4th International Conference on Applications of Neuroimaging to Alcoholism
ICANA-4

July 19-21, 2019
Yale School of Medicine

The Anlyan Center (TAC)
300 Cedar Street, New Haven, CT

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Dear Colleagues,

Welcome to the 4th International Conference on Applications of Neuroimaging to Alcoholism (ICANA-4). ICANA-4 is part of the NIAAA Center for the Translational Neuroscience of Alcoholism (CTNA) based at the Yale University Department of Psychiatry.

Our goal is to build on the success of past ICANA conferences and continue to foster interest, career development, research, and collaboration in this ever-expanding area of neuroscience technology. We have brought together neuroimagers with expertise in a wide variety of imaging techniques and with clinical expertise to discuss the numerous ways of applying imaging to alcoholism research. Distinct to ICANA-4 is our focus on the use of multiple imaging techniques to approach the same topical issue within the field of alcohol research.

We are delighted to welcome you to Yale. We look forward to our discussions and continuing to foster growth and advances in this exciting area of research.

Sincerely,

John H. Krystal, M.D.

Robert L. McNeil, Jr. Professor of Translational Research
Chair, Department of Psychiatry, Yale University School of Medicine
Director, NIAAA Center for the Translational Neuroscience of Alcoholism
Chair, ICANA-4

Yale Organizing Committee: Philip Corlett, Kelly Cosgrove, Kelly DeMartini, Halppen Donoghoe, Chris Gardner, Hedy Kober, Stephanie O'Malley, Graeme Mason, Godfrey Pearlson, Diane Redding

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10:15am to 11:30am	**Plenary Lecture: "Neurobiology of Alcohol Use Disorder: A Heuristic Framework for Future Research"** George F. Koob, NIAAA Director
12:00pm to 1:15pm	**Lunch (TAC Upper Level Lobby)**
1:15pm to 3:30pm	**Session I: Stress and Craving of Alcoholism** Rajita Sinha & Hedy Kober, Yale University (Chairs) Hedy Kober, Yale University Mauricio Delgado, Rutgers Colleen Hanlon, MUSC Howard Becker, MUSC
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3:45pm to 6:00pm	**Session II: Inflammation of Alcoholism** Stephanie O'Malley & Kelly Cosgrove, Yale University (Chairs) Kimberly Nixon, U Texas at Austin Corinde Weirs, NIAAA Intramural Natalie Zahr, Stanford Ansel Hillmer, Yale University
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Saturday, July 20, 2019	
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10:00am to 10:15am	**Break (TAC Upper and Lower Level Lobbies)**
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	Sunday, July 21, 2019
7:30am to 8:30am	**Continental Breakfast (TAC Upper Level Lobby)**
8:30am to 8:45am	**Welcome** John Krystal, CTNA Director, ICANA-4 Chair Yale Dept. of Psychiatry Chair
8:45am to 9:45am	**Plenary Lecture: "Investigating Alcohol-Induced Functional and Longitudinal Changes in Brain Circuitry with MRI Imaging in Monkeys"** Kathleen A. Grant, Chief and Professor Oregon National Primate Research Center and Professor of Behavioral Neuroscience, Oregon Health and Sciences University
9:45am to 10:00am	**Poster Awards**
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12:45pm	**Discussion & ICANA4 Summary** John Krystal, CTNA Director, ICANA-4 Chair Yale Dept. of Psychiatry Chair

PLENARY LECTURE

Neurobiology of Alcohol Use Disorder: A Heuristic Framework for Future Research

Friday, July 19

Speaker: George F. Koob, Director, NIAAA

Dr. Koob received his Ph.D. in Behavioral Physiology from Johns Hopkins University in 1972. He spent much of his early career at the Scripps Research Institute as the Director of the Alcohol Research Center, and as Professor and Chair of the Scripps' Committee on the Neurobiology of Addictive Disorders. He has contributed to our understanding of the neurocircuitry associated with the acute reinforcing effects of alcohol and drugs of abuse and the neuroadaptations of the reward and stress circuits associated with the transition to dependence. Dr. Koob has published over 700 peer-reviewed papers and several books including the "Neurobiology of Addiction." He is the Director of NIAAA as of 2014. He is also a Senior Investigator at the Intramural Research Program of NIDA where he directs the Neurobiology of Addiction Laboratory in the Integrative Neurosciences Research Branch. He is the recipient of many honors, including membership in the National Academy of Medicine and award of the Legion of Honor (France).

Abstract: Alcohol use disorders cause an enormous amount of human suffering, loss of productivity and cost to our medical system and the nation's economy. Conceptualizing alcohol use disorder from a heuristic framework of a binge/intoxication stage, a withdrawal/negative affect stage, and a preoccupation/anticipation (craving) stage representing the domains of incentive salience, negative emotional states and executive function has allowed identification of key neurocircuits: basal ganglia, extended amygdala, and frontal cortex, respectively, that underlie addiction to alcohol. Alcohol can usurp and overpower the reward function of endogenous opioids, drive incentive salience and engage pathological habits via molecular and neurocircuitry neuroadaptations within the reward system. Alcohol withdrawal produces a negative emotional state (hypohedonia, dysphoria, anxiety, hyperalgesia, irritability, and sleep disturbances, termed hyperkatifeia), providing an additional source of motivation for compulsive drug seeking in alcohol addiction. The negative emotional state that drives negative reinforcement is hypothesized to derive from the within-system dysregulation of key neurochemical circuits that mediate incentive-salience/reward systems (dopamine, opioid peptides) in the ventral striatum and from the between-system recruitment of brain stress systems (corticotropin-releasing factor, dynorphin, norepinephrine, hypocretin, vasopressin, glucocorticoids, and neuroimmune factors) in the extended amygdala. Chronic alcohol administration also engages powerful glutamatergic pathways from the frontal cortex and allocortex to drive craving while in parallel impairing executive function. Compelling evidence indicates that plasticity in the brain incentive salience, emotional and cognitive systems is triggered by acute excessive alcohol intake, is sensitized during the development of compulsive drug taking with repeated withdrawal, persists into protracted abstinence, and contributes to the development and persistence of compulsive alcohol-seeking behavior. Such a neurobiological knowledge base provides a heuristic framework for the development of novel, science-based approaches to diagnosis, prevention and treatment of alcohol use disorders.

PLENARY LECTURE

Corticostriatal Computations in Learning and Decision Making

Saturday, July 20

Speaker: Michael J. Frank, Edgar L. Marston Professor of Cognitive, Linguistic & Psychological Sciences and Psychiatry and Human Behavior, Brown University

Dr. Frank received his PhD in Neuroscience and Psychology in 2004 at the University of Colorado, following undergraduate and master's degrees in electrical engineering and biomedicine (Queen's University (Canada) and University of Colorado). Dr. Frank's work focuses primarily on theoretical models of frontostriatal circuits and their modulation by dopamine, especially in terms of their cognitive functions and implications for neurological and psychiatric disorders. The models are tested and refined with experiments involving pharmacological manipulation, deep brain stimulation, EEG, fMRI and genetics. Honors include Kavli Fellow (2016), the Cognitive Neuroscience Society Young Investigator Award (2011), the Janet T Spence Award for early career transformative contributions (Association for Psychological Science, 2010) and the DG Marquis award for best paper published in Behavioral Neuroscience (2006). Dr Frank is a senior editor for *eLife*, associate editors for *Behavioral Neuroscience* and the *Journal of Neuroscience*, and member of Faculty of 1000 (Theoretical Neuroscience section). Dr. Frank directs the Initiative for Computation in Brain and Mind within the Carney Institute for Brain Science at Brown University.

Abstract: The basal ganglia and dopaminergic systems are well studied for their roles in reinforcement learning and reward-based decision making. Much work focuses on "reward prediction error" (RPE) signals conveyed by dopamine and used for learning. Computational considerations suggest that such signals may be enriched beyond the classical global and scalar RPE computation to support more structured learning and motivational signals in distinct sub-circuits ("vector RPEs"). I will present experimental data from both mouse (calcium imaging of dopamine terminals in striatum) and humans which provide preliminary support for this notion.

PLENARY LECTURE

Investigating Alcohol-Induced Functional and Longitudinal Changes in Brain Circuitry with MRI Imaging in Monkeys

Sunday, July 21

Speaker: Kathleen A. Grant, Professor & Chief, Div. of Neuroscience, Oregon National Primate Research Center; Professor, Dept. of Behavioral Neuroscience, Oregon Health & Science Univ.

Dr. Grant received her doctorate degree in Physiological Psychology from the University of Washington in Seattle followed by post-doctoral training at the University of Chicago where she incorporated rhesus monkeys into her investigations of behavioral pharmacology of alcohol. She continued her post-doctoral training in molecular pharmacology at the intramural laboratories of the NIAAA and then joined the faculty of Wake Forest University School of Medicine where she began using *in vivo* imaging (PET and MRI) to assess stress and chronic alcohol self-administration of macaque monkeys. In 2005 Dr. Grant accepted a position as Professor in the Department of Behavioral Neurosciences at Oregon Health & Science University (OHSU) and became the Chief of the Division of Neuroscience at the Oregon National Primate Research Center in 2011. At OHSU she began her fruitful collaborations in MRI with Dr. Chris Kroenke and the Advanced Imaging Research Center. Dr. Grant has served as the Director of numerous collaborative research projects on understanding the behavioral and endocrine risk factors for chronic heavy drinking and the underlying brain circuitry mediating this risk.

Abstract: Neuroimaging studies of nonhuman primates (NHPs) contribute important translational linkages between controlled animal model systems and observations in human subjects. Here, an overview of neuroimaging studies performed over the past decade at the Oregon National Primate Research Center is provided. In the adult macaque brain, voluntary alcohol drinking leads to a dose-dependent reduction in cerebral cortical brain volume of 0.11% per average daily drink, and this reduction is associated with an increase in the ethanol methyl ^{1}H T_2 value. Prior to middle age, during the transition from late adolescence to early adulthood, the rhesus macaque brain volume increases with age, similar to the human brain. In this dynamic context, alcohol drinking diminishes the rate of brain growth by a factor of 0.06 mL per year per average daily drink, decreases whole brain white matter and thalamic volume. Functional connectivity MRI approaches of brain areas related to associative, sensory motor or limbic in late adolescence are predictive of both future heavy alcohol drinking status and performance on the cognitive flexibility task of attentional set-shifting. In further extension of these studies to the earliest stages of brain development, *in utero* MRI procedures reveal attenuated cerebellar growth and widespread alterations of white matter maturation in the third trimester following 1.5 g/kg/day alcohol exposure only during the first trimester of pregnancy. In the adult, adolescent, and fetal brains, the effects of alcohol are closely associated with synaptic mechanisms, as assessed with *ex vivo* electrophysiological recordings. These studies across the lifespan leverage similarities between NHP and human subjects in development, physiological processes, and behaviors related to alcohol drinking. They enable the interpretations of human neuroimaging studies to be validated, and contribute new perspectives for future strategies to use imaging methods to understand how alcohol affects the brain and behavior.

SESSION I
Stress and Craving of Alcoholism

Friday, July 19

Co-Chair: Rajita Sinha, Ph.D. Foundations Fund Endowed Professor in Psychiatry and Professor of Neuroscience and in Child Study at the Yale University School of Medicine. Chief of the Psychology Section in Psychiatry and Co-Director of Education for the Yale Center for Clinical Investigation.

Dr. Sinha is an internationally renowned clinical scientist with expertise on stress and trauma mechanisms that promote risk of alcoholism, drug addiction and overeating and risk of relapse. She is the founding director of the Yale Interdisciplinary Stress Center that focuses on understanding the neurobiology of stress, trauma and resilient versus vulnerable coping mechanisms that promote neuropsychiatric diseases, including addiction and other chronic diseases. Her lab also develops and tests novel treatments to address these processes to prevent relapse and risk of stress-related addictive disorders. Her research has been supported by a series of NIH funded research projects continuously for over 20 years and she has published over 275 scientific peer reviewed publications in these areas. She currently serves on the NIH/NIAAA Advisory Council and is also on the Expert Scientific Panel for the NIH Common Fund's Science of Behavior Change program.

Co-Chair: Hedy Kober, Ph.D. Associate Professor of Psychiatry and Psychology, Yale University

Dr. Kober is the director of Yale's Clinical and Affective Neuroscience Laboratory. She received her Ph.D. in psychology with a focus on cognitive and affective neuroscience from Columbia University in 2009. Dr. Kober's scientific research has been published in high-impact journals, including Brain and Behavioral Sciences, Proceedings of the National Academy of Sciences (PNAS), Biological Psychiatry, Clinical Psychology Review, and Neuropsychopharmacology. Her work has been very well-cited, and is funded by multiple grants from the National Institute of Health as well as private foundations. She has also received multiple fellowships and awards including from the National Institute of Drug Abuse, the College on Problems of Drug Dependence, the Helmesley Charitable Trust, the Mind and Life Institute, and Yale's Center for Clinical Investigation. In addition, her research was featured on popular media outlets including CNN, NPR, New York Magazine, LA Times, Boston Globe, USA Today, Discover Magazine, Forbes, and the Huffington Post.

