Neuroscience and the Future of Psychiatric Diagnosis: Updates on Development of the Fifth Edition of Diagnostic and Statistical Manual of Mental Disorders

Chair: David J. Kupfer

8:30 a.m.   Autism Spectrum Disorder in DSM5
Edwin H. Cook

9:00 a.m.   DSM-5 Schizophrenia Spectrum: Major Changes, Controversies, and Linkage with the NIMH Research Domain Criteria
William Carpenter

9:30 a.m.   Anxiety Disorders, Obsessive-compulsive and Related Disorders, Trauma- and Stressor-Related Disorders, and Dissociative Disorders: Changes for DSM-5
Katharine A. Phillips

PA

10:00 a.m.   A Potential Biomarker for Addiction
Charles P. O'Brien

10:30 a.m.   Discussant: *Darrel A. Regier*

8:30 a.m. – 11:00 a.m.
Panel
Regency Ballroom 3

Developmental Programming of the Brain: Implications for Shared Mechanisms Across Neuropsychiatric Disorders

Chair: Jill M. Goldstein
Co-Chair: Paul J. Harrison

8:30 a.m.   Genome-wide Analysis Identifies Loci with Shared Effects on
                 Five Major Psychiatric Disorders
                      Jordan W. Smoller

9:00 a.m.   Shared Fetal Programming of Sex Differences in Stress
                 Response Circuitry and Endocrine Deficits in Schizophrenia and
                 Depression: Shared Mechanisms but Different Disorders
                      Jill M. Goldstein

9:30 a.m.   Long-term, Sex-specific Effects of Developmental Exposure to
                 Excess Glucocorticoids on Gene Expression in the Hypothalamus
                      Robert J. Handa

10:00 a.m.   Trans-generational Effects of Endocrine Disrupting Compounds
                 on Brain and Behavior
                      Emilie Rissman

10:30 a.m.   Discussant: *Paul J. Harrison*

PA

8:30 a.m. – 11:00 a.m.
Panel
Regency Ballroom 1

One Size Doesn't Fit All: Molecular Mechanisms Underlying Diverse Estradiol Signaling in the Brain

Chair: David Rubinow

8:30 a.m.   Roles of ERβ in the CNS
                Jan-Ake Gustafsson

9:00 a.m.   Development of Ligands for Estrogen Receptor Beta and
                the Genomic vs. Non-Genomic Pathway: Appreciating and
                Exploiting the Many Dimensions of Activity and Selectivity
                John Katzenellenbogen

9:30 a.m.   Acute Estrogen Modulation of Synapses in the Hippocampus
                Catherine Woolley

10:00 a.m.   Serotonin Transporter Function: Interaction among Ovarian
                Steroids and Antidepressants
                Alan Frazer

10:30 a.m.   Discussant: *Tracy Bale*

PA

8:30 a.m. – 11:00 a.m.
Panel
Diplomat Ballroom 1 & 2

Optimizing Cognitive Interventions for Schizophrenia: Predictive Biomarkers and Pharmacologic Enhancement

Chair: Neal R. Swerdlow

8:30 a.m.   Predictors of Cognitive Improvement after "Neuroplasticity-based" Computerized Cognitive Training in Schizophrenia
Sophia Vinogradov

9:00 a.m.   Neuroanatomical Predictors of Response to Cognitive Remediation
Matcheri Keshavan

9:30 a.m.   Combining a Cognitive Enhancer and Cognitive Training: Proof of Principle and Potential Complexities in Real-life
Shitij Kapur

10:00 a.m.   Memory Consolidation Deficits in Schizophrenia and the Combination of D-cycloserine with Cognitive Remediation
Donald Goff

10:30 a.m.   Discussant: *Deanna Barch*

PA

The Developmental Trajectory of Cannabis Effects on Neurobiological Functioning

Chair: Barbara J. Mason
Co-Chair: Yasmin Hurd

8:30 a.m.   Cannabis and the Adolescent Brain: Differentiating Vulnerability from Pathology
Dan I. Lubman

9:00 a.m.   Trajectory of Adolescent THC Exposure on Mesocorticolimbic Molecular, Epigenetic and Structural Modifications: Transgenerational Effects
Yasmin Hurd

9:30 a.m.   Δ9-tetrahydrocannabinol Impairs Reversal Learning and Visuo-spatial Associative Memory in Rhesus Macaques
Michael Taffe

10:00 a.m.   Effects of Cannabis Abuse on the Functional Brain Architecture for Visual Learning and Recognition Memory: Psychopharmacological and Developmental Evidence before and after Sustained Abstinence
Frank Haist

10:30 a.m.   Discussant: *Deborah Yurgelun-Todd*

PA

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8:30 a.m. – 11:00 a.m.
Panel
Atlantic Ballroom 3

Multi-level Classification of Schizophrenia and Bipolar Disorder: New Evidence and Controversies

Chair: Michael Davidson

8:30 a.m.   Cognitive Heterogeneity in Bipolar Disorder: Implications for Overlap with Schizophrenia
Katherine E. Burdick

9:00 a.m.   Cognitive and Functional Deficits in Schizophrenia and Bipolar Disorder vary by Psychosis Presence and History
Christopher R. Bowie

9:30 a.m.   MRI can be used to Differentiate Schizophrenia Patients from Those with Bipolar Disorder: Clinical and Theoretical Implications
Rene Kahn

10:00 a.m.   Developmental Trajectories in Schizophrenia and Bipolar Disorder: Evidence for Distinct Etiologies
Michael Davidson

10:30 a.m.   Discussant: *Avi Reichenberg*

PA

Immune Modulation of Neurodevelopment in Schizophrenia and Autism

Chair: Alan Brown
Co-Chair: Karoly Mirnics

8:30 a.m.   Novel Roles for Immune Molecules in Early Postnatal Cortical Development: Implications for Schizophrenia and Autism Spectrum Disorders
        Kimberley McAllister

9:00 a.m.   Neuroimmune Changes in a Mouse Model of the Maternal Infection Risk Factor for Schizophrenia and Autism
        Paul H. Patterson

9:30 a.m.   Elevated Maternal C-Reactive Protein and Autism in a National Birth Cohort
        Alan Brown

10:00 a.m.   Neuroimmune Changes in the Brain of Subjects with Schizophrenia or Autism
        Karoly Mirnics

10:30 a.m.   Discussant: *John H. Gilmore*

PA

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Data Blitz Session

Chair: William Carlezon

This session is comprised of rigorously timed 5 minute presentations by 17 young investigators.

11:15 a.m.   Early Exposure to Antidepressants does not Recapitulate Constitutive Serotonin Transporter Deficiency
Anne M. Andrews

11:22 a.m.   Activity-dependent Phosphorylation of MeCP2 T308 Regulates Interaction with NCoR Co-repressor Complex
Daniel H. Ebert

11:29 a.m.   A Potential Mechanism of Behavioral Alteration by Genome Diversification: The Role of Neural MILI/piRNA Complexes on De Novo L1 Retrotransposition
Daisy Lin

11:36 a.m.   Top-down Control of Raphe Circuits in Affective Resilience: Key Role of Raphe GABA Interneurons
Olivier Berton

11:43 a.m.   Compared to What? Reappraising the Early Brain Overgrowth Hypothesis in Autism
Armin Raznahan

11:50 a.m.   Allele-specific DNA deMethylation in FKBP5: A Molecular Mediator of Gene x Environment Interactions with Childhood Trauma
Tortsen Klengal

11:57 a.m.   Differential Control of Learning and Anxiety along the Dorso-ventral Axis of the Dentate Gyrus
Mazen A. Kheirbek

PL

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

12:04 p.m.   Broader Autism Phenotype: Relationships between Maternal/
              Paternal BAP, Parental SSRI Treatment, WB 5-HT and Child's
              Autism Symptoms
                  Suma Jacob

12:11 p.m.   The Functional Significance of Antipsychotic-related Cortical
              Thinning in First Episode Schizophrenia
                  Tyler A. Lesh

12:18 p.m.   Imaging the Sensitivity of [123I]5-IA-85380 to Increases in
              Acetylcholine at the Beta2-nicotinic Acetylcholine Receptors in
              Human Subjects
                  Irina Esterlis

12:25 p.m.   Self-regulation of Amygdala Activity with Real-time fMRI
              Neurofeedback in Patients with Depression
                  Kymberly Young

12:32 p.m.   Cannabinoid Facilitation of Extinction Recall via Increased
              Recruitment of Prefrontal-hippocampal Circuitry in Healthy
              Humans
                  Christine A. Rabinak

12:39 p.m.   A Brief Monetary Progressive Ratio Task Predicts Clinical
              Amotivation and Ventral Striatum Activation in Schizophrenia
                  Daniel Wolf

12:46 p.m.   The Neurosteroids Allopregnanolone and DHEA Enhance
              Emotion Regulation Neurocircuits and Modulate Memory for
              Emotional Stimuli
                  Rebecca K. Sripada

12:53 p.m.   Neuronal Signatures of Self-control in Anterior Cingulate Cortex
                  Benjamin Hayden

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

1:00 p.m.   Impaired Reward Responsiveness during Nicotine withdrawal
                 in Rats and Humans Assessed in a Translational Behavioral
                 Procedure
                 Andre Der-Avakian

1:07 p.m.   Long Acting Injectable vs. Oral Antipsychotics in Schizophrenia:
                 A Systematic Review and Meta-analysis of Mirror-image Studies
                 Taishiro Kishimoto

PL

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Early Exposure to Antidepressants does not Recapitulate Constitutive Serotonin Transporter Deficiency

Monday, Poster #64

Stefanie Altieri, Hongyan Yang, Hannah O'Brien, Julie G. Hensler, <u>Anne M. Andrews</u>
University of California, Los Angeles

Background: Administration of serotonin transporter inhibiting antidepressants (SSRIs) during a critical early postnatal period in rodents is postulated to reproduce changes in behavior arising from constitutive reductions in serotonin transporter (SERT) expression. Both animal models have medical significance related to neonatal exposure to SSRIs and differential SERT expression associated with human *Sert* gene polymorphisms, respectively.

Methods: We investigated the effects of postnatal administration of escitalopram (SCIT) or fluoxetine *vs* constitutive SERT deficiency in mice on emotion-related behaviors, presynaptic 5-HT1A receptor expression and function, and extracellular serotonin levels in adolescence and late into adulthood. SSRIs were administered daily during postnatal days 5-21. Behavior was assessed in the elevated plus maze, open field, forced swim test, and sucrose preference test. Thermic responses to the 5-HT1A receptor agonist 8-OH-DPAT were investigated. *In vivo* microdialysis and zero-net-flux analysis were used to evaluate changes in extracellular serotonin levels.

