3rd International Conference on

Applications of Neuroimaging to Alcoholism (ICANA-3)

PROGRAM

Yale SCHOOL OF MEDICINE

Center for the Translational Neuroscience of Alcoholism (CTNA)

3rd International Conference on Applications of Neuroimaging to Alcoholism
ICANA-3

February 16 – 18, 2013
Yale School of Medicine

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

Sponsored by:

NIAAA
National Institute on Alcohol Abuse and Alcoholism

With additional support from:

SIEMENS

Dear Colleagues,

Welcome to the "3rd International Conference on Applications of Neuroimaging to Alcoholism (ICANA-3)" as part of the NIAAA Center for the Translational Neuroscience of Alcoholism (CTNA) based at Yale University Department of Psychiatry!

Building on the success of past ICANA conferences, ICANA-3 will foster interest, career development, research and collaboration in this rapidly expanding area of neuroscience technology. The conference will bring together neuroimagers with diverse technical and clinical expertise to consider methodological applications to alcoholism research. A distinctive feature of the design of this meeting is its focus on multi-modality imaging (sMRI, DTI, fMRI, MRS, PET, SPECT), promoting interdisciplinary crosstalk. As with past conferences, ICANA-3 highlights "hot" issues in the field for special focus and emerging technologies within each neuroimaging modality.

We are delighted to welcome you to Yale, to discuss and promote 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
CTNA Director & ICANA-3 Chair

Yale Organizing Committee: Alan Anticevic, Phil Corlett, Kelly DeMartini, Elise Devito, Halppen Donoghoe, Elaine Horn, Hedy Kober, Graeme Mason, Stephanie O'Malley, Godfrey Pearlson, Aleksandar Savic, Shane Seger

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Saturday, February 16, 2013	
7:30 am to 8:30 am	**Registration & Continental Breakfast (TAC Upper Level Lobby)**
8:30 am to 8:40 am	**Welcome** John Krystal, CTNA Director, ICANA Chair, and Yale Department of Psychiatry Chair
8:40 am to 9:00 am	**Introduction from NIAAA** Kenneth R. Warren, NIAAA Acting Director
9:00 am to 10:00 pm	**Plenary Lecture: "Detecting Laminar Specific Neural Plasticity in the Rodent Brain with MRI"** Alan P. Koretsky, Director, Laboratory of Functional and Molecular Imaging, National Institute on Neurological Disease and Stroke
10:00 am to 10:15 am	**Break (Upper and Lower Level Lobbies)**
10:15 am to 12:45 pm	**Session I (MRS): "Neurochemical and Energetic Effects of Chronic Alcohol Consumption"** Graeme Mason, Yale University (Chair) Tim Durazzo, UCSF Gabriele Ende, Mannheim University Robert Thoma, University of New Mexico Natalie Zahr, Stanford University
12:45 pm to 1:45 pm	**Lunch and Poster Viewing (Upper and Lower Level Lobbies)** (#1-14)
1:45 pm to 4:15 pm	**Session II (fMRI): "Brain Mechanisms of Reward and Cognition as Substrates of Addictive Behavior"** Theodora Duka, University of Sussex (Chair) Hedy Kober, Yale University Trevor Robbins, Cambridge University Robert Rogers, Oxford University Susan Tapert, UCSD Reinout Wiers, University of Amsterdam
4:15 pm to 5:15 pm	**Posters** (#1-14)
6:00 pm	**1st Pre-arranged Transportation to Yale Peabody Museum***
6:30 pm	**2nd Pre-arranged Transportation to Yale Peabody Museum***
7:00 pm	**Reception at Yale Peabody Museum**

* Transportation leaves from New Haven Hotel (arranged transportation back to the hotel at 10:00 & 10:30 pm)

Sunday, February 17, 2013	
7:30 am to 8:45 am	**Registration & Continental Breakfast (TAC Upper Level Lobby)**
8:45 am to 9:00 am	**Welcome** Stephanie O'Malley, CTNA Co-Director; Director, Yale Div. of Substance Abuse
9:00 am to 10:00 am	**Plenary Lecture: "Acute and Chronic Effects of Alcohol on the Human Brain"** Nora D. Volkow, NIDA Director
10:00 am to 10:15 am	**Break (Upper and Lower Level Lobbies)**
10:15 am to 12:45 pm	**Session III (Imaging Genomics): "Structural & Functional Genomics of Alcoholism"** Godfrey Pearlson, Yale University (Chair) Hugh Garavan, University of Vermont David Glahn, Yale University Mary Heitzeg, University of Michigan Kent Hutchison, University of Colorado Dieter Meyerhoff, UCSF Marc Potenza, Yale University
12:45 pm to 1:45 pm	**Lunch and Poster Viewing (Upper and Lower Level Lobbies)** (#15-27)
1:45 pm to 4:15 pm	**Session IV (PET): "Imaging the Molecular Mechanisms of Vulnerability and Dependence with PET"** Anissa Abi-Dargham, Columbia (Chair) Kelly Cosgrove, Yale University Marco Leyton, McGill University Alexander Neumeister, NYU Karmen Yoder, Indiana University Henry Huang, Yale University David Nutt, Imperial College, London
4:15 pm to 5:15 pm	**Posters** (#15-27)
6.30 pm	**Informal Dinner (BAR Restaurant, 254 Crown St.)** Location is one block from the New Haven Hotel, see map.

Monday, February 18, 2013	
7:30 am to 8:30 am	**Continental Breakfast (TAC Upper Level Lobby)**
8:30 am to 8:45 am	**Welcome** John Krystal, CTNA Director, ICANA Chair, and Yale Department of Psychiatry Chair
8:45 am to 9:45 am	**Plenary Lecture: "Charting the Human Connectome"** David C. Van Essen, Chairman of Neurobiology, Washington University in St. Louis
9:45 am to 10:00 am	**Poster Awards**
10:00 am to 10:15 am	**Break (Upper and Lower Level Lobbies)**
10:15 am to 12:45 pm	**Topical Session: "A Translational Approach to Alcoholism: Understanding Addictive Goals and Habits via Computation, Representation and Neural Instantiation"** Philip Corlett, Yale University (Chair) Paul Fletcher, Cambridge University Michael Frank, Brown University Scott Grafton, UC Santa Barbara Nathaniel Daw, NYU Yael Niv, Princeton University
12:45 pm	**Discussion & ICANA Summary** John Krystal, CTNA Director, ICANA Chair, and Yale Department of Psychiatry Chair

PLENARY LECTURE

Detecting Laminar Specific Neural Plasticity in the Rodent Brain with MRI

Saturday, February 16

Speaker: Alan P. Koretsky, Director, Laboratory of Functional and Molecular Imaging, National Institute on Neurological Disease and Stroke, NIH, Bethesda, MD.

Dr. Koretsky received his B.S. degree from the Massachusetts Institute of Technology and Ph.D. from the University of California at Berkeley. He performed postdoctoral work in the NHLBI at NIH studying regulation of mitochondrial metabolism using optical and NMR techniques. Dr. Koretsky spent twelve years on the faculty in the Department of Biological Sciences at Carnegie Mellon University where he was the Eberly Professor of Structural Biology and Chemistry. In summer 1999, he moved to NINDS as Chief of the Laboratory of Functional and Molecular Imaging and Director of the NIH MRI Research Facility. Dr. Koretsky's laboratory is interested in two main areas. They are actively developing novel imaging techniques to visualize brain function and study the regulation of cellular energy metabolism combining molecular genetics with non-invasive imaging tools.

Abstract: Functional MRI techniques have found widespread use to measure brain neural circuits that are used for a large number of behaviors. When circuit activity changes due to plasticity, it remains a challenge to identify sites of synaptic changes responsible for the circuit level changes measured in the human brain. Of particular interest are the long range cortical rearrangements that have been detected in the human brain after injury. Rodent models that mimic some of these cortical rearrangements are being used to develop MRI techniques that may enable determination of the synaptic sites responsible for the plasticity. We have developed a model of adult cortical plasticity due to peripheral somatosensory nerve damage that is being used to develop MRI tools that can pinpoint sites of synaptic changes. Two weeks after peripheral denervation of one side of the forepaw, hindpaw, or whisker pathway there is a large up-regulation of cortical activity from the spared side and a large up-regulation of callosal inputs from the spared cortex to the cortical representation of the denervated area. A combination of functional MRI and laminar specific neural track tracing using manganese enhanced MRI predicted changes in thalamo-cortical inputs to layer IV that contribute to the up-regulation of cortical activity along the spared whisker barrel pathway. Slice electrophysiology confirmed that the thalamic inputs on layer IV stellate cells were strengthened by a post-synaptic mechanism. Sites of plasticity that explain the up-regulation of the callosal communication have also been studied with MRI. High temporal-spatial resolution fMRI demonstrates that up-regulation of the communication between the spared and denervated cortices likely occur through callosal inputs. These fMRI results are consistent with manganese enhanced MRI that predict a strengthening of inputs into layer 2/3 and 5. Taken together these results demonstrate that MRI is positioned to begin to give laminar specific information about mechanisms of cortical plasticity.

PLENARY LECTURE

Acute and Chronic Effects of Alcohol on the Human Brain

Sunday, February 17

Speaker: Nora D. Volkow, NIDA Director

Dr. Volkow attended the Modern American School, and earned her medical degree from the National University of Mexico in Mexico City. Her psychiatric residency was at New York University. Dr. Volkow spent most of her professional career at the Department of Energy's Brookhaven National Laboratory (BNL) in Upton, New York, where she held several leadership positions including Director of Nuclear Medicine, Chairman of the Medical Department, and Associate Director for Life Sciences. In addition, Dr. Volkow was a Professor in the Department of Psychiatry and Associate Dean of the Medical School at the State University of New York (SUNY)-Stony Brook. Dr. Volkow has published more than 530 peer-reviewed articles and written more than 80 book chapters and non-peer reviewed manuscripts, and has also edited three books on neuroimaging for mental and addictive disorders. Dr. Volkow became Director of the National Institute on Drug Abuse (NIDA) at the National Institutes of Health in May 2003. NIDA supports most of the world's research on the health aspects of drug abuse and addiction.

Abstract: Low to moderate doses of alcohol result in significant reductions in glucose metabolism in the human brain (range 10-30%) that are not associated with the behavioral effects seen with intoxication. Moreover, alcoholics show much greater reductions in regional brain glucose metabolism during intoxication than in healthy controls despite the fact that for the doses given the alcoholics in contrast to the controls showed no evidence of behavioral intoxication (Volkow et al., 1990). This led us to postulate that brain glucose metabolic decrements could reflect utilization of acetate as an alternative source of energy for the brain during alcohol intoxication. To test this hypothesis we separately assessed the effects of alcohol intoxication on brain glucose and on acetate metabolism using Positron Emission Tomography (PET). We found that alcohol intoxication significantly decreased whole brain glucose metabolism (measured with FDG) with the largest decrements in cerebellum and occipital cortex and the smallest in thalamus. In contrast, alcohol intoxication caused a significant increase in [1-11C]acetate brain uptake (measured as standard uptake value, SUV, which was used as marker of acetate metabolism), with the largest increases occurring in cerebellum and the smallest in thalamus. In heavy alcohol drinkers [1-11C]acetate brain uptake during alcohol challenge trended to be higher than in occasional drinkers ($p < 0.06$) and the increases in [1-11C]acetate uptake in cerebellum with alcohol were positively associated with the reported amount of alcohol consumed ($r=0.66$, $p<0.01$). That is the higher the reported alcohol intake the greater the brain [1-11C]acetate uptake. Our findings document that alcohol intoxication results in an increase in regional brain acetate uptake that is opposite to the decreases in regional brain glucose metabolism. Thus these findings support the hypothesis that during alcohol intoxication the brain may rely on acetate as an alternative brain energy source and provides evidence that heavy alcohol exposures may facilitate the use of acetate as an energy substrate. These findings raise the question of the potential therapeutic benefits that increasing plasma acetate concentration (ie ketogenic diets) may have in alcoholics undergoing alcohol detoxification.

PLENARY LECTURE

Charting the Human Connectome

Monday, February 18

Speaker: David C. Van Essen, Chairman of Neurobiology, Washington University in St. Louis.

Dr. Van Essen received his undergraduate degree in Chemistry in 1967 from Caltech and his graduate degree in neurobiology in 1971 from Harvard. He was a postdoctoral fellow at Harvard under Drs. David Hubel and Torsten Wiesel and did additional postdoctoral work in Norway and England before returning to Caltech in 1976. He was a faculty member in the Division of Biology at Caltech until 1992, during which time he served as Executive Officer for Neurobiology (1982-1989) and Option Representative for the Computation and Neural Systems program (1986-1991). In 1992 he became Edison Professor of Neurobiology and Head of the Department of Anatomy and Neurobiology at Washington University School of Medicine. Dr. Van Essen is currently Edison Professor and Head of the Anatomy & Neurobiology Department at Washington University in St. Louis. He has served as Editor-in-Chief of the Journal of Neuroscience, founding chair of the Organization for Human Brain Mapping, and President of the Society for Neuroscience. He is a fellow of the AAAS and has received the Peter Raven Lifetime Achievement Award from the St. Louis Academy of Science and the Krieg Cortical Discoverer Award from the Cajal Club. He and his colleagues have developed powerful new techniques in computerized brain mapping to analyze these visual areas in humans as well as nonhuman primates. This work includes the continued development of an integrated suite of software tools for surface-based analyses of cerebral cortex. These methods are applied to the analysis of cortical structure and function in humans, monkeys and rodents. A broad objective is to develop probabilistic surface-based atlases that accurately convey commonalities as well as differences between individuals.

Abstract: Recent advances in noninvasive neuroimaging have set the stage for the systematic exploration of human brain circuits in health and disease. One such effort is the Human Connectome Project (HCP), which will characterize brain circuitry and its variability in healthy adults. A consortium of investigators at Washington University, University of Minnesota, University of Oxford, and 7 other institutions is engaged in a 5-year project to characterize the human connectome in 1,200 individuals (twins and their non-twin siblings). Information about structural and functional connectivity will be acquired using diffusion MRI and resting-state fMRI, respectively. Additional modalities will include task-evoked fMRI and MEG/EEG, plus extensive behavioral testing and genotyping. Advanced visualization and analysis methods will enable characterization of brain circuits in individuals and group averages at high spatial resolution and at the level of functionally distinct brain parcels (cortical areas and subcortical nuclei). Comparisons across subjects will reveal aspects of brain circuitry which are related to particular behavioral capacities and which are heritable or related to specific genetic variants. Data from the HCP will be made freely available to the neuroscience community. A user-friendly informatics platform will enable investigators around the world to carry out many types of data mining on these freely accessible, information-rich datasets. Altogether, the HCP will provide invaluable information about the healthy human brain and its variability. It will also set the stage for characterizing abnormal brain connectivity in a variety of brain disorders and diseases.

SESSION I (MRS)
Neurochemical and Energetic Effects of Chronic Alcohol Consumption

Saturday, February 16

Chair: Graeme F. Mason, Ph.D. Professor of Diagnostic Radiology and Psychiatry, Yale University, School of Medicine

Graeme Mason's research focuses on quantitative neurochemical studies of the brain, particularly with respect to energetic and amino acid neurotransmission. Professor Mason received his Ph.D. in 1991 in Molecular Biophysics & Biochemistry at Yale University, where he studied MRS methodology and quantitative studies of brain metabolism under Professor Robert Shulman. After a postdoctoral traineeship with Hoby Hetherington and a brief faculty stint at the University of Alabama at Birmingham, he was recruited back to Yale in 1997 by Professor John Krystal, who introduced Dr. Mason to Psychiatry, in particular the field of alcohol research. Dr. Mason applies magnetic resonance spectroscopy and metabolic modeling to study acute and chronic effects of alcohol and nicotine on the brain, in addition to collaborative studies in other psychiatric conditions.

Timothy C. Durazzo, Ph.D. Assistant Professor, Department of Radiology and Biomedical Imaging, University of California, San Francisco, Center for Imaging of Neurodegenerative Diseases, San Francisco VA Medical Center

Timothy C. Durazzo, Ph.D. is an Assistant Professor in the Department of Radiology and Biomedical Imaging. His research focuses on employing magnetic resonance methods and neuropsychological assessment to better understand how chronic cigarette smoking and alcohol use disorders affect human brain biology and function in several populations. Dr. Durazzo is also interested in combining the use of magnetic resonance neuroimaging methods and neuropsychological assessment to assist in identifying the biological and cognitive factors that contribute to relapse in alcohol dependence and other forms of substance abuse.

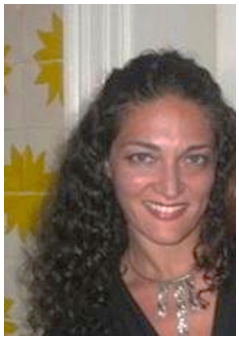
Gabriele Ende, Dr. rer. nat. Provisional head of the Department of Neuroimaging, Central Institute of Mental Health, Mannheim, University of Heidelberg, Germany

Gabriele Ende is a Provisional head of the Department of Neuroimaging, Central Institute of Mental Health in Mannheim, Germany. She received the title of Dr. rer. nat. in physics at the Ruprecht-Karls-Universität Heidelberg in 1993. Dr. Ende was a Postdoctoral Fellow at the University of California, San Francisco, USA. In 2005 she attained habilitation in Medical Physics at the University of Heidelberg, Medical Faculty in Mannheim,

Germany. Her research interests include magnetic resonance research in psychiatry using MR spectroscopy/spectroscopic imaging, morphometry, functional MRI, real-time fMRI, hyperscanning, as well as diffusion tensor imaging. Dr. Ende wrote 61 original papers, 6 reviews, 4 book chapters, more than 150 reviewed abstracts.

