THE ADDICTED BRAIN AND NEW TREATMENT FRONTIERS: *Sixth Annual Aspen Brain Forum*

May 18 – 20, 2016

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The New York Academy of Sciences

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WELCOME

The Aspen Brain Forum Foundation, **The New York Academy of Sciences**, and ***Science Translational Medicine*** are pleased to welcome you to the **Sixth Annual Aspen Brain Forum**, ***The Addicted Brain and New Treatment Frontiers***. This multidisciplinary program will convene leading researchers, clinicians, government and industry representatives, and non-profit leaders, to explore the latest scientific advances in the field of addiction, with the end goal of reducing the impact of addiction on individuals, families, and society.

Substance and alcohol-use disorders — characterized by continued, compulsive, stimulus-seeking behaviors despite serious negative physical, emotional, and social consequences — impose significant human health, economic, and legal burdens on society. Although research suggests that addiction is strongly related to neurobiological changes in the brain, implementation of neuroscience-based therapeutic strategies to address addiction is a relatively nascent development. As such, patients in need of treatment for addiction may not be receiving short- and long-term care that considers neurobiological, molecular, and/or genetic aspects of addiction.

The conference will begin with an evening Public Lecture and Panel Discussion, "***Arrested Development: The Teenage Brain and Substance Abuse***" followed by a **networking reception**. The scientific sessions will feature **keynote addresses** from **U.S. National Institute on Drug Abuse Director**, **Nora D. Volkow**, MD and **U.S. National Institute on Alcohol Abuse and Alcoholism Director**, **George F. Koob**, PhD, along with an interactive poster session, invited lectures, and short Hot Topic presentations selected from submitted abstracts. Speakers will present the latest developments on the neural circuitry of addiction, neuroplasticity, susceptibility of the developing adolescent brain, and new treatment strategies, and will draw on speakers from the fields of neuroscience, behavioral physiology/medicine, cognitive and clinical neuroimaging, pharmacogenetics, neurobiology, psychology, epigenetics, genetic medicine, criminal justice, policy, and economics. Presentations in the final session will be dedicated to the social and governmental environment within which addiction occurs, and we are pleased to welcome **The Honorable Patrick Kennedy** to deliver a

special **closing keynote address** on the importance of including mental health issues as a component of addiction treatment.

The **Sixth Annual Aspen Brain Forum** represents a partnership between **The New York Academy of Sciences**, **The Aspen Brain Forum Foundation**, and ***Science Translational Medicine***, which is intended to build a live and virtual network of innovators that will lead to new collaborations and breakthroughs. We hope that this conference will provide a unique forum for communication between scientists, clinicians, and other specialists who are directly involved in the treatment of patients with substance and alcohol-use disorders. The conference will assist in the bidirectional flow of information, resulting in improved understanding of addiction and the creation of more successful treatment programs. In order to disseminate the proceedings of the conference to a global audience, a comprehensive, open-access multimedia conference report with a selection of presenters' slides and audio — known as an Academy eBriefing — will be made available on the Academy's website (www.nyas.org) later this year.

We ask you to take a moment to give us your feedback and help us further improve our scientific programming by completing the online survey for this event at www.surveymonkey.com/r/Addiction2016. We hope that this conference will meet your expectations, stimulate exciting discussions, and lead to fruitful new collaborations. Please do not hesitate to notify our staff of any questions, concerns, or suggestions.

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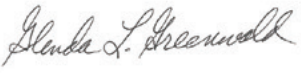

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AGENDA

DAY 1: WEDNESDAY, MAY 18, 2016

5:00 PM **Registration**

5:45 PM **Welcome and Introductory Remarks**
Includes special Introductory Remarks from New York City First Lady **Chirlane McCray** *(via video address)*

6:00 PM **Public Lecture**
Arrested Development: The Teenage Brain and Substance Abuse
Moderator: Claudia Wallis, Managing Editor, *Scientific American Mind*
Panelists:
Nora D. Volkow, MD, Director, National Institute on Drug Abuse, U.S. National Institutes of Health
Honorable Gregory P. Canova, JD, Judge, King County Superior Court (2000 – 2015); King County Drug Court (2012 – 2015)
Jeremy Waletzky, MD, Clinical Professor, The George Washington University

7:00 PM **Reception**

7:45 PM **Public Lecture Adjourns**

DAY 2: THURSDAY, MAY 19, 2016

7:30 AM **Registration, Continental Breakfast, and Poster Session Set Up**

8:30 AM **Opening Remarks**

8:45 AM **KEYNOTE ADDRESS #1**
Disease of Addiction: Significance to Brain Development, Function, and Behavior
Nora D. Volkow, MD, National Institute on Drug Abuse, U.S. National Institutes of Health

SESSION I: MECHANISMS OF NEUROPLASTICITY IN ADDICTION

Session Chair: George F. Koob, PhD, National Institute on Alcohol Abuse and Alcoholism, U.S. National Institutes of Health

9:30 AM ***Synaptic Plasticity and Circuitry Mediating Relapse to Drug Use***
Peter W. Kalivas, PhD, Medical University of South Carolina

10:00 AM ***The Neural Basis of Learning Mechanisms Underlying Addiction***
Barry J. Everitt, ScD, University of Cambridge

10:30 AM ***Deconstructing Aversive Brain Networks that Drive Addiction***
Thomas L. Kash, PhD, University of North Carolina School of Medicine

11:00 AM **Networking Coffee Break**

11:30 AM ***Tolerance and Dependence: Neural Adaptations to Chronic Drug and Alcohol Exposure***
David M. Lovinger, PhD, National Institute on Alcohol Abuse and Alcoholism, U.S. National Institutes of Health

12:00 PM ***Optical De(Re)construction of Neural Systems: Applications to Research on Addiction Neuroscience***
Michael R. Bruchas, PhD, Washington University School of Medicine

12:30 PM **Networking Lunch**

1:00 PM **Early Career Investigator Mentoring Workshop**
Recommended for Graduate Students, Post-doctoral Fellows, and Junior Faculty

Editor's Guide to Writing and Publishing Your Paper
Brooke Grindlinger, PhD, The New York Academy of Sciences
Former Editor, *The Journal of Clinical Investigation*

In this 45-minute workshop participants will gain an inside look into the editorial review process and how to best present the results of their work for publication.

