8:30 a.m – 11:30 a.m.
***Neuropsychopharmacology Reviews* Plenary**
Regency Ballroom 1 & 2

PL

Neuropsychopharmacology Reviews Plenary

"Epigenetics"

Co-Chairs: Eric Nestler and Schahram Akbarian

8:30 a.m. Epigenetics Mechanisms in Memory Regulations
David Sweatt

8:55 a.m. The Role of Histone Deacetylase 3 (HDAC3) in the Acquisition and Extinction of Cocaine-context Associated Memories
Marcelo Wood

9:20 a.m. The Impact of MeCP2 Loss- or Gain-of-Function on Synaptic Plasticity
Lisa Monteggia

9:45 a.m. microRNA miR-128 Controls Dopamine-mediated Locomotor Behavior and Prevents Fatal Epilepsy-like Disease in Mice
Anne Schaefer

10:10 a.m. Epigenetics of Complex Behaviors and Their Inheritance in Mammals
Johannes Bohacek

10:35 a.m. Discussion
Eric Nestler and Schahram Akbarian

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Epigenetics Mechanisms in Memory Regulations

David Sweatt
University of Alabama at Birmingham Medical School

Epigenetic mechanisms typically involve alterations in chromatin structure, which in turn regulate gene expression. "Epigenetics" is functionally equivalent to the mechanisms allowing stable maintenance of gene expression that involve physically "marking" DNA or its associated proteins through post-translational modification. Thus, regulation of chromatin structure and regulation of direct methylation of DNA are the principal mechanisms of epigenetic regulation. This presentation will address the idea that conservation of epigenetic mechanisms for information storage represents a unifying model in biology, with epigenetic mechanisms being utilized for cellular memory at levels from behavioral memory to development to cellular differentiation. Do epigenetic mechanisms operate in behavioral memory formation? We have generated several lines of evidence that support this idea that I will discuss. 1. Contextual fear conditioning triggers alterations in hippocampal DNA methylation and histone post-translational modifications. 2. Inhibitors of DNA methylation block both hippocampal LTP and associative learning in vivo. 3. Remote contextual fear memory is associated with persisting changes in DNA methylation in the Anterior Cingulate Cortex, and DNMT inhibition can reverse established remote memory. 4. Histone acetylation increases in memory formation, and histone deacetylase (HDAC) inhibitors enhance both memory formation and hippocampal long-term potentiation.

David Sweatt obtained his B.S. in Chemistry before attending Vanderbilt University, where he was awarded a Ph.D. for studies of intracellular signaling mechanisms. He then did a post-doctoral Fellowship at the Columbia, working on memory mechanisms in the laboratory of Nobel laureate Eric Kandel. From 1989 to 2006 he was a member of the Neuroscience faculty at Baylor College of Medicine in Houston, Texas. He is currently the Evelyn F. McKnight endowed Chairman of the Department of Neurobiology at UAB Medical School. Dr. Sweatt's laboratory studies biochemical mechanisms of learning and memory. In addition, his research program also investigates mechanisms of learning and memory disorders, such as mental retardation and aging-related memory

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Epigenetics Mechanisms in Memory Regulations (continued)

David Sweatt

dysfunction. Dr. Sweatt has won numerous awards and honors, including an Ellison Medical Foundation Senior Scholar Award, and election as a Fellow of the American Association for the Advancement of Science. This year he won the Ipsen Foundation International Prize in Neural Plasticity.

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The Role of Histone Deacetylase 3 (HDAC3) in the Acquisition and Extinction of Cocaine-context Associated Memories

Marcelo Wood
University of California, Irvine

How do drugs of abuse, such as cocaine, cause stable changes in neural plasticity that in turn drive long-term changes in behavior? What kind of mechanism can underlie such stable changes in neural plasticity? One prime candidate mechanism is epigenetic mechanisms of chromatin regulation. Chromatin regulation has been shown to generate short-term and long-term molecular memory within an individual cell. They have also been shown to underlie cell fate decisions (or cellular memory). Now, there is accumulating evidence that in the CNS, these same mechanisms may be pivotal for drug-induced changes in gene expression and ultimately long-term behavioral changes. As these mechanisms are also being found to be fundamental for learning and memory, an exciting new possibility is the extinction of drug-seeking behavior by manipulation of epigenetic mechanisms. In particular, we have focused on understanding the role of histone deacetylase 3 (HDAC3) in the acquisition and extinction of cocaine-context associated memories. We have found that HDAC3 is pivotal for both the acquisition and the persistent extinction of drug-seeking behavior.

Dr. Wood received his Ph.D. from the Department of Molecular Biology at Princeton University in molecular cancer biology. He then switched fields to study the neurobiology of learning and memory at the University of Pennsylvania for his postdoctoral fellowship. He is currently an associate professor in the Department of Neurobiology and Behavior at the University of California Irvine. He is also the Director of the Interdepartmental Neuroscience Program. His research program focuses on understanding the molecular mechanisms underlying long-term memory formation and drug-seeking behavior.

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The Impact of MeCP2 Loss- or Gain-of-Function on Synaptic Plasticity

Lisa Monteggia
University of Texas, Southwestern Medical Center, Dallas

Methyl-CpG-binding protein 2 (MeCP2) is a transcriptional regulator of gene expression that is an important epigenetic factor in the maintenance and development of the central nervous system. The neurodevelopmental disorders Rett syndrome and MECP2 duplication syndrome arise from loss of function and gain of function alterations in MeCP2 expression, respectively. Several animal models have been developed to recapitulate the symptoms of Rett syndrome and MECP2 duplication syndrome. Cell morphology, neurotransmission, and cellular processes that support learning and memory are compromised as a result of MeCP2 loss- or gain-of-function. Interestingly, loss of MeCP2 function and MeCP2 overexpression trigger diametrically opposite changes in synaptic transmission. These findings indicate that the precise regulation of MeCP2 expression is a key requirement for the maintenance of synaptic and neuronal homeostasis and underscore its importance in central nervous system function. This review highlights the functional role of MeCP2 in the brain as a regulator of synaptic and neuronal plasticity as well as its etiological role in the development of Rett syndrome and MECP2 duplication syndrome.

Dr. Monteggia's research interests focus on the molecular and cellular basis of neural plasticity as it pertains to psychiatric disorders. She utilizes molecular, cellular, behavioral, biochemical and electrophysiological approaches to elucidate how specific genes may contribute to psychiatric disorders, specifically focusing on better understanding Depression and Rett Syndrome/Autism. Dr. Monteggia is Ginny and John Eulich Professor in Autism Spectrum Disorders, and Associate Professor of Psychiatry, at University of Texas Southwestern Medical Center in Dallas. She is currently an associate editor of Neuropsychopharmacology, on the editorial board of Biological Psychiatry , as well as on several national advisory and review boards. She has received several awards for her research, including the Daniel X. Freedman Award for outstanding basic research achievement from NARSAD, the Rising Star Basic Research Award from the International Mental Health Research Organization, and the Daniel H. Efron Award from ACNP.

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***Neuropsychopharmacology Reviews* Plenary**
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microRNA miR-128 Controls Dopamine-mediated Locomotor Behavior and Prevents Fatal Epilepsy-like Disease in Mice

Anne Schaefer
Friedman Brain Institute, Mount Sinai School of Medicine

MiR-128 is one of the most abundant, postnatal brain-enriched miRNAs and is encoded by two different genes, miR-128-1 and miR-128-2. We found that the majority of miR-128 in the adult brain originates from the miR-128-2 gene. Loss of miR-128-2 in postnatal forebrain neurons causes a fatal epilepsy-like disease, characterized by hyperlocomotion, increased exploratory activity and spontaneous, recurrent seizures. Moreover, deficiency of miR-128-2 specifically in dopamine 1 receptor (Drd1) expressing neurons is sufficient to reproduce the epilepsy-like disease and is associated with an enhanced neuronal responsiveness to Drd1 stimulation. Using cell-type specific mRNA analysis of miR-128-2 deficient Drd1 neurons combined with neuron-specific analysis of Ago2 associated mRNA targets in neurons in the adult brain we identified >30 miR-128 target genes. The nature of these targets and their potential contribution to the development of the epilepsy-like disease in mice will be discussed.

Dr. Schaefer is Assistant Professor of Neuroscience and Psychiatry and named Seaver Fellow at the Friedman Brain Institute at Mount Sinai School of Medicine. She did her graduate studies at the Johannes Gutenberg University, the Charité University Berlin and The Rockefeller University in New York. In 2004 she joined Paul Greengards Laboratory at The Rockefeller University where she completed her postdoctoral studies. She joined the Friedman Brain Institute at Mount Sinai School of Medicine to start her own laboratory in 2011. Her research is focused on understanding how epigenetic mechanisms contribute to maintenance of specialized neuronal functions and their alteration during psychiatric and neurodegenerative diseases.