Robert J. Thoma, Ph.D. Associate Professor and Clinical Neuropsychologist, University of New Mexico School of Medicine, Department of Psychiatry, Center for Neuropsychological Services

Robert J. Thoma, Ph.D. is an Associate Professor specializing in clinical neuropsychology in the University of New Mexico Department of Psychiatry. He also serves as an Associate Research Scientist at the nearby MIND Research Network neuroimaging facility. He has an active neuropsychology and neuroimaging research lab, and current projects include studies the effect of alcohol on brain structure and function, and the study of neurodevelopmental changes in adolescents who abuse alcohol and other substances. His current research involves an investigation of the neural substrates of auditory verbal hallucinations; a project that is supported by a grant from NCATS COBRE mechanism (P20RR021938).



Natalie M. Zahr, Ph.D. Research Scientist, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine; Neuroscience Department, SRI International

Natalie M. Zahr, Ph.D. is a research scientist at Stanford University and SRI International. Her graduate education in the basic sciences included the study of neuro- anatomy, physiology, and pharmacology. After she completed graduate training as an electrophysiologist, she began postdoctoral training as a magnetic resonance imaging (MRI) scientist. Her work currently focuses on translational approaches using in vivo MR imaging and spectroscopy in studies of human alcoholics and rodent models of alcoholism with the goal of identifying mechanisms of alcohol toxicity on the brain.

SESSION II (fMRI)

Brain Mechanisms of Reward and Cognition as Substrates of Addictive Behavior

Saturday, February 16

Chair: Theodora Duka, M.D. Ph.D. Professor of Experimental Psychology, Behavioural and Clinical Neuroscience group, School of Psychology, University of Sussex, United Kingdom

Theodora Duka is since 2000 Professor of Experimental Psychology in the Behavioural and Clinical Neuroscience group of School of Psychology in University of Sussex. She was elected to be President of the European Behavioural Pharmacology Society (2013-2015), currently appointed as president elect. Her work focusing in translating ideas and methodologies from animals to humans has been influential in particular with regard to research in addictive behaviours. Dr. Duka's investigations early in her career led to the first demonstration of a relationship between benzodiazepines and endogenous opiate systems, which has generated twenty years of research effort. During 10 years in the pharmaceutical industry in the sector of clinical psychopharmacology, she was involved in the study of the mechanisms underlying memory impairment. Her current work focuses on the brain mechanisms underlying the acute effects of alcohol on cognition and emotional sensitivity in social drinkers and the long term effects of alcohol on the same aspects in binge drinkers and alcoholics. She uses functional and structural imaging to reveal these mechanisms. Her work is supported by the Medical Research Council the Biotechnology and Biological Sciences Research Council, the European Commission and the National Institute of Health.

Hedy Kober, Ph.D. Assistant Professor of Psychiatry and Psychology, Yale University

Hedy is an Assistant Professor of Psychiatry and Psychology at Yale University. She was born and raised in Israel, and began her undergraduate studies at the University of Tel Aviv at age 16. After she completed her mandatory service in the Israeli Defense Forces she moved to NY and completed her undergraduate degree at Columbia University. She then completed her Ph.D. at Columbia University's Social, Cognitive and Affective Neuroscience (SCAN) Unit in the Psychology department in 2009. Subsequently, she joined Yale University's Psychiatry department, where her lab explores issues related to cognition-emotion interaction in substance use disorders and treatment, with a focus on regulation of craving.

Trevor W. Robbins, CBE FRS FMedSci FBrPS Ph.D. Professor of Cognitive Neuroscience, Head of Department, Department of Psychology, University of Cambridge, United Kingdom

Trevor was appointed in 1997 as Professor of Cognitive Neuroscience and elected to the Chair of Expt. Psychology (and the Head of Department of the recently-formed Department of Psychology) at the University of Cambridge from October 2002. He was Chairman of the MRC Neuroscience and Mental Health Board from 1996-1999. He has been President of the British Neuroscience Association (2008-2010), the British Association for Psychopharmacology (1994-1996) and the European Behavioural Pharmacology Society (1992-1994), winning the latter Society's inaugural Distinguished Scientist Award in 2001. He also co-shared the IPSEN FONDATION 'Neuroplasticity Prize' in 2005 and gave the F. Kavli Distinguished International Lecturer at the Society for Neuroscience meeting in the same year. He recently received the prestigious Distinguished Scientific Contribution Award for 2011 by the American Psychological Association. He has published about 700 full papers or chapters, and has an H index of about 136. Currently, he directs the MRC/Wellcome Trust-funded 'Behavioural and Clinical Neuroscience Institute', the mission of which is to enhance translation from basic to clinical neuroscience. His interest in this area began with his co-invention of the CANTAB computerised neuropsychological battery which is currently used in over 500 institutes and clinical centers world-wide.

Robert D. Rogers, DPhil, CPsychol. Professor of Cognitive Neuroscience, Department of Psychiatry, Department of Experimental Psychology, University of Oxford, United Kingdom

Robert Rogers is an experimental psychologist, with a background in cognitive psychology and cognitive neuroscience. Robert holds a Ph.D. in Cognitive Psychology from Cambridge University. His post-doctoral research, also Cambridge, investigated neuropsychological impairments associated with orbitofrontal dysfunction in substance misuse. Robert was appointed University Lecturer in (non-clinical) psychology of the Department of Psychiatry at Oxford University in 1999 and Professor in Cognitive Neuroscience in 2007. He is a Senior Research Fellow at Jesus College, Oxford and is also a chartered psychologist with the British Psychological Society (BPS). In September 2013, he is moving to the School of Psychology at the Bangor University, North Wales. Currently, Robert's research group is investigating the psychological and neural mechanisms associated with behavioural addictions, such pathological gambling, as well as substance-related addictive disorders. These experiments involve a mixture of cognitive testing, brain-imaging and pharmacological techniques. Much of this work is focused upon the role of mood disturbances in these illnesses. Other work is examining how disturbances in neuromodulator activity influence social behaviour and play a role in the social isolation that enhances the likelihood of psychological distress.

Susan F. Tapert, Ph.D. Professor of Psychiatry, University of California, San Diego

Dr. Tapert's research focuses on brain functioning in adolescents with substance use disorders, using magnetic resonance imaging (MRI), functional MRI, diffusion tensor imaging, and neuropsychological testing. She also evaluates brain functioning in youth at risk for substance use disorders, typical adolescent brain development, and gender differences. Recent work has focused on longitudinal relationships between brain functioning and the progression of substance involvement, including the formation of alcohol and drug expectancies, coping skills, and brain response to substance-related stimuli to investigate the neural substrates of cue reactivity and craving. She has been awarded ten research grants from the National Institutes of Alcohol Abuse and Alcoholism and the National Institute on Drug Abuse, in 2008 was honored with the APA Division 50 Distinguished Scientific Early Career Contribution Award, and in 2010 was elected to Fellow status in the American Psychological Association. Dr. Tapert is Chief of the Psychology Service in the VA San Diego Healthcare System, and a clinical psychologist licensed in the state of California.

Reinout W. Wiers, Ph.D. Professor of Developmental Psychopathology, University of Amsterdam, Netherlands

Dr. Wiers' research focuses on increasing the understanding into the (neuro-) cognitive processes involved in the etiology of addiction and related disorders and to use this knowledge to develop interventions. Dr. Wiers' work on implicit cognitive processes in addiction is internationally known. Dr. Wiers' published well over 100 international papers and many chapters, mostly on this subject and received the prestigious VIDI (2002) and VICI (2008) research grants from the Dutch National Science Foundation (N.W.O.) for research on implicit cognition and addiction. Together with his colleagues, Dr. Wiers developed the alcohol-related approach avoidance task (AAT) as a novel measure of automatic, implicit appetitive tendencies toward alcohol. Based on the AAT, his group subsequently developed automatic action tendency retraining as an implicit intervention designed to reduce appetitive tendencies toward alcohol and thereby decrease alcohol consumption in students, and increase abstinence in alcoholic patients. His group also conducted the first randomized clinical trial on attentional re-training in alcoholism, and conducted research on neurocognitive predictors of trajectories of addiction, as well as on the effects of various novel interventions for addiction.

SESSION III (IMAGING GENOMICS)
Structural & Functional Genomics of Alcoholism

Sunday, February 17

Chair: Godfrey D Pearlson, MBBS, M.D. Professor of Psychiatry and of Neurobiology, Yale University, School of Medicine

Dr. Pearlson is currently founding director of the Olin Neuropsychiatry Research Center, a 50-person organization consisting of 4 component labs. The Center specializes in the translational neuroscience of major mental illness, including dementias, mood disorders, substance abuse, schizophrenia and psychotic bipolar disorder, PTSD, autism and other conditions spanning childhood to old age. Dr. Pearlson's research uses neuroimaging as a tool to address a broader array of questions regarding the neurobiology of major mental disorders, primarily psychosis and substance abuse. Dr. Pearlson is a current NIMH MERIT awardee and holds six R01 grants from NIAAA, NIDA and NIMH. He has been awarded a NARSAD distinguished investigator award and a Michael visiting professorship from the Weizmann Institute. He is published ~275 peer-reviewed research articles. He is also co-founder of the annual BrainDance competition for high school and college students across New England. These competitive awards encourage students to gain knowledge about psychiatric diseases and to develop a more tolerant and realistic perspective towards people with severe psychiatric problems.

Hugh Garavan, Ph.D. Associate Professor, Departments of Psychiatry and Psychology, University of Vermont

Hugh Garavan received his undergraduate degree in Psychology from University College Dublin in Ireland and his Ph.D. in Cognitive Psychology from Bowling Green State University in Ohio. He held postdoctoral positions at Cornell University and the Medical College of Wisconsin before a faculty appointment at Trinity College Dublin. He returned to the US in January 2011 where is an Associate Professor in the Departments of Psychiatry and Psychology at the University of Vermont. His research employs functional and structural brain imaging to study cognitive and reinforcement-related processes and his primary clinical interest is human addiction.

David C. Glahn, Ph.D. Associate Professor of Psychiatry, Olin Neuropsychiatry Research Center, Yale University

The research focus of Dr. Glahn's laboratory is on the genetics of brain structure and function. Their goals include elucidation of the neurobiological roots of major mental illnesses through the integration of cognitive neuropsychological, functional and structural neuroimaging, and behavioral and molecular genetic approaches. The ultimate goals of this

research is the identification of genes involved in affective and psychotic illnesses as well as genes that influence non-pathological brain structure and function. Localization of genes involved in mental illness should significantly contribute to an understanding of the underlying biology of these complex diseases, which in turn should improve future treatments and create the potential for prevention strategies.

Mary M. Heitzeg, Ph.D. Assistant Professor, Department of Psychiatry, Addiction Research Center, University of Michigan

Mary M. Heitzeg is Assistant Professor in the Department of Psychiatry and the Addiction Research Center at the University of Michigan. Dr. Heitzeg received her Ph.D. in Biological Psychology from the University of Michigan and completed her postdoctoral training at the Addiction Research Center. Her primary research focus is on developmental neuroimaging targeted at investigating genetic, neuropsychological and behavioral risk factors for substance abuse and the effects of alcohol and other drugs on the developing brain. Dr. Heitzeg is the recipient of the 2010 NIDA Early Career Investigator award from the Division of Clinical Neuroscience and Behavioral Research for her work during her Mentored Research Scientist Development award on functional brain endophenotypes modulating vulnerability to substance abuse. She developed and leads the neuroimaging component of the ongoing Michigan Longitudinal Study, a prospective, high-risk study of the emergence of risk and the development of alcohol abuse, dependence, and related symptomatology.

Kent Hutchison, Ph.D. Professor, Psychology & Neuroscience Department, CU, Director of Clinical & Population Neuroscience, Intermountain Neuroimaging Consortium, CU, Director of Neuroscience Core, Mind Research Network, New Mexico

Dr. Hutchison received a Ph.D. in clinical psychology in 1995 from Oklahoma State University and then completed four years of postdoctoral training in addiction research at Brown University. He joined the psychology department at the University of Colorado in 1998 as an assistant professor. Currently, Dr. Hutchison is the Chief Science Officer at the Mind Research Network and a Professor of Psychology and Neuroscience at the University of Colorado. Dr. Hutchison's program of research is focused on integrating neuroimaging and genetic approaches to the study of addiction in order to identify biomarkers that may be used predict the success of current treatment approaches or may be used to develop new treatments for addiction. Dr. Hutchison is involved in teaching and mentoring at the undergraduate, graduate, and post graduate levels and has a very active program of research with several grants from NIH, mostly focused on alcohol and tobacco dependence.

Dieter J. Meyerhoff, Dr. rer. nat., Professor in Residence, Department of Radiology and Biomedical Imaging, UCSF and VA Medical Center San Francisco

Dr. Meyerhoff is Professor in Residence in the Department of Radiology and Biomedical Imaging at the University of California San Francisco. He received his Ph.D. in Chemistry from the Westfaelische-Wilhelms-Universitaet in Muenster, Germany. He received postdoctoral training in NMR spectroscopy at the University of California, Berkeley, and then joined the Department of Radiology at the University of California San Francisco in 1987 and the department's faculty there in 1993. He has been a founding member of the Center for Imaging of Neurodegenerative Diseases (CIND) at the VA Medical Center in San Francisco and has Senior Investigator status at the SF VA. Dr. Meyerhoff has been investigating the effects of substance abuse (alcohol, cocaine, tobacco) on the brains of treatment-seeking and community-based populations, using various in-vivo MR methods, cognitive testing, and genotyping. His primary focus is on the neurobiological recovery from brain injury in abstinent alcoholics, under special consideration of the comorbid effects of chronic smoking and other substance use disorders. His other research areas include neuroimaging of HIV infection, posttraumatic stress disorder, and Gulf War syndrome.

Marc N. Potenza, Ph.D. M.D. Professor of Psychiatry, Child Study and Neurobiology, Yale University, School of Medicine

Dr. Potenza is a board-certified psychiatrist with sub-specialty training and certification in addiction psychiatry. Currently, he is a Professor of Psychiatry, Child Study and Neurobiology at the Yale University School of Medicine where he is Director of the Problem Gambling Clinic, the Center of Excellence in Gambling Research, and the Women and Addictive Disorders Core of Women's Health Research at Yale. He is on the editorial boards of ten journals and has received multiple national and international awards for excellence in research and clinical care. He has consulted to the Substance Abuse and Mental Health Services Administration, National Registry of Effective Programs, National Institutes of Health, American Psychiatric Association and World Health Organization on matters of addiction. Dr. Potenza's research has focused on the neurobiology and treatment of substance and non-substance addictions and other disorders characterized by impaired impulse control, particularly the disorders characterized in DSM-IV as “Impulse Control Disorders Not Elsewhere Classified.” The majority of this work has focused on understanding clinical and neurobiological underpinnings of these disorders, and their co-occurrences with other mental health disorders, in order to advance prevention and treatment strategies. This work has involved a developmental perspective, with a focus on adolescence. Dr. Potenza's research has applied brain imaging, genetic, epidemiological and clinical trials methodologies to gain knowledge and improve prevention and treatment strategies for addictive disorders. This work has also involved a specific focus on gender and identifying potential intermediary phenotypes, like facets of impulsivity, that may in part explain the high rates of co-occurrence between impulse control disorders and other mental health conditions, and might represent novel targets for prevention and treatment strategies.

SESSION IV (PET)
Imaging the Molecular Mechanisms of Vulnerability and Dependence with PET

Sunday, February 17

Chair: **Anissa Abi-Dargham,** M.D. Professor of Clinical Psychiatry (in Radiology), Columbia University, Director of the Division of Translational Imaging, Director of Clinical and Imaging Research, Lieber Center for Schizophrenia Research, NYSPI

Dr. Abi-Dargham's research focus is on using molecular imaging techniques (SPECT and PET) to study the pathophysiology of schizophrenia, schizophrenia related spectrum disorders and addiction. Her work has resulted in seminal publications describing the complex alterations of dopamine transmission in schizophrenia and their relationship to clinical symptoms, cognition and response to treatment, as well as their interrelatedness to glutamate dysfunction in schizophrenia. The work with cortical D1 receptor has provided added rationale for testing D1 agonists in schizophrenia. A new direction for work in her imaging group now is dual diagnosis patients with comorbid schizophrenia and cannabis. Ultimately this work is relevant to developing biomarkers and more focused treatment interventions for these disorders. She received numerous awards, and published over 100 articles in major scientific journals. Dr. Abi-Dargham is Past President for the Brain Imaging Council for the Society of Nuclear Medicine and Associate Editor for Neuropsychopharmacology for Brain Imaging and she has a large portfolio of federal, charitable and industry funded studies, including a Translational Conte Center funded by NIMH for the study of "Dopamine Dysfunction in Schizophrenia".

