244), which included on-site screening, motivational-enhanced education and counseling, on-site vaccination, and case management services. Compared with the control group, intervention group participants were significantly more likely (odds ratio [OR] = 41.8; 95% confidence interval [CI] = 19.4, 90.0) to receive their first vaccine dose within 30 days and to receive an HCV evaluation within 6 months (OR = 4.10; 95% CI = 2.35, 7.17). A combined intervention adherence outcome that measured adherence to HAV-HBV vaccination, HCV evaluation, or both strongly favored the intervention group (OR = 8.70; 95% CI = 5.56, 13.61). Hepatitis care coordination was efficacious in increasing adherence to HAV-HBV vaccination and HCV clinical evaluation among methadone patients.

[Managing Psychiatric Comorbidity within Versus Outside of Methadone Treatment Settings: A Randomized and Controlled Evaluation.](#) Brooner RK, Kidorf MS, King VL, Peirce J, Neufeld K, Stoller K, Kolodner K. *Addiction.* 2013; 108 (11): 1942-1951.

Integrating psychiatric services within substance abuse treatment settings is a promising service delivery model, but has not been evaluated using random assignment to psychiatric treatment setting and controlled delivery of psychiatric care. This study evaluates the efficacy of on-site and integrated psychiatric service delivery in an opioid-agonist treatment program on psychiatric and substance use outcomes. Participants at the Addiction Treatment Services (ATS) were assigned randomly to receive on-site and integrated substance abuse and psychiatric care (on-site: n = 160) versus off-site and non-integrated substance abuse and psychiatric care (off-site: n = 156), and observed for 1 year. On-site participants received all psychiatric care within the substance abuse program by the same group of treatment providers. The same type and schedule of psychiatric services were available to off-site participants at a community psychiatry program. All participants received routine methadone maintenance at the ATS program in Baltimore, Maryland, USA. Participants were opioid-dependent men and women with at least one comorbid psychiatric

disorder, as assessed by the Structured Clinical Interview for DSM-IV and confirmed by expert clinical reappraisal. Outcomes included psychiatric service utilization and retention, Hopkins Symptom Checklist Global Severity Index (GSI) change scores and urinalysis test results. On-site participants were more likely to initiate psychiatric care 96.9 to 79.5%; $P < 0.001$), remain in treatment longer (195.9 versus 101.9 days; $P < 0.001$), attend more psychiatrist appointments (12.9 versus 2.7; $P < 0.001$) and have greater reductions in GSI scores (4.2 versus 1.7; $P = 0.003$) than off-site participants; no differences were observed for drug use. On-site and integrated psychiatric and substance misuse services in a methadone treatment setting might improve psychiatric outcomes compared with off-site and non-integrated substance misuse and psychiatric care. However, this might not translate into improved substance misuse outcomes.

Is The Relationship Between Early-Onset Cannabis Use and Educational Attainment Causal Or Due To Common Liability? Verweij KJH, Huizink AC, Agrawal A, Martin NG, Lynskey MT. *Drug Alcohol Depend.* 2013; 133(2): 580-586.

Several studies have shown that early cannabis use is correlated with poor educational performance including high school drop-out. The predominant explanation for this relationship is that cannabis use causes disengagement from education. Another explanation is that the association between early cannabis use and educational attainment is not causal, but the result of overlapping risk factors that increase the likelihood of both early cannabis use and disengagement from education. These confounding factors could be of genetic and/or environmental origin. Here the authors use data from a large community-based sample of adult twins ($N=3337$) who completed a comprehensive semi-structured telephone interview. They first apply the classical twin-design to determine whether genetic and/or environmental influences underlie the relationship between early-onset cannabis use (prior to age 18) and early school leaving. Next, with a co-twin control design the authors investigate whether the relationship between the two variables is more likely due to direct causality or overlapping risk factors. They find a significant phenotypic correlation between early-onset cannabis use and early school leaving ($r=0.26$), which could be explained by familial influences (of genetic and/or shared environmental origin). The pattern of odds ratios found in the co-twin control design is not consistent with direct causation, but rather suggests that the association is due to shared environmental factors influencing both variables. These findings suggest that the relationship between early-onset cannabis use and school leaving is due to shared environmental risk factors influencing both the risk of early-onset cannabis use and early school leaving.

Using Genetically Informed, Randomized Prevention Trials To Test Etiological Hypotheses About Child and Adolescent Drug Use and Psychopathology. Brody GH, Beach SRH, Hill KG, Howe GW, Prado G, Fullerton SM. *Am J Public Health.* 2013; 103 Suppl 1: S19-24.

In this essay, the authors describe a new era of public health research in which prevention science principles are combined with genomic science to produce gene-intervention (G-I) research. They note the roles of behavioral and molecular genetics in risk and protective mechanisms for drug use and psychopathology among children and adolescents, and the results of first-generation genetically informed prevention trials are reviewed. They also consider the need for second-generation research that focuses on G-I effects on mediators or intermediate processes. This research can be used to further understanding of etiological processes, to identify individual differences in children's and adolescents' responses to risk, and to increase the precision of prevention programs. The authors note the caveats about using genetic data to select intervention participants.

Longitudinal Twin Study of Borderline Personality Disorder Traits and Substance Use in Adolescence: Developmental Change, Reciprocal Effects, and Genetic and Environmental Influences. Bornovalova MA, Hicks BM, Iacono WG, McGue M. *Personal Disord.* 2013; 4(1): 23-32.

Although the comorbidity between borderline personality disorder (BPD) and substance abuse is well established, there are few longitudinal studies that have examined its developmental origins or whether the comorbidity is due to common genetic or environmental risk factors. To fill this gap, the authors used a large sample of female adolescent twins ($N = 1,280$) to examine the developmental course, reciprocal influences, and the genetic and environmental factors underlying the co-occurrence of BPD traits and substance use from age 14 to 18. Rank-order stability was moderate to high for both BPD traits ($r = .58$) and substance use ($r = .51$), whereas mean levels of substance use increased substantially from age 14 to 18 ($d = 0.77$) and BPD traits showed a small decline ($d = -0.21$). BPD traits and substance use exhibited concurrent and prospective associations; however, the longitudinal associations dropped to non-significance after accounting for the temporal stability of each trait. Twin analyses revealed that shared environmental factors accounted for the association between BPD traits and substance use at age 14, but genetic factors accounted for the association at age 18. These results indicate that, at least in adolescence, the comorbidity between BPD traits and substance use is a consequence of common risk factors rather than due to one being a casual antecedent of the other.

Tests of A Direct Effect of Childhood Abuse on Adult Borderline Personality Disorder Traits: A Longitudinal Discordant Twin Design. Bornovalova MA, Huibregtse BM, Hicks BM, Keyes M, McGue M, Iacono W. *J Abnorm Psychol.* 2013; 122(1): 180-194.

The authors used a longitudinal twin design to examine the causal association between sexual, emotional, and physical abuse in childhood (before age 18) and borderline personality disorder (BPD) traits at age 24 using a discordant twin design and biometric modeling. Additionally, they examined the mediating and moderating effects of symptoms of childhood externalizing and internalizing disorders on the link between childhood abuse and BPD traits. Although childhood abuse, BPD traits, and internalizing and externalizing symptoms were all correlated, the discordant twin analyses and biometric modeling showed little to no evidence that was consistent with a causal effect of childhood abuse on BPD traits. Instead, these results indicate that the association between childhood abuse and BPD traits stems from common genetic influences that, in some cases, also overlap with internalizing and externalizing disorders. These findings are inconsistent with the widely held assumption that childhood abuse causes BPD, and they suggest that BPD traits in adulthood are better accounted for by heritable vulnerabilities to internalizing and externalizing disorders.

Methadone Dose at the Time of Release from Prison Significantly Influences Retention in Treatment: Implications from a Pilot Study of HIV-Infected Prisoners Transitioning to the Community in Malaysia. Wickersham JA, Zahari MM, Azar MM, Kamarulzaman A, Altice FL. *Drug Alcohol Depend.* 2013; 132(1-2): 378-382.

The objective of this study was to evaluate the impact of methadone dose on post-release retention in treatment among HIV-infected prisoners initiating methadone maintenance treatment (MMT) within prison. Thirty HIV-infected prisoners meeting DSM-IV pre-incarceration criteria for opioid dependence were enrolled in a prison-based, pre-release MMT program in Klang Valley, Malaysia; 3 died before release from prison leaving 27 evaluable participants. Beginning 4 months before

release, standardized methadone initiation and dose escalation procedures began with 5mg daily for the first week and 5mg/daily increases weekly until 80 mg/day or craving was satisfied. Participants were followed for 12 months post-release at a MMT clinic within 25 kilometers of the prison. Kaplan-Meier survival analysis was used to evaluate the impact of methadone dose on post-release retention in treatment. Methadone dose ≥ 80 mg/day at the time of release was significantly associated with retention in treatment. After 12 months of release, only 21.4% of participants on < 80 mg were retained at 12 months compared to 61.5% of those on ≥ 80 mg (Log Rank $\chi(2)=(1,26)$ 7.6, $p < 0.01$). Higher doses of MMT at time of release are associated with greater retention on MMT after release to the community. Important attention should be given to monitoring and optimizing MMT doses to address cravings and side effects prior to community re-entry from prisons.

Mindfulness Training Improves Attentional Task Performance In Incarcerated Youth: A Group Randomized Controlled Intervention Trial. Leonard N, Jha A, Casarjian B, Goolsarran M, Garcia C, Cleland C, Gwadz M, Massey Z. *Front. Psychol.* 2013; 4(792).

The authors investigated the impact of cognitive behavioral therapy and mindfulness training (CBT/MT) on attentional task performance in incarcerated adolescents. Attention is a cognitive system necessary for managing cognitive demands and regulating emotions. Yet persistent and intensive demands, such as those experienced during high-stress intervals like incarceration and the events leading to incarceration, may deplete attention resulting in cognitive failures, emotional disturbances, and impulsive behavior. The authors hypothesized that CBT/MT may mitigate these deleterious effects of high stress and protect against degradation in attention over the high-stress interval of incarceration. Using a quasi-experimental, group randomized controlled trial design, they randomly assigned dormitories of incarcerated youth, ages 16–18, to a CBT/MT intervention (youth $n = 147$) or an active control intervention (youth $n = 117$). Both arms received approximately 750 min of intervention in a small-group setting over a 3–5 week period. Youth in the CBT/MT arm also logged the amount of out-of-session time spent practicing MT exercises. The Attention Network Test was used to index attentional task performance at baseline and 4 months post-baseline. Overall, task performance degraded over time in all participants. The magnitude of performance degradation was significantly less in the CBT/MT vs. control arm. Further, within the CBT/MT arm, performance degraded over time in those with no outside-of-class practice time, but remained stable over time in those who practiced mindfulness exercises outside of the session meetings. Thus, these findings suggest that sufficient CBT/MT practice may protect against functional attentional impairments associated with high-stress intervals.

Division of Pharmacotherapies and Medical Consequences of Drug Abuse (DPMCDA)

Combination Varenicline and Bupropion SR For Tobacco-Dependence Treatment In Cigarette Smokers: A Randomized Trial. Ebbert JO, Hatsukami DK, Croghan IT, Schroeder DR, Allen SS, Hays JT, Hurt RD. *JAMA.* 2014 Jan 8; 311(2): 155-163. doi: 10.1001/jama.2013.283185.

Combining pharmacotherapies for tobacco-dependence treatment may increase smoking abstinence. The purpose of the study was to determine efficacy and safety of varenicline and bupropion sustained-release (SR; combination therapy) compared with varenicline (monotherapy) in cigarette smokers. This was a randomized, blinded, placebo-controlled multicenter clinical trial with a 12-

week treatment period and follow-up through week 52 conducted between October 2009 and April 2013 at 3 midwestern clinical research sites. Five hundred six adult (≥ 18 years) cigarette smokers were randomly assigned and 315 (62%) completed the study. Primary outcome was abstinence rates at week 12, defined as prolonged (no smoking from 2 weeks after the target quit date) abstinence and 7-day point-prevalence (no smoking past 7 days) abstinence. Secondary outcomes were prolonged and point-prevalence smoking abstinence rates at weeks 26 and 52. Outcomes were biochemically confirmed. At 12 weeks, 53.0% of the combination therapy group achieved prolonged smoking abstinence and 56.2% achieved 7-day point-prevalence smoking abstinence compared with 43.2% and 48.6% in varenicline monotherapy (odds ratio [OR], 1.49; 95% CI, 1.05-2.12; $P=.03$ and OR, 1.36; 95% CI, 0.95-1.93; $P=.09$, respectively). At 26 weeks, 36.6% of the combination therapy group achieved prolonged and 38.2% achieved 7-day point-prevalence smoking abstinence compared with 27.6% and 31.9% in varenicline monotherapy (OR, 1.52; 95% CI, 1.04-2.22; $P=.03$ and OR, 1.32; 95% CI, 0.91-1.91; $P=.14$, respectively). At 52 weeks, 30.9% of the combination therapy group achieved prolonged and 36.6% achieved 7-day point-prevalence smoking abstinence compared with 24.5% and 29.2% in varenicline monotherapy (OR, 1.39; 95% CI, 0.93-2.07; $P=.11$ and OR, 1.40; 95% CI, 0.96-2.05; $P=.08$, respectively). Participants receiving combination therapy reported more anxiety (7.2% vs 3.1%; $P=.04$) and depressive symptoms (3.6% vs 0.8%; $P=.03$). Among cigarette smokers, combined use of varenicline and bupropion, compared with varenicline alone, increased prolonged abstinence but not 7-day point prevalence at 12 and 26 weeks. Neither outcome was significantly different at 52 weeks. Further research is required to determine the role of combination therapy in smoking cessation.

Maintenance Treatment with Varenicline for Smoking Cessation in Patients with Schizophrenia and Bipolar Disorder: A Randomized Clinical Trial. Evins AE, Cather C, Pratt SA, Pachas GN, Hoepfner SS, Goff DC, Achtyes ED, Ayer D, Schoenfeld DA. JAMA 2014; 311(2): 145-154.

