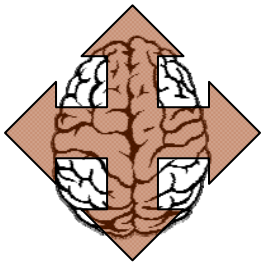

PROGRAM

Scientific Meeting of the International Society for Research on Impulsivity

Manchester Grand Hyatt, San Diego, CA
June 20, 2009

www.impulsivity.org

THE INTERNATIONAL SOCIETY FOR RESEARCH ON IMPULSIVITY AND IMPULSE CONTROL DISORDERS

2009 Officers

Executive Committee

President:
Marc N. Potenza, M.D., Ph.D.

Secretary Treasurer:
Christopher Reist, M.D., M.B.A.

At Large Executive Members:
Franck Bayle, M.D
Jon Grant, M.D.
Marc N. Potenza, M.D., Ph.D.
Christopher Reist, M.D., M.B.A.

Executive offices:
Executive Officer
Alan C. Swann, M.D.

Managing Secretary
Amy Hollas, B.S.

SUPPORT:
This conference was supported in part by a grant from National Institute on Alcohol Abuse and Alcoholism: R13 AA018234

About the International Society for Research on Impulsivity

The International Society for Research on Impulsivity is a nonprofit scientific society founded to promote research collaboration on impulsivity and impulse control disorders by scientists around the world.

The purpose of this society is to foster international research collaboration on impulsivity and its psychiatric and social consequences.

What is Impulsivity?

Impulsivity has been variously defined as human behavior without adequate thought, the tendency to act with less forethought than do most individuals of equal ability and knowledge, or a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions.

Impulsivity is implicated in a number of psychiatric disorders including Mania, Personality Disorders, and Substance Use Disorders; yet, there is significant disagreement among researchers and clinicians regarding the exact definition of impulsivity and how it should be measured.

Impulsivity is also a key construct in many social decisions. For example, in jurisprudence, forensic psychiatrists often testify in mens rea decisions. If an alleged criminal act like murder is shown to be impulsive, the penalty is different than if it is premeditated.

The goals of this society include:

1) Establishment of guidelines for measurement of impulsivity which would make comparisons across research projects more meaningful

2) Examination of the current diagnostic criteria for disorders of impulse control based on results of biological, social, cognitive, and behavioral research

3) Dissemination of clinical and pre-clinical impulsivity research to other researchers and clinicians through symposia, publication, and newsletters.

Meeting Schedule

SATURDAY, JUNE 20, 2009

7:30 - 8:00 am	Registration and Continental Breakfast
8:00 - 8:30 am	Overview and Introduction
8:30 - 9:30 am	Plenary: Trevor W. Robbins, PhD - "Impulsivity and Addiction"
9:30 – 10:45 am	***Session 1***: Defining and Assessing Impulsivity in Animal Models Chair: Catharine Winstanley, PhD **1.)** Catharine Winstanley, PhD - "The Neural and Neurochemical Basis of Impulsivity: Insight from Rodent Models" **2.)** David Belin, PhD - " Ventral and Dorsal Striatal Involvement in Impulsive and Compulsive Behaviors" **3.)** Peter Olausson, PhD – "Neural Mechanisms of Cognitive-Motivational Dysfunction in Addiction " **4.)** J. David Jentsch, PhD - " Genetic and Neurochemical Correlates of Impulsivity in Monkeys"
10:45 - 11:00 am	Break
11:00 - 12:15 pm	***Session 2***: Defining and Assessing Impulsivity in Human Studies Chair: Robert Rogers, PhD **1.)** F. Gerard Moeller, MD - "Clinical Neurobiology of Impulsivity: Relationship to Substance Abuse" **2.)** Robert Rogers, PhD - "The role of dopamine and serotonin in persisting gambling behavior: Implications for the persistence of alcohol and substance misuse behaviors" **3.)** Alan Swann, MD - "Impulsivity and Mood: State and Trait Mechanisms in Bipolar Disorder" **4.)** Luke Clark, PhD - "Neural and Neurocognitive Aspects of Impulsivity in Pathological Gambling"

12:15 – 1:45 pm	Lunch (many local restaurant options)
1:45 – 2:45 pm	***Session 3***: Alcohol and Impulsivity: Animal Studies
	Chair: Harriet de Wit, PhD
	1.) Harriet De Wit, PhD – "Impulsivity as a Determinant of Drug Use: Relationship to Reward?"
	2.) Suzanne H. Mitchell, PhD – "Measures of impulsivity in drug-naive rats and mice can be associated with alcohol consumption"
	3.) Dai Stephens, PhD – "Evidence for Reduced Ability to Suppress Pre-potent Responses in Multiply Detoxified Alcoholics, Binge-drinkers, and in a Rodent Model of Binge Drinking: Cause or Consequence of Alcohol Abuse?"
2:45 - 3:00 pm	Break
3:00 – 4:15 pm	***Session 4***: Alcohol and Impulsivity: Human Studies
	Chair: John Krystal, MD
	1.) Rajita Sinha, PhD – "Stress, Self-Control and Alcohol Relapse Risk: fMRI Studies"
	2.) Michael Stevens, PhD – "fMRI Studies of Reward Processing and Impulsivity, Related to Family History of Alcoholism"
	3.) David Goldman, MD – "The Gene-by-Environment Interface in Aggression and Addiction"
	4.) Carl Lejuez, PhD – "Behavioral Assessment of Risk-taking and Alcohol Use in Adolescents"
4:15 – 4:45 pm	Closing Remarks
4:45 - 6:30 pm	Poster Session

PLENARY ABSTRACT:

Impulsivity and addiction

TW Robbins, Behavioural and Clinical Neuroscience Institute, and Dept. of Expt. Psychology, University of Cambridge

Much evidence now supports the view that drug addiction results in part from aberrant learning mediated by dopamine-dependent processes of the limbic-striatal interface. In particular, drug addiction may involve a 'switch' between instrumental behaviour controlled by its outcome and habitual responding mediated by stimulus-response associations, corresponding hypothetically to a devolution of behavioural control from the ventral to the dorsal striatum. However, this hypothesis fails to take into account evident individual differences in the propensity to addiction, or the temporal course of the addictive process. Recent data suggest that impulsivity associated with ventral striatal dopamine D2/3 receptor down-regulation in the rat is predictive of the tendency toward compulsive drug seeking behaviour and other behavioural correlates of addiction. These data distinguish effects of sensation- (or novelty-) seeking which appear to predispose towards a sensitivity to the rewarding effects of stimulants without, however, enhancing compulsive drug-seeking behaviour. These findings, together with complementary results in non-human primates, help us to disambiguate the effects of drug-induced neurotoxicity from predisposing influences in accounting for drug-addictive behaviour in humans. However, how behaviour that is habitual becomes 'compulsive' in the drug-taking context requires further explanation, and I will consider three possible accounts. Finally, we will consider how well this hypothesis, developed to account for stimulant drug addiction, applies to other forms of addiction.

SPEAKER ABSTRACTS:

The Neural and Neurochemical Basis of Impulsivity: Insight from Rodent Models

Catherine Winstanley, Ph.D., University of British Columbia

Background: High levels of impulsivity are associated with numerous psychiatric disorders, including borderline personality disorder, attention-deficit hyperactivity disorder, mania, pathological gambling and addiction. However, there is little common consensus in terms of the treatment of impulse control deficits. Factor analysis of self-report questionnaires designed to measure impulsivity indicates that impulsivity is made up of a number of independent dimensions. The degree to which these different aspects of impulse control are subserved by similar neural and neurochemical systems is an important empirical question: such knowledge could contribute to our understanding of the basis of impulse control disorders, and optimize therapeutic interventions based on symptom profiles.

Methods: Through fractionating impulsivity into its component parts, it has proved possible to design neuropsychological tests which measure different forms of impulsivity, many of which have been successfully translated into rodents. These include the five-choice serial reaction time task (based on the continuous performance task), delay-discounting paradigms, and, more recently, models of gambling-related decision-making.

Results: The nucleus accumbens and frontal cortices are critical sites for the regulation of different forms of impulsive behaviour, and manipulations which target both serotonin and dopamine can modulate impulsivity. However, the results of both lesions and drug challenges are not uniform across different paradigms, such that drugs like amphetamine or lesions to the orbitofrontal cortex (OFC) can reduce intolerance to delayed gratification but increase premature responding. Furthermore, the effects of locally modulating dopamine within the OFC may depend on basal levels of impulse control.
Conclusions: Research so far indicates that the effects of drug treatments may vary depending on the nature of the impulse control deficit, and also on how impulsive individual subjects are. Through the examination of rodent approximations to human behaviour, greater insight can be gained into the neurobiological systems regulating the complex behavioural trait of impulsivity.