Kelly P. Cosgrove, Ph.D. Assistant Professor, Departments of Psychiatry and Diagnostic Radiology, Yale University, School of Medicine

Kelly Cosgrove is an Assistant Professor in the Departments of Psychiatry and Diagnostic Radiology. She conducts PET and SPECT imaging studies in human subjects and in nonhuman primates examining the chemical changes that occur during the recovery from tobacco smoking and alcohol dependence. She also has a primary interest in investigating sex differences in brain chemistry and she collaborates on the use of PET imaging in other psychiatric disorders including schizophrenia and major depression.

Marco Leyton, Ph.D. Professor, Department of Psychiatry, William Dawson Research Chair, McGill University, Canada

Dr. Leyton is Professor of Psychiatry and a William Dawson Research Chair at McGill University, and immediate Past-President of the CCNP (Canadian College of Neuropsychopharmacology). The focus of his research is the neurobiology of addictions and addiction related disorders, particularly the search for pre-existing vulnerability traits. The studies use a combination of functional neuroimaging (PET/MRI), drug self-administration paradigms, and manipulations of monoamine synthesis.

Alexander Neumeister, M.D. Professor of Psychiatry and Radiology, New York University

Dr. Neumeister is a Professor of Psychiatry and Radiology and the Director of the Molecular Imaging Program for Mood and Anxiety Disorders, New York University Langone Medical Center (NYULMC). His work aims to evaluate brain mechanisms, which contribute to the development of major psychiatric disorders such as posttraumatic stress disorder, depression or addiction disorders. Using positron emission tomography (PET) as well as other functional and structural imaging modalities, his group aims to identify novel mechanisms in the etiology of these disorders with the possibility of finding novel targets that are suitable for treatment development and prevention strategies. He has been awarded numerous national and international awards, notably the Max Hamilton Award of the CINP, the A.E. Bennett Award of the Society of Biological Psychiatry and the 2012 ISTSS Robert S. Laufer, Ph.D., Memorial Award for Outstanding Scientific Achievement in PTSD.

Karmen K. Yoder, Ph.D. Assistant Professor, Center for Neuroimaging, Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis

Dr. Yoder's laboratory uses PET to examine the neurochemistry of psychiatric and neurological disorders, with an emphasis on the role of dopamine in cognitive processes in alcoholism and pain disorders. Within the field of alcohol research, Dr. Yoder investigates how the dopamine system differs in nontreatment-seeking alcoholics relative to social drinkers, with special focus on dopaminergic cognitive processes that may underlie the transition to hazardous drinking. Currently, the laboratory has NIAAA support to study dopamine release in response to positive prediction error - unexpected alcohol delivery – as a proxy for determining how dopamine codes for salience attribution to alcohol intoxication. Other ongoing funded projects include: characterizing the dopamine system in pain disorders with [18F]fallypride; methods development of quantitative approaches for [11C]PBR28 (a marker for neuroinflammation) in rodents and humans; and determination of changes in brain blood flow and metabolism in a mouse model of traumatic brain injury. Dr. Yoder works closely with faculty within the Indiana University Center for Neuroimaging, the NIAAA-supported Indiana Alcohol

Research Center, and the NIA-supported Indiana Alzheimer's Disease Center Neuroimaging Core. Currently funded collaborations include using RAC PET to study striatal dopamine responses to alcohol-related chemosensory cues in risky drinkers, determination of the temporal course of neuroinflammation (with [11C]PBR28) and amyloid deposition (with [11C]PiB) in normal aging, cognitive decline, and dementia, and using [11C]PE2I (a dopamine transporter ligand) to assess striatal dopamine neuron integrity in a rodent model of manganese exposure.

Henry Yiyun Huang, Ph.D. Associate Professor of Diagnostic Radiology; Co-Director of Yale PET Center & Director of Chemistry

Dr. Henry Yiyun Huang is an Associate Professor of Diagnostic Radiology, Yale School of Medicine and Co-director of the Yale PET Center. Dr. Huang's research is directed toward the development, validation and application of PET radiotracers to investigate psychiatric, neurologic and other diseases. His CNS PET tracer development work encompasses multiple neurotransmitter systems, such as the dopamine, serotonin, norepinephrine, glutamate, cannabinoid and opioid systems. His most recent contribution includes the first-in-human evaluation of selective agonist and antagonist radiotracers for PET imaging of the kappa opioid receptors.

David Nutt, DM, FRCP, FRCPsych, FSB, FMedSci Professor of Neuropsychopharmacology, Director, Neuropsychopharmacology Unit, Division of Brain Sciences, Imperial College, London, United Kingdom

David Nutt is currently the Edmund J Safra Professor of Neuropsychopharmacology and Head of the Centre for Neuropsychopharmacology in the Division of Brain Science, Dept of Medicine, Hammersmith Hospital, Imperial College London.
He is currently Chair of the Independent Scientific Committee on Drugs (ISCD) and Past-President of the European College of Neuropsychopharmacology (ECNP), Vice-President of the European Brain Council and President of the British Neuroscience Association. In addition he is a Fellow of the Royal Colleges of Physicians, of Psychiatrists and a Fellow of the Academy of Medical Sciences. He is also the UK Director of the European Certificate and Masters in Affective Disorders Courses and a member of the International Centre for Science in Drug Policy. He has edited the Journal of Psychopharmacology for over a decade and acts as the psychiatry drugs advisor to the British National Formulary. He has published over 400 original research papers, a similar number of reviews and books chapters, eight government reports on drugs and 26 books. Previously he has been member and Chair of the Advisory Committee on the Misuse of Drugs (ACMD – 1998-2009), President of the British Association of Psychopharmacology (BAP), member of the HEFCE/NHS Senior Lecturer Selection Panel and member of the MRC Neuroscience Board. Other previous national contributions include serving as the medical expert on the Independent Inquiry into the Misuse of Drugs Act (2000 Runciman report), and membership of the Committee on Safety of Medicines, the Committee on NHS drugs and the Ministry of Defence Science Advisory Board. He was the clinical scientific lead on the 2004/5 UK Government Foresight initiative "Brain science, addiction and drugs" that provided a 25-year vision for this area of science and public policy and in 2006 he was Director of Bristol Neuroscience.

TOPICAL SESSION

A Translational Approach to Alcoholism: Understanding Addictive Goals and Habits via Computation, Representation and Neural Instantiation

Monday, February 18

Chair: **Philip R. Corlett,** Ph.D. Assistant Professor of Psychiatry, Yale University, School of Medicine

Dr. Philip Robert 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 Ph.D. 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 has continued to explore the cognitive and biological mechanisms of delusional beliefs as well as predictive learning, habit formation and addiction.

Paul Fletcher, Ph.D., M.R.C.Psych Bernard Wolfe Professor of Health Neuroscience, department of Psychiatry, University of Cambridge, United Kingdom

Paul Fletcher trained in medicine before taking a Ph.D. in cognitive neuroscience. He was elected to the Bernard Wolfe Professorship of Health Neuroscience, University of Cambridge, in 2008 and was also awarded a Wellcome Trust Senior Clinical Fellowship in Clinical Science. His clinical work is on Huntington's Disease and psychosis. His research uses combinations of functional neuroimaging and psychopharmacological manipulations to explore the brain basis of disturbances in learning, inference, motivation and decision-making. Early work developing an understanding of the contributions of the frontal lobes to human learning were followed by a series of studies aimed at furthering understanding of dynamic brain responses during associative learning, demonstrating that key parts of the mesocorticolimbic system are disrupted in psychosis for both classical causal learning tasks and operant, reward-based learning. He has gone on to explore learning and motivational changes that characterise the health-harming behaviours of hyperphagia and obesity. This has led to collaborations with metabolic physicians, aiming at drawing together neurobehavioural insights from hyperphagic patients who have undergone sophisticated metabolic characterisation but in whom reward-related behaviour has been only sparsely studied.

Michael J. Frank, Ph.D. Associate Professor, Brown Institute for Brain Science at Brown University

Michael J. Frank is Associate Professor of Cognitive, Linguistic & Psychological Sciences and Psychiatry in the Brown Institute for Brain Science at Brown University. He directs the Laboratory for Neural Computation and Cognition. He received an undergraduate degree in Electrical Engineering at Queen's University (Canada), followed by a Master's degree in biomedicine Engineering at the University of Colorado at Boulder, where he went on to receive a Ph.D. in Neuroscience and Psychology in 2004. His work focuses primarily on theoretical models of basal ganglia, frontal cortex 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 by empirical studies using a variety of methods. Received the Cognitive Neuroscience Society Young Investigator Award (2011) and the Janet T Spence Award for early career transformative contributions (APS 2010).

Scott Grafton, M.D. Professor, Department of Psychological & Behavioral Sciences, UC Santa Barbara

Scott Grafton is recognized for developing multimodal brain mapping techniques combined with state of the art bioengineering methods for accelerating discovery and diagnosis of the nervous system. He is associate director at the Institute for Collaborative Biotechnologies, which draws on bio-inspiration and innovative bioengineering solutions for both non-medical and medical challenges posed by the defense and medical communities. He received his M.D. degree from the University of Southern California and completed residencies in Neurology at the University of Washington and Nuclear Medicine at UCLA. He developed brain imaging programs at University of Southern California, Emory University and Dartmouth College. He joined the UCSB faculty in 2006 and directs the UCSB Imaging Center. He uses fMRI, magnetic stimulation and high density EEG to characterize the neural basis of goal directed behavior with an approach grounded in 20 years of clinical experience.

Nathaniel Daw, Ph.D. Associate Professor of Neural Science and Psychology, New York University

Nathaniel Daw is Associate Professor of Neural Science and Psychology and Affiliated Associate Professor of Computer Science at New York University. He received his Ph.D. in computer science from Carnegie Mellon University before conducting postdoctoral research at the Gatsby Computational Neuroscience Unit at UCL. His research concerns computational approaches to reinforcement learning and decision making, and particularly the application of computational models in the laboratory, to the design of experiments and the analysis of behavioral and neural data. He is the recipient of a McKnight Scholar Award, a NARSAD Young Investigator Award, a Scholar Award in Understanding Human Cognition from the MacDonnell Foundation, and the 2012 Young Investigator Award from the Society for Neuroeconomics.

Yael Niv, Ph.D. Assistant Professor, Princeton Neuroscience Institute & Psychology Department, Princeton University

Yael Niv is assistant professor of Psychology and Neuroscience at Princeton University. Her work utilizes computational models and empirical investigations of rat and human learning and decision making, as well as human neuroimaging, to investigate the processes of reinforcement learning in the brain. In particular, she is trying to understand how reinforcement learning occurs in tasks of real-world complexity: how do we learn with highly multidimensional stimuli, from tasks that have hierarchical or other hidden structure, and how do learning predispositions affect this process.

CONFERENCE SPEAKER SESSION ABSTRACTS

SESSION I (MRS)
Neurochemical and Energetic Effects of Chronic Alcohol Consumption

Acute and Chronic Energetic Effects of Alcohol on the Brain

[1,2]J. Wang; [2]L.H. Jiang; [2]G.F. Mason

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Abstract: Energetic effects of ethanol on brain may have implications for alcohol withdrawal via generation of adenosine and acetaldehyde. The liver converts ingested alcohol to acetate, which circulates in the blood and is oxidized in brain, generating adenosine, which is sedating. Ethanol oxidation generates acetaldehyde, which in brain is rewarding. Measuring 13C-glutamate and glutamine with 13C magnetic resonance spectroscopy (MRS) while infusing 13C-acetate or ethanol, we quantified brain acetate and ethanol oxidation. Study 1) 13C-acetate was infused in Heavy Drinkers (HD) and Light Drinkers (LD). At acetate levels like those from 2-3 drinks (1-2 mM), HD consumed more acetate (0.068±0.008 vs 0.046±0.005 mmol/kg/min; P=0.05) (6-10% of oxidative metabolism). Brain acetate consumption is increased by alcohol exposure. Study 2) Rats treated three weeks with alcohol vapor or room air were administered [2-13C]ethanol. 13C-acetate appeared in the blood, and chronically treated rats showed increased 13C consumption by brain ($p<0.01$), probably from circulating acetate. The brain consumes acetate from alcohol, and chronic exposure increases consumption. Study 3) Naïve and vapor-treated rats received co-infusions of [2-13C]ethanol and [1, 2-13C2]acetate, and doubly-labeled and singly labeled glutamate and glutamine were measured. Both groups had more GlnC4/GlnC45 and GluC4/Glu45 than AcC2/AcC12 ($p<0.001$), proving intracerebral Etoh oxidation. Brain ethanol oxidation was ~0.03 mmol/min/g, with chronic exposure increasing the glial component. Carbon from ethanol is consumed by the brain, primarily as acetate, and oxidation of both sources can be stimulated by chronic exposure. It may be important to consider substrate oxidation in the contexts of damage and withdrawal.

Chronic Cigarette Smoking in Healthy Controls and Alcohol Use Disorders: Effects on Regional Brain Metabolites.

Timothy C. Durazzo

Abstract: Chronic cigarette smoking in healthy controls and those with alcohol use disorders is associated with multiple neurobiological and neurocognitive abnormalities. The majority of neuroimaging studies have focused on structural measures. Proton magnetic resonance spectroscopic imaging (1H MRSI) enables the non-invasive quantitation of several metabolites from multiple brain regions. 1H MRSI permits the assessment of neurophysiological consequences of a disease/condition that may precede any associated gross morphological changes. The effects of chronic smoking on regional brain metabolites, and their associations with neurocognition, were evaluated with multislice 1H MRSI at 1.5T in healthy controls (CON) and treatment-seeking alcohol dependent participants (ALC). Smoking CON compared to non-smoking CON, showed a lower concentration of N-acetylaspartate (NAA: marker of neuronal integrity) in the frontal gray matter (GM) and white matter (GM), and higher creatine (Cr; marker of cellular bioenergetics) in the parietal WM, and choline (Cho; marker of membrane

turnover/synthesis) in the temporal WM. Higher frontal GM NAA was associated with better performance on multiple cognitive measures, while higher parietal WM creatine was related to poorer neurocognition. Never-smoking CON and never-smoking ALC had higher NAA concentrations than actively smoking ALC in the frontal and parietal GM and WM. Former-smoking ALC had NAA concentrations that were intermediate to never-smoking and actively smoking ALC. There were no differences between never-smoking CON and never-smoking ALC on any regional metabolite level. Overall, results indicated chronic smoking in both healthy controls and those with an alcohol use disorder were associated with neurometabolite abnormalities in multiple brain regions.

Metabolite Changes Associated With Various States of Alcohol Use, Abuse or Withdrawal in Humans and Rats

Gabriele Ende

Abstract: Introduction: There is a still growing literature on MRS detectable metabolite changes found in detoxified alcoholics. We tried to observe metabolite changes at various less extensively studied stages of alcohol use and abuse by investigating social light drinkers, non-treatment seeking heavy drinkers and alcohol dependent patients on the first day of withdrawal admitted to inpatient detoxification. In a translational approach we investigated a rat model of alcoholism. Methods: Human studies were conducted at 1.5T using MR spectroscopic imaging (TR = 1.8 s, TE = 135 ms, quantifying N-acetylaspartate and N-acetylaspartylglutamate (tNAA), choline-containing compounds (tCho) and creatine plus phosphocreatine (tCr)) and at 3T with single voxel MRS (TR = 3 s, TE = 80 ms, additionally quantifying glutamate (Glu)). Whereas animals were examined at 9.4 T using single voxel MRS (TR = 4s, TE = 12ms, quantifying various additional metabolite resonances). Results: In social drinkers we observed a significant positive correlation of alcohol consumption quantified by alcohol consumption timeline follow-back (TLFB) with frontal tCho values from MRSI measures. At 3T we corroborated a significant tCho difference between light social drinkers and subjects with heavy alcohol consumption in frontal white matter. Here we additionally quantified Glu and observed a negative correlation of Glu with the DSM IV sum scale for alcohol addiction. The lowest Glu was observed in heavy drinking subjects reporting a loss of control on time and amount of alcohol consumption. Finally, during withdrawal from alcohol patients exhibited elevated Glu in the anterior cingulate cortex. These findings are paralleled by the MRS findings in the rat model of alcoholism. Conclusions: Combined animal and human MRS studies seem to have a strong and valid translational component, essentially demonstrating that a given animal model is indeed relevant to the human condition and therefore useful for expanding mechanistic insight into psychiatric disorders.

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Divergent 1H-MRS Neurometabolite Profiles Associated with Risk and Consequences of Adolescent Alcohol Use Disorders.