SESSION II: ADOLESCENT BRAIN DEVELOPMENT AND SUSCEPTIBILITY IN ADDICTION

Session Chair: Nora D. Volkow, MD, National Institute on Drug Abuse, U.S. National Institutes of Health

2:00 PM ***Transcriptional and Epigenetic Mechanisms of Addiction***
Eric J. Nestler, MD, PhD, Icahn School of Medicine at Mount Sinai Hospital

2:30 PM ***Alcohol's Dynamic Effect on Neurodevelopment***
Susan F. Tapert, PhD, University of California San Diego; Veterans Affairs San Diego Healthcare Systems

3:00 PM ***Cannabis and Neurodevelopment in Adolescence***
Staci A. Gruber, PhD, McLean Hospital, Harvard Medical School

3:30 PM **Networking Coffee Break**

4:00 PM ***Neurobiologic Approaches to Teenage Addiction Treatment and Prevention***
Diana L. Fishbein, PhD, and **Emma J. Rose**, PhD, Pennsylvania State University

4:30 PM ***Electronic Cigarettes and Adolescents***
Thomas Eissenberg, PhD, Virginia Commonwealth University

SESSION III: HOT TOPIC TALKS FROM SUBMITTED ABSTRACTS

Session Chair: Joseph Dial, The Aspen Brain Forum Foundation

5:00 PM ***Neural Predictors of Initiating Alcohol Use during Adolescence***
Lindsay M. Squeglia, PhD, Medical University of South Carolina

5:15 PM ***Perceived Susceptibility to Nicotine Addiction as a Predictor of E-cigarette Use***
Olusegun Owotomo, MD, MPH, University of Texas at Austin

5:30 PM **Networking Reception and Poster Session**

7:00 PM **Conference Day 2 Adjourns**

DAY 3: FRIDAY, MAY 20, 2016

7:30 AM **Continental Breakfast**

8:15 AM **KEYNOTE ADDRESS #2**
Dark Side of Addictions: Alcohol Abuse and the Stress System
George F. Koob, PhD, National Institute on Alcohol Abuse and Alcoholism, U.S. National Institutes of Health

SESSION IV: NEW HORIZONS FOR TREATMENT STRATEGIES

Session Chair: Orla Smith, PhD, *Science Translational Medicine*

9:00 AM ***Optogenetically-inspired Deep Brain Stimulation Reverses Cocaine-evoked Synaptic Plasticity***
Meaghan Creed, PhD, University of Geneva

9:30 AM ***Immune-based Therapies for Substance Dependence***
Ronald G. Crystal, MD, Weill Cornell Medical College

10:00 AM **Networking Coffee Break**

10:30 AM ***Pharmacologic Approaches to Resolving the Opioid Epidemic***
David R. Gastfriend, MD, Treatment Research Institute; American Society of Addiction Medicine

11:00 AM ***Personalized Treatment Using Genetics: An Illustration from Tobacco***
Rachel F. Tyndale, PhD, Centre for Addiction and Mental Health; University of Toronto

SESSION V: HOT TOPIC TALKS FROM SUBMITTED ABSTRACTS

Session Chair: Rachel F. Tyndale, PhD, Centre for Addiction and Mental Health; University of Toronto

11:30 AM ***Temporal Discounting as an Individualized Computational Marker of Treatment Efficacy for Opioid Use Disorder***
Silvia Lopez-Guzman, MD, New York University

11:45 AM ***Accumbens nNOS Interneurons Underlie Cued Relapse to Cocaine Seeking***
Michael D. Scofield, PhD, Medical University of South Carolina

12:00 PM **Networking Lunch**

SESSION VI: NEUROSCIENCE TO ACTION: WHAT'S WRONG AND WHAT CAN WE FIX?

Session Chair: Peter W. Kalivas, PhD, Medical University of South Carolina

1:30 PM	***State of the Science of Cannabis Research: Update from the NIH Marijuana Summit, March 2016*** **Susan R. B. Weiss**, PhD, National Institute on Drug Abuse, U.S. National Institutes of Health
2:00 PM	***Translational Overview of the Neurobiology of Addiction and Societal Implications*** **Yasmin Hurd**, PhD, Icahn School of Medicine at Mount Sinai Hospital
2:30 PM	***Neurobiology of Decision-making and Willful Choice in the Context of Addiction*** **P. Read Montague**, PhD, Virginia Polytechnic Institute and State University; University College London
3:00 PM	**Networking Coffee Break**
3:30 PM	***Optimizing Public Health and Safety in the Face of Addiction*** **Mark A. R. Kleiman**, MPP, PhD, New York University, Marron Institute of Urban Management
4:00 PM	***Healthcare Systems and Policy in the Management of Care for Addiction*** The Peter G. Dodge Foundation Lecture **A. Thomas McLellan**, PhD, Treatment Research Institute
4:30 PM	**CLOSING LECTURE KEYNOTE ADDRESS** Introduction by **Nora D. Volkow**, MD, National Institute on Drug Abuse, U.S. National Institutes of Health ***My Journey: Making Mental Health Essential Health*** **The Honorable Patrick J. Kennedy**, Former U.S. Representative, Rhode Island; Co-Founder, One Mind; and Founder, Kennedy Forum
5:00 PM	**Closing Remarks**
5:15 PM	**Conference Concludes**

ABSTRACTS

DAY 1: WEDNESDAY, MAY 18, 2016

PUBLIC LECTURE

Arrested Development: The Teenage Brain and Substance Abuse

Although rates of adolescent alcohol and substance use have declined in recent years, both remain a pervasive problem in the United States. Underlying youth addiction is a complex network of neurological, psychological, social, and political factors that interplay with one another. Changes in the brain's inhibition and reward centers that promote the transition from voluntary to compulsive drug use, psychosocial influences that shape both the process and treatment of addiction, personal family perspectives, and the diversion of eligible, drug-addicted offenders into substance abuse treatment programs by drug courts will be explored in this evening event by a panel of experts in neurobiology, psychology, and criminal justice.

DAY 2: THURSDAY, MAY 19, 2016

KEYNOTE ADDRESS #1

Disease of Addiction: Significance to Brain Development, Function, and Behavior

Nora D. Volkow, MD, National Institute on Drug Abuse, U.S. National Institutes of Health, Bethesda, Maryland, United States

Advances in neurobiology have begun to clarify the mechanisms underlying the profound disruptions in decision-making ability and emotional balance that characterize addicted individuals. These advances provide critical insights into the ways in which disruptions in fundamental biological processes can alter voluntary behavioral control, not just in drug addiction but also in other disorders of self-regulation, like obesity and excessive video gaming. The recognition that addiction is a disease that emerges gradually, with a typical

onset in adolescence, has been especially consequential, because during this highly vulnerable period, the still-developing brain is particularly sensitive to the effects of drugs, a factor that contributes to adolescents' greater risk for drug experimentation and addiction.

The concept of addiction as a disease of the brain will no doubt continue to be questioned, for it challenges deeply ingrained values about self-determination and personal responsibility. However, this fact should not deter us from acting on the broad public health implications of this evidence-based model. The disease model of addiction, by providing knowledge of individual and social risk factors and the neurobiological and functional changes associated with the various stages of substance use disorders, allows us to tailor more effective individual as well as universal prevention strategies. Similarly, the opportunities that emerge from our understanding of neurobiological changes in addiction provide new targets and intervention strategies to help restore healthy function and improve behavior and outcomes in those suffering from a substance use disorder.

Any reference to NIDA or the NIH, or Dr. Volkow, should not be viewed as an endorsement of the New York Academy of Sciences, its products or services.