Ventral and Dorsal Striatal Involvement in Impulsive and Compulsive Behaviors
David Belin, Ph.D., Cambridge University
Drug addiction is being more generally defined as a compulsive habit over drug taking behaviour, accompanied by a very high vulnerability to relapse. In the past four years we have investigated the psychobiological and neurobiological substrates of the establishment of habitual and compulsive cocaine self-administration in rats. At the neurobiological level we have established that a serial functional connectivity between the ventral and the dorsolateral striatum (DLS) through recurrent spiralling connections with ventral midbrain dopaminergic neurons underlies the instantiation of habitual cocaine seeking behaviour, dependent upon the DLS. At the psychological level, we have established that high impulsivity and high novelty-seeking traits predict the transition from controlled to compulsive cocaine self-administration after protracted exposure to the drug. Based on the neurobiological correlates of these behavioural traits we propose a functional framework whereby a shift occurs from the ventral to the dorsolateral striatum in the development of compulsive habitual cocaine self-administration. A new incentive habit hypothesis of drug addiction will be presented in light of recent literature supporting a ventral to dorsal striatum shift in the control over cocaine taking behaviour in the course of self-administration history. A broader view will also be presented regarding the psychological mechanisms involved in vulnerability to opiate addiction, focusing on the role of impulsivity.

Neural Mechanisms of Cognitive-Motivational Dysfunction in Addiction
Peter Olausson, Ph.D., Yale University School of Medicine
Drugs of abuse produce cellular adaptations in the cortico-limbic-striatal brain circuits thought to mediate compulsive drug-seeking/taking behavior. While the precise neurobiological mechanisms by which drug use progresses to addiction are not fully understood, drug-induced alterations in synaptic plasticity within these cortico-limbic-striatal networks that subserve learning, memory, motivational processes and behavioral control have been established, and a role for the
prefrontal cortex (PFC) has emerged. We, and others, have proposed that the transition to addiction is critically dependent on deficient PFC-mediated inhibitory control functions, resulting in an increase in the motivational significance of drug-associated

stimuli. The orbitofrontal cortex (OFC) which promotes behavioral flexibility by coordinating inhibitory control related to the probabilistic and incentive value of reward, appears particularly sensitive to repeated cocaine exposure. Addicts display deficits in such flexible decision-making, and these behavioral observations are concurrent with abnormal brain activation patterns in this region and its limbic-striatal targets. Our experimental evidence now suggests a correlation between drug-induced alterations in OFC-dependent cognitive and motivational functions (i.e., reversal learning deficits and increased motivational effects of reward-associated cues). In animals, such deficits are linked to low striatal dopamine D2 receptor availability, consistent with low D2 levels in cocaine abusers. Reduced DA D2 receptor expression has been found in rodent and monkey OFC after repeated cocaine. Altered cortico-limbic-striatal cAMP-regulated signaling also suggests that these adaptations may underlie loss of inhibitory control. Indeed, when we identified synaptic changes produced by prior chronic cocaine exposure in monkeys using proteomics, a number of proteins involved in synaptic function and activity-dependent plasticity were regulated within distinct cortico-striatal regions. A majority of these proteins are associated with cAMP-regulated signaling, cytoskeletal function, vesicle trafficking and metabolic processes. Evidence for the causal relationships between these synaptic neuroadaptations and frontal-striatal dysfunction are beginning to be elucidated and integrated with current research is using animal models to probe the contributions of drug-induced and pre-existing cortical dysfunction in the transition to addiction.

Genetic and Neurochemical Correlates of Impulsivity in Monkeys

David Jentsch, Ph.D., University of California, Los Angeles

Non-human primates exhibit naturally-occurring, genetically-determined individual differences in their reaction to novel and risky situations, much like humans. Remarkably, behavior genetic data indicate that certain alleles (e.g., variable number tandem repeat polymorphisms in the dopamine D4 receptor gene) influence novelty-seeking and impulsivity across primate species, suggesting that a mechanistic understanding of impulsivity in primates will expand our understanding of the molecular basis of human disorders involving poor impulse control. Recent work in our group indicates that impulsive temperament is associated with, and probably determined by, an impairment in spatial working memory maintenance and difficulty with inhibiting pre-potent responses.

Collectively, we believe these cognitive deficits lead to a myopic and inflexible behavioral style. At a molecular level, selective alterations in dopamine D2-dependent signaling may be critical, relationships supported by behavioral pharmacological and molecular neuroimaging studies in high and low impulsivity subjects. On-going behavior genetic studies will no doubt provide even more critical insights into the molecular determination of impulsivity, and correspondingly, to liability for impulse control disorders.

Neurobiology of Impulsivity: Relationship to Substance Abuse

F. Gerard Moeller, M.D., University of Texas Health Science Center-Houston

F. Gerard Moeller, M.D., Joel L. Steinberg, M.D., Khader M. Hasan, Ph.D., Liangsuo Ma, Ph.D., Kimberly L. Kjome, M.D., Ponnada A. Narayana, Ph.D.

Background: There is a large body of literature linking impulsivity to drug and alcohol abuse. Recent studies have suggested that white matter pathology may play a role in the relationship between impulsivity and substance abuse.
Methods: Two groups of cocaine dependent subjects underwent diffusion tensor imaging (DTI) scans along with a questionnaire measure of impulsivity (the Barratt Impulsiveness Scale) and laboratory measures of behavioral inhibition (the Immediate Memory Task) and decision-making (the Iowa Gambling Task).
Results: Results of these studies were that cocaine dependent subjects showed evidence of subtle white matter pathology in the corpus callosum and in right frontal and parietal regions. Specifically, cocaine dependent subjects had lower fractional anisotropy (FA) and higher radial diffusivity than non-drug abusing control subjects. There was also a correlation between impairment on impulsivity and decision-making measures and white matter deficits seen on DTI.
Conclusions: These data support: 1) cocaine dependence is associated with evidence of subtle white matter pathology on DTI; 2) these changes on DTI are correlated with impaired decision making and impulsivity seen in these subjects. This is consistent with the premise that white matter changes in substance abuse may be responsible for at least some of the well-documented increase in impulsivity and impaired decision-making seen in these individuals.

The role of dopamine and serotonin in persistent gambling behaviour: implications for the persistence of alcohol and substance misuse behaviours.
Robert Rogers, Ph.D., Oxford University
Alcohol dependence, and other substance misuse disorders, are characterised by the persistence of behaviours that carry increasing risks of worse and worse health outcomes. In the context of gambling, this involves continued play to recover previous losses and is known as 'loss-chasing'. Despite the centrality of loss-chasing to pathological gambling, little is known about the neural systems that mediate this behaviour, or the way in which the neuromodulators that mediate impulse control and reinforcement processing might influence loss-chasing behaviour. Such information could inform our understanding of how pharmacological treatments might help to treat gambling problems and, perhaps, persisting alcohol and substance misuse.
Recently, we have used a simple 'double or quits' model of loss-chasing in non-clinical, healthy adult volunteers. Participants were required to choose repeatedly between (i) gambling to recover the loss of a reward at the risk of doubling its size or (ii) deciding to sustain that loss and quit the chase. Using functional magnetic resonance imaging, we have found that chasing losses is associated with increased activity in areas linked to incentive-motivation and reward expectancy. By contrast, quitting the chase was associated with decreased activity in these areas, but increased activity in areas linked to anxiety and conflict monitoring (Campbell-Meiklejohn, Woolrich, Passingham, & Rogers, 2008). Here, I review 3 separate pharmacological manipulations of loss-chasing behaviour in non-clinical healthy adults (when compared against control or placebo treatments). These include manipulations of central serotonin activity (tryptophan depletion), D_2/D_3 receptor activity (a single 176mcg dose of pramipexole), and beta-adrenoceptor activity (a single 80mg dose of propranolol). While tryptophan depletion influenced the number of consecutive decisions participants made to keep

gambling (i.e. the length of the chase during a run of losing gambles), a single dose of pramipexole influenced the size of the losses that participants were prepared to gamble in order to recover. Propranolol had much weaker effects on all measures. These results provide the first pharmacological investigation of loss-chasing behaviour in the laboratory and suggest that serotonin and dopamine have dissociable effects on this central feature of gambling behaviour. They also suggest these neurotransmitter systems may play distinct roles in the persistence of alcohol- and substance-seeking behaviours.