Mauricio Delgado, Ph.D. Professor and Chair, Department of Psychology, Rutgers University-Newark.

Dr. Delgado is the Director of the Social and Affective Neuroscience Lab and the Associate Director of the Rutgers University Brain Imaging Center (RUBIC). He received his Ph.D. from the University of Pittsburgh with Dr. Julie Fiez and completed a post-doctoral fellowship at New York University with Dr. Elizabeth Phelps. Dr. Delgado's research program investigates how the human brain learns from rewards and punishments, how it uses this information to guide behavior during both simple decisions (e.g., learning actions which lead to desired outcomes) and complex social interactions (e.g., learning to trust another person), and how it controls our emotions to avoid maladaptive decision-making.

Colleen Hanlon, Ph.D. Associate Professor, Departments of Psychiatry and Neurosciences, Medical University of South Carolina.

Dr. Hanlon leads a human addiction research laboratory dedicated to mapping and modulating frontal-striatal-thalamic systems that contribute to the cycle of initiation, use, and relapse among multiple substance dependent populations. The majority of her work to date has focused on functional neuroimaging and brain stimulation in heavy alcohol users, tobacco smokers, and chronic cocaine users. She has published over 50 manuscripts related to neuroimaging and brain stimulation in substance dependence patients. In 2011 she was honored with an Early Career Investigator award from the National Institute of Drug Abuse. In 2017 her NIH-funded brain stimulation research was highlighted in National Geographic (Sept 2017) and Science Magazine (Sept 2017). She serves as the Associate Director of the Brain Stimulation Core at MUSC, is the Director of the Advanced TMS Training Course sponsored by the MUSC National Center for Neuromodulation for Rehabilitation, is an active member of the NIAAA P50 Charleston Alcohol Research Center, and holds leadership positions in several scientific organizations. In addition to primary clinical research, she also has strong collaborations with several preclinical drug and alcohol use researchers.

Howard Becker, Ph.D. Professor, Department of Psychiatry and Behavioral Sciences and Department of Neuroscience, Medical University of South Carolina. Senior Research Career Scientist at the RHJ Department of Veterans Affairs Medical Center. Director, Charleston Alcohol Research Center.

Dr. Becker is an established investigator in the alcohol and addiction neuroscience field, with over 30 years of experience in addressing factors that influence and mechanisms that underlie alcohol addiction. The overall focus of his research program is elucidating biological underpinnings and environmental factors that govern sensitivity to alcohol, as well as adaptive changes resulting from chronic alcohol exposure that play a role in driving/promoting excessive alcohol drinking and enhanced relapse vulnerability. His research program utilizes behavioral, neurochemical, and molecular biology approaches in studying brain mechanisms that facilitate transition to uncontrolled drinking, with the goal of identifying and evaluating new therapeutic targets and strategies for treating problem drinking and alcoholism. Dr. Becker's research program has been continually supported by multiple concurrent grants from the NIH/NIAAA and VA Medical Research for over 30 years. He is widely recognized as a leader in the alcohol research field, as evidenced by his published research accomplishments, editorial and grant reviewing service, and being frequently invited to present his research findings at numerous national and international scientific conferences.

SESSION II
Inflammation of Alcoholism

Co-Chair: Stephanie S. O'Malley, Ph.D. Elizabeth Mears and House Jameson Professor of Psychiatry and the Deputy Chair for Clinical Research in the Department of Psychiatry at the Yale School of Medicine. Director of the Division of Substance Abuse Research in the Department of Psychiatry at the Yale University School of Medicine.

Dr. O'Malley received her Ph.D. in 1983 in Clinical Psychology from Vanderbilt University and joined the faculty of Yale University School of Medicine in 1984. The major focus of her research is on the development of more effective treatments for substance use disorders, primarily alcohol and tobacco. Dr. O'Malley's study on the efficacy of naltrexone was pivotal to the approval of this medication by the Food and Drug Administration for use in the treatment of alcoholism in 1994. She has continued to study the efficacy of opiate antagonists and other pharmacotherapies using human laboratory paradigms and clinical trials. Dr. O'Malley is the Deputy Director of the NIAAA funded Center for the Translational Neuroscience of Alcoholism and co-leads the Yale Tobacco Center for Regulatory Science. Dr. O'Malley is actively involved in mentoring junior faculty and co-leads a NIDA supported Clinician Scientist Training program for faculty level investigators.

Co-Chair: Kelly Cosgrove, Ph.D. Associate Professor, Departments of Psychiatry, Neuroscience, Radiology and Biomedical Imaging.

Dr. Cosgrove uses positron emission tomography (PET) to gain insights into the brains of people after they've stopped using alcohol and tobacco. Trained as a clinical psychologist who worked with individuals suffering from drug addiction, Dr. Cosgrove transitioned to conducting research in order to find more effective ways of helping patients recover from addiction and avoid relapse. Her laboratory develops and uses creative PET imaging paradigms to track changes in critical neurochemicals during the recovery from addiction.

Kimberly Nixon, Ph.D. Associate Professor of Pharmacology and Toxicology, The University of Texas at Austin and James T. Doluisio Fellow at The University of Texas at Austin and Waggoner Center for Alcohol and Addiction Research

Dr. Nixon received her Ph.D. in Behavioral Neuroscience at The University of Texas at Austin followed by a postdoctoral fellowship at the Bowles Center for Alcohol Studies at the University of North Carolina at Chapel Hill. Prior to moving to UT Austin, Dr. Nixon rose through the ranks to full professor at the University of Kentucky Department of Pharmaceutical Sciences. Dr. Nixon's lab focuses on elucidating novel druggable targets and mechanisms in the causes and consequences of alcoholic neurodegeneration, specifically the role of the innate immune system in the development of addiction behaviors in alcohol use disorders. She is a recipient of the 2008 Research Society on Alcoholism Young Investigator Award and a 2009 Presidential Early Career Award for Scientists and Engineers (PECASE)

Corinde Weirs, Ph.D. Research Fellow, NIAAA

Dr. Weirs is a Research Fellow at the National Institute on Alcohol Abuse and Alcoholism, in the Laboratory of Neuroimaging of Nora D. Volkow, M.D. After her studies in Psychology and Psychobiology at the University of Amsterdam (Netherlands) and Sussex University (UK) in 2010, she completed her PhD in Psychology at the Berlin School of Mind and Brain and Free University Berlin (Germany) in 2014, where she investigated neural underpinnings of automatic approach behavior to alcohol cues, and neural effects of behavioral trainings in patients with alcohol use disorder. The main goal of Dr. Wiers' research is to understand cognitive, neurobiological and (epi) genetic processes involved in alcohol and drug addiction, using functional MRI, PET, psychophysics and molecular techniques. She currently works on the effects of a ketogenic diet intervention on alcohol withdrawal and brain energetics in AUD patients undergoing detoxification.

Natalie Zahr, Ph.D. Research Scientist, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

Dr. Zahr's research interests focus on identifying mechanisms of brain pathology due to HIV and alcoholism. Her basic science foundation enables development of mechanistic and testable hypotheses using novel magnetic resonance imaging (MRI) techniques. She is particularly interested in how peripheral physiological processes initiated by HIV or alcoholism, including hepatic, nutritional, and neuroimmune signaling, may contribute to changes in the central nervous system. In the past several years, she has developed a translational approach by conducting human and rodent studies using in vivo MR imaging and spectroscopy. Her published work reflects the investigation of the brain in the context of changes to the peripheral system, in particular, the relationships between blood markers and brain measures.

Ansel Hillmer, Ph.D. Assistant Professor, Departments of Radiology & Biomedical Imaging and of Psychiatry, Yale University

Dr. Hillmer's received his Ph.D. in Medical Physics from the University of Wisconsin, Madison in 2014. His research focuses on the characterization and application of PET imaging paradigms to study psychiatric (and other) diseases, with particular emphasis on applications to substance use (alcohol, tobacco, cannabis). Current research projects include assessing dynamic responses of neuroimmune and glutamate signaling to alcohol challenge, and the development of multimodal data integration approaches.

SESSION III
Reward and Habit Learning

Co-Chair: Jane Taylor, Ph.D. Charles B.G., Murphy Professor of Psychiatry, Psychology and Neuroscience at Yale University School of Medicine and Yale University

Dr. Taylor is an expert in behavioral neuroscience with interests in decision-making, learning, memory, and motivational processes that relate to addiction, alcoholism, depression, stress and other psychiatric diseases. She received her undergraduate training at the University of Sussex and her graduate training at the University of Cambridge, UK. Her laboratory in the Division of Molecular Psychiatry at Yale combines sophisticated behavioral analyses in rodents with pharmacologic, optogenetic, viral, molecular/cellular and computational analyses. Dr. Taylor's research program aims to integrate translational and basic neuroscience approaches to understanding mental illness through collaborate research. Her key findings have been on topics such as decision-making, inhibitory control, habits, motivation, memory and reinforcement learning, the role plasticity-associated signaling mechanisms in frontal limbic-striatal circuits, and the impact of sex differences on behavior and in normal and pathophysiological states.

Co-Chair: Philip Corlett, Ph.D. Associate Professor, Department of Psychiatry, Yale University School of Medicine

Dr. Corlett trained in Experimental Psychology, Cognitive Neuroscience and Psychiatry with Professors Trevor Robbins and Paul Fletcher at the University of Cambridge. He won a Wellcome Trust Prize Studentship and completed his PhD on the brain bases of delusion formation in the Brain Mapping Unit, Department of Psychiatry. After a short postdoc, he was awarded the University of Cambridge Parke- Davis Exchange Fellowship in Biomedical Sciences which brought him to the Yale University Department of Psychiatry to explore the maintenance of delusions with Professors Jane Taylor and John Krystal. He was named a Rising Star and Future Opinion Leader by Pharmaceutical Marketing Magazine and joined the Yale faculty in 2011 where he continues to explore the cognitive and biological mechanisms of delusional beliefs as well as predictive learning, habit formation and addiction.

Jacqueline Barker, Ph.D. Assistant Professor, Department of Pharmacology and Physiology, Drexel University College of Medicine

Dr. Barker's research focuses on understanding the neural circuits and molecular targets that regulate response strategy selection and reward seeking behavior. Her primary interests include glutamatergic neurocircuitry, sex differences in the consequences of drug and alcohol use on circuit function and behavior, and the neurobiological substrates of outcome encoding. To investigate these topics, the Barker lab combines established and novel behavioral models with cutting-edge tools such as photometry and chemogenetics and established techniques including *in vivo* electrophysiology.

Andrew Holmes, Ph.D. Senior Investigator, Laboratory of Behavioral and Genomic Neuroscience, NIAAA

Dr. Holmes received his undergraduate degree in Psychology in 1995 from the University of Newcastle, Caltech and his graduate degree in behavioural pharmacology in 1998 from the University of Leeds. He was a postdoctoral fellow at the National Institute of Mental Health under Dr. Jacqueline Crawley. He joined the National Institute on Alcohol Abuse and Alcoholism in 2004 as a Section Chief, and became Chief of the Laboratory of Behavioral and Genomic Neuroscience in 2011, which remains his current position. The overarching mission of the Holmes lab is to understand the neural basis of cognitive and emotional regulation and how these critical mental processes are mediated by discrete neural circuits and moderated in function by genetic variation and environmental insults, including stress and alcohol.

Sanne de Wit, Ph.D. Associate Professor, Department of Clinical Psychology, University of Amsterdam

Dr. de Wit obtained her PhD degree in 2006 at the Dept. of Experimental Psychology, University of Cambridge. Since 2008 she works at the University of Amsterdam, presently as an Associate Professor at the Dept. of Clinical Psychology. She studies the role of fundamental learning mechanisms in the flexibility versus efficiency of human behaviour and decision making, with a special interest in habitual behaviour and habit interventions. Her research lies at the interface between associative learning theory, behavioural neuroscience, and clinical psychology.

Alexander Genauck, M.Sc. Doctoral Candidate, Department of Computational and Clinical Neuroscience, Charité Berlin/Bernstein Center for Computational Neuroscience.

Mr. Genauck has a M.Sc. in psychology from Humboldt-Universität zu Berlin. He's currently finishing his publication-based PhD in computational and clinical neuroscience at Charité Berlin/Bernstein Center for Computational Neuroscience with Prof. Andreas Heinz and Prof. Nina Romanczuk-Seiferth. His thesis is on loss aversion and cue-induced decision making in alcohol dependence and gambling disorder. He works mainly with functional MRI. He is interested in behavioral and neural models of human value-based decision-making, as well as machine learning/predictive modeling as a tool in neuroscience.