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***Neuropsychopharmacology Reviews* Plenary**
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Epigenetics of Complex Behaviors and Their Inheritance in Mammals

Johannes Bohacek
The University of Zurich

The development and expression of behaviors in mammals are strongly influenced by environmental factors. When favorable and positive, these factors facilitate appropriate responses and allow normal behaviors, but when adverse and negative, they can lead to behavioral alterations. Stressful and traumatic events early in life are particularly negative risk factors that can induce behavioral and psychiatric conditions such as depression, personality disorders and antisocial behaviors. Such disorders can further not only affect the individuals directly exposed to trauma, but they can also be transmitted and similarly expressed in the following generations. The mechanisms underlying the etiology and inheritance of behavioral symptoms induced by early traumatic stress have been proposed to involve epigenetic processes, but remain undefined. This talk will present an experimental model of early traumatic stress in mice and provides initial evidence for the contribution of epigenetic mechanisms to the impact of negative factors on behavior across generations. This model shows that chronic and unpredictable maternal separation combined with maternal stress causes depressive and impulsive behaviors, social withdrawal and cognitive defects in adult mice, and that these symptoms are transmitted to the following offspring across several generations. It further shows that these alterations are associated with persistent changes in DNA methylation in the promoter-associated CpG island of several genes, both in the germline of the stressd animals and in the brain of the offspring. These findings suggest the implication of epigenetic processes in the impact of negative environmental conditions on behavior.

Johannes Bohacek received a diploma in Psychology at the University of Graz, Austria in 2003. He then moved to the United States to complete a Master's degree in Applied Biopsychology at the University of New Orleans, and in 2009 he earned a PhD in Neuroscience from Tulane University. He then joined the laboratory of Isabelle Mansuy as a Postdoc at the Swiss Federal Institute of Technology (ETHZ) and the University Zurich. He has been coordinating a

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Epigenetics of Complex Behaviors and Their Inheritance in Mammals (continued)

Johannes Bohacek

3-year collaboration with Roche to investigate the role of epigenetic factors in the inheritance of disease, and has been funded by a Postdoctoral Fellowship from the ETHZ. His main research interest focuses on the transgenerational effects of early life stress as a risk factor for the inheritance of neuropsychiatric disease.

1:00 p.m. – 2:30 p.m.
Institute Director's Session
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NIH Institute Director's Session

Chair: John Krystal

Panelists:

Kenneth Warren
NIAAA

Thomas Insel
NIMH

Nora Volkow
NIDA

Neil Buckholtz
NIA

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2:30 p.m. – 6:30 p.m.
Hot Topics
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Hot Topics

Co-Chairs: Anissa Abi-Dargham and Randy Blakely

2:30 p.m. The Sex Biased Phosphoproteome: A Novel Approach Towards Understanding The Molecular Basis for Sex Differences in Neuropsychiatric Diseases
Rita Valentino

2:42 p.m. Alarm Pheromone Processing Areas are Involved in the Intergenerational Social Transfer of Emotional Trauma
Jacek Debiec

2:54 p.m. Epigenetics, Neurodevelopment, and Risk for Anxiety and Depression in Model Rats
Sarah M. Clinton

3:06 p.m. Astrocyte-specific Ablation in the Mouse Prefrontal Cortex Induces Depressive-like and Anxiety-like Deficits
Mounira Banasr

3:18 p.m. Reduced Mitochondrial Energy Production in Major Depressive Disorder: Associations with the Serotonin Transporter and Glutamine Synthetase Genes
Chadi G. Abdallah

3:30 p.m. Adolescent Stressors to Epigenetic Modulation in Dopaminergic Neurons Via Glucocorticoids: A Novel Model for Psychotic Depression
Akira Sawa

3:42 p.m. Stress Response Systems in Adolescent Girls and Boys with Major Depression: A Multi-modal Approach
Kathryn R. Cullen

2:30 p.m. – 6:30 p.m.
Hot Topics
Regency Ballroom 1 & 2

Hot Topics (continued)

Co-Chairs: Anissa Abi-Dargham and Randy Blakely

3:54 p.m. PTSD is Associated with an Increased Prevalence of Autoimmune Disorders
Thomas Neylan

4:06 p.m. The Peripheral Immune System Functionally Contributes to Susceptibility to Repeated Social Defeat Stress
Georgia E. Hodes

4:18 p.m. Pain-related Depression of the Mesolimbic Dopamine System in Rats: Expression, Blockade by Analgesics, and Role of Endogenous Kappa Opioids
Steve Negus

4:30 p.m. Evidence of an Inflammatory Pathway Leading to Psychosis in Bipolar Disorder
Mikael Landen

4:42 p.m. Mapping Brain Metabolic Connectivity in Awake Rats with MicroPET and Optogenetic Stimulation
Panayotis Thanos

4:54 p.m. Fine-grained Working Memory Load Manipulation Reveals Absence of Normative Inverted-U Activation in Schizophrenia
Jared X. Van Snellenberg

5:06 p.m. BDNF Val66Met Modulates BOLD Response to Affective Instrumental Learning in Humans
Mbemba Jabbi

PL

2:30 p.m. – 6:30 p.m.
Hot Topics
Regency Ballroom 1 & 2

Hot Topics (continued)

Co-Chairs: Anissa Abi-Dargham and Randy Blakely

5:18 p.m. "Erasing" a Cocaine-cue Memory in Mice: Potential Implications for Relapse to Drug Taking
Sheena Josselyn

5:30 p.m. Markedly Reduced mGluR5 Receptor Binding in Smokers and Ex-smokers Determined by [11C]ABP688 Positron Emission Tomography
Gregor Hasler

5:42 p.m. Differentiating Neural Networks with Interleaved TMS-BOLD Imaging: Insight into Addiction
Colleen A. Hanlon

5:54 p.m. Treatment of Depression with Botulinum Toxin A: A Randomized, Double-Blind, Placebo Controlled Trial
Eric Finzi

6:06 p.m. A Randomized Controlled Crossover Trial of Ketamine in Obsessive-Compulsive Disorder
Carolyn I. Rodriguez

6:18 p.m. Effects of Oxytocin on Social Cognition and Olfaction in Adults with Schizophrenia and Healthy Subjects
Josh Woolley

2:30 p.m. – 6:30 p.m.
Hot Topics
Regency Ballroom 1 & 2

PL

The Sex Biased Phosphoproteome: A Novel Approach Towards Understanding The Molecular Basis for Sex Differences in Neuropsychiatric Diseases

Tuesday, Poster #138

Rita Valentino, Debra Bangasser, Zach Plona, Hua Ding, Christopher McKennan, Steven Seeholzer
The Children's Hospital of Philadelphia

Background: Stress-related psychiatric disorders (e.g., depression, post-traumatic stress disorder) are nearly two fold more prevalent in females compared to males. Our recent studies implicated sex differences in signaling and trafficking of the receptor for corticotropin-releasing factor (CRF), the molecule that orchestrates the stress response, as a molecular mechanism for these differences. In females the CRF receptor (CRF1) was more highly coupled to its GTP-binding protein (Gs) and it did not associate with b-arrestin 2 following stress as seen in males. These sex differences rendered neurons of female rats more sensitive to CRF and less able to adapt to excess CRF through b-arrestin 2-mediated CRF1 internalization. In addition to promoting receptor internalization, b-arrestin 2 also acts as a scaffold linking receptors to G-protein independent signaling pathways. This suggests that CRF1 signaling is sex biased, such that in females signaling is preferentially through Gs-protein related pathways whereas in males it can involve b-arrestin 2-related, Gs-protein independent pathways. By engaging different signaling cascades stressors can have sex-specific cellular, physiological, behavioral and pathological consequences. Because Gs-protein and b-arrestin 2 signaling regulate phosphorylation dynamics in cells we tested the hypothesis that the excessive CRF that occurs in stress-related psychiatric disorders could result in sex specific phosphoprotein profiles. Keys to understanding sex differences in stress-related psychiatric disorders may lie in the differences between these profiles. This was tested by performing a deep phosphoproteomic analysis of cortex of male and female CRF overexpressing (CRF-OE) mice using stable isotope labeling of whole mouse (SILAM) and high resolution mass spectrometry. **Methods:** Experimental protocols were approved by IACUC of The Children's Hospital of Philadelphia and were in accordance with the NIH *Guide for the Care*

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The Sex Biased Phosphoproteome: A Novel Approach Towards Understanding The Molecular Basis for Sex Differences in Neuropsychiatric Diseases

Tuesday, Poster #138 (continued)

Rita Valentino

and Use of Laboratory Animals. Male and female CRF-OE transgenic mice with the mMt-1 promoter driving the CRF gene (including introns) backcrossed onto the C57BL/6 mouse strain were purchased from Jackson Labs. Cortical protein homogenates were obtained from experimental subjects and protein from male and female SILAM brains obtained from mice on a stable isotope labeled amino acid diet was added to experimental samples as an internal standard. After tryptic digest, phosphoproteins were enriched and separated by hydrophyllic interaction chromatography in conjunction with immobilized metal affinity chromatography. Samples were subjected to reversed phase LC-MSMS. Raw data were analyzed using MaxQuant 1.2.7.4 and Andromeda search engine.
Results: Over 5300 unique phosphopeptides were identified that were present in both female CRF-OE mice (FOE) and male CRF-OE mice (MOE). Approximately 14% of these differed between groups with 269 being more abundant in FOE and 131 being more abundant in MOE (1%FDR). Kinases were prominent in the FOE group (44 kinases) and were not as well represented in the MOE (10 kinases). Additionally, more phosphatases and phosphodiesterases were represented in the FOE compared to the MOE group.The different types of kinases in the two groups supported the concept that signaling was different between FOE and MOE mice. Calcium/calmodulin kinase (CAMK) subunits and serine/threonine kinases were prominent in the FOE group, whereas no specific kinase was more apparent in the MOE group. Analysis of the overrepresented amino acid motifs in both groups showed some overlap between the groups but also identified motifs that distinguished the groups. Finally, analysis of protein domains using PROSITE revealed that protein kinase domains dominated the FOE group and PDZ and Src domains were most representative in the MOE group. These initial findings support the hypothesis that sex biased CRF receptor signaling translates

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The Sex Biased Phosphoproteome: A Novel Approach Towards Understanding The Molecular Basis for Sex Differences in Neuropsychiatric Diseases

Tuesday, Poster #138 (continued)

Rita Valentino

to different profiles of phosphoproteins in brain. Finally, an initial functional pathway analysis strongly implicated the FOE phosphoproteome in calcium signaling with >20 phosphoproteins related to this and also in Alzheimer's disease with key phosphoproteins related to amyloid b (A4) precursor protein binding and processing, including beta secretase and phosphorylation of tau, including tau tubulin kinase and CAMK.