Impulsivity and Mood: State and Trait Mechanisms in Bipolar Disorder

Alan Swann, M.D., University of Texas Health Science Center-Houston
Alan C. Swann, Marijn Lijffijt, Blake Cox, Scott D. Lane, Joel L. Steinberg, F. Gerard Moeller
Department of Psychiatry and Behavioral Sciences, the University of Texas Health Science Center at Houston.

Background: Impulsivity is prominent in manic episodes of bipolar disorder and in its behavioral complications. Impulsivity represents several dimensions of the initiation of action, where responses to stimuli occur without the opportunity to reflect and conform behavior to its context. Mechanisms include rapid-response impulsivity, where responses occur before stimuli have been fully evaluated, and reward-delay impulsivity, with inability to delay a response for a larger reward. There is relatively little evidence about relationships between these aspects of impulsivity and the time course, compared to symptomatic states, of bipolar disorder.

Methods: Subjects were recruited from the community. DSM-IV diagnosis was rendered by the Structured Clinical Interview for DSM-IV. Psychaitric symptoms were assessed using the Schedule for Affective Disorders and Schizophrenia, Change version (SADS-C). Trait-like impulsivity was assessed using the BIS-11. Rapid-response impulsivity was assessed by the Immediate Memory Task (a Continuous Performance Test), and reward-delay impulsivity by the Single-Key Impulsivity Paradigm (SKIP), a free operant responding task, and the Two-Choice Impulsivity Paradigm, where subjects choose between smaller-sooner and larger-later rewards.

Results: BIS-11 scores correlated differentially with depression (elevated attentional and nonplanning scores) and mania (elevated attentional and motor scores). Symptoms correlating with BIS-11 scores were not related to subjective mood, but included hyperactivity, anhedonia, and hopelessness. Manic symptoms correlated with commission errors on the IMT. Manic symptoms during depressive episodes were also correlated with BIS-11 scores and multiple complications of the course of illness. There were no relationships between acute symptoms and reward-based impulsivity. After correction for symptoms, BIS-11 scores were still markedly elevated in bipolar disorder (effect size = 1.45 vs controls) and were related to recurrent course of illness and comorbid substance use disorders. IMT performance and inability to delay rewarded responses on the SKIP were also strongly related to the diagnosis of bipolar disorder regardless of state. Multivariate analyses showed that BIS-11 and measures of rapid-response impulsivity were related to severity of recurrence, history of suicide attempts, and substance-use disorders.

Conclusions: Increased impulsivity has state- and trait-like aspects in bipolar disorder. So-called trait impulsivity is also significantly related to acute symptoms, possibly because of differences in mania- and depression-prone subjects. Rapid-response impulsivity is related to acute symptoms and to the life course of bipolar disorder. Reward-based impulsivity was not as strongly related to symptoms or course of illness.
Support: R01 MH069944

Neural and Neurocognitive Aspects of Impulsivity in Pathological Gambling

Luke Clark, Ph.D., Cambridge University
Luke Clark[1], Henry Chase[2]
[1] Behavioural and Clinical Neuroscience Institute (BCNI), University of Cambridge, Cambridge, UK.
[2] School of Psychology, University of Nottingham, Nottingham, United Kingdom

Background: Problem gambling is a putative 'behavioural addiction' associated with elevated trait impulsivity. Cognitive models of problem gambling emphasise the role of distorted beliefs about winning, fuelled by multiple features of gambling games including near-miss outcomes. In non-gambling volunteers, we showed that near-miss outcomes recruited reward-related circuitry (Clark et al 2009 Neuron).
Methods: 20 regular gamblers, comprising a mixture of recreational and problem gamblers, received an fMRI scan whilst performing a computerised slot machine task. Gambling severity was measured with the South Oaks Gambling Screen (SOGS) and Gambling-Related Cognitions Scale (GRCS).
Results: Consistent with our previous study, 1) winning outcomes (minus all non-win outcomes) recruited ventral striatum, midbrain, insula and thalamus, 2) near-misses (minus full-misses) recruited ventral striatum, insula and thalamus. Regression of the near-miss response against gambling severity (SOGS, GRCS-Inability to Stop) showed significant positive associations in the midbrain. Gambling severity did not predict win-related responses in midbrain, striatum or elsewhere.
Conclusions: In games of chances (like slot machines), near-miss outcomes do not provide a valid signal of future success. The association between midbrain activity (proximal to substantia nigra/VTA) and gambling severity implicates dopamine activity in the response to near-miss outcomes in more severe problem gamblers.

Impulsivity as a determinant of drug use: Relationship to reward?

Harriet De Wit, Ph.D., University of Chicago

Susceptibility to use or abuse drugs is thought to be controlled by both the reward value of the drug and by the tendency to be impulsive, i.e., the ability to refrain from using the drug inappropriately. Several studies have shown that impulsive individuals (nonhumans and humans) are more likely to use drugs. However, little is known about the relationship between impulsivity and the reward value of the drug. That is, impulsive individuals may use drugs more readily either because of their impulsive tendencies, or because they are also more, or less, sensitive to the reward value of the drug. In an analysis of a large ongoing study, we compared the euphorigenic effects of d-amphetamine (20 mg) in healthy young adults in relation to their performance on three behavioral measures of impulsivity: behavioral inhibition, delay discounting, and lapses of attention. We found that subjects who exhibited the most lapses of attention reported

smaller increases in ratings of drug liking. This was consistent with a previous finding (de Wit et al, 2002), indicating that subjects who exhibited a higher rate of false alarms on a go-no-go task reported less euphoria from d-amphetamine (20 mg). That is, impulsivity by these measures was correlated with *lower* sensitivity to the rewarding effects of d-amphetamine. Delay discounting tended to have the opposite relationship: High delay discounting was non-significantly associated with greater increases in Positive Mood after amphetamine. These findings suggest that certain impulsive behaviors may be related to sensitivity to reward.
Supported by DA09133 and DA021336.

Measures of impulsivity in drug-naive rats and mice can be associated with alcohol consumption

Suzanne H. Mitchell, Ph.D., Oregon Health and Science University

Relative levels of delay aversion (delay discounting) have been used to index impulsivity in human and animal subjects. Data will be described to show that this measure of impulsivity has a genetic component in rats and in mice. Further, a series of studies using rat and mouse lines, which were selected to consume large or small amounts of alcohol, will be described. The results indicate that high consumption lines exhibit higher levels of delay aversion than lines selected to consume low amounts. However, this result is not consistent across all pairs of selected lines, indicating that genes associated with high levels of alcohol consumption are not perfectly cosegregated with those associated with high levels of delay aversion. These data have implications for the identification of the genetically-driven individual differences in delay aversion. They also suggest that individuals who are family-history positive for alcoholism may differ in their levels of impulsivity, which in turn may affect the likelihood of their progression to high levels of alcohol use.

Evidence for reduced ability to suppress pre-potent responses in multiply detoxified alcoholics, binge-drinkers, and in a rodent model of binge drinking: cause or consequence of alcohol abuse?

David Stephens, Ph.D., University of Sussex
D.N. Stephens, L. Hoang, K. Pulman, L. Trick and T. Duka
Department of Psychology, University of Sussex, Falmer, Brighton, BN1 9QG, UK

Repeated episodes of alcohol withdrawal are a common feature of both alcoholism and binge drinking. We have studied the relationship of repeated detoxification and of binge drinking to cognitive and emotional functioning in young adults. Since in human studies it is difficult to know whether such behavioural changes predate, or are a consequence of patterns of alcohol abuse, we have also studied parallel behaviours in a rodent model, in which rats are exposed to intermittent episodes of alcohol consumption and withdrawal (repeated withdrawal; RWD). Both multiply detoxified patients and binge drinkers showed increased errors of commission in a vigilance task of the Gordon Diagnostic Battery. In addition, binge drinkers reacted faster in a matching to sample visual search task and in a simple reaction task, whilst patients responded faster in the delay task of the Gordon diagnostic, tasks associated with motor impulsivity. Currently abstaining alcoholic patients were also impaired in inhibiting inappropriate responses during performance of a negative patterning task in which they received monetary

reinforcement for responding to either of two stimuli, but were punished by loss of money for responses during compound presentation of the stimuli. Such impairments are consistent with high impulsivity, which may result from, or contribute to alcohol abuse. Rats exposed to repeated episodes of withdrawal showed similar impairments in a negative patterning task as alcoholic patients, suggesting that impulsive behaviours may result from, rather than precede alcohol abuse. However, we found no effects of RWD on rats' performance of a 2-choice serial reaction time task (CSRTT), or mouse performance of a 5-CSRTT), in which ethanol given acutely was effective in inducing impulsive performance. Thus the motor impulsivity seen in binge drinkers and patients may precede alcohol abuse, while impulsivity in the negative patterning task may be a consequence.