SESSION IV
Structural and Functional Connectivity in Alcoholism

Co-Chair: Godfrey Pearlson, M.D. Professor, Departments of Psychiatry and Neuroscience, Yale University; Director, Olin Neuropsychiatry Research Center, Institute of Living/Hartford Hospital.

Dr. Pearlson's research uses neuroimaging as a tool to address a broad array of questions regarding the neurobiology of major mental disorders, primarily psychosis and drug/alcohol abuse. Important "firsts" in his research career include showing that structural and functional brain changes associated with schizophrenia also occur in psychotic bipolar disorder, the relationship of abnormalities in the superior temporal gyrus and hallucinations in schizophrenia, and the first demonstration of human in-vivo cocaine-mediated dopamine release using PET ligands. Dr. Pearlson is an NIMH MERIT awardee and has held RO1 grants from NIAAA, NIDA, NIA and NIMH. He has received a series of research awards & is on the editorial board of several psychiatry and neuroimaging journals. He has published >700 peer-reviewed research articles. He is also co-founder of the annual BrainDance Competition, open to high school and college students across New England. The BrainDance Awards encourage students to gain knowledge about psychiatric diseases and to develop a more tolerant and realistic perspective toward people with severe psychiatric problems.

Co-Chair: Suchitra Krishnan-Sarin, Ph.D. Professor, Department of Psychiatry, Yale University.

Dr. Krishnan-Sarin's research is focused on developing a bio-behavioral understanding of substance use behaviors in adult and adolescent substance users, with the goal of developing optimal prevention and cessation interventions.

Kilian Pohl, Ph.D. Associate Professor, Department of Psychiatry and Behavioral Sciences, Stanford University

Dr. Kilian M Pohl is an Associate Professor of Psychiatry and Behavioral Sciences at Stanford University and has a secondary appointment as Program Director of Biomedical Computing at SRI International. Over 15 years ago, Kilian joined the Artificial Intelligence Laboratory at the Massachusetts Institute of Technology to advance neuroscientific research through the use of machine learning technology and has continuously published in that domain since then. He now focuses on computational science aimed at identifying biomedical phenotypes improving the mechanistic understanding, diagnosis, and treatment of neuropsychiatric disorders. His research is supported by funding from multiple NIH institutions, in particular NIAAA. Kilian is a multiple Principal Investigator of the Data Analysis Resource of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) and a key investigator of the Adolescent Brain Cognitive Development (ABCD) study.

Mary Heitzeg, Ph.D. Associate Professor, Department of Psychiatry and Addiction Center, University of Michigan.

Dr. Heitzeg's primary research focus is on developmental neuroimaging targeted at investigating two related themes relevant to adolescent substance use: 1) how early individual differences in brain function relate to susceptibility to alcohol and other drug use and problems; and 2) how substance use impacts the developing brain and, in consequence, risk trajectories across adolescence. She is PI of the ongoing neuroimaging component of the Michigan Longitudinal Study, a prospective, high-risk study of the emergence of risk and the development of alcohol use disorder and related symptomatology. She is also PI of the University of Michigan site for the Adolescent Brain Cognitive Development (ABCD) Study, which is tracking neural and behavioral development through adolescence in over 11,000 youth across the country.

Susan F. Tapert, Ph.D. Vice Chair, Academic Affairs, Department of Psychiatry, University of California San Diego

Dr. Tapert became interested in addictive behavior research as an undergraduate at University of Washington, working with Dr. G. Alan Marlatt at the Addictive Behaviors Research Center. Her focus on adolescence started during graduate studies with Dr. Sandra A. Brown in the SDSU-UCSD Joint Doctoral Program in Clinical Psychology, where she specialized in neuropsychology and behavioral medicine. Following an APA clinical psychology internship at Brown University, she completed a post-doctoral fellowship at UC San Diego on functional magnetic resonance imaging. Dr. Tapert's research focuses on understanding neural sequelae of and risk factors for adolescent substance use. Her work uses magnetic resonance imaging (MRI), functional MRI, diffusion tensor imaging, and neuropsychological testing. Her studies evaluate adolescent brain development and sex differences. She has been awarded over 20 research grants, most from the National Institutes of Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse. Dr. Tapert is Consortium Coordinator and site PI for the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA), and Associate Director and site PI for the Adolescent Brain Cognitive Development (ABCD) study, which launched in 2015 to explore the development of over 11,000 children.

Alecia Dager, Ph.D. Assistant Professor, Department of Psychiatry, Yale University

Dr. Dager completed her Ph.D. in experimental psychology at the University of California San Diego, focusing on the influence of heavy marijuana use on brain functioning during adolescent neurodevelopment. She joined the faculty at Yale in 2008, where she is an Assistant Professor in the Olin Neuropsychiatry Research Center. She has contributed to numerous fMRI studies of alcohol use in adolescents and young adults, including investigations of both risks and consequences of alcohol use in young people. Most recently, this work has been expanded to comprise structural MRI, functional MRI, and magnetic resonance spectroscopy in order to characterize multiple facets of alcohol and marijuana use in young adulthood.

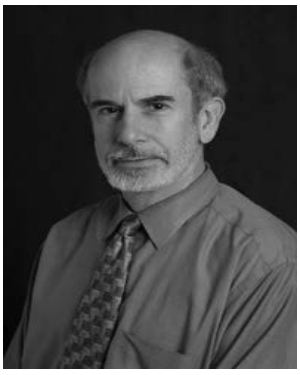
SESSION V
Pharmacoimaging

Co-Chair: Graeme F. Mason, Ph.D. Professor of Radiology and Biomedical Engineering and Psychiatry, Yale University.

Dr. Mason began his studies of brain metabolism with magnetic resonance Spectroscopy in 1986. He focuses on (1) quantitative methods to study metabolism, (2) application of those methods to neuropsychiatric disorders such as alcohol use disorders, and (3) dissemination and training related to imaging methods. With these areas, he has collaborated extensively with Psychiatry to investigate amino acid and energy neurotransmission in depression and other disorders. Dr. Mason also maintains a long-standing interest in dissemination and interdisciplinary training to foster collaborations between investigators in imaging methodologies and researchers who focus on applications in neuropsychiatric research.

Co-Chair: Anissa Abi-Dargham, M.D. The Lourie Endowed Chair in Psychiatry, Professor of Psychiatry and Radiology, Vice Chair for Research, Department of Psychiatry, Stony Brook University, Renaissance School of Medicine.

Dr. Abi-Dargham is a member of the National Academy of Medicine and a Special Lecturer at Columbia University in New York, where she spent the last twenty-two years of her career prior to her move to Stony Brook University in 2016. She directs the Multi Modal Translational Imaging Lab and oversees a multidisciplinary team with expertise in multiple neuroimaging modalities used in tandem to address important questions about the brain mechanisms of schizophrenia. She is an internationally recognized leader in the use of molecular imaging of the human brain to study schizophrenia and its comorbidity with addiction. She has received funding from NIMH, NIDA, NIAAA, NARSAD, Lilly, BMS, GSK, Forest, and Peirre-Fabre. Her work has shown precise topographical alterations in dopamine function and their relationship to various functional domains within schizophrenia spectrum disorders.



Lawrence Kegeles, M.D., Ph.D. Associate Professor, Departments of Psychiatry and Radiology, Columbia University College of Physicians and Surgeons and the New York State Psychiatric Institute

Dr. Kegeles' area of research is imaging the neurochemistry of the brain using positron emission tomography (PET) and magnetic resonance spectroscopy (MRS). His investigations have focused on schizophrenia, anxiety disorders such as OCD, and substance use disorders. He has also examined changes in brain chemistry acutely induced in healthy volunteers by administering pharmacological agents including amphetamine, and ketamine to further our understanding of the neurochemical abnormalities that underlie or accompany psychiatric conditions.

Isabelle Bioleau, Ph.D. Senior Clinical Research Scientist, Centre for Addiction and Mental Health

Dr. Boileau's research is in the area of substance use disorders and addictions. She is the Head of the Addiction Imaging Research Group at the Centre for Addiction and Mental Health in Toronto, Canada and an Associate Professor at the University of Toronto in the Department of Psychiatry. Her lab's primary focus has been to develop a multimodal imaging approach to investigate the neurochemistry and neural basis of substance use and co-morbid conditions. The common thread running through her research activities is an interest in uncovering neurochemical and neuro-functional markers and therapeutically useful mechanisms of risk for the development and maintenance of addictions. She has received funding from the Canadian Institute for Health Research (CIHR), National Institute of Health (NIH), Ontario Mental and Health Foundation (OMHF) and Canadian Institute for Military and Veteran Heath Research (CIMVHR). Currently she is conducting NIH funded research using positron emission tomography probes which were developed at the Centre for Addiction and Mental Health and target enzymes of the endocannabinoid and monoamine systems.

Lorenzo Leggio, M.D., Ph.D., M.Sc. Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, NIAAA Division of Intramural Clinical and Biological Research and NIDA Intramural Research Program; Medication Development Program, NIDA Intramural Research Program; Center for Alcohol and Addiction Studies, Brown University

Dr. Lorenzo Leggio is a Senior Investigator at the NIH intramural research program (IRP), where he serves as the Chief of the Section on Clinical Psychoneuroendocrinology and Neuropsychopharmacology, a joint NIAAA and NIDA laboratory. Dr. Leggio received his M.D. and Ph.D. from the Catholic University of Rome and 'Agostino Gemelli' hospital, where he also completed residency and received Board Certification in Internal Medicine. He also received a Masters in 'Alcohol-related diseases and problems' from the University of Florence. He was a visiting research associate, then postdoctoral research associate in Psychiatry and Human Behavior at Brown University, Providence, RI. In 2010-2012, Dr. Leggio joined the faculty of the Brown University Medical School as Assistant Professor and Core Faculty at the Brown University Center for Alcohol and Addiction Studies (CAAS), where he is still on faculty as an Adjunct Professor. He was recruited by the NIH IRP in 2012 and received tenure in 2018. Dr. Leggio's clinical research has been primarily focused on medication development towards the treatment of alcohol and substance use disorders. The main focus of his laboratory is the role of gut-brain as well as GABAergic pathways in alcohol and substance use disorder

Dieter Meyerhoff, Dr. rer. nat. Professor of Radiology and Biomedical Imaging, University of California San Francisco, School of Medicine and DVA Medical Center San Francisco

Dr. Meyerhoff has been performing magnetic resonance neuroimaging research in Alzheimer's disease, HIV infection, PTSD, alcohol and other substance abuse (primarily nicotine, stimulants, and opioids) for more than three decades. In collaboration with colleagues from psychiatry and psychology, he has contributed to our better understanding of the neural and cognitive effects of these our society's major ailments, and he has demonstrated convincingly the adverse effects of chronic tobacco use on neural health and the health of the brain in recovery from long-term alcohol and other substance abuse.

CONFERENCE SPEAKER SESSION ABSTRACTS

SESSION I
Stress and Craving of Alcoholism

Stress, Craving, and the Regulation of Craving: Using Meta-Analysis and Neuroimaging to Guide Treatments

Hedy Kober

Abstract. I will open the symposium by discussing the role of stress and craving in drug use broadly and in alcohol drinking specifically. To illustrate this, I will present data from a quantitative meta-analysis of >200 clinical studies (representing nearly 50,000 participants) that shows that drug cue exposure, stress, and craving prospectively and reliably predict drug use and relapse. I will focus on finding from >70 alcohol studies representing >16,000 participants that directly link alcohol cues, stress, and alcohol craving to drinking and relapse to alcohol – underscoring their importance in substance use disorders, including alcohol use disorder. Then, I will show data from a meta-analysis of 127 published neuroimaging studies (representing nearly 4,000 participants) that identifies the neural systems most consistently linked to cue reactivity and craving across drugs, and in alcohol in particular. In the final part of my talk, I will describe the regulation of craving (ROC) task. We have used the ROC task (1) to measure the effects of various regulatory strategies on craving (e.g., CBT-based, mindfulness-based), (2) to study the neural mechanisms underlying such strategies, and (3) as the basis of for a new ROC-based intervention that reduces smoking and unhealthy eating (with pilot data in alcohol).

Acute Stress Influences on Reward-Related Processes

Mauricio Delgado

Abstract. The experience of acute stress can have significant consequences for an individual's day to day activities and long-term well-being. Acute stress can elicit negative emotion (Lazarus & Folkman, 1984) while compromising cognitive resources and neural mechanisms (Arnsten, 2009) necessary for controlling emotional responses (Raio et al., 2013), Further, stress can significantly impact mechanisms of reward valuation and contribute to maladaptive decision making (e.g., craving and drug-seeking; Sinha, 2008). In this talk, we will highlight the influence of acute stress on reward-related neural mechanisms. Then, we will focus on the effect of acute stress exposure on decision making, in particular decisions to persist with a goal. Finally, we will discuss the use of positive emotion induction as a strategy for coping with the deleterious effects of acute stress.