It is estimated that more than half of those with serious mental illness smoke tobacco regularly. Standard courses of pharmacotherapeutic cessation aids improve short-term abstinence, but most who attain abstinence relapse rapidly after discontinuation of pharmacotherapy. The objective of this study was to determine whether smokers diagnosed with schizophrenia and bipolar disease have higher rates of prolonged tobacco abstinence with maintenance pharmacotherapy than with standard treatment. This was a randomized, double-blind, placebo-controlled, parallel-group, relapse-prevention clinical trial conducted in 10 community mental-health centers. Of 247 smokers with schizophrenia or bipolar disease recruited from March 2008-April 2012, 203 received 12-weeks' open-label varenicline and cognitive behavioral therapy and 87 met abstinence criteria to enter the relapse prevention intervention. Participants who had 2 weeks or more of continuous abstinence at week 12 of open treatment were randomly assigned to receive cognitive behavioral therapy and double-blind varenicline (1 mg, 2 per day) or placebo from weeks 12 to 52. Participants then discontinued study treatment and were followed up to week 76. Main outcomes and measures included: seven-day rate of continuous abstinence at study week 52, the end of the relapse-prevention phase, confirmed by exhaled carbon monoxide. Secondary outcomes were continuous abstinence rates for weeks 12 through 64 based on biochemically verified abstinence and weeks 12 through 76, based on self-reported smoking behavior. Sixty-one participants completed the relapse-prevention phase; 26 discontinued participation (7 varenicline, 19 placebo) and were considered to have relapsed for the analyses; 18 of these had relapsed prior to dropout. At week 52, point-prevalence abstinence rates were 60% in the varenicline group (24 of 40) vs 19% (9 of 47) in

the placebo group (odds ratio [OR], 6.2; 95% CI, 2.2-19.2; $P < .001$). From weeks 12 through 64, 45% (18 of 40) among those in the varenicline group vs 15% (7 of 47) in the placebo group were continuously abstinent (OR, 4.6; 95% CI, 1.5-15.7; $P = .004$), and from weeks 12 through 76, 30% (12 of 40) in the varenicline group vs 11% (5 of 47) in the placebo group were continuously abstinent (OR, 3.4; 95% CI, 1.02-13.6; $P = .03$). There were no significant treatment effects on psychiatric symptom ratings or psychiatric adverse events. Among smokers with serious mental illness who attained initial abstinence with standard treatment, maintenance pharmacotherapy with varenicline and cognitive behavioral therapy improved prolonged tobacco abstinence rates compared with cognitive behavioral therapy alone after 1 year of treatment and at 6 months after treatment discontinuation.

[Buprenorphine Implants For Treatment Of Opioid Dependence: Randomized Comparison To Placebo and Sublingual Buprenorphine/Naloxone.](#) Rosenthal RN, Ling W, Casadonte P, Vocci F, Bailey GL, Kampman K, Patkar A, Chavoustie S, Blasey C, Sigmon S, Beebe KL. *Addiction*. 2013 Dec; 108(12): 2141-2149. Epub 2013 Sep 18.

The aim of this study was to evaluate the safety and efficacy of buprenorphine implants (BI) versus placebo implants (PI) for the treatment of opioid dependence. A secondary aim compared BI to open-label sublingual buprenorphine/naloxone tablets (BNX). The study design was a randomized, double-blind, placebo-controlled trial. Subjects received either four buprenorphine implants (80mg/implant) ($n=114$), four placebo implants ($n=54$) or open-label BNX (12-16mg/day) ($n=119$). Treatment setting comprised twenty addiction treatment centers. Participants were adult out-patients (ages 18-65) with DSM-IV-TR opioid dependence. The primary efficacy end-point was the percentage of urine samples negative for opioids collected from weeks 1 to 24, examined as a cumulative distribution function (CDF). The BI CDF was significantly different from placebo ($P < 0.0001$). Mean [95% confidence interval (CI)] proportions of urines negative for opioids were: BI=31.2% (25.3, 37.1) and PI=13.4% (8.3, 18.6). BI subjects had a higher study completion rate relative to placebo (64 versus 26%, $P < 0.0001$), lower clinician-rated ($P < 0.0001$) and patient-rated ($P < 0.0001$) withdrawal, lower patient-ratings of craving ($P < 0.0001$) and better subjects' ($P=0.031$) and clinicians' ($P=0.022$) global ratings of improvement. BI also resulted in significantly lower cocaine use ($P=0.0016$). Minor implant-site reactions were comparable in the buprenorphine [27.2% (31 of 114)] and placebo groups [25.9% (14 of 54)]. BI were non-inferior to BNX on percentage of urines negative for opioids [mean (95% CI)=33.5 (27.3, 39.6); 95% CI for the difference of proportions=(-10.7, 6.2)]. The authors conclude that compared with placebo, buprenorphine implants result in significantly less frequent opioid use and are non-inferior to sublingual buprenorphine/naloxone tablets.

[Increased Efficacy Of A Trivalent Nicotine Vaccine Compared To A Dose-Matched Monovalent Vaccine When Formulated With Alum.](#) Villiers SH, Cornish KE, Troska AJ, Pravetoni M, Pentel PR. *Vaccine*. 2013 Dec 16; 31(52): 6185-6193.

Vaccination against nicotine is a potential treatment for tobacco smoking. Clinical trials show effect only in high antibody responders; therefore it is necessary to increase the effectiveness of nicotine vaccines. The use of a multivalent vaccine that activates several B cell populations is a possible approach to increase antibody response. The aim of this study was to investigate whether three different nicotine immunogens could be mixed to generate independent responses resulting in additive antibody titers, and whether this would alter nicotine distribution to a greater extent than antibodies generated by a monovalent vaccine. When immunogens were administered s.c. with

alum adjuvant, the trivalent vaccine generated significantly higher titers and prevented the distribution of an i.v. nicotine dose to brain to a greater extent than an equivalent dose of a monovalent vaccine. The number of rats with antibody titers $>1:10,000$ was significantly increased in the trivalent group compared to the monovalent group. There were no correlations between the titers generated by the different nicotine immunogens in the trivalent vaccine, supporting the hypothesis that the immunogens generated independent responses from distinct populations of B cells. In contrast, when administered i.p. in Freund's adjuvant, the trivalent nicotine vaccine was not more immunogenic than its component monovalent vaccine. Vaccine immunogenicity was suppressed if unconjugated protein was added to the monovalent vaccine formulated in Freund's adjuvant, compared to monovalent vaccine alone. These data suggest a protein-protein interaction that affects titers negatively and is apparent when the vaccines are formulated with Freund's adjuvant. In summary, a trivalent nicotine vaccine formulated with alum showed significantly higher efficacy than a dose-matched monovalent vaccine and may offer a strategy for increasing nicotine vaccine immunogenicity. This approach may be generalizable to other nicotine immunogens or vaccines for other addictive drugs.

[Topiramate For The Treatment Of Cocaine Addiction: A Randomized Clinical Trial.](#) Johnson BA, Ait-Daoud N, Wang XQ, Penberthy JK, Javors MA, Seneviratne C, Liu L. *JAMA Psychiatry*. 2013 Oct 16. doi: 10.1001/jamapsychiatry.2013.2295. [Epub ahead of print].

No medication has been established as an efficacious treatment for cocaine dependence. The authors hypothesized that dual modulation of the mesocorticolimbic dopamine system by topiramate—a glutamate receptor antagonist and γ -aminobutyric acid receptor agonist—would result in efficacious treatment for cocaine dependence compared with placebo. The objective of this study was to determine the efficacy of topiramate vs placebo as a treatment for cocaine dependence. This was a double-blind, randomized, placebo-controlled, 12-week trial of 142 cocaine-dependent adults in clinical research facilities at the University of Virginia between November 22, 2005, and July 25, 2011. Topiramate ($n=71$) or placebo ($n=71$) in escalating doses from 50 mg/d to the target maintenance dose of 300 mg/d in weeks 6 to 12, were combined with weekly cognitive-behavioral treatment. For the efficacy period, weeks 6 to 12, the primary outcome was the weekly difference from baseline in the proportion of cocaine nonuse days; the secondary outcome was urinary cocaine-free weeks, and exploratory outcomes included craving and self- and observer-rated global functioning on the Clinical Global Impression scales. Using an intent-to-treat analysis, topiramate was more efficacious than placebo at increasing the weekly proportion of cocaine nonuse days, irrespective of whether missing data were not or were imputed conservatively to the baseline value (13.3% vs 5.3%, 95% CI for the estimated mean difference, 1.4%-14.6%, $P=.02$ or 8.9% vs 3.7%, 95% CI for the estimated mean difference, 0.2%-10.1%, $P=.04$, respectively). Topiramate also was associated, significantly more than placebo, with increasing the likelihood of urinary cocaine-free weeks (16.6% vs 5.8%; odds ratio, 3.21; 95% CI, 1.24-8.32; $P=.02$), as well as decreasing craving and improving observer-rated global functioning (all $P \leq .05$). The authors conclude that topiramate is more efficacious than placebo at increasing the mean weekly proportion of cocaine nonuse days and associated measures of clinical improvement among cocaine-dependent individuals. TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00249691.

Gradual and Immediate Nicotine Reduction Result In Similar Low-Dose Nicotine Self-Administration.

Smith TT, Levin ME, Schassburger RL, Buffalari DM, Sved AF, Donny EC. Gradual and immediate nicotine reduction result in similar low-dose nicotine self-administration. *Nicotine Tob Res* 2013 Nov; (11): 1918-1925.

Food and Drug Administration-mandated product standards that drastically reduce nicotine content in cigarettes aim to decrease smoking and thus improve health outcomes for millions of U.S. smokers. Researchers have suggested that nicotine reduction should be implemented gradually, but a gradual nicotine reduction may shift the minimum level of nicotine required to reinforce behavior or may result in different levels of compensatory smoking behavior. Rats were given the opportunity to acquire nicotine self-administration at 60 $\mu\text{g}/\text{kg}/\text{infusion}$ nicotine with a cocktail of other tobacco constituents included as the vehicle. Rats were subsequently assigned to one of six immediate dose reductions (30, 15, 7.5, 3.75, 1.875, or 0.0 $\mu\text{g}/\text{kg}/\text{infusion}$) for 10 sessions (n = 9-15). Rats in the 30 $\mu\text{g}/\text{kg}/\text{infusion}$ reduction group continued to have their nicotine dose reduced by half after at least 10 sessions at each dose until reaching 1.875 $\mu\text{g}/\text{kg}/\text{infusion}$ (i.e., gradual reduction). For both methods of reduction, reduction to 3.75 $\mu\text{g}/\text{kg}/\text{infusion}$ resulted in significant decreases in behavior. Reduction to doses above 3.75 $\mu\text{g}/\text{kg}/\text{infusion}$ resulted in only limited compensation. The largest compensation was temporary. There was no compensation following reduction to 3.75 $\mu\text{g}/\text{kg}/\text{infusion}$ or below. This study suggests that reduction to the same nicotine dose will result in similar reductions in behavior for both gradual and immediate reductions, and both methods result in similar compensation. Future studies using humans should investigate differences in other outcomes such as withdrawal and craving.

Reducing Cannabinoid Abuse and Preventing Relapse By Enhancing Endogenous Brain Levels Of Kynurenic Acid.

Justinova Z, Mascia P, Wu HQ, Secci ME, Redhi GH, Panlilio LV, Scherma M, Barnes C, Parashos A, Zara T, Fratta W, Solinas M, Pistis M, Bergman J, Kangas BD, Ferré S, Tanda G, Schwarcz R, Goldberg SR. *Nat Neurosci.* 2013 Nov; 16(11): 1652-1661.

In the reward circuitry of the brain, α -7-nicotinic acetylcholine receptors (α 7nAChRs) modulate effects of Δ (9)-tetrahydrocannabinol (THC), marijuana's main psychoactive ingredient. Kynurenic acid (KYNA) is an endogenous negative allosteric modulator of α 7nAChRs. Here the authors report that the kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 increases brain KYNA levels and attenuates cannabinoid-induced increases in extracellular dopamine in reward-related brain areas. In the self-administration model of drug abuse, Ro 61-8048 reduced the rewarding effects of THC and the synthetic cannabinoid WIN 55,212-2 in squirrel monkeys and rats, respectively, and it also prevented relapse to drug-seeking induced by reexposure to cannabinoids or cannabinoid-associated cues. The effects of enhancing endogenous KYNA levels with Ro 61-8048 were prevented by positive allosteric modulators of α 7nAChRs. Despite a clear need, there are no medications approved for treatment of marijuana dependence. Modulation of KYNA offers a pharmacological strategy for achieving abstinence from marijuana and preventing relapse.

Hepatitis C Virus Maintains Infectivity for Weeks after Drying on Inanimate Surfaces at Room Temperature: Implications for Risks of Transmission.

Painstil E, Binka M, Patel A, Lindenbach BD, Heimer R. *J Infect Dis.* 2013 Nov 23. [Epub ahead of print].

Healthcare workers may come into contact with fomites containing infectious HCV during preparation of plasma, or following placement or removal of venous lines. Similarly, injection drugs users may come into contact with fomites. Hypothesizing that prolonged viability of HCV in fomites may contribute significantly to incidence, the authors determined the longevity of virus

infectivity and the effectiveness of antiseptics. They determined the volume of drops misplaced during transfer of serum or plasma. Aliquots equivalent to the maximum drop volume of plasma spiked with 2a HCV reporter virus were loaded into 24-well plates. Plates were stored uncovered at three temperatures: 4°, 22°, and 37°C for up to 6 weeks before viral infectivity was determined in a microculture assay. The mean volume of an accidental drop was 29 µl (min - max of 20 - 33 µl). At storage temperatures 4° and 22°C, we recovered viable HCV from the low titer spots for up to 6 weeks of storage. The rank order of HCV virucidal activity of commonly used antiseptics was bleach (1:10) > cavicide (1:10) > ethanol (70%). The hypothesis of potential transmission from fomites was supported by the experimental results. The anti-HCV activity of commercial antiseptics varied.

Effect Of Micronutrient Supplementation On Disease Progression In Asymptomatic, Antiretroviral-Naive, HIV-Infected Adults In Botswana: A Randomized Clinical Trial. Baum MK, Campa A, Lai S, Sales Martinez S, Tsalaile L, Burns P, Farahani M, Li Y, van Widenfelt E, Page JB, Bussmann H, Fawzi WW, Moyo S, Makhema J, Thior I, Essex M, Marlink R. JAMA. 2013 Nov 27;310(20):2154-63. doi: 10.1001/jama.2013.280923.