Stress, Self-control and Alcohol Relapse Risk: fMRI studies

Rajita Sinha, Ph.D., Yale University School of Medicine
Rajita Sinha, Helen Fox, Dongju Seo, Kwang-ik Hong, Keri Bergquist

Introduction: Difficulties in self control (impulse control) have been documented in alcoholism and are also observed in other psychiatric disorders (ADHD, personality disorders). It is also well known that self control decreases under periods of high emotional stress and heightened arousal. Our previous research has documented emotion regulation and impulse control difficulties in treatment engaged abstinent alcoholics. We've also shown alcohol-related dysregulation in stress pathways along with persistent increases in stress and cue-induced alcohol craving during early alcohol abstinence. Here we examined whether functional magnetic resonance imaging (fMRI) responses to stress and alcohol cue exposure are associated with impulse control problems in alcoholics and whether such neural responses are predictive of return to drinking post-treatment. Method: Inpatient treatment-engaged alcohol dependent (AD) individuals participated in brief trials of exposure to script-guided imagery of personal stress, alcohol cue and neutral relaxing situations while blood oxygenation level-dependent (BOLD) signals of their brain response were acquired in a 3T MRI scanner. The Difficulties in Emotion Regulation Scale (DERS) was used to assess self/impulse control and all patients were prospectively followed after discharge from the inpatient research treatment unit to assess returnt o alcohol use during a 90-day follow-up period. Results: AD patients showed significant activity in the medial prefrontal cortex (mPFC, ACC and ventromedial PFC/OFC), ventral striatum, VTA, thalamus and posterior cingulate cortex during stress and alcohol cue relative to neutral relaxing exposure. However, relapsers showed blunted mPFC/OFC and ventral striatum responses to stress and cues relative to non-relapsers, resulting from hyperresponsvity of these regions during neutral relaxed imagery. Poor impulse control scores was associated with blunted stress-related activity in the prefrontal cortex, and blunted prefrontal cortex response to stress and high mPFC response to the neutral-relaxing imagery were both predictive of relapse outcomes. Conclusion: The findings indicate blunted prefrontal responses to stress which were associated with poor impulse control and greater risk of alcohol relapse. Self control processes involve the medial prefrontal cortex and this region is important in emotional stress regulation. Dysfunction of this region contributes to impulse control difficulties commonly seen in alcoholism and also predicts high risk of alcohol relapse. (Supported by R01-AA013892 and UL1-DE019586).

fMRI Studies of Reward Processing and Impulsivity, Related to Family History of Alcoholism

Michael Stevens, Ph.D., Yale University School of Medicine

Part of the inherited vulnerability to substance abuse may involve impulsivity, defined both by 1) abnormal reward sensitivity, often operationalized as deficient activation in neural circuitry engaged by delayed reward tasks, and 2) risky or impulsive decision making, which biases such individuals towards immediate rewards and risky decisions. Reward sensitivity-based fMRI paradigms such as the Monetary Incentive Delay task separate appetitive and consummatory aspects of rewards, and activate a *reward circuit* that includes ventral striatum (nucleus accumbens, NAcc), amygdala, ventral tegmental area (VTA), mesial prefrontal cortex, caudate, putamen, hippocampus, anterior cingulate, insula and orbitofrontal cortex (OFC). Previous fMRI studies indicate reduced NAcc activation during reward anticipation in abstinent alcoholics. This could represent an inherited risk-related response, a consequence of alcohol abuse, or both. We hypothesized that persons genetically at risk for alcoholism by virtue of having multiple affected first-degree relatives with the disorder, but who are not themselves alcohol abusers, would have reduced NAcc activation during reward anticipation. We also expected to observe elevated impulsivity and abnormal reward sensitivity on a battery of trait- and laboratory-based measures in these family-history positive (FHP) persons, as has frequently been seen in alcohol abusers. 30 FHN and 19 age/sex/ethnicity matched (FHP) underwent fMRI using the MID task. These participants were part of a larger sample of 176 FHP/FHN persons who completed a dual-factor impulsivity test battery that was examined by factor analysis. We found significant MID task activation differences in FHP during reward anticipation, including reduced NAcc activity, as well as less response in insula, orbitofrontal cortex, and putamen. There also was greater activation in FHP relative to FHN in NAcc during the cues signaling the prospect of reward, but diminished FHP NAcc activation during reward outcome. Although FHP were not more impulsive based on impulsivity factor scores, several impulsivity measures across the entire FHP+FHN sample correlated with fMRIactivation patterns in a manner consistent with our original hypotheses. The increased reward prospect NAcc finding and the decreased NAcc reward anticipation/outcome findings support both a *reward sensitivity* and *reward deficit* hypothesis, respectively. One explanation is that FHP persons are overly reward-focused, but cannot sustain neuralresponse in NAcc signaling of the likelihood of reward over time.

The gene-by-environment interface in aggression and addiction

David Goldman, M.D., NIAAA

Stress exposure, including activations of the brain and HPA stress axis, play a powerful role in vulnerability to addictions and several other psychiatric disorders. Genes that alter stress resilience and vulnerability play a powerful role via G x E interactions. In African American opioid, cocaine, and alcohol dependent patients, we showed that the serotonin transporter promoter polymorphism predicts a high rate of suicidality (Roy et al). MAOA, a gene that influences behavioral dyscontrol, does so in the context of early life stress exposure, as shown classically by Caspi et al for dimensionally measured

behavioral dyscontrol. We have found that the combination of the low activity MAOA and childhood sexual trauma is predictive of alcoholism and ASPD in women (Ducci et al). In men, the effect of testosterone to increase aggression is strongly moderated, or dependent, on the low MAOA genotype (Sjoberg et al). The Finnish subjects in that study included controls and patients with alcoholism and/or ASPD who had also been convicted of various serious crimes. African-Americans have high prevalences of certain illicit substance use disorders (cocaine, heroin) but not others (amphetamine), leading to discussion of whether their differences in outcome are due to intrinsic or extrinsic (environmental) differences. Using a large panel of highly informative ancestry markers, we showed that African ancestry was slightly, but significantly, protective. However, in the same largely economically poor population (as shown by census tract data), childhood trauma assessed by the Childhood Trauma Questionnaire, was strongly predictive of risk of cocaine, heroin and alcohol dependency (Ducci et al, in press). These findings emphasize the powerful roles of poverty and stress exposure for diseases of addiction and behavioral dyscontrol that are, paradoxically, moderately to strongly heritable.

Behavioral Assessment of Risk-taking and Alcohol Use in Adolescents

Carl Lejuez, Ph.D., University of Maryland
C. W. Lejuez, Laura MacPherson, & Elizabeth K. Reynolds

Alcohol misuse in adolescence continues to grow despite large-scale public health efforts to reduce both its incidence and prevalence (Bukstein & Winters, 2004; Waldron & Kaminer, 2004). This is troubling given that adolescent alcohol initiation and subsequent misuse often signals future impairments in physical health (Jones et al., 2004), mental health (McGue & William, 2005), and social and occupational functioning (Friedman, Terras & Zhu, 2004). Further, alcohol use is associated with risky sexual behavior and is the primary contributor to injury-related death, which is the number one cause of death in youth under age 21 (NIAAA, 2004). To enhance prevention efforts, theorists have attempted to understand factors that contribute to the etiology and maintenance of alcohol misuse. There exist several models to understand the personality factors that lead adolescents to alcohol initiation and subsequent misuse (e.g., Sher, Bartholow, & Wood, 2000; Zuckerman & Kuhlman, 2000). Predominantly, these models focus on some aspect of positive reinforcement, that is, how risk taking is influenced by the novelty, excitement and/or arousal associated with alcohol use. In line with these models, researchers have attempted to use self-report measures of risk-taking to identify and predict vulnerability to alcohol misuse. However, self-report measures have their limitations for such purposes because adolescents often are unable to accurately report on their own risk tendencies (Ladouceur et al., 2000; Turner et al., 1998) and may be suspicious of assessments that they worry could be used to uncover their substance use. To address this, behavioral measures have been developed to capture snap shots of reward seeking in a less transparent and potentially more accurate way. One empirically validated and commonly used behavioral measure to index reward seeking is the Balloon Analogue Risk Task (BART; Lejuez et al., 2002). Several studies indicate that risky responding on the task is related to excessive risk behaviors including problematic alcohol use in both community (Aklin et al., 2005; Lejuez et al., 2005; 2007) and clinical samples (Crowley, Lejuez et al., 2006). This