From Neural Mapping to Neural Modulation: Developing of TMS as a Non-Invasive Strategy to Decrease Dinging in Individuals with AUD - A Series of 5 Studies

Colleen Hanlon

Abstract. Alcohol Use Disorder is a chronically relapsing condition which likely involves multiple dysfunctional frontal-striatal circuits. Through advances in preclinical research in the last decade, we now have an unprecedented understanding of the neural control of alcohol taking behavior. In both rodent models and human clinical neuroimaging studies, it is apparent that medial frontal-striatal limbic circuits regulate alcohol cue triggered behavior. While non-human preclinical studies can use invasive stimulation techniques to inhibit drug cue-evoked behavior, in human clinical neuroscience we are pursuing non-invasive theta burst stimulation (TBS) as a novel therapeutic tool to inhibit drug cue-associated behavior. Our laboratory and others have spent the last 9 years systematically and empirically developing a non-invasive, neural circuit based intervention for alcohol use disorder. Utilizing a multimodal approach of functional brain imaging and brain stimulation we have attempted to design and optimize an rTMS treatment protocol which is now being evaluated in clinical trials. This talk will briefly review the data that motivated our selection of candidate neural circuits, and summarize the results of the 5 studies, culminating in the first double-blinded, sham controlled clinical trial of TMS as a treatment adjuvant for treatment-engaged cocaine users. The intent of this talk is to highlight one example of a systematic path for TMS treatment development in AUD patients. This path is not necessarily optimal, exclusive, or appropriate for every substance use disorder. Rather, it is one example of a reasoned, empirically-derived pathway which we hope will serve as scaffolding for future investigators seeking to develop TMS treatment protocols.

Stress and Alcohol Interactions: Mechanisms and Potential Therapeutics

Howard C. Becker

Abstract. While it is generally acknowledged that stress is an important factor in promoting heavy alcohol drinking and triggering relapse, the interaction between stress and alcohol is complex and not fully understood. The dynamic interplay between a host of biological and environmental variables, along with experiential factors (prior stress and/or alcohol experience) plays a critical role in defining response to stress and how stress impacts decisions about alcohol drinking. Preclinical studies have shown that stress and alcohol exposure influence common neural systems and pathways in the brain, provoking adaptations that facilitate and/or drive transition to excessive, uncontrolled alcohol consumption. This presentation will describe the role of two neuropeptide systems in animal models demonstrating the ability of stress to enhance alcohol drinking and relapse-like behavior: the pro-stress dynorphin/kappa opioid receptor (DYN/KOR) system and the anti-stress neuropeptide oxytocin (OT) system. The DYN/KOR system is known to produce stress-like (aversive/dysphoric) effects and is engaged following heavy drinking associated with dependence. Using pharmacological and chemogenetic approaches, evidence will be presented showing that DYN/KOR activity within extended amygdala circuitry (central amygdala (CeA) – bed nucleus of the stria terminalis (BNST) pathway) contributes to stress-enhanced escalated drinking in dependent mice. Aside from its hormonal role in parturition and maternal behaviors, the OT system is known to produce stress-buffering effects and contribute to regulation of social behaviors. The OT system also has been implicated in a number of neuropsychiatric disorders involving social deficits, including alcohol (and other drug) addiction. Evidence will be presented that systemic administration of OT blocks the ability of stress to provoke relapse-like behavior in mice as well as prevent a sensitized stress effect in a mouse model of PTSD-AUD comorbidity. Additionally, using transgenic mice and chemogenetics, activating endogenous hypothalamic release of OT mimics these effects, demonstrating that these effects are mediated by central actions of OT. Collectively, these studies implicate important roles for these neuropeptide systems in influencing stress-alcohol interactions. Further, these results point to KOR antagonists and OT receptor agonists as potential therapeutics for treatment of stress-related excessive alcohol drinking and relapse vulnerability.

SESSION II
Inflammation of Alcoholism

Primed for alcoholism: Microglia phenotypes in an adolescent model of an alcohol use disorder

Kimberly Nixon[1], Hui Peng[2], Catherine Van Doorn[2], Jennifer K. Melbourne[1], S. Alex Marshall[3], Jim Pauly[2]

1. The University of Texas at Austin, College of Pharmacy, Division of Pharmacology & Toxicology, Austin, TX. 2. University of Kentucky, College of Pharmacy, Department of Pharmaceutical Sciences, Lexington, KY 3. High Point University, College of Pharmacy, Department of Basic Pharmaceutical Sciences, High Point, NC

Abstract. Activation of the innate immune system as a consequence of excessive alcohol intake may be a key driver in the development of an alcohol use disorder (AUD). Adolescents who begin drinking alcohol prior to age 13 are significantly more likely to develop an AUD in adulthood, which parallels the adolescent's greater susceptibility to the damaging effects of alcohol on brain structure and function. A key player in both the innate immune system and the response to insult in the brain is microglia, the macrophage of the central nervous system. Microglia have been observed across a spectrum of phenotypes that correspond to the nature of the activating insult but also predict their diverse roles from cytotoxicity (pro-inflammatory) to neuroprotection (anti-inflammatory). This talk focuses on our most recent data in an adolescent rodent model of binge-like alcohol exposure where dynamic effects are observed in microglia. Immediately after alcohol exposure, a loss of microglia has been observed according estimates of Iba-1-positive microglia in the hippocampus and entorhinal cortex, both of which are targets of alcohol's toxic effects to neurons. After multiple days in abstinence, innate immune system activation becomes more evident according to [^{3}H] PK-11195 radioligand binding for the 18-kDa translocator protein (TSPO) and changes in microglia morphology, gene expression, microglia surface antigen expression (flow cytometry) and functional assays of microglia priming. Altogether our multidisciplinary approach continues to support limited pro-inflammatory phenotypes with stronger evidence for anti-inflammatory or alternative activation phenotypes. Appreciating the dynamic and complex effects alcohol has on microglia phenotype is critically important for our understanding of the role of microglia in the development of AUDs.

TSPO as a Marker of Neuroinflammation in Alcohol Use Disorder in Humans and Rodents

Corinde E. Wiers, Sung Won Kim, Leandro F. Vendruscolo, George F. Koob, Gene-Jack Wang, Nora D. Volkow

National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, 20892 MD, USA

Abstract. Neuroinflammation appears to contribute to neurotoxicity observed with heavy alcohol consumption. In a series of experiments we explored expression of the 18-kDa translocator protein (TSPO), a biomarker of neuroinflammation, in both human patients with Alcohol Use Disorder (AUD) and a rat model of alcohol dependence. Using PET and [^{11}C]PBR28, a marker for TSPO expression, we and others reported decreased TSPO expression in patients with an alcohol use disorder (AUD) compared to controls. In contrast, postmortem human AUD brain tissue revealed upregulated TSPO mRNA expression in the amygdala and prefrontal cortex compared to tissue from non-dependent controls. We found a similar discrepancy between *in vivo* and *in vitro* results in rats: While alcohol-dependent and control rats did not differ in [^{11} C]PBR28 brain uptake *in vivo*, autoradiography measures in brain slices of the same rat model revealed significantly higher binding in alcohol-dependent rats for both [^{3} H] PBR28 and [^{3} H]PK11195 (another marker for TSPO expression) in thalamus and hippocampus (trend level for [^{3} H]PBR28) compared to nondependent rats. Thus, our human postmortem and *in vitro* animal data showing evidence of overexpression of TSPO, are consistent with neuroinflammation associated with chronic alcohol exposure. Failure to observe similar increases in [^{11} C]PBR28 binding *in vivo* in both humans and rats suggests the possibility that a mechanism mediated by chronic alcohol exposure interferes with [^{11} C]PBR28 binding to TSPO *in vivo*. Because TSPO plays a central role in cholesterol transport into mitochondria, and plasma cholesterol levels are upregulated in AUD, we measured the correlation between plasma cholesterol and [^{11} C]PBR28 binding in brain in AUD and observed a significant negative association, consistent with upregulated cholesterol being a potential competitor of TSPO binding *in vivo*.

Imaging Neuroinflammation?

Natalie M. Zahr

Abstract. Classical inflammation in the central nervous system (CNS) includes a response to bacteria, parasites, or viruses or is “sterile” as a reaction to stroke or trauma. Neuroinflammation requires a stereotyped response including presence of infiltrating mobile cells of the innate immune system and compromise of the blood-brain barrier. Regardless of the underlying primary pathology, it is clear that in a variety of CNS disorders microglial activation, neuroinflammation, and neurodegeneration are intimately connected. Thus, the identification of markers that can distinguish between component processes of these independent mechanisms is important in elucidating a better understanding of brain pathology. One of our goals has been to document a unique in vivo imaging phenotype of “neuroinflammation”. To that end, I will present human data including peripheral cytokine quantification in individuals with alcohol use disorders relative to those infected with HIV, a disease with a well-described neuroinflammatory component. I will also review our animal studies including in vivo neuroimaging responses to thiamine deficiency relative to chronic alcohol exposure and in response to peripheral LPS injections. Our most recent work suggests that while there may be an in vivo neuroimaging signature related to neuroinflammation, including an increase in brain temperature, it is still not clear that this signature is selective, robust, and reliable as a marker for neuroinflammation.

Imaging the 18-kDa Translocator Protein in Alcohol Dependence: Findings and Interpretations

Hillmer AT, Sandiego CM, Hannestad J, Angarita GA, Kumar A, Huang YY, O'Connor KC, Carson RE, O'Malley SS, Cosgrove KP

Depts. of Psychiatry, Radiology; Yale PET Center; Yale University School of Medicine

Abstract. Chronic alcohol use is thought to disturb brain homeostasis by influencing microglial function. Positron emission tomography (PET) imaging of the 18-kDa translocator protein (TSPO), an imaging marker influenced by microglia number, was measured with the radioligand [^{11}C]PBR28. TSPO levels were measured in 15 healthy controls and 15 alcohol-dependent subjects after 1-4 days (n=14) or 24 days (n=1) of alcohol abstinence. TSPO was quantified by estimating total distribution volumes (V_T) using multilinear analysis with arterial blood sampling to measure the parent [^{11}C]PBR28 input function. Alcohol dependent subjects exhibited significantly lower [^{11}C]PBR28 levels than healthy controls ($p=0.034$). On average, TSPO levels were 10% lower in alcohol dependent subjects. Exploratory analyses suggested a negative relationship of TSPO levels in hippocampus and striatum with alcohol dependence severity ($p<0.035$). In a subset of subjects, peripheral immune responsivity was assessed by culturing monocytes extracted from venous blood samples both with and without lipopolysaccharide (LPS). Monocyte response was quantified by measuring the fold-change of cytokine levels in LPS-stimulated cultures relative to saline cultures. Peripheral monocyte response to immune stimulus was lower in alcohol dependent subjects for the pro-inflammatory cytokines interleukin-6 and interleukin-8. The imaging data indicate lower TSPO levels throughout the brain and a smaller peripheral pro-inflammatory response in alcohol dependent subjects compared to healthy controls. These findings could be attributed to lower numbers of microglia in alcohol use disorder. Importantly, [^{11}C]PBR28 V_T is significantly reduced in a preclinical model of microglial depletion, demonstrating that [^{11}C]PBR28 is sensitive to settings of reduced microglia number. Taken together, this work suggests altered microglia homeostasis in alcohol dependence, implying a potential role for pharmaceuticals tuning the neuroimmune system as therapeutics for alcohol dependence.

SESSION III
Reward and Habit Learning

Corticoaccumbens glutamate signaling in response strategy selection

Laura L Giacometti[1], W Bailey Glen[2], L Judson Chandler[2], Jacqueline M Barker[1]

[1]Department of Pharmacology and Physiology, Drexel University College of Medicine
[2]Department of Neuroscience, Medical University of South Carolina

Abstract. Prefrontal subregions have been shown to have distinct contributions to response strategy selection. The ventromedial infralimbic prefrontal cortex appears to be necessary for the development and expression of habitual behaviors and may critically contribute to compulsive-like reward seeking. We examined the function of infralimbic pyramidal neurons during habitual and goal-directed reward seeking, demonstrating that encoding of behavioral outcomes is lost during habitual behavior. The infralimbic prefrontal cortex sends extensive glutamatergic projections to the nucleus accumbens shell, which our findings suggest is a key regulator of contingency-mediated behaviors including goal-directed actions. Chronic alcohol exposure is known to dysregulate accumbens glutamate signaling and may promote the loss of goal-directed behavior in a sex-specific manner, such that males exhibit facilitated expression of habitual behavior while females exhibit increased sensitivity to aversive experiences. Our published and unpublished findings will describe potential mechanisms by which chronic alcohol exposure may act to differentially impair reward seeking behavior in males and females by dysregulating accumbens glutamate levels. In particular, we highlight sex differences in accumbens astrocyte immunoreactivity and calcium signaling following chronic alcohol exposure and the potential for astrocyte function to serve as a key target in rescuing chronic alcohol-induced deficits in behavior.