Conclusions: Here we used a proteomic approach to test a hypothesis generated from receptor immunoprecipitation studies. A deep phosphoproteomic analysis comparing cortical tissue of male and female CRF-OE mice to mimic the CRF overactivity of stress-related psychiatric disorders revealed that a substantial proportion of the phosphoproteome differed significantly between the sexes. The different pattern of kinases and protein domains represented in the two groups supported the notion of sex biased CRF signaling. The finding that many phosphoproteins associated with Alzheimer's disease are exclusively present in the FOE phosphoproteome suggests a sex by stress interaction in this disease that may play a role in determining vulnerability.

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Hot Topics
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Alarm Pheromone Processing Areas are Involved in the Intergenerational Social Transfer of Emotional Trauma

Monday, Poster #60

Jacek Debiec, Regina M. Sullivan
University of Michigan, Ann Arbor

Background: A number of studies suggest that psychological trauma can be transmitted to subsequent generations and potentiate the emergence of mental disorders, such as depression, PTSD and specific phobias (Cameron et al., 2005; Yehuda et al., 1998; de Rosnay et al. 2006). We have recently proposed a rat model of a transgenerationally transmitted trauma (Debiec and Sullivan, ACNP 2011). Using 2-DG autoradiographic imaging, we have shown that the lateral nucleus of the amygdala, a key structure underlying associative fear learning, is involved in the transfer of fear responses from mothers to infants (Debiec and Sullivan, ACNP 2011). We have demonstrated that in our paradigm, the social transmission of fear from mothers to their pups is mediated by maternal alarm odor (Debiec and Sullivan, ACNP 2011). Here we ask whether brain structures which are known to process alarm pheromones are also involved in the acquisition of socially transmitted fear.
Methods: Female rats that had undergone olfactory fear conditioning training were re-exposed to their conditioning stimulus (CS) in the presence of the pups ("Paired-CS" ; n=7). Controlled groups included pups exposed to mothers that had been previously conditioned but were not re-exposed to the CS ('Paired-No CS"; n=4) and pups exposed to mothers that had been previously exposed to unpaired presentations of CS odor and electric shock ("Unpaired-CS"; n=6). All pups were injected with ^{14}C S 2-DG prior to their exposure in order to assess the neural changes during acquisition. Following exposure to their mothers, 2-DG reuptake in pups' brains was assessed.
Results: Statistical analysis revealed that "Unpaired-CS" group exhibited decrease of 2-DG uptake in the granular part of the accessory olfactory bulb (AOB) as compared to two other groups [ANOVA, $F(2, 14) = 6.089$; $p<0.02$; post hoc Newman-Keuls Multiple Comparison Test $p< 0.05$]. "Paired-CS" group showed significant increase of 2-DG uptake in necklace glomeruli (NG) [ANOVA,

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Alarm Pheromone Processing Areas are Involved in the Intergenerational Social Transfer of Emotional Trauma

Monday, Poster #60 (continued)

Jacek Debiec

F(2, 14) = 8.438; p<0.004; post hoc Newman-Keuls Multiple Comparison Test p< 0.05].

Conclusions: Our data demonstrate that the acquisition of socially transmitted fear in rat pups involves the AOB and the NG which are both involved in processing of intraspecific chemical alarm signaling (Chamero *et al*., 2012; Luo, 2008). Interestingly, there was no difference in 2-DG uptake in the AOB between the "Paired-CS" and "Paired-No CS" groups suggesting that the history of trauma (fear conditioning) predicts fear and the AOB activation. In contrast, the 2-DG uptake in the NG was significantly increased as compared to two other groups. This pattern of findings suggests that the NG activity underlies acquisition of socially transmitted fear.

This research was supported by grants NIDCD DC009910 and NIMH MH091451 to RMS and NARSAD Young Investigator Award from the Brain & Behavior Research Foundation to JD.

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Epigenetics, Neurodevelopment, and Risk for Anxiety and Depression in Model Rats

Tuesday, Poster #152

Sarah M. Clinton, Rebecca K. Simmons, Matthew E. Glover, Phyllis C. Pugh, Huda Akil
University of Alabama, Birmingham

Background: Individual differences in human temperament powerfully shape ability to cope with stress as well as vulnerability to mental illness. Our ongoing work utilizes rats to model individual differences in temperament to understand molecular and neuroanatomical changes in the developing brain that may put an individual at risk for a depressive/anxiety-like phenotype. The hippocampus emerged as a particularly important node in shaping temperament differences, as we found altered hippocampal volume, cell proliferation, gene expression, and epigenetic (DNA methylation) changes in the developing brain of "depression prone" versus "depression resistant" rats. The current experiments highlight similar changes in the developing amygdala – an area well-known for regulating emotion, in part via interconnections with the hippocampus.
Methods: In rats selectively-bred for differences in locomotor response to novelty, low novelty responders(bLR) exhibit high levels of behavioral inhibition, anxiety- and depression-like behavior, compared to high novelty responders (bHR), which are highly aggressive, impulsive and prone to drug-taking. The bLR/bHR phenotypes are highly predictable across generations and emerge as early as the second week of life. Brains were collected from developing bLR/bHR pups at three time points (postnatal days (P)7, 14, and 21). The amygdala was dissected, and RNA and DNA were extracted for Affymetrix microarray gene expression and Epigentek global DNA methylation assays, respectively.
Results: The microarray experiment revealed dramatic global gene expression differences in the developing amygdala of bLR vs. bHR rats. At P7 and P14, approximately 400 genes were differentially expressed between the strains, and by P21, nearly 700 genes were differentially expressed. At P7, 15% of altered genes were downregulated in bLR vs. bHR, while 85% was upregulated. This pattern dramatically changed at the later timepoints, with approximately 80% of altered genes being downregulated in bLR vs. bHR at P14 and P21, while approximately

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Epigenetics, Neurodevelopment, and Risk for Anxiety and Depression in Model Rats

Tuesday, Poster #152 (continued)

Sarah M. Clinton

20% were upregulated. The global DNA methylation assay revealed robustly increased DNA methylation in the amygdala of bLR (vs. bHR) rats specifically at P7. There were no group differences at the other ages (P14 and P21), and we did not see differences at any timepoint for several other brain areas, including the hippocampus, caudate putamen, or septum. Ongoing studies are evaluating methylation status of specific genes in P7 amygdala samples from bLR/bHR rats. **Conclusions:** Our earlier work pointed to marked differences in developing hippocampus of bLR vs. bHR rats, suggesting a possible neurodevelopmental underpinning of their distinct behavioral phenotypes. Here we report remarkable bLR/bHR differences in the developing amygdala. Microarray results revealed substantial gene expression changes at P7 and P14 that expand with age (nearly doubling the number of genes changed at P21 vs. P14). This finding is quite interesting as the pattern differs from our prior microarray study in hippocampus; there we found robust bLR/bHR differences at P7 and P14, with extremely few changes at P21. We also discovered robustly increased global methylation in the P7 amygdala of bLR vs. bHR rats. DNA methylation is typically thought to suppress gene expression, so this dramatic DNA methylation difference may contribute to P14 and P21 gene expression differences where 80% of differing genes were downregulated in bLR vs. bHR rats. Ongoing work aims to identify specific gene targets that are differentially methylated in bLR/bHR rats, and determine whether manipulating methylation in the developing brain can ameliorate some aspects of the bLR/bHR phenotypes. Furthermore, we are also exploring possible differences in hippocampal-amygdala connectivity in developing bLR/bHR rats to identify neural circuit differences that correspond with observed molecular changes. Overall this body of work aims to provide insight into the possible genesis of individual differences in emotionality and related risks for the emergence of emotional disorders (e.g. the anxiety-prone nature of bLRs or drug addiction proclivity of bHRs), and delineate the role of epigenetic processes in these phenomena.