R.J. Thoma, R.A.Yeo, and C. Gasparovic

Abstract: Introduction: Adolescence is a time of continuous and concurrent neural, cognitive, behavioral and emotional development. During this stage, adolescents are particularly susceptible to the neurotoxic consequences of alcohol and drug misuse. However, in order for researchers to determine the effects of substances of abuse on neural growth and development, it must first be determined what deficits may have been present prior to the initiation of substance use. Method:

To investigate the difference between risk and consequences of substance use, data were collected for three groups of adolescents; healthy minimally-drinking controls (N = 12; Control), healthy, minimally drinking controls who were children of at least one parent with an AUD (N = 12; High Risk), and a currently drinking group diagnosed with Alcohol Dependence (N = 15; AUD). Neurometabolite levels derived from 1H-MRS analyses included combined N-acetyl-aspartyl groups (NAA, associated with neuronal metabolism), combined creatine and phosphocreatine (Cre; reflecting energy metabolism), choline compounds (Cho, a marker of membrane breakdown), myo-inositol (mI, found in glial cells), glutamate (Glu; excitatory neurotransmitter), and glutamine (Gln; a metabolite of Glu). Form-90 percent days drinking, marijuana use, and tobacco use were used quantify drinking frequency. Behavioral Assessment Scales for Children (second edition, BASC-2) internalizing score, sex and age were considered as covariates. To maximize statistical power the non-drinking groups were combined (Control + High Risk), and the effect of high risk (High Risk+AUD=RISK) was represented by dummy codes. Two MANCOVAs covarying for age, sex, (BASC-2) internalizing score, and RISK were applied separately for gray and white matter neurometabolites. Follow-up analyses included partial correlations of the three substance abuse variables with selected neurometabolites linked with RISK or Group. Results: In the gray matter specific analysis, a significant main effect for group ($p = .033$) on neurometabolite concentrations was found ($p<.05$), with the most striking effect being higher NAA in the AUD group than in the non-drinkers. For the white matter specific analysis there was a significant main effect of group ($p = .01$) for neurometabolite concentrations. At a univariate level, the AUD group had significantly lower Glu than the non-drinkers. The effect of RISK was also significant, as high risk was associated with lower WM mI and higher Cre. Partial correlations (controlling for age, sex, RISK, and Internalizing) revealed these correlations of substance abuse variables with gray matter NAA drinking = .38 ($p < .05$), nicotine = .33 ($p = .06$), and marijuana = .38 ($p < .05$). partial correlations with white matter Glu: drinking = -.49 ($p < .01$), nicotine = -.47 ($p < .05$), and marijuana = -.32 ($p = .07$). Discussion: The AUD group had higher NAA than the non-drinkers, consistent with the findings of Bartsch et al (2007) and Yeo et al (2012), who proffered that higher NAA is associated with recent onset of abstinence. The negative correlation between substances of abuse and WM Glu levels suggest that lower WM Glu is an effect of AUD. In addition to its role as the brain's major excitatory neurotransmitter at synapses, Glu is known to also play a role in signaling between the axon and oligodendrocytes, which may be related to the regulation of myelin growth and repair (Kukley et al., 2007). Analyses suggest that increasing risk is characterized by lower WM mI and higher WM Cre. Reduction in mI may reflect osmoregulator dysfunction (Walecki et al, 2011), and increase in WM Cre suggests a role for energy metabolism in the development of AUD.

Translational Studies in Alcoholism: In Search of a Neuroimaging Biomarker for Alcohol Use Disorders

Natalie M. Zahr

Abstract: Magnetic resonance imaging (MRI) of human alcoholics and animal models of alcoholism can identify in vivo markers of the effects of alcohol on the brain. A concomitant of alcoholism is nutritional deficiency, especially for thiamine (vitamin B1). We validated a model of thiamine deficiency (TD) in the rat by replicating the in vivo neuroradiological signature observed in human Wernicke's Encephalopathy (WE), a syndrome precipitated by TD. Our animal model confirmed thiamine diphosphate (TDP) as a better predictor than thiamine of biologically relevant thiamine levels, a finding immediately translated for use in our human studies. Using indices of cell damage determined with proton MR spectroscopy (MRS), our animal models demonstrated a dissociable pattern between alcohol exposure and TD effects. Alcohol consistently caused an increase in the signal from choline-containing compounds (Cho), while TD resulted in lower Cho

levels suggesting that different mechanisms underlie the changes associated with TD relative to alcoholism. We determined whether meeting historical criteria for unsuspected WE explains why some human alcoholics have severe neuropsychological deficits, whereas others, with a similar drinking history, exhibit preserved performance. Neuropsychological performance of the alcoholic subgroups was graded, with those meeting zero criteria not differing from controls, those meeting one criterion presenting mild-to-moderate deficits on some of the functional domains, and those meeting two or more criteria having the most severe deficits on each of the domains examined. TDP levels were selectively related to memory performance in the alcoholics. A next challenge will be to test whether MRS-detectable Cho can discriminate subpopulations of human alcoholics.

SESSION II (fMRI)
Brain Mechanisms of Reward and Cognition as Substrates of Addictive Behavior

Brain mechanisms of behavioral changes associated with reward and behavioural control, promoting relapse in alcohol dependent individuals.

Theodora Duka

Abstract: In introducing the session on reward and cognition as substrates of addictive behaviours, I will present how alcoholic patients, as their alcohol dependence increases, become increasingly impaired in performing a task that captures two of the basic features of addictive behavior – cue-induced motivation to seek a reward, and failure to inhibit such motivation when reward seeking is inappropriate. Performance deficits in this task reflect alcohol-induced impairments in prefrontal subfields essential for regulating emotional conflict and subsequently for remaining in abstinence. I will also demonstrate how, under emotional challenge, multiple detoxified alcoholics show decrease in integration of neural networks in cortical regions responsible for a top-down emotional regulation, whilst integration of neural networks in sub-cortical regions, underlying a bottom up emotional input, is increased. The data in this presentation will add to our understanding of how addiction to alcohol develops to reach a severe inability to abstain.

Cognition-emotion interaction in Substance-Use Disorders: Regulation of Craving

Hedy Kober

Abstract: Craving has long been considered a key factor in substance use disorders, and recent findings have more clearly linked cue-induced craving and drug use. Specifically, craving has been shown to rise prior to drug use, to predict drug use, and to predict relapse after treatment. Theoretically, it has been suggested that diminished cognitive control over cue-induced craving may underlie compulsive drug taking. Clinically, the ability to regulate craving has been shown to reduce drug craving, drug use, and relapse after treatment. In the course of treatment, the acquisition of such skills is associated with better long-term outcomes, and instances of regulation of craving with cognitive strategies leads to greater treatment success. We developed a laboratory Regulation of Craving (ROC) task that allows us to directly measure cue-induced craving as well as ability to use regulation strategies during cue-induced craving. In this task, drug users are exposed to picture drug cues and, on alternating trials, are asked to use a cognitive regulation strategy drawn from cognitive-behavioral treatments during craving. We have shown that smokers of cigarettes, cocaine, and methamphetamines can use such strategies to reduce self-reported craving. Using fMRI, we have shown that such regulation of craving depends on recruitment of prefrontal regions associated with cognitive control (e.g., dlPFC, vlPFC) which in turn modulate subcortical regions associated with craving, emotion, and motivation (e.g., ventral striatum, subgenual cingulate). I intend to discuss the basic findings from this line of work, and how we are currently applying this to alcohol-use disorders.

Neurobehavioural phenotypes for stimulant abuse and addiction

Trevor W. Robbins

Abstract: I will review recent data relevant to the definition of risk factors, mainly for stimulant abuse and addiction, using structural and functional magnetic resonance imaging (MRI) (in

collaboration with KD Ersche, ET Bullmore and others). Compulsive stimulant abusers and their non-drug abusing siblings exhibit impairments in cognitive control (on the stop-signal reaction time task) concomitantly with reduced functional anisotropy in the vicinity of the right inferior frontal gyrus, as well as increased grey matter within the putamen and changes in the medial temporal lobe and the insular cortex. These findings of candidate neurobehavioral endophenotypes will be contrasted with recent results obtained in non-dependent recreational drug users, suggestive of two distinct phenotypes that do not suggest a common aetiology or trajectory towards dependence. Moreover, they will be compared with functional magnetic resonance studies showing: (i) different patterns of findings, as compared with structural MRI, for compulsive drug users and their siblings performing the stop-signal reaction time task, suggestive of functional compensations of deficits in cognitive control; and (ii) distinctive impulsivity neuroendophenotypes associated with the abuse of alcohol, nicotine and other drugs, as compared with incipient symptoms of attention deficit hyperactivity disorder, in an fMRI study of the stop-signal reaction time task in about 2000 healthy adolescents. Overall, these results contribute to our understanding of the antecedents, as well as the consequences, of stimulant drug abuse and may be readily related to recent data from preclinical models. Supported by the MRC, Wellcome Trust, and the E.U. FP-6 project, IMAGEN.

Mood Elevation, Risky Choice, Rewards and Alcohol

Robert D. Rogers

Abstract: Bipolar disorders (BDs) are associated with elevated lifetime prevalence rates of alcohol use disorders (AUDs). Recent research highlights how repeated experiences of elevated mood (hypomanic experiences) are common in young people and linked to alcohol use and increased rates of depression and anxiety. However, little is known about the link between these experiences, altered decision-making, and the processing of different rewards including alcohol. In this talk, I will review recent experimental evidence gathered in our laboratory that explores these connections. Our data show that individuals with hypomanic experiences report diminished subjective intoxication effects ('low-level-responses') compared with individuals without these experiences, while also reporting heightened expectations of alcohol's positive effects; potentially explaining increased alcohol misuse in this population. These latter expectations point towards broader changes in the consummatory processing of different kinds of rewards, rather than changes in action selection per se. Two fMRI experiments with large samples of young, unmedicated individuals (n= 80) with and without histories of mood elevation or positive diagnoses of BD-II/NOS show blunted BOLD amplitudes within the ventral striatum while processing positive monetary outcomes, and/or blunted amplitudes within the insula cortex while anticipating and processing reinforcement events. Collectively, our data suggest that mood elevation as part of a phenotype for BD or diagnoses of BD-II/NOS is associated with the disrupted representation of future rewards, and their value, within fronto-striatial-thalamic circuits in ways that enhance the likelihood of AUDs and substance use disorders.

This is Your Brain on Alcohol: Brain Function in Heavy Drinking Adolescents

Susan F. Tapert

Abstract: Alcohol and other drug use reach lifetime peak prevalence during late adolescence and early adulthood, as the brain is completing important neuromaturational processes. This session will present recent cross-sectional and longitudinal data highlighting neural features that may be linked to risk for subsequent heavy substance use, and indicators that heavy drinking during this period may alter some features of adolescent neurodevelopment. First, data from several

samples and tasks have suggested that lower levels of frontal activation during inhibition and working memory demands has been linked to greater probability of substance use initiation and progression in subsequent years. Second, youth who have initiated heavy episodic drinking show increasing levels of activation during cognitive tasks, as compared to youth who remained substance free and to their own activation levels evidenced prior to the initiation of drinking. Third, heavy substance using youth show enhanced response of the insular cortex during positively valenced interoceptive probes. Fourth, the enhanced reactivity evidenced by heavy drinking youth to alcohol stimuli appears to abate with abstinence.

Can we use brain function to predict the course of cannabis use towards dependence? Results and treatment implications from a prospective neuroimaging study.

[1]Reinout W Wiers, [1,2]Janna Cousijn, [1]Anna E Goudriaan, [1,3]K Richard Ridderinkhof, [2]Wim van den Brink, [2,4]Dick J Veltman

[1]Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands; [2]Amsterdam Institute for Addiction Research, Department of Psychiatry, Academic Medical Centre, University of Amsterdam, Amsterdam, the Netherlands3; Cognitive Science Center Amsterdam, University of Amsterdam, Amsterdam, the Netherlands; [4]Department of Psychiatry, VU-MC, Amsterdam, the Netherlands

Abstract: One in ten heavy cannabis users meets the DSM-criteria for cannabis dependence. Still, relatively little is known about the neural mechanisms involved in the transition from recreational toward compulsive cannabis use. Models of addiction suggest that strong automatically triggered motivations to use combined with sub-optimal regulatory functions play an important role in the development of addictive behaviors. With neuropsychological tasks and Functional Magnetic Resonance Imaging (fMRI) we investigated if we could use brain function to predict the course of cannabis use. Different motivational (craving, approach action tendencies) and regulatory processes (decision-making, working-memory) were compared between heavy cannabis users (n = 33) and matched controls (n = 42) and we investigated if these processes could predict cannabis use and related problems after six months. The results showed that a behavioural approach-bias towards cannabis, self-reported craving, and brain functionality during a monetary decision-making (Iowa Gambling Task) task and a working-memory task (N-Back) predicted escalation of cannabis use six months later. Together with a measure of baseline cannabis use, these measures together explained 87 percent of the variance in cannabis use six months later. In addition, functionality of the dorsolateral prefrontal cortex (DLPFC) and anterior frontal cortex (ACC) during approach and avoidance of cannabis stimuli was associated with a decrease in cannabis-related problems after six months. These results suggest that both motivational and regulatory processes play an important role in progression of cannabis use towards dependence. By studying neurocognitive predictors of the course of cannabis use towards dependence, one of the primary aims of this study was to identify new targets for prevention and treatment. This talk will therefore conclude with a discussion on the treatment implications for cannabis dependence and other substance use disorders (i.e., cognitive bias modification, working-memory training, neuro-modulation, pharmacological interventions).

SESSION III (IMAGING GENOMICS)

Structural & Functional Genomics of Alcoholism

Neuroimaging and Genetic Markers for Risk of Alcohol Use: Evidence from the Longitudinal IMAGEN Project.

Hugh Garavan

Abstract: The IMAGEN project is a multi-site neuroimaging study of 2,400 adolescents that includes extensive phenotyping and genotyping in eight sites in Ireland, England, Germany and France. Participants, all fourteen years of age, completed a motor response inhibition STOP task, which provides a measure of prefrontally-mediated cognitive control, and a Monetary Incentive Delay (MID) task, which provides measures of cortical and subcortical activity during reward anticipation and reward delivery. Analyses of the STOP task revealed reduced activation in orbitofrontal cortex in those adolescents who had experience with alcohol (approximately 60% of the sample). Notably, this effect was not related to the severity of alcohol use and, indeed, was observed in those participants who had no more than 4 drinks in their lifetimes, a result which is suggestive of a pre-existing trait that predisposed towards alcohol use at an early age. Conversely, right prefrontal activation showed elevated levels of activity, relative to alcohol-naïve controls, but only in those participants who had experience with alcohol, nicotine and other drugs. Activation in right prefrontal cortex also increased as a function of the extent of drug use, thereby suggesting that the alcohol-related effects in this area arose from use. Activity levels in this same right prefrontal region were also related to genetic variation in a norepinephrine transporter gene, with mediation analyses identifying allelic variation in norepinephrine to be related to brain activity which, in turn, was related to individual differences in inhibitory control performance. Ventral striatal activation during reward anticipation on the MID task was reduced in drinkers relative to alcohol-naïve participants. This effect was present in very light drinkers but was also related to the extent of drinking so may reflect a pre-existing trait and/or a dose-related neurotoxic effect. Follow-up data on alcohol use obtained two years later provides an opportunity to test for baseline neurobiological predictors of the transition to binge drinking. This presentation will discuss some of the considerable methodological and analytic challenges associated with this type of investigation. Initial results suggest that some of the effects that discriminated drinkers from non-drinkers at baseline also predict the transition to heavy alcohol use in those who reported no drinking at baseline. For example, activity related to reward anticipation in medial prefrontal cortex at baseline was lower in those participants who were binge drinking two years later compared to those who remained alcohol-naïve or who were relatively light drinkers two years later. Similarly, orbitofrontal activation on the STOP task at baseline was reduced in those who transitioned to heavier drinking relative to those who remained zero-to-low drinkers. Combined, these results suggest certain brain differences that precede alcohol use and might therefore be hypothesized to confer risk for alcohol use and other brain differences that are affected in a dose-response manner by use. The longitudinal nature of this research, combined with its large sample size, offers insights into the roles played by both cognitive control and reward-related processes that confer risk for, or arise from, early adolescent alcohol use.

Alcoholism's Effects on Neuroanatomy: Genetic and Environmental Influences

David C. Glahn

Abstract: Alcoholism is associated with pervasive brain shrinkage due to loss of gray and white matter volume. Although some of the alcoholism-related brain damage appears to be reversible with abstinence, some residual tissue deficits persist even in long-abstinent alcoholics. Yet, it is less clear if genetic factors play a roll in these neuroanatomical changes. That is, it is possible that the same genetic factors that predispose one towards alcoholism also influence the size of brain regions associated with the disorder. Here, we examined high-resolution MRI images from 872 Mexican-American individuals from extended pedigrees to determine if (1) individuals with a current (n=188) or past (n=109) alcoholism diagnosis showed aberrant subcortical volumes and (2) to determine if these volumes were also altered in their non-alcoholic relatives (n=348) or unrelated controls (n=227). We show reduced caudate and hippocampal volumes in current and past alcoholics compared to controls. Current, but not past, alcoholics show reduced accumbens and increased lateral ventricular volumes compared to controls. None of these anatomic differences were observed in unaffected relatives. These data suggest that while heavy drinking is associated with reduced subcortical volumes, these effects do not appear to be genetically mediated

The Impact of GABRA2 Genotype on Nucleus Accumbens Response to Incentive Stimuli from Adolescence to Young Adulthood

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Abstract: Associations have been found between GABRA2, a gene encoding the alpha 2 subunit of the γ-aminobutyric acid A receptor (GABAA), and alcoholism, as well as some of the strongest precursive risk factors for alcoholism, including childhood conduct disorder and externalizing behavior. These studies suggest that GABRA2 may be involved in alcoholism risk via a general externalizing pathway. Furthermore, it has been shown that the influence of GABRA2 on these behaviors may change across developmental stages. However, the neural mechanism through which GABRA2 influences risk remains largely unstudied. Drugs of abuse exert their reinforcing properties by activating the mesolimbic dopamine circuitry, which originates in the ventral tegmental area and projects to the nucleus accumbens. This pathway is regulated by GABAergic interneurons. We tested the hypothesis that GABRA2 genetic variation is linked to individual differences in nucleus accumbens response to salient stimuli. We investigated this across development from adolescence to young adulthood in a combined cross-sectional and longitudinal design. 60 youth were scanned at age 12-16 and 93 young adults were scanned at ages 18-21, 54 of whom were scanned again between the ages of 22 and 26. A modified monetary incentive delay task was used to probe nucleus accumbens functioning in response to incentive stimuli. SNPs rs279858 and rs279847 were genotyped by TaqMan using inventoried assays of primers and probes (Applied Biosystems, ABI Foster City, CA). Both SNPs were associated with nucleus accumbens response to incentive stimuli in the 12-16 year old sample (n=60) and in the 18 to 21 year old sample (n=93). In the subset of the young adults who underwent longitudinal scanning (n=54), the genotype effect was apparent at ages 18 to 21 but not at ages 22 to 26. This work uncovers a neural pathway through which GABRA2 genotype may influence risk for alcoholism and suggests a specific developmental period during which this influence may occur.