Prefrontal regulation of punished ethanol self-administration

Andrew Holmes

Abstract: A clinical hallmark of alcohol use disorder (AUD) is that drinking persists despite an awareness of the potential adverse consequences. The ventral (vmPFC) and dorsal (dmPFC) medial prefrontal cortex are positioned to exert top-down control over subcortical regions, such as the nucleus accumbens shell (NAcS) and basolateral amygdala (BLA), encoding the positive and negative valence of EtOH-related stimuli. Prior studies in rodents have implicated these prefrontal regions in the regulation of punished EtOH self-administration (EtOH-SA). This presentation will describe experiments in which we conducted in vivo electrophysiological recordings in the vmPFC and dmPFC to obtain neuronal correlates of footshock-punished EtOH-SA in mice. Ex vivo recordings were performed in NAcS D1-positive MSNs receiving vmPFC input to examine punishment-related changes in this pathway. To assess the functional contribution of the vmPFC and dmPFC neurons, and vmPFC projections to the NAcS or BLA, these regions/pathways were optogenetically-silenced during testing. In response to punishment, mice exhibited approaches to the EtOH-lever but aborted making an actual lever-press, leading to a reduction in the rate of EtOH-lever pressing. Neurons in both vmPFC and dmPFC exhibited phasic firing related to both aborts and EtOH-lever pressing, but population-level coding of aborts was only evident in the vmPFC. Photosilencing the vmPFC, but not dmPFC, reversed punished-suppression of EtOH-SA. Punished-suppression was associated with plasticity at vmPFC inputs to D1-MSNs in the NAcS, and photosilencing vmPFC-NAcS projections, but not vmPFC-BLA, partially reversed punished-suppression. These data identify a corticostriatal circuit regulating EtOH-SA after punishment, with implications for understanding the neural basis of compulsive drinking in AUDs.

The Challenge of Studying Habits in Humans

Sanne de Wit

Abstract. Animal research has provided support for the influential theory that habits play a role in the transition from goal-directed towards compulsive drug seeking. However, direct evidence from human research is still lacking. This may at least in part be related to the challenge of capturing habits in humans in the lab. During recent years, several studies have used computerized tasks to provide evidence for a general imbalance between habitual and goal-directed control in people with substance or alcohol abuse. However, the behavioural inflexibility observed in those studies may in fact be predominantly due to impairments in goal-directed control. Furthermore, these studies have investigated general tendencies as opposed to the habit status of drug seeking specifically. In my talk, I will discuss strengths and weaknesses of current approaches to habit research in humans. Furthermore, as an alternative to studying habits in the lab, I will present our most recent attempt to study real-life habit formation in healthy, young adults. In this study, we used the Self-Report Behavioural Automaticity Index to investigate gradual automatisation of an everyday behaviour (namely taking a placebo pill on a daily basis), and related subjective automaticity of this behaviour to individual differences in the integrity of frontostriatal circuitries (using Diffusion Tensor Imaging and Voxel Based Morphometry) in a healthy population. Our findings provide preliminary support for the validity of this approach to studying habits in humans.

Cue-Induced Changes in Decision-Making and Reduced Model-Based Control in Alcohol Use Disorder and Gambling Disorder

Alexander Genauck

Abstract. Patients suffering from addictive disorders show increased cue-reactivity with regards to stimuli related to the addictive behavior. Furthermore, addiction research suggests impaired decision-making in addicted patients due to the dominance of the habitual, model-free at the expense of the goal-directed, model-based decision system. Both processes, high cue reactivity and reduced model-based behavior, may increase the propensity for relapse and for the persistence of addictive behavior in affected patients. In the current talk I would like to present studies from our lab at Charité Berlin that have investigated cue induced changes in decision-making and decreases in model-based behavior in both alcohol dependence (AD) and gambling disorder (GD). Methods: I will present data on whether cue-induced decision-making (pavlovian-to-instrumental transfer, PIT) is enhanced in young men with high-risk social drinking and in AD patients. Moreover, I will cover the relation between PIT and impulsivity, polygenic risk for alcohol consumption, prospective relapse and neural activation in AD subjects. To expand on this, I will present a study testing whether neural responses during alcohol-related PIT predict future relapse in AD patients and future drinking behavior in adolescents using a multivoxel out-of-sample classification scheme. Further, I will present a study that elucidates whether cue-induced decision-making is also a phenotype of GD (behaviorally and neurally), using also an out-of-sample classification scheme. Lastly, I will present studies based on a Markov decision (2-step) task that try to uncover the neural basis of reduced model-based behavior in AD subjects.

Results:
Behavioral PIT was enhanced in high- compared to low-risk drinkers and in AD patients compared to matched controls. Moreover, behavioral PIT was associated with impulsivity in both cohorts and with polygenic risk for alcohol consumption in social drinkers. On a neural level, PIT activated the amygdala in social drinkers and the nucleus accumbens predicted relapse in the cohort of AD patients. PIT activation patterns predicted future relapse with 71.2% accuracy, whereby mainly activation patterns in medial prefrontal cortex helped predicting. Cross-validated diagnosis prediction (GD vs. HC) based on behavioral an neural PIT yielded an area under the receiver operating curve (AUC-ROC) of 68.9% and 70.0%, respectively. Lastly, patients who relapsed displayed reduced medial prefrontal cortex activation during model-based decision making and high alcohol expectancies were associated with low model-based control in relapsers, while the opposite was observed in abstainers and healthy control subjects. However, reduced model-based control per se was not associated with subsequent relapse.
Conclusion: Cue-induced changes in decision-making and PIT seem to be important mechanisms that are associated not only with at-risk but also with chronic alcohol consumption and gambling disorder. Moreover, we found multi-level evidence that PIT is related to potential risk factors for the development and maintenance of alcohol use disorders such as polygenic risk for alcohol consumption and impulsivity. Further, relapse does not simply result from a shift from model-based to model-free control but is instead dependent on the interaction between high drug expectancies and low model-based decision making.

SESSION IV
Structural and Functional Connectivity in Alcoholism

Identifying Alcohol Specific Brain Phenotypes via Machine Learning Technology

Kilian M. Pohl

Abstract. The World Health Organization estimates a 12-month prevalence rate of above 13% for an alcohol use disorder (AUD) diagnosis in people age 15 years and older in the United States, presenting significant health risks that have the potential of accelerating. Numerous studies are investigating the impact of alcohol on the brain and risk factors predictive of AUD. This talk complements the findings of these expert-guided, group-level studies with phenotypes identified by novel data-driven machine learning approaches, which predict appreciable alcohol use from MRIs. Phenotypes specific to regular alcohol drinking adolescents were extracted from the micro and macro structural MRIs of 705 youth of the National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA). Significantly more accurate in predicting drinking in individuals than expert-guided analysis, these phenotypes consisted of structural MRI volumes of the lateral ventricles, centrum semiovale, corpus callosum, and cingulate gyrus and microstructural DTI measures of the fornix, corona radiata, and thalamic radiations.

Alcohol and cannabis effects on cognition, hippocampal structure and function in the BARCS college student study

Godfrey Pearlson

Abstract. The NIAAA-funded Brain and Alcohol Research in College Students (BARCS) study tracked 2100 freshman students at Trinity College and Central Connecticut State University for 24 months, capturing 99% of the incoming first-year students over the study period. Students were assessed using a wide variety of measures to derive both baseline predictors of future dysfunctional alcohol use and subsequent consequences of both alcohol and cannabis use on brain development and cognitive trajectories. All students were tested cognitively and genotyped at study entry: 420 randomly chosen students received baseline structural and functional MRIs, and EEGs: these were repeated conclusion of the study. All participants logged into a confidential website where they provided monthly self-reports of alcohol and recreational drug use in terms of quantity, frequency and consequences. This presentation will focus on four aspects of the study findings; 1. Longitudinal relationship of alcohol consumption on hippocampal structural MRI volumes. 2. Cross-sectional correlations of alcohol consumption on performance and regional brain BOLD signal during performance of a hippocampal- and frontal lobe-dependent virtual water maze task. 3. Cross-sectional prediction of transition to later alcohol use disorders using a functional alcohol cue reactivity task and 4. Cross-modal interrelationships of hippocampal structural and functional findings. Study was funded by R01AA016599.

Multimodal signatures of externalizing behaviors

Mary M. Heitzeg and Chandra Sripada

Abstract. Externalizing problems often precede the initiation of alcohol use and are associated with a more severe and persistent course of alcohol use disorder. An externalizing risk pathway is characterized by problems with self-regulation such as aggression, impulsivity, sensation-seeking, and rule-breaking, with the primary deficit being one of behavioral undercontrol or disinhibition. There is evidence that individual differences in traits underlying externalizing problems differentiate substance abusing subgroups on the basis of age of onset, patterns of use, and susceptibility to co-morbid psychopathology; however, neural underpinnings of these traits may represent more robust predictors of distinct trajectories of alcohol and other substance use problems than the traits themselves. Furthermore, neurodevelopmental processes that contribute to serious mental health problems such as substance abuse are unlikely to affect a single region or single modality. It is more likely that they involve interactive networks across distributed regions; thus, understanding emerging psychopathology in the context of brain networks is critical. The goal of the current study is to uncover distinct neurofunctional phenotypes related to externalizing behavior, which may be predictive of problem alcohol use. Specifically, we investigate the relationship between externalizing behaviors and cohesive patterns of brain function across multiple modalities in 200 offspring drawn from a prospective, high-risk study of the development of alcohol use disorder and related symptomatology.

Structural and functional neuroimaging markers of risk for heavy drinking in youth: Results from longitudinal and consortium projects

Susan F. Tapert

Abstract. Dr. Tapert will present data from longitudinal and multi-site consortia that have identified structural and functional neuroimaging markers of risk for heavy drinking in youth. Our long-term longitudinal studies of relatively high functioning youth with no history of substance use at project baseline identified neural candidate markers of risk. These including thinner cortices and less brain activation in diffusely distributed regions of the brain that predicted initiation of moderate-to-heavy drinking by age 18. In a separate cohort, have seen that lower white matter integrity in the fornix and superior corona radiata predicted heavier amounts of substance use years later. The National Consortium on Alcohol and NeuroDevelopment in Adolescence (NCANDA) recruited 831 12-21 year-olds across 5 research sites in 2012-2013, to focus on neural sequelae of and risk factors for adolescent substance use. The Adolescent Brain Cognitive Development (ABCD) study recruited 11,878 9-10 year-olds from 21 research sites across the United States, from 2016-2018. Data from these consortium that distinguish youth with and without major risk factors for alcohol use disorder, including presence of early alcohol use and family history of alcohol use disorder, will be discussed.

fMRI Response Patterns and Predictors of Use in College Drinkers

Alecia Dager

Abstract. Emerging adults ages 18-25 show the highest rates of alcohol use and escalation to heavy drinking. Identifying the neural risks and consequences of heavy drinking in this age range could have an important impact on public health. To this end, the NIAAA-funded Brain and Alcohol Research in College Students (BARCS) study ascertained neuroimaging and substance use over 2 years in college students. Participants reported substance use quantity, frequency, and consequences via monthly online surveys. Functional MRI tasks included alcohol cue reactivity, figural memory, and go/nogo. This presentation will focus on describing 1) fMRI response differences between heavy drinkers and controls, including the influence of family history of alcohol dependence, and 2) fMRI response patterns related to the subsequent transition to heavy drinking. These findings add to our understanding of alcohol use in college students and provide possible targets for intervention efforts. Funded by R01AA016599 to Godfrey Pearlson.

SESSION V
Pharmacoimaging

Expectation effects on striatal dopamine responses to alcohol – an indicator of risk?

Lawrence S. Kegeles, Guillermo Horga, Rassil Ghazzaoui, Rachel Rosengard, Najate Ojeil, Xiaoyan Xu, Mark Slifstein, Ismene Petrakis, Stephanie S. O'Malley, John H. Krystal, and Anissa Abi-Dargham

Department of Psychiatry (LSK, GH, RG, RR, NO, XX), Columbia University and the New York State Psychiatric Institute; Department of Psychiatry (MS, AA-D), Stony Brook University; Department of Psychiatry (IP, SSO, JHK), Yale School of Medicine.