Results: Increased anxiety-related behavior, which is highly characteristic of SERT-deficient mice and humans with low-expression *Sert* alleles, was notably absent or potentiated in mice postnatally exposed to SSRIs. Furthermore, whereas 5HT1A-mediated decreases in body temperature were attenuated in SERT-deficient mice, SSRI-treated mice showed pronounced hypothermia after 8OHDPAT. Moreover, postnatal treatment with SCIT resulted in 5-HT1A autoreceptor *hyper*sensitivity. Extracellular serotonin levels have been shown to be elevated in mice with constitutive reductions in SERT, however, mice exposed to SSRIs during early postnatal development showed reduced extracellular serotonin levels as adults.

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Early Exposure to Antidepressants does not Recapitulate Constitutive Serotonin Transporter Deficiency

Monday, Poster #64 (continued)

Anne M. Andrews

Conclusions: Transient *vs* constitutive SERT deficiency produces opposing and long-lasting changes in regulation of extracellular serotonin and 5-HT1A autoreceptor function evident as early as adolescence. Persistent changes in presynaptic serotonergic circuitry are hypothesized to contribute to differential emotional phenotypes associated with these two models. Ongoing work is aimed at investigating mechanisms of differential serotonin and 5HT1A regulation. These findings have important implications for antidepressant use during pregnancy and neonatal life in humans, which corresponds to the early postnatal period in rodents. They further clarify genetic influences associated with differential SERT expression regarding effects on behavior and underlying neurotransmission.

PL

Activity-dependent Phosphorylation of MeCP2 T308 Regulates Interaction with NCoR Co-repressor Complex

Monday, Poster #77

Daniel H. Ebert, Michael E. Greenberg
Massachusetts General Hospital and Harvard Medical School

Background: Rett syndrome (RTT) is a neurodevelopment disorder with features of autism that is caused by mutations in *MeCP2*. In addition, less severe mutations in *MeCP2* can lead to a wider spectrum of neuropsychiatric disorders, including autism and psychotic spectrum disorders. MeCP2 is a nuclear protein that binds DNA at methylated cytosines and represses transcription. In neurons, MeCP2 is expressed at high levels, stochiometrically equivalent to core histones and is bound broadly across the genome. The molecular mechanisms of how loss of MeCP2 leads to RTT are not well understood. Neuronal activity triggers the phosphorylation of MeCP2 at S421. While S421A knock-in mice have defects in synapse development and behavior, the mutation had no detected effect on transcription. In addition, the proximal molecular impact of phosphorylation at S421 on MeCP2 is not known. Mass spectrometry studies have revealed many additional sites of phosphorylation in MeCP2; however, no other phosphorylation site has reproducibly been shown to be induced by neuronal activity. We hypothesized that multiple post-translational modifications of MeCP2, bound broadly across the genome, dynamically regulate its activity, modifying transcription and chromatin.

Methods: To identify novel sites of activity-dependent phosphorylation, we used phosphotryptic mapping of MeCP2 derived from ^{32}P-orthophosphate-labeled primary cortical neurons that had been left untreated or membrane-depolarized. To identify the sites of phosphorylation that correspond to the phospho-peptide spots that appeared with membrane-depolarization, we generated phosphotryptic maps of MeCP2, wildtype or with missense mutations at putative sites of phosphorylation, which had been phosphorylated using *in vitro* kinase assays. We generated phospho-site specific antibodies to each site of phosphorylation. We used these antibodies in Western blotting to determine if various stimuli in neuronal cell culture, or *in vivo*, induce the phosphorylation at each site in MeCP2.

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Activity-dependent Phosphorylation of MeCP2 T308 Regulates Interaction with NCoR Co-repressor Complex

Monday, Poster #77 (continued)

Daniel H. Ebert

We used synthetic peptides in pull-down assays and co-immunoprecipitation assays to determine if phosphorylation of T308 altered MeCP2's ability to bind co-factors. We used organotypic hippocampal cultures biolistically transfected with MeCP2 variants to determine the role of phosphorylation of MeCP2 T308 in regulating dendritic arborization.

Results: Using phosphotryptic mapping, we found multiple sites of activity-induced phosphorylation of MeCP2. Phosphorylation of these sites are differentially induced by neuronal activity, brain-derived neurotrophic factor, or agents that elevate the intracellular level of cAMP, suggesting that MeCP2 functions as an epigenetic regulator of gene expression that integrates diverse signals from the environment. By Western blotting with the phospho-site specific antibodies to MeCP2 pT308, we find that the phosphorylation of MeCP2 T308 is induced by neuronal activity upon calcium influx into neurons via L-type calcium channels and NMDA receptors. We find that the common RTT missense mutations at R306, by disrupting the basophilic kinase recognition motif, prevent phosphorylation of MeCP2 T308. Phosphorylation of MeCP2 T308 abrogates an interaction of MeCP2 with NCoR co-repressor complex and impairs the ability of MeCP2 to provide transcription repression. We find that phosphorylation of MeCP2 T308 regulates dendritic arborization, a phenotype altered in RTT.

Conclusions: These findings indicate that neuronal activity induces phosphorylation of MeCP2 at T308 and that phosphorylation at this site disrupts an interaction with NCoR co-repressor complex and regulates MeCP2's ability to mediate transcription repression. The NCoR co-repressor complex contains HDAC3, a histone deacetylase. The regulated interaction between MeCP2 and NCoR may modulate histone acetylation in response to neuronal activity to control transcription in neurons. The phosphorylation of T308 has not been observed previously in mass spectrometry studies from many different laboratories, indicating the utility of phosphotryptic mapping in identifying sites

PL

Activity-dependent Phosphorylation of MeCP2 T308 Regulates Interaction with NCoR Co-repressor Complex

Monday, Poster #77 (continued)

Daniel H. Ebert

of activity-dependent phosphorylation. The common RTT missense mutations at R306 both disrupt an interaction with NCoR and prevent experience triggered phosphorylation of MeCP2 at T308. The loss of this regulated interaction between MeCP2 and the NCoR co-repressor complex may underlie critical aspects of RTT. Investigation of activity-dependent phosphorylation of MeCP2 may help identify targets for novel therapeutics for RTT and the broader spectrum of neuropsychiatric disorders caused by mutations in *MeCP2*.

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

A Potential Mechanism of Behavioral Alteration by Genome Diversification: The Role of Neural MILI/piRNA Complexes on De Novo L1 Retrotransposition

Monday, Poster #114

Daisy Lin, Jay A. Gingrich
Columbia University/New York State Psychiatric Institute

Background: Mobile retrotransposable elements, such as the long interspersed element (LINE) L1, can insert copies of themselves throughout the genome and influence the expression of nearby genes. This is one of the mediators of genome diversification. Recent findings show that L1 element insertion can occur in dividing neurons, resulting in somatic cell diversification and possibly neuropsychiatric disorders such as Rett syndrome and schizophrenia. Our group is interested in developmental pathways leading to neuropsychiatric disorders. As such, while examining mechanisms of paternal influence on offspring behavioral outcomes, we discovered a possible role of the MILI/piRNA system as mechanism of neural L1 suppression. The mouse MILI gene is a member of the well-conserved PIWI family of proteins that are expressed across phylogenetically diverse species. Canonically, the MILI/piRNA complex has been shown to suppress L1 activity in the male germline, but a role for regulating L1 expression in dividing neurons has not been established. We hypothesized that there is a MILI/piRNA system in the brain and it has a direct impact on the behavior of the mouse by the regulation of L1 activity.

Methods: The expression of MILI in the mouse brain was detected by: real-time PCR, western blot hybridization and *in situ* hybridization (data taken from Allen Brain Atlas). Brain samples from wildtype (WT) and MILI$^{+/-}$ mice of C57BL/6 background were used to compare MILI expression change between the two sets of samples. In order to understand the impact of neural MILI on neuronal L1 expression, semi-quantitative reverse transcription PCR probing the expression of a retrotransposition competent L1 transcript from the L1 A subfamily was performed. To examine whether there are changes in the behavior of these two sets of mice, our breeding approach was to mate C57BL/6 MILI+/+ and +/- sires (but not -/- sires, since they are sterile) with WT C57BL/6 females. We then

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

A Potential Mechanism of Behavioral Alteration by Genome Diversification: The Role of Neural MILI/piRNA Complexes on De Novo L1 Retrotransposition

Monday, Poster #114 (continued)

Daisy Lin

examined several different behavioral dimensions using an array of behavioral tests such as: the open field, light-dark choice test, social interaction (SI), elevated plus maze and forced swim test (FST).

Results: Contrary to what is generally thought to be a male mouse germline specific gene, here we show that, MILI, is also expressed in the mouse brain. Both MILI mRNA and protein expression are significantly reduced in the brains of MILI$^{+/-}$ compared to MILI$^{+/+}$ mice. We further observed that L1 expression is significantly increased in the brains of MILI$^{+/-}$ offspring compared to MILI$^{+/+}$ offspring of the same fathers. We observed that MILI$^{+/-}$ offspring had depression and SI related behavioral changes compared to MILI$^{+/+}$ offspring (demonstrated by increased floating duration during FST and increased time spent with social target during SI test, respectively). It could be argued that this change in MILI$^{+/-}$ offspring is due to inheritance of genetic diversity that arose in the germline of MILI$^{+/-}$ fathers, in this case we would observe changes in all offspring of MILI$^{+/-}$ fathers compared to offspring of MILI$^{+/+}$ fathers. However, changes in behavior were only observed in MILI$^{+/-}$ offspring, but not MILI$^{+/+}$ offspring of the same MILI$^{+/-}$ fathers. Based on the data, we now know that changes in the behavior of MILI$^{+/-}$ offspring is due to a direct effect of the MILI gene and independent of paternal germline MILI expression.

Conclusions: In the course of examining the effect of reduced paternal MILI expression on offspring behavior, we unexpectedly observed an independent effect of inheriting a null MILI allele on offspring behavior. This observation surprised us because MILI activity (if indeed testes specific) should not affect the brain. Here, we show that MILI is expressed in the brain. We wondered whether the MILI/piRNA complex might also function in dividing neurons. If so, the MILI haploinsufficient mice might exhibit behavioral differences due to an increase in *de novo* L1 insertions. Indeed, we observed increased L1 expression in the

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Data Blitz Session
Regency Ballroom 2

A Potential Mechanism of Behavioral Alteration by Genome Diversification: The Role of Neural MILI/piRNA Complexes on De Novo L1 Retrotransposition

Monday, Poster #114 (continued)

<u>Daisy Lin</u>

brains of MILI$^{+/-}$ mice. Together, these observations will allow future work to directly assess the presence of piRNA species in neurons and determine whether MILI/piRNA complexes control *de novo* L1 insertion in neurons. Somatic L1 insertions in neural populations has been proposed as a mechanism for generating behavioral diversity as well as a potential etiology for neuropsychiatric disorders. A better understanding of the role of the MILI/piRNA system in L1-mediated neuronal genome diversification may lead to new insights into the origins of certain neuropsychiatric disorders as well as new preventative strategies.