Alcohol Dependence: Leveraging Intermediate Phenotypes to Uncover Epigenetic Biomarkers

Kent E. Hutchison, Nicole Harlaar, Angela Bryan

Abstract: While the field has been focused on genetic research for some time, research designed to identify epigenetic biomarkers associated with course of addiction is relatively nascent. The etiology of alcohol dependence is related to changes in the neuronal systems involved in the anticipation of reward and executive control. Epigenetic variations that are associated with individual differences in these mechanisms may be important in terms of predicting the course of dependence as well as treatment outcomes. We recently developed an approach that leverages intermediate phenotypes to link epigenetic variation to changes in neuronal function and clinical measures. In a recent study, an exploratory epigenome wide analysis identified several promising DNA methylation sites that were associated with measures of alcohol dependence. These methylation sites are near the ALDH1A2, DRD2, and HTR3D genes. Additional analyses indicated that methylation at the ALDH1A2 CpG site is associated with the amount of time necessary to reach a target breath alcohol level during an ethanol infusion, the subjective experience of intoxication, and loss of white matter integrity, suggesting that this methylation site may be associated with metabolism of ethanol. CpG sites near the DRD2 and HTR3D genes are more strongly associated with responses to alcohol cues. In post-mortem samples, greater methylation of these sites was also associated with decreases in mRNA. Additional results from the epigenome wide analysis will also be presented.

Candidate Genotypical Influences on Neurobiology and Cognition in Recovering Alcoholics

Dieter J. Meyerhoff

Abstract: Neuroimaging and cognitive testing helps understand behaviorally relevant brain characteristics in individuals dependent on alcohol (ALC). The wide variance of neurobiological and neurocognitive measures in ALC as a group appears to be not only associated with substance use, life style and behavior, but it is also determined by genetics. Therefore, we have started to perform candidate genotyping for more comprehensive analyses of select determinants of neurobiology and cognition in alcohol dependence. Here, we will focus on the influence of BDNF (rs6265) and COMT (rs4680) genotype on neurobiology and cognition.

Cross-sectional analyses indicate that BDNF genotype does not affect the volumes of the major lobes in ALC during early abstinence; however, BDNF val/val had thicker cortices in critical components of the brain reward/executive oversight system (BREOS) than val/met and lower NAA, Cr, and Cho concentrations in lobar gray and white matter, subcortical structures, and top-down BREOS components. Over four weeks after drinking cessation, alcohol dependent BDNF val/val had greater longitudinal increases of frontal cortical volume than val/met, whereas BDNF genotype had the opposite effect on lobar white matter volume recovery. While COMT genotype did not predict any of these neurobiological measure in our ALC studies, alcohol dependent COMT Met carriers demonstrated better performance on measures of executive skills and general intelligence than COMT val homozygotes.

Our findings suggest that BDNF genotype contributes to the variance of brain structural and metabolic measures in ALC after correcting for drinking severity and to neurobiological recovery dynamics during abstinence and COMT genotype influences ALC neurocognition.

Genetic Influences on Motivational Neurocircuitry Function in Substance and Non-Substance Addictions

Marc N. Potenza

Abstract: Over the past decade, data have suggested similarities between non-substance-related psychiatric disorders and substance addictions, and these data have resulted in the proposal to classify pathological gambling with substance-use disorders in DSM-5. As an "addiction without the drug", pathological gambling thus offers a complementary comparison disorder that may help better understand addictive processes and the potential impacts of substances on brain substrates. In this presentation data describing similarities and differences between pathological gambling and drug dependence in brain structure and function will be described, as will data on how allelic variants relating to dopaminergic and noradrenergic function relate to the processing of emotional and motivational (craving/urge) cues in addiction. Implications for alcohol abuse and dependence will be discussed.

SESSION IV (PET)
Imaging the Molecular Mechanisms of Vulnerability and Dependence with PET

Imaging GABAA-Benzodiazepine Receptors During Acute and Prolonged Withdrawal from Chronic Alcohol Consumption

Kelly P. Cosgrove

Abstract: GABA receptors are the primary mechanism for modulating inhibitory synaptic transmission in the brain, and they play a central role in modulating the effects of ethanol in the central nervous system. Acute exposure to ethanol potentiates GABA-gated currents and long-term ethanol exposure significantly interferes with GABA transmission, function and neuronal excitability, mainly by reducing GABA inhibition, which is clearly evidenced by seizure activity during ethanol withdrawal. These alterations in GABA-ergic neurotransmission are associated with symptoms of alcohol tolerance, dependence and withdrawal. In vivo PET and SPECT studies consistently demonstrate lower GABAA-benzodiazepine receptor (GABAA-BZR) availability in alcohol dependent subjects at approximately 1 and 3 months withdrawal. We have conducted a translational study to investigate the changes in GABAA-BZRs during acute and prolonged withdrawal from chronic alcohol in alcohol dependent individuals and in an animal model of alcohol self-administration. Methods: Adult males with alcohol dependence were admitted to an inpatient unit for up to 1 month and participated in one MRI, and [123I]iomazenil SPECT scans at 1-3, 9-12 and 30 days after the last drink. Adolescent male rhesus macaques underwent baseline [11C]flumazenil PET scans and one MRI. Then, animals self-administered alcohol (up to 6 g/kg/day) for 5-6 months and were scanned at the following withdrawal time points: 1 day, 8 days, and 12 weeks. Emission scans were reconstructed, attenuation corrected, coregistered to template MRs and region-of-interest templates were applied. SPM analyses are being conducted. Results and Conclusions: Alcohol dependent humans (n=27) and age-matched controls (n=25) and 8 monkeys have been scanned and the data is currently being analyzed. Relationships between GABAA-BZR availability and characteristics of alcohol dependence will be examined. Findings from this study will determine the time course of GABAA-BZR changes during acute and prolonged withdrawal and the relationship to alcohol dependence correlates.

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Vulnerability to Addictions: Dopamine Studies in Humans

Marco Leyton

Abstract: Background: Animal studies suggest that dopamine neurotransmission influences responses to reward-related stimuli and susceptibility to drug-seeking behavior. The relevance of this work for humans, though, has been unclear. Methods: During the past 15 years, we have conducted a series of studies using positron emission tomography (PET) and acute phenylalanine/tyrosine depletion (APTD) to measure dopamine release and its behavioral significance. Results: The studies suggest that, in humans, abused drugs, across pharmacological classes, increase extracellular dopamine levels. With repeated drug administration, these dopamine responses can become progressively greater (sensitized) and conditioned to environmental cues. Diminishing the drug-induced dopamine responses does not alter the substance's pleasurable effects, consistently diminish conscious craving, or change the

self-administration of easily available drugs. However, decreasing dopamine transmission does reduce the ability to respond preferentially to rewards and the willingness to sustain effort to get them (alcohol, cigarettes, money). In people at risk for addictions, these drug-induced dopamine responses are markedly altered, differences that remain after controlling for past drug use. Discussion: Together, these studies might identify more closely the specific role of dopamine in drug-taking behavior. Since the studies also provide the evidence of disturbed drug-induced dopamine responses in people at elevated risk for addiction, disturbed dopamine responsivity might reflect a pre-existing vulnerability trait.

Stress Mechanisms Contribute to the Etiology of Alcohol Dependence – Evidence from PET Imaging Studies

Alex Neumaister

Abstract: Background: Norepinephrine (NE) and endogenous cannabinoids (eCBs) contribute to the adaptive and maladaptive consequences of stress exposure. Both systems are involved in alcohol dependence (AD). To understand the relative contribution of these connected neurobiological systems in the neurobiology of AD we conducted a series of molecular brain imaging studies using positron emission tomography (PET) and radioligands designated (S,S)-[11C]MRB and [11C]OMAR which are selective for the NE transporter, (NET), and the CB1 receptor, respectively. Methods: Patients with AD, and normal social drinker control subjects were recruited. Following a transmission scan, [11C]MRB and [11C]OMAR were injected by pump over one min and HRRT list mode data were acquired for 120 min. Regional time-activity curves (TACs) were fitted with the Logan graphical method, with and without k2 correction, and analyses were performed using the multilinear reference tissue model, MRTM2 to produce images of binding potential (BPND) for the NET. To measure CB1 receptor density, we determined volume of distribution (VT) values. All subjects were medication-free and alcohol dependent individuals were studied 4 weeks after their last drink after controlled abstinence. Results: We show differences in NET BPND between AD patients relative to healthy control subjects in the thalamus and the locus coeruleus (LC), brain regions which exhibit high NET concentrations in humans. No between-group difference in BPND was found between AD and obsese people. In alcoholics relative to healthy controls, [11C]OMAR VT values were elevated by ~20% (p=.023) in a circuit, including the amygdala, hippocampus, putamen, insula, anterior and posterior cingulate cortices and orbitofrontal cortex. Age, body mass index or smoking status did not influence the outcome. Obese subjects did not differ from healthy controls in their [11C]OMAR VT data. Conclusions: Our NET PET data suggest a role for abnormal NET density in alcohol addictions. The [11C]OMAR VT data agree with preclinical evidence and implicate brain CB1 receptors in AD. The current study design does not answer the question of whether elevated CB1 receptors are a pre-existing vulnerability factor for AD or whether elevations develop as a consequence of AD.

Why You Shouldn't Drink in the Scanner: Advances and Advantages in PET Study Design With IV Alcohol Infusion

Karmen K. Yoder

Abstract: Over the last decade, the literature from animal studies has shown us that dopamine is involved in multiple processes that subserve the development and maintenance of alcoholism and other addictions. The role of dopamine goes beyond the familiar constructs of "liking" and "wanting." For example, dopamine drives both goal-directed and habitual behaviors for the acquisition and consumption of alcohol. Additionally, dopamine informs organisms of the presence of alcohol, encodes the conditioned cues associated with drinking and its effects, and tells the organism how important alcohol is (salience attribution). When an organism's expectations of alcohol delivery or availability in the environment are violated, dopamine is the brain syntax of these "prediction errors". The use of PET and [11C]raclopride (RAC) to study changes in striatal dopamine in human subjects is a well-accepted method, but this approach is not immune to problems inadvertently induced by study design. For example, variable timing and dosing of a challenge stimulus can result in variance in the measurement of the binding potential (BP, the primary dependent variable) across subjects. Factors such as subject expectation influence striatal dopamine levels, even during a "baseline" state. Therefore, RAC PET experiments with alcohol must be carefully designed to avoid methodological confounds inherent to PET, the properties of alcohol, and the cognitive state of the subject. Our laboratory utilizes an intravenous (IV) alcohol "clamp" technique that permits us to precisely control timing and dose of alcohol administration. IV alcohol also has the added advantage of providing unique experimental opportunities to probe cognitive processes, such as prediction error, that are coded for by striatal dopamine and which depend on manipulation of subject expectation. RAC PET data from paradigms involving IV alcohol infusion in several cohorts of social drinkers and nontreatment-seeking alcoholics will be presented. We will explore evidence that alcoholics and social drinkers differ in both (1) how the dopamine system processes information about alcohol intoxication and/or the presence of alcohol, and (2) how dopamine encodes prediction errors regarding expectation of delivery of IV alcohol. Supported by ABMRF/The Foundation for Alcohol Research (KKY), NIAAA P60AA007611 (pilot P50 to KKY), NIAAA R21AA016901 (KKY), R01AA018354 (KKY) and the Indiana Clinical and Translational Sciences Institute (NIH TR000006, Indiana Clinical Research Center).

PET Radiotracers for Imaging the Kappa Opioid Receptors in Alcoholism

Henry Y. Huang

Abstract: The role of the opioid system in alcohol addiction and treatment is well established, as the non-selective opioid antagonist naltrexone is effective in the prevention of relapse in alcoholics. Endogenous opioid mediated reward and reinforcement pathways may play a significant role in the development and maintenance of alcohol dependence. Alcohol intake elevates endogenous opioids, and administration of selective kappa opioid receptor (KOR) agonist increases alcohol intake or preference for alcohol, whereas non-selective opioid receptor antagonists such as naltrexone and naloxone or the selective KOR antagonist nor-BNI suppress alcohol intake in rodents. The involvement of the KOR is thought to be through its ability to modulate dopamine (DA) function. Activation of the KOR by dynorphin or administration of KOR agonists inhibits psychostimulant-induced DA release in the nucleus accumbens, and attenuation of DA release has been shown to inhibit both the psychomotor effects and reinforcing behaviors of psychostimulants. Repeated administration of drugs of abuse leads to the dysregulation of the dynorphin/KOR modulatory system. Hence, PET imaging with KOR selective radiotracers will be

a valuable tool to probe the involvement of KOR in alcohol abuse. In this paper we present our work in the development and validation of the KOR-selective agonist [11C]GR103545 and antagonist [11C]LY2795050 as PET imaging agents, and how these radiotracers can be used to investigate the function of KOR and its potential dysregulation in alcoholism and other addictive disorders.

PET Imaging of Opioid and GABA-A Receptors Alcoholism

David Nutt, Anne Lingford-Hughes, Jim Myers, Paul Stokes

Abstract: Our group has been using PET to explore receptor dysfunction in alcoholism for over a decade using [11C]-diprenorphine for opioid receptors and [11C]-flumazenil and then [11C]Ro15-4513 for GABA-A receptors and its subtypes. In early alcohol abstinence we found increased density of 11C-diprenorphine binding that correlated with craving [1]. In 3 of the 4 individuals who stayed abstinent there was no change with abstinence, with levels reducing in one individual. Using a midazolam challenge with [11C]-flumazenil we have shown that the subsensitivity of GABA-A systems in alcoholism is due to functional dynamic changes in brain rather than from kinetic changes [2]. Subsequently using the partially subtype-selective tracer [11C]Ro15-4513 we have demonstrated significant reductions in receptor density in nucleus accumbens and hippocampus [3]. These changes may reflect trait vulnerability to alcoholism as there is a significant negative correlation between [11C]Ro15-4513 density and impulsivity. Additionally using more sophisticated analysis we are now able to simultaneously estimate the density of both intra (a1) and extra (a5)-synaptic receptors in some brain regions and these data in alcoholism are in preparation. We thank the MRC for program support for this work

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[3] Lingford-Hughes A, Reid AG, Myers J, Feeney A, Hammers A, Taylor L, Rosso L, Turkheimer F, Brooks DJ, Grasby P, Nutt DJ. (2012) A [11C]Ro15 4513 PET study suggests that alcohol dependence in man is associated with reduced {alpha}5 benzodiazepine receptors in limbic regions. J Psychopharmacol. 26(2):273-81.

TOPICAL SESSION

A Translational Approach to Alcoholism: Understanding Addictive Goals and Habits via Computation, Representation and Neural Instantiation

Hunger in the brain: is addiction a useful explanation for over-eating and obesity?

Paul C. Fletcher

Abstract: There is a growing interest in the concept of "food addiction" as an explanation for the rapid and disturbing worldwide increase in obesity. Indeed, many already accept the importance of addiction-like processes as important drivers to over-eating, arguing that therapeutic and policy decisions should be shaped accordingly. Yet how strong is the evidence for this position? And to what extent do sophisticated cognitive neuroscientific models of substance addiction, notably those shaped by theoretical and empirical distinctions between goal-driven and habitual actions, plausibly map onto eating behavior? I would like to consider these questions, reviewing in particular the evidence from studies on eating and obesity in humans. While there is clear theoretical value in applying concepts developed and refined in the addiction fields, I suggest that the current evidence does not support food addiction as a major drive towards abnormal eating behavior. I will go on to consider ways in which insights from studies of reward and reinforcement may assist in refining and developing our understanding of pathways towards obesity.

A model of interactive effects of learning and choice incentive in the striatal dopamine system

Michael Frank

Abstract: The striatum and dopaminergic systems have been strongly implicated in reward-based behavior, with debates focusing on the relative roles of this system in reinforcement learning, motor performance, and incentive motivation. Neural network models implicate the corticostriatal dopamine system at the intersection of all of these functions -- not independently, but interactively. Dopaminergic modulations directly influence action selection and choice incentive, i.e. the degree to which decisions are based primarily based on learned prospective gains vs losses, encoded in D1 and D2 expressing medium spiny neuron populations. Reciprocally, phasic dopamine signals involved in learning progressively modulate synaptic weights and hence activity levels, which in turn influence not only action selection, but also the eligibility for further learning. We present a novel algorithmic model summarizing these fundamental interactive properties of the neural implementation, incorporating both incentive and learning effects into a single theoretical framework suitable for formal analysis and quantitative fits. In contrast to standard reinforcement learning frameworks, this model simultaneously captures documented effects of dopamine on both learning and choice incentive across a variety of studies, as well as their interactive effects on motor skill learning.