SESSION I: MECHANISMS OF NEUROPLASTICITY IN ADDICTION

Synaptic Plasticity and Circuitry Mediating Relapse to Drug Use
Peter W. Kalivas, PhD, Medical University of South Carolina, Charleston, South Carolina, United States

The repeated use of addictive drugs changes synaptic connections in the brain to create the various symptoms of addiction, including an enduring vulnerability to relapse to drug use. This plasticity in synaptic connections is facilitated by the shared characteristic of all addictive drugs to release dopamine. However, the enduring changes in the brain that create and sustain addictive behaviors reside more in the circuitry regulating top-down control over behavior. Like dopamine transmission for developing addicted drug use, this circuit is shared by all classes of addictive drugs and involves glutamate synapses from the prefrontal cortex into the striatum. In particular, glutamate

synapses in the ventral striatum (nucleus accumbens) serve as a portal whereby motivationally important stimuli guide the initiation and execution of behavior. These synapses undergo enduring synaptic plasticity in animals trained to use addictive drugs, and when stimuli associated with drug use, such as conditioned cues, are presented, the synapses undergo additional marked, but transient potentiation that parallels performance of drug-seeking behavior. I will describe the relevant enduring and transient plasticity induced by addictive drugs and cue-induced drug seeking. In doing so, we will explore a few molecular mechanisms that have the potential to be developed into pharmacotherapeutic targets that can modulate enduring and transient plasticity and thereby reduce relapse in animal models of addiction. In particular, we will explore involvement of glutamate transporters that have been pharmacologically targeted in recent clinical trials for treating marijuana, cocaine, and nicotine use.

The Neural Basis of Learning Mechanisms Underlying Addiction

Barry J. Everitt, ScD, Department of Psychology, University of Cambridge, Cambridge, United Kingdom

Drug addiction can be understood as the endpoint of a series of transitions from recreational, voluntary drug use, through loss of control over drug seeking behavior such that it becomes less goal-directed and more habitual, elicited by drug-associated conditioned stimuli (CSs); ultimately drug seeking becomes compulsive. These behavioural transitions depend on interactions between pavlovian and instrumental learning and memory processes. Neurally, the transition from goal-directed to habitual drug seeking reflects a shift in control over behaviour from ventral to dorsal domains of the striatum, mediated by serial interactions with midbrain dopaminergic circuitry and, ultimately, loss of prefrontal inhibitory control over drug seeking as it emerges as compulsive. As well as eliciting the performance of drug-seeking habits underpinned by implicit processes, drug-associated CSs also elicit craving and relapse. Pharmacological and/or psychological treatments that diminish the impact of drug CSs on drug seeking and relapse may therefore have clinical utility. Pharmacological agents from several drug classes, e.g. a μ-opioid receptor antagonist, can prevent cocaine, heroin, and alcohol seeking and thereby promote abstinence. Retrieving drug memories by presenting drug CSs

results in their destabilisation in the brain and they must undergo restablilisation, or 'reconsolidation', in order to persist. Preventing drug memory reconsolidation, for example by anatagonising NMDA or ß-adrenoceptors given at memory retrieval, can result in the long-term reduction or elimination of the ability of drug CSs to elicit drug seeking and relapse. The potential of translation to the clinic of these treatment approaches will be discussed.

Deconstructing Aversive Brain Networks that Drive Addiction

Thomas L. Kash, PhD[1,2], Catherine Marcinkiewcz, PhD[1,2], Chris Mazzone, BS[1,2], and Zoe McElligott, PhD[2,3]
[1]Department of Pharmacology, University of North Carolina School of Medicine Chapel Hill, North Carolina, United States;
[2]Bowles Center for Alcohol Studies, University of North Carolina School of Medicine Chapel Hill, North Carolina, United States;
[3]Department of Psychiatry, University of North Carolina School of Medicine Chapel Hill, North Carolina, United States

Drug and alcohol abuse are highly comorbid with anxiety and depression. In keeping with this, a large body of work from multiple laboratories points to the critical role of aversive brain systems in driving behavioral pathologies associated with addiction. The broad focus of my laboratory is to identify how discrete circuits in the brain can drive aversive behavior, and understand mechanistically how alcohol and drugs of abuse can dysregulate these circuits. Our goal is to identify novel circuit-based approaches to treat addiction. Here I will discuss recent work that highlights the role of discrete circuits in the brain, centered on the extended amygdala, in driving aversive behavior. Specifically, I will discuss how signaling in a discrete population of neurons that express corticotrophin releasing factor in the extended amygdala can drive both reward-related behavior, such as binge-like alcohol consumption, and aversive behavior, such as fear learning.

Tolerance and Dependence: Neural Adaptations to Chronic Drug and Alcohol Exposure

David M. Lovinger, PhD, Laboratory for Integrative Neuroscience, National Institute on Alcohol Abuse and Alcoholism, U.S. National Institutes of Health, Bethesda, Maryland, United States

Drugs of abuse alter the function of cortical and basal ganglia circuits, and these effects contribute to drug use disorders. While the majority of work in this area has focused on the limbic striatum, it is becoming clear that dorsal striatal circuitry also contributes to reward, drug actions, and addiction. We examine acute and chronic drug effects on synaptic transmission and plasticity in dorsal striatum, using both mouse and rhesus macaque monkey models. Acute alcohol exposure has differential effects on GABAergic synaptic transmission in different striatal subregions that control goal-directed versus habitual behavior. Chronic alcohol exposure suppresses GABAergic transmission, particularly in the dorsolateral striatum, a subregion with crucial roles in habitual behavior. The hypo-GABAergic state is observed in both mouse and monkey, and persists after prolonged abstinence in the primate model. This synaptic change is strongly correlated with alcohol intake and accompanies a shift from variable to highly stable drinking. *In vivo* exposure to opiates, cannabinoids, and alcohol alters endocannabinoid-mediated, presynaptically-expressed long-term depression at cortical synapses onto dorsolateral striatum neurons, likely enhancing the output of habit-controlling striatal circuitry. The cellular and molecular bases of these drug actions will be discussed in relation to the effects of addictive substances on behaviors controlled by the striatum. Evidence that drugs of abuse promote habitual behaviors, including habitual drug seeking, will also be discussed. New techniques for *in vivo* measurement of the activity of specific corticostriatal afferents during behavior will also be discussed, with an eye toward their use in examining drug-related behaviors.

Optical De(Re)construction of Neural Systems: Applications to Research on Addiction Neuroscience

Michael R. Bruchas, PhD, Washington University School of Medicine, St. Louis, Missouri, United States

Motivated behaviors are largely controlled by specific neurotransmitters and their receptors in the central nervous system. Many of these signals

are conveyed through activation of both neuropeptide (i.e., CRF and opioid) and monoamine (norepinephrine, dopamine, and serotonin) receptor systems. These receptors are seven transmembrane spanning G-protein coupled receptors (GPCR) and they can stimulate a variety of signaling cascades following neurotransmitter/neuropeptide release. Neuropeptide and monoamine circuits are engaged by reward and stress, and elicit a complex array of behavioral responses relevant to anxiety, addiction, and depression. These systems and circuits have classically been studied using pharmacological approaches, *in vivo* and *in vitro* electrophysiology, and biochemical methods. Here we will describe recent advances in optogenetic technology including development and implementation of cellular-scale wireless optogenetic and optofluidic devices for *in vivo* behavioral measures. In addition, we report divergence of behavioral responses using optical control of discrete brain region subnuclei containing dynorphin-expressing neurons in the nucleus accumbens. We find that optical control of this neuropeptide system in select regions results in differences in reward and aversion behavior. Finally, we will also discuss recent advances in controlling monoamine and peptide GPCR signaling pathways with optogenetic strategies and how these technologies reveal novel insights into neuromodulator function in motivated behaviors. In sum, we will highlight some recent advances from our laboratory that dissect the role of neuromodulatory circuits in motivated behaviors. Supported by the U.S. National Institute on Drug Abuse.