PL

Top-down Control of Raphe Circuits in Affective Resilience: Key Role of Raphe GABA Interneurons

Monday, Poster #115

Collin Challis, Julie Espallergues, Sheryl Beck, <u>Olivier Berton</u>
University of Pennsylvania

Background: Imaging studies have revealed dysfunctions in the ventromedial prefrontal cortex (vmPFC) of patients with major depressive disorder (MDD). Deep brain stimulation (DBS) targeting the vmPFC is therapeutic in patients suffering from treatment resistant depression and produces antidepressant-like responses in rodents. Lesion studies in rodents suggest that serotonin (5-HT) partly mediates this antidepressant-like therapeutic activity of vmPFC DBS. The top-down control exerted by vmPFC over raphe circuits has also been implicated in stress coping and the expression of affective resilience. Underlying circuit mechanisms are poorly understood. The median and dorsal Raphe Nuclei (RN) receive strong excitatory inputs from the vmPFC. Although the RN contains a large proportion of 5-HT neurons, previous reports suggest that excitatory mPFC inputs preferentially synapse onto GABAergic interneurons. Given their position as primary postsynaptic target for vmPFC inputs in the RN, we hypothesized that Raphe GABA interneurons may be pivot to regulate vmPFC-RN connectivity during stress and the expression of affective resilience

Methods: We used combined genetic, electrophysiological and behavioral approaches to dissect the function of RN GABA interneurons in the social defeat (SD) mouse model of depression. Reporter mice with fluorescently-tagged GABA (GAD-Tomato) or 5-HT neurons (Pet1-tomato) were exposed to 10 days of social defeat and were segregated into resilient and vulnerable subpopulations based on social avoidance tests. SD-induced cFos was mapped using immunohistochemistry. Whole cell recordings of genetically identified neurons were conducted to characterize SD-induced changes in intrinsic properties of RN neurons and their synaptic inputs. mPFC-RN connectivity was assessed morphologically using viral-mediated track tracing and functionally using optogenetic stimulation and cFos mapping. To examine the role of RN excitatory inputs, ChR2 was targeted to vmPFC pyramidal neurons using an AAV vector under the control CamK2a

PL

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Top-down Control of Raphe Circuits in Affective Resilience: Key Role of Raphe GABA Interneurons

Monday, Poster #115 (continued)

Olivier Berton

promoter. Axon terminals of transduced neurons were photostimulated locally in the DR. To examine the role of local 5-HT and GABA neurons in the expression of vulnerable and resilient behavioral phenotypes, the proton pump Arch was targeted to GABA or 5-HT neurons thereby allowing selective photosilencing of each cell populations. Photostimulation and photosilencing were conducted in freely moving mice, either during the sensory phase of social defeat training or during social interaction tests.

Results: We found GABA neurons to be preferentially activated over 5HT neurons after repeated experiences of SD. cFos induction by SD was significantly greater in stress-resilient than vulnerable mice and was topographically distributed in the RN. A strikingly similar pattern of activation was observed following direct photostimulation of vmPFC terminals in the RN. Using AAV-mediated anterograde tracing we observed a topographical overlap between the distribution of cFos expressing GABA neurons in the RN and the distribution of mPFC terminals, a result suggesting that vmPFC inputs drive GABAergic activation in RN during defeat stress and the degrees of this mPFC-driven GABAergic activation predicts subsequent social avoidance. In contrast to cFOS data, whole-cell electrophysiology of genetically identified GABA neurons revealed a diminished glutamatergic input in resilient mice. These results suggest that repeated phasic activation of RN GABA neurons during SD in resilients may trigger neuroadaptations that result in a tonic reduction of glutamatergic synaptic inputs. Lastly, we found that photosilencing DRN GABA neurons during the sensory contact period that follows physical defeat but not social interaction test, promoted the expression of a resilient phenotype and fully prevented social avoidance.

Conclusions: These results highlight a key role for DRN GABAergic neurons in expression of resilience to social defeat and stress induced neuroplasticity of mPFC raphe circuits.

PL

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Compared to What? Reappraising the Early Brain Overgrowth Hypothesis in Autism

Monday, Poster #125

<u>Armin Raznahan</u>, Rhoshel Lenroot, Audrey Thurm, Marta Gozzi, Sarah Spence, Susan Swedo, Jay Giedd
National Institute of Mental Health

Background: The presence of a robust association between Autism Spectrum Disorder (ASD) and early brain overgrowth (EBO) is widely accepted, prominent in lay understanding of the condition, and continues to influence the cutting edge of ASD research. The bulk of published data regarding early brain growth in ASD comes from studies of head circumference (HC), an excellent proxy for brain size in early childhood. Two developments since last systematic review of EBO studies in ASD urge reappraisal of the evidence base behind the influential notion in ASD research however: (i) multiple independent studies outside the field of ASD research have found that large contemporary samples of typically developing children appear to show EBO relative to HC reference norms (HCRNs) that have been used by several seminal EBO reports in ASD, and (ii) multiple new longitudinal tests of the EBO hypothesis have been published which build on earlier work by using larger sample sizes and contrasting HC growth in ASD with locally recruited controls (LRCs) as well as HCRNs.

PL

Methods: We systematically review all published HC tests of the EBO hypothesis in ASD (34 studies encompassing ~ 3k ASD and 60k LRC participants), and analyze new data from a cohort of 57 preschool-aged male Caucasian children (35 ASD, 22 LRCs) with ~ 330 longitudinal HC measures between birth and age 18 months. Our study (i) distinguishes cross-sectional analyses of mean HC in ASD within a given age-range from longitudinal analyses that can measure brain size change, and (ii) assesses the dependence of evidence for EBO on the type of control data with which HC data in ASD are compared. We supplement traditional sources of HCRNs in ASD research [such as the Center for Disease Control (CDC)] with recently published "Primary Care Norms" (PCNs): the largest (~500k HC measures between birth and 18 months) contemporary set of US-based HCRNs.

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Compared to What? Reappraising the Early Brain Overgrowth Hypothesis in Autism

Monday, Poster #125 (continued)

Armin Raznahan

Results: Systematic Review: The majority (> 65%) of HC studies in ASD are cross-sectional. Of the 11 existent longitudinal HC studies, 10 have been published since the EBO hypothesis was last subjected to systematic review. 85% of all HC studies in ASD make use of HCRNs. Cross-sectional studies that do not find evidence for brain enlargement in ASD tend to include a comparison with LRCs rather than solely relying on HCRNs (p=0.0006), and tend to use smaller age-ranges for calculating mean HC (p=0.03). All published comparisons of HCRN-defined macrocephaly rate in ASD vs. LRC groups have been negative. Elevated macrocephaly rates in ASD relative to HCRN-defined null of 3% vary 6-fold, with older HCRNs tending to identify higher rates (p=0.04). Over 85% of all longitudinal HC tests of the EBO hypothesis have compared ASD data to CDC HCRNs and identified rapid HC centile increases in ASD between birth and ~age 12 months. In contrast, most studies comparing HC growth between ASD participants and LRCs do not find evidence for EBO in ASD during the first year of life. By transforming existing HC reports into a common CDC reference frame we confirm the well-replicated pattern of EBO in ASD relative to CDC HCRNs, but show that the timing of this EBO is almost perfectly recapitulated by (i) 2012 PCN HCRNs which incorporate > 500k HC measures from typically developing children in the US, *and* (ii) a weighted mean summary of HC growth for all LRCs included in ASD research. New Data Analysis: We did not find any cross-sectional differences in raw HC between ASD and LRCs at any pediatric surveillance time-point in the first 24 months of life, or group differences in raw HC change between time-points. Both ASD and LRC groups showed abnormally accelerated HC growth relative to CDC HCRNs, but had a stable mean PCN HC centile that remained within normal ranges between birth and 24 months.

Conclusions: By combining systematic review with analysis of new data and comparisons across multiple HCRNs we find several lines of evidence that oppose the hypothesis of EBO in ASD as currently formulated. Specifically

Compared to What? Reappraising the Early Brain Overgrowth Hypothesis in Autism

Monday, Poster #125 (continued)

Armin Raznahan

(i) EBO in ASD relative to CDC appears to reflect a mis-match between CDC norms and contemporary patterns of HC growth that is shared by large samples of healthy children, (ii) HCRN-defined macrocephaly rates in ASD have usually been indistinguishable from those in contemporaneously ascertained LRCs, and (iii) macrocephaly rate reports that lack parallel LRC comparison appear to vary as a function of how old the HCRNs used define macrocephaly were. Existing data potentially provide partial support for a subtle divergence of HC growth between a sub-group of children with ASD and LRCs during the second year life that (i) results in ~5mm group difference in mean HC at 24 months, and (ii) may index body size and SES related confounds.

PL

11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Allele-specific DNA deMethylation in FKBP5: A Molecular Mediator of Gene x Environment Interactions with Childhood Trauma

Tuesday, Poster #6

Torsten Klengel, Divya Mehta, Christoph Anacker, Jens C. Pruessner, Carmine M. Pariante, Thaddeus WW. Pace, Kristina B. Mercer, Helen S. Mayberg, Bekh Bradley, Charles Nemeroff, Florian Holsboer, Christine M. Heim, Kerry J. Ressler, Theo Rein, Elisabeth Binder
Max-Planck-Institute of Psychiatry

Background: For most psychiatric diseases neither a genetic disposition nor environmental factors on its own are sufficient to elicit a specific disorder. Rather, genetic variation and environmental exposure interact to shape the development and function of the human brain and ultimately moderate the risk to suffer from psychiatric disorders. Here, we delineate an epigenetic mechanism for the gene x environment (GxE) interaction of the gene with childhood abuse on the development of post-traumatic stress disorder (PTSD) in adulthood.

Methods: Data from this study were collected as part of the Grady Trauma Project and replication was performed in data from the Conte Center Study for the Psychobiology of Early-Life Trauma (Emory University, Atlanta, GA, USA). Individuals were assessed using different measures for PTSD and childhood abuse. For genotyping and pyrosequencing, DNA was extracted from peripheral blood. Methylation analysis was performed by pyrosequencing of bisulfite treated genomic DNA. The functional impact of differential methylation was analyzed using a CpG free luciferase reporter construct and an GR sensitivity assay. In addition, we used a multipotent hippocampal progenitor cell line to assess the methylation status of FKBP5in human neuronal cells in response to dexamethasone stimulation.

Results: FKBP5 rs1360780 interact with child abuse exposure (CTQ) on the development of current PTSD symptoms (mPSS) in adulthood ($F_{1963,2} = 4.40$, $P = 0.012$). The risk to suffer from lifetime PTSD (CAPS) is significantly increased by exposure to early trauma in *FKBP5* risk allele carriers ($X^2 = 28.6$, df $= 2$, $P < 0.001$), but not in carriers of the protective genotype ($X^2 = 2.02$, df $= 2$, $P = 0.36$).