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Astrocyte-specific Ablation in the Mouse Prefrontal Cortex Induces Depressive-like and Anxiety-like Deficits

Monday, Poster #18

Mounira Banasr, Meiyu Xu, Gerard Sanacora, Christopher Pittenger, Ronald S. Duman
Yale University School of Medicine

Background: Growing evidence implicates glia in the pathophysiology of depression. Reductions in the number of astrocytes have been reported in postmortem studies examining brain tissue from patients with major depression. Preclinical studies have confirmed some of these changes in both the hippocampus and the prefrontal cortex (PFC) in rodent models of depression based on chronic stress. More specifically we have reported that chronic unpredictable stress reduced number of astrocytes expressing GFAP (glial fibrillary associated protein) and others have emonstrated that the S100Beta-positive cell population was unaffected. We have also demonstrated that rat prefrontal cortex (PFC) glial ablation using local infusion of a gliotoxin induces behavioral deficits similar to chronic stress, including anhedonia, anxiety and helplessness. However, the specific contribution of each subtype of glial cell in the development of depressive-like symptoms remains to be characterized.
Methods: To answer this question, we examined the behavioral consequences of targeted ablation of GFAP-positive cells in the PFC in baseline and stress conditions on anhedonia, anxiety and helplessness. To achieve this goal, we developed an approach adapted from *cre/loxP system* strategy in which GFAP-positive cells of the PFC are altered to express the diphtheria toxin (DT) receptor (DTR), and thereby made sensitive to DT exposure. Adult GFAP-*cre* mice and wild type (WT) littermates were infused with AAV5 virus in the PFC. The viral construct was design to express DTR only in *cre* expressing cells; more specifically the *loxp* sequences were strategically positioned around the CMV promoter to induce the flipping of the promoter thereby inducing expression of DTR in *cre*-cells. Three weeks after bilateral infusion of the virus (AAV5-fCMV-DTR) in the PFC, animals were injected i.p. daily with saline or DT at 3 different doses (0.1, 5, 20 ug/kg) for 4 days and daily sucrose (1%) consumption over 24h-period

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Astrocyte-specific Ablation in the Mouse Prefrontal Cortex Induces Depressive-like and Anxiety-like Deficits

Monday, Poster #18 (continued)

Mounira Banasr

was measured. When an effect on sucrose consumption was observed, we also analyzed the effect of glial ablation in other behavioral tests known to be affected by stress and antidepressant treatment.

Results: Two days after the first injection of DT, GFAP*cre*+AAV5-fCMV-DTR mice injected with 20ug/kg of DT showed a significant decrease in sucrose consumption when compared with GFAP*cre*+AAV5-fCMV-DTR mice injected with saline or the 0.1 ug/kg DT. On day 3, both 5 and 20 ug/kg GFAP*cre*+AAV5-fCMV-DTR mouse groups showed reduced sucrose consumption when compared with the saline or the low DT dose group. WT mice infused with AAV5-fCMV-DTR showed no change in sucrose consumption when injected with saline or the different doses of DT. We also measured water consumption on day 5 and found no significant difference in WT or GFAP*cre* mice injected with saline or the various doses of DT. We found that animals GFAP*cre*+AAV5-fCMV-DTR injected with 5 and 20 ug/kg still showed decreased sucrose consumption on day 8, but not day 14 (4 or 10 days after the last injection of DT, respectively). We also examined the consequences of the cell ablation in behaviors measuring the anxiety-like state of the animals. Overall, we found that although the effects were not always significant, the GFAP*cre*+AAV5-fCMV-DTR animals treated with DT tend to exhibit more anxiety-like deficits when compared to the GFAP*cre*+AAV5-fCMV-DTR animals injected with saline. More precisely, we found that GFAP*cre*+AAV5-fCMV-DTR animals treated with the 3 doses of DT showed a significant increase in their latency to drink a milk solution in the novelty induced hypophagia test ($P<0.05$), a trend toward increased latency to feed in the novelty suppressed feeding test ($P=0.15$) and a trend to spend less time in the center in the open field test ($P=0.13$).

Conclusions: Our results demonstrate that selective ablation of GFAP-positive cells in the PFC induces rapid anhedonia- and anxiety-like deficits that persist for at least 8 days but are transitory and not observed at day 14; this reversal could

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Astrocyte-specific Ablation in the Mouse Prefrontal Cortex Induces Depressive-like and Anxiety-like Deficits

Monday, Poster #18 (continued)

Mounira Banasr

be due to glial renewal after cessation of DT infusion, a possibility that we are currently testing. These findings demonstrate that loss of GFAP-positive cells in the PFC is sufficient to cause depressive behavior, supporting the hypothesis that glial loss in depressed patients contributes to depressive symptoms. Moreover, this cell selective ablation approach will allow us to further study the cellular consequences of this astrocyte-specific cortical ablation on the function of the PFC, as well as the contribution of other populations of cells (glial or neuronal) in the development of depressive-like behavior.

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Reduced Mitochondrial Energy Production in Major Depressive Disorder: Associations with the Serotonin Transporter and Glutamine Synthetase Genes

Monday, Poster #91

Chadi G. Abdallah, Graeme F. Mason, Henk De Feyter, Madonna Fasula, Ben Kelmendi, Arthur Simen, Lihong Jiang, John H. Krystal, Douglas L. Rothman, Gerard Sanacora
Yale University

Background: Proton magnetic resonance spectroscopy (^{1}H-MRS) studies have demonstrated altered concentration of aminoacid neurotransmitters in the occipital brain of patients with major depressive disorder (MDD). However, the functional implications of this alteration in total glutamate and GABA levels are not well understood. To elucidate the underlying neuronal mechanisms, we employed ^{13}C magnetic resonance spectroscopy (^{13}C-MRS) to investigate neurotransmitter fluxes and mitochondrial neuroenergetics in MDD subjects.
Methods: 21 medication-free patients with MDD and 14 age- and gender-matched healthy controls had ^{1}H-MRS and ^{13}C-MRS scans with viable data. A subset of the subjects was genotyped for the serotonin transporter (5-HTTLPR) and glutamine synthetase (GLUL) genes. ^{1}H-MRS measured total glutamate and GABA concentration in a single voxel placed in the occipital cortex. [1-^{13}C]-glucose was infused intravenously during ^{13}C-MRS acquisition, which provided *in vivo* measures of neuronal and astrocytic tricaboxilic acid cycle (V_{TCAn} and V_{TCAa}) for mitochondrial energy production, GABA synthesis (V_{GAD}), and glutamate-glutamine cycle (V_{cycle}), which is a measure of glutamate release and uptake.
Results: Patients with MDD had a 26% reduction in mitochondrial energy production of glutamatergic neurons [Mean ±*SEM*; MDD V_{TCAn} = 0.36 ±*0.03* mM, Healthy $V_{TCA\ n}$ = 0.49 ±*0.05* mM, t = 2.30, n = 35, p = 0.028]. GABA and glutamate concentrations, V_{cycle}, and V_{GAD} did not differ between groups ($p > 0.1$). Among the MDD subjects, carriers of the short allele of 5-HTTLPR (SS or SL) have reduced neuronal V_{TCA} compared to those homozygous for the long allele (LL) [t = 2.86, n = 12, p = 0.017]. In addition, we found a significant association [$p < 0.009$] between astrocytic V_{TCA} and 3 GLUL SNPs (rs12136955; rs12735664; rs4652705).

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Reduced Mitochondrial Energy Production in Major Depressive Disorder: Associations with the Serotonin Transporter and Glutamine Synthetase Genes

Monday, Poster #91 (continued)

Chadi G. Abdallah

Conclusions: The reduction of glutamatergic neuronal energy production (V_{TCAn}) in the occipital brain of depressed subjects raises two possibilities: (1) reduced activity of glutamatergic neurons in this brain region or (2) impaired mitochondrial function. Although we did not detect a difference in activity (as measured through V_{cycle}), this may be due to the V_{cycle} measurement with 1-^{13}C glucose being less precise than the V_{TCAn} measurement. However with the recent demonstration that combined use of ^{13}C glucose and ^{13}C acetate enhances the precision of measuring V_{cycle} several fold, it would be possible to distinguish these possibilities in future studies, as well as further explore the impact of MDD on the astrocytic TCA cycle. Finally, the serotonin transporter and glutamine synthetase genes were associated with mitochondrial energy production in glutamatergic neurons and astrocytes, respectively. Further exploration, in future studies, of these intriguing preliminary findings may provide insight in the mechanisms through which these genes affect cerebral function and psychopathology.

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Adolescent Stressors to Epigenetic Modulation in Dopaminergic Neurons Via Glucocorticoids: A Novel Model for Psychotic Depression

Monday, Poster #61

Minae Niwa, Akira Sawa
Johns Hopkins University School of Medicine

Background: Human behavior in adulthood is crucially influenced by various environmental conditions during childhood and adolescence. Nonetheless, individual responses to such environmental factors vary, mainly because of different genetic predispositions among individuals. These gene-environmental interactions may also underlie a variety of neuropsychiatric disorders. Elucidation of the underlying mechanisms and mediators should help development of a means to intervene in such disorders, including prophylactic environmental readjustment.
Methods: A genetic model with isolation stress was examined by behavioral assays and neurochemical assessments. A glucocorticoid receptor antagonist RU38486 (mifepristone) was used. The nuclei of mesocortical and mesolimbic dopaminergic neurons in ventral tegmental area were enriched by labeling with fluorescent retrograde beads and fluorescence-activated cell sorting in a projection-specific manner. Epigenetic modification of the gene for tyrosine hydroxylase was examined by bisulfite sequencing.
Results: We exposed a genetic model (DISC1 mutant mice) to 3-week isolation stress during adolescence (from 5 to 8 weeks of age) and observed behavioral deficits (prepulse inhibition, forced swim test, and locomotor activity) and neurochemical changes associated with dopamine in adulthood. Two distinct dopaminergic projections (mesocortical and mesolimbic) originating from the ventral tegmental area was differentially affected in this model. A mild isolation stress with the genetic risk affected only mesocortical, but not mesolimbic, projection of dopaminergic neurons in which DNA hypermethylation of the tyrosine hydroxylase gene was elicited. The epigenetic alternations were long-lasting, evident in adult animals even if they were maintained in the normal group housing until 20 weeks after the transient adolescent isolation. These molecular, neurochemical, and behavioral deficits in this model were normalized

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Adolescent Stressors to Epigenetic Modulation in Dopaminergic Neurons Via Glucocorticoids: A Novel Model for Psychotic Depression

Monday, Poster #61 (continued)

Akira Sawa

by an administration of a glucocorticoid receptor antagonist RU38486. Given that behavioral deficits may be relevant to endophenotypes of psychotic depression and that RU38486 uniquely benefits this condition, this model of gene-environmental interaction may be a promising tool to study psychotic depression.
Conclusions: This study shows a novel link between adolescent stressors and epigenetic controls in dopaminergic neurons via glucocorticoids, which addresses a central question of neurobiology of how adult behavior patterns are formed by a combination of genetic factors and environmental stressors. Interestingly, the epigenetic modifications by the primary stressor are maintained for long (the isolation stress during adolescence leads to a long-lasting change in adulthood). The present study also offers an innovative mouse model for psychotic depression, a common and debilitating psychiatric disease. The availability of a preclinical model would allow us to study underlying pathological mechanisms, including those in the premorbid and prodromal stages, and explore novel therapeutic strategies. Such a model could provide a good template not only for screening compounds with better efficacy and fewer side effects, but also for prophylactic environmental readjustment, which is crucially important in clinical psychiatry.