Abstract. We used PET imaging with [11C]raclopride to examine the effects of consumption of alcohol or placebo beverage by participants with alcohol use disorder (AUD) compared with healthy participants with and without family history of AUD. We sought to assess dopamine release following alcohol exposure in relation to AUD risk. Participants consumed a placebo or alcohol beverage in counterbalanced order before PET scanning. Binding potential (BPND) in the two drink conditions and the percent change in BPND between conditions were evaluated across striatal subregions. Alcohol resulted in greater dopamine release than did placebo in the ventral striatum ($p < .001$). There were no main effects of group, drink order, or sex on ventral striatum BPND or percent change in BPND. However, there was a drink order-by-group interaction ($p = .02$) whereby family history-positive participants who received placebo first had both lower placebo BPND and less difference between placebo and alcohol BPND than all other groups, consistent with expectation of alcohol powerfully evoking dopamine release in this group. Subjective responses showed the same order-by-group interaction. This hyper-responsivity of the dopaminergic system in family history-positive participants to expectation of alcohol may contribute to the expression of familial risk for AUD.

Endocannadinoid Metabolism in Brain of Alcohol Users: PET Studies with the Fatty Acid Amine Hydrolase Radioligand [C-11]CURB

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Abstract. Fatty acid amide hydrolase (FAAH) is the catabolic enzyme for the major endocannabinoid neurotransmitter anandamide and a target for medication development. Preclinical and genetic studies of a functional polymorphism in the FAAH gene (C385A, rs342240) suggest that lower FAAH levels might be associated with risk for alcohol use disorder (AUD). Here, we investigated whether lower brain FAAH level is associated with AUD, family history of AUD and /or behavioural phenotypes related to risk for AUD. Methods: FAAH brain levels were measured with positron emission tomography using the FAAH radioligand [C-11]CURB in healthy controls (n = 25), in heavy-drinking youth with positive (n = 14) or negative family history of AUD (n = 17) and in subjects with AUD at two time points (~5 and ~25 days of monitored abstinence: n = 14; n = 11). Heavy-drinking youth completed an intravenous alcohol infusion session and blood samples were taken in all participants to assess FAAH C385A genotype and plasma endocannabinoid levels at multiple time points. Results: [C-11]CURB binding was globally lower than controls during early but not protracted abstinence and significantly correlated with drinks per week and with plasma concentrations of anandamide. Family history of AUD did not affect [C-11]CURB binding, however higher alcohol consumption and hazardous use (Alcohol Use Disorders Identification Test (AUDIT)) in heavy-drinking youth, as well as lower sedative effects of alcohol during intravenous administration (Biphasic Effects of Alcohol Scale) was related to lower [C-11]CURB binding. Conclusion: In line with preclinical studies our findings that lower FAAH is related to higher alcohol consumption (in AUD and in non-AUD heavy drinking youth) may be an acute consequence of recent chronic alcohol use (in AUD) and or a predating factor increasing vulnerability for hazardous use. Although clinical significance of low FAAH in AUD remains to be established, treatment approaches targeting FAAH should consider that increased endocannabinoid tone during early abstinence could drive drinking however some aspects could be beneficial.

Developing novel pharmacological treatments for alcohol use disorder via gut-brain pathways: recent translational efforts

Lorenzo Leggio

Abstract. Dr. Leggio will present recent data from his laboratory on the role of gut-brain neuroendocrine pathways, as possible new neuropharmacological targets for the treatment of alcohol and substance use disorders. His laboratory conducts clinical and translational inpatient and outpatient studies to identify possible novel medications for addiction. His group uses a combination of state-of-the-art, innovative bio behavioral, pharmacological and neuroimaging procedures performed under well-controlled human laboratory conditions. While the laboratory focuses primarily on clinical studies, both preclinical and human approaches are under development to shed light on the possible role of gut-brain and other neuroendocrine pathways in alcohol and substance use disorders.

Recent 1H MRS Studies to Measure the Effects of GABA-ergic Medication on Brain Metabolites

Dieter J. Meyerhoff

Abstract. Very few non-invasive methods allow to measure the effects of medications on human neurochemistry. Proton (1H) MR spectroscopy can measure region-specific brain metabolites associated with neuronal and glial processes. We have used 1H MRS for many years to observe the chronic effects of alcohol and other substance abuse on the brain as well as the effects of neuroplasticity and metabolic recovery after cessation of substance abuse. Only more recently has the clinical treatment field begun to offer more routinely pharmacotherapy for the treatment of alcohol use disorder (AUD). Here, we will present absolute metabolite concentration data from two separate 1H MRS studies: a) cross-sectional 4T MRS data obtained after chronic oral administration of gabapentin to a convenience sample of treatment seekers several weeks into abstinence from alcohol, and b) pre- and post-treatment 3T MRS data obtained in a double-blind placebo controlled clinical trial of topiramate to reduce drinking and PTSD symptoms in a sample of heavily-drinking Veterans with dual diagnoses. Regarding the first study, daily gabapentin treatment at an average of 1,600 mg/day for at least one week was not associated with altered cortical GABA or glutamate concentrations but with lower glutamate in frontal white matter. For the topiramate clinical trial, serial prefrontal, insular and temporal 1H MRS data have been processed (MEGA-PRESS for GABA and semiLASER for other metabolites) but the study blind will not be broken before the end of June. Here, we expect to present hot-off-the-press newly unblinded data on regional cortical metabolite concentration outcomes as a function of study medication in more than 40 PTSD patients with AUD.

Potential for Ketone Bodies to Support Sobriety

Graeme F. Mason

Abstract. Ethanol, a fermentation product of yeast, contains a large quantity of energy, and so the body oxidizes ethanol both directly and in the form of acetate that the liver generates from ethanol. Among the tissues that consume this energy is the brain. Perhaps with chronic misuse of alcohol, the brain comes to rely on acetate and ethanol and so during withdrawal suffers an energetic perturbation in addition to the loss of the pharmacologic activities that are normally associated with dependence. This presentation will show data acquired with Magnetic Resonance Spectroscopy (MRS) to assess the consumption of ethanol and acetate as related to alcohol abuse and discuss how energetic supplementation may provide a benefit during ethanol withdrawal. Overall, ^{13}C MRS was used *in vivo* to track the consumption of ethanol and acetate in the brains of light drinkers and non-dependent heavy drinkers. We observed that heavy drinkers' brains consume more ethanol and acetate than light drinkers. We also found that while acetate supplies energy for glia, ethanol fuels neurons directly. This duality of consumption of the energy directly from ethanol and indirectly from hepatically generated acetate allows the provision of large quantities of energy for neurons and glia. When ethanol is withdrawn, the brain loses this supply of energy, and one may hypothesize that energetic replacements could alleviate some problems that could result from the energy loss. Some evidence suggests that ketone bodies, energy-rich and readily consumed by both neurons and glia, could provide such a source.

POSTER PRESENTATIONS

POSTER 1: The Kappa Opioid Receptor Levels in Alcohol-Dependent Heavy Drinkers is Associated with Reductions in Drinking and Craving Following Naltrexone

Authors: B de Laat, A Goldberg, N Nabulsi, Y Huang, SS O'Malley, ED Morris and S Krishnan-Sarin

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Abstract. Naltrexone is a non-selective opioid receptor antagonist approved for the treatment for alcohol use disorder (AUD) with modest efficacy. We used positron emission tomography (PET) to investigate the role of the kappa opioid receptor (KOR) in the therapeutic effect of naltrexone in alcohol dependent heavy drinkers. *Methods:* Non-treatment seeking heavy drinkers meeting criteria for AUD participated in two alcohol drinking paradigm (ADP) sessions; one before and one after a week of 100 mg/day naltrexone. Subjects also underwent a [^{11}C]-LY2795050 PET scan to measure KOR availability in the amygdala, hippocampus, pallidum, striatum, cingulate, and prefrontal cortex on a separate day prior to starting naltrexone. The primary behavioral outcomes were reduction in number of consumed drinks during ADP1 and ADP2 (Ddrinks), and craving during each ADP quantified via the Alcohol Urge Questionnaire (AUQ) and Yale Craving Scale (YCS). The primary imaging outcome was volume of distribution of [^{11}C]-LY279505 (V_T^K) – a measure of available KOR. Associations between V_T^K were assessed with mixed models for craving and with Lasso regression for Ddrinks. In addition, voxel-wise analysis of the PET data was performed with either craving or Ddrinks as a covariate. *Data:* Forty-eight participants (16F) drinking 47 ± 16 drinks per week per TLFB at intake participated. *Results:* During the second ADP participants consumed fewer drinks (-3.7 ± 4, $p < 0.0001$) and experienced less craving (YCS: -11 ± 1, $p < 0.0001$; AUQ: -6 ± 0.6, $p < 0.0001$). Higher V_T^K in the striatum ($p = 0.005$), cingulate ($p = 0.023$) and prefrontal cortex ($p = 0.018$) was associated with smaller Ddrinks. YCS scores were positively associated with V_T^K in all evaluated brain regions (all $p < 0.01$). AUQ scores were also positively associated with V_T^K in the hippocampus ($p = 0.0007$), cingulate ($p = 0.007$), and prefrontal cortex ($p = 0.048$). Voxel-wise analysis identified clusters in the bilateral insula, prefrontal, and cingulate cortex associated with Ddrinks ($p < 0.0001$). *Conclusion:* Higher KOR levels appear to be associated with greater craving during an ADP and less reduction in drinking following a week of treatment with naltrexone.

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POSTER 2: Occupancy of the Kappa Opioid Receptor Predicts Reduction in Drinking after Naltrexone

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Abstract: Naltrexone is a non-selective opioid receptor antagonist approved for the treatment for alcohol use disorder (AUD) with modest efficacy. The ability to identify predictors of treatment response could improve clinical practice. *Methods:* Non-treatment seeking heavy drinkers meeting criteria for AUD underwent [^{11}C]-LY2795050 PET before and after the week of naltrexone treatment. Occupancy was estimated using volume of distribution of [^{11}C]-LY279505 before and after naltrexone using a Lassen plots. Subjects also participated in alcohol drinking paradigm (ADP) sessions before and after naltrexone week. The primary behavioral outcomes were reduction in number of consumed drinks from ADP1 to ADP2 (Ddrinks) and craving during each ADP. Associations with KOR occupancy were assessed with mixed models for the reported craving levels, and with multivariable regression for the reduction in drinking ("Drinks). A logistic regression was performed to evaluate if associated variables could predict a reduction of >50% in drinking from ADP1 to ADP2 ("Drinks_50%). *Data:* Forty-eight participants (16F, 32M) drinking 47 ± 16 drinks per week participated in the study. *Results:* Participants were balanced in FH (41% negative, 59% positive) and smoking status (57% non-, 43% smokers). High occupancy (92 ± 1%) was achieved by the 100 mg naltrexone regimen. No effects of gender nor FH on occupancy were observed. Occupancy was associated with the number of years participants had been drinking (YOD) and this association was significantly different between FH positive and FH negative participants ($p = 0.0003$). ΔDrinks was associated with FH, YOD, and occupancy ($p = 0.032$). A logistic regression model including these 3 variables achieved an 84% prediction accuracy for ΔDrinks_50%. Higher KOR occupancy by naltrexone was associated with higher craving levels during an ADP ($p < 0.03$). *Conclusion:* The relationship between occupancy and ΔDrinks differed by FH status, which could be underlie our previous finding that only in FH positive individuals a higher naltrexone dose was associated with a larger reduction in drinking (Krishnan-Sarin, 2007). In conclusion, occupancy of KOR by naltrexone measured by PET combined with key demographics could provide valuable predictions of who will respond to naltrexone for the treatment of alcoholism.