Micronutrient deficiencies occur early in human immunodeficiency virus (HIV) infection, and supplementation with micronutrients may be beneficial; however, its effectiveness has not been investigated early in HIV disease among adults who are antiretroviral therapy (ART) naive. The objective of the study was to investigate whether long-term micronutrient supplementation is effective and safe in delaying disease progression when implemented early in adults infected with HIV subtype C who are ART-naive. This was a randomized clinical trial of supplementation with either daily multivitamins (B vitamins and vitamins C and E), selenium alone, or multivitamins with selenium vs placebo in a factorial design for 24 months. The study was conducted in 878 patients infected with HIV subtype C with a CD4 cell count greater than 350/µL who were not receiving ART at Princess Marina Hospital in Gaborone, Botswana, between December 2004 and July 2009. Interventions were daily oral supplements of B vitamins and vitamins C and E, selenium alone, or multivitamins plus selenium, compared with placebo. Main outcomes and measures included reaching a CD4 cell count less than 200/µL until May 2008; after this date, reaching a CD4 cell count of 250/µL or less, consistent with the standard of care in Botswana for initiation of ART at the time of the study. There were 878 participants enrolled and randomized into the study. All participants were ART-naive throughout the study. In intent-to-treat analysis, participants receiving the combined supplement of multivitamins plus selenium had a significantly lower risk vs placebo of reaching CD4 cell count 250/µL or less (adjusted hazard ratio [HR], 0.46; 95% CI, 0.25-0.85; P=.01; absolute event rate [AER], 4.79/100 person-years; censoring rate, 0.92; 17 events; placebo AER, 9.22/100 person-years; censoring rate, 0.85; 32 events). Multivitamins plus selenium in a single supplement, vs placebo, also reduced the risk of secondary events of combined outcomes for disease progression (CD4 cell count ≤250/µL, AIDS-defining conditions, or AIDS-related death, whichever occurred earlier [adjusted HR, 0.56; 95% CI, 0.33-0.95; P=.03; AER, 6.48/100 person-years; censoring rate, 0.90; 23 events]). There was no effect of supplementation on HIV viral load. Multivitamins alone and selenium supplementation alone were not statistically different from placebo for any end point. Reported adverse events were adjudicated as unlikely to be related to the intervention, and there were no notable differences in incidence of HIV-related and health-related events among study groups. The authors conclude that in ART-naive HIV-infected adults, 24-month supplementation with a single supplement containing multivitamins and selenium was safe and significantly reduced the risk of immune decline and

morbidity. Micronutrient supplementation may be effective when started in the early stages of HIV disease.

Dual-Mixed HIV-1 Coreceptor Tropism and HIV-Associated Neurocognitive Deficits.

Morris SR, Woods SP, Deutsch R, Little SJ, Wagner G, Morgan EE, Heaton RK, Letendre SL, Grant I, Smith DM. *J Neurovirol.* 2013 Oct; 19(5): 488-494.

HIV coreceptor usage of CXCR4 (X4) is associated with decreased CD4+ T-cell counts and accelerated disease progression, but the role of X4 tropism in HIV-associated neurocognitive disorders (HAND) has not previously been described. This longitudinal study evaluated data on 197 visits orshfrom 72 recently HIV-infected persons who had undergone up to four sequential neurocognitive assessments over a median of 160 days (IQR, 138–192). Phenotypic tropism testing (Trofile ES, Monogram, Biosciences) was performed on stored blood samples. Multivariable mixed model repeated measures regression was used to determine the association between HAND and dual-mixed (DM) viral tropism, estimated duration of infection (EDI), HIV RNA, CD4 count, and problematic methamphetamine use. Six subjects (8.3 %) had DM at their first neurocognitive assessment and four converted to DM in subsequent sampling (for total of 10 DM) at a median EDI of 10.1 months (IQR, 7.2–12.2). There were 44 (61.1 %) subjects who demonstrated HAND on at least one study visit. HAND was associated with DM tropism (odds ratio, 4.4; 95 % CI, 0.9–20.5) and shorter EDI (odds ratio 1.1 per month earlier; 95 % CI, 1.0–1.2). This study found that recency of HIV-1 infection and the development of DM tropism may be associated with HAND in the relatively early stage of infection. Together, these data suggest that viral interaction with cellular receptors may play an important role in the early manifestation of HAND.

Integration Of Health Services Improves Multiple Healthcare Outcomes Among HIV-Infected People Who Inject Drugs In Ukraine. Bachireddy C, Soule MC, Izenberg JM, Dvoryak S, Dumchev K, Altice FL. *Drug Alcohol Depend.* 2014 Jan 1;134C:106-114. doi: 10.1016/j.drugalcdep.2013.09.020. Epub 2013 Sep 27.

People who inject drugs (PWID) experience poor outcomes and fuel HIV epidemics in middle-income countries in Eastern Europe and Central Asia. The authors assess integrated/co-located (ICL) healthcare for HIV-infected PWID, which despite international recommendations, is neither widely available nor empirically examined. This was a 2010 cross-sectional study of randomly sampled 296 HIV-infected opioid-dependent PWID from two representative HIV-endemic regions in Ukraine where ICL, non-co-located (NCL) and harm reduction/outreach (HRO) settings are available. ICL settings provide onsite HIV, addiction, and tuberculosis services, NCLs only treat addiction, and HROs provide counseling, needles/syringes, and referrals, but no opioid substitution therapy (OST). The primary outcome was receipt of quality healthcare, measured using a quality healthcare indicator (QHI) composite score representing percentage of eight guidelines-based recommended indicators met for HIV, addiction and tuberculosis treatment. The secondary outcomes were individual QHIs and health-related quality-of-life (HRQoL). On average, ICL-participants had significantly higher QHI composite scores compared to NCL- and HRO-participants (71.9% versus 54.8% versus 37.0%, $p < 0.001$) even after controlling for potential confounders. Compared to NCL-participants, ICL-participants were significantly more likely to receive antiretroviral therapy (49.5% versus 19.2%, $p < 0.001$), especially if $CD4 \leq 200$ (93.8% versus 62.5% $p < 0.05$); guideline-recommended OST dosage (57.3% versus 41.4%, $p < 0.05$); and isoniazid preventive therapy (42.3% versus 11.2%, $p < 0.001$). Subjects receiving OST had significantly higher HRQoL than those not receiving it ($p < 0.001$); however, HRQoL did not differ

significantly between ICL- and NCL-participants. These findings suggest that OST alone improves quality-of-life, while receiving care in integrated settings collectively and individually improves healthcare quality indicators for PWID.

Correlates of Elevated Interleukin-6 and C-Reactive Protein in Persons With or at High Risk for HCV and HIV Infections. Salter ML, Lau B, Mehta SH, Go VF, Leng S, Kirk GD. *J Acquir Immune Defic Syndr.* 2013 Dec 15;64(5):488-95. doi: 10.1097/QAI.0b013 e3182a7ee2e.

HIV and hepatitis C virus (HCV) infections may increase interleukin-6 (IL-6) and C-reactive protein (CRP). However, relationships between inflammatory biomarkers, chronic viral infections, clinical factors, and behavioral factors remain poorly understood. Using linear regression, the authors modeled cross-sectional associations between loge IL-6 or loge CRP levels and HCV, HIV, injection drug use, and comorbidity among 1191 injection drug users. Mean age was 47 years, 46.0% reported currently injecting drugs, 59.0% were HCV monoinfected, and 27% were HCV/HIV coinfecting. In multivariable models, higher loge IL-6 was associated with HCV monoinfection [$\beta = 0.191$, 95% confidence interval (CI): 0.043 to 0.339] and HCV/HIV coinfection ($\beta = 0.394$, 95% CI: 0.214 to 0.574). In contrast, HCV monoinfection ($\beta = -0.523$, 95% CI: -0.275 to -0.789) and HCV/HIV coinfection ($\beta = -0.554$ 95% CI: -0.260 to -0.847) were associated with lower CRP. Lower CRP with HCV infection was independent of liver fibrosis severity, synthetic function, or liver injury markers; CRP decreased with higher HCV RNA. Increased injection intensity was associated with higher IL-6 ($P = 0.003$) and CRP ($P < 0.001$); increasing comorbidity ($P < 0.001$) and older age ($P = 0.028$) were associated with higher IL-6; older age was associated with higher CRP among HCV-uninfected participants ($P = 0.021$). The authors conclude that HIV and HCV infections contribute to chronic inflammation; however, reduced CRP possibly occurs through HCV-mediated mechanisms. Findings highlight potentially modifiable contributors to inflammation.

AIDS Research Program (ARP)

Directly Administered Antiretroviral Therapy For HIV-Infected Individuals In Opioid Treatment Programs: Results From A Randomized Clinical Trial. Lucas GM, Mullen BA, Galai N, Moore RD, Cook K, McCaul ME, Glass S, Oursler KK, Rand C. *PLoS One.* 2013 Jul 16;8(7):e68286. doi: 10.1371/journal.pone.0068286. Print 2013.

Data regarding the efficacy of directly administered antiretroviral therapy (DAART) are mixed. Opioid treatment programs (OTPs) provide a convenient framework for DAART. In a randomized controlled trial, the authors compared DAART and self-administered therapy (SAT) among HIV-infected subjects attending five OTPs in Baltimore, MD. HIV-infected individuals attending OTPs were eligible if they were not taking antiretroviral therapy (ART) or were virologically failing ART at last clinical assessment. In subjects assigned to DAART, the authors observed one ART dose per weekday at the OTP for up to 12 months. SAT subjects administered ART at home. The primary efficacy comparison was the between-arm difference in the average proportions with HIV RNA <50 copies/mL during the intervention phase (3-, 6-, and 12-month study visits), using a logistic regression model accounting for intra-person correlation due to repeated observations. Adherence was measured with electronic monitors in both arms. The authors randomized 55 and 52 subjects from five Baltimore OTPs to DAART and SAT, respectively. The average proportions with HIV RNA <50 copies/mL during the intervention phase were 0.51 in DAART and 0.40 in SAT

(difference 0.11, 95% CI: -0.020 to 0.24). There were no significant differences between arms in electronically-measured adherence, average CD4 cell increase from baseline, average change in log₁₀ HIV RNA from baseline, opportunistic conditions, hospitalizations, mortality, or the development of new drug resistance mutations. In this randomized trial, the authors found little evidence that DAART provided clinical benefits compared to SAT among HIV-infected subjects attending OTPs.

Center for Clinical Trials Network (CCTN)

[A Randomized Trial of Concurrent Smoking-Cessation and Substance Use Disorder Treatment in Stimulant-Dependent Smokers.](#) Winhusen TM, Brigham GS, Kropp F, Lindblad R, Gardin II JG, Penn P, Hodgkins C, Kelly TM, Douaihy A, McCann M, Love LD, DeGravelles E, Bachrach K, Sonne SC, Hiott B, Haynes L, Sharma G, Lewis DF, VanVeldhuisen P, Theobald J, Ghitza U. *J Clin Psychiatry* 2013 Dec 10. [Epub ahead of print].

The objective of this study was to evaluate the impact of concurrent treatments for substance use disorder and nicotine-dependence for stimulant-dependent patients. A randomized, 10-week trial with follow-up at 3 and 6 months after smoking quit date conducted at 12 substance use disorder treatment programs between February 2010 and July 2012. Adults meeting *DSM-IV-TR* criteria for cocaine and/or methamphetamine dependence and interested in quitting smoking were randomized to treatment as usual (n = 271) or treatment as usual with smoking-cessation treatment (n = 267). All participants received treatment as usual for substance use disorder treatment. Participants assigned to treatment as usual with concurrent smoking-cessation treatment received weekly individual smoking cessation counseling and extended-release bupropion (300 mg/d) during weeks 1–10. During post-quit treatment (weeks 4–10), participants assigned to treatment as usual with smoking-cessation treatment received a nicotine inhaler and contingency management for smoking abstinence. Weekly proportion of stimulant-abstinent participants during the treatment phase, as assessed by urine drug screens and self-report, was the primary outcome. Secondary measures included other substance/nicotine use outcomes and treatment attendance. There were no significant treatment effects on stimulant-use outcomes, as measured by the primary outcome and stimulant-free days, on drug-abstinence, or on attendance. Participants assigned to treatment as usual with smoking-cessation treatment, relative to those assigned to treatment as usual, had significantly better outcomes for drug-free days at 6-month follow-up ($\chi^2_1 = 4.09, P < .05$), with a decrease in drug-free days from baseline of -1.3% in treatment as usual with smoking-cessation treatment and of -7.6% in treatment as usual. Participants receiving treatment as usual with smoking-cessation treatment, relative to those receiving treatment as usual, had significantly better outcomes on smoking point-prevalence abstinence (25.5% vs 2.2%; $\chi^2_1 = 44.69, P < .001; OR = 18.2$). These results suggest that providing smoking-cessation treatment to illicit stimulant-dependent patients in outpatient substance use disorder treatment will not worsen, and may enhance, abstinence from nonnicotine substance use.

[Effect of Risk-Reduction Counseling with Rapid HIV Testing on Risk of Acquiring Sexually Transmitted Infections: the AWARE Randomized Clinical Trial.](#) Metsch LR, Feaster DJ, Gooden L, Schackman BR, Matheson T, Das M, Golden MR, Huffaker S, Haynes LF, Tross S, Malotte CK, Douaihy A, Korthuis PT, Duffus WA, Henn S, Bolan R, Philip SS, Castro JG,

Castellon PC, McLaughlin G, Mandler RN, Branson B, Colfax GN. JAMA. 2013 Oct 23; 310(16): 1701-1710.

To increase human immunodeficiency virus (HIV) testing rates, many institutions and jurisdictions have revised policies to make the testing process rapid, simple, and routine. A major issue for testing scale-up efforts is the effectiveness of HIV risk-reduction counseling, which has historically been an integral part of the HIV testing process. The objective of this study was to assess the effect of brief patient-centered risk-reduction counseling at the time of a rapid HIV test on the subsequent acquisition of sexually transmitted infections (STIs). From April to December 2010, Project AWARE randomized 5012 patients from 9 sexually transmitted disease (STD) clinics in the United States to receive either brief patient-centered HIV risk-reduction counseling with a rapid HIV test or the rapid HIV test with information only. Participants were assessed for multiple STIs at both baseline and 6-month follow-up. Participants randomized to counseling received individual patient-centered risk-reduction counseling based on an evidence-based model. The core elements included a focus on the patient's specific HIV/STI risk behavior and negotiation of realistic and achievable risk-reduction steps. All participants received a rapid HIV test. The prespecified outcome was a composite end point of cumulative incidence of any of the measured STIs over 6 months. All participants were tested for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum* (syphilis), herpes simplex virus 2, and HIV. Women were also tested for *Trichomonas vaginalis*. There was no significant difference in 6-month composite STI incidence by study group (adjusted risk ratio, 1.12; 95% CI, 0.94-1.33). There were 250 of 2039 incident cases (12.3%) in the counseling group and 226 of 2032 (11.1%) in the information-only group. Risk-reduction counseling in conjunction with a rapid HIV test did not significantly affect STI acquisition among STD clinic patients, suggesting no added benefit from brief patient-centered risk-reduction counseling.

Treating Nicotine Dependence by Targeting Attention-Deficit/ Hyperactivity Disorder (ADHD) With OROS Methylphenidate: The Role of Baseline ADHD Severity and Treatment Response Nunes EV, Covey LS, Brigham G, Hu MC, Levin FR, Somoza EC, Winhusen TM. J Clin Psychiatry 2013; 74(10): 983–990.