SESSION II: ADOLESCENT BRAIN DEVELOPMENT AND SUSCEPTIBILITY IN ADDICTION

Transcriptional and Epigenetic Mechanisms of Addiction

Eric J. Nestler, MD, PhD, Department of Neuroscience; Friedman Brain Institute, Icahn School of Medicine at Mount Sinai, New York, New York, United States

Drug addiction involves potentially life-long behavioral abnormalities that are caused in vulnerable individuals by repeated exposure to a drug of abuse. The persistence of these behavioral changes suggests that long-lasting alterations in gene expression, within particular regions of the brain, contribute importantly to the addiction phenotype. Work over the past decade has demonstrated a crucial

role for epigenetic mechanisms in driving lasting changes in gene expression in diverse tissues, including brain. This has prompted recent research aimed at characterizing the influence of epigenetic regulatory events in mediating the lasting effects of drugs of abuse on the brain in animal models of drug addiction and in validating such findings in postmortem human brains. We have used next generation sequencing methods, RNA-seq and ChIP-seq — the latter focusing on numerous histone modifications and regulatory enzymes, DNA methylation, chromatin remodeling proteins, and transcription factor — to obtain a more complete view of cocaine-induced changes in gene expression and associated adaptations in numerous modes of chromatin regulation in the nucleus accumbens, a key brain reward region. We have identified "chromatin signatures" that predict an altered steady-state of transcription or altered inducibility (priming or desensitization) of affected genes in response to subsequent drug exposures. We are using engineered zinc finger proteins and related approaches to target a single type of chromatin modification to a single gene within a single cell type of the nucleus accumbens *in vivo* and to study the downstream consequences of such regulation. This work is providing novel causal evidence for an important role played by individual forms of epigenetic regulation in the control of gene expression in this brain region and downstream neural and behavioral consequences. These findings establish chromatin modifications as crucial regulatory mechanisms underlying aspects of drug addiction, work that can now be mined to develop improved diagnostic tests and treatments for addictive disorders.

Alcohol's Dynamic Effect on Neurodevelopment

Susan F. Tapert, PhD[1,2]
[1]Department of Psychiatry, University of California San Diego, La Jolla, California, United States;
[2]Veterans Affairs San Diego Healthcare System, La Jolla, California, United States

Alcohol use is common in adolescence, and rates of binge drinking remain high. Neuropsychological and brain imaging studies have shown that the brain continues to develop into young adulthood, and may be more vulnerable to the effects of heavy doses of alcohol and to other substance use at this developmental phase. This lecture

will discuss how a healthy brain progresses through adolescence and young adulthood. Data will be shown suggesting that binge drinking appears to affect the brain, and is linked to changes in thinking abilities over time. The role of the media in alcohol use decisions of young people and implications for prevention will be discussed.

Cannabis and Neurodevelopment in Adolescence

Staci A. Gruber, PhD[1,2,3]
[1]Cognitive and Clinical Neuroimaging Core, McLean Hospital, Belmont, Massachusetts, United States;
[2]Marijuana Investigations for Neuroscientific Discovery (MIND) Program, Belmont, Massachusetts, United States;
[3]Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, United States

The most recent national survey data indicate that for the first time, more high school seniors report smoking marijuana (MJ) daily than smoke cigarettes (6% vs 5.5%), and perception of risk and harm related to MJ use is now at an all-time low. This is likely related to the fact that, as legislation related to MJ continues to make headlines across the country, benefits of use are often underscored, while negative effects may be overshadowed. However, this shift in national attitudes is occurring despite mounting evidence of the potentially deleterious effects of MJ, particularly on the developing brain. Although once considered to be complete by early adolescence, longitudinal studies have demonstrated that the brain continues to develop well into adulthood, leaving adolescents and emerging adults particularly vulnerable to the effects of MJ. This presentation will highlight data from neurocognitive and multimodal imaging studies which underscore the impact of early onset MJ use on cognitive performance, brain structure, and function. Findings from these studies have demonstrated a relationship between earlier age of MJ onset, poorer neurocognitive performance, increased impulsivity, and white matter alterations, providing evidence of structural and functional changes secondary to early MJ exposure. As states consider legislation regarding MJ use, it is imperative to determine safe guidelines that consider the impact of MJ on the brain, particularly during critical periods of neurodevelopmental vulnerability. Implications of these data will be discussed including the importance of early identification, education, and intervention.

Neurobiological Underpinnings of Adolescent Drug Abuse and Implications for Prevention

Diana H. Fishbein, PhD and **Emma J. Rose**, PhD, The Pennsylvania State University, University Park, Pennsylvania, United States

Adolescents at risk for substance abuse exhibit specific behavioral problems that parallel neurodevelopmental trajectories. Behavioral patterns in adolescence are often characterized by increased impulsivity, inattention, and aggression, leading to high-risk behaviors and clinical outcomes, including drug abuse, traumatic stress symptoms, and mood disorders. Neuroimaging studies document adolescent variability in underlying neural functioning, including altered forebrain connectivity and "vertical control" (top-down cognitive regulation of affect) deficits. Psychophysiological studies provide further evidence of adolescent-specific risk, suggesting differences in arousal and stress reactivity in youth at increased risk for substance abuse. Together, these findings indicate impaired maturation of frontal networks in at-risk youth, giving rise to cognitive, behavioral, and affective patterns that increases propensity for substance abuse.

Childhood neuroplasticity is considerable, particularly in frontostriatal networks, and contributes to neurodevelopmental variability for better or for worse. For worse, stressful, suboptimal socio-environmental conditions (e.g., poverty, trauma, and maltreatment) increase substance abuse risk via adverse neurodevelopmental effects and subsequent behavior (e.g., increased reward sensitivity, maladaptive decision-making, and executive dysfunction). For better, neuroplasticity provides opportunity for well-targeted interventions to improve neurodevelopment and reinforce normative developmental pathways. Such interventions can potentially buffer or reverse the neurobiological impact of maladaptive socio-environmental experiences. It is also possible that neurodevelopmental integrity is a prerequisite for adaptive responses to socio-environmental challenges and preventive interventions. Indeed, cognitive and emotional regulatory deficits characterizing neurodevelopmental delays can compromise intervention effects, potentially explaining differential outcomes for even the most highly regarded and efficacious programs. Knowledge regarding malleable conditions propagating this cascade — from adversity to neurodevelopment to behavior — and factors predicting differential outcomes provides a roadmap to

develop more effective preventive interventions, i.e., what works for whom, why, and under which circumstances. Addressing impactful socio-environmental conditions may improve neurodevelopmental indicators of plasticity and cognitive functioning, and in turn, improve self-regulatory capacities and ultimate behavioral outcomes.