Overlearned behaviors are cortical… Insights from the cognitive neuroscience of physical skills

Scott Grafton

Abstract: Textbook accounts of habits and automaticity often conclude that subcortical systems, including the basal ganglia are the storehouse of well-learned behaviors. Despite this prevalent view, it remains difficult to find studies where over-learned behavior is erased by a basal ganglia

stroke, stereotactic ablation, deep brain stimulation or pharmacotherapy. Here, we examine the role of the basal ganglia in supporting changes of cortico-cortical connections that mediate the formation and retention of long term physical skills during early skill learning. In this alternate account, the skill itself is ultimately represented in cortical connections, with the dopaminergic BG involved in reward based learning that is mainly involved early in training. Furthermore, there is evidence that learning dynamics within different cortical regions reflect change over multiple time scales. Some motor areas change quickly, others slowly. Multiple time scales undermine the notion of distinct “stages” of learning. These observations with physical skills have implications for interpreting the learning and retention of normal as well as pathologic appetitive and social behaviors.

Goals and Habits, Learning and Compulsion

Nathaniel Daw

Abstract: I discuss the relationship between the categories of goal-directed and habitual behavior, and different computational strategies for trial-and-error learning in decision making, known as model-based and model-free learning. Model-free learning is the theory associated with predominant accounts of the dopaminergic response and its action in striatum, producing behavior with many of the properties of habits. Model-based learning instead evaluates actions using a learned cognitive map or model, and may serve as a computational theory of goal-directed behaviors. Having detailed computational theories of the learning processes underlying goal-directed and habitual behavior permits teasing apart these processes' dynamic effects on behavior and associated neural signals in humans with precision while avoiding laborious manipulations such as devaluation or overtraining. This enables us to examine how these processes contribute under different circumstances and in different populations. I discuss the implications of these results for drug abuse, and report new experiments demonstrating an abnormal balance between these processes in the initial acquisition of new learned behaviors in human patients with disorders involving compulsion.

State space representations --- where habits and goal-directed behavior meet

Yael Niv

Abstract: The first ingredient in any reinforcement learning model is the state space -- a description of the task in terms of a sequence of situations (states). For many tasks, the state space is not trivial, and must be learned. I will first demonstrate that state spaces are learned using a simple perceptual judgment task in humans and a learning task in rats, and then argue that the orbitofrontal cortex (OFC), a region well known for its pervasive yet subtle influence on decision making, encodes a map of the states of the current task and their inter-relations. This map provides a state space for reinforcement learning elsewhere in the brain, and is especially critical in complex tasks. Importantly, this state space is likely shared between model-based (goal directed) and model-free (habitual) decision making processes, explaining the importance of OFC in both types of actions. I will use this hypothesis to explain extant data on the neural and behavioral consequences of compromising the OFC, and lay out a number of testable experimental predictions that can distinguish our theory from other accounts of OFC function.

POSTER PRESENTATIONS
Saturday

POSTERS 1-14

POSTER 1: Influence of Binge Drinking on the Neural Correlates of Inhibitory Control during Emotional Distraction in Young Adults

Author Names: Julia E. Cohen-Gilbert, Zachary J. Schwab, William D.S. Killgore, David J. Crowley, Marisa M. Silveri

Affiliations: McLean Hospital - Brain Imaging Center, and Harvard Medical School - Dept. of Psychiatry

Abstract: Heavy episodic alcohol use, or binge drinking, peaks in early adulthood, a period during which prefrontal cortex (PFC) and frontolimbic connections continue to develop. Binge drinking potentiates impulsive actions, particularly in emotion-laden circumstances, and may have lasting deleterious effects on brain regions critical to cognitive and emotional regulation. This study used functional magnetic resonance imaging (fMRI) to record brain activity during a task that required participants to ignore background images that were positive, negative, neutral, or scrambled, while performing an inhibitory control task (go-nogo). Subjects were young adults (18-24 years) who were either binge drinkers (BD) or light drinkers (LD). In a preliminary sample of 10 subjects, LD demonstrated lower accuracy on inhibitory trials with negative backgrounds compared all other background types. BD, however, performed equally poorly on inhibitory trial in all background conditions, and showed a trend towards increased total impulsive errors compared to LD. With regard to brain activity, contrasts of negative versus neutral trials across groups revealed PFC regions with greater activation in the LD versus the BD group. These preliminary data suggest that higher rates of impulsive errors observed in the BD group may, in part, reflect less efficient recruitment of the prefrontal cortex during inhibitory control efforts in the presence of emotional distractors. These differences in PFC recruitment may result from binge drinking during the late stages of frontolimbic development or may reflect pre-existing differences in brain functioning that predispose individuals to engage in more risky behaviors, such as binge drinking.

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POSTER 2: Can sitting still teach us how to stop drinking? Meditation training is associated with differences in default mode network activity and connectivity.

Author Names: Judson A. Brewer, Patrick D. Worhunsky, Jeremy R. Gray, Yi-Yuan Tang, Jochen Weber, and Hedy Kober

Affiliations: Yale University School of Medicine (JAB, PDW, HK), Michigan State University (JRG), University of Oregon (YYT), Columbia University (JW).

Abstract: Mindfulness training (MT) is an emerging treatment for addictions. It has produced promising results for nicotine, cocaine and alcohol dependence, demonstrating greater efficacy than other cognitive treatments in randomized controlled trials (Brewer 2011). MT has recently

been shown to moderate the decoupling of craving and use (e.g. smoking, Elwafi 2012), but the neural mechanisms of this process remain unclear. Core to mindfulness is the ability to pay attention, notice when one's attention has wandered, and return it to an object of focus. One might hypothesize that this would involve brain regions implicated in self-monitoring and cognitive control (e.g. dorsal anterior cingulate, dACC and dorsolateral prefrontal cortex, dlPFC, Kober 2010 and others). To examine potential neural mechanisms of MT, novice and experienced meditators (n = 12/group) performed 3 types of meditation while undergoing fMRI scanning. Results revealed that across all meditation conditions, experienced meditators demonstrated decreased activity in the posterior cingulate cortex (PCC), a default mode network region associated with craving (Garavan 2000 and others). Importantly, experienced meditators also showed increased functional connectivity between the PCC and both dACC and dlPFC. These findings suggest that MT may act by increasing self-monitoring and cognitive control to help individuals notice craving and its pull when it arises rather than habitually and mindlessly acting on it.

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POSTER 3: Common patterns of social drinking influence brain GABA levels measured using magnetic resonance spectroscopy

Author Names: David J. Crowley, Michael J. Covell, J. Eric Jensen, Julia E. Cohen-Gilbert, Jennifer T. Sneider, Marisa M. Silveri.

Affiliations: Neurodevelopmental Laboratory for Addictions and Mental Health, McLean Hospital, Belmont, MA; Department of Psychiatry, Harvard Medical School

Abstract: Over 20% of Americans over age 12 drink heavily (binge drink) at least twice per month. Magnetic resonance spectroscopy (MRS) studies have reported that levels of the neurotransmitter gamma-aminobutyric acid (GABA) are significantly reduced following an acute alcohol challenge, as well as some evidence that GABA levels are reduced in alcohol-dependent patients. However, there has been no research to date on the effects of binge drinking in non-dependent individuals on brain GABA levels. Given the prevalence of this common drinking pattern in community samples, the objective of the current study was to determine whether binge drinking is associated with altered GABA in a non-alcohol dependent population. Proton MRS data were acquired using MEGAPRESS from voxels placed in the anterior cingulate cortex (ACC) and in a comparison region, the parieto-occipital cortex (POC) in 18-24 year olds classified as light drinkers (LD, N=28) or binge drinkers (BD, N=19). Participants also completed a battery of clinical and neuropsychological tests. GABA/Cr levels were significantly lower in BD compared to LD (p=.04), but only in the ACC. Groups did not differ significantly on mood measures, but there was evidence of worse performance on some cognitive tasks in BD compared to LD. These findings suggest that frequent binge drinking is associated with low GABA levels that are selective to the prefrontal cortex. Results from MRS studies of GABA in community samples could therefore be significantly influenced by this common drinking pattern. Future studies should carefully screen for alcohol use using multiple objective measures of consumption.

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POSTER 4: Oxidation Behavior and Chronic Alcohol Effect of Ethanol in the Rat Brain

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Abstract: Previous studies in humans and rats have shown ethanol (EtOH) consumption to decrease brain glucose utilization, and ethanol, which is converted to acetate (Ac), increases brain Ac uptake. It is unknown if Ac only or if Ethanol also directly provides energy to the brain. Rats were treated 3 weeks with ~23 mg/L Etoh vapor (treated), or room air (naïve), for 8hr/day. Naïve and treated rats received co-infusions of EtOH-C2 and [1, 2-13C2]Ac (AcC12) to maintain blood Ethanol at ~28 mM and Ac at ~3 mM for 2 hours. Blood samples were collected from saphenous vein, and plasma was obtained. Then the brain was fixed by focused microwave and the cortex extracted for MRS analysis of double-labeled and single-labeled Glu and Gln. MRS detection were also used to analysis Plasma samples to measure the labeling AcC2 and AcC12. Both groups had significantly more GlnC4/GlnC45 and GluC4/Glu45 than AcC2/AcC12 ($p<0.001$), proving intracerebral Ethanol oxidation. In naïve rats Ethanol provided 6.8±0.8% and 3.4±0.4% of glial and neuronal oxidation, respectively, and for treated rats the figures were 11.0±0.8% ($p=0.0015$ increase with treatment) and 3.3±0.1%. Using published glial and neuronal Krebs cycle rates, we estimate brain Etoh oxidation at ~0.03 mmol/min/g. Chronic alcohol exposure can enhance the oxidation of ethanol in astroglia. Furthermore, Oxidation of EtOH generates acetaldehyde, which in the brain is rewarding, but it also creates oxidative stress and might be pro-inflammatory in the brain. Ethanol can provide energy for the brain, directly and via Ac, but the oxidation may theoretically be damaging.

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POSTER 5: Adolescent Brain Development in Wistar Rats

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Abstract: Adolescence is a developmental period in humans and other mammalian species characterized by high social and play activity, risk taking, thrill seeking that may be reflected in structural maturation of the brain. To investigate Wistar rat brain development we determined MRI across rat adolescence into young adulthood, e.g . postnatal days 28, 42 and 80. Both live and post-mortem MRI scans were done at all 3 ages. A unique sacrifice-perfusion procedure with contrast agent coupled with post-mortem whole head MRI scans was found to replicate in-vivo brain regional volumes while increasing image resolution and ease of experimental design. Rats body weight increased 4.5 fold (e.g. 100 to 450 gm) from P28 (early adolescence) to P80 (young adulthood) that correlated closely with a brain volume increase of 33%. Hippocampus and thalamus were progressively increased across these ages by 27% and 48% respectively. Ventricles and cerebellum rapidly increased in volume during adolescence, e.g. P28-42, by 34% and 29% respectively, and continued to grow, although at a slower rate, into young adulthood

(P80). In contrast, dorsal striatum grew only 5% between P28-42, but expanded 22% between P42-P80. Neocortex increased 9% between P28-42 and 8% between P42-P80. These findings indicate adolescent rat growth contributes to brain volume increases, although different brain regions grow at different rates dependent upon age. Further, we find MRI can be used to investigate development of brain structures during adolescence. (Supported by the NADIA of NIAAA).

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POSTER 6: Effects of the Oxytocin Gene Variant in Children and Adolescents at High Risk for Alcoholism

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Abstract: Studies have showed that oxytocin modulates responses to drugs of abuse. The genetic polymorphisms associated with this effect, however, have not been identified, although oxytocin and oxytocin receptor gene variants have been linked to impaired social behaviors. In a longitudinal sample at high risk for alcoholism, we examined the influence of an oxytocin gene SNP (rs4813625) on social behaviors at age 12-14 and drinking related problems at age 18. The results showed that C allele carriers scored lower on social acceptance and close friendship scales (n=168), and exhibited more drinking related problems (n=66) as compared to GG homozygotes. In addition, nucleus accumbens (NAcc) activation during reward anticipation was examined using fMRI in a monetary incentive delay task in a child group (n=24; average age = 10) and an adolescent group (n=51; average age=21) drawn from the same sample. A significant interaction between sex and genotype was found in both age groups. Specifically, female C allele carriers exhibited greater NAcc activation than GG homozygotes, while males showed the opposite pattern. In sum, the oxytocin gene variant explains individual differences in social behaviors in children and alcohol use in adolescents. In addition, the neuroimaging findings suggest that oxytocin affects these behaviors potentially by interacting with the dopaminergic reward system in a sex-dependent manner.

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POSTER 7: The BDNF Val66Met Polymorphism Moderates the Association between Childhood Maltreatment and Subcortical Brain Volumes in Treatment-Seeking Alcoholics

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Abstract: Early life stress (ELS) is a robust predictor of alcohol dependence (AD) in adulthood, but the mechanisms underlying this association are unclear. The current study builds on our earlier finding of positive associations between ELS and brain volume in a sample of treatment-seeking alcoholics by exploring the moderating role of brain-derived neurotrophic factor (BDNF) genotype. Participants included 214 alcoholics undergoing inpatient treatment at the NIH Clinical Center. ELS was assessed using the Childhood Trauma Questionnaire (CTQ) and quantified as a categorical severity score. BDNF Val66Met genotype was determined using the Illumina® OmniExpress BeadChip. Participants underwent structural MRI scans on a 3T scanner and brain and subcortical volumes were determined using FSL. Genotyping results found 73.8% of the sample were Val/Val; 26.2% were Met carriers. A significant genotype X CTQ severity interaction was found for right accumbens ($F=2.97$, $p=0.05$) and left hippocampus ($F=3.19$, $p=0.04$) volumes. There was a trend-level significant main effect of genotype on right accumbens volume. The addition of depression scores (from MADRS) into the model eliminated the significant interaction for right accumbens; the interaction was reduced to trend level significance for left hippocampus. Further, there was a significant interaction between emotional abuse severity and Val66Met genotype on right accumbens volume ($F=4.18$, $p=0.017$) even after controlling for depression. In all cases, Met carriers with the highest trauma severity scores had larger subcortical volumes than Val/Val homozygotes. These findings suggest a BDNF gene X environment interaction underlying the relationship between ELS and brain volume in alcoholics.

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POSTER 8: Hippocampal subfield volumes in chronic alcoholism: Associations with drinking history and memory ability

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Abstract: Chronic alcohol abuse adversely impacts neuropsychological functions supported by the hippocampus. While hippocampal morphometry also is negatively affected by chronic alcoholism, the distribution of these effects across the hippocampal subfields in humans remains to be explored. Participants in this study were abstinent alcoholic men (n=21) and women (n=19) and healthy nonalcoholic controls (n=38, 19 women). Multi-echo MPRAGE scans were collected for each participant, and volumes of the hippocampi and their component subfields were calculated by an automated segmentation algorithm using FreeSurfer 5.1.0. Correcting for age and intracranial volume, the resulting hippocampal volumes were examined for alcoholism and gender effects, as well as for associations with drinking variables and Wechsler Memory Scale (WMS-IV) and Wechsler Adult Intelligence Scale (WAIS-IV) composite scores. Controls had higher Visual Working Memory and Processing Speed scores than alcoholics. Alcoholics had smaller total right hippocampal volumes than controls, with alcoholic men being more affected than alcoholic women. Analysis of hippocampal subfield volumes revealed that these effects were strongest in the right hemisphere presubiculum, subiculum, CA2/3, and CA4/dentate gyrus. Among alcoholics, more severe drinking histories were associated with smaller presubiculum and subiculum volumes. Across the hippocampal subfields, larger volumes were associated with higher WMS-IV and WAIS-IV composite scores among controls, while this effect was relatively

absent among alcoholics. This work confirms previous reports of abnormal hippocampal structure and memory dysfunction in chronic alcoholics, and extends these findings by localizing effects to component hippocampal subfields.

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POSTER 9: Effects of smoking on D2/D3 Striatal Receptor Availability in Alcoholics and Social Drinkers

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Abstract: Objective: Studies have reported lower striatal D2/D3 receptor availability in both alcoholics and cigarette smokers relative to healthy controls. These substances are commonly co-abused, yet the relationship between comorbid alcohol/tobacco use and striatal D2/D3 receptor availability has not been examined. We sought to determine the degree to which dual use of alcohol and tobacco is associated with lower D2/D3 receptor availability. Method: Eighty-one subjects (34 nontreatment-seeking alcoholic smokers [NTS-S], 21 social-drinking smokers [SD-S], and 26 social-drinking non-smokers [SD-NS]) received baseline [11C]raclopride scans. D2/D3 binding potential (BPND ≡ Bavail/KD) was estimated for ten anatomically defined striatal regions of interest (ROIs). Results: Significant group effects were detected in bilateral pre-commissural dorsal putamen, bilateral pre-commissural dorsal caudate; and bilateral post-commissural dorsal putamen. Post-hoc testing revealed that, regardless of drinking status, smokers had lower D2/D3 receptor availability than non-smoking controls. Conclusions: Chronic tobacco smokers have lower striatal D2/D3 receptor availability than non-smokers, independent of alcohol use. Additional studies are needed to identify the mechanisms by which chronic tobacco smoking is associated with striatal dopamine receptor availability.