The objective of this study was to determine whether treatment of attention-deficit/hyperactivity disorder (ADHD) with osmotic-release oral system (OROS) methylphenidate promotes abstinence from smoking among smokers with ADHD who have greater severity of ADHD symptoms at baseline or greater improvement in ADHD during treatment. This is a secondary analysis of data from a randomized, double-blind, 11-week trial conducted between December 2005 and January 2008 at 6 clinical sites; the original trial was sponsored by the National Drug Abuse Clinical Trials Network. Adult cigarette smokers (aged 18–55 years) who met *DSM-IV* criteria for ADHD were randomly assigned to OROS methylphenidate (72 mg/d) ($n = 127$) or matching placebo ($n = 128$). All participants received nicotine patches (21 mg/d) and weekly individual smoking cessation counseling. Logistic regression was used to model prolonged abstinence from smoking (ascertained by self-report and breath carbon monoxide testing) as a function of treatment, baseline ADHD Rating Scale-IV (ADHD-RS) score, change in ADHD-RS score during treatment, and their interactions. Treatment interacted with both ADHD-RS score at baseline ($P = .01$) and change in ADHD-RS score during treatment ($P = .008$). Among patients with higher ADHD-RS scores (> 36) at baseline and the most improvement in ADHD during treatment (ADHD-RS change score ≥ 24), 70.0% of those who took OROS methylphenidate achieved abstinence from smoking compared to 36.8% of those who took placebo ($P = .02$). In contrast, among patients with the lowest ADHD-RS

baseline scores (≤ 30), 30.3% of those who took OROS methylphenidate achieved abstinence from smoking compared to 60.7% of those who took placebo ($P = .02$). OROS methylphenidate, in combination with nicotine patch, may be an effective treatment for nicotine dependence among smokers with more severe ADHD and more robust response of ADHD symptoms to medication. OROS methylphenidate may be counterproductive among smokers with lower severity of ADHD.

Intramural Research Program (IRP)

Neural Estimates of Imagined Outcomes in the Orbitofrontal Cortex Drive Behavior and Learning.

Takahashi YK, Chang CY, Lucantonio F, Haney RZ, Berg BA, Bonci A, Schoenbaum G. *Neuron* 2013; 80: 507-518.

Imagination, defined as the ability to interpret reality in ways that diverge from past experience, is fundamental to adaptive behavior. This can be seen at a simple level in our capacity to predict novel outcomes in new situations. The ability to anticipate outcomes never before received can also influence learning if those imagined outcomes are not received. The orbitofrontal cortex is a key candidate for where the process of imagining likely outcomes occurs; however, its precise role in generating these estimates and applying them to learning remain open questions. Here the authors address these questions by showing that single-unit activity in the orbitofrontal cortex reflects novel outcome estimates. The strength of these neural correlates predicted both behavior and learning, learning that was abolished by temporally specific inhibition of orbitofrontal neurons. These results are consistent with the proposal that the orbitofrontal cortex is critical for integrating information to imagine future outcomes.

Reducing Cannabinoid Abuse and Preventing Relapse by Enhancing Endogenous Brain Levels Of Kynurenic Acid.

Justinova Z, Mascia P, Wu HQ, Secci ME, Redhi GH, Panlilio LV, Scherma M, Barnes C, Parashos A, Zara T, Fratta W, Solinas M, Pistis M, Bergman J, Kangas BD, Ferré S, Tanda G, Schwarcz R, Goldberg SR. *Nature Neuroscience* 2013; 16(11): 1652-1661.

In the reward circuitry of the brain, α -7-nicotinic acetylcholine receptors (α 7nAChRs) modulate effects of Δ (9)-tetrahydrocannabinol (THC), marijuana's main psychoactive ingredient. Kynurenic acid (KYNA) is an endogenous negative allosteric modulator of α 7nAChRs. Here the authors report that the kynurenine 3-monooxygenase (KMO) inhibitor Ro 61-8048 increases brain KYNA levels and attenuates cannabinoid-induced increases in extracellular dopamine in reward-related brain areas. In the self-administration model of drug abuse, Ro 61-8048 reduced the rewarding effects of THC and the synthetic cannabinoid WIN 55,212-2 in squirrel monkeys and rats, respectively, and it also prevented relapse to drug-seeking induced by reexposure to cannabinoids or cannabinoid-associated cues. The effects of enhancing endogenous KYNA levels with Ro 61-8048 were prevented by positive allosteric modulators of α 7nAChRs. Despite a clear need, there are no medications approved for treatment of marijuana dependence. Modulation of KYNA offers a pharmacological strategy for achieving abstinence from marijuana and preventing relapse.

Large-Scale Brain Networks in the Awake, Truly Resting Marmoset Monkey.

Belcher, AM, Yen, CC, Stepp, H, Gu, H, Lu, H, Yang, Y, Silva, AC, Stein, EA. *Journal of Neuroscience* 2013; 33:16796-16804.

Resting-state functional MRI is a powerful tool that is increasingly used as a noninvasive method for investigating whole-brain circuitry and holds great potential as a possible diagnostic for disease.

Despite this potential, few resting-state studies have used animal models (of which nonhuman primates represent our best opportunity of understanding complex human neuropsychiatric disease), and no work has characterized networks in awake, truly resting animals. Here the authors present results from a small New World monkey that allows for the characterization of resting-state networks in the awake state. Six adult common marmosets (*Callithrix jacchus*) were acclimated to light, comfortable restraint using individualized helmets. Following behavioral training, resting BOLD data were acquired during eight consecutive 10 min scans for each conscious subject. Group independent component analysis revealed 12 brain networks that overlap substantially with known anatomically constrained circuits seen in the awake human. Specifically, the authors found eight sensory and "lower-order" networks (four visual, two somatomotor, one cerebellar, and one caudate-putamen network), and four "higher-order" association networks (one default mode-like network, one orbitofrontal, one frontopolar, and one network resembling the human salience network). In addition to their functional relevance, these network patterns bear great correspondence to those previously described in awake humans. This first-of-its-kind report in an awake New World nonhuman primate provides a platform for mechanistic neurobiological examination for existing disease models established in the marmoset.

[Resting-State Glutamate and GABA Concentrations Predict Task-Induced Deactivation In the Default Mode Network.](#) Hu Y, Chen X, Gu H, Yang Y J. *Neuroscience* 2013; 33: 18566-18573.

Deactivation of the human brain's default mode network (DMN) is regarded as suppression of endogenous activity to support exogenous task-related processes. This phenomenon has important functional relevance and insufficient DMN deactivation has been implicated in several neuropsychiatric disorders. However, the neurochemical mechanism of the DMN's deactivation remains largely unknown. In the present study, the authors test the hypothesis that the major excitatory and inhibitory neurotransmitters, glutamate and GABA, respectively, are associated with DMN deactivation. They used magnetic resonance spectroscopy to measure neurotransmitter concentrations in the posterior cingulate cortex/precuneus (PCC/PCu), a key component of the DMN, and functional magnetic resonance imaging to evaluate DMN deactivation induced by an n-back working memory task. Results demonstrate significant associations of glutamate and GABA with DMN deactivation. Specifically, high regional GABA concentration in the PCC/PCu area is associated with enhanced deactivation induced by the task in the same region, whereas high glutamate concentration is associated with reduced deactivation. Furthermore, the association between GABA and DMN deactivation increases with the cognitive loads. These neurochemical characteristics of DMN deactivation may provide novel insights toward better understanding of the DMN's functions under normal physiological conditions and dysfunction in neuropsychiatric disorders.

[Methamphetamine Downregulates Striatal Glutamate Receptors Via Diverse Epigenetic Mechanisms.](#) Jayanthi S, McCoy MT, Chen B, Britt JP, Kourrich S, Yau HJ, Ladenheim B, Krasnova IN, Bonci A, Cadet JL. *Biol Psychiatry* 2013; Oct 16. pii: S0006-3223(13)00915-3. doi: 10.1016/j.biopsych.2013.09.034. [Epub ahead of print]

Chronic METH decreased transcript and protein expression of GluA1 and GluA2 alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPA) and GluN1 N-methyl-D-aspartate receptor subunits. These changes were associated with altered electrophysiological glutamatergic responses in striatal neurons. Chromatin immunoprecipitation-polymerase chain reaction revealed

that METH decreased enrichment of acetylated histone H4 on GluA1, GluA2, and GluN1 promoters. Methamphetamine exposure also increased repressor element-1 silencing transcription factor (REST) corepressor 1, methylated CpG binding protein 2, and histone deacetylase 2 enrichment, but not of sirtuin 1 or sirtuin 2, onto GluA1 and GluA2 gene sequences. Moreover, METH caused interactions of REST corepressor 1 and methylated CpG binding protein 2 with histone deacetylase 2 and of REST with histone deacetylase 1. Surprisingly, methylated DNA immunoprecipitation and hydroxymethylated DNA immunoprecipitation-polymerase chain reaction revealed METH-induced decreased enrichment of 5-methylcytosine and 5-hydroxymethylcytosine at GluA1 and GluA2 promoter sequences. Importantly, the histone deacetylase inhibitor, valproic acid, blocked METH-induced decreased expression of AMPAR and N-methyl-D-aspartate receptor subunits. Finally, valproic acid also attenuated METH-induced decrease H4K16Ac recruitment on AMPAR gene sequences. These observations suggest that histone H4 hypoacetylation may be the main determinant of METH-induced decreased striatal glutamate receptor expression.

Critical Role Of Peripheral Drug Actions In Experience-Dependent Changes In Nucleus

Accumbens Glutamate Release Induced By Intravenous Cocaine. Wakabayashi KT, Kiyatkin EA. Journal of Neurochemistry. Oct 1, 2013. doi: 10.1111/jnc.12472. [Epub ahead of print]

Recent studies reveal that cocaine experience results in persistent neuroadaptive changes within glutamate (Glu) synapses in brain areas associated with drug reward. However, it remains unclear whether cocaine affects Glu release in drug-naïve animals and how it is altered by drug experience. By using high-speed amperometry with enzyme-based and enzyme-free biosensors in freely moving rats, the authors show that an initial intravenous cocaine injection at a low self-administering dose (1 mg/kg) induces rapid, small and transient Glu release in the nucleus accumbens shell (NAc), which with subsequent injections rapidly becomes a much stronger, two-component increase. Using cocaine-methiodide, cocaine's analogue that does not cross the blood-brain barrier, the authors confirm that the initial cocaine-induced Glu release in the NAc has a peripheral neural origin. Unlike cocaine, Glu responses induced by cocaine-methiodide rapidly habituate following repeated exposure. However, after cocaine experience this drug induces cocaine-like Glu responses. Hence, the interoceptive actions of cocaine, which essentially precede its direct actions in the brain, play a critical role in experience-dependent alterations in Glu release, cocaine-induced neural sensitization and may contribute to cocaine addiction.

Detecting Resting-State Brain Activity By Spontaneous Cerebral Blood Volume Fluctuations Using Whole Brain Vascular Space Occupancy Imaging.

Miao X, Gu H, Yan L, Lu H, Wang DJ, Zhou XJ, Zhuo Y, Yang Y. NeuroImage 2014; 84: 575-584.

Resting-state brain activity has been investigated extensively using BOLD contrast. However, BOLD signal represents the combined effects of multiple physiological processes and its spatial localization is less accurate than that of cerebral blood flow and volume (CBF and CBV, respectively). In this study, the authors demonstrate that resting-state brain activity can be reliably detected by spontaneous fluctuations of CBV-weighted signal using whole-brain gradient and spin echo (GRASE) based vascular space occupancy (VASO) imaging. Specifically, using independent component analysis, intrinsic brain networks, including default mode, salience, executive control, visual, auditory, and sensorimotor networks were revealed robustly by the VASO technique. The authors further demonstrate that task-evoked VASO signal aligned well with expected gray matter areas, while blood-oxygenation level dependent (BOLD) signal extended outside of these areas probably due to their different spatial specificity. The improved spatial localization of VASO is

consistent with previous studies using animal models. Moreover, the authors showed that the 3D-GRASE VASO images had reduced susceptibility-induced signal voiding, compared to the BOLD technique. This is attributed to the fact that VASO does not require T2* weighting, thus the acquisition can use a shorter TE and can employ spin-echo scheme. Consequently VASO-based functional connectivity signals were well preserved in brain regions that tend to suffer from signal loss and geometric distortion in BOLD, such as orbital prefrontal cortex. This study suggests that 3D-GRASE VASO imaging, with its improved spatial specificity and less sensitivity to susceptibility artifacts, may have advantages in resting-state fMRI studies.

NIH/HHS POLICY UPDATES

For a complete list see <http://grants.nih.gov/grants/policy/policy.htm>

2014

January 16 [NIH Operates Under a Continuing Resolution](#)

2013

December 18 [Notice of Reissuance of the Parent Research Career Development \(K\) Award Funding Opportunity Announcements](#)

December 6 [Notice of Reissuance of Ruth L. Kirschstein National Research Service Award \(NRSA\) Institutional Research Training Grant \(Parent T32\) and Short-Term Institutional Research Training Grant \(Parent T35\)](#)

December 4 [Change in the NIH Continuous Submission Policy](#)

November 25 [Update to the Interim Agency Policy, NIH Extramural and Intramural Research Involving Chimpanzees](#)

November 25 [Annual Reports to the Office of Laboratory Animal Welfare due January 31, 2014](#)

November 25 [NIH Will Require Use of Research Performance Progress Report \(RPPR\) for All Multi-Year Funded Awards](#)

November 25 [NIH Reminds Applicants to Use Updated Electronic Application Forms \(FORMS-C\) for F, K, T and D Submissions with Due Dates on/after January 25, 2014](#)

November 7 [Status of Peer Review Meetings Scheduled to Take Place During the Recent Lapse in Appropriations](#)

October 29 [Additional Clarification on Resumption of NIH Extramural Activities Following the Recent Lapse in Appropriations](#)

October 25 [Publication of the Revised NIH Grants Policy Statement \(Rev. 10/1/2013\)](#)

October 25 [NIH Operates Under a Continuing Resolution](#)

October 25 [Amendment to Small Business Innovation Research \(SBIR\) Program Contract Solicitation \(PHS 2014-1\)](#)

October 22 [Revised Guidance on Resumption of NIH Extramural Activities Following the Recent Lapse in Appropriations](#)

October 18 [Interim Guidance on Resumption of NIH Extramural Activities](#)

October 18 [Guidance on Resumption of NIH Extramural Activities Following the Recent Lapse in Appropriations](#)

October 18 [Update on the NIH RPPR Phase II Pilot Training Webinar for Demonstration Partnership Members](#)