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Data Blitz Session
Regency Ballroom 2

Allele-specific DNA deMethylation in FKBP5: A Molecular Mediator of Gene x Environment Interactions with Childhood Trauma

Tuesday, Poster #6 (continued)

Torsten Klengel

Pyrosequencing of bisulfite treated DNA of highly traumatized individuals and controls revealed a significant demethylation of CpGs around glucocorticoid responsive elements (GREs) of *FKBP5* in abused individuals. We found a significant interaction of *FKBP5* genotype and childhood abuse on DNA methylation level in 3 CpGs in intron 7 ($F_{73,1}$ = 31.01, P_{corr} < 0.001). When correlating level of child abuse using the Childhood Trauma Questionnaire (CTQ) with the methylation of intron 7, significant differences in the correlation coefficients were observed between the risk allele carriers and carriers of the protective allele (R=-0.646, *P<0.001* and R=0.414, *P*=0.078, Fisher Z-score of -4,23, *P*-value=7.0×10^{-5}). This emphasizes the effects of early trauma severity on *FKBP5* demethylation in risk allele carriers, but not in carriers of the protective allele. Replication in an independent cohort from the Conte Center Study confirm these findings. Employing a CpG-free reporter construct, we demonstrate that changes in DNA methylation in intron 7 alter glucocorticoid responsiveness of *FKBP5 in vitro*. An *ex-vivo* GR sensitivity assay demonstrate that intron 7 DNA methylation alters the ultra-short feedback loop between GR and *FKBP5* and thus GR sensitivity with reduced methylation in intron 7 associated with higher induction of FKBP5 by GR, representing an enhancement of the ultra-short feedback loop leading to increased GR resistance. In a multipotent human hippocampal progenitor cell line we show that *FKBP5* demethylation is initiated by GR-activation with dexamethasone which led to a highly significant DNA demethylation in CpGs in intron 7 similar to the CpGs in intron 7 affected by early trauma in *FKBP5* risk allele carriers (average of 17.1% demethylation in these 3 CGs, *P<0.001*). We currently extend these results comparing DNA methylation changes in dexamethasone treated hippocampal progenitor cells with trauma exposed individuals on Illumina's 450k methylation bead chip. Preliminary data suggest a strong allele-dependent overlap between methylation in neuronal cells and childhood abused individuals.

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Allele-specific DNA deMethylation in FKBP5: A Molecular Mediator of Gene x Environment Interactions with Childhood Trauma

Tuesday, Poster #6 (continued)

Torsten Klengel

Conclusions: *FKBP5*, an important regulator of the stress hormone system, increase the risk of developing PTSD by allele-specific, childhood trauma-dependent demethylation of CpGs in functional GREs of *FKBP5*. For the first time, we delineate a molecular mechanism by which environmental impact in early life is encoded in epigenetic modifications and moderated by genetic predisposition influencing the development of psychiatric symptoms in later life. Our findings might be of particular relevance for the developing organism since the effects on DNA methylation seemed to be restricted to exposure to childhood trauma and were not influenced by traumatic experiences in adulthood, suggesting a possible sensitive period in early development for these epigenetic effects.

PL

Differential Control of Learning and Anxiety along the Dorso-ventral Axis of the Dentate Gyrus

Tuesday, Poster #22

Mazen A. Kheirbek, Liam J. Drew, Daniel Costantini, Nesha Burghardt, Lindsay Tannenholz, Susanne E. Ahmari, Hongkui Zeng, Andre Fenton, Rene Hen
Columbia University

Background: The hippocampus, in addition to its role in learning and memory, is increasingly implicated in the pathophysiology of anxiety disorders. The hippocampus shows marked variation along its dorso-ventral axis in terms of both afferent and efferent connectivity, yet it is unclear if this heterogeneity mediates its differential contributions to memory processing and to anxiety-like behavior, whether the three primary subregions of the hippocampus (dentate gyrus, CA3 and CA1) perform the same operations along the dorso-ventral axis, or if real-time activity changes in the hippocampal circuitry can acutely affect emotional state. Granule cells (GCs) of the dentate gyrus subregion of the hippocampus are implicated in affective processing, as they are especially susceptible to damage by elevated stress hormone levels, and adult neurogenesis, a unique feature of the DG, modulates emotional states and is required for some of the behavioral effects of antidepressants. To test the specific contribution of DG GCs to emotional behavior we examined the effects of acutely increasing or decreasing activity in DG GCs in tests of cognition and mood.

Methods: We used optogenetic techniques to modulate activity in DG GCs in real-time. To target opsin expression selectively to GCs we used a POMC-Cre line crossed to conditional eNpHR3.0-EYFP and ChR2-tdTomato lines. Mice were implanted with fiber optics targeted to either the dorsal or the ventral DG, and tested for behavioral effects of light induced inhibition or excitation. To test the role of DG GCs in learning and anxiety-like behavior, mice were tested in contextual fear conditioning, active place avoidance, elevated plus maze and open field test.

Results: Dependent on their position along the dorso-ventral axis of the hippocampus, GCs control specific features of anxiety-related behavior and

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Data Blitz Session
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Differential Control of Learning and Anxiety along the Dorso-ventral Axis of the Dentate Gyrus

Tuesday, Poster #22 (continued)

Mazen A. Kheirbek

contextual learning. In mice expressing eNpHR3.0 in the DG, inhibition GCs in the dorsal, but not ventral, DG blocks the encoding, but not the retrieval, of contextual fear memories and the rapid and flexible encoding of spatial information in active place avoidance, while having no effect on anxiety-related behaviors. In contrast, elevating the activity of GCs in the dorsal DG with ChR2 resulted in a dramatic increase in exploratory behavior, while elevating activity in the ventral DG powerfully suppressed innate anxiety.

Conclusions: By using optogenetic techniques that allow neural activity in DG GCs to be acutely, reversibly and bidirectionally manipulated, this study supports the hypothesis that the dorsal and ventral poles of the hippocampus are functionally distinct and demonstrates that hippocampal activity not only has a mnemonic function but can also strongly influence anxiety-related behaviors. Specifically, dorsal GCs were shown to contribute to spatial and contextual learning, where they were required for rapid encoding of contextual information, but not for memory retrieval. Surprisingly, elevating dorsal DG activity also induced a dramatic increase in exploratory behavior in novel environments. The ventral DG was not required for contextual fear learning, but was found to exert a major influence on innate anxiety-like behavior. Recent studies employing deep brain stimulation to ameliorate symptoms of treatment resistant depression highlight the effectiveness of circuit based approaches for the treatment of psychiatric illness. Our results provide the first evidence that increasing activity in the ventral DG can reduce innate anxiety without affecting learning. The clear dissociation between the contributions of the dorsal and ventral poles of the DG to cognitive function and anxiety offers a rationale for pursuing strategies that target the ventral DG to treat anxiety with minimal cognitive side effects.

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Data Blitz Session
Regency Ballroom 2

Broader Autism Phenotype: Relationships between Maternal/paternal BAP, Parental SSRI Treatment, WB 5-HT and Child's Autism Symptoms

Tuesday, Poster #53

Tal Levin-Decanini, Nell Maltman, Guter Stephen, Edwin H. Cook, <u>Suma Jacob</u>
University of Illinois, Chicago

Background: Subtle expression of related traits in relatives of persons with autism spectrum disorders (ASD), known as the broader autism phenotype (BAP) has been demonstrated previously. Elevated whole blood serotonin (WB 5-HT) is the most long-standing and best-replicated biological findings in ASD. Previous research has shown a relationship between whole blood serotonin levels and parental ratings of depression but those studies did not include measurement of BAP. The present study focused on the relationship between parental BAP and sex, selective serotonin reuptake inhibitor (SSRI) treatment, and the child's autism symptoms.

Methods: Subjects included 197 children with ASD, and 357 of their parents (n=357). Of these parents, 25 were taking SSRIs. Proband symptoms were measured using the ADOS, ADI-R, CRI, and RBS-R domain scores. Parental BAP was measured by the Broader Autism Phenotype Questionnaire (BAPQ). In addition to total BAPQ, Aloofness, Rigidity, Pragmatic Language subscores, nine clinical expert raters identified items that measure autism-related "insistence on sameness" (IS) in order to examine those characteristics in the parent measure that may be more closely related to proband characteristics and WB 5-HT. The BAP-IS subscale was obtained by summing responses across six statements in the Rigid subscale of the BAPQ. MANCOVAs were performed to explore relationships between sex and SSRI medication use on the subscales of parent BAPQ and proband symptom scores.

Results: There were significantly different average BAPQ scores across sex and medication groups, although the effect size was modest (Wilks' $\Lambda = 0.881$, $F(12,709) = 2.897$, p $=0.001$; $\eta_\rho^2 = 0.041$). Sex and medication had significant effects on the Total score ($F(3,271) = 5.103$, p $= 0.002$; $\eta_\rho^2 = 0.058$) and on Aloof ($F(3,271) = 6.015$, p $= 0.001$; $\eta_\rho^2 = 0.062$), Rigid ($F(3,271) = 5.212$, p $= 0.001$; $\eta_\rho^2 = 0.055$)

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Broader Autism Phenotype: Relationships between Maternal/paternal BAP, Parental SSRI Treatment, WB 5-HT and Child's Autism Symptoms

Tuesday, Poster #53 (continued)

Suma Jacob

and the subset of items related to IS (F(3,271) = 5.103, p = 0.002; η_p^2 = 0.053). Post-hoc analyses showed mothers others taking SSRIs also had higher Total (p=0.021) and Rigid subscale scores (p = 0.026) than those mothers not on SSRI medications. Fathers not taking SSRIs had higher Aloof and Rigid scores compared to mothers not taking SSRIs.

Conclusions: The results of this study showed that among parents not on SSRI medication, fathers score significantly higher on multiple measures of the BAPQ than mothers, namely BAP Total, Aloof and IS-related items. We did not find a relationship between parental Rigid scores and child Insistence on Sameness scores. However, we did confirm correlation of WB 5-HT between parents and children and found higher Aloof and Rigid scores in fathers compared to mothers. The increase in BAPQ scores in our subsample of mothers being treated with SSRIs was unexpected and requires careful interpretation and further study.