Electronic Cigarettes and Adolescents

Thomas Eissenberg, PhD, Center for the Study of Tobacco Products, Department of Psychology, Virginia Commonwealth University, Richmond, Virginia, United States

Electronic cigarettes (ECIGs) are a class of tobacco products that use an electrically powered heating element to aerosolize for user inhalation, a liquid that contains solvents, flavorants, and, usually, the psychomotor stimulant drug nicotine. ECIG use among adolescents in the U.S. has been increasing in recent years, with nationally representative data showing that it has surpassed every other form of tobacco use, including combustible tobacco cigarettes, among high school students. This increased prevalence of ECIG use among adolescents is troubling for several reasons, including the fact that nicotine has long-term effects on the adolescent brain. In addition, great variability has been observed in the nicotine delivery profile of this product class, with some ECIGs delivering very little nicotine and others exceeding the nicotine delivery profile of a tobacco cigarette under similar use conditions. This variability has led to the suggestion that low nicotine delivery ECIGs may function as "starter" products that allow nicotine-naïve adolescents to "graduate" to higher nicotine delivery ECIGs that may engender dependence. This presentation focuses on understanding ECIG nicotine delivery profile and explores the factors that influence it. Results will be discussed in the context of adolescent users who may, with experience, receive more nicotine from ECIGs than they might receive with tobacco cigarettes.

SESSION III: HOT TOPIC TALKS FROM SUBMITTED ABSTRACTS

Neural Predictors of Initiating Alcohol Use during Adolescence

Lindsay M. Squeglia, PhD[1], Tali M. Ball, PhD[2], Joanna Jacobus, PhD[3,4], Ty Brumback, PhD[3,4], Benjamin S. McKenna, PhD[3], Tam T. Nguyen-Louie, MS[5], Scott F. Sorg, PhD[3,4], Martin P. Paulus, MD[6], and Susan F. Tapert, PhD[3]

[1]Medical University of South Carolina, Charleston, South Carolina, United States;
[2]Stanford University, Stanford, California, United States;
[3]University of California San Diego, La Jolla, California, United States;
[4]VA San Diego Healthcare System, La Jolla, California, United States;
[5]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California, United States;
[6]Laureate Institute for Brain Research, Tulsa, Oklahoma, United States

Background: Underage drinking is widely recognized as a leading public health and social problem for adolescents in the United States. Being able to identify at-risk children before they initiate heavy alcohol use could have immense clinical and public health implications; however, few investigations have explored individual-level precursors of adolescent substance use. This prospective investigation used machine learning with demographic, neurocognitive, and neuroimaging data in substance-naïve adolescents to predict alcohol use initiation by age 18.

Methods: Participants (N = 137) were healthy substance-naïve adolescents (ages 12 – 14) who underwent neuropsychological testing and structural and functional magnetic resonance imaging (sMRI and fMRI), then were followed annually. By age 18, 70 youth (51%) initiated moderate-to-heavy alcohol use and 67 remained non-users. Random forest classification generated individual alcohol use outcome predictions based on demographic, neuropsychological, sMRI, and fMRI data.

Results: The final random forest model was 74% accurate, with good sensitivity (74%) and specificity (73%) and included 34 predictors contributing to alcohol use by age 18, including several demographic and behavioral factors (being male, higher socioeconomic status, early dating, more externalizing behaviors, positive alcohol expectancies),

worse executive functioning, and thinner cortices and less brain activation in diffusely distributed regions of the brain. Inclusion of neuropsychological, sMRI, and fMRI data significantly increased the prediction accuracy of the model.

Discussion: Random forest models of demographic, behavioral, neuropsychological, and neuroimaging data can provide single-subject predictions of who is at an elevated risk for initiating alcohol use during adolescence. Identification of at-risk youth is highly important for alcohol prevention efforts.

Perceived Susceptibility to Nicotine Addiction as a Predictor of E-cigarette Use

Olusegun Owotomo, MD, MPH, and Julie Maslowsky, PhD
University of Texas at Austin, Austin, Texas, United States

Background: Prevalence of e-cigarette use is increasing among U.S. adolescents, recently surpassing cigarette smoking; however, not all factors contributing to this behavior have been identified. This study aims to identify factors predicting e-cigarette use among U.S. adolescents.

Methods: Nationally representative sample of 12th grade students (N = 2,122) in 2014 was obtained from Monitoring the Future, a national cross-sectional survey. Dependent variable was e-cigarette use in the past 30 days, dichotomized (No / Yes). Independent variables were perceived susceptibility to nicotine addiction, perceived peer smoking, grade when (if ever) cigarette was first smoked, and risk-taking propensity. Sociodemographic (control) variables were urbanicity (rural / urban), race, gender, and age (<18 / ≥18 years). Binary logistic regression was conducted to investigate the relationship between independent variables and e-cigarette use while controlling for sociodemographic variables.

Results: Prevalence of e-cigarette use was 18%, and was highest among White (21.4%), urban (19.7%), and male (21.7%) students. No significant age difference in e-cigarette use. After controlling for sociodemographic variables, low perceived susceptibility to nicotine addiction, high perceived peer smoking, smoking first cigarette at higher class grade, and greater propensity for risk taking were all

significantly associated with increased use of e-cigarettes. The model accounted for 30.7% of variation in e-cigarette use.

Conclusion: Perceived susceptibility to nicotine addiction, perceived peer smoking, and risk-taking propensity predict e-cigarette use among adolescents; these factors should be considered in future research and intervention design. Lack of age difference (<18 versus ≥18 years) in e-cigarette use may indicate ease of access to e-cigarettes and need for further regulation.

DAY 3: FRIDAY, MAY 20, 2016

KEYNOTE ADDRESS #2

Dark Side of Addiction: Alcohol Abuse and the Stress System

George F. Koob, PhD, National Institute on Alcohol Abuse and Alcoholism, U.S. National Institutes of Health, Bethesda, Maryland, United States

Addiction to alcohol and drugs has been conceptualized to involve three stages; binge/intoxication stage, withdrawal/negative affect stage, and preoccupation-anticipation stage. The construct of negative reinforcement, defined here as drug taking that alleviates a negative emotional state created by drug abstinence, is particularly relevant as a driving force in both the withdrawal/negative affect and preoccupation-anticipation stages in alcohol addiction. The negative emotional state that drives such negative reinforcement is hypothesized to derive from dysregulation of key neurochemical circuits that form the brain stress systems within the extended amygdala. Specific neuroplasticity in these circuits includes the extrahypothalamic corticotropin releasing factor (CRF) stress systems, and the dynorphin – μ opioid aversive systems the in the extended amygdala. Excessive alcohol taking also engages activation of CRF and dynorphin in the medial prefrontal cortex and is accompanied by deficits in executive function that may facilitate the transition to compulsive-like responding and relapse. Thus, compelling evidence exists to argue that plasticity in the brain stress systems, a heretofore largely neglected component of addiction, is triggered by acute excessive alcohol intake, is sensitized during repeated withdrawal, persists into protracted abstinence,

and contributes to the development and persistence of addiction. The neuroplasticity of the brain stress systems in alcohol addiction not only provides understanding of the neurobiology of negative reinforcement mechanisms in all forms of addiction, but also provides key insights into how the brain processes negative emotions.