- September 26 [Update on the NIH Research Performance Progress Report \(RPPR\) Phase II Pilot for Federal Demonstration Partnership Members](#)
- September 26 [NIH Reminds Applicants to Use Updated Electronic Application Forms \(FORMS-C\) for Due Dates on or after September 25, 2013](#)
- September 26 [NIH Domestic Awards to Transition to Payment Management System Subaccounts in FY 2014 and FY 2015](#)
- September 17 [Notice of Intent to Publish the Reissuance of the Funding Opportunity Announcement Ruth L. Kirschstein National Research Service Award \(NRSA\) Institutional Research Training Grants \(Parent T32\)](#)
- September 17 [New Program Certifications Required for SBIR and STTR Awards](#)
- September 16 [Review of Grants Information for Fiscal Year 2013](#)
- September 12 [NIH Opens the Research Performance Progress Report \(RPPR\) Phase II Pilot to Federal Demonstration Partnership Members](#)
- September 3 [NIH to Transition Payment for Individual Fellowships at Foreign and Federal Sponsoring Institutions, and Awards to Federal Institutions to Payment Management System Subaccounts in FY 2014](#)
- September 3 [NIH Domestic Awards to Transition to Payment Management System Subaccounts in FY 2014](#)
- August 28 [Notice of Special Terms and Conditions for NIH Hurricane Sandy Recovery Awards](#)
- August 28 [NIH Offers Niche Assessment Program to SBIR and STTR Phase I Awardees](#)

CONGRESSIONAL AFFAIRS

(Prepared January 22, 2014)

APPROPRIATIONS

Recently-signed legislation will fund NIH and NIDA for the balance of FY 2014. As described by the Congress, the bill includes \$29.9 billion for the NIH, \$1 billion above the fiscal year 2013 level. This funding will continue support for basic biomedical research and translational research through the programs like the Clinical and Translational Science Awards (CTSA) and Institutional Development Award (IDeA) to support scientists as they conduct research to discover cures. Further, it provides full support for the NIH Office of Science Education and programs like the Science Education and Partnership Awards (SEPA) to support biomedical research for the future. Within the NIH amount, NIDA will receive an appropriation of \$1,025,435,000. This represents an approximate increase of 3.2% above the FY 2013 “actuals” level of \$993,403,793. Further, the Congress showed that it is focused on some drug abuse and addiction issues. In the statement of the managers, there is NIDA-specific language regarding research on opioids, medications development etc:

Opioid Drug Abuse -- Opioid narcotics are frequently abused through injection, inhalation, crushing, or oral overdose to create a highly addictive euphoria. According to some reports, more than 35 million Americans have abused prescription opioids at some point in their lifetimes. In addition, the June 2011 Institute of Medicine report on relieving pain indicates that such abuse and misuse resulted in an annual estimated cost to the nation of \$72.5 billion. The National Institute of Drug Abuse (NIDA) is expected to support meritorious scientific activities that provide companies with the basic science to develop and implement innovative strategies to reduce opioid drug abuse. Such strategies may include new chemical molecule structures, coatings, agents, or other appropriate scientifically sound processes with a goal of providing barriers to abuse while still providing the pain relief necessary for appropriate patient care. The NIDA is strongly urged to continue its support of research on pain, including the development of pain medications with reduced abuse liability. In addition, NIDA should continue to fund research to better prevent and treat prescription drug abuse. The NIDA shall provide an update in the fiscal year 2015 budget request on activities related to addressing the opioid drug abuse problem.

CONGRESSIONAL HEARINGS/MEETINGS

Synthetic Drugs Hearing -- On September 25, 2013, the Senate Caucus on International Narcotics Control held a hearing on “Dangerous Synthetic Drugs.” NIDA Director Dr. Nora Volkow was one of the witnesses who testified. According to the Caucus, “The hearing examined the impact of dangerous synthetic drugs, such as Molly, K2, Spice and so-called “bath salts” and ways in which drug traffickers are circumventing existing law. Senator Feinstein recently introduced the Protecting Our Youth from Dangerous Synthetic Drugs Act of 2013 to combat synthetic drugs designed to mimic the effects of controlled substances like ecstasy, PCP and LSD, as well as THC, the principal chemical in marijuana. These controlled substance analogues are currently inadequately controlled under existing federal drug laws.” All testimonies and an archived video file of the hearing can be seen at <http://www.drugcaucus.senate.gov/hearings.html>.

Treatment Medications – On September 30, 2013, the American Society of Addiction Medicine hosted a Congressional Briefing titled *Advancing Access to Addiction Treatment Medications*. Dr. Jack Stein, the Director of NIDA’s Office of Science Policy and Communications, was one of the panelists focusing on this important topic. More information on the briefing can be found at <http://www.asam.org/advocacy/aaam/hill-briefing>.

SOME BILLS OF INTEREST

HR 486 – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

HR 498 – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. Representatives Rosa DeLauro (D-CT), and Frank Wolf (R-VA) were the only two original co-sponsors of the legislation. The bill was referred to the House Committee on Energy and Commerce.

HR 499 – On February 5, 2013, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

HR 672 -- On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

HR 1263 – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

HR 1285 – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary, and Judiciary. See also S 621. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

HR 1366 – On March 21, 2013, Representative Stephen Lynch (D-MA) introduced the Stop Oxycontin Abuse Act of 2013, to direct the Commissioner of Food and Drugs to modify the approval of any drug containing controlled-release oxycodone hydrochloride to limit such approval to use for the relief of severe-only instead of moderate-to-severe pain, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

HR 1523 – On April 12, 2013, Representative Dana Rohrbacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

HR 3717 – On December 12, 2013, Representative Tim Murphy (R-PA) introduced the Helping Families in Mental Health Crisis Act of 2013, to make available needed psychiatric, psychological, and supportive services for individuals diagnosed with mental illness and families in mental health crisis, and for other purposes. The bill was referred to the House Committees on: Energy and Commerce; Judiciary; Energy and the Workforce; Ways and Means; and Science, Space and Technology.

S 237 – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

S 264 – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

S 265 – On February 7, 2013 Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

S 348 – On February 14, 2014, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

S 621 – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

S 644 – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

S 1277 – On July 10, 2013, Senator Barbara Boxer (D-CA) introduced the Combating Prescription Drug Abuse Act, to establish a commission for the purpose of coordinating efforts to reduce prescription drug abuse, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

PROGRAM ACTIVITIES/FOAS

New NIDA RFAs

On January 17, 2014, NIDA, with NIMH, issued an RFA entitled **Tools for Monitoring and Manipulating Modified RNAs in the Nervous System (R43/R44) [RFA-DA-15-001](#), (R41/R42) [RFA-DA-15-002](#)**. The purpose of this initiative is to incentivize small businesses to generate tools and products specifically for monitoring and manipulating covalently modified eukaryotic mRNAs and regulatory RNAs. Open date: March 24, 2014. Application due date(s): April 24, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

New NIDA Program Announcements

On August 26, 2013, NIDA issued a PA entitled **Neuroscience Research on Drug Abuse (R03) [PA-13-336](#), (R21) [PA-13-337](#), (R01) [PA-13-338](#)**. The goals of this FOA are to understand the neurobiological mechanisms underlying drug abuse and addiction, with special emphasis on changes that occur during chronic drug use, withdrawal and relapse. An understanding of the basic mechanisms underlying drug addiction can help to identify targets for prevention and treatment interventions. Research utilizing basic, translational, or clinical approaches is appropriate. Open date: January 5, 2014. 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 September 11, 2013, NIDA issued a PAR entitled **Early Career Award in Chemistry of Drug Abuse and Addiction (ECHEM) (R21/R33) [PAR-13-350](#)**. This PAR seeks to facilitate the entry of new-to-NIH investigators into basic chemistry research applied to drug abuse and addiction. Open date: September 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 November 7, 2013, NIDA issued a PA entitled **Development of Opioid and Adjuvant Fixed Combination Dosage Forms for the Treatment of Chronic Pain with Reduced Addiction Potential (R43/R44) [PA-13-387](#), (R41/R42) [PA-13-388](#)**. The purpose of this announcement is to fund meritorious applications from small business organizations that aim to develop of opioid and adjuvant drug combinations within a single dosage form for treatment of a pain condition. The drug combination should provide improved analgesia when compared with the same dose (morphine equivalents) of opioid monotherapy. Such dosage forms should minimize opioid exposure while optimizing analgesia, in order to reduce risk of addiction and limit severity of other opiate adverse effects. Open date: March 5, 2014. 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 November 22, 2013, NIDA issued a PAR entitled **Identification of Gene Variants for Addiction Related Traits by Next-Gen Sequencing in Model Organisms Selectively Bred for Addiction Traits (UH2/UH3) [PAR-14-010](#)**. The goals of this initiative are to: 1) develop

strategies and methodologies for the sequencing, mapping and genomic analyzing of established phenotypes of selectively bred animal models with addiction traits, and 2) identify, from new or existing selectively bred animal models, genetic variants with implications for addiction related traits. Open date: December 31, 2013. Application due date(s): January 31, 2014; June 30, 2014; October 31, 2014; June 30, 2015; October 31, 2015; June 30, 2016; by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 5, 2013, NIDA issued a PA entitled **Functional Genetics, Epigenetics, and Non-coding RNAs in Substance Abuse (R21) [PA-14-013](#), (R01) [PA-14-014](#)**. This Funding Opportunity Announcement encourages basic functional genetic and genomic research in two areas: 1. functional validation to determine which candidate genes/variants/epigenetic/non-coding RNA features have an authentic role in addictive processes, and 2. detailed elucidation of the molecular pathways and processes modulated by candidate genes/variants, particularly for those genes with an unanticipated role in addiction. Open date: January 5, 2014 (R01), January 16, 2014 (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 December 6, 2013, NIDA issued a PAS entitled **Public Health Impact of the Changing Policy/Legal Environment for Marijuana (R01) [PAS-14-020](#)**. This initiative encourages research on the impact of changing marijuana policies and laws on public health outcomes, including marijuana exposure among children, adolescents, and adults; other licit and illicit drug use; education and professional achievement; social development; risky behaviors (e.g., drugged driving); mental health; HIV, etc. Open date: May 5, 2014. 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 10, 2013, NIDA issued a PA entitled **Discovering Novel Targets: The Molecular Genetics of Drug Addiction and Related Co-Morbidities (R01) [PA-14-025](#)**. This FOA encourages applications for research projects that identify and/or validate chromosomal loci and variations in genes that are associated with vulnerability to addiction and that inform the likelihood of responsiveness to treatment. Applications that propose to examine intermediate phenotypes or endophenotypes to assess the molecular genetics of drug addiction, addiction vulnerability and/or their associated co-morbidities and how they are related to drug addiction are especially encouraged. Open date: January 5, 2014. 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 FOAs Issued by the NIH Roadmap

On November 14, 2013, the NIH Common Fund issued a Roadmap Administrative Supplement entitled **Collaborative Activities to Promote Metabolomics Research (Admin Supp) [PA-14-003](#)**. This administrative supplement funding opportunity is part of the Common Fund Metabolomics Program created to increase and improve the nation's ability to undertake metabolomics analyses in translational and clinical research. Metabolomics has great potential to

advance our understanding of human diseases, but requires specialized expertise in metabolomics study design, technology, and data analysis and interpretation. This FOA supports supplemental funds to current NIH-funded research projects for new interactive collaborations between basic or clinical researchers and metabolomics experts to add biomedical studies requiring a metabolomics approach. In addition to enhancing the parent grant by adding metabolomics analyses, collaborative projects must include activities to increase the expertise of the biomedical research group in key aspects of metabolomics study design, analysis, and data interpretation. Open date: January 15, 2014. Application due date(s): February 14, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 10, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Computational Analyses Exploiting Reference Epigenomic Maps (R01)** [RFA-RM-14-001](#). This FOA, part of the NIH Common Fund program in Epigenomics, seeks applications from investigators proposing computational analyses that will take advantage of the publicly available reference epigenomic maps generated as part of the Roadmap Epigenomics Program. Open date: February 3, 2014. Application due date(s): March 3, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 12, 2013, the NIH Common Fund issued a Roadmap Administrative Supplement entitled **Administrative Supplement to Existing NIH Director's Biomedical Research Workforce Innovation Award: Broadening Experiences in Scientific Training (BEST) (Admin Supp)** [PA-14-040](#). The purpose of this FOA is to notify all Program Directors/Principal Investigators (PDs/PIs) of the Director's Biomedical Research Workforce Innovation Award: Broadening Experiences in Scientific Training (BEST) Program ([RFA-RM-12-022](#)) that funds are available for administrative supplements to parent awards in order to help meet the goals of the program. The Administrative Supplement awardee will establish and maintain electronic resources to support the BEST Award investigators in the coordination, collection, and dissemination of approaches and activities that broaden and complement traditional research training in biomedical sciences. The awardee will achieve these goals by developing, facilitating, and managing BEST Award program website(s) and/or portal(s), monthly teleconferences, and the annual meeting in collaboration with NIH personnel. Open date: February 24, 2014. Application due date(s): March 24, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Revisions to Add Single Cell Analysis to Active Research Projects (R01)** [RFA-RM-13-022](#), (U01) [RFA-RM-13-023](#). The purpose of this funding opportunity is to stimulate the adoption and validation of novel powerful single cell analysis (SCA) approaches by supporting collaborations of currently funded U01 investigators with developers of the SCA approaches. The collaborations must be new, possess the potential to substantially further the aims of the U01 project, and provide iterative and informed feedback to the SCA developers for continued refinement. By strengthening the interface between users and developers, the objective is to accelerate the discovery of fundamental new biological insights and translation of new diagnostic and therapeutic methods that analysis at the single cell level will allow. Open date: March 4, 2014. Application due date(s): April 4, 2014, by 5:00 PM local time of applicant

organization. AIDS application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Revisions to Add Single Cell Analysis to Active Research Projects (R21) [RFA-RM-13-021](#)**. This Funding Opportunity Announcement (FOA) issued by the National Institutes of Health, solicits early stage, high-risk/high-impact applications to develop next-generation tools that distinguish heterogeneous states among cells in situ. Applications should define the current state of technology as a benchmark against which the new tool(s) will be measured and should propose proof-of-concept testing of the tool(s) in a complex biological tissue or living organism. The new tools should provide substantially increased sensitivity, selectivity, spatiotemporal resolution, scalability of multiple global or functional measures of single cells. A particular emphasis for this FOA is on measures that minimize cell perturbation and permit viability of cells for repeated measures over time. These novel technologies will aid in obtaining a fine-grained, integrative and dynamic view of heterogeneous cellular states/classes and will provide innovative platforms to transform research into the cellular basis of diseases. Open date: March 4, 2014. Application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **Validation and Advanced Development of Technologies for the Study of Biological Properties of Single Cells (R33) [RFA-RM-13-020](#)**. This Funding Opportunity Announcement (FOA) invites applications that propose to accelerate the development of promising technologies for single cell analysis by taking them through the downstream optimization and validation process and establishing them as robust, well-characterized tools ready to transform our understanding of the biological properties of individual cells and the role those properties have in modulating the states of surrounding cells, tissues, and organs. This FOA solicits projects where proof-of-principle of the proposed technology or methodology has been established and supportive preliminary data are available. A current R21 award is not necessary. Projects should reflect the potential of single cell analysis to have a major impact on our understanding of biomedical processes, fulfill a critical unmet need by offering compelling advantages to end-users, and demonstrate the technology can be applied to multiple types of cells. It is expected that applications will have well-defined goal(s) with intermediate quantitative milestones. Projects proposing to use established technologies where the novelty resides in the biological or clinical question being pursued will be considered non-responsive and will not be reviewed. Open date: March 4, 2014. Application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): April 4, 2014, by 5:00 PM local time of applicant organization.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH National Research Mentoring Network (NRMN) (U54) [RFA-RM-13-017](#)**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage organizations with experience in the mentorship of individuals from diverse backgrounds as they pursue careers in biomedical research to submit grant applications for the NIH National Research Mentoring Network (NRMN). The NRMN will be a nationwide consortium to enhance the training and career development of individuals from diverse backgrounds who are pursuing biomedical, behavioral, clinical, and social science research careers (collectively termed biomedical research careers), through enhanced networking and mentorship

experiences. Application due date(s): March 2, 2014. AIDS application due date(s): Not Applicable.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Building Infrastructure Leading to Diversity (BUILD) Initiative (U54) [RFA-RM-13-016](#)**. The NIH encourages institutions that seek to engage undergraduate students in innovative mentored research training programs to submit applications for cooperative agreement awards through the NIH Building Infrastructure Leading to Diversity (BUILD) initiative, one of three new Common Fund initiatives that together aim to enhance diversity in the biomedical, behavioral, clinical, and social sciences research workforce. Addressing a major leakage point in the research workforce pipeline, BUILD awards are intended to support the design and implementation of innovative programs, strategies and approaches to transform undergraduate research training and mentorship. BUILD awards will also support institutional and faculty development to further strengthen undergraduate research training environments. Application due date(s): March 2, 2014. AIDS application due date(s): Not Applicable.