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Data Blitz Session
Regency Ballroom 2

The Functional Significance of Antipsychotic-related Cortical Thinning in First Episode Schizophrenia

Tuesday, Poster #60

Tyler A. Lesh, Costin Tanase, Tara Niendam, Jong Yoon, J Daniel Ragland, Michael Minzenberg, Marjorie Solomon, Cameron Carter
University of California, Davis

Background: Findings of structural and functional brain abnormalities are consistently replicated in magnetic resonance imaging (MRI) studies of patients with schizophrenia. Studies using voxel-based morphometry and measurements of cortical thickness identify gray matter reductions and cortical thinning in prefrontal and temporal structures, as well as increased volume in the basal ganglia. Schizophrenia patients typically show altered activation of these same regions, particularly reduced activity in dorsolateral prefrontal cortex, during fMRI tasks tapping the fronto-parietal cognitive control circuit (e.g., AX-CPT, N-back). However, the degree to which antipsychotic medications are associated with changes in brain structure, function, and behavioral performance within the illness are poorly understood. We sought to examine these effects in first episode schizophrenia patients, who were evaluated within one year of illness onset, utilizing cortical thickness measurements and fMRI. Cortical thickness measurements were derived from surface-based registration methods where homologous regions are matched, as opposed to relying upon spatial smoothing of VBM analyses, potentially offering increased sensitivity to subtle cytoarchitectural changes. The AX-CPT was used as a measure of functional fronto-parietal recruitment. When compared to healthy controls, we hypothesized that patients with schizophrenia would show thinner cortex and reduced activation of dorsolateral prefrontal cortex, as well as lower performance reflecting impaired cognitive control. Additionally, we anticipated that patients receiving antipsychotic medication compared to those who were unmedicated would show more extensive prefrontal cortical thinning in the context of improved functional activity and better behavioral performance. **Methods:** Medicated (n=24) and unmedicated (n=21) first episode schizophrenia patients as well as healthy control participants (n=28) were identified from referrals to the UC Davis Early Detection and Preventative Treatment clinic

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Data Blitz Session
Regency Ballroom 2

The Functional Significance of Antipsychotic-related Cortical Thinning in First Episode Schizophrenia

Tuesday, Poster #60 (continued)

Tyler A. Lesh

using the Structured Clinical Interview for DSM-IV. Images were obtained on a 1.5-Tesla General Electric scanner and processed using Freesurfer 4.1 (structural analysis) and SPM8 (fMRI analysis). Statistical analyses of structural data were conducted using a vertex-wide threshold of $p < .01$ followed by a cluster-wise correction for multiple comparisons (5000 Monte Carlo simulations, $p < 0.05$). Statistical analysis of AX-CPT fMRI data focused on CueB versus CueA trials and both whole-brain cluster-corrected and DLPFC region of interest analyses were performed.

Results: Analyses of structural data revealed significant cortical thinning in medicated patients with schizophrenia relative to healthy controls in dorsolateral prefrontal and orbitofrontal cortices. Unmedicated schizophrenia patients demonstrated no significant cortical thickness differences from healthy controls after cluster-wise correction. A comparison of medicated and unmedicated patients revealed significant cortical thinning in medicated patients only in the DLPFC. With regard to brain activation during the AX-CPT, both patient groups showed reduced activity in frontal and parietal regions compared to healthy controls. However, medicated schizophrenia patients also demonstrated higher DLPFC activation compared to unmedicated patients. A similar pattern emerged in behavioral performance, in which medicated patients showed higher performance (as indexed by d'-context scores) than unmedicated patients.

Conclusions: These findings highlight the complex relationship between antipsychotic treatment and the structural, functional, and behavioral deficits repeatedly identified in schizophrenia. Although treatment with antipsychotic medications was associated with prefrontal cortical thinning, treatment was also related to better cognitive control and increased prefrontal functional activity that was comparable to healthy controls. This study also highlights the critical importance of multi-modal analyses in understanding the complex nature of structural and functional neurophysiological changes in the disorder.

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Data Blitz Session
Regency Ballroom 2

Imaging the Sensitivity of [123I]5-IA-85380 to Increases in Acetylcholine at the Beta2-nicotinic Acetylcholine Receptors in Human Subjects

Tuesday, Poster #74

Irina Esterlis, Jonas Hannestad, Frederic Bois, Andrew Sewell, Rachel Tyndale, John Seibyl, Marina Picciotto, John H. Krystal, Marc Laruelle, Richard Carson, Kelly Cosgrove
Yale University

Background: Introduction: Acetylcholine is one of the major neurotransmitters in the brain and has been implicated in psychiatric and medical illnesses. Our evaluation of the nicotinic acetylcholine system (β_2*-nAChR) in vivo in individuals with current and remitted major depressive disorder demonstrated significantly lower receptor availability associated with current depression (and less so with remitted depression) compared to controls. We followed up with a postmortem study to quantify β_2-nAChR density under the conditions where endogenous acetylcholine is washed out, and observed no difference in β_2-nAChR density between individuals with and without major depressive disorder. An interpretation of these results is β_2*-nAChRs might be lower in depression, and/or that increased acetylcholine concentration in the vicinity of β_2*-nAChR might reduce the availability of these receptors to the binding of the radioligand. Previously, Fujita and colleagues showed that the high affinity β_2*-nAChRradioligand [123I]5-IA-85380 ([123I]5-IA) may be sensitive to extracellular increases in acetylcholine in baboons [1]; however, such an examination in humans has lagged. Given that acetylcholine is one of the major neurotransmitters in the brain and has been implicated in the psychiatric andmedical illnesses, we developed a paradigm to interrogate the cholinergic system in vivo via use of [123I]5-IA single photon emission computed tomography (SPECT) imaging and physostigmine, a centrally-acting acetylcholinesterase inhibitor.
Methods: Six healthy subjects (3 men, 3 women; 31±4.1yrs) participated in one [123I]5-IA SPECT study and one magnetic resonance imaging (MRI) scan. MRI was used to guide placement of regions of interest for SPECT scans. [123I]5-IA was administered as a bolus plus constant infusion (B/I 7.0h); total injected dose

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Imaging the Sensitivity of [123I]5-IA-85380 to Increases in Acetylcholine at the Beta2-nicotinic Acetylcholine Receptors in Human Subjects

Tuesday, Poster #74 (continued)

Irina Esterlis

was 390.2±13.2MBq. After three 30-min baseline scans at 6-8h post infusion, physostigmine (1-1.5mg) was administeredIV over 60 min, and nine additional 30-min scans were collected during the next 6h. The outcome measure was V_s/f_p (specific volume of distribution), calculated as V_T/f_p (estimated receptor availability) minus V_{ND}/f_p (nondisplaceable binding; previously estimated in a smoking to satiety paradigm [2]).

Results: We observed a peak average decrease in V_s/f_p of 25±15% in cortical regions (t=3.2, p=0.03), 15±11% in thalamus (t=2.8, p=0.05), 16±14% in striatum (t=2.6, p=0.06), and 35±34% in cerebellum (t=2.8, p=0.05). This effect reflected a combination of a significant decrease in tissue concentration of 5-IA (7-16% region specific, p<0.05) and a significant increase in plasma parent concentration (8%, p<0.05). There were no significant changes in subjects' self-reported mood symptoms after physostigmine challenge.

Conclusions: We developed a paradigm to interrogate the cholinergic system *in vivo* in human subjects and observed a significant decrease in specific binding of [123I]5-IA following physostigmine challenge, consistent with an increase in endogenous extracellular ACh levels. This confirms a previous study in baboons (Fujita et al. 2003). This imaging tool may have enormous potential to facilitate the development of innovative medicines aimed at modulating the cholinergic system. This study is inherently innovative in the use of neuroreceptor imaging techniques to interrogate the ACh system *in vivo* in human subjects. 1. Fujita M, Al-Tikriti M, Tamagnan G, et al. Influence of acetylcholine levels on the binding of a SPECT nicotinic acetylcholine receptor ligand [123I]5-I-A-85380. *Synapse.* 2003;48:116-122. 2. Esterlis I, Cosgrove K, Batis J, et al. Quantification of smoking induced occupancy of β2-nicotinic acetylcholine receptors: estimation of nondisplaceable binding. *Journal of Nuclear Medicine.* 2010;51:1226-1233.

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Data Blitz Session
Regency Ballroom 2

Self-regulation of Amygdala Activity with Real-time fMRI Neurofeedback in Patients with Depression

Tuesday, Poster #91

<u>Kymberly Young</u>, Raquel Phillips, Vadim Zotev, Wayne C. Drevets, Jerzy Bodurka
Laureate Institute for Brain Research

Background: Up to two-thirds of patients with major depressive disorder (MDD) who seek standard pharmacological and/or psychological interventions will not respond, while only one-half who do will achieve sustained remission. Cognitive-behavioral therapy (CBT), the most commonly implemented psychological treatment for MDD, is most effective for mildly to moderately depressed patients. In severely ill patients, CBT is often ineffective, and treatments available for these severally ill non-responders (such as electroconvulsive therapy, vagus nerve stimulation, and deep brain stimulation) are invasive, expensive, and pose significant risks. Therefore, there is a need to develop novel and non-invasive treatments for MDD. MDD is associated with the deregulation of brain emotional circuitry, with significant changes in amygdala activity. Research has shown that the hemodynamic response of the amygdala is exaggerated to negative stimuli in MDD, with further evidence that amygdala responses to *positive* stimuli are *attenuated* in MDD, and that this later response normalizes with remission. The availability of real-time functional magnetic resonance imaging (rtfMRI) and recent advances in rtfMRI neurofeedback (rtfMRI-nf) permit, for the first time, direct targeting of this region. The current study aims to determine whether individuals with MDD are able to use rtfMRI-nf to enhance the hemodynamic response of the amygdala to positive stimuli, and whether this ability will correspond to alterations in mood.

Methods: Unmedicated participants with a current diagnosis of MDD participated in the current study (n=19). Twelve received active rtfMRI-nf with the left amygdala (LA) as the target region of interest (ROI), and 7 received sham feedback in which the target ROI was the left horizontal segment of intraparietal sulcus (HIPS), a region putatively not involved in emotional regulation. In each of four 8min runs, alternating 40s blocks of Rest, Count, and Happy were

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Self-regulation of Amygdala Activity with Real-time fMRI Neurofeedback in Patients with Depression

Tuesday, Poster #91 (continued)

<u>Kymberly Young</u>

presented. During Rest blocks participants were instructed to clear their minds and focus on the screen. During Count blocks participants were instructed to count backwards from 300 by the number provided. During Happy blocks, the cue "Happy" and two colored bars (red, blue) were displayed on the screen. The red bar represented the actual BOLD neurofeedback signal from the target ROI, which was updated every 2s by changing the height of the bar. Subjects were instructed to retrieve and contemplate positive autobiographical memories while also attempting to increase the level of the red bar to that of the fixed target level displayed by the blue bar. The target blue bar level was increased from run to run. A final 8min Transfer run was presented in which no feedback was provided. Additionally, an 8min rest run was included at the beginning and end of the fMRI session. All imaging was conducted on a GE Discovery MR750 3T MRI scanner with an 8-channel receive-only brain coil. Single shot gradient-recalled EPI with sensitivity encoding (SENSE) was used for fMRI with FOV/slice=240/2.9mm, TR/TE=2000/30ms, SENSE=2, 96×96 matrix, flip=90°, 34 axial slices. A T1-weighted MPRAGE sequence was used for anatomical reference and to define ROIs. Neurofeedback was implemented using a custom real-time fMRI system utilizing AFNI real-time features and a custom GUI software. For each subject, three spherical ROIs (7 mm radius in Talairach space) were centered, respectively, at the left and right amygdala and the HIPS region. The fMRI data analysis was based on GLM and performed in AFNI.
Results: Four of the MDD patients in the active rtfMRI-nf group were unable to learn to successfully regulate their amygdala (defined as LA BOLD response no different from 0 during the transfer run) and were therefore excluded from the group analysis. These patients were significantly younger and had increased fatigue ratings compared to those patients in the active group who successfully regulated their LA. The remaining 8 participants in the active rtfMRI-nf group significantly increased their LA response (BOLD response for Happy-Rest

Self-regulation of Amygdala Activity with Real-time fMRI Neurofeedback in Patients with Depression

Tuesday, Poster #91 (continued)

Kymberly Young

condition > 0) and maintained this elevated activity during the transfer run in which no neurofeedback was provided (p=0.03). In the sham neurofeedback group, the BOLD response within the LA did not significantly increase from 0 in any of the training or transfer runs (ps>0.10). The difference between the active and sham groups in LA activity was significant for the last training run and the transfer run (ps<0.05). BOLD activity did not significantly change within the right amygdala or HIPS for either the active or sham groups (ps>0.11). State measures of happiness significantly increased, while state measures of depression significantly decreased in the group receiving active rtfMRI-nf (ps<0.05), but did not change significantly in the group that received sham feedback (ps>0.15).