SESSION IV: NEW HORIZONS FOR TREATMENT STRATEGIES

Optogenetically-inspired Deep Brain Stimulation Reverses Cocaine-evoked Synaptic Plasticity

Meaghan Creed, PhD, University of Geneva, Geneva, Switzerland

Exposure to addictive drugs, such as cocaine, induces characteristic forms of synaptic plasticity, for example a potentiation of glutamatergic inputs onto medium spiny neurons of the nucleus accumbens (NAc). One behavioral correlate of this plasticity is locomotor sensitization, a phenomenon in which repeated exposure to equivalent doses of cocaine induces progressive increases in locomotor activity. Deep brain stimulation (DBS) is a surgical therapy in which electric current is passed through electrodes implanted into specific brain nuclei. We sought to reverse cocaine-evoked plasticity and behavior using DBS applied to the fiber bundle of excitatory projections originating in the mPFC and targeting the NAc shell. We found that classical DBS protocols (high frequency: 130 Hz, 100 μA) effectively decreased the locomotor response to cocaine. However, this effect was transient. In line with these behavioral observations, the cocaine-induced enhancement of excitatory inputs onto MSNs was unchanged. We then demonstrated that depotentiating the projection from the medial prefrontal cortex (mPFC) to the NAc using optogenetic stimulation delivered at 12 Hz *in vivo* restores normal synaptic transmission and abolished locomotor sensitization to cocaine, which we then attempted to mimic with DBS. However, given that the 12 Hz protocol is dependent on mGluR activation, and that signaling through dopamine D1-receptors in MSNs opposes mGluR signaling, we hypothesized that D1 antagonism may be necessary to unmask a DBS-induced depotentiation onto MSNs. Indeed, when we administered the D1 antagonist SCH23390 in conjunction with DBS, cocaine sensitization and cocaine-evoked plasticity were abolished. Taken together, our results provide a proof of principle that combined with pharmacology, DBS may be used to reverse to

cocaine-induced synaptic plasticity and drug-adaptive behavior, which may have important implications for the clinical application of DBS for the treatment of addictive disorders.

Immune-based Therapies for Substance Dependence

Ronald G. Crystal, MD, Weill Cornell Medical College, New York, New York, United States

Addiction to drugs is a major worldwide problem for which there is no effective therapy. Using cocaine and nicotine as examples, we have developed two platform strategies to evoke high-titer antibodies specific for the anti-addictive drug. In the first strategy, based on the highly immunogenic nature of the adenovirus capsid, analogs of the addictive drug are bound to adenovirus capsid proteins to create active vaccines that generate high-titer anti-drug antibodies. In the second strategy, the gene coding sequences for monoclonals against the addictive drug are expressed by adeno-associated virus gene transfer vectors capable of generating, with a single administration, persistent high titers of anti-drug antibodies. In experimental animal models, both strategies are highly effective, providing new paradigms for anti-addictive molecular vaccines.

Pharmacologic Approaches to Resolving the Opioid Epidemic

David R. Gastfriend, MD[1,2]
[1]Treatment Research Institute, Philadelphia, Pennsylvania, United States;
[2]American Society of Addiction Medicine, Bethesda, Maryland, United States

In the opioid epidemic, 2,100,000 Americans have opioid use disorder. Overdose deaths can be reduced with the rapid-acting μ-opioid antagonist naloxone. Although counseling alone dominates the treatment field, combining U.S. Food and Drug Administration (FDA)-approved pharmacotherapies with counseling is clearly superior. These agents stabilize dopamine release in the shell of the nucleus accumbens. Slow onset, long-acting, μ-agonist (methadone) or partial μ-agonist (buprenorphine) agents stabilize craving, opioid use, medical problems, criminality, and disease transmission. Buprenorphine's ceiling

effect makes it safer in overdose, with improved accessibility and less overall cost. Both agents are safe and effective during pregnancy. They are also easy to initiate but sustain physiological opioid dependence, causing discontinuation withdrawal and necessitating long-term or indefinite treatment. The μ-opioid antagonist, oral naltrexone, is no more effective than placebo in general populations due to poor daily adherence. Intramuscular extended-release naltrexone, however, sustains month-long μ-opioid blockade. Work on rapid detoxification/induction is still needed, but it has no discontinuation withdrawal, and therefore may not require extended treatment. Newer preparations (surgically implanted buprenorphine and naltrexone) are not FDA-approved. Increased availability of agonists and the extended-release antagonist in addition to counseling would help resolve the opioid epidemic. Research is needed, however, on pain threshold and stress system effects and management, treatment selection, duration, sequencing criteria, and care coordination. Comparative effectiveness designs are confounded by patient choice issues, cultural factors, unblinding, and the possibility of differential effective treatment duration. Unanswered questions, legacy myths, controversies, stigma, unavailability, and reimbursement problems abound and hobble the adoption of these agents — exacerbating the epidemic.

Personalized Treatment Using Genetics: An Illustration from Tobacco

Rachel F. Tyndale, PhD[1,2,3]
[1]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada;
[2]Department of Pharmacology & Toxicology, University of Toronto, Toronto, Ontario, Canada;
[3]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Heritability (genetics) accounts for a substantial degree of variation in risk for drug dependence, how much of a drug is used, and in treatment response. Here we will illustrate these different aspects of genetic risk using smoking behaviors and tobacco cessation treatment.

Nicotine is the main psychoactive component in cigarettes. The majority of nicotine is metabolically inactivated by a liver enzyme, CYP2A6. CYP2A6 is highly genetically variable resulting in a wide

range of rates of nicotine inactivation. Genetically slow CYP2A6 nicotine inactivators are generally less tobacco dependent, smoke fewer cigarettes per day, and inhale less deeply.

Variation in the rate of nicotine metabolism is also associated with differences in the ability to quit smoking during spontaneous quitting, behaviorally-assisted cessation, and pharmacotherapy-assisted cessation. Using a prospective clinical trial design, randomized based on the rate of nicotine metabolism, we found that for normal metabolizers, varenicline was superior to nicotine patch, while for slow metabolizers they were equally efficacious; slow metabolizers had more adverse side effects on varenicline. Brain imaging studies illustrate some of the potential mechanisms (i.e., differing smoking cue-reactivity, nicotinic receptor availability, functional connectivity) behind these differing cessation rates among slow and normal metabolizers.