On December 19, 2013, the NIH Common Fund issued a Roadmap RFA entitled **NIH Coordination and Evaluation Center for Enhancing the Diversity of the NIH-Funded Workforce Program (U54) [RFA-RM-13-015](#)**. The purpose of this Funding Opportunity Announcement (FOA) is to encourage institutions with expertise in data coordination and evaluation of research training, career development, and mentoring programs to submit applications for the establishment and operation of the Coordination and Evaluation Center (CEC) for the NIH Enhancing the Diversity of the NIH-Funded Workforce Program. This program will consist of three integrated initiatives: the Building Infrastructure Leading to Diversity (BUILD) initiative, the National Research Mentoring Network (NRMN) and the CEC. Awardees funded through these initiatives will work together as a consortium which will be coordinated by the CEC. The CEC will facilitate the establishment of program-wide goals and agreed upon hallmarks of successful biomedical researchers at multiple career stages. The CEC will develop appropriate instruments and processes to assess the impact of BUILD and NRMN activities on attainment of these hallmarks by program participants. It will coordinate the collection of data from BUILD and NRMN awardees and other sources, assess the data in an ongoing way, provide feedback to the consortium and facilitate an iterative process of program adjustment to maximize the research benefit of BUILD and NRMN activities. Application due date(s): March 2, 2014. AIDS application due date(s): Not Applicable.

New RFAs Issued as Part of Collaborative Research on Addiction (CRAN)

On January 3, 2014, NIDA, NIAAA and NCI issued an RFA entitled **Using Social Media to Understand and Address Substance Use and Addiction (R01) [RFA-CA-14-008](#), (R21) [RFA-CA-14-009](#)**. This Funding Opportunity Announcement (FOA) is part of a trans-NIH initiative known as Collaborative Research on Addiction (CRAN). The goal of this FOA is to inspire and support research projects investigating the role of social media in risk behaviors associated with the use and abuse of alcohol, tobacco, and other drugs (hereafter referred to as "ATOD") and projects using social media to ameliorate such behaviors. Each research project proposed in response to this FOA must be focused on one of the two distinct areas: 1) observational research using social media

interactions as surveillance tools to aid in the understanding of the epidemiology, risk factors, attitudes, and behaviors associated with ATOD use and addiction, or 2) intervention research measuring the reach, engagement, and behavioral and health impact of social media-based interventions for the screening, prevention, and treatment, of ATOD use and addiction. Original research preliminary data are not required but all projects are expected to be supported by a strong rationale that is based on integrating to the extent possible the available relevant information from various sources. Open date: February 25, 2014. Application due date(s): March 25, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

New PAs Issued as Part of Collaborative Research on Addiction (CRAN)

On August 28, 2013, NIAAA and NIDA issued a PA entitled **Mechanisms of Alcohol and Stimulant Co-Addiction (R01) PA-13-339, (R21) PA-13-340**. This FOA encourages applications from institutions/organizations that propose to study the neurobiological and behavioral mechanisms that might explain how alcohol and stimulants interact at genetic, epigenetic, cellular, neurocircuitry and behavioral levels to promote co-addiction. Open date: January 5, 2014 (R01) January 16, 2014 (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.

On December 11, 2013, NIDA with NIAAA, issued a PA entitled **Basic Mechanisms of Brain Development for Substance Use and Dependence (R01) PA-14-026**. This Funding Opportunity Announcement (FOA) encourages Research Project Grant (R01) applications from institutions/organizations that propose to study the developing brain or brain areas that play significant roles in mediating emotional and motivated behavior and in substance use and dependence. All stages of brain development are of interest, but a new emphasis of the current reissue of this initiative is to support basic neuroscience research on fundamental mechanisms of brain development during prepuberty and the adolescent period in relation to the problems of substance abuse and co-morbidity with psychiatric disorders. Topics of interest pertaining to brain development of this initiative include, but are not limited to, the euphoric properties of abused substances, actions of psychotherapeutic agents, and their consequences on memory, cognitive and emotional processes. An additional major goal of this initiative is to understand how exposure to substances of abuse affects the cellular and molecular mechanisms underlying nervous system development and neural circuit functions implicated in substance use and addiction. Open date: January 5, 2014. 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 12, 2013, NIDA, with NIAAA, issued a PA entitled **Women & Sex/Gender Differences in Drug and Alcohol Abuse/Dependence (R21) PA-14-036, (R03) PA-14-037, (R01) PA-14-038**. The purpose of this Funding Opportunity Announcement (FOA) is to advance research on male-females differences in drug and alcohol abuse and addiction and on factors specific to women. Both human and animal model studies are sought. Open date: January 16, 2014. 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 7, 2014, NIDA, with NIAAA, issued a PA entitled **Substance Use and Abuse, Risky Decision Making and HIV/AIDS (R01) [PA-14-061](#), (R21) [PA-14-062](#), (R03) [PA-14-063](#)**. This Funding Opportunity Announcement (FOA) is intended to stimulate model-driven research to understand the ways that people make decisions about engaging in behaviors that impact the risk of acquiring or transmitting HIV, or to adhere to treatments for HIV. Decision making processes may contribute to both substance use/abuse and other HIV acquisition or transmission risks. A better understanding of decision making processes in the context of brain neural networks and their associated functions would lead to the development of better strategies to reduce the frequency of HIV-risk behaviors. Therefore, this FOA encourages applications to study 1) cognitive, motivational or emotional mechanisms and/or 2) brain neuroendocrine and reinforcement systems that related to HIV-risk behaviors or treatment non-compliance. Open date: April 7, 2014. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization. The first application due date for this FOA is June 5, 2014. AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization. The first AIDS application due date for this FOA is May 7, 2014.

New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant

Interpreting Variation in Human Non-Coding Genomic Regions Using Computational Approaches and Experimental Assessment (R01) [RFA-HG-13-013](#)

Low-Cost, Pragmatic, Patient-Centered Randomized Controlled Intervention Trials (UH2/UH3) [RFA-HL-14-019](#)

Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) for Neuroscience and Disorders of the Nervous System (R01) [RFA-MH-14-214](#)

BD2K-LINCS-Perturbation Data Coordination and Integration Center (DCIC) (U54) [RFA-HG-14-001](#)

Development of an NIH Data Discovery Index Coordination Consortium (U24) [RFA-HL-14-031](#)

Mentored Career Development Award in Biomedical Big Data Science for Clinicians and Doctorally Prepared Scientists (K01) [RFA-HG-14-007](#)

Open Educational Resources for Biomedical Big Data (R25) [RFA-HG-14-009](#)

Courses for Skills Development in Biomedical Big Data Science (R25) [RFA-HG-14-008](#)

New PAs Issued by Other NIH/HHS Components in which NIDA is a participant

NIH Support for Conferences and Scientific Meetings (Parent R13/U13) [PA-13-347](#)

Academic Research Enhancement Award (Parent R15) [PA-13-313](#)

Opportunities for Collaborative Research at the NIH Clinical Center (U01) [PAR-13-358](#)
Pre-application: Opportunities for Collaborative Research at the NIH Clinical Center (X02)
[PAR-13-357](#)

Development of Assays for High-Throughput Screening for Use in Probe and
Pre-therapeutic Discovery (R01) [PAR-13-364](#)

Research on the Health Determinants and Consequences of Violence and its Prevention,
Particularly Firearm Violence (R21) [PA-13-369](#), (R03) [PA-13-368](#), and (R01) [PA-13-363](#)

Analysis of Genome-Wide Gene-Environment (G x E) Interactions (R21) [PAR-13-382](#)

Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research
Training Grant (Parent T32) [PA-14-015](#)

NIH/PEPFAR Collaboration for Implementation Science (Admin Supp) [PA-14-024](#)

Administrative Supplements for Research on Sex/Gender Differences (Admin Supp)
[PA-14-027](#)

Centers for AIDS Research and Developmental Centers for AIDS Research (P30)
[PAR-14-041](#)

Mentored Patient-Oriented Research Career Development Award (Parent K23) [PA-14-049](#)

Mentored Quantitative Research Development Award (Parent K25) [PA-14-048](#)

Midcareer Investigator Award in Patient-Oriented Research (Parent K24) [PA-14-047](#)

Mentored Clinical Scientist Research Career Development Award (Parent K08) [PA-14-046](#)

Independent Scientist Award (Parent K02) [PA-14-045](#)

Mentored Research Scientist Development Award (Parent K01) [PA-14-044](#)

NIH Pathway to Independence Award (Parent K99/R00) [PA-14-042](#)

PHS 2014-02 Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business
Innovation Research Grant Applications (Parent SBIR [R43/R44]) [PA-14-071](#)

PHS 2014-02 Omnibus Solicitation of the NIH for Small Business Technology Transfer Grant
Applications (Parent STTR [R41/R42]) [PA-14-072](#)

New RFAs Issued by the NIH Blueprint for Neuroscience Research

BRAIN Initiative: Integrated Approaches to Understanding Circuit Function in the Nervous System (U01) [RFA-NS-14-009](#)

BRAIN Initiative: Optimization of Transformative Technologies for Large Scale Recording and Modulation in the Nervous System (U01) [RFA-NS-14-008](#)

BRAIN Initiative: New Technologies and Novel Approaches for Large-Scale Recording and Modulation in the Nervous System (U01) [RFA-NS-14-007](#)

BRAIN Initiative: Planning for Next Generation Human Brain Imaging (R24) [RFA-MH-14-217](#)

BRAIN Initiative: Development and Validation of Novel Tools to Analyze Cell-Specific and Circuit Specific Processes in the Brain (U01) [RFA-MH-14-216](#)

BRAIN Initiative: Transformative Approaches for Cell-Type Classification in the Brain (U01) [RFA-MH-14-215](#)

COMMUNICATIONS

PUBLICATIONS/VIDEOS

NIDA Publications and Online Resources

“Seeking Drug Abuse Treatment: Know What to Ask” (Revised June 2013):

<http://www.drugabuse.gov/publications/seeking-drug-abuse-treatment>

“Marijuana Facts for Teens” (Revised Oct. 2013):

<http://www.drugabuse.gov/publications/marijuana-facts-teens>

“Research Report Series: Methamphetamine” (Revised September 2013):

<http://www.drugabuse.gov/publications/research-reports/methamphetamine-abuse-addiction>

“Heads Up” (Scholastic/NIDA) 2012-13 Teacher’s Compilation:

http://www.scholastic.com/smp/pdfs/nida/NIDA_YR11-TE_Comp.pdf

“Heads Up” (Scholastic/NIDA) 2012-13 Student’s Compilation:

http://www.scholastic.com/smp/pdfs/nida/NIDA_YR11-Stu_Comp.pdf

NIDA Notes (now online only)

Twenty new articles have been posted on the [NIDA Notes homepage](#). Three new videos ([Dave Thomas](#), [Marilyn Huestis](#), [Madeleine Meyer](#)), also available as podcasts, were posted. In addition, the NIDA Notes Homepage was redesigned, improving the search engine, increasing internal referencing and linking, and adding a subscription page for podcasts. NIDA sent out three content e-blasts to 20,000 subscribers and 1 subscription e-blast to NIDA grantees. NIDA Notes had 32,000 page views from mid-October to mid-November.

“Principles of Adolescent Substance Use Disorder Treatment: A Research Based Guide” (Released January 2014)

<http://www.drugabuse.gov/publications/principles-adolescent-substance-use-disorder-treatment-research-based-guide>

“Substance Use Disorders in Adolescents: Screening and Engagement in Primary Care Settings” (Released January 2014)

http://webcampus.drexelmed.edu/nida/module_2/default_FrameSet.htm

Heads Up: “Drugs and Your Body: It Isn’t Pretty” (Scholastic/NIDA) (January 2014)

<http://www.scholastic.com/drugs-and-your-body>

A new Web interactive designed for grades 7-12 that uses graphics, videos and quizzes to demonstrate the wide-ranging harmful effects of drugs on the brain and body.