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POSTER 10: Assessing the effect of acute alcohol administration on amygdala-prefrontal activity at rest

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Abstract: Previous research demonstrates that anxiety is linked to compromised interactions between amygdala and dorsal and ventral medial prefrontal cortex at rest (Kim et al., 2011). Specifically, participants low in state anxiety exhibited positively correlated spontaneous fluctuations in amygdala and ventral mPFC activity. This was not observed in high state anxious participants. Here, individuals were given a fixed amount of alcohol and then completed ~8 minutes of a resting state fMRI run. We assessed functional connectivity between amygdala and dorsal and ventral medial prefrontal cortex at rest. We hypothesized that, in the high anxious

participants, an acute dose of alcohol would produce coherence between amygdala and ventral mPFC activity (i.e., positive correlation) in high state anxious subjects. In other words, alcohol should cause the high anxiety group to look more like the low anxious group. Preliminary results show that participants given a fixed amount of alcohol show a positive correlation between amygdala and ventral mPFC activity, similar to the previous pattern observed in low anxious subjects. Further, we found a positive correlation between amygdala and dorsal mPFC activity at rest. We aim to extend these data to include enough subjects to provide the requisite variability in anxiety levels to test our working hypothesis, namely, that the neural substrates of the anxiolytic effects of acute alcohol administration can be visualized in terms of the pattern of amygdala-prefrontal interactions at rest.

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POSTER 11: Diffusion tensor imaging (DTI) reveals age- and adolescent binge ethanol exposure-induced alterations of brain regional volumes and diffusivity in adult rats.

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Abstract: Adolescence is a developmental period that occurs in humans and other mammalian species, and is characterized by increased social interaction and risk-taking that coincides with brain maturation. Since adolescent humans engage in high levels of alcohol binge drinking, we used DTI to assess the effect of adolescent intermittent ethanol (AIE) exposure (5 g/kg, i.g., 2-day on/2-day off from postnatal day (P)25 to P55) on brain regional volumes and diffusivity in adult male rats (P80 and P220). Aging exerted the largest effect, with body weight increasing 55% from P80 to P220, and a 9% increase in brain volume at P220 that was associated with a 25% and 17% increase in neocortical and basal forebrain volumes, respectively. In contrast, hippocampal volumes were decreased by 28%, and cerebellar volumes did not change as a function of age. AIE did not alter overall brain volumes, but did significantly reduce neocortex volumes by 5% at P80. Assessment of overall measures of diffusivity found age-associated reductions across the hippocampus, neocortex, and basal forebrain from P80 to P220. We found that AIE treatment reduced axial diffusion in the hippocampus (8%), and reduced axial, radial, and mean diffusion in neocortex and cerebellum by 11%, and the basal forebrain by 15%. These findings indicate that adult rat growth contributes to overall brain growth, which appears to be the result of brain region specific. Further, AIE did not exert any volumetric changes in the adult brain, but did alter tissue integrity throughout the brain. (Supported by the NADIA of NIAAA)

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POSTER 12: Brain activation, alcohol cues, and craving

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Abstract: We sought to identify brain regions implicated in alcohol craving as evidenced by changes in the BOLD response to visual alcohol cues and to examine the level of craving for alcohol in relation to drinking history. We hypothesized that in brain regions implicated in alcohol craving, alcoholic beverages for which alcoholics reported a high subjective level of craving would elicit a greater BOLD response than those for which they reported a low level of craving. Abstinent alcoholic participants (n=46) completed an fMRI working memory task. One of three types of distractors was presented prior to each recognition trial: alcoholic beverages, nonalcoholic beverages, and visual noise. Following the scan, participants rated their craving level for all the beverage images. These ratings were used for post-hoc trial sorting, allowing comparisons of BOLD response during presentation of high- versus low-craving alcohol cues. Measures of drinking history and general levels of alcohol craving (Penn Alcohol Craving Scale; PACS) were obtained. There was higher activity in the left amygdala and right hippocampus when participants viewed alcoholic beverages for which they reported high craving compared to alcoholic beverages for which they reported low craving, whereas the right nucleus accumbens and right pallidum showed the opposite relationship. Subjective level of craving for the beverage images changed in relation to drinking history. On the PACS, duration of abstinence was related to general craving. Our results suggest that brain regions associated with increased response to alcohol cues may also be sensitive to subjective alcohol craving levels among alcoholics.

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POSTER 13: Naltrexone effects on ethanol-induced brain activation and emotional processing in alcoholics

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Abstract: Clinical studies have shown that the mu-opioid antagonist naltrexone (NTX) is effective in the treatment of alcoholism; however the underlying mechanism of this effect is not well-understood. This study examined the effects of naltrexone on striatal BOLD response to alcohol and on alcohol-induced brain activation during emotional processing in treatment-seeking alcoholics. Sixty-three hospitalized alcoholics were randomized following detoxification to receive NTX (50 mg/day) or placebo. On day 9, participants underwent fMRI scanning to collect BOLD response to emotional facial stimuli, while receiving IV infusions of saline followed by alcohol to a target blood alcohol level of 0.08g%. Subjective responses to alcohol were measured using rating scales. There was no significant difference in striatal BOLD response between saline and alcohol infusions, and no effect of NTX or placebo treatment on the BOLD response. NTX group

participants had greater BOLD response to fearful compared to neutral faces, particularly in the amygdala, this was not seen in the placebo group. Unexpectedly, NTX group participants experienced greater subjective high (p=0.02) and intoxication (p=0.03) following alcohol compared to the placebo group. Regardless of NTX or placebo, alcoholics did not show striatal activation in response to alcohol, probably related to chronic alterations in neural mechanisms underlying positive reinforcement. NTX did enhance emotional processing of fearful stimuli, as measured by BOLD responses to fearful faces. Since alcoholics typically fail to effectively avoid and process cues that signal threat, these data suggest that NTX may act to restore this process, by blocking mu-opioid receptors specifically localized in the amygdala.

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POSTER 14: Acute alcohol effects on behavioural reward-seeking responses

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Abstract: Previous data suggested a positive association between the behavioural disinhibiting effects of acute alcohol [as measured by the Stop-Signal reaction time (SSRT)], and the increase in the probability to respond to a stimulus signalling loss of money [Loeber and Duka (2009)]. Twenty-seven moderate-to-heavy social-drinkers received a drink containing no alcohol, or a low (0.4g/kg), or a high (0.8g/kg) dose of alcohol, in a randomized double-blind design, and were then placed in a 1.5T scanner, and underwent a forced choice instrumental reward-seeking procedure, with abstract stimuli serving as S+ (always predicted winning 10 pence) and S- (always predicting losing 10 pence). Participants pressed one key to obtain a reward-outcome ("press-key"), and a different key to indicate that they did not wish to press ("do-not-press-key"). Stimulus–outcome contingencies were acquired before alcohol administration to ensure no group differences. A visual Stop-Signal task was also administered. Groups did not differ in the rate of responding to obtain the reward-outcome in the presence of the S+ or the S-. However, both the low and the high dose impaired SSRTs relative to placebo [t(24)=2.5,p=0.02; and t(24)=3.64,p=0.001, respectively]. The rate of responding to the S- tended to correlate positively with SSRT (r=0.3,p=0.06). A one-way ANOVA compared activations to the S->S+ between groups. A one-sample T-test tested significant activations to successful stop-trials relative to go-trials in the placebo group. Conjunction analyses (p<0.005,k=13) revealed a significant linear reduction in activation in Inferior orbitofrontal cortex (BA47). The data suggest that alcohol affects behavioural control to signals associated with punishment.

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POSTER PRESENTATIONS
Sunday

POSTERS 15-27

POSTER 15: Dopamine D3 receptors in Alcohol Dependence; [11C]PHNO-PET With Selective D3 Receptor Blockade.

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Abstract: Animal studies are in support for a role of the dopamine D3 receptor (DRD3) in alcohol reinforcement or liking1. Sustained voluntary alcohol drinking in rats has been associated with an upregulation of striatal DRD3 gene expression2, and selective blockade of DRD3 in rat reduces ethanol preference, consumption3, and cue-induced reinstatement. Brain DRD3 status was compared between 16 male alcohol dependent patients (ADP) (abstinent for 415, range 39 to 893, days) and 13 healthy non-dependent males matched for age using the DRD3-preferring agonist positron emission tomography (PET) radioligand [11C]PHNO and a selective DRD3 antagonist (GSK598809 60mg p.o.). In striatal regions of interest, baseline [11C]PHNO binding levels did not differ but was significantly higher in ADP compared with CTR in hypothalamus (VT: 16.5±4 vs 13.7±2.9, p=0.040), a region in which the [11C]PHNO signal in healthy controls almost entirely reflects DRD3 availability. The reductions in regional receptor binding (VT) following a single 60 mg dose of GSK598809 were consistent with those observed in previous studies across all regions4. There were no differences in regional changes in VT following DRD3-blockade between the two groups, indicating the regional fractions of DRD3 are similar in the two groups and the increased [11C]PHNO binding in the hypothalamus in APD is explained by elevations of the DRD3 in this group. This preliminary finding of regionally increased DRD3 binding is relevant to future therapeutic strategies targeting the DRD3.

1) Heidbreder, 2008, 2) Jeanblanc, 2006, 3) Thanos, 2005, 4) Searle, 2010

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POSTER 16: Self-reported Deficits in Emotion Regulation Predict Brain Response to Stress in Alcohol-Dependent Adults

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Abstract: Individuals with alcohol dependence (AD) exhibit difficulties in emotion regulation and altered brain response to salient, emotionally-evocative information. However, prior studies have not investigated brain activity related to emotion regulation difficulties during emotion provocation

tasks in AD. Using functional magnetic resonance imaging (fMRI), we examined the neural correlates of specific enduring difficulties in emotion regulation, e.g. impulse control, during brief individualized imagery exposure to emotional stress cues, alcohol cues and neutral-relaxing cues in 37 early abstinent recovering AD inpatients and 37 matched healthy control participants. Emotion regulation ability and its dimensions were measured using the Difficulties in Emotion Regulation Scale. At admission, the AD group reported impairment in multiple dimensions of emotion regulation ability in comparison to their healthy peers. AD participants improved or normalized on most aspects of emotion regulation over the course of 4 weeks of inpatient treatment, but reported persistent impairments in impulse control abilities in response to highly emotional situations. In contrast to controls, abstinent AD patients showed decreased responses in the medial prefrontal cortex (PFC) and limbic regions during stress relative to neutral-relaxing cues. Overlapping stress-related reductions in medial PFC and limbic activation were associated with greater impairments in impulse control, suggesting impairments in top-down regulation of emotions and behavior in recovering alcohol dependent individuals. Dysfunction of the medial PFC and related limbic network may perpetuate impulse control problems and jeopardize recovery from alcohol dependence.

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POSTER 17: Hypoactive response to stress in frontal-striatal regions as a risk factor of alcoholism in non-dependent heavy social drinkers

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Abstract: Stress dysregulation is a significant risk factor of alcoholism, and altered stress circuits associated with compulsive alcohol seeking and early relapse have been reported in alcohol-dependent patients. However, few studies have examined the integrity of stress-related neural circuit and its association with alcohol-related behaviors in non-dependent social drinkers. The current study aims to examine the neural correlates of stress and alcohol-related risk factors in social drinkers using functional magnetic resonance imaging. We compared brain activity of 27 heavy social drinkers with 23 age-, gender-, and intelligence- matched light social drinkers during brief exposure to alcohol cue, stress, and neutral-relaxing imagery. A pulse oximeter was used for heart rate monitoring. Heavy social drinkers displayed greater dysregulation in autonomic and craving responses marked by increased basal heart rate and greater stress-induced alcohol craving relative to light drinkers ($ps<0.05$). fMRI results indicated that heavy social drinkers showed hypoactive response to stress in a frontal-striatal circuit including the medial prefrontal cortex (PFC), anterior cingulate cortex (ACC), ventral striatum, putamen, posterior insula, and temporal gyrus compared to light drinkers ($p<0.05$, whole-brain corrected). Moreover, during stress exposure, high alcohol craving was significantly associated with hypoactivity in the ventromedial PFC, ACC, and dorsolateral PFC in all social drinkers ($p<0.05$, whole-brain corrected). Stress-specific hypoactivity in the frontal-striatal circuit in heavy social drinkers suggests disrupted stress-related neural pathways and poor regulatory control during stress over alcohol-related processes such as high alcohol craving. Altered neuroadaptive response in stress regulatory regions may be a potential risk factor of the development of alcoholism in non-dependent social drinkers (Supported by R01-AA013892; UL1-DE019586; PL1-DA24859).

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POSTER 18: Relationships Between Impulsivity, Reward Sensitivity and Family History of Alcoholism during an Interactive Competitive fMRI Task

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Abstract: As an initial step to deconstruct the complex attributes of impulsivity, our group previously reported the results of a principal component analysis of multiple self-report and behavioral impulsivity measures to create five impulsivity domains. Individuals with a positive family history for alcoholism (FHP) often show impulsive behavior traits that are higher than those lacking such a history (FHN). Our previous work also shows that healthy FHP individuals exhibit differences in reward sensitivity during an fMRI monetary incentive delay task. In the current study, we ask if a) impulsivity domain factors can be used to predict neural activity in response to reward sensitivity, and b) whether family history (FH) of alcoholism is associated with either impulsivity factor scores or neural reward response during an interactive two-player fMRI task. 29 FHN and 40 FHP subjects with no history of Axis I disorders, alcohol dependence or abuse were scanned while playing the Domino game task to explore the neural correlates of simultaneous implicit 'on-line' mentalization and reward-related motivation processes. FHP individuals show significantly higher factor 2 domain scores (p=.004) and BIS-11 scores (p=.027) than FHN subjects. This factor is comprised of Padua and SPSRQ scores to address self-reported compulsivity and reward/punishment sensitivity. Whole brain multiple regression analysis using reward masking reveals significant correlation between factor 5 scores (behavioral risk taking) and right caudate activation under reward > punishment contrast (peak FWE corrected .006, T=4.75). These data suggest that behavioral risk taking scores may be more closely associated with neural reward response than FH or impulsivity self-report measures alone.

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POSTER 19: A longitudinal study of the relationship between fMRI response to alcohol pictures and change in drinking patterns among college students

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Abstract: Recent fMRI studies have examined neural indicators of risk for AUDs. It is possible that greater alcohol cue reactivity presages heavy drinking and alcohol-related problems. In this longitudinal study, we examined the relationship between fMRI response to alcohol pictures and subsequent drinking among college students. Participants were selected from a large (total N=2100) ongoing NIAAA-funded longitudinal neuroimaging study of college drinkers (BARCS). The current study included 43 18- to 21-year-olds who underwent scanning and completed monthly surveys ascertaining alcohol use and alcohol-related problems over the following year. Participants were categorized into groups at baseline (BL) and one-year follow-up (FU) as defined

previously (Dager et al., 2012). Consistently moderate (CM, n=13) drinkers were not heavy drinkers at BL or FU, consistently heavy (CH, n=16) drinkers were heavy drinkers at both BL and FU, and transitioned-to-heavy (TH; n=14) drinkers were not heavy drinkers at BL but were so by FU. Importantly, CM and TH were comparable on demographics and baseline alcohol involvement. During fMRI scanning at BL, participants viewed alcohol and matched non-alcohol beverage images. Participants also completed several impulsivity assessments at BL. TH showed greater fMRI response to alcohol cues than CM and CH in bilateral caudate, orbitofrontal cortex, medial frontal cortex/anterior cingulate, and left insula (clusters > 2619 µl, $F(2, 40) > 3.23$, $p < .05$ whole-brain corrected). Additional analyses in CM and TH indicated that fMRI response did not predict subsequent alcohol-related consequences (e.g., hangover, passing out), but that greater reward sensitivity (Sensitivity to Punishment and Sensitivity to Reward Questionnaire) did. Conversely, reward sensitivity predicted consequences but not drinking amount. Our results demonstrate enhanced neural response to alcohol cues among college students who subsequently transitioned from moderate to heavy drinking. Greater cue reactivity predicted larger increases in drinking, regardless of baseline drinking, whereas reward sensitivity better predicted subsequent alcohol-related problems. Together, cue reactivity and reward sensitivity measures could provide markers to identify individuals at greatest risk for future heavy drinking and consequences. This work was supported by NIAAA (AA016599 & AA19036; Pearlson) and the Alcohol Beverage Medical Research Foundation (Anderson).