Together this provides one example of how genetic variation can alter drug dependence and clinical treatment. Genetically tailored personalized medicine should assist in increasing the success rates of drug dependence treatment.

SESSION V: HOT TOPIC TALKS FROM SUBMITTED ABSTRACTS

Temporal Discounting as an Individualized Computational Marker of Treatment Efficacy for Opioid Use Disorder

Silvia Lopez-Guzman, MD[1], Anna B. Konova, PhD[1], Adelya Urmanche, BA[1], Stephen Ross, MD[2,3], John Rotrosen, MD[2], and Paul W. Glimcher, PhD[1,4]

[1]Center for Neural Science, New York University, New York, New York, United States;

[2]Department of Psychiatry, New York University School of Medicine, New York, New York, United States;

[3]Division of Alcoholism and Drug Abuse, Bellevue Hospital Center, New York, New York, United States;

[4]Institute for the Interdisciplinary Study of Decision Making, New York University, New York, New York, United States

Temporal discounting (TD), or the tendency to forfeit future larger rewards in favor of sooner smaller ones, is an increasingly widespread

proxy measure of impulsivity in studies of substance use disorder. By employing this model-based approach, we derive a parameter — the discount rate (DR) — that encompasses the individual's degree to which a reward loses its value as a function of time, that is, their level of TD. In the specific case of opioid use disorder (OUD), previous studies have indicated how patients exhibit higher DRs compared to controls and how patients' discounting shows a decrease between baseline and a short opioid substitute treatment period. Treatment is aimed at reducing opioid use and achieving abstinence; we therefore sought to investigate, in a continuous fashion, TD's relation to opioid use in a cohort of 25 individuals seeking outpatient maintenance treatment for OUD over a 7-month follow up period. Participants attended regular sessions during which they completed a decision-making task for estimation of their DR and provided a self-report of their drug use over the previous week that was crosschecked with their routine urine drug tests. Our results indicate DRs follow each patient's clinical state through recovery, decreasing progressively with abstinence. Interestingly, DRs also correlate with relapse events, peaking when these occur. We conclude that TD, when assessed repeatedly over the course of treatment, could be used as a behavioral signature of an individual patient's evolution and potentially serve as a useful predictor of prognosis and treatment adherence for OUD.

Accumbens nNOS Interneurons Underlie Cued Relapse to Cocaine Seeking

Michael D. Scofield, PhD[1], Jasper A. Heinsbroek[1], Heather A. Boger PhD[1], Cassie D. Gipson PhD[2], and Peter W. Kalivas, PhD[1]
[1]Department of Neurosciences, Medical University of South Carolina, Charleston, South Carolina, United States;
[2]Department of Psychology, Arizona State University, Tempe, Arizona, United States

The gaseous transmitter nitric oxide (NO) is produced in the nucleus accumbens core (NAcore) by a subpopulation of interneurons that express neuronal nitric oxide synthase (nNOS). Among other things, NO plays a critical role in the nitrosylation and activation of matrix metalloproteinases (MMPs) by drug-conditioned cues, a signaling event upstream of dendritic spine head expansion on medium spiny neurons (MSNs) and the initiation of cued cocaine seeking. Consistent with

a role for NO in reinstated drug seeking, inhibition of the nNOS enzyme with N-Propyl-L-Arginine (NPLA) inhibits cue-induced activation of MMPs and cued cocaine seeking. Remarkably, infusion of the mGluR5 agonist CHPG into the NA core produced drug seeking in the absence of cues, which was blocked by the co-infusion of NPLA. We hypothesize that cue-induced glutamate release in the NA core engages NO production and drug seeking. To verify that stimulation of glutamate receptors enhances NO release, NO levels were measured in anesthetized animals using multi electrode arrays. Puff application of glutamate or CHPG in the NAcore produced a dose-dependent increase in NO release, which was inhibited by the mGluR5 antagonist MTEP or NPLA, respectively. Further, NO efflux was dose-dependently evoked by stimulation of Gq-coupled designer receptors exclusively activated by designer drugs (DREADDs), expressed in NA core nitrergic interneurons. Akin to CHPG, activation of Gq-DREADD receptors in nNOS interneurons promoted drug seeking in the absence of cues. Combined, these data indicate NO release is a crucial step in the signal transduction cascade between cue-induced glutamate release in the NA core and cued cocaine seeking.

SESSION VI: NEUROSCIENCE TO ACTION: WHAT'S WRONG AND WHAT CAN WE FIX?

State of the Science of Cannabis Research: Update from the NIH Marijuana Summit, March 2016

Susan R. B. Weiss, PhD, National Institute on Drug Abuse, U.S. National Institutes of Health, Bethesda Maryland, United States

Cannabis policy is changing rapidly in the U.S. and globally. Currently, 23 states plus the District of Columbia (DC) have legalized marijuana for medical use; four states plus DC have legalized its recreational use for individuals over age 21; and several 2016 ballot initiatives relate to marijuana legalization. While there is general agreement in some areas (i.e., cannabis use is risky for children and adolescents; its criminalization has had a disproportionate adverse impact on minority populations); many topics of growing contention remain and there is insufficient research regarding both its adverse and potential therapeutic uses.

In March 2016, the U.S. National Institutes of Health (NIH) convened a summit entitled **Marijuana and Cannabinoids: A Neuroscience Research Summit** to address the need for additional scientific information and identify important research questions to inform practice and policy. With a focus on neurological and psychiatric effects of marijuana, other cannabinoids, and the endocannabinoid system, and discussion of both the adverse and the potential therapeutic effects; the goal of this summit was to review the state of the science on marijuana, solicit input, and disseminate information to a wide range of stakeholders including policymakers, other Federal agencies, and the scientific community. The meeting was sponsored by several NIH Institutes and Centers: the National Institute on Drug Abuse; the National Institute on Alcohol Abuse and Alcoholism; the National Center for Complementary and Integrative Health; the National Institute of Mental Health; and the National Institute of Neurological Disorders and Stroke. The presentation today will highlight the discussion and findings from the NIH summit.

Translational Overview of the Neurobiology of Addiction and Societal Implications

Yasmin Hurd, PhD, Icahn School of Medicine at Mount Sinai Hospital, New York, New York, United States

Drug addiction continues to be of substantial public health concern with significant burden to the individual, their families, the communities, and healthcare systems with profound impact on the U.S. economy exceeding over half trillion dollars yearly. Research efforts in recent years have begun to more thoroughly address the complex nature of substance use disorders based on individual differences to vulnerability. Although many young people experiment with drugs, only a select number will ultimately progress to addiction. Multiple factors including genetics, behavioral traits, psychiatric comorbidity, as well as environmental conditions during neurodevelopment have been acknowledged to contribute to addiction risk. Delineating the underlying neurobiology linked with these factors can help in the prevention and intervention of substance use disorders. A major component of our research is dedicated to expanding knowledge about the molecular neuropathophysiology of drug addiction based on studies of gene expression, neuronal circuits, genetic variants, and

epigenetic mechanisms directly in the human brain. Complementary animal models help to facilitate the development of novel treatments that leverages translational strategies such as chemogenetic to target discrete neural circuits linked with addiction-related phenotypes. Moreover, these models allow the opportunity to investigate the long-term neurobiological impact of developmental drug exposure into adulthood and even across generations as apparent with cannabis, a drug with significant societal implications given its recent expanded use for recreational and medicinal purposes.