Videos

- **CEWG Region Report: Drug Abuse in Philadelphia, June 2013** <http://youtu.be/CiAxo0MFEXo>
- **NIDA NOTES: NIDA@Work Presents, Dr. Dave Thomas** <http://youtu.be/c-Wixxy5IYA>
- **National Drug Facts Week: Do You Have Something to Say? Teens Do.** <http://youtu.be/JIihA4FeT2c>
- **CEWG Region Report: Drug Abuse in Detroit, Wayne County, and Michigan, June 2013** <http://youtu.be/jwRWmgniF6Q>
- **What's New at NIDA: Office of Science Policy and Communication Director's notes** <http://youtu.be/PyFYgxR-4sk>
- **Chat Day, NDFW, release June 2013** <http://www.youtube.com/watch?v=1HlsRRjwa2I>
- **I-Science Chief Resident Program, June 2013** http://www.youtube.com/watch?v=iBRL_KkwxI8
- **Jane Maxwell, CEWG, Emerging Drug, Lean** <http://youtu.be/RJfybUfDaqI>
- **Carol Boyd, CEWG, Prescription Drug Use** <http://youtu.be/bORYUoQrfDU>
- **Drs. Brooks, NIDATV** <http://www.youtube.com/watch?v=U7hOpCiJISQ>
- **What's New at NIDA/Jack Stein, August Insite** http://youtu.be/D_tlCecHEDk
- **I-Science, Evidence Based Practices** <http://youtu.be/b3zNDnBoZLY>
- **I-Science: NIDA's Look into Old Designer Drugs, New Cultural Phenomenon** <http://youtu.be/FZMgIO2tC18>
- **I-Science: NIDA's Look into the Risks of Designer Drugs** <http://youtu.be/-WwNwW0aDh4>
- **NIDA TV Spotlight on the Iraqi Community Epidemiology Work Group (CEWG)** <http://youtu.be/3mnM5nxZgIs>
- **NIDATV Scientist Spotlight (Cannabinoid), release Aug 2013** <http://youtu.be/Zyh-N3k30jg> and http://youtu.be/DsE9_aJfZGw
- **Duke University Dr. Meier Interview, Aug 2013** <http://youtu.be/qJXnxHYapbE>
- **Teen MOTS, August 2013** <http://youtu.be/dWfnzQqVMVs>
- **Avant-Garde Award 2013** <http://youtu.be/J9sZmWwBqbk>
- **Dr. Volkow: Addicted Human Brain (For CMI)** <http://www.youtube.com/watch?v=1J87LFHlkp8>
- **NIDA TV Spotlight: "Recovery: What's Research Got to do with It, Part II"** <http://youtu.be/QYxi4HhpXhw>
- **NIDA TV Spotlight: "Recovery: What's Research Got to do with It, Part I"** <http://youtu.be/2M4rYZU48EM>
- **NIDA NOTES: NIDA@Work Presents, Dr. Marilyn Huestis** <http://youtu.be/hn2jVa5Izrg>
- **2013 ISEF Addiction Science Award Winners Visit NIDA** <http://youtu.be/ZjLfwyyEILU>
- **I-Science: NIDA's Look into what we still need to know about Synthetic Cannabinoids** <http://youtu.be/SP667cI6NA>

- **NIDATV Scientist Spotlight (E-cig), Release Oct 2013**
<http://www.youtube.com/watch?v=Iz67IqkLwYs>
- **MTF: Dr Volkow on Marijuana**
<http://www.youtube.com/watch?v=piN8m2OfimM&feature=c4-overview&list=UUfXHx9qyqeB3ezHQnHk8zXA>
- **MTF: Drs. Volkow and Compton**
<http://www.youtube.com/watch?v=Ki5k4Xetv3I&feature=c4-overview&list=UUfXHx9qyqeB3ezHQnHk8zXA>
- **MTF: Dr. Johnston** http://www.youtube.com/watch?v=_4KkEAXUYuM&feature=c4-overview&list=UUfXHx9qyqeB3ezHQnHk8zXA

CTN-Related Publications

Six 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 28 CTN studies are now available on the NIDA Data Sharing website <http://www.nida.nih.gov/CTN/Data.html>. Over 2,000 data sets have been downloaded by researchers from 45 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.

COMMUNITY AND PRESS EVENTS

2013 winners of Addiction Science Award present at NIDA

The 2013 winners of NIDA's Addiction Science Awards, part of the Intel International Science and Engineering Fair (ISEF), presented their projects to NIDA Director Nora Volkow and other NIDA scientists on August 13, 2013, and were given a tour of the NIH campus. The Addiction Science Awards are coordinated by NIDA as well as Friends of NIDA, a private group dedicated to furthering NIDA's mission. ISEF is the world's largest science competition for high school students.

NIDA participates in Facebook Chat with Partnership at DrugFree.org.

On September 16, 2013, Dr. Volkow participated in a live Facebook chat with the Partnership at Drugfree.org for its "Meet the Parents Hour," which aims to provide science-based information to parents and those affected by drugs and alcohol. Over 3,300 people were reached during the hour-long chat, with close to 40 questions answered.

Dr. Nora Volkow Honored at Child Mind Institute Event

On October 1, 2013, the Child Mind Institute hosted its third annual *On the Shoulders of Giants* scientific symposium, honoring NIDA Director Nora Volkow and two of her scientific mentees.

Dr. Volkow's pre-recorded video presentation summed up her groundbreaking work in drug addiction and focused on chemical dependency as a disease of the brain.

NIDA IRP Hosts Mentor Foundation USA "Shatter the Myths" Event

On October 30, 2013, NIDA provided press support to an IRP event with the Mentor Foundation USA in an effort to "Shatter the Myths" about drug abuse. Nearly 200 high school students were in attendance at the Johns Hopkins Bayview Medical Center in Baltimore, MD. The goal of the event was to give teenagers a forum to learn about the dangers of drug abuse, ask questions and get scientific answers about substance abuse. IRP Scientific Director Dr. Antonello Bonci was interviewed by *A&E TV* and *WBAL-11* (a local NBC affiliate) regarding his presentation. NIDA staff live-tweeted from the event. Other speakers included Baltimore City Mayor Stephanie Rawlings-Blake, Office of National Drug Control Policy Deputy Director David Mineta, and Dr. Lonise Bias, mother of the late Len Bias.

NIDA Director and other thought leaders meet with His Holiness the Dalai Lama

On October 30, 2013, Dr. Volkow participated in *Mind and Life XXVII: Craving, Desire, and Addiction*, a conference of the Mind and Life Dialogues between His Holiness the Dalai Lama and other leading scientists and philosophers. The meeting, which took place at His Holiness the Dalai Lama's private residence in Dharamasala, India, brought together contemplative practitioners, Buddhist and Christian scholars, and leading scientific researchers to achieve new understandings that may ultimately lead to improved treatment of the root causes of craving, desire and addiction. An audience of about 200 included His Holiness the Dalai Lama, Tibetan monastics, scientists, scholars, contemplatives, Mind & Life Institute staff, and special guests. Dr. Volkow gave an overview titled *The Role of Dopamine in the Addicted Human Brain*, which described addiction as a disease and detailed the latest in neuroscience. Her presentation and interaction with the Dalai Lama are posted on the NIDA Web site (<http://www.drugabuse.gov/about-nida/noras-blog/2013/11/talking-to-dalai-lama-about-addiction-science>)

Dr. Nora Volkow participated in NIH-Sponsored Press Conference at SfN

On November 10, 2013, Dr. Volkow presented the status of NIDA's research at the Society of Neuroscience in San Diego, CA. NIDA posted tweets on its Twitter account surrounding the event.

Press Releases

- August 29, 2013** [2013 Avant-Garde Awards explore HIV without AIDS, protective genes](#)
- September 9, 2013** [National Drug Facts Week 2014 begins January 27](#)
- October 21, 2013** [NIDA's drug abuse information for teens goes mobile](#)
- November 8, 2013** [Dr. Wilson Compton named Deputy Director, National Institute on Drug Abuse](#)
- December 10, 2013** [Stimulant-addicted patients can quit smoking without hindering treatment](#)

December 18, 2013 [Sixty percent of 12th graders do not view regular marijuana use as harmful](#)

January 3, 2014 [Severe mental illness tied to higher rates of substance use](#)

January 23, 2014 [New substance abuse treatment resources focus on teens](#)

Science Spotlights and Announcements

August 12, 2013 [Statement from NIDA Director Nora Volkow on NIDA's commitment to marijuana research.](#)

August 21, 2013 [Parents and siblings influence future drug risk in different ways.](#)

August 21, 2013 [NIDA and Lightlake Therapeutics partner to expand access to medication to treat opioid overdose.](#)

September 20, 2013 [NIDA updates its consumer treatment guide in recognition of National Recovery Month.](#)

October 23, 2013 [No added benefit from risk-reduction counseling at HIV testing.](#)

October 29, 2013 [Medication to treat marijuana addiction may be on the horizon.](#)

November 1, 2013 [Gene variant may predict whether a person will benefit from nicotine replacement therapies.](#)

November 7, 2013 [NIDA's Dr. Wilson Compton receives Health and Human Services Meritorious Service Award.](#)

November 21, 2013 [New breath test may detect recent marijuana use.](#)

November 22, 2013 [New study shows that drug overdose is the leading cause of death in former prisoners.](#)

December 12, 2013 [Three NIH Institutes highlight collaboration for addiction research.](#)

December 16, 2013 [National Institute on Drug Abuse to announce results of 2013 Monitoring the Future Survey.](#)

December 19, 2013 [Registration open for Drug Facts Chat Day; 2014 Drug IQ Challenge preview available.](#)

December 26, 2013 [Research suggests new genetic target to treat cocaine addiction.](#)

January 24, 2014 [*NIDA's Dr. Marilyn Huestis chosen for new National Commission on Forensic Science*](#)

Meetings/Conferences

Select Meetings and Conferences in which NIDA played a significant role

NIDA involvement at the **American Academy of Child and Adolescent Psychiatry (AACAP) Annual Meeting**, held in Orlando, Florida, October 22-27, 2013 included two symposia and a grant writing workshop. Cheryl Boyce, Ph.D. (NIDA) and Brooke S.G. Molina, Ph.D. (University of Pittsburgh School of Medicine) co-chaired a session titled "Understanding ADHD and Smoking: Current Issues and Perspectives". Presenters included Scott H. Kollins, Ph.D. (Duke University Medical Center), Alexandra Potter, Ph.D. (University of Vermont), Stephanie Cardoos, M.A. (University of California, Berkley), and Timothy Wilens, M.D. (Massachusetts General Hospital). Geetha Subramaniam, M.D. (NIDA) and Howard Moss, M.D. (NIAAA) co-chaired a session titled "Medication Therapies for Youth with Alcohol and Other Substance Use Disorders- a Hands-on Educational Experience". Kevin Gray, M.D. (University of South Carolina) participated as a presenter. NIDA staff presented a grant writing workshop titled "NIH Research Priorities & Competitive Grant Writing".

SFN/ENDURE: NIDA's Office of Diversity and Health Disparities Acting Director, Dr. Albert Avila, co-organized and presented at the NIH Blueprint initiative "**Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (ENDURE)**" pre-meeting at SFN on November 9, 2013. This initiative aims to raise interest and opportunities in neuroscience research for individuals who are typically underrepresented in the neurosciences. The goal is to provide such individuals with training at the undergraduate level, so that they are prepared to enter and successfully complete neuroscience Ph.D. programs. Dr. Avila gave a presentation on NIH research funding opportunities.

NIDA's Office of Diversity and Health Disparities Acting Director, Dr. Albert Avila, in collaboration with staff from the National Institute of Biomedical Imaging and Bioengineering organized a pre-meeting workshop on Wednesday, November 13th at the **Annual Biomedical Research Conference for Minority Students** for students from the UMBC Meyerhoff and Savannah State undergraduate STEM scholars program. The meeting provided over 40 students valuable information and advice on transitioning from undergraduate to a graduate program, graduate school admission and expectations, and small group sessions focused on addressing individual questions ranging from research proposals to funding sources.

On September 11, 2013, NIDA, in conjunction with NIAAA, NICHD, NIMH and NINDS, held "**Views By Two: Addressing Health Disparities Through Neuroscience**" with speakers, Drs. Barry Jordan (Burke Rehabilitation Hospital) and Shari Wade (Cincinnati Children's Hospital Medical Center), who presented on the topic "Fundamental Mechanisms of TBI and Implications for Health Disparities Research." The goal of the series is to increase awareness of health disparities relating to neuroscience through a collegial discussion between 2 renowned scientists on

a shared topic. Flair Lindsey, Program Analyst, Special Populations Office, represents NIDA on this inter-agency planning committee.

On September 19-20, 2013, the NIDA Office of Diversity and Health Disparities hosted a two-day **NIDA Special Populations Research Development Seminar Series Workshop** in Bethesda, Maryland. Chaired by Flair Lindsey, Program Analyst, this workshop convened 15 new substance abuse investigators and NIDA-supported faculty mentors in an intensive grants development workshop setting. During the workshop, new investigators learned of NIDA's research and funding priorities and the NIH grants submission and review process, met with NIDA program staff and NIDA funded researchers, and received feedback on research proposals.

PLANNED MEETINGS (pending approval)

2014 Community Anti-Drug Coalitions of America (CADCA) National Forum– National Harbor, MD, February 3-6, 2014.

NIDA staff will deliver two sessions at the CADCA National Forum. Ruben Baler, Ph.D. (NIDA) will present “Where do Addictions Come from?” and Jacqueline Lloyd, Ph.D., (NIDA) will chair a session on “Cultural and Contextual Adaptation of Evidence-Based Prevention Interventions for Real World Community and Practice Settings.” The session will highlight the ongoing research being conducted by Dr. Jeanne Poduska (American Institutes for Research, Baltimore, MD) on the Good Behavior Game, which is an evidence-based classroom behavior management strategy. Dr. Volkow will deliver the plenary address, and there will be a Power Session delivered by Drs. Wilson Compton and Jack Stein titled *Science Update from NIDA: Spotlight on Marijuana-Related Research*

2014 American Psychiatric Association Annual (APA) Meeting – New York, NY, May 3-7, 2014.

NIDA will hold a track of sessions at the APA Annual Meeting. Dr. Nora Volkow is scheduled to deliver the Frontiers of Science Lecture, and hold an interactive session with residents. NIDA staff will chair sessions on a variety of substance abuse related topics including: Cannabis Use and Youth: Risk Assessment and Implications for Clinical Practice, The Role of Substance Use in Violence Against Self and Others, Persistence and Desistance of Comorbid Drug Abuse and Psychiatric Disorders in Adolescence, Biological Approaches To Treat Substance Use Disorders, and Diagnostic and Assessment Considerations for the Treatment of Comorbid Opioid Addiction and Chronic Pain.

College on Problems of Drug Dependence (CPDD) Annual Scientific Meeting – San Juan, Puerto Rico, June 14–19, 2014.

The National Institute on Drug Abuse (NIDA) will sponsor a Grant-Writing and Career Development Workshop at the CPDD Annual Scientific Meeting. The Grant/Career Workshop provides new or junior investigators with information and skills to advance their research careers, with a heavy emphasis on NIDA funding opportunities, grantsmanship, and the grant application process. NIDA will also be offering a limited number of travel awards to partially defray the cost of attending this conference. Only NIDA-supported NRSA trainees, NRSA fellows, and Minority

Supplement recipients are eligible for this award. The application deadline for these awards was December 19, 2013.

The NIDA CTN Steering Committee Meeting will be held March 11-13, 2014 in Gaithersburg, MD.

GRANTEE HONORS AND AWARDS

Carolyn Mazure, Ph.D., Director of Women's Health at Yale, was named to a new endowed professorship that provides permanent leadership for Women's Health Research at Yale, the University's interdisciplinary research center focused on women's health and gender differences. Dr. Mazure, who founded Women's Health Research at Yale in 1998 and has been Director from the start, is the inaugural Norma Weinberg Spungen and Joan Lebson Bildner Professor of Women's Health Research at Yale.

David Olds, Ph.D., Professor of pediatrics, nursing, psychiatry and public health at the University of Colorado School of Medicine and founder of the Nurse –Family Partnership (NFP) program is the 2012-2013 recipient of the Chase Faculty Community Service Award. Each year a faculty member at the University of Colorado who provided exceptional service to the community is honored. Dr. Olds is recognized for the extraordinary impact and benefits of his work to children and families worldwide.