presentation focuses on a study of 221 10-12 year old youth assessed annually for three years aimed at examining the utility of the BART for predicting alcohol initiation and use. We also included sensation seeking given its documented association with youth alcohol use; BART was related to sensation seeking only at Year 3 ($r = .19$, $p < .01$). The concurrent or cross-sectional correlation between BART and alcohol use showed a modest increase in the robustness of the correlations across each year, $r = .10$ (ns), .14 ($p < .05$), and .19 ($p < .01$) respectively. The correlation between sensation seeking and alcohol use was significant each year, with the weakest correlation in Year1; $r = .15$ ($p < .05$), .27 ($p < .01$), and .25 ($p < .01$) across subsequent years respectively. Further, BART score assessed at Year1 was examined as a prospective predictor of odds of alcohol use over time in a generalized estimating equations analysis for binomial outcomes. After covarying for the main effects of age, gender, baseline sensation seeking, and the linear effect of time, greater riskiness indexed by the final 10 balloons on the BART significantly predicted a higher odds of alcohol use across three waves of data (AOR = 1.02, $p = .04$). Despite promising results, tasks such as the BART tap only positive reinforcement/reward seeking processes and do not address adolescents' use of alcohol in response to aversive stimuli, including coping with negative feelings or experiences (Kuntsche et al., 2005). For this reason, we introduce a version of the BART that addresses negative reinforcement theory pathways to alcohol use and misuse (e.g., Baker et al., 2004). Finally, we discuss the extension of this work with biological and environmental measurement and implications for prevention.

POSTER PRESENTERS:

Iris Balodis, Yale University School of Medicine

Recreational Drug Use and Impulsivity in an Undergraduate Population

I.M. Balodis[1]; M.N. Potenza[1]; M.C. Olmstead[2]
[1]*Yale University School of Medicine, New Haven, CT*
[2]*Queen's University, Kingston, Ontario, K7L 3N6, Canada*

Illicit drug use during adolescence is associated with health and behavioral problems and is a strong predictor of substance dependence in adulthood. The consumption of drugs during adolescence may be particularly detrimental, as brain development is still occurring at this time. We gathered information on the recreational drug use habits, impulsivity scores and the drinking habits of 205 (105 female) undergraduate students. In the current sample, 64% of the students reported having used marijuana at least once. These individuals were also more likely to report binge drinking. There were no significant gender differences in reports of recreational drug use, multiple drug use or impulsivity scores. Multiple drug use, defined as using marijuana and at least one other illicit substance, was reported by 20% of students. These individuals reported a greater number of drinking occasions per month, however, they were no more likely to be binge drinkers than individuals who reported marijuana use. Multiple drug users were also more likely to have higher levels of trait impulsivity, as measured by the Barratt Impulsiveness Scale and its associated cognitive, motor and nonplanning subscales. Given the high rates of marijuana experimentation reported by students, our data suggest that, rather than initial marijuana use, trait impulsivity may be an important

predictor of illicit drug use. Longitudinal studies examining the initiation of drug use should assess the contribution of impulsivity to the initiation and experimentation with illicit drugs. The recreational drug use rates reported by students are similar to those reported in national surveys and suggest increases in experimentation with specific illicit drugs.

Eliza Congdon, Ph.D., University of California, Los Angeles

Impulsivity and Clinical Symptoms among Girls with Repeated Suicide Attempts

E. Congdon[1,2], J. Mumford[1], E. Miller[1], Cohen, J., Aron, A. & R. A. Poldrack[1]

[1]Department for Psychology, University of California Los Angeles; [2]Center for Neurobehavioral Genetics, University of California Los Angeles

Despite the important role of impulsivity in multiple psychiatric disorders, our understanding of its role remains limited because impulsivity is multidimensional and there are several psychological processes that could potentially underlie impulsive behavior, including response inhibition, or the ability to suppress a prepotent response. In order to better characterize the neural correlates of response inhibition across adults representing a range of impulsivity, we conducted a meta-analysis of three fMRI studies (n = 86), in which participants were scanned while performing a Stop-signal task. Each study used an adaptive procedure to ensure approximately 50% inhibition, in order to estimate a ”stop signal reaction time” (SSRT) indexing the speed of the inhibitory process. Our meta-analysis provides further evidence for the role of a frontostriatal network (primarily the right IFC, preSMA, basal ganglia) underlying response inhibition, with more medial-frontal areas showing activation during failed inhibition. Our results also demonstrate significant individual differences, as activation during both stopping and going correlates with task performance. These results demonstrate the robustness of the neural signal elicited during performance of the Stop-signal task, and suggest that the pattern of neural activation during response inhibition is a suitable candidate for continued investigations into the neurobehavioral correlates of impulsivity.

[This work was supported by NIH T32 NS048004 and PL1 MH083271 grants and the James S. McDonnell Foundation.]

Blake Cox, B.A., University of Texas Health Science Center-Houston

Impaired decision-making in antisocial personality disorder with past poly-substance abuse

Department of Psychiatry and Behavioral Sciences, Mental Science Institute, University of Texas at Houston, Houston, USA

Background: Antisocial personality disorder (ASPD) has been associated with impaired decision-making measured by the Iowa Gambling Task (IGT), which is related to increased trait impulsivity or current substance abuse. Limited information is available on decision-making in subjects with ASPD without current alcohol and drug abuse, or on relationships between decision-making and impulsivity or ASPD severity.

Methods: Twenty-five subjects met criteria for childhood-onset (n = 22) or adulthood-onset (n = 3) ASPD; 45 subjects were included as normal controls. Impulsivity was measured with the Barratt Impulsiveness Scale (BIS-11). Severity was measured by histories of alcohol or drug abuse, and conduct disorder or adulthood ASPD symptom counts.

Results: Subjects with ASPD had increased BIS-11 and lower IGT total scores than control subjects. BIS-11 scores and symptom counts did not relate to IGT performance. However, subjects with ASPD and past alcohol and drug (poly-substance) abuse had significantly worse IGT performance than controls, whereas subjects without past poly-substance abuse did not.
Conclusions: Subjects with ASPD and past poly-substance abuse perform worse on the IGT and score higher on the BIS-11, suggesting impaired decision-making and heightened impulsivity

Melissa Cyders, M.S., University of Kentucky
Biological Underpinnings of Positive and Negative Urgency and Their Importance for Treatment Implications
Cyders. M.A., Smith, G.T.
Background: Researchers have acknowledged that the trait "impulsivity" is a poorly defined term encompassing many different tendencies toward rash action. Evidence has shown that the emotion-based dispositions toward rash action, namely negative urgency (rash action in response to a negative emotional state) and positive urgency (rash action in response to a positive emotional state) have unique predictive roles for a variety of maladaptive and problematic behaviors. Given that fact, it is important to provide a theoretical framework for understanding these traits as specific risk factors for maladaptive behaviors and to understand the treatment implications of these traits. This is the goal of this presentation. Results: To summarize, it appears that positive and negative urgency have important biological underpinnings that may involve the dual activation of (1) related brain processes, (2) reciprocal modulation of brain regions (specifically, the interaction between the amygdale and motor cortex regions), and (3) neurotransmitter systems that underlie both approach behaviors and emotional experiences (serotonin and dopamine) (Cyders & Smith, 2008). Conclusions: These traits are a common factor among impulse control disorders. Given this, treatment implications and directions will be discussed. This research was supported by NIAAA.