Conclusions: Our results show that by using rtfMRI-nf from the LA during recall of positive autobiographical memories, a subset of individuals with MDD can learn to self-regulate their amygdala BOLD responses. We also found an association between the ability to regulate the LA and reductions in depression ratings, as well as improvements in happiness ratings. These preliminary results suggest applications for rtfMRI-nf training and positive autobiographical memory recall in the treatment of MDD.

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Data Blitz Session
Regency Ballroom 2

Cannabinoid Facilitation of Extinction Recall via Increased Recruitment of Prefrontal-hippocampal Circuitry in Healthy Humans

Tuesday, Poster #164

Christine A. Rabinak, Mike Angstadt, Chandra Sripada, Mohammed R. Milad, Israel Liberzon, K. Luan Phan
University of Michigan

Background: Enhancing extinction learning may optimize gains achieved by exposure therapy for anxiety disorders (e.g., maintenance of effects, hastened pace of improvement, greater generalization outside therapeutic context). Emerging evidence from animal studies suggest that enhancing cannabinoid system within the ventromedial prefrontal cortex (vmPFC) and hippocampus (HPC), brain structures critical to fear extinction, enhances fear extinction and its retention. However, the role of cannabinoids on the retention of extinction memory and its effect on the underlying neural circuits in humans remains unknown.

Methods: We conducted an fMRI study using a randomized, double-blind, placebo-controlled, between-subjects design, coupled with a standard Pavlovian fear extinction paradigm and simultaneous skin conductance response (SCR) recording with an acute pharmacological challenge with oral dronabinol (synthetic Δ^9-tetrahydrocannibinol; THC, n = 15) or placebo (PBO, n = 15) 2 hours prior to extinction learningin healthy adult volunteers to assess the effects of THC on vmPFC and HPC activation when tested for recall and maintenance of extinction learning at 24 hours and 1 week after training, respectively.

Results: Compared to subjects who received PBO, those who received THC showed increased vmPFC activation and functional coupling with the HPC, as well as low SCR to a previously extinguished CS when extinction memory recall was tested, suggesting that THC prevented the recovery of fear via increased recruitment of the vmPFC and HPC.

Conclusions: These results advance the neurobiology of extinction learning and prompt development of novel pharmacological modulators of the cannabinoid system to maximize the potency of exposure therapy for anxiety disorders.

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A Brief Monetary Progressive Ratio Task Predicts Clinical Amotivation and Ventral Striatum Activation in Schizophrenia

Wednesday, Poster #47

Jacob Kantrowitz, Natalie Katchmar, Theodore Satterthwaite, Lillie Vandekar, Ruben Gur, Raquel Gur, Daniel Wolf
University of Pennsylvania

Background: Motivational deficits play a central role in disability due to negative symptoms of schizophrenia, which constitute a major unmet therapeutic need in psychiatry. Despite this importance, amotivation in schizophrenia has been understudied and its pathophysiology remains largely unknown. Negative symptoms of schizophrenia have previously been linked to hypofunction in ventral striatum (VS), a crucial component of the mesolimbic dopamine motivation circuitry. However, further work is needed to determine whether specific negative symptoms such as amotivation drive this relationship. This effort can be facilitated by new interview-based assessments like the Clinical Assessment Interview for Negative Symptoms (CAINS), which distinguishes amotivation from related negative symptoms such as anhedonia and asociality by emphasizing both subjective experience and objective behaviors. In addition, improved reliability, validity and translatability to animal models will require applying neurobehavioral measures of amotivation in the laboratory. Here we report initial validation of a brief, computerized progressive ratio task (PRT) that quantifies effort exerted in pursuit of monetary reward. We show that motivation assessed dimensionally with this PRT predicts both clinical amotivation on the CAINS and VS fMRI responses to monetary reward.

Methods: 41 patients with schizophrenia (SCH, stable/medicated) and 37 group-matched controls (CTR) performed a brief computerized PRT to earn money. The PRT required repetition of easy but attention-requiring trials (choosing which of 2 numbers was larger). Within each of three runs, an increasing number of repetitions was required to obtain the monetary reward. Across the three runs, the amount of reward progressively decreased (50 cents, 25 cents, 10 cents). A run ended when the subject chose not to attempt or complete the required number of repetitions. This "breakpoint" was used to quantify motivation, and was defined here as the

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A Brief Monetary Progressive Ratio Task Predicts Clinical Amotivation and Ventral Striatum Activation in Schizophrenia

Wednesday, Poster #47 (continued)

Daniel Wolf

ratio of effort (maximum number of performed trials) to monetary value, averaged across runs. Prior to the PRT, subjects performed BOLD fMRI at 3T including a monetary guessing paradigm that robustly activates VS. VS activation measures (win>lose) were extracted and correlated with PRT breakpoints. Psychopathology was evaluated with self-report and interview scales; the CAINS provided the primary measure of clinical amotivation.

Results: Total PRT duration averaged 16 min (+/-14), without group differences. PRT breakpoints ranged widely in both groups, from ~0.1 trials per cent (tpc) up to ~10 tpc. As expected, average PRT motivation was reduced in patients [SCH 2.3 tpc (+/-2.8), CTR 4.3 tpc (+/-3.7), 1-tail p=0.03]. In SCH, the predicted inverse correlation of PRT with CAINS amotivation was significant (r = -0.40, 1-tail p=0.005). The same relationship was found in CTR (r=-0.29, 1-tail p=0.04). When the relationship of PRT breakpoint to both diagnosis and CAINS amotivation were tested in a multiple regression, the effect of CAINS was significant (2 tail p=0.002) but not diagnosis (p=0.75), indicating that the group difference in PRT was attributable to individual differences in motivation as assessed with the CAINS, rather than to a simple categorical effect of diagnosis. Correlations between PRT and other negative symptom domains were also negative, but less robust. Potential confounds including socioeconomic status, cognition, reaction time, smoking, depression, and positive symptoms did not explain the relationship between PRT breakpoint and CAINS amotivation. In SCH, lower PRT motivation also predicted reduced VS activation to monetary reward (r=0.36, 2-tail p=0.03).

Conclusions: We report one of the first applications of PRT in schizophrenia, and provide initial evidence of its construct validity in relationship to clinical motivation and an fMRI measure of motivation circuit function. It is striking that a brief laboratory measure of motivation shows even these moderate correlations with a clinical measure that is inevitably impacted by various life circumstances operative outside, but not necessarily inside, the laboratory. The

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A Brief Monetary Progressive Ratio Task Predicts Clinical Amotivation and Ventral Striatum Activation in Schizophrenia

Wednesday, Poster #47 (continued)

Daniel Wolf

brief computerized PRT described here has advantages over clinical measures of motivation, including translatability to non-human models, greater objectivity, and potentially greater specificity. The observed correlation with VS activation supports further use of the PRT in studies aiming to identify neural circuit, molecular-genetic, and psychiatric symptom correlates of motivation, and for assessing and predicting response to novel therapeutic interventions.

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Data Blitz Session
Regency Ballroom 2

The Neurosteroids Allopregnanolone and DHEA Enhance Emotion Regulation Neurocircuits and Modulate Memory for Emotional Stimuli

Wednesday, Poster #76

Rebecca K. Sripada, Christine E. Marx, Anthony P. King, Sarah N. Garfinkel, James L. Abelson, Israel Liberzon
University of Michigan

Background: Allopregnanolone (ALLO) and dehydroepiandrosterone (DHEA) are endogenously-produced neurosteroids with neuroprotective, anxiolytic, antidepressant, and antiglucocorticoid effects. Dysregulated release of these neurosteroids has been extensively linked to mood and anxiety disorders. Both neurosteroids are endogenously released in response to stress, and reduce negative affect when administered exogenously. Though these antidepressant and anxiolytic effects have been well established, no research to date has examined the neural pathways involved. In particular, brain imaging has not been used to link neurosteroid effects to emotion regulation neurocircuitry.

Methods: To investigate the brain basis of ALLO and DHEA's impact on emotional response and regulation, subjects were administered 400mg of pregnenolone (N=16), 400mg of DHEA (N=14), or placebo (N=15) and underwent 3T fMRI while performing the Shifted-Attention Emotional Appraisal Task (SEAT), a test of emotional processing and regulation. FMRI data were analyzed in SPM8 random-effects models ($p<0.05$, FWE-corrected for whole brain analyses, small-volume-corrected [SVC] for ROIs).

Results: Compared to placebo, ALLO and DHEA both reduced activity in the amygdala ([27,-1,-17]; $F(1,29)=9.97$; [27,-10,-14]; $F(1,27)=6.9$, $p<.05$, SVC). ALLO decreased activity in the insula ([42,8,4]; $F(1,29)=10.97$, $p<.05$, SVC), whereas DHEA decreased activity in the hippocampus ([-33,-28,-11]; $F(1,29)=22.07$, $p<.05$, SVC) and enhanced connectivity between the amygdala and hippocampus ([30,-13,-11]; $z=3.40$, $p<.05$, SVC). DHEA enhanced activity in the rostral anterior cingulate cortex ([3,41,-2]; $F(1,29)=13.3$, $p<.05$, SVC), whereas ALLO increased activity in the dorsal medial prefrontal cortex ([3,56,37]; $F(2,232)=6.41$, $p<.05$, SVC) and enhanced connectivity between the amygdala

The Neurosteroids Allopregnanolone and DHEA Enhance Emotion Regulation Neurocircuits and Modulate Memory for Emotional Stimuli

Wednesday, Poster #76 (continued)

Rebecca K. Sripada

and dorsal medial prefrontal cortex ([-30,-1,-23]; t=4.8, p<.001), an effect that was associated with reduced self-report anxiety (r=-.52, p=.046). DHEA reduced memory accuracy for emotional stimuli (conjunctive d'; $t(27)$=2.31, p=.029), and reduced activity in regions associated with conjunctive memory encoding.
Conclusions: These results demonstrate that ALLO and DHEA reduce activity in regions associated with generation of negative emotion and enhance activity in regions linked to regulatory processes. Considering that activity in these regions is altered in mood and anxiety disorders, our results provide initial neuroimaging evidence that these neurosteroids may be useful as pharmacological interventions for these conditions and invite further investigation into the brain basis of neurosteroid emotion regulatory effects.