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POSTER 3: Disrupted Neural and Autonomic Response to Sustained Stimuli Linked to High Craving in Patients with Alcohol Use Disorder

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Abstract. Previous studies have noted neural and autonomic disruption in patients with alcohol use disorder (AUD). However, few have examined these two systems simultaneously. Our study focused on basal/tonic and phasic disruption of the ventromedial prefrontal cortex (vmPFC) and autonomic nervous system (ANS) functioning and its relationship to high craving in AUD patients. We performed both functional magnetic resonance imaging (fMRI) and electrocardiogram (ECG) methods and collected ratings on craving, stress and arousal in 23 AUD patients and 19 light drinkers during sustained exposure to stress (S), alcohol cue (A) and neutral (N) pictures. We analyzed fMRI data with BioImageSuite and AFNI, and processed ECG data through MATLAB and Kubios software for heart rate, low-frequency power (LF) and approximate entropy (ApEn). We found that, at the basal state level, AUD patients exhibit significantly disrupted behavioral and autonomic response prior to and during visual provocation, relative to light drinkers. Across conditions, AUD patients reported higher craving (S: $t=3.72$, A: $t=3.74$, N: $t=3.44$; $ps<0.01$), exhibited higher overall heart rate (S: $t=2.36$, A: $t=2.18$, N: $t=2.07$; $ps<0.05$) and displayed higher baseline ApEn (S: $t=2.35$, A: $t=2.49$, N: $t=2.24$; $ps<0.05$), which is an indicator of autonomic irregularity and disruption. We also observed significant relationships between ANS dysfunction and craving. During the alcohol cue condition, we found that time-related increased craving associated with greater basal heart rate ($r=.485$, $p<0.05$) in AUD patients. During the stress condition, craving positively correlated with LF power ($r=.473$, $p<0.05$) in AUD patients whereas craving in light drinkers did not. At the basal state level, we observed vmPFC hyperactivity in AUD patients that predicted higher heart rate during stress ($p<0.05$), relative to light drinkers. Our current study suggests a basal/tonic disruption in neural and autonomic pathways that relates to functional alterations in physiologic and craving response to sustained stress and cue stimuli in AUD patients. In highly susceptible environments involving alcohol, higher craving in AUD patients may result from basal state dysfunction such as autonomic irregularity and vmPFC hyperactivity. Constant exposure to such settings may further increase vulnerability to high craving and aggravate addiction severity in AUD patients.

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POSTER 4: Disrupted Neural and Autonomic Response to Sustained Stimuli Linked to High Craving in Patients with Alcohol Use Disorder

Authors: J. Weafer[1], M. Dzemidzic[2], D. Kareken[2], and H. de Wit[1].

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Abstract. Alcohol abuse has been traditionally considered a male-oriented problem and as a consequence research on risk factors specific to women has been minimal. However, the sex gap in alcohol abuse is closing rapidly, and both animal and human studies suggest that females are actually more vulnerable to substance use than males. As such, it is important to understand the biological basis of sex differences to develop sex-specific prevention and treatment efforts. Here we examined neurobiological factors underlying poor inhibitory control, a risk factor that we and others have shown is more strongly linked to heavy drinking in women than in men. Methods: Female and male heavy drinkers, matched on demographic and alcohol consumption measures, performed the stop signal task to assess inhibitory control while undergoing fMRI. Women were tested once in the early follicular phase of their menstrual cycle (when estradiol levels are low) and once in the late follicular phase (when estradiol levels peak), and men were tested twice at similar intervals. Blood samples were taken to assess serum levels of estradiol at both sessions. Data and Results: To date 21 women and 11 men have completed the study. Preliminary analyses confirmed low levels of estradiol in the early follicular phase (mean = 48.1 pg/ml), and high levels in the late follicular phase (mean = 201.9 pg/ml). Women showed less brain engagement in the early compared to the late follicular phase in right frontal regions, including the right inferior frontal gyrus, middle frontal gyrus, and supplementary motor area. Further, women had less brain activation compared to men when tested in the early follicular phase, but no sex differences were observed when women were tested in the late follicular phase. Conclusions**:** These data suggest that the inhibitory impairments observed in heavy-drinking women are influenced by menstrual cycle phase. Specifically, they suggest that inhibitory deficits may be exacerbated in the early follicular phase, possibly contributing to increased difficulty controlling alcohol consumption during this time. Identification of such vulnerable periods for problematic alcohol consumption could have important implications for prevention and treatment of alcohol use disorders in women. Research supported by NIAAA grant K01AA024519 (JW).

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POSTER 5: Risky Drinkers Show Biased Habit-Like Learning for Alcohol Cues

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Abstract. Addiction is broadly characterized as a disorder of learning and memory, in which users form strong habitual associations between drug cues and drug use behaviors, thus driving maladaptive drug taking. This suggests that individuals with addiction (e.g., patients with alcohol use disorder [AUD]) would show enhanced habit learning relative to social drinkers. However, laboratory findings have been inconsistent, and it remains unclear whether non-dependent individuals who engage in risky drinking behavior would show differences in learning. We developed a novel task in which cues (alcohol and neutral object images) are probabilistically associated with simple motor sequences, associations that recruit similar neural circuitry to habit formation. Non-dependent high-risk drinkers (meeting NIAAA criteria for binge and/or heavy drinking, N = 16), non-dependent low-risk drinkers (N = 36), and treatment-seeking AUD participants (N = 35) completed the experiment. Overall, participants successfully learned the associations (main effect of block: $F(1,926) = 127.57$, $p < .001$) and responded differently for alcohol and neutral objects (main effect of cue: $F(1,926) = 6.62$, $p = .01$). Crucially, drinking status was associated with differences in both learning (controlling for age and IQ: group [AUD, high-risk, low-risk] x block x cue: $F(2,926) = 9.54$, $p = .002$) and the speed of the correct motor sequence (group x cue: initiating sequence - $F(2,926) = 11.25$, $p < .001$; completing sequence – $F(2,926) = 16.56$, $p < .001$). High-risk drinkers were quicker to learn associations with alcohol cues (Block 1, alc v neut: $t(15) = 2.13$, $p = .05$), a bias that differed from both AUD (cue x group: est = .17 [.06], $p = .006$) and low-risk participants (est = .14 [.06], $p = .02$). By the end of learning, high-risk drinkers were faster to initiate correct sequences for alcohol cues ($t(15) = -1.79$, $p = .09$), whereas low-risk drinkers showed the opposite ($t(35) = 2.24$, $p = .031$; cue x group: est = 231.26 [99.27], $p = .02$). Together, these results demonstrate that risky drinking behavior is associated with differences in habit-like learning, particularly for alcohol cues. Planned analyses for a follow-up neuroimaging study will be discussed.

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POSTER 6: Greater Hippocampal Activation during Memory Retrieval in Women: Impact of Depression and Risk for Alcohol Use Disorder

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Abstract. Major depressive disorder (MDD) is a debilitating condition that interferes with daily functioning, and which occurs at a markedly higher rate in women relative to men. Evidence of memory deficits, along with structural and functional alterations inhippocampus, have also been reported in MDD, which likely contribute to the multifaceted impact of this condition. This study aimed to examine the intersection between depression and risk for an alcohol use disorder in women using a virtual translation of the Morris Water Task (MWT), a classic probe of hippocampal-mediated spatial memory function. Multiband blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) data were acquired during performance of the MWT in a sample of 22 women, across a clinical spectrum of depressed mood, from no depression to current MDD, and stratified into no/low (n=16) and some risk (n=6) groups using the Alcohol Use Disorders Identification Test (AUDIT). fMRI data were analyzed using FSL. While depression scores on the Beck Depression Inventory (BDI) were not significantly different between groups, women in the alcohol risk group reported significantly higher anhedonic depression on the Mood and Anxiety Symptom Questionnaire (MASQ, p=.032) and lower self-efficacy measured using the NIH Toolbox Emotion Measures (p=.05) relative to the no/low risk group. In an fMRI contrast comparing BOLD activation during memory retrieval relative to motor control, significantly greater hippocampal activation was observed in the alcohol risk group (p=.022) relative to the no risk group. This hippocampal hyperactivation was observed in the absence of any MWT performance differences between groups. Greater hippocampal activation during a spatial memory task may reflect neural compensation, i.e., greater utilization of neuronal resources, in those at risk, to perform at levels equivalent to the no/low risk group. It was surprising that depressive symptoms and self-efficacy did not further impact hippocampal differences beyond risk for alcohol misuse. However, these preliminary findings emphasize the importance of characterizing drinking behavior within the context of depression, which may in turn help inform prevention and treatment strategies in co-occurring disorders, in order to help to alleviate suffering from this debilitating condition. Funding Source: NARSAD Young Investigator Grant (Sneider)

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POSTER 7: Greater Hippocampal Activation during Virtual Morris Water Task Prospectively Predicts Substance Use Initiation by Age 15.5

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Abstract. Early age of onset of alcohol and other substance use is considered one of the most important risk factors in the later development of an alcohol use disorder (AUD). While much recent research has examined age of onset together with other risk factors for AUD, little is known about the neurobiological markers predictive of early use itself. Additionally, research on neurobiological markers of substance use risk has focused largely on the prefrontal cortex and mesolimbic systems for their roles in inhibitory control and in reward-seeking, respectively. However, recent models have highlighted the relevance of hippocampal function (especially developmentally) in determining substance use risk, given its role in both emotion regulation and in adaptive learning. The purpose of the current study was to examine hippocampal activation as it prospectively relates to earlier substance use initiation. This longitudinal study enrolled 13-14-year-old healthy, drug- and alcohol-naïve adolescents for a baseline visit, during which multiband blood oxygen level dependent (BOLD) functional magnetic resonance imaging (fMRI) data were acquired while participants performed a virtual translation of the classic Morris Water Task (vMWT), which tests spatial memory retrieval. Participants were then followed for 3 years via quarterly substance use assessments and stratified into those who initiated use before age 15.5 (n=8) and those who did not (n=19). Those who initiated substance use by age 15.5 showed significantly greater hippocampal activation during memory retrieval on the vMWT at baseline than those who did not initiate by this age (p=0.03). No significant differences in activation were found for any prefrontal cortex regions examined (middle frontal gyrus, anterior cingulate cortex, and frontal medial cortex). These results suggest inefficient hippocampal function may be a risk factor for early substance use. The findings shed light on neurobiological patterns that predict and, importantly, predate use (allowing these patterns to be distinguished from consequences of early initiation on brain development), and help to identify specific neurobiological vulnerabilities predictive of later risky behavior during adolescence. Funding Sources: R01 AA022493 and K24 AA025977 (Silveri); F31 AA025844 (Oot)

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POSTER 8: Experimental Alcohol Exposure Predicts Cerebral Metabolites on the Descending Limb in Healthy Adults: A Preliminary H MRS Study

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Abstract: Chronic exposure to alcohol induces neuroadaptation and allostasis, but mechanisms are not well understood. Neuroimaging studies have used magnetic resonance spectroscopy (MRS) to identify cerebral metabolite changes under acute alcohol in healthy individuals. However, previous experimental studies have focused solely on ascending or peak blood alcohol concentration. This pilot study used MRS to gain insight into neurometabolic activity on the descending limb of acute alcohol in healthy moderate drinkers. We predicted changes in choline, myo-inositol, glutathione, and the summed peak of glutamate and glutamine (Glx) on the descending limb. Method: Participants completed an MRI scan prior to receiving a moderate alcohol dose (.60 g/kg). A second MRI was collected approximately 4.5 hours after alcohol consumption. Cerebral metabolites were assessed using single voxel spectroscopy in the thalamus and frontal white matter. Metabolite concentrations were referenced to creatine (Cr). Breath alcohol concentration area under the curve, a measure of cumulative alcohol exposure during the session, was used to predict changes in neurometabolites from pre-alcohol baseline to descending limb. Results: The sample (N=13) was 26.4+2.8 years of age (mean + standard deviation) and 62% female. Participants consumed an average of 3.3+1.8 drinks per week. Breath alcohol peaked at .070+.008% 60 minutes after alcohol consumption and was 0.025+.011% at the second MRI. On the descending limb, relative to baseline, we found significant increases in levels of choline/Cr, Glx/Cr, and glutathione/Cr in the thalamus and Glx/Cr in frontal white matter (p_'s_<0.05). Myo-inositol did not change significantly in either voxel. Breath alcohol area under the curve was a significant predictor of all metabolite increases (p_'s_<0.045). Conclusion: This MRS study is the first to report increased levels of choline, Glx, and glutathione on the descending limb of alcohol. Metabolite increases were predicted by a cumulative measure of acute alcohol exposure, supporting the notion that they were alcohol-induced. Findings suggest heightened glutamatergic activity, cellular membrane turnover, and antioxidant activity in the brain during alcohol clearance in healthy moderate drinkers. In the context of chronic drinking, these neurometabolic changes may contribute to alcohol-induced neuroadaptation and allostasis.