Jodie Finlayson-Burden, University of Nottingham
The role of impulsivity and related traits in predicting behavior within a bipolar continuum sample
Authors and affiliations: Ms. Jodie Finlayson-Burden, BSc, PhD Student, Division of Psychiatry, QMC; Dr. Rhiannon Corcoran, PhD, Associate Professor, Division of Psychiatry, QMC; Prof. Richard Morriss, PhD, Professor, Division of Psychiatry, Institute of Mental Health
Background: Impulsivity has been shown to be of great importance in the prediction of certain behaviours in bipolar disorder, particularly suicidal behaviour. As the first study in a series, this experiment will use a sample of students with high levels of hypomania to tease out the relationships between particular strands of impulsivity and a variety of behaviours common to bipolar disorder.
Methods: The study will take the form of an online questionnaire. The Mood Disorders Questionnaire will be used to assess hypomania, with both the Barratt Impulsiveness Scale and the UPPS Impulsive Behaviour Scale measuring various forms of impulsivity. A newly designed selection of questions investigates the occurrence of certain

behaviours thought to be linked to high levels of impulsivity in bipolar spectrum individuals, such as reckless driving, drug and alcohol use and suicide.
Results and conclusions: *The study is in progress and results have not yet been collected, though data and analysis will be complete by the time of the conference in June 09. The results are expected to demonstrate the links between particular forms of impulsivity and impulsive-type behaviour within the bipolar spectrum, and as such will have implications for the prevention of risk taking behaviour and suicide in at-risk bipolar patients.*

Regan E. Fried, B.A., University of Kentucky
The Measurement of Dispositions to Rash Action in Children
Fried, R. E.[1], Cyders, M. A.[2], & Smith, G. T.[1]
[1]University of Kentucky
[2]Indiana University Purdue University at Indianapolis
This paper describes the first longitudinal test of a model specifying a process by which impulsivity-related personality traits influence psychosocial learning, which in turn leads to increases in quantity of alcohol consumption and problem drinking. Prior research has demonstrated the importance of emotion-based dispositions to rash action for the prediction of problem drinking. The present study extended this research by testing a specified mechanism for how those dispositions ultimately influence problem drinking. The authors studied 418 individuals making the transition to college independence across three longitudinal waves. In one longitudinal model, the trait of positive urgency (the tendency to act rashly when experiencing extremely positive affect), measured at the start of college, predicted subsequent increases in expectancies that alcohol provides positive, arousing effects, and those expectancies in turn predicted increased drinking quantity by the end of the first year of college. In a second model, negative urgency (the tendency to act rashly when experiencing extremely negative affect), again measured at the start of college, predicted subsequent increases in the motive to drink to cope with distress, which in turn predicted increased drinking quantity by the end of the first year of college. This research was supported by NIAAA.

Robert Leeman, Ph.D., Yale University School of Medicine
Impaired Control Mediates Associations Between Impulsivity and Alcohol-Related Problems
R. F. Leeman1; M. Fenton2; M. Kulesza3; D. W. Stewart3; L. A. Taylor4; and A. L. Copeland3
1 Yale University School of Medicine, New Haven, CT2 Columbia University, New York, NY 3 Louisiana State University, Baton Rouge, LA4 Scripps College, Claremont, CA
Background: Impaired control is “a breakdown of an intention to limit consumption in a particular situation” (Heather et al., 1993). Both impulsivity and impaired control involve difficulties with self-restraint and both have been associated with problem drinking. The goal of this study was to determine whether impaired control—given that it is more proximal to alcohol use—mediates associations between impulsivity and problem drinking. Methods: Data were from an anonymous survey conducted at a state university in Connecticut (N = 395). Results: Impaired Control Scale scores significantly predicted binge drinking, however none of the subscales of the Barratt Impulsiveness

Scale did. The attentional and nonplanning, but not the motor subscale, were significant predictors of alcohol-related problems, however these effects lost significance when controlling for impaired control. These findings, plus its significance in predicting alcohol-related problems, suggested a mediating effect of impaired control. Mediation was confirmed by significant Sobel tests (attentional: $Z = 2.49$, $p = 0.013$; nonplanning: $Z = 2.62$, $p = .009$). Conclusions: Much of the association between impulsivity and alcohol-related problems could be accounted for by its association with impaired control. A potential implication is that impulsivity leads to impaired control, which in turn, leads to alcohol-related problems.
Supported by R01 AA016621 (P.I.: S. O'Malley)

Marijn Lijffijt, Ph.D., University of Texas Health Science Center-Houston
Sensory Gating and Severity of Course of Illness in Antisocial Personality Disorder
Marijn Lijffijt, Blake Cox, F. Gerard Moeller, Scott D. Lane, Joel L. Steinberg, Alan C. Swann
Department of Psychiatry and Behavioral Sciences, Mental Science Institute, University of Texas at Houston, Houston, USA
Background: Antisocial personality disorder (ASPD) has been associated with recurrent impulsive behaviors and deficient information processing which could be related to impaired gating of information to higher order functions for more elaborate stimulus processing. We studied relationships between ASPD and sensory gating as the difference in P50, N100 or P200 amplitude from an initial stimulus (S1) to a second stimulus (S2) using the paired-click paradigm. A smaller S1-S2 difference indicates diminished gating.
Methods: Thirty-six subjects were included with childhood-onset (n = 26) or adulthood-onset (n = 10) ASPD; 43 subjects were included as healthy controls. Severity of ASPD was measured independently by the Barratt Impulsiveness Scale (BIS-11), conduct disorder and ASPD symptom counts, and history of substance (alcohol or drug) abuse.
Results: General Linear Model (GLM) analysis showed reduced N100 and P200 S1-S2 differences in subjects with ASPD which correlated positively with BIS-11 total scores and with adulthood ASPD symptom count. Additionally, N100 difference score was smaller in ASPD subjects with a history of substance abuse, but not in subjects without such a history.
Conclusions: Subjects with ASPD with greater symptom severity show diminished N100 and P200 sensory gating.

Andrew Littlefield, M.A., University of Missouri-Columbia
Developmental Trajectories of Impulsivity and Their Association with Alcohol Use and Other Outcomes During Emerging and Young Adulthood
A. K. Littlefield, K. J. Sher, & D. Steinley; University of Missouri-Columbia and the Midwest Alcoholism Research Center, Columbia, MO 65211
Background: Research has documented normative patterns of personality change during emerging and young adulthood that reflect decreases in traits associated with substance use, such as impulsivity. However, evidence suggests variability in these developmental changes. This study examined trajectories of impulsivity and their association with substance use and other outcomes from ages 18-35.

Methods: Data were taken from a longitudinal study of 489 first-year college students (54% women; 52% with paternal history of alcoholism; baseline age = 18.5) who completed measures of impulsivity at ages 18, 25, 29, and 35. Mixture modeling identified 5 trajectory groups that differed in baseline levels of impulsivity and developmental patterns of change.
Results: Trajectory groups that exhibited high and non-decreasing levels of impulsivity were less likely to decrease in alcohol use compared to a trajectory group that exhibited high but decreasing levels of impulsivity. Among other outcomes, trajectory groups that failed to decline in impulsivity were more likely to be male, higher in baseline psychoticism, and less likely to be married at subsequent assessments.
Conclusions: Findings suggest trajectory groups characterized by distinctive patterns of stability and change in impulsivity are associated with changes in alcohol use, adult role transitions, and other outcomes during emerging and young adulthood.
Supported by NIAAA grants AA013987, K05AA017242, and T32AA013526 to Kenneth J. Sher and AA11998 to Andrew C. Heath.

Shijing Liu, Ph.D., University of Texas Health Science Center-Houston
The relationship between the responsivity to cocaine-related stimuli and other cognitive performance
S. Liu1, F.G. Moeller1, S.D. Lane1 and K.A. Cunningham2
1Department of Psychiatry and Behavioral Sciences, University of Texas Medical School, Houston, TX and 2Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX
Background: Cocaine users exhibit an attentional bias for drug-related stimuli and are more impulsive in different cognitive tasks than controls. However, the relationship between the responsivity to cocaine-related stimuli and the performance on other tasks is not well explored.
Methods: We compared the performance of cocaine-dependent and control subjects on a cocaine word-based emotional Stroop task, probabilistic reversal learning task and two different measures of impulsivity. We specifically analyzed the relationship between the response time to cocaine vs. neutral words in the Stroop task and performance on the above cognitive tasks.
Results: Our preliminary data show that response time difference (cocaine words – neutral words) of cocaine-dependent subjects (n = 11) in Stroop task was significantly larger than that of controls (n=12; $p < 0.05$). This response time difference was positively correlated with the number of incorrect responses on the reversal learning task ($P < 0.05$), but not with response inhibition or delay discounting.
Conclusions: The significant correlation between Stroop and reversal learning performance, but not with performance on tests of impulsivity provides preliminary evidence that attentional bias and reversal learning (compulsiveness) may be independent from response inhibition and temporal discounting (impulsivity); though both are prominent features of cocaine dependence.
Support: DA024157, DA009262