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Neuronal Signatures of Self-control in Anterior Cingulate Cortex

Wednesday, Poster #105

Benjamin Hayden, Tommy Q. Blanchard
University of Rochester

Background: Addiction, obsessive compulsive disorder (OCD), and Tourette Syndrome (TS) are diseases in which the core symptoms include deficits in self-control. Recent studies have begun to identify the key brain areas that govern our ability to resist temptation, but the circuit-level mechanisms of self-control remains poorly understood. Of the core elements of self-control, delay of gratification, or persistent commitment to the choice of a delayed option, has been identified as especially important. Inspired by the recent development of delay-of-gratification tasks for rhesus macaques, we have developed corresponding tasks that are usable with single unit recordings. We focused on the dorsal anterior cingulate cortex (dACC). The dACC has been linked overcoming impulsive behaviors, to self-control, and to executive control more broadly. Lesions to dACC produce frank deficits in self-control and variations in structure and function in dACC predict susceptibility to addiction, OCD, and TS.

Methods: On each trial of our task, one of several possible options (colored rectangles) appears at the top of a computer monitor and quickly glides down the screen. Monkeys can accept or reject this option by fixating on it. Once an option is accepted, the monkey must maintain gaze on it for several seconds in order to obtain a reward. Failures to maintain gaze for the duration of the shrinking period (several seconds) are considered persistence failures and lead to no reward. Options vary in their benefit (reward amount offered) and cost (delay until reward). We recorded firing rate activity of 125 single neurons in the dACC while two macaques performed this task.

Results: We found that monkeys' chose approximately optimally and that their choices reflected a balance between costs and benefits for each option. Neuronal activity was tonically enhanced throughout the hold period, suggesting that it contributes to active resistance to temptation. Consistent with this idea, we found that variations in dACC activity predicted accept or reject decisions for individual stimuli, and in approximately one quarter of neurons, firing rate during the second

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Data Blitz Session
Regency Ballroom 2

Neuronal Signatures of Self-control in Anterior Cingulate Cortex

Wednesday, Poster #105 (continued)

<u>Benjamin Hayden</u>

before the stimulus appeared predicted the monkeys decision. When monkeys made a decision and stuck with it past 750 ms, they proceeded to successfully maintain gaze on it for about 90-95% of trials. On the remaining trials they failed to maintain gaze and let the option disappear. These trials are demonstrably suboptimal because, due to the structure of the task, it was always better to reject any option immediately. We therefore classify these trials as self-control failures. In approximately 20% of dACC neurons, we found a slight but significant suppression in neuronal activity during the half second before the failed self-control gaze shifts. These reductions in activity are therefure predictive of self-control failures. **Conclusions:** Our results indicate that dACC plays a direct role in controlling delay-of-gratification decisions in a macaque self-control task. Specifically, they suggest that dACC provides a proactive control signal that facilitates persistent commitment to an abstemious decision. These results therefore constitute the first putative self-control signal observed at the single neuron level in macaques. Past studies have generally emphasized the importance of dACC for monitoring and for reactive control; the present results demonstrate its key role in proactive control as well. It is likely that dACC is only one of several brain areas important for self-control. The dorsolateral prefrontal cortex and ventromedial prefrontal cortex has been hypothesized to play distinct roles in self-control decisions as well. Our results suggest that dACC may be a high-level controller that tunes activity in these other areas during self-control decisions. More broadly, these results offer a potential explanation for the observed diminution in self-control that accompanies addiction, OCD, and other diseases associated with aberrant structure and function of the dACC. Finally, these results suggest that dACC may be a good target for future therapies, such as deep brain stimulation, that aim to improve self-control in severe psychiatric conditions.

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Impaired Reward Responsiveness during Nicotine Withdrawal in Rats and Humans Assessed in a Translational Behavioral Procedure

Wednesday, Poster #111

Andre Der-Avakian, Michele L. Pergadia, Manoranjan S. D'Souza, Pamela AF. Madden, Andrew C. Heath, Saul Shiffman, Diego A. Pizzagalli, Athina Markou
University of California, San Diego

Background: Nicotine withdrawal produces negative affective symptoms similar to those seen in depression. It is hypothesized that chronic drug exposure and withdrawal promotes the abnormal processing of rewards, which may contribute to addictive behaviors and negative affect during withdrawal that in turn may lead to relapse. Clinical evidence suggests that depressed subjects display abnormal processing of positively reinforcing stimuli (i.e., anhedonia, or decreased interest in rewards) when assessed using the Response Bias Probabilistic Reward Task [Pizzagalli et al. (2008) J Psychiatr Res *43*, 76-87]. Briefly, this task involves exposure to two different visual stimuli that are difficult to discriminate, each requiring a different response to lead to reinforcement. Correct responses to one stimulus are rewarded three times more frequently (i.e., rich) compared to correct responses to the other stimulus (i.e., lean). Non-depressed human subjects modulate their behavior during testing as a function of prior reinforcement by gradually developing a biased response toward the rich stimulus. In contrast, depressed subjects fail to develop this response bias for the more frequently rewarded stimulus. The result is a quantitative task that objectively measures deficits in reward processing in depressed individuals. The goal of the present study was to determine whether nicotine withdrawal is associated with impaired reward responsiveness similarly in rats and humans using the Response Bias Probabilistic Reward Task originally developed in humans and recently adapted for rats. We hypothesized that nicotine withdrawal would be associated with similarly decreased reward responsiveness in rats chronically exposed to nicotine and heavy smoking human subjects.
Methods: Rats: Male Wistar rats were food restricted and trained in operant boxes to press a lever to receive a food pellet as a reward. Rats were then presented with

Impaired Reward Responsiveness during Nicotine Withdrawal in Rats and Humans Assessed in a Translational Behavioral Procedure

Wednesday, Poster #111 (continued)

Andre Der-Avakian

either a short or long tone (identical in all parameters other than duration) and trained to discriminate the tones by pressing one of two levers associated with each tone duration. Once these associations were learned, defined as more than 70% accuracy, the difference between the two tone durations was made more ambiguous during a 100-trial test session split into three blocks. Correct responses on the lever associated with either the short or the long tone (counterbalanced) were reinforced three times more frequently (i.e., rich) than correct responses on the other lever (i.e., lean). After this baseline test, rats were surgically prepared with subcutaneous osmotic minipumps delivering either 6.32 mg/kg/day nicotine (base) or saline vehicle for 28 days. After 28 days, minipumps were removed and rats were tested again 24 hr later during withdrawal. Humans: Participants classified as heavy smokers were presented on a computer screen with one of two mouths varying slightly in length on a schematic face, and instructed to discriminate the mouths by pressing one of two keys on a keyboard associated with each mouth length. During a 300-trial session split into three blocks, correct responses for either the long or short mouth (counterbalanced) resulted in presentation of a monetary reward (5 cents) three times more frequently than correct responses for the other mouth. At the end of the session, participants were given the amount of money won. In one session, participants were smoking at their usual rate prior to testing. In another session, participants were instructed to be 24 hr smoke-free prior to testing (i.e., withdrawal), which was biologically verified. The smoking and abstinence sessions were randomly counterbalanced across subjects and were approximately one-week apart.
Results: Rats: Saline-treated rats developed a response bias towards the rich stimulus, which was comparable to the response bias previously quantified in non-depressed human subjects. In contrast, response bias was significantly decreased in rats exposed to nicotine withdrawal ($p < 0.05$). Humans: In heavy smokers,

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Impaired Reward Responsiveness during Nicotine Withdrawal in Rats and Humans Assessed in a Translational Behavioral Procedure

Wednesday, Poster #111 (continued)

Andre Der-Avakian

response bias was significantly decreased within subjects during 24 hr abstinence relative to the smoking session (p<0.05).Collectively, control rats and heavy smokers when smoking (relative to their abstinence day) responded more toward the rich stimulus than the lean stimulus. However, rats and humans experiencing withdrawal from nicotine responded similarly with less overall responsiveness toward the rich stimuli despite the fact that correct responses for the rich stimuli were reinforced more frequently.

Conclusions: The results indicate that withdrawal from nicotine significantly impairs reward responsiveness in both rats and humans as assessed using the Response Bias Probabilistic Reward Task. This impairment of reward responsiveness is reflected by an inability to alter behavioral responding as a function of prior reinforcement experience. Being able to identify reward processing impairments that are analogous across species will facilitate translational research investigating the behavioral and neurobiological mechanisms that underlie nicotine reward and withdrawal.

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11:15 a.m. - 1:30 p.m.
Data Blitz Session
Regency Ballroom 2

Long Acting Injectable vs. Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-analysis of Mirror-image Studies

Wednesday, Poster #175

Taishiro Kishimoto, Masahiro Nitta, Michael Borenstein, John Kane, Christoph U. Correll
The Zucker Hillside Hospital, Glen Oaks, New York

Background: As psychopathology and social functioning can worsen with repeated psychotic episodes in patients with schizophrenia, relapse prevention is critical. High non-adherence rates in this population can limit the efficacy of pharmacotherapy, therefore, the use of long-acting injectable antipsychotics (LAIs) is considered to be an important treatment option. However, new, large, randomized controlled trials (RCTs) showed no significant benefit of LAIs over oral antipsychotics (OAPs) (e.g., Rosenheck et al. 2011; Schooler et al. 2011). Moreover our latest meta-analysis of RCTs showed no superiority of LAIs over OAPs (Kishimoto et al. in submission: Studies=21, n=4,950, RR=0.93, 95%CI: 0.80-1.08, p=0.35). However, clinical trials might over-represent patients with better treatment adherence and lower illness severity. In addition, patients in clinical trials are likely to receive more and different types of attention than those in routine care, such as measures of adherence, reminders to attend clinical/research assessment sessions, etc. Therefore, the standard RCT might not be the best strategy to examine the efficacy of LAIs, and this possibility needs to be examined carefully. Mirror image studies, which compare the periods pre- and post-LAI introduction within subjects might be a more informative design to examine the effect of LAIs in the targeted population, even though mirror image studies have their own limitations.