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POSTER 20: The Brain Response to Oral Sucrose Stimulation: Association With Recent Drinking

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Abstract: Background: A preference for sweet tastes has been repeatedly shown to be associated with alcohol preference in both animals and humans. In this study, we tested the extent to which recent drinking is related to blood oxygen dependent (BOLD) activation from an intensely sweet solution in orbitofrontal areas known to respond to primary rewards. Methods: Sixteen right-handed, non-treatment seeking, healthy volunteers (mean age 26 years; 75% male) with a range of recent drinking (mean drinks/week= 7.1, SD= 4.9) were recruited from the community. All underwent a taste test using a range of sucrose concentrations, as well as functional magnetic resonance imaging (fMRI) during pseudorandom, event-driven stimulation with water and a 0.83M concentration of sucrose in water. Results: [Sucrose > Water] provoked significant BOLD activation ($p< 0.05$, FWE corrected for a priori search regions) in primary gustatory cortex. Activation ($p< 0.05$, FWE corrected) was also present in the associative regions of the dorsal amygdala and in the orbital areas that respond to primary rewards. Drinks/drinking day (90-day timeline followback) correlated significantly with extracted left orbital activation ($r = 0.52$, $p = 0.02$). Using stepwise multiple regression, adding sucrose liking accounted for significantly more incremental variance in drinks/drinking day than did left orbital activation alone (multiple $R= 0.79$, $p = 0.002$). Conclusions: Both the orbitofrontal response to an intensely sweet taste, as well as rated liking of that taste, accounted for significant variance in drinking behavior. The brain response to sweet tastes may be an important phenotype of alcoholism risk.

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POSTER 21: Cortical Dopamine release During a Behavioral Response Inhibition Task in Social Drinkers

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Abstract: Alcoholism is marked by impulsive behavior and loss of control over drinking. Dysregulation of dopamine (DA) within fronto-striatal circuitry may underlie cognitive processes involved in impulsivity and alcohol use disorders. To date, no one has directly demonstrated the role of cortical dopamine during tasks related to impulsivity. The goal of the current study was to determine whether a response inhibition task (stop signal) would elicit detectable extrastriatal DA release in social drinkers. We hypothesized that DA release would be detected in regions implicated in different aspects of inhibitory control, including frontal cortex, anterior cingulate cortex, and insula. [18F]Fallypride (FAL) PET scanning was used to assess changes in cortical DA during a stop-signal task relative to a baseline "go" task. Six healthy, social-drinking males (23.3 ± 6.1 y.o.) underwent scanning procedures. On separate days, subjects received one FAL scan during a "go" control task and one FAL scan during the stop-signal task. Task-order was counter-balanced. Parametric BPND images were generated and analyzed with SPM8. Preliminary voxel-wise analysis indicated DA release during the stop-signal task relative to the "go" task in several cortical regions, including insula, anterior cingulate cortex, dorsolateral prefrontal cortex, and posterior parietal cortex. Additionally, we observed a correlation between D2 availability and stop-signal reaction time in the insula, anterior cingulate, and dorsal caudate. These data support the feasibility of using FAL-PET to study DA release during a response inhibition task. Future work will use this paradigm to investigate the relationships between DA function, impulsivity, and heavy drinking.

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POSTER 22: Beer flavor induces orbitofrontal BOLD activation and correlated striatal dopamine release in heavy drinkers

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Abstract: Background: Alcohol's flavor predicts intoxication, and therefore should be a potent conditioned stimulus. We previously showed that the flavor of a preferred beer (absent intoxication) decreased binding potential of the D2/D3 radioligand [11C]raclopride. We hypothesized that orbitofrontal cortex (OFC), which projects to the ventral striatum, would likewise activate in response to beer flavor, and that BOLD fMRI responses in OFC would correlate positively with striatal DA release. Method: Male heavy drinkers (n=30, age=24 ± 2, drinks/drinking day =5 ± 3, mean ± SD) who had participated in our earlier PET study were also assessed with fMRI on a 3T Siemens Trio-Tim scanner using a similar flavor cue paradigm. The flavors of subjects' preferred beer and an appetitive control, Gatorade®, were sprayed onto the tongue, analogous to the PET study. Subjects rated craving and flavor qualities while in the scanner. Results: Flavor intensity did not differ between flavors. Beer flavor increased craving for

beer and activated the right OFC relative to Gatorade (pFWE = 0.011, corrected for an a priori OFC ROI). We also detected a positive correlation in this OFC ROI between BOLD activation to beer flavor and ventral striatal DA release from the PET study (pFWE = 0.045). Conclusions: In male heavy drinkers, the alcohol flavor cue alone was sufficient to induce right OFC activation- an area that responds to primary reinforcers. The correlation between OFC BOLD activation to beer flavor and DA release suggests measurable associations in fronto-striatal circuits known to be important in addiction. AA017661 to DAK, AA007462 to BGO

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POSTER 23: Glutamate and Choline Levels in the Anterior Cingulate are Associated with Measures of Social Cognition in Abstinent Long-Term Alcoholics

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Abstract: Background: Alcoholics have shown deficits in social cognition (conspecific social abilities that are represented in the brain). Although magnetic resonance spectroscopy (MRS) has been used to measure brain metabolite concentrations in recently abstinent alcoholic (ALC) individuals, little is known about metabolite levels after long-term abstinence. Objective: We assessed the relationships between measures of social cognition and brain metabolite concentrations of glutamate and choline in the anterior cingulate region (important in emotional and decision-making functions). Methods: Participants were 35 ALC (16 men; mean 6.73 years of sobriety) and 33 nonalcoholic (NC) age-equivalent controls (16 men). The Advanced Clinical Solutions (ACS) portion of the Wechsler Adult Intelligence Scale-IV was administered. Proton MRS was employed at 3T (TE=30 ms) to acquire metabolite data from a single voxel in the anterior cingulate region. Metabolites were quantified using LCModel and normalized to creatine levels. Results: The groups did not differ on behavioral measures of the ACS. However, relationships between ACS Social Cognition scores and brain metabolite levels differed significantly between groups. Increased scores on four subtests (Social Perception, Social Perception Affect Naming, Social Perception Prosody, and Social Perception Pairs) were associated with higher glutamate levels in the NC group and lower glutamate levels in the ALC group. A similar interaction of choline levels and groups also was significant for three of the Social Cognition measures (Social Perception, Affect Naming, and Prosody). Conclusion: These data suggest that brain metabolite levels in abstinent long-term alcoholics are negatively associated with performance on measures of social cognition.

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POSTER 24: Functional Connectivity of the Default Mode Network and Temporal Discounting of Reward in Alcoholism

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Abstract: In a recent meta-analysis, we reported that two posterior parietal regions, the posterior cingulate cortex (PCC) and precuneus, most consistently demonstrated greater alcohol cue-elicited activation among alcoholics relative to controls (Schacht et al., 2013). Intriguingly, both regions are part of the default mode network (DMN), which is comprised of areas that normally display task-induced deactivation and whose activity fluctuates synchronously at rest. However, alcoholics display cue-elicited hyperactivation of DMN areas and reduced resting connectivity of this network (Chanraud et al., 2011), perhaps contributing to these individuals' cognitive impairment and behavioral dysregulation. In particular, alcoholics tend to make more impulsive choices, opting for smaller immediate rewards rather than larger delayed ones. This study investigated whether the propensity to make such choices was related to resting connectivity of the DMN. Twenty-one non-treatment-seeking alcoholics completed a temporal discounting task and underwent a resting fMRI scan. For each subject, reversal points between impulsive and restrained choices were used to fit a hyperbolic discounting function. To determine resting DMN connectivity, correlations between a seed in the right PCC and every other voxel in the brain were calculated. On average, subjects demonstrated significant temporal discounting of delayed reward as well as resting connectivity between PCC and precuneus, lateral parietal cortex, hippocampus, and medial prefrontal cortex (mPFC). Reduced connectivity between PCC and mPFC was associated with greater temporal discounting. These data suggest that impulsive choice in alcoholism may be related to DMN dysregulation, providing a neural signature of impulsivity that may have diagnostic and treatment implications. Supported by T32 AA007474 (Schacht), K01 MH090548 (Cortese), K05 AA017435 (Anton), and P50 AA010761 (the Charleston Alcohol Research Center).

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POSTER 25: Neural and Behavioral Signatures of Conflict for Two Stroop Tasks in Heavy and Light Drinkers

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Abstract: Structural and functional changes in the frontostriatal circuitry that underlie cognitive control result from problem drinking. To identify differences associated with alcohol context, conflict type, and drinking severity, 25 heavy drinkers and matched light-drinking controls performed two distinct Stroop tasks, pictorial-alcohol and color-word, while undergoing fMRI. In the alcohol Stroop, heavy drinkers responded faster than light drinkers, whereas there were no differences for the color-word Stroop. In the alcohol Stroop, reaction times were slowest for non-

alcohol target pictures with alcohol word distracters regardless of drinking group. BOLD activity corresponding to these trials was found in rIFG, a cognitive control region. Regional beta weights were compared, and revealed similar activity patterns, but with lower magnitudes in heavy drinkers. Comparing overall task-related activity, BOLD activity was greater for light drinkers. In the color-word Stroop, incongruent trials were associated with prefrontal activations, with little difference between drinking groups. To relate drinking magnitude with neural activity, the number of consumed drinks per day was correlated with BOLD activity for each subject. In the alcohol Stroop, this measure negatively co-varied with activations in parahippocampal, cingulate, thalamus, and PFC. In the color-word Stroop, this measure co-varied with activations in cingulate and PFC distinct from those of the alcohol Stroop. While each Stroop task revealed activations in distinct brain regions, the patterns were similar between groups save that magnitudes were reduced for heavy drinkers. Such changes in control circuitry are associated with particular cognitive deficits, and thus provide a mechanism for maladaptive behaviors associated with alcohol use.

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POSTER 26: Intravenous Alcohol Increases Functional Connectivity in the Brain

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Abstract: Alcohol can fundamentally alter the way in which an individual feels. Even low to moderate doses can decrease anxiety, and impair decision-making. Our previous research used fMRI to show that activation of the amygdala, a region involved in threat detection, is altered under intoxication (Gilman et al., 2008). This raises the hypothesis that functional connectivity between the amygdala and other regions may be altered as a result of alcohol exposure. We administered intravenous alcohol as a 6% (v/v) solution in saline, or placebo, to 20 social drinkers, based on a pharmacokinetic model for alcohol (Ramchandani et al., 1999). During the infusions, participants were scanned using a 3T MRI scanner, and shown emotional facial expression images. Scans were analyzed using FSL (FMRIB Software Library v5.0). We investigated functional connectivity by completing a psycho-physiological interaction analysis (PPI), a method for investigating whether the correlation in activity between brain areas is different during different psychological contexts. We chose seed regions in the left and right amygdala. Alcohol exposure increased connectivity between the amygdala and several areas, including subgenual cingulate, subcallosal cortex, left thalamus, and frontal and parietal regions. Connectivity was increased during alcohol in both the neutral and fearful face condition. Connectivity between the amygdala and the dorsolateral prefrontal cortex correlated positively with stimulation, and negatively with sedation. Alcohol affects a range of neurotransmitter systems, and enhances inhibition through facilitation of GABAA receptors (Koob et al 1998). A recent study showed that alcohol increased connectivity of the resting-state network (Lithari, 2012). Our findings suggest that intoxication increases connectivity during task-related activation as well. This enhanced connectivity, presumably driven by inhibitory connections, may, in part, explain alcohol's effects on behavior.

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POSTER 27: Gray matter volume correlates of global positive alcohol expectancy in non-dependent adult drinkers

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Abstract: Alcohol use and misuse is known to involve structural brain changes. Numerous imaging studies have examined changes in gray matter (GM) volumes in dependent drinkers, but there is little information on whether non-dependent drinking is associated with structural changes and whether these changes are related to psychological factors – such as alcohol expectancy – that influence drinking behavior. We used voxel based morphometry (VBM) to examine whether the global positive scale of alcohol expectancy, as measured by the Alcohol Expectancy Questionnaire AEQ-3, is associated with specific structural markers and whether such markers are associated with drinking behavior in 113 adult non-dependent drinkers (66 women). Alcohol expectancy is positively correlated with GM volume of left precentrral gyrus (PCG) in men and women combined and bilateral superior anterior prefrontal gyricortices (SFGAPFC) in women, and negatively correlated with GM volume of the right ventral putamen in men. Furthermore, mediation analyses showed that the GM volume of PCG mediate the correlation of alcohol expectancy and the average number of drinks consumed per occasion and monthly total number of drinks in the past year. When recent drinking was directly accounted for in multiple regressions, GM volume of bilateral dorsolateral prefrontal cortices (DLPFC) correlated positively with alcohol expectancy in the combined sample. To our knowledge, these results are the first to identify the structural brain correlates of alcohol expectancy and its mediation of drinking behaviors.

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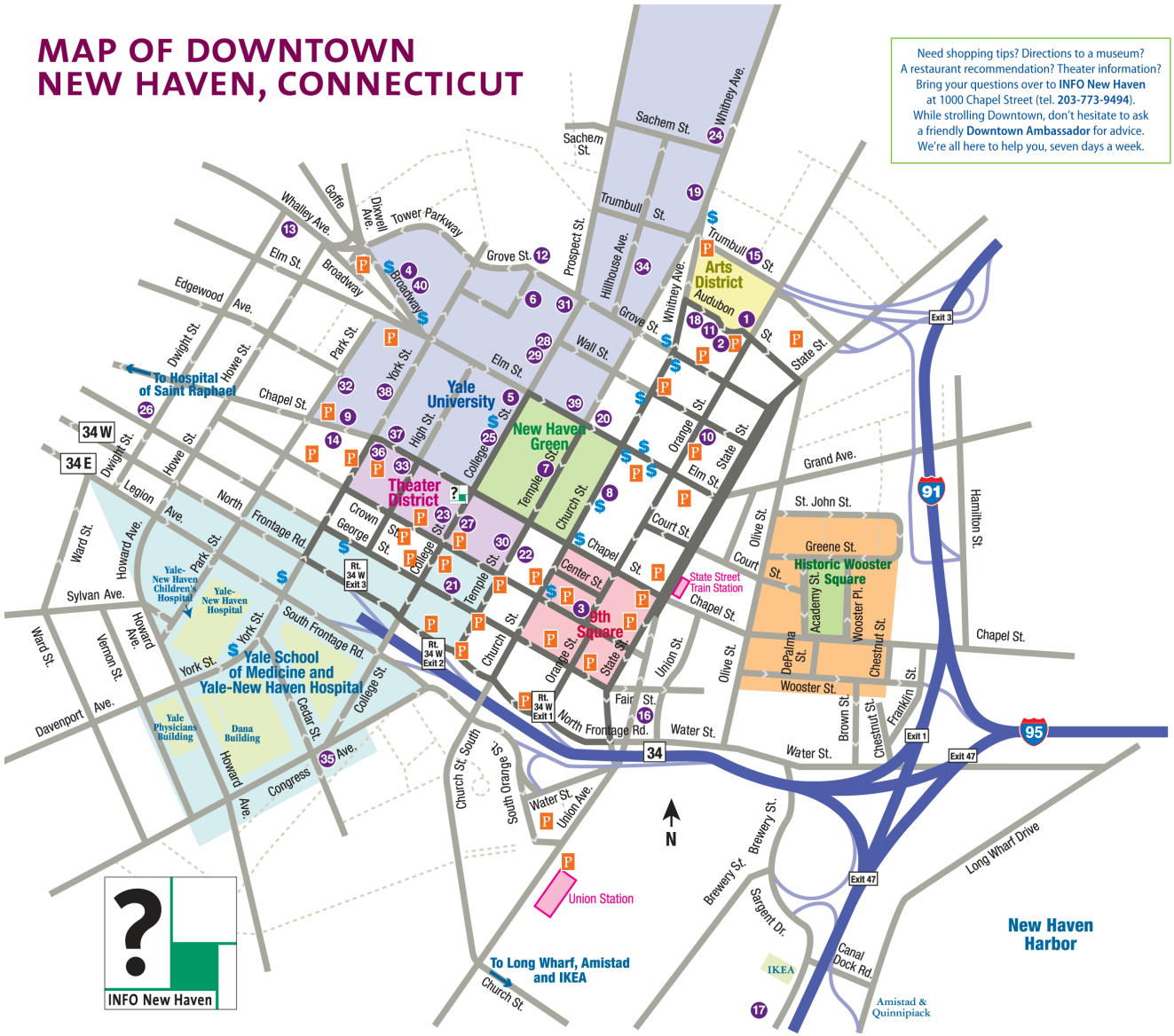

- $ ATM
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1. ACES/ECA/The Little Theater
2. Arts Council
3. Artspace
4. Barnes & Noble Yale Bookstore
5. Battell Chapel
6. Beinecke Rare Book Library
7. Center Church on the Green/Crypt
8. City Hall
9. Colony Inn
10. CT Children's Museum
11. Creative Arts Workshop
12. Grove Street Cemetery
13. Holiday Inn at Yale
14. H.T. Green Hall/New Theater/DCMA
15. John Slade Ely House
16. Knights of Columbus Museum
17. Long Wharf Theatre
18. Neighborhood Music School
19. New Haven Colony Historical Society
20. New Haven Free Public Library
21. New Haven Hotel
22. Omni New Haven Hotel at Yale
23. Palace Theater
24. Peabody Museum of Natural History
25. Phelps Gate/Yale's Old Campus
26. Ronald McDonald House
27. Shubert Theater
28. Sprague Hall/Morse Recital Hall
29. Sudler Hall/WLH
30. Temple Street Plaza
31. Woolsey Hall
32. Yale Cabaret
33. Yale Center for British Art
34. Yale Collection of Musical Instruments
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36. Yale Repertory Theatre
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39. Yale Visitor Center
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