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Stress Response Systems in Adolescent Girls and Boys with Major Depression: A Multi-modal Approach

Monday, Poster #139

Kathryn R. Cullen, Bonnie Klimes-Dougan, Alaa Houri, Kelvin O. Lim
University of Minnesota Medical School

Background: The pathophysiology of major depressive disorder (MDD) involves impairment within the neurobiological systems that underlie the response to stress. The neuroendocrine stress response system, encompassed by the Hypothalamic Pituitary Adrenal (HPA), is centrally implicated in MDD. Additionally, fronto-limbic neural circuitry is (a) implicated in MDD, (b) associated with stress response and (c) tightly linked with the HPA system. Core components of this network include the amygdala and the rostral anterior cingulate cortex (rACC). Sex differences have previously been identified in brain development and in stress response. However, the functioning of neurobiological stress systems in adolescents has been understudied. This research is particularly important in adolescence as neurobiological systems are still undergoing development. The goal of the present study was to examine the neurobiological stress systems in adolescent girls and boys with MDD.
Methods: Participants included 54 adolescents aged 12-19, including 39 with MDD (22 unmedicated, 17 medicated) and 15 healthy comparison volunteers. All participants underwent diagnostic evaluation, the Trier Social Stress Test (TSST), and brain imaging (which included a T1 anatomical scan). Statistical analyses were conducted using SPSS. In the TSST, participants were asked to prepare and deliver a short speech to a strange audience. Salivary cortisol measurements were taken at the beginning and immediately following the procedure, and at 15 minutes intervals afterward for a total of five time points. Repeated measures analysis was conducted on the cortisol levels, including group (control, medicated depressed and unmedicated depressed) and sex as fixed effects. Multivariate regression analyses were also conducted on peak cortisol levels and area under the curve measurements to assess for effects of group and sex. Analysis of anatomical imaging data was conducted using the FreeSurfer software to extract brain volumes from key regions of interest. A multivariate regression analysis

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Stress Response Systems in Adolescent Girls and Boys with Major Depression: A Multi-modal Approach

Monday, Poster #139 (continued)

Kathryn R. Cullen

was conducted on key fronto-limbic brain regions that were hypothesized to relate to MDD and the stress system: bilateral amygdala volumes and bilateral rACC volumes, including group and sex as fixed effects, and intracranial volume as a covariate. Finally, we examined correlations between cortisol measurements (peak levels and area under the curve) and brain volumes (amygdala and rostral anterior cingulate.)

Results: For the TSST, repeated measures analysis revealed a significant group by time effect ($F=3.4$, $p=0.002$) and a trend-level sex effect ($F=2.0$, $p=0.1$). The control group exhibited a normative elevation in cortisol followed by return to baseline; the unmedicated group showed elevated baseline cortisol levels, peaked higher and remained elevated at the end of the experiment; and the medicated group showed a marked decrease during the task followed by a return to baseline. Examination of the results separately by sexes showed that while depressed boys tended to show an over-responding pattern, the depressed girls showed an under-responding pattern. Medication seemed to flatten responses for both boys and girls. Multivariate analyses revealed of peak and summary cortisol measures showed significant effects for group ($F=3.7$, $p=0.000$), sex ($F=2.6$, $p=0.03$), and a group by sex interaction ($F=2.8$, $p=0.003$). Whereas unmedicated boys had much higher peak and summary levels than both controls and medicated boys, the female groups were more similar. Finally, although we did not identify significant group effects with respect to brain volumes for our regions of interest, we did find significant correlations between both left and right amygdala volume and peak cortisol during the recovery phase of the experiment (left: $r = -0.4$, $p=0.006$; right: $r = -0.3$, $p = 0.03$) as well as with the summary measure (area under the curve) (left: $r = -0.4$, $p=0.008$, right: $r = -0.3$, $p =0.03$.)

Conclusions: We report results from a multi-method study that examined stress systems in adolescents with MDD. Our findings suggest that the systems that underlie the stress response in adolescents with depression are abnormal,

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Stress Response Systems in Adolescent Girls and Boys with Major Depression: A Multi-modal Approach

Monday, Poster #139 (continued)

Kathryn R. Cullen

with unmedicated adolescents showing elevated stress responses and delayed recovery. Current treatment with medication appears to dampen the biological response to social stress. These cross sectional results suggesting the impact of treatment on HPA responding should be followed by longitudinal studies to directly test whether treatment mitigates the stress response in depressed teens. Although this study included fewer boys than girls, tentatively our results suggest that unmedicated depressed boys show an over-responding pattern, whereas for girls the pattern is that of under-responding. The sex effects noted in this study require confirmation with larger and more balanced samples. Finally, although fronto-limbic brain volumes did not differentiate groups, they were inversely related to cortisol measures in the adolescents of this study. Additional research using multi-modal approaches is needed to further delineate the inter-dependent relationships across neurobiological stress systems.

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PTSD is Associated with an Increased Prevalence of Autoimmune Disorders

Wednesday, Poster #137

Aoife O'Donovan, Beth Cohen, Daniel Bertenthal, Mary Margaretten, Karen Seal, Thomas Neylan
University of California, San Francisco

Background: Accumulating evidence links post-traumatic stress disorder (PTSD) with elevated inflammatory activity. However, the clinical significance of this association is unclear. Though inflammation could increase the risk of autoimmune disease, little is known about whether patients with PTSD are at increased risk of developing autoimmune disorders.
Methods: We conducted a retrospective cohort study of 673,277 Iraq and Afghanistan veterans under 55 years old who received VA healthcare from October 1, 2005 to March 31, 2012 with at least one year of follow up. Department of Veterans Affairs administrative data were used to identify ICD-9 codes for mental health and autoimmune disorders and to obtain sociodemographic, military service, and health service utilization information. Generalized Linear Models were used to ascertain the association of PTSD with subsequent autoimmune diagnoses after adjusting for age, race and number of primary care visits.
Results: The sample was 88% male and 49% white with a mean age of 31.3 years (+/- 8.7). PTSD was diagnosed in 206,623 (31%) veterans and mental health disorders other than PTSD were diagnosed in an additional 132,242 (20%) veterans. Compared to veterans with no mental health diagnoses, those diagnosed with PTSD had increased risk for subsequent diagnosis with thyroiditis (Adjusted Relative Risk [ARR] = 1.74; 95% CI, 1.67, 1.82), rheumatoid arthritis, (ARR = 1.92, 95% CI, 1.67, 2.20), inflammatory bowel disease (ARR = 1.32, 95% CI, 1.20, 1.46), multiple sclerosis (ARR = 2.23, 95% CI, 1.88, 2.64), systemic lupus erythematous (ARR = 1.81, 95% CI, 1.48, 2.23) and any of these disorders alone or in combination (ARR = 1.50, 95% CI, 1.45, 1.56). Moreover, while there was an increased risk for each of these disorders in veterans with mental health disorders other than PTSD, the risk was consistently higher in those diagnosed

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PTSD is Associated with an Increased Prevalence of Autoimmune Disorders

Wednesday, Poster #137 (continued)

Thomas Neylan

with PTSD. Women had significantly higher risk for autoimmune disorders overall, but the pattern of results was similar in men and women.
Conclusions: Veterans with PTSD appear to be at increased risk for autoimmune disorders compared to those with no or other mental health diagnoses. Future prospective longitudinal cohort studies are needed to establish causality, measure inflammatory markers in conjunction with PTSD, and evaluate whether successful treatment of PTSD reduces risk of autoimmune disorders.

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The Peripheral Immune System Functionally Contributes to Susceptibility to Repeated Social Defeat Stress

Monday, Poster #13

Georgia E. Hodes, Sam A. Golden, Daniel J. Christoffel, Madeline Pfau, Mitra Heshmati, Marylene Leboeuf, Miriam Merad, Scott Russo
Mount Sinai School of Medicine

Background: Subjects with major depression have increased circulating levels of pro- inflammatory cytokines, such as Interleukin-6 (IL-6), which is thought to reflect hyperactivity of their peripheral immune system (Dowlati et al., 2009). We have previously shown similar increases in serum IL-6 levels following repeated social defeat stress (RSDS), a mouse model of mood and anxiety disorders. Mice that are susceptible to RSDS initially have an exaggerated release of IL-6 and exhibit sustained increases of IL-6 levels for at least 1 month following the last defeat. Thus, we predict that there are innate differences in the immune response to stress in susceptible mice that drives depression- and anxiety-like behavioral phenotypes.
Methods: We used RSDS to examine individual differences in response to stress; some animals termed susceptible show a spectrum of depression-like behavior, whereas resilient animals are more similar to controls. To determine whether IL-6 release can be used as a predictive biomarker, we isolated and cultured peripheral blood mononuclear cells (PBMCs) prior to exposure to RSDS, stimulated with the endotoxin lipopolysaccharide (LPS), and then measured IL-6 using enzyme linked immunosorbent assays (ELISA). To determine if peripheral IL-6 was necessary for the development of susceptibility to RSDS, we systemically injected a separate group of animals with an antibody that neutralizes IL-6 in the periphery and tested them for social avoidance, anhedonia (sucrose preference) and anxiety (elevated plus maze). To examine whether the peripheral immune system was sufficient to functionally drive these behavioral adaptations to RSDS, we first ablated the peripheral immune system of naïve mice using irradiation. We then replaced their immune system with bone marrow either from a susceptible mouse following 10 days of RSDS, or a control mouse with a little or no IL-6 response to endotoxin challenge. We then exposed mice to a sub-threshold micro-defeat and tested for depression and anxiety-like behavior.