Charles Mathias, Ph.D., University of Texas Health Science Center- San Antonio
Impulsivity and Clinical Symptoms among Girls with Repeated Suicide Attempts

Authors: Charles W. Mathias, Michael A. Dawes, Dawn M. Richard, and Donald M. Dougherty
Affiliation: Neurobehavioral Research Laboratory and Clinic,
The University of Texas Health Science Center at San Antonio
Background: Adults with repeated suicide attempts have a more severe clinical presentation than those who attempt only one time. Impulsivity is an important component of the clinical presentation of those who attempt or die by suicide. Preliminary work has explored behavioral impulsivity among adult repeated suicide attempters, although this work is yet to be replicated or extended to the adolescent age range. The purpose of this study was to test impulsivity and standard clinical symptom scales among adolescent girls with repeated suicide attempts.
Methods: Eighty-one adolescent girls were recruited into one of four groups: community controls, or psychiatric inpatients with either zero, one, or more than one suicide attempts. The assessment included measures of impulsivity (stop task and consequence sensitivity procedure) and clinical symptom scales (depression, hopelessness, suicidal ideation, suicide intent, and aggression).
Results: Inpatients were generally more impaired than controls in terms of clinical symptoms, and girls with repeated suicide attempts were differentiated from single attempters in terms of depression, aggression, and consequence sensitivity.
Conclusions: Assessments of tolerance of delay gratification, as measured by consequence sensitivity procedures, may be a valuable tool for use in assessing risk and the needs of individual patients in suicide intervention programs.

Ian Mendez, M.A.,Texas A&M University
The Roles of Nicotinic and Muscarinic Cholinergic Receptors in Decision Making
Ian A. Mendez* & Barry Setlow.
Behavioral and Cellular Neuroscience Program, Department of Psychology, Texas A&M University.
Risky decision making is a characteristic of several psychopathological conditions. Although the role of several neurotransmitter systems in such behavior has been thoroughly investigated, little is known about the involvement of the cholinergic system. The overall goal of these experiments was to determine how cholinergic signaling is involved in risky decision making. Fifteen male Long-Evans rats were trained in a probability discounting task, in which they chose between a small guaranteed food reward and a large food reward that was delivered with varying probabilities ranging from 100% to 0% within a single session. Using acute drug administration in a within-subjects design, the acetylcholinesterase inhibitor donepezil decreased risky choices (increased choice of the small guaranteed reward), but only in rats with high baseline levels of risky choices. Nicotine increased risky choices, whereas the muscarinic receptor agonist oxotremorine may have decreased risky choices but also non-specifically disrupted performance. Findings from these experiments suggest that the cholinergic system is indeed involved in risky decision making, and preliminary data suggest a dissociation between cholinergic receptor subtypes. Ongoing experiments are investigating the effects of cholinergic antagonists on the probability discounting task, as well as on impulsive choice in a delay discounting task.

Melissa Miller, B.A., University of Kentucky

Levels of impulsivity in drinkers predict the degree of attentional bias toward alcohol
Melissa A. Miller and Mark T. Fillmore
University of Kentucky

Background: Attentional bias toward alcohol-related stimuli is thought to be a conditioned process that is linked to alcohol-seeking behavior. Response times to alcohol-related stimuli have typically been used to measure attentional bias. The current study aimed to validate this measure using eye-tracking techniques to directly measure subjects' visual fixations on alcohol-related stimuli. The study also tested the hypothesis that individuals with greater levels of trait impulsivity would demonstrate greater attentional bias toward alcohol-related stimuli.

Methods: Young adult alcohol drinkers (N=25) completed two measures of attentional bias to alcohol-related visual stimuli: 1) A dot-probe task that measured the subject's reaction times to alcohol versus neutral stimuli; and 2) An eye-tracking measure of the subject's gaze times on alcohol versus neutral stimuli. Participants' trait impulsivity was measured by the Barratt Impulsiveness Scale (BIS-11).

Results: Participants demonstrated attentional bias toward alcohol-related stimuli as measured by faster reaction times and increased gaze durations to alcohol versus neutral stimuli. Also, greater attentional bias to alcohol was associated with higher impulsivity.

Conclusions: The results of the eye-tracking assessment validate the use of dot-probe tasks as a measure of attentional bias. Additionally, results suggest that greater attentional bias to alcohol-related stimuli could be linked reduced impulse control.

Marci Mitchell, B.S., Texas A&M University

mpaired probabilistic decision making in aging.
M.R. Mitchell, N.W. Simon, B. Setlow, J.L. Bizon

Decision making can be impaired in aging and such deficits impact financial security and overall quality of life. Naturalistic rodent models mimic human aging in other cognitive domains and may afford the opportunity to examine effects of age on decision-making, relatively uncontaminated by experiential factors. Young adult (6 mo.) and aged (24 mo.) male Fischer 344 rats were trained on a probabilistic discounting task in which they could choose between two levers, one that delivered a certain reward (1 food pellet) and one that delivered a large but uncertain reward (2 food pellets with varying probabilities of delivery). Young adult rats accurately detected within-session changes in probability, and adjusted their choices away from the large reward when the probability of its delivery decreased. Aged rats were impaired in adjusting their choices, and continued to choose the large reward even with low probabilities of delivery. Control measures indicated that age-related differences in probabilistic decision making were not likely due to perseveration or alterations in reward magnitude perception. These findings suggest that advanced age impairs the ability to detect and/or respond to changes in reward probability, and this rodent model should be useful for investigating neurobiological substrates underlying these deficits.

Supported by R01 AG029421 (JLB & BS) and F31 DA023331 (NWS)

Brandon Oberlin, B.S., Indiana University School of Medicine

Responding For Ethanol Reduces Impulsivity In Female High Alcohol Preferring Mice In A Delay Discounting Task

B.G. Oberlin; C.J. Frye; N.J. Grahame. Indiana University Schools of Science and Medicine, Indianapolis, IN 46202.

Human alcoholism and other addictive behaviors have been correlated with greater impulsivity as measured by a delay discounting (DD) task. Although we previously showed that selectively bred High Alcohol Preferring (HAP) mice are more impulsive than the Low Alcohol Preferring (LAP) line in the DD task, the influence of alcohol itself on impulsivity as measured by the DD task is not clearly delineated in the literature. Here we addressed the hypothesis that ethanol would increase impulsivity in HAP mice.

We used an adjusting amount version of the DD task which gave HAP mice concurrent choice between a larger delayed reinforcer and a smaller immediate reinforcer. Mice could titrate the value of the immediate reinforcer until it was equivalent to the fixed, delayed reinforcer, thus giving a measure of subjective reward size. In study 1, HAP mice (n = 20) were injected with ethanol (1.5 & 2.0 g/kg) and amphetamine (1.2 mg/kg) and responded for saccharin (0.0316% w/v) reinforcement. Delays to the fixed reinforcer were 0.5 sec. or 10 sec, assigned in a between-subjects fashion. In study 2, HAP mice (n = 39) responded for ethanol (8% v/v) or saccharin (0.01% w/v) reinforcement at delays of 1, 2, 4, and 8 sec.

Amphetamine, a positive control, showed a strong trend of decreasing impulsivity in study 1. We were not able to detect an effect of injected ethanol on impulsivity, although the trend was a decrease rather than the hypothesized increase. In study 2, mice responding for and consuming ethanol during the DD sessions were less impulsive than mice responding for saccharin. This effect was driven by females, perhaps due to their higher self-administered ethanol doses than males (2.50 ± 0.10 and 1.89 ± 0.10 g/kg/hr ± SEM, respectively). Also consistent with a dose-dependent effect of ethanol in reducing impulsivity was a negative correlation between the transformed best-fit parameter *k* and ethanol dose consumed (r = -0.64), but not saccharin consumption (r = -0.17). These results were opposite of our hypothesis. Although study 1 may have been underpowered, the data from study 2 were in the same direction as study 1, in that ethanol decreased impulsivity. Together, these studies suggest that like amphetamine, ethanol decreases impulsive choice, consistent with similar effects reported in some human studies, but contrary to the widely held view that acute ethanol increases impulsivity. AA13483 to NJG, AA07611 to David Crabb, F31AA016430 to BGO.

Erik Ostling, B.A., University of Kentucky

Tolerance to Alcohol Effects of Ihhibitory and Activational Mechanisms of Behavioral Control.