CTN New England Consortium Node

John Hamilton, LMFT, CEO of Recovery Network of Programs, Inc. (Connecticut) was one of 8 recipients of the 2013 *Nyswander/Dole "Marie" Award*. Awardees are nominated and selected by their peers for outstanding service in the opioid treatment community. The awards were presented at the 2013 American Association for the Treatment of Opioid Dependence, Inc. (AATOD) Conference in Philadelphia on November 12, 2013. Dr. Vincent Dole and Dr. Marie Nyswander were the first recipients of this Award in 1983. The Association has been responsible for bestowing this honor since the first Regional Conference of 1984 in New York.

Shelly F. Greenfield, M.D., M.P.H. from the New England Consortium Node was recently awarded the R. Brinkley Smithers Distinguished Scientist Award from the American Society of Addiction Medicine (ASAM) for 2014. The award was established by ASAM in 1995 and is presented annually. Dr. Greenfield has been invited to receive the award and deliver the keynote plenary address at the society's annual medical scientific conference on April 11, 2014, in Orlando, Florida. The 45th Annual Medical-Scientific ASAM Conference is scheduled for April 10-13, 2014.

CTN Southern Consortium Node

Kathleen T. Brady, M.D., Ph.D., Distinguished University Professor and Principal Investigator of the Southern Consortium Node, received the 2013 Medical University of South Carolina's (MUSC) Women Scholars Faculty Advancement Award. This award recognizes the MUSC faculty member who best demonstrates excellence in his/her commitment to the advancement of women faculty. In recognizing Dr. Brady, the Women Scholars Initiative Committee welcomed the opportunity to publicly recognize her and thank her for the vision and opportunities she provides to women faculty.

MacArthur Foundation Award

Dr. Susan Murphy, Ph.D., received the prestigious John D. and Catherine T. MacArthur Foundation Award. Dr. Murphy is a statistician who is developing new methodologies to evaluate courses of treatment for individuals coping with chronic or relapsing disorders such as depression or substance abuse. Her work has influenced many in the CTN.

AMERSA Awardees from the CTN

The Association for Medical Education and Research in Substance Abuse (AMERSA) held its 37th National Conference in Bethesda, Maryland, November 7-9, 2013. The conference brought together researchers and health professional educators to learn about scientific advances and teaching approaches. Several CTN members were recognized at this meeting:

- George Woody, M.D., received the John P. McGovern Award.
- David Liu, M.D./Marc Fishman, M.D./Ned Nunes, M.D., received the Best Workshop Award.
- Jennifer McNeely, M.D., received the John Nelson Chappel Research Award.
- Joshua Lee, M.D., received Best Research Abstract Semi-finalist Award.

STAFF HIGHLIGHTS

Staff Honors and Awards

Donna Calu, Ph.D., IRP, received the 2014 Winter Conference in Brain Research Travel Fellowship and is an invited lecturer at the 47th Winter Conference in Brain Research in Steamboat Springs, Colorado.

Chien-Ying Chuang, Ph.D., IRP, was the recipient of an NIH FARE award.

Lori Ducharme, Ph.D., DESPR, Services Research Branch, was appointed to the Executive Committee of the Veteran's Administration's Substance Use Disorder Quality Enhancement Research Initiative (QUERI).

Marilyn Huestis, Ph.D., IRP, was reappointed to the World Anti-doping Agency Prohibited Drug List Committee that determines the list of prohibited substances for all elite sports.

Anton Ilango Micheal, Ph.D., IRP, received the 2014 NIDA-IRP postdoctoral FARE award.

Mary Pfeiffer, Ph.D., Assistant Director, Office of Education and Career Development, IRP, received the NIH Director's Award for her work on the Feds Feed Families project.

Tsung-Ping Su, Ph.D., IRP, was appointed by the Johns Hopkins University in October as a member of the Johns Hopkins Graduate Board of Examiners in October 2013.

Dong Wang, Ph.D., IRP, received the 2014 NIDA-IRP postdoctoral FARE award.

Staff Changes

New Employees

Sandrine Pirard Janne d'Othee, M.D., Ph.D., M.P.H. joined the Chemistry and Drug Metabolism Section, IRP, as staff clinician in August 2013.

Heather Kimmel, Ph.D. joins the Epidemiology Research Branch in DESPR. Dr. Kimmel received her undergraduate degree in biology from Wake Forest University and her Ph.D. in neuroscience from Emory University. As a faculty member at Emory University, she examined the effects of psychostimulants on neuropharmacology and behavior in rodent and nonhuman primate models of addiction, and was also involved in medication development efforts to help treat those addicted to psychostimulants. She comes to us more recently from an AAAS Science & Technology Policy fellowship in the Economics, Exposure, and Technology Division at US EPA. Heather will be developing the tobacco program in DESPR, including activities relating to the PATH study and other collaborations with the Center for Tobacco Products at FDA.

Avni Shah, M.D., M.P.H. joins DESPR and the PATH Study. Dr. Shah comes to us most recently from Georgetown University, where she worked on several clinical trials. By way of training, Avni is a medical doctor, holds an MPH in Environmental Health Sciences, and earned a graduate certificate in biostatistics (while she was working at Georgetown). Avni joins the PATH Study to increasingly assume responsibilities in the areas of data management and data analysis (both topics are becoming increasingly demanding and important for PATH), and to contribute substantively to the long-term plans for bio specimens. She also has experience with tobacco-cessation interventions, and will likely contribute to plans/papers/analyses on topics related to cessation.

Eric Wargo, Ph.D. joined the Science Policy Branch, Office of Science Policy and Communications (OSPC) in December 2013 as a Health Science Policy Analyst. Dr. Wargo received his Ph.D. in Anthropology from Emory University in 2000 and has since worked as a writer and editor in Washington, D.C. From 2005 through 2011, he was Editorial Director at the Association for Psychological Science (APS) and Managing Editor of the APS journals *Current Directions in Psychological Science* and *Psychological Science in the Public Interest*. He joined the Science Policy Branch of OSPC as a science writer contractor in January 2012.

Rachel Wolf joined the Office of Science Policy and Communications' Public Information and Liaison Branch in November 2013 as the NIDA Deputy Press Officer. Before joining NIDA, Rachel was a CDC contractor working for the Oak Ridge Institute for Science and Education and on other CDC contracts as well as working with the CDC communications office. Rachel has a Bachelor's in Biology and a Masters in Behavioral Sciences and Health Education.

New Appointments/Transfers

Wilson Compton M.D., M.P.E. of the Division of Epidemiology, Prevention, Research and Services Branch (DESPR), is appointed as the Deputy Director for the National Institute on Drug Abuse (NIDA). Dr. Wilson Compton is a well-recognized expert in the addiction field with over two decades of research, clinical, and administrative experience. For the past 10 years, he has been the Director of the Division of Epidemiology, Services and Prevention Research (DESPR) at NIDA where he very competently and creatively managed a large and complex research program of national and international scope spanning a broad range of population-based science. Prior to joining NIDA, Dr. Compton was Associate Professor of Psychiatry and Director of the Master in Psychiatric Epidemiology Program at Washington University in Saint Louis as well as Medical Director of Addiction Services at the Barnes-Jewish Hospital in Saint Louis. He received his undergraduate education from Amherst College and attended Washington University School of Medicine where he also completed his residency training in psychiatry and later graduated from the Master in Psychiatric Epidemiology program. In 2008, he received the Senior Scholar Health Services Research Award from the American Psychiatric Association and in 2010 the Paul Hoch Award from the American Psychopathological Association. Dr. Compton is highly respected as a scientist and has been a prolific author of over 100 articles, book chapters, research manuals, and invited publications.

Redonna Chandler, Ph.D. assumed the position of Acting Director for the Division of Epidemiology, Services, and Prevention Research, National Institute on Drug Abuse, Bethesda, MD. Dr. Chandler is an expert in the treatment of substance use disorders with experience in research, clinical practice, and science administration. For the past 12 years she has served in numerous positions at NIDA including 7 years as the Chief of the Services Research Branch where she managed a portfolio of research intended to improve the quality of treatment services effectively addressing substance use disorders and HIV. Prior to joining NIDA, Dr. Chandler worked for the Bureau of Prisons implementing and evaluating substance abuse treatment programs for federally sentenced offenders and served as an adjunct professor at the University of Kentucky. Dr. Chandler earned her Ph.D. in psychology from the University of Kentucky and has authored numerous peer-reviewed articles and book chapters. Dr. Chandler has been recognized with several awards for her scholarship and leadership in drug abuse research.

Lori Ducharme, Ph.D. is serving as Acting Deputy Branch Chief, Division of Services Research Branch, DESPR.

David Daubert has been appointed NIDA's Deputy Executive Officer. Dave has provided administrative leadership at NIDA for the past eleven years, serving first as Deputy Chief of OM's Administrative Management Branch (AMB) and then Chief, AMB since 2005. Prior to joining NIDA, he served as a Budget Analyst at NIMH's Intramural Research Program and an Administrative Officer at NIMH's Extramural Program. Dave has been a leader on several NIH-level groups and initiatives including the Extramural Administrative Management Council and the NIH Administrative Strategic Plan. Dave holds a degree in Management Technology and has received numerous performance awards including the NIH Director's Award.

Nathaniel Fredericks is serving as Acting Chief of OM's Administrative Management Branch for a 90-day period effective January 1, 2014.

Sheri Grabus, Ph.D. was appointed as the NIDA Press Officer in December 2013. Dr. Grabus previously served as the Acting NIDA Press Officer for the past year and before that served as the NIDA Deputy Press Officer for 3 years.

Dionne Jones, Ph.D. is serving as Acting Branch Chief, Division of Services Research Branch, DESPR.

Departures

Helio Chaves, NIDA's Deputy Executive Officer, has accepted a new position as Deputy Executive Officer at the FDA, Center for Food Safety and Applied Nutrition (CFSAN), Office of Management. In his new role, Helio will support the CFSAN's mission of ensuring the nation's food supply is safe, by supporting and overseeing Business Informatics, Administrative Services, Acquisition Management, Budget, Workforce Management and Facilities. Helio has been with NIDA since March of 2012 and has played a key role in the oversight of the Office of Management's myriad operations, the transformation of several business processes, and has also served as Acting IRMB and AMB Chief.

Gaya Dowling, Ph.D. left NIDA after 10 years in the Science Policy Branch, OSPC in December. As Chief of the Science Policy branch, Gaya's contributions to NIDA have been enormous. Her scientific and policy expertise have helped shape a host of critically important projects ensuring information was scientifically accurate, well written, and reflective of the latest research. Dr. Dowling is currently serving as the Acting Director of the Office of Science and Technology with the National Heart, Lung, and Blood Institute (NHLBI) where she will be leading the coordination and assessment of progress on cardiovascular, lung, and blood diseases.

Denise Pintello, Ph.D., OD, left NIDA in December 2013 to become the Program Chief of the NIMH Child and Adolescent Services Research portfolio. Denny began her 11-year career at NIDA in OSPC, where she oversaw NIDA's Blending Research and Practice Initiative.

In 2005 she was selected to serve as the Special Assistant to NIDA's Deputy Director, where she worked closely with national leaders from NIDA's National Advisory Council on Drug Abuse to coordinate Council review workgroups and prepared ten final reports including: NIDA's Blue Ribbon Task Force on Health Services Research, the National Drug Abuse Treatment Clinical Trials Network, NIDA's Medications Development Program, NIDA's Science of Genetics Review and most recently, the Blue Ribbon Task Force on NIDA's Intramural Research Program. While at NIDA, Denny was selected to receive multiple awards including the NIDA Director's Award for the Roadmap Behavioral and Social Sciences Initiative, the Blending Intramural and Extramural Collaboration and in 2013, the NIH Director's Award for the NIH Pain Consortium's Centers of Excellence in Pain Education.

Petra Jacobs, M.D., Acting Deputy Director for CCTN, left NIDA in November 2013 to join her husband and family in Ecuador. Geetha Subramaniam, MD, FAPA, who previously served as Team Leader and Medical Officer in the CCTN, was appointed the Deputy Director, CCTN, NIDA in September 2013.

Scott Chen, Ph.D., SRO, OEA, transitioned to a position with NCI on December 28, 2013.

Chien-Ying Chuang, IRP, was appointed an Assistant Professor of Neuroscience at the Biomedical Institute of the Taipei Medical University, Taipei, Taiwan, in August, 2013.

Teruo Hayashi, IRP, was appointed as the Executive Director of the Nishikawa Hospital in Shimane prefecture, Japan.

Retirements

Jerry Frankenheim, Ph.D., DBNBR, is retiring after 25 years at NIDA. Jerry was trained as a pharmacologist and earned his PhD at the University of Mississippi Medical Center. He has been a member of DBNBR's neuroscience branch under Roger Brown and Nancy Pilotte. During his time at NIDA, Jerry's interests have focused on the neural mechanisms of drug abuse, circuitry, neuroplasticity and neurotoxicity. He has developed a wide-ranging portfolio in emergent drugs of abuse including the hallucinogens, GHB and MDMA. Jerry has been an active member of the Neuroscience Consortium and has worked with the Office of Special Populations to support the minority supplement program. Jerry has many interests, and when he is not skiing or cycling his

way through retirement, he will volunteer his time to help us to think about how drug abuse accelerates aging.

Amrat Patel, Ph.D, Director of the Pharmacokinetics Program, DPMCDA, retired on January 11, 2014 after 23 years of federal service. Prior to joining DPMCDA in 1998, Dr. Patel had 10 years of research experience in receptor pharmacology and drug abuse research at the University of Virginia and the NIDA IRP, as well as 2 years of FDA experience in bioequivalence/ pharmacokinetics. He brought to DPMCDA a broad knowledge of both basic research and regulatory science. During his first 5 years at DPMCDA, he served as a pharmacologist for the Addiction Treatment Discovery Program, where he was responsible for the identification of new compounds for the treatment of drug abuse. In 2003, he assumed the responsibility for directing the pharmacokinetic and metabolism projects pertaining to medications development. He was a member of various medication development project teams and NIDA workgroups including the Genetics Work Group and the Special Populations Review group. He made significant contributions to NIDA's medications discovery and development program

Jane Smither retired from the Science Policy Branch, OSPC in September 2013, with 34 years of government service, 17 with NIDA. Ms. Smither joined OSPC in October 1996 as a Program Analyst. While she played a key role in all aspects of NIDA public outreach activities, her primary role was that of NIDA Constituent Relations Liaison, which encompassed a wide range of activities, special projects, and collaborations with key outside organizations to advance NIDA's mission. Prior to NIDA, Ms. Smither served as a senior staff member to Congressman E. (Kika) de la Garza of South Texas for 16 years.