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The Peripheral Immune System Functionally Contributes to Susceptibility to Repeated Social Defeat Stress

Monday, Poster #13 (continued)

Georgia E. Hodes

Results: PBMCs isolated prior to social defeat from mice that later developed a susceptible phenotype had a larger release of IL-6 following LPS stimulation compared to mice that went on to become resilient. Systemic injections of an IL-6 neutralizing antibody in the periphery blocked RSDS-induced social avoidance and anhedonia. Finally, mice that received bone marrow transplants from a susceptible mouse showed greater social avoidance, anhedonia, and anxiety-like behavior following a sub-threshold micro-defeat.
Conclusions: These studies indicate that the peripheral immune system contributes to the development of susceptibility to social defeat stress. We found that a hyperactive peripheral immune response to stress is a risk factor for the development of depression and anxiety-like behavior. We also show a direct functional role of the peripheral immune response to stress in regulating depression and anxiety like behaviors. Together these studies indicate that innate differences in the immune responses to stress may underlie the development of depression like behavior and serve as a novel therapeutic target for treatment.

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Pain-related Depression of the Mesolimbic Dopamine System in Rats: Expression, Blockade by Analgesics, and Role of Endogenous Kappa Opioids

Monday, Poster #52

Steve Negus, Michael Leitl, Matthew L. Banks
Virginia Commonwealth University

Background: Pain is often associated with depression of behavior and mood, and relief from pain-related depression is a common goal of treatment with analgesic drugs. This preclinical study tested the hypothesis that pain-related depression of behavior in rats results from activation of endogenous kappa opioidergic systems and subsequent kappa receptor-mediated inhibition of mesolimbic dopamine neurons. We have reported previously that a common visceral noxious stimulus, intraperitoneal (IP) injection of dilute acid, produces an analgesic-reversible depression of operant responding in an assay of intracranial self-stimulation (ICSS) in rats. The present study compared effects of IP acid and the exogenous kappa agonist U69593 on ICSS and on microdialysis measures of mesolimbic nucleus accumbens dopamine levels in rats. The nonsteroidal anti-inflammatory drug ketoprofen, the mu opioid receptor agonist morphine, and the kappa opioid receptor antagonist norbinaltorphimine were then evaluated for their ability to block acid- and U69593-induced depression of ICSS and nucleus accumbens dopamine. Our hypothesis predicted that both IP acid and U69593 would depress ICSS and nucleus accumbens dopamine levels, and that effects of acid would be blocked by analgesics and by the kappa antagonist.
Methods: Adult male Sprague-Dawley rats were prepared either with intracranial electrodes targeting the medial forebrain bundle (for behavior studies of intracranial self-stimulation) or cannulae targeting the nucleus accumbens (for microdialysis studies of mesolimbic dopamine). Rats in behavioral studies were trained to lever press under a fixed-ratio 1 schedule for electrical brain stimulation, and daily experimental sessions were composed of multiple 10 min components. During each component, the frequency of brain stimulation was systemically varied from 158-56 Hz in ten 0.05 log unit steps, and the primary dependent variable was the total number of stimulations delivered across all frequencies. On test days, ICSS

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Pain-related Depression of the Mesolimbic Dopamine System in Rats: Expression, Blockade by Analgesics, and Role of Endogenous Kappa Opioids

Monday, Poster #52 (continued)

Steve Negus

components were conducted before and after experimental treatments, and ICSS data determined after each treatment were expressed as a percent of the baseline data collected before treatment on that day. Rats in neurochemical studies were fitted with microdialysis probes on the day of the experiment, and samples were collected at 6-min intervals before and after experimental treatments. The primary dependent variable was the concentration of dopamine in each sample determined by high performance liquid chromatography coupled to electrochemical detection. Dopamine levels determined after each treatment were expressed as a percent of the baseline data collected before treatment on that day. In both types of studies, rats were treated with vehicle (-30 min), 3.2 mg/kg ketoprofen (-30 min), 3.2 mg/kg morphine (-30 min) or 32 mg/kg norbinaltorphimine (-24 hr) before subsequent treatment with vehicle, 0.56 mg/kg U69593 or dilute lactic acid (1.8 or 5.6% in water). All studies were approved by the Virginia Commonwealth University IACUC and were conducted in accordance with the National Institutes of Health *Guide for the Care and Use of Laboratory Animals*.

Results: The acid noxious stimulus produced a concentration- and time-dependent depression of both ICSS and nucleus accumbens dopamine, and effects of the highest acid concentration (5.6%) in both assays were similar in magnitude to effects of 0.56 mg/kg U69593. Acid-induced depression of ICSS and nucleus accumbens dopamine was blocked by pretreatment with the analgesics ketoprofen and morphine, but not by the kappa antagonist norbinaltorphimine. Conversely, U69593-induced depression of ICSS and dopamine was blocked by norbinaltorphimine but not by ketoprofen; morphine produced intermediate effects. Neither ketoprofen nor norbinaltorphimine altered ICSS or dopamine levels when administered alone without acid. Morphine alone significantly increased basal dopamine, and produced biphasic effects on ICSS manifested as facilitation of low ICSS rates maintained by low brain stimulation frequencies and

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Pain-related Depression of the Mesolimbic Dopamine System in Rats: Expression, Blockade by Analgesics, and Role of Endogenous Kappa Opioids

Monday, Poster #52 (continued)

Steve Negus

reduction in high ICSS rates maintained by high brain stimulation frequencies. **Conclusions:** These results support a role for the mesolimbic dopamine system, but not of endogenous kappa opioid systems, in mediating pain-related depression of behavior in rats. Further research to investigate mechanisms of pain-related depression of behavior and mesolimbic dopamine levels may reveal new targets for analgesic drug development.

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Evidence of an Inflammatory Pathway Leading to Psychosis in Bipolar Disorder

Tuesday, Poster #135

Mikael Landén, Carl Sellgren, Magdalena Kegel, Carl-Johan Ekman, Patrick Sullivan, Jordan W. Smoller, Pamela Sklar, Göran Engberg, Sophie Erhardt
The Sahlgrenska Academy at Gothenburg University

Background: Family history is the strongest risk factor for bipolar disorder. Yet it has been difficult to identify susceptibility gene variants. An alternative approach to unearth causal genetic mutations is to focus on biomarkers, i.e., measurable key components in biological pathways between genotype and disease. We therefore conducted a genome wide association study (GWAS) of kynurenic acid (KYNA) in cerebrospinal fluid (CSF), based on that elevation of KYNA in brain is a consistently found biochemical aberration in psychotic disorders. We then studied the genetic finding in relation to psychotic symptoms, cognition, and brain gray matter volume. Lastly, we used an *in vitro* model to test if IL-1b is the link between the genetic variant and elevated CSF levels of KYNA.
Methods: CSF was collected from patients with bipolar disorder (N=76) and a genome-wide association study in relation to CSF KYNA was conducted. Patients underwent magnetic resonance imaging (MRI) scans of the brain and a neurocognitive test battery. Human cortical astrocytes were cultured and stimulated with recombinant human IL-1b (10ng/ml). Analysis of KYNA was performed using an isocratic reversed-phase high-performance liquid chromatography (HPLC) system.
Results: One SNP located on chromosome 1 reached genome-wide statistical significance in relation to CSF KYNA (rs10158645, b=1.05, P=3.85x10^{-8}, MAF=0.15).The minor allele of rs10158645 was associated with increased risk of psychotic features (n=76, OR=4.0, 95%CI:1.4-12) , increased verbal working memory (n=108, b=1.8, P=0.019) and increased gray matter thickness in corresponding brain regions (n=138, P=0.02, voxel-level FWE-corrected). the *in vitro* results showed that IL-1b increases KYNA levels in human cortical astrocytes by inducing the rate-limiting enzyme TDO2.

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Evidence of an Inflammatory Pathway Leading to Psychosis in Bipolar Disorder

Tuesday, Poster #135 (continued)

Mikael Landén

Conclusions: The minor allel of rs10158645 has previously been coupled to a decreased expression of sortin nexin 7 (SNX7), which in turn activates caspase-8 that increases IL-1β. Here we found that IL-1β stimulates KYNA, known to be increased in psychotic disorders. This raises the possibility that SNX7-induced IL-1b dependent activation of the kynurenine pathway is a molecular pathway underlying psychosis in bipolar disorder.