Background: Recent behavioral studies of alcohol have employed cognitive models to examine behavioral control as the net effect of countervailing activational and inhibitory influences. Studies show that acute doses of alcohol impair the ability to activate behavior and to inhibit action. Evidence also shows that activational, but not inhibitory mechanisms, demonstrate acute tolerance to the impairing effect of alcohol during a single dose. Lack of tolerance development to the impairing effects on inhibitory control could prolong the disinhibiting effects of alcohol.

Method: The present study built on this finding by examining tolerance development to impaired inhibitory and activational mechanisms across repeated doses of alcohol. Subjects (N=24) performed the cued go/go-go task. Half were tested under the 0.65 g/kg dose; administrated twice, on two different days. The other half served as control and were tested under placebo during those days.
Results: Alcohol initially impaired response activation and inhibition. During the second alcohol administration, tolerance was observed to the impairing effects on response activation, but not to the impairing effects on response inhibition.
Conclusions: This suggests that inhibitory mechanisms are particularly vulnerable to impairment under alcohol, and that the disinhibiting effects of the drug might persist despite repeated, heavy drinking.
Research supported by NIAAA grant R01 AA012895 and NIDA grants R21 DA021027.

Barry Setlow, Ph.D., Texas A&M University
Self-administered cocaine causes lasting increases in impulsive choice in a delay discounting task
Barry Setlow, Ian A. Mendez, Nicholas W. Simon, Nigel Hart, Marci R. Mitchell, Jack R. Nation, & Paul J. Wellman
Cocaine use is associated with increased impulsive choice (preference for immediate over delayed rewards), but it is not clear whether cocaine use *causes* increased impulsive choice, or whether increased impulsive choice is solely a predisposing factor for cocaine use. This study examined the effects of prior cocaine self-administration experience on rats performing a delay discounting task commonly used to measure impulsive choice.
Rats self-administered at least 30 mg/kg/day cocaine HCl (approx. 0.5 mg/kg/infusion) for 14 consecutive days (a control group received yoked saline infusions). Following three weeks of withdrawal, rats began training on the delay discounting task. On each trial, rats were given a choice between two levers. A press on one lever delivered a small reward immediately, and a press on the other delivered a large reward after a variable delay period.
Rats that self-administered cocaine displayed greater impulsive choice behavior (i.e. - enhanced preference for the small immediate over the large delayed reward) compared to saline controls. These data suggest that cocaine use can cause lasting increases in impulsive choice, and that increased impulsive choice observed in human cocaine addicts may be due in part to long-term effects of cocaine on brain function.

Nicholas Simon, M.S., Texas A&M University
A rat model of risky decision-making
Nicholas W. Simon, Ian A. Mendez, Jennifer L. Bizon & Barry Setlow
When deciding upon a course of action, individuals must weigh the risks and benefits of each of their choices in order to make optimal decisions. We developed a behavioral protocol in rats to assess the influence of risk of punishment on reward-related decision-making. Male Long-Evans rats were given choices between a small food reward and a large food reward associated with risk of punishment (footshock). Each session consisted of 5 blocks of 10 choice trials, with punishment probability (risk) increasing with each consecutive block (0, 25, 50, 75, 100%). Preference for the large, risky reward decreased with increased punishment probability (i.e. – risk of punishment

discounted the value of the large reward). Further behavioral testing showed that risky decision-making was not correlated with impulsive choice (assessed with a delay-discounting task), but was correlated with some measures of impulsive action (assessed with a differential reinforcement of low rates of responding task) and with performance on a probabilistic discounting task. Finally, acute amphetamine administration reduced preference for the large, risky reward in a dose-dependent fashion. This line of research has implications for psychopathological conditions characterized by excessive risk-taking behavior, such as drug addiction and ADHD.
Supported by NIDA F31DA0233312 (NWS)

Gregory Smith, Ph.D., University of Kentucky

Understanding the Construct of Impulsivity and its Relationship to Alcohol Use Disorders

Danielle M. Dick[1], Gregory Smith[2], Peter Olausson[3], Suzanne H. Mitchell[4], Robert F. Leeman[3], Stephanie S. O'Malley[3], & Kenneth Sher[5]
[1]Virginia Institute for Psychiatric & Behavioral Genetics, Virginia Commonwealth University
[2]Department of Psychology, University of Kentucky
[3]Department of Psychiatry, Yale University School of Medicine
[4]Departments of Behavioral Neuroscience & Psychiatry, Oregon Health & Science University
[5]Department of Psychological Sciences, University of Missouri

This poster presents a review of both the human and animal literatures on the assessment of impulsivity and its role in alcohol use. The review was motivated by the need to understand and develop consilience of phenotypes between human and animal studies of alcohol problems. There are multiple lines of evidence from both human and animal studies linking impulsivity and alcohol use disorders, including evidence that (a) impulsivity may increase risk for disorder onset and (b) impulsivity may be increased secondary to the disorder. Recently, it has become clear that the term "impulsivity" has been used to refer to at least five different personality trait processes: positive and negative urgency (the tendency to act rashly when experiencing intensely positive and intensely negative emotion, respectively), lack of planning, lack of persistence, and sensation seeking. The five traits predict different aspects of risky behavior. Similarly, tasks used in the laboratory and those used with animals are also heterogeneous: they include processes such as prepotent response inhibition, resistance to distractor interference, delay aversion, and others. We present evidence describing the overlap between certain trait measures and certain laboratory tasks (e.g., urgency with prepotent response inhibition deficits). We offer suggestions for future research.

Jessica Weafer, M.S., University of Kentucky

Increased Senisitivity to the Disinhibiting Effects of Alcohol in Adults with ADHD

Weafer; M.T. Fillmore. University of Kentucky, Lexington, KY 40506.

Little is known about the acute impairing effects of alcohol in individuals with disorders characterized by poor impulse control, such as those with ADHD. Given the high levels of impulsivity and pre-existing deficits involving inhibitory control in adults with ADHD, it is possible that alcohol could produce greater disinhibition in these individuals

compared with adults with no history of ADHD. The present study tested this hypothesis. Adults with ADHD (*N* = 10) and controls (*N* = 12) performed the cued go/no-go task, which requires quick responses to go targets and suppression of responses to no-go targets following the presentation of cues (valid or invalid), under 3 doses of alcohol: 0.65 g/kg, 0.45 g/kg, and 0.0 g/kg (placebo). Consistent with prior research, alcohol dose-dependently increased inhibitory failures in controls in the invalid, but not the valid, cue condition. By contrast, those with ADHD displayed significant alcohol impairment regardless of cue condition. Thus, unlike controls, valid cues offered little protection from the disinhibiting effects of alcohol in drinkers with ADHD, suggesting an increased sensitivity to alcohol-impairment of inhibitory control. This heightened sensitivity among those with ADHD could help explain why this group is at greater risk of developing alcohol use problems.
Research supported by NIAAA grant R01 AA012895 and NIDA grant R21 DA021027 and T32 DA007304.

Tamika Zapolski, M.S., University of Kentucky
The Measurement of Dispositions to Rash Action in Children
Tamika C. B. Zapolski, Regan E. Fried, Agnes M. Stairs, Jessica L. Combs, Gregory T. Smith
University of Kentucky, Psychology Department
Among adolescents and adults, there appear to be at least four different personality traits that dispose individuals to rash or ill-advised action: sensation seeking, urgency, lack of planning, and lack of perseverance. The four have been found to be only moderately correlated and play different roles in dysfunction. For example, urgency predicts problem levels of risky behavior, whereas sensation seeking only predicts frequency of such involvement. Because individual differences in personality are understood to influence subsequent developmental trajectories, including risk for psychopathology and alcohol abuse, it is important to determine whether the traits are present among preadolescents. In a three-part study with 94 children (30% clinical cases), we (a) assessed the traits reliably by both questionnaire and interview; (b) showed good convergent and discriminant validity in this assessment using the multitrait, multimethod technique; and (c) showed that the different traits correlated with different dysfunctional behaviors as predicted by theory. Thus, the four traits appear to be present, distinct, and play different roles in relation to dysfunction prior to adolescence. Clinical researchers can now assess these four traits in children and use the findings to inform theories of etiology and shape risk reduction interventions.
Funded by NIAAA and NIDA.

TRAVEL AWARDEES:

Iris Balodis,
David Belin,
Luke Clark,
Melissa Cyders,
Jodie Finlayson-Burden,
Regan Fried,
Robert Leeman,
Andrew Littlefield,
Marijn Lijffijt,
Shijing Liu,
Ian Mendez,
Melissa Miller,
Erik Ostling,
Nicholas Simon,
Gregory Smith,
Jessica Weafer,
Tamika Zapolski,

NOTES

NOTES