Methods: A systematic review/meta-analysis was conducted of mirror image studies following patients at least 12 months (at least 6 months each on OAP and LAI). Co-primary outcomes were hospitalization rate and number of hospitalizations. Pooled risk ratio or rate ratio together with their 95% confidence intervals (CIs) were calculated, using random-effects model. Number-needed-to-treat (NNT) was calculated where appropriate. With regard to the heterogeneity, τ^2, I^2, Q, p values were reported.

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Data Blitz Session
Regency Ballroom 2

Long Acting Injectable vs. Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-analysis of Mirror-image Studies

Wednesday, Poster #175 (continued)

Taishiro Kishimoto

Results: We identified a total of 26 studies across 22 countries including 5,940 participants. LAIs showed strong superiority over OAPs in preventing a next hospitalization (18 studies, n=2722, risk ratio=0.44, 95%CI: 0.38-0.52, p<0.001, NNT=3; heterogeneity: τ^2=0.078, I^2=79%, Q=81.4, df=17, p<0.001). LAIs also showed strong superiority over OAPs in decreasing the number of hospitalizations (19 studies, 7034 person years, rate ratio=0.40, 95%CI: 0.31-0.51, p<0.0001; heterogeneity: τ^2=0.266, I^2=93.8%, Q=288.2, df=18, p<0.001) Although substantial heterogeneity was seen, all studies except one each consistently showed significant superiority regarding the rate and number of hospitalizations favoring of LAIs. This strong superiority remained across all of the following subgroups: first-generation antipsychotic-LAIs, second-generation antipsychotic-LAIs, studies published before 2000 and studies published after 2000, studies applying intention-to-treat analysis and those reporting observed cases. The extent to which publication bias might have contributed to these findings will be further discussed.

Conclusions: Result from mirror image studies in patients eligible for clinical use of LAIs showed strong superiority of LAIs compared to OAPs in preventing hospitalization. The results are in contrast with the meta-analysis of RCTs, which showed non-superiority of LAIs. However, given the possible biases in mirror image studies; i.e., expectation bias, time effect, etc., a cautious interpretation is required. Nevertheless, the population in mirror image studies better reflects the population receiving LAIs in clinical practice. Future RCTs may benefit from including patients at high-risk for relapse and those more closely reflecting routine clinical care.

References: [1] Rosenheck RA, Krystal JH, Lew R, Barnett PG, Fiore L, Valley D, Thwin SS, Vertrees JE, Liang MH; CSP555 Research Group., 2011. Long-acting risperidone and oral antipsychotics in unstable schizophrenia. N Engl J Med. 64(9):842-51. [2] Schooler NR, Buckley PF, Mintz J, et al. PROACTIVE: Initial

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Long Acting Injectable vs. Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-analysis of Mirror-image Studies

Wednesday, Poster #175 (continued)

Taishiro Kishimoto

results of an RCT comparing long-acting injectable risperidone to 2nd generation oral antipsychotics. American College of Neuropsychopharmacology 50th annual meeting. Kona, Hawaii, USA; 2011 [3] Kishimoto T. Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU. Long-acting injectable vs. oral antipsychotics for relapse prevention in schizophrenia: A meta-analysis of randomized trials.

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1:30 p.m. - 3:00 p.m.
Associate Member Session
Regency Ballroom 1

Special Session for Associate Members

"Ask the Experts: Peer Review"

<u>Panelists:</u>

Bill Carlezon   John Krystal
Marlene Freeman   Lisa Monteggia
Bob Friedman   Nora Volkow

Peer review is a critical centerpiece of the academic process, determining which articles get published and which grants are funded. Despite its importance, there is little formal training in how to become a useful peer reviewer. This workshop will provide a panel discussion on how to perform an optimal peer review for journal articles and grant proposals. The panel will consist of editors of top psychiatric journals and NIH staff. The discussion will be moderated by members of the ACNP Member Advisory Task Force and will begin with a small number of structured questions followed by audience participation. Topics to be discussed will include, but not be limited to: Why should I review (I'm so busy!)? What are some tips for writing a good review? Are there any common mistakes/pitfalls to avoid? How long should a review be – should I mention every problem I see or just the major issues? What are the boundaries determining relevant conflict of interest? What should I do if I know something about the study (that affects my judgment) that isn't transparent in the proposal/article? How does one become an Editorial Board Member of a journal? Through this session, it is expected that participants will improve their understanding of how to perform a useful peer review, and will also gain a better understanding of the peer review process. It is expected that the latter understanding will enhance writing of articles and grants and responding to reviews.

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Rescuing Novel Mechanisms: Minimizing Placebo Response and Optimizing Signal Detection in Proof of Concept Trials

Chair: Michael Thase
Co-Chair: William Z. Potter

3:00 p.m.   Decline in Signal Detection: Background and Proposed Strategies
       Michael Thase

3:25 p.m.   Missing Data, Placebo Response, and Positive Controls: How They Influence Signal Detection
       Craig H. Mallinckrodt

3:50 p.m.   First, Do No ... Help!?: The Problems with Therapeutic Alliance and Expectation Bias in Clinical Trials
       Michael Detke

MP

4:15 p.m. – 5:30 p.m.
Mini Panel
Diplomat Ballroom 1 & 2

Exploring Therapeutic Use of Psilocybin, A Classic Hallucinogen

Chair: Roland Griffiths

4:15 p.m.   Experimental Studies of Psilocybin in Healthy Volunteers:
              Persisting Attribution of Positive Changes in Attitudes, Mood
              and Behavior
                    Roland Griffiths

4:40 p.m.   Psilocybin Treatment for Anxiety in Patients with Advanced-
              Stage Cancer
                    Charles Grob

5:05 p.m.   Effects of Psilocybin in the Treatment of Addictions: A Review
              and Preliminary Results from Two Ongoing Trials
                    Michael P. Bogenschutz

MP

New Perspectives on the Role of Glutamatergic Neurotransmission in Alcoholism and Drug Addiction

Chair: Mary-Anne Enoch

3:00 p.m.   Translational Support for the Glutamate Hypothesis of Addiction
Derik Hermann

3:30 p.m.   The Effects of Chronic, Heavy Alcohol and Cocaine Use
on Glutamatergic Gene Expression in Postmortem Human
Hippocampus
Mary-Anne Enoch

4:00 p.m.   Adaptations of Glutamatergic Transmission in Extended
Amygdala in Stress and Reward
Danny Winder

4:30 p.m.   A Functional Grm2 Stop Codon Increases Alcohol Preference in
Alcohol Preferring (P) Rats
David Goldman

5:00 p.m.   Discussant: *Gary Aston-Jones*

PA

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3:00 p.m. – 5:30 p.m.
Panel
Atlantic Ballroom 2

High Anxiety: Endocannabinoid Regulation of the Stress Response and Emotional Behavior

Chair: Alexander Neumeister

3:00 p.m.   PET Reveals Abnormal CB1 Receptor Binding in PTSD
               Alexander Neumeister

3:30 p.m.   Reduced Plasma Endocannabinoid Levels in PTSD
               Rachel Yehuda

4:00 p.m.   The Endocannabinoid System as a Therapeutic Target for Stress-
               related Disorders
               Daniele Piomelli

4:30 p.m.   Stress-induced Regulation of Endocannabinoid Signaling in the
               Amygdala: Mechanisms and Functional Implications
               Matt Hill

5:00 p.m.   Discussant: *Ken Mackie*

PA

Longitudinal Neuroimaging of Emerging Substance Use: Brain Indicators of Early Risk and Effects of Use

Chair: Mary Heitzeg
Co-Chair: Godfrey D. Pearlson

3:00 p.m.   Individual Differences in Control and Reward and Their Relationship to Substance Use Risk: The IMAGEN Study
          Hugh Garavan

3:30 p.m.   Longitudinal fMRI Studies of Impulse Control and Incentive Responding: Effects of Risk and Alcohol Use
          Mary Heitzeg

4:00 p.m.   Effects of Alcohol use Initiation on Brain Structure and Behavioral Functions in Adolescents
          Monica Luciana

4:30 p.m.   Longitudinal Studies of Alcohol Effects on Academic Grades and MRI Hippocampal Volumes in the BARCS College Sample
          Godfrey D. Pearlson

5:00 p.m.   Discussant: *Edith Sullivan*

PA

3:00 p.m. – 5:30 p.m.
Panel
Regency Ballroom 2

Neuropeptide Receptor Ligands in Psychiatric Diseases: New Hopes after Multiple Failures

Chair: Stephen Stahl
Co-Chair: Guy Griebel

3:00 p.m.   Neuropeptides to Treat Affective Disorders: Did Animal Model Fail to be Predictive, or did Clinical Research Fail to Detect Effects?
Catherine Belzung

3:30 p.m.   Neuropeptides and Major Depression/Depression-like Behavior: Focus on Substance P and Galanin
Tomas Hokfelt

4:00 p.m.   Hypocretin/orexin, Sleep and Narcolepsy: Immune and Pharmacological Implications
Emmanuel Mignot

4:30 p.m.   Identifying the Right Patient for Neuropeptide Receptor Ligands - Biomarkers for Central CRH Overexpression
Marcus Ising

5:00 p.m.   Discussant: *Thomas Steckler*

PA

3:00 p.m. – 5:30 p.m.
Panel
Atlantic Ballroom 1

Are We at a Turning Point in Psychiatric Genetics?

Chair: Kalpana Merchant
Co-Chair: David A. Collier

3:00 p.m.   How Common and Rare Variants are Beginning to Provide Insights into Biological Mechanisms Underlying Psychiatric Disorders
David A. Collier

3:30 p.m.   Dissecting Complexity in Neuropsychiatric Genetics with Network Inference
Neelroop N. Parikshak

4:00 p.m.   Modelling Schizophrenia Using Induced Pluripotent Stem Cells
Kristen Brennand

4:30 p.m.   Optogenetics and Psychiatric Disease: Focus on Social Behaviors
Karl Deisseroth

5:00 p.m.   Discussant: *Kalpana Merchant*

PA

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3:00 p.m. – 5:30 p.m.
Panel
Atlantic Ballroom 3

The Ups and Downs of AKT Signaling:
A Nexus of Risk for Psychiatric Disorders

Chair: Daniel R. Weinberger
Co-Chair: Thomas F. Franke

3:00 p.m.   Dissecting the Role of the AKT/PKB Family in
                 Neurodevelopment and Schizophrenia
                      Amanda Law

3:30 p.m.   Integrated Approaches to Understand the Actions of GPCRs:
                 The β-arrestin-dependent D2R Signaling Axis
                      Marc G. Caron

4:00 p.m.   DISC1 Regulation of Neural Development through
                 AKT-mTOR-CYFIP1 Signaling
                      Guo-li Ming

4:30 p.m.   Studying AKT1 Signaling in Human Brain
                      Daniel R. Weinberger

5:00 p.m.   Discussant: *Thomas F. Franke*

PA