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Mapping Brain Metabolic Connectivity in Awake Rats with MicroPET and Optogenetic Stimulation

Wednesday, Poster #46

Panayotis Thanos, Lisa Robison, Eric Nestler, Ronald Kim, Mike Michaelides, Mary Kay Lobo, Nora D. Volkow
National Institute on Alcohol Abuse and Alcoholism

Background: Optogenetics allows researchers to map neuronal circuit function in the rodent brain in vivo (Zhang et al., 2010; Lee and Deisseroth, 2012). The combined use of optogenetics and functional magnetic resonance imaging (fMRI) has been used to investigate functional connectivity in the rodent brain (Lee et al., 2010; Lee 2012; Lee and Deisseroth, 2012); however, these are limited by the use of anesthesia, which affects neuronal activity (Qiu et al., 2008; Tsurugizawa et al., 2010). Positron emission tomography (PET) using [^{18}F] 2-fluoro-2-deoxy-D-glucose (FDG), however, allows researchers to non-invasively measure regional brain glucose metabolism (BGluM), a marker of brain activity, in the awake rodent. The present study used mPET with FDG to measure optogenetic stimulation (OGS) of the nucleus accumbens (NAc). We tested the hypothesis that excitation of the NAc by OGS would increase metabolism in the NAc and in its downstream projection regions. In parallel, we mapped c-Fos expression to corroborate regional activation by OGS.
Methods: Male Sprague Dawley rats (8-10 weeks) were anesthetized and Adeno-associated virus serotype 2 (AAV2)-hsyn-ChR2-EYFP (n=8/group) or AAV2-GFP control virus (n=9/group) was infused into the right NAc core (AP +1.7, ML +1.5, DV -6.5 from bregma) through a 20 gauge cannula. Rats recovered for a minimum of two weeks while waiting for optimal AAV expression. The experiment was conducted in accordance with the Guide for the Care and Use of Laboratory Animals (1996) and approved by the BNL Institutional Animal Care and Use Committee (IACUC). Each rat was scanned twice using FDG-mPET, one week apart (counterbalanced design): once at baseline (optical fiber attached but no stimulation applied) and once following OGS. Rats were placed in a small plexiglass cage to restrict movement and minimize activation from motor behavior. Blue (473 nm) light stimulation, pulsed at 10Hz, was applied

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Mapping Brain Metabolic Connectivity in Awake Rats with MicroPET and Optogenetic Stimulation

Wednesday, Poster #46 (continued)

Panayotis Thanos

through the optical fiber at 30 second intervals for five minutes (light turned off for the baseline scan). Rats were injected intraperitoneally with ~0.5 mCi of FDG (30 minute awake uptake), during which time blue light stimulation was continued, and locomotor activity was measured. After the uptake period, rats were anesthetized and scanned on an R4 mPET tomograph for 30 minutes. Statistical Parametric Mapping (SPM) analysis was performed using paired t-tests for each group (GFP and ChR2) comparing regional brain glucose metabolism between the baseline and the stimulation scans [threshold: $p<0.005$, $K_e>100$, $T>5.7$]. A region of interest (ROI) was manually drawn in the NAc cluster that was significantly activated in the ChR2 group, and activity was measured for the baseline and stimulation condition for the GFP and ChR2 rats. Rats (GFP: n=4; ChR2: n=6) were again stimulated with blue light for ten minutes, and 90 minutes later, rats were anesthetized, perfused, and brain harvested to assess c-Fos immunofluorescence in the NAc.

Results: Brain metabolic differences between baseline and OGS stimulation of the NAc were determined both for activation (stimulation > baseline) and inhibition (stimulation < baseline). OGS in the ChR2 group resulted in five activated and two inhibited clusters. Activation was seen in the NAc, dorsal hippocampus and stria terminalis; secondary somatosensory cortex and caudate/putamen; globus pallidus, ventral pallidum, and amygdala; and periaqueductal gray. Inhibition was seen in the retrosplenial cortex, anterior cingulate gyrus and secondary motor cortex. The ROI analysis determined that the NAc of each rat in the ChR2 group was activated between the baseline and stimulation scans. Only ChR2 rats showed a significant increase (16% ±3) in BGluM in NAc ROI from baseline to stimulation scans ($p<0.01$; group x intervention [$F(1,15)=9.332$, $p<0.01$]). Locomotor measures determined only a significant main effect of time [$F(4,56)=5.188$, $p=0.001$]; as expected, rats were more active during the habituation sessions compared to the mPET sessions. Analysis of c-Fos

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Mapping Brain Metabolic Connectivity in Awake Rats with MicroPET and Optogenetic Stimulation

Wednesday, Poster #46 (continued)

Panayotis Thanos

expression in the NAc following OGS found that c-Fos expression was greater in ChR2 rats compared to GFP rats [$F(1,8)=20.392$; $p<0.01$], and changes in brain glucose metabolism in the NAc (baseline vs. stimulation) and c-Fos expression were significantly correlated ($R=0.77$, $p<0.01$).

Conclusions: OGS of the NAc increased c-Fos expression and BGluM in the region of stimulation, and these measures were correlated. This is consistent with fMRI results reporting BOLD increases in the area of stimulation (Lee and Deisseroth, 2012). We also observed increased metabolism in regions connected to the NAc including the basal ganglia (caudate, putamen, globus pallidus, and ventral pallidum) and limbic regions (amygdala, hippocampus). Interestingly, we showed decreased metabolic activity in the restrosplenial cortex (posterior cingulate gyrus) and anterior cingulate gyrus, which are regions that form part of the default mode network (DMN), which in conjunction with brain imaging findings in humans (Tomasi et al., 2009; Dang et al., 2012), suggests that activation of the NAc may facilitate DMN inhibition. These results demonstrate the feasibility of using mPET with FDG in conjunction with OGS to map connectivity in the awake rat brain.

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Fine-grained Working Memory Load Manipulation Reveals Absence of Normative Inverted-U Activation in Schizophrenia

Wednesday, Poster #123

Jared X. Van Snellenberg, Ragy R. Girgis, Christina Read, Judy L. Thompson, Jochen Weber, Tor D. Wager, Mark Slifstein, Jeffrey A. Lieberman, Anissa Abi-Dargham, Edward E. Smith
Columbia University College of Physicians & Surgeons

Background: Patients with schizophrenia exhibit serious and clinically relevant deficits in working memory (WM). However, investigations of WM in patients with schizophrenia using functional Magnetic Resonance Imaging (fMRI) have largely failed to reveal a consistent abnormality in brain activation in patients. One hypothesis is that patients exhibit a disordered relationship between the extent of activation in dorsolateral prefrontal cortex (DLPFC) and WM load, for example a left-shift in an inverted-U relationship (Callicott et al., 2003; Manoach, 2002, 2003), such that patients exhibit greater activation relative to healthy individuals at low WM loads and less activation at high loads. To test this hypothesis, we employed a version of the self-ordered working memory task (SOT) for use with fMRI that provides a finer-grained variation in WM load than existing tasks.
Methods: Thirteen patients with schizophrenia and eighteen control participants matched on age, gender, and parental socio-economic status performed the SOT during the acquisition of Blood-Oxygen Level Dependent fMRI images from a Philips 1.5 Tesla Intera scanner (2 s TR, 40 slices of a 64 x 64 plane, 3 mm isotropic voxels). In each trial of the SOT participants are presented with eight line drawings of 3D objects in an array. On each step of the trial the object positions are pseudo-randomly rearranged, and participants must select any object that they have not previously selected, thereby producing a gradual increase in WM load over the eight steps of each trial. Whole-brain fMRI activation data during correctly performed steps was analyzed in a two-way between-groups repeated measures ANOVA with factors Diagnosis (two levels) and Step (eight levels), using the Greenhouse-Geisser correction for non-sphericity. Regions showing a main effect of Step in either group were further analyzed in a random-effects polynomial regression to determine the shape of the change in activation over steps.

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Fine-grained Working Memory Load Manipulation Reveals Absence of Normative Inverted-U Activation in Schizophrenia

Wednesday, Poster #123 (continued)

Jared X. Van Snellenberg

Results: Patients and controls exhibited above chance accuracy and monotonic declines in performance from steps two through eight, with patients also performing significantly worse than controls at these steps. Healthy controls exhibited a significant ($p < 0.05$, FDR corrected) negative quadratic polynomial (inverted-U) response to increasing WM load in the SOT in bilateral DLPFC, posterior parietal cortex (PPC), lateral occipital cortex, fusiform gyrus, and left putamen. Patients with schizophrenia exhibited no significant main effect of step in any brain region, even at a relaxed statistical threshold ($p > 0.25$, FDR corrected). Significant between-group differences in the pattern of activation was observed at a relaxed threshold ($p < 0.25$, FDR corrected) in bilateral DLPFC, right PPC, and right cuneus and fusiform gyrus.
Conclusions: The present findings support the hypothesis of an inverted-U relationship between DLPFC activation and WM load in healthy individuals, as proposed by Callicott et al. (2003) and Manoach (2002, 2003), and this relationship was also observed in several other brain regions known to be involved in WM. However, there was no evidence to suggest a left-shift in this inverted-U in patients with schizophrenia; rather, the normative inverted-U relationship was absent in patients. While specification of the functional significance of this inverted-U relationship remains somewhat speculative, the fact that healthy individuals maintained high levels of performance at later steps, and yet showed decreasing activation during correct performance in brain regions known to subserve WM, suggests that healthy individuals may have exhibited a flexible shift in strategy (e.g. to a familiarity-based long-term memory strategy) as their WM capacity was exceeded. Critically, patients with schizophrenia failed to show this shift at high WM load, raising the possibility that they either have a fundamental impairment that makes such a strategy shift a non-optimal approach to performing the task, or that they were exhibiting perseveration on the earlier-adopted strategy. This study is arguably the most comprehensive investigation of the impact of variation

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Fine-grained Working Memory Load Manipulation Reveals Absence of Normative Inverted-U Activation in Schizophrenia

Wednesday, Poster #123 (continued)

Jared X. Van Snellenberg

in WM load on brain activation in patients with schizophrenia and matched controls carried out to date, and reveals several new directions for research into the functional impairment underlying WM deficits in patients with schizophrenia.