Neurobiology of Decision-making and Willful Choice in the Context of Addiction

P. Read Montague, PhD[1,2]
[1]Virginia Polytechnic Institute and State University, Blacksburg, Virginia, United States;
[2]Wellcome Trust Centre for Neuroimaging, University College London, London United Kingdom

The initiation and sustenance of addiction requires the interaction of many neural systems operating in particular contexts — typically socially relevant contexts. In this talk, we focus on the role that computational models now play in understanding some of the interacting processes that lead to an addicted state — one that repeatedly chooses actions that lead to drug taking or its proxies. These computational models have been mapped onto the activity of dopaminergic systems at the levels of spiking and neurotransmitter release at the synaptic level. We have developed a new capacity to extract sub-second dopamine and serotonin signals from the striata of conscious humans playing a simple sequential choice task and show some of the surprising new findings of how these important neuromodulators relate to one another and to computational models formerly used to understand dopaminergic function. One of the interpretations of the data is that actual experience and counterfactual experience are being combined in a composite dopamine and serotonin signal and this possibility has consequences for understanding valuation disease like addiction.

Optimizing Public Health and Safety in the Face of Addiction

Mark A. R. Kleiman, PhD, New York University, Marron Institute of Urban Management, New York, New York, United States

Addiction — more formally, substance use disorder (SUD) — is a persistent state of impaired volition with respect to drug consumption. While drug consumption remains somewhat responsive to contingencies, those who suffer from SUD continue to engage in behavior despite knowledge of its negative consequences.

SUD thus undermines one of the central ideas underlying the liberal order: that individuals are, in general, good stewards of their own welfare, capable of taking actions that satisfy their preferences and reflect their beliefs about their own welfare. That condition poses a threat to health insofar as the drugs involved have toxic effects.

All use of intoxicating drugs poses risks of intentional and unintentional injury; addiction increases the threat by diminishing the user's capacity to manage the frequency, intensity, and times and places of intoxication.

Thus, in the absence of any special laws controlling them, addictive intoxicants would create harms to health and safety. That observation creates some justification for such special laws. However, the laws themselves can become threats to health and safety, both by increasing the harmfulness of drugs consumed and by generating illicit-market side effects including violence and disorder, and enforcement side-effects including arrest and incarceration.

Thus, the optimal drug policy from the perspective of public health and safety would minimize the sum of harms from use and intoxicated behavior, and harms from illicit transactions and enforcement efforts. The optimal policy may vary over variations in drugs, times, and places.

Healthcare Systems and Policy in the Management of Care for Addiction

This lecture is generously supported by The Peter G. Dodge Foundation.

A. Thomas McLellan, PhD, Treatment Research Institute, Philadelphia, Pennsylvania, United States

Although substance use disorders are serious public health problems in their own right, and they affect the quality and costs of many other

forms of healthcare, they have been segregated from the rest of mainstream healthcare. Most insurance plans have not fully covered addiction treatment and less than 10% of medical, nursing, or pharmacy schools offer even a one-semester course in substance use disorders. Thus, specialty addiction treatment programs regularly fail to recognize and treat the medical problems that occur in over 50% of their patients; and general medical care regularly fails to recognize or address even severe addictions that occur in 20 ~ 60% of patients in healthcare settings. This has been a costly mistake. Unrecognized and unaddressed substance use disorders cost mainstream healthcare over $120 billion annually in misdiagnosis, poor adherence, rapid re-admissions to hospitals, and fatal medical errors. The presentation will discuss the history and rationale behind this system segregation, detail some of the most significant healthcare management problems segregation has caused, and describe examples of how integrated care has increased the quality and reduced the costs of mainstream medicine.

CLOSING LECTURE KEYNOTE ADDRESS

My Journey: Making Mental Health Essential Health

The Honorable Patrick J. Kennedy[1,2,3]
[1]Former U.S. Representative, Rhode Island, United States;
[2]Co-Founder, One Mind, Island Heights, New Jersey, United States;
[3]Founder, Kennedy Forum, Island Heights, New Jersey, United States

Since his earliest days in public service, **Patrick J. Kennedy** believed that mental health should be a national priority. After 16 years in Congress, and countless bills passed, one stands out among the rest for the impact it has on the lives of all Americans — the *Mental Health Parity and Addiction Equity Act of 2008*. This bill ensures that mental health is treated on-par with physical health, breaking down decades-old practices in the health care system that kept those two areas separate from one another, often with dire consequences. This presentation will focus on the necessary steps that will fulfill President Kennedy's vision of ensuring the best possible mental well-being for every American. Discussion topics will include implementation of the *Mental Health Parity and Addiction Equity Act*, ways to accelerate advances in diagnostics, treatments and cures, and how we can integrate mental health into the mainstream of American medicine. The result will be improved outcomes for patients and lower costs for everyone.

NOTES

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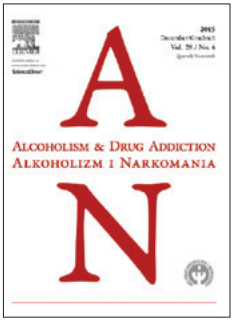

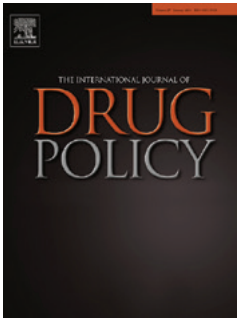

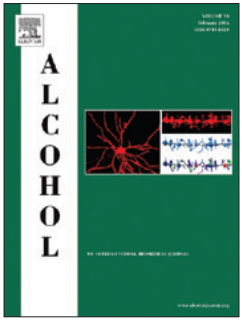

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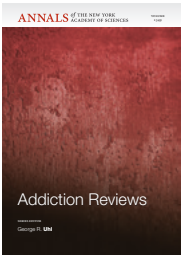

Addiction Reviews

Edited by **George R. Uhl** (U.S. National Institutes of Health, Baltimore, Maryland, United States)
Volume 1349, September 2015
126 Pages, 6 Papers

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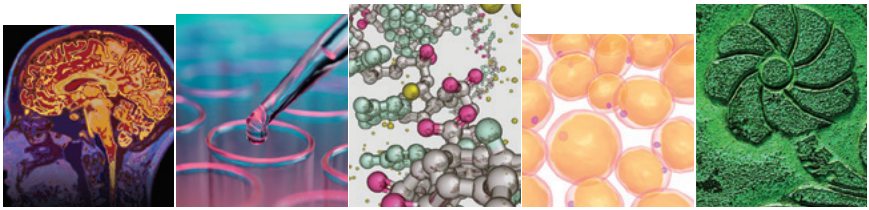

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