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POSTER 9: In Vivo Imaging of 11β-HSD1 with [^{18}F]AS2471907 in Trauma-Exposed Individuals and in AUD: Implications for Stress and Alcohol Use

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Abstract. Stress is a potent activator of the HPA axis, and the amount of glucocorticoids (e.g., cortisol, cortisone) present in the brain is dependent on the enzyme 11β-HSD1. 11β-HSD1 catalyzes the conversion of cortisone to cortisol and amplifies the action of glucocorticoids in the brain. High brain glucocorticoid levels, driven by 11β-HSD1 and induced by stress, may contribute to problem alcohol use. We used PET imaging with the 11β-HSD1 specific radioligand [18F]AS2471907 to assess 11β-HSD1 expression in subjects with history of trauma exposure and alcohol use. Methods: This study included 18 trauma-exposed individuals (n=11 men, n=7 women), with or without posttraumatic stress disorder (PTSD; n=1 risky drinker, n=1 with severe AUD). Participants received 95±13 MBq [^{18}F]AS2471907 as a bolus injection and were imaged for 180-240 minutes on the High-Resolution Research Tomograph. 11β-HSD1 levels were estimated as [^{18}F]AS2471907 volume of distribution (V_T), an equilibrium ratio of tissue-to-plasma [^{18}F]AS2471907 radioactivity concentration. Individuals were required to be overnight abstinent from drinking. Levels of 11β-HSD1 were correlated with stress measures (i.e., childhood trauma, mood, anxiety, depression) and alcohol use. Preliminary data using this methodology have also been collected for individuals with AUD (n=5) versus healthy controls (n=12). Results: Exploratory analyses found a positive association of 11β-HSD1 levels in the caudate, cerebellum, anterior cingulate, hippocampus, insula, putamen, temporal cortex, ventromedial prefrontal cortex (PFC), and whole brain with childhood physical abuse (p=0.01-0.03). For alcohol-related outcomes, preliminary analyses found positive associations of 11β-HSD1 levels in the caudate with drinks per week (p=0.02; mean=11.04, SD=30.94) and average drinks per drinking day (p=0.04; mean=2.50, SD=4.65) during the month prior to study participation. Regarding AUD, current data are highly preliminary but suggest that 11β-HSD1 levels may be elevated in amygdala, hippocampus, ventromedial PFC, and caudate in AUD individuals compared to healthy controls. Conclusions: These preliminary findings suggest a role for 11β-HSD1 in early stress exposure and alcohol use. This work is also consistent with findings that early life stress alters caudate volume and work demonstrating increased drug craving-related caudate activity. Consideration of 11β-HSD1 inhibitors as a target for stress-related disorders or alcohol use may be a relevant future pharmacotherapeutic avenue.

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POSTER 10: Association between Impulsivity and Neural Activation to Alcohol Cues in Heavy Drinkers

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Abstract. Impulsivity is a multifaceted construct. Convergent preclinical and clinical evidence indicates that impulsivity is both a risk factor for and a consequence of alcohol use and misuse. Moreover, frontostriatal circuits have been linked to both impulsivity and addiction-related behaviors, including neural response to alcohol cues. The present study aimed to extend the literature on impulsivity and neural alcohol cue-reactivity by examining associations between two measures of impulsivity, behavioral via the delay discounting task and self-reported via the UPPS-P, and brain response to alcohol taste cues. Methods: Non-treatment-seeking heavy drinkers (n=55; 32M/23F; age = 34.00±11.99) completed an fMRI alcohol taste cue-reactivity paradigm. They also completed two impulsivity questionnaires: (1) the monetary choice questionnaire (MCQ), a behavioral impulsivity measure where participants were asked to make a series of choices between smaller, sooner rewards and larger, later rewards; and (2) the UPPS-P Impulsive Behavior Scale, a self-report measure which assess five impulsivity factors: negative urgency, lack of premeditation, lack of perseverance, sensation seeking, and positive urgency. General linear models were run in FSL to identify associations between neural alcohol taste cue-reactivity and behavioral and self-reported impulsivity. Age, gender, and smoking status were included as nuisance covariates. Results: Sensation seeking was positively associated with brain activation to alcohol taste cues in the caudate, thalamus, insula, and cingulate ($Z>2.3$, $p<0.05$, corrected). Delay discounting scores were negatively associated with alcohol taste cue-reactivity in the posterior cingulate, precuneus, occipital cortex, and middle frontal gyrus ($Z>2.3$, $p<0.05$, corrected). There were no significant associations between the other self-reported impulsivity sub-scales and brain activation to alcohol taste cues. Conclusions: This study highlights the multifaceted nature of impulsivity. Self-reported sensation seeking was positively associated with alcohol taste cue-elicited activation in frontostriatal regions, such that individuals who reported higher sensation seeking displayed greater neural response to alcohol taste cues. Conversely, delay discounting was negatively associated with alcohol taste cue-elicited activation in frontoparietal regions, such that individuals who reported greater discounting had less neural response to alcohol taste cues. Together these results indicate that sensation seeking is associated with reward responsivity, while delay discounting is associated with recruitment of self-control circuitry.

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POSTER 11: Impact of Binge Drinking on Salience and Executive Network Activation during Emotional Response Inhibition in College Freshmen

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Abstract. The transition to college is associated with an increase in heavy episodic alcohol use, or binge drinking, during a time when the prefrontal cortex and prefrontal-limbic circuitry continue to mature. Traits associated with this immaturity, including impulsivity in emotional contexts, may contribute to risky and heavy episodic alcohol consumption. Methods: Functional magnetic resonance imaging (fMRI) was used to assess brain network activation during a task that required participants to ignore background images with positive, negative, or neutral emotional valence while performing an inhibitory control task (Go-NoGo). Data: Subjects were 49 college freshmen (18-20 years) who engaged in a range of drinking behavior (past three months' binge episodes range = 0-20, mean = 3.8, total drinks consumed range = 0-104, mean = 31.1). To disentangle activation of networks implicated in inhibitory control during negative emotion, network template spatial maps derived from Human Connectome Project data were regressed against the full set of brain activation maps for Negative NoGo > Neutral NoGo contrast, generating estimates of the impact of negative emotional stimuli during response inhibition on the strength of activation of each associated network. Subjects' network loadings generated for the salience network and central executive networks were examined relative to alcohol use and task performance. Results: Activation strength in the salience network was negatively associated with binges in the past three months (p=.032) and with reduced NoGo trial accuracy on negative (p=.001) and neutral (p=.042) trials. Activation of the right frontoparietal central executive network also was significantly negatively associated with binge episodes (p=.003) and AUDIT total score (p=.001). Conclusions: These findings suggest that in emerging adults with heavier recent binge drinking, processing of negative emotional images interferes more with engagement of inhibitory control neurocircuitry than in emerging adults who do not binge drink often. This pattern of altered frontal lobe activation associated with binge drinking may serve as an early marker of risk for future self-regulation deficits that could increase problematic alcohol use. These findings underscore the importance of understanding the impact of emotion on cognitive control and associated brain network function in binge drinking behaviors among emerging adult college students. Funding sources: K01 AA022392 (PI: Cohen-Gilbert), R21 AA024565 (PI: Nickerson) and R01 AA018153 (PI: Silveri)

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POSTER 12: When Only Alcohol Will Do: Understanding Neural Predictors of Relapse in Veterans with AUD

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Abstract. Augmenting our understanding of the brain circuit mechanisms underlying alcohol use disorders (AUD) to predict relapse is a critical step toward improving AUD outcomes for Veterans who suffer from this destructive disorder. The hijack theory of addiction suggests that following chronic substance use, individuals will demonstrate blunted response to conventional reward and preferential response to their drug of choice. To explore mechanisms underlying AUD outcomes, we examine the impact of demographic, social, psychiatric and neural characteristics associated with relapse in Veterans with AUD. A total of 84 treatment seeking Veterans (14 females; mean age=46 years) with AUD were enrolled in the study and completed 6 months of outcome follow-ups. Participants completed demographic and symptom questionnaires, psychodiagnostic interview, computerized and standard neuropsychological testing, and a 2-hour neuroimaging session, including fMRI tasks of reward and cue reactivity. Participants were contacted vis phone call at 1, 3, and 6 months following participant in the study to determine treatment outcome. T-tests and chi-squared were used to understand difference between relapsers and abstainers. Logistic' regressions were employed to predict risk of relapse versus abstinence. Results revealed that 68% of participant consumed an alcoholic beverage, or relapsed, within 6 months following participation. Smoking status, symptoms of anhedonia, days since last drink, and race were related to relapse status. In addition, differential BOLD signal was detected in medial frontal and bilateral inferior frontal regions during the reward and cue tasks. Specifically, relapsers had blunted activation to monetary rewards (gain vs no gain) compared with abstainers. Conversely, relapsers demonstrated heightened activation to alcohol cues (alcohol vs neutral) compared with abstainers. Demographics, social and psychiatric symptoms classified 77% of the sample into treatment outcome groups. When neuroimaging metrics where added to the model, classification increased to 85%. Identification of predictors of relapse in Veterans with AUD is critical in improving treatment outcomes for those at highest risk. Modifiable risk factors were identified, and adding neuroimaging response increased classification ability by 8%. Future studies are needed to replicate these findings in a larger sample and clinical trials are needed to understand which interventions will help those most likely to relapse.

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POSTER 13: Multi-Modal MRI Data Fusion Reveals Interactions between Sex and Alcohol Use Disorder in Brain Structure Related to Social Processing

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Abstract. Prior neuroimaging investigations of brain structure in individuals with alcohol use disorder (AUD) suggest that men with AUD have greater alterations in brain structure than women, although findings are equivocal. The present study aims to assess sex differences in gray and white matter structural architecture in individuals with AUD via data fusion of multi-modal magnetic resonance imaging (MRI) data. Methods and Data: Human Connectome Project data from participants with AUD (N=129, 63F/66M) and matched controls (N=125, 67F/58M) were examined in this study. Indices of white matter integrity, e.g. fractional anisotropy, mean diffusivity, and tensor mode, were calculated from diffusion images (using FSL). Gray matter density (GM; FSLVBM), cortical thickness (CT; Freesurfer), and pial surface area (PSA; Freesurfer) were calculated from T1 images. All six features were included in a linked independent component analysis to identify 50 multi-modal spatial patterns and their participant-level strengths (loadings). Three components associated with AUD diagnosis (uncorrected) were subsequently assessed for AUD x Sex interactions using PALM non-parametric permutation testing ($p<0.05$, corrected for family structure). Results: Two multi-modal components showed a significant interaction, with AUD men having the highest loadings on both patterns, and AUD women showing a weaker effect in the same direction. The first component (interaction $p=0.009$) reflected greater GM and PSA among anterior temporal, ventral prefrontal, insula, hippocampus, and angular gyrus, reduced GM in fusiform and temporo-occipital areas, and reduced integrity of inferior fronto-occipital fasciculus (IFOF). The second component ($p=0.01$) reflected greater GM and PSA among lateral orbitofrontal and temporal regions, reduced GM in ventromedial striatum and regions overlapping with dorsal attention network, reduced CT in ventral insula and dorsal anterior cingulate, and reduced integrity of cingulum and IFOF. Both components were associated with age of first alcohol use and impulsivity ($p<0.05$, uncorrected). Conclusions: Participants with AUD show alterations in structural architecture of spatially distributed brain regions previously shown to support social processing, with greater effects in AUD men. Associations of these effects with drinking age of onset suggest observed effects may be related to sex differences in brain development co-occurring with onset of alcohol drinking. Further work will investigate associations between these patterns and social function/social cognition. Support: NIAAA R21 AA024565 and NIHM K00 MH119603.
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POSTER 14: Alcohol Use and Responses to Anti-drinking Messages among Emerging Adults: an fMRI Study

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Abstract. Among youth, most alcohol is consumed by binge drinking, and two out of three young adults report binge drinking in the past month. Some will transition out of risky drinking behavior, while others will maintain/exacerbate use into adulthood. Public health campaigns depicting the negative consequences of drinking have shown some efficacy at reducing this behavior. However, substance use in dependent individuals is governed by automatic/habitual responses to drug cues rather than the consequences. Here we studied how young adults who binge drink (≥1 day past month) responded to messages about the health and social consequences of drinking in an online study (N=100, 50F, 23±1.7yr.) and a separate fMRI study (N=19, 12F, 20.8±1.9yr.). In the online study, intent to binge drink decreased pre- to post-task ($p<.001$). Youth who rated antidrinking messages as more effective showed a greater reduction in intent to binge drink ($p=.026$). Reduction in intent to binge drink was maintained at one month follow up ($p<.001$). Finally, past month drinking frequency was reduced at one month ($p<.001$), and was related to the reduction in intent to binge drink from pre-task to one month ($p=.001$). In the fMRI study, young adults first completed a drinking cue-reactivity task (i.e., alcohol-related images) and then completed a task in which the drinking cues were paired with antidrinking messages (simultaneous audio/text). Intent to binge drink decreased pre- to post-fMRI ($p=.002$). Activity in the ventral striatum –a brain region implicated in reward processing –decreased between drinking cues and cues paired with antidrinking messages ($p=.034$). This decrease was less pronounced in young adults who had reported higher past month drinking quantity ($p=.017$; controlling for sex/gender, $p=.02$). Reduction in intent to binge drink was maintained at one month follow up ($p=.001$), and there was a reduction in past month drinking quantity at one month ($p=.037$). Finally, young adults who showed greater activity in the medial prefrontal cortex in response to antidrinking messages –a brain region implicated in processing message self-relevance –reported a greater reduction in drinking frequency at one month ($p=.049$). These findings may help to differentiate who is at risk for continued heavy drinking as adults and may inform interventions to reduce drinking among young adults.

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