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BDNF Val66Met Modulates BOLD Response to Affective Instrumental Learning in Humans

Wednesday, Poster #205

Mbemba Jabbi, Brett Cropp, Tiffany Nash, Philip Kohn, Raghav Mattay, Shane Kippenhan, Bhaskar S. Kolachana, Daniel R. Weinberger, Karen F. Berman
National Institute of Mental Health

Background: Preclinical models implicate the BDNF Val66Met polymorphism in impaired fear extinction and anxiety phenotypes (Chen et al., 2006; Lipsky and Marini 2007), but the role of this genotype in human adaptive learning requiring both avoidance of adverse circumstances as well as attainment of rewarding experiences remains largely unknown. Here, we assessed this SNP's influence on the amygdala and hippocampus, two key regions involved in emotional regulation and learning (Ledoux 2000; Farinelli et al., 2006; Herry et al., 2008) during higher-order reinforcement learning whereby videos of fearful and happy expressions predicted choice-related monetary loss and gain respectively.
Methods: Thirty-three healthy participants (12 met carriers, 21 val homozygotes) underwent fMRI (at 3T; 16 channel head coil) while passively viewing dynamic happy, fearful, and neutral facial expressions. In addition, 61 participants including the 33 passive viewing cohort (21 met carriers, 40 val homozygote) underwent reinforcementlearning during fMRI (3T, 16 channel head coil), while they *1*) watched a cue video of emotional or neutral expression; *2*) made a choice between two non-face pictures simultaneously presented, with one of the pictures portraying emotional content concordant with the preceding video; and *3*) saw an outcome cue delineating monetary reward if the concordant picture was correctly chosen, or loss if the non-concordant picture was chosen. Preprocessing (8mm smoothing), first-level analysis with SPM5, and random-effects ANOVAs were performed to assess BOLD response to passive viewing and during establishment of cue-outcome association. We tested for regional specificity of Val66Met influence on BOLD response to higher-order emotional cues in amygdala and hippocampus, given their intimate inter-connectivity and collective mediation of learning and LTP and their role in regulation of emotions (Ledoux 2000; Dolan 2002; Farinelli et al., 2006; Herry et al., 2008). To this aim, we extracted

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BDNF Val66Met Modulates BOLD Response to Affective Instrumental Learning in Humans

Wednesday, Poster #205 (continued)

Mbemba Jabbi

percentage BOLD signal change from manually segmented whole amygdala and hippocampal regions of interest (ROI) for each emotional viewing condition separately for each of the 33 individuals who participated in passive viewing, and while they underwent affective reinforcement learning.
Results: Using a 2 *by 2 by* 3 repeated measures ANOVA (task ['passive viewing vs. higher-order emotional conditioning'] *by* region ['whole amygdala and hippocampus'] *by* valence) with Val66Met genotype as the between-subjects factor, we found a task *by* region *by* BDNF interaction ($F_{2, 30} = 3.71$, $p = 0.032$). Whereas the hippocampal response was not affected by genotype, there was a decreased BOLD response to reinforced emotional cues in the amygdala of met carriers. To further assess valence-specific BDNF influence on neural coding of predictive emotional cues during reinforcement learning, we extracted BOLD signals measured during viewing of loss and gain predictive fear and happy cues from left and right amygdala and hippocampal ROIs in all 61 reinforcement learning participants. Using a 2 *by* 2 *by* 3 repeated measures ANOVA (region *by* hemisphere 'left vs. right' *by* valence) with BDNF Val66Met genotype as the between subjects factor, we found an interaction between region and hemisphere at $F_{2,58} = 18.21$, $p = 10^{-}4$, driven by a marked reduction in left amygdala BOLD signals. Importantly, no main effects of BDNF genotype and no interaction between genotype and valence was found on neural coding of predictive emotional cues, supporting aVal66Met influence on these regions that is not fear specific. The observed BOLD response pattern was in line with previous research (Soliman et al., 2010; Andero et al., 2012), in that met carriers showed a consistent overall decrease in BOLD response to reinforced emotional cues. To assess the behavioral utility of the Val66Met genotype, we used a 3 *by* 2 (valence *by* conditioning) repeated-measures ANOVA on choice-related performance scores, with BDNF as between-subjects factor. We found main effects of genotype ($F_{1, 59} = 4.392$, $p = 0.040$) and valence ($F_{2, 58} = 100.59$, $p < 10^{-5}$), with choice accuracy during

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BDNF Val66Met Modulates BOLD Response to Affective Instrumental Learning in Humans

Wednesday, Poster #205 (continued)

Mbemba Jabbi

affectively-relevant instrumental choice behavior surpassing chance-level for the aversive and rewarding conditions only, and more so for the met carriers.
Conclusions: Here, we demonstrated that met carriers performed better by gaining more money while avoiding losses in the subsequent choice behavior. This behavioral pattern was associated with an overall decrease in amygdala BOLD response to facial cues, and this neural response pattern was shown to be specific to emotional cues carrying loss/gain predictive value. Together, these findings suggest an adaptive utility of the pronounced decrement in amygdala BOLD response found in the met carriers. By demonstrating that the BDNF Val66Met polymorphism mediates flexible adaptive behavior in both reward and aversive learning, these data may demonstrate a neurogenetic mechanism underlying emotionally meaningful adaptive behavior, and thereby provide a possible framework for understanding the neurogenetic correlates of mood and anxiety disorders.

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"Erasing" a Cocaine-cue Memory in Mice: Potential Implications for Relapse to Drug Taking

Monday, Poster # 81

Sheena Josselyn, Hwa-Lin (Liz) Hsiang, Michel van den Oever, Chen Yan, Asim Rashid, Paul Frankland
University of Toronto

Background: One significant obstacle for the treatment of drug addiction is the high incidence of relapse to drug-taking following months, or even years, of abstinence. Exposure to stimuli that were previously associated with prior drug use can awaken powerful memories that may trigger drug craving and provoke a relapse. Therefore, understanding how animals learn and remember the association between a cue and a drug of abuse (such as cocaine) is a crucial step to develop more effective treatment strategies for preventing and treating relapse in humans. Here we examined the neural mechanisms that mediate how cues become associated with the rewarding properties of cocaine to determine if disrupting expression of this cue-reward memory can help prevent relapse.
Methods: CREB (cAMP/Ca^{2+} responsive element binding protein) is a transcription factor that has a well-documented role in neuronal plasticity and long-term memory formation. Previously we found that increasing levels of the transcription factor CREB in a subset of lateral amygdala (LA) neurons in mice enhanced the formation of a fear memory and that selectively ablating these neurons post-training essentially "erased" the fear memory (Han et al., *Science*, 2007, 2009). We took advantage of this approach to investigate whether LA neurons are also critically involved in a cocaine-cue associated memory. To assess cocaine-cue memory, we used the conditioned place preference (CPP) paradigm. In this task, an otherwise neutral environment is paired with cocaine administration. A second neutral environment is paired with saline administration. Drug-free mice are then given the opportunity to spend time in each of these environments. Mice that have learned and remember the association between the particular environment and cocaine spend more time in this drug-paired environment.
Results: To increase CREB function in a subset of LA neurons, we microinjected replication-defective herpes simples virus (HSV) vectors encoding CREB or GFP (control) into the LA of mice. Increasing CREB in a small subset of

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"Erasing" a Cocaine-cue Memory in Mice: Potential Implications for Relapse to Drug Taking

Monday, Poster # 81 (continued)

Sheena Josselyn

LA neurons during (but not after) conditioning (pairing cocaine with a neutral environment) enhanced cocaine-CPP memory. To determine if these LA neurons with increased CREB function comprised a crucial component of the "cocaine memory-trace", we used inducible diphtheria toxin receptor (iDTR) transgenic mice to selectively ablate just these neurons after conditiioning. Deletion of LA neurons with increased CREB function (but not a similar proportion of random neurons) blocked expression of a previously acquired cocaine-CPP memory. That is, we were able to disrupt expression of a cocaine CPP by simply ablating a small portion of LA neurons that overexpressed CREB during conditioning. In contrast to extinction training, the disruption of CPP produced by ablating neurons overexpressing CREB was resistant to reinstatement following a low priming dose of cocaine. These findings suggest that a critical component of the cocaine-CPP memory is essentially erased. Next, rather than (irreversibly) ablating these neurons overexpressing CREB, we took advantage of the DREADD (designer receptors exclusively activated by designer drug) system to temporarily inactivate neurons overexpressing CREB. hM4Di is an engineered receptor that is coupled to Gi protein; binding of hM4Di by clozapine-N-oxide (CNO), an otherwise pharmacologically inert compound, promotes neuronal inhibition. We microinjected viral vectors expressing both CREB and hM4Di and found that "silencing" neurons overexpressing CREB before CPP testing similarly inhibited the expression of cocaine CPP memory.

Conclusions: Our results indicate that, similar to a conditioned fear memory, a small population of LA neurons is critically involved in a cocaine-associated memory. Not only do the results of these studies inform us as to the biology underlying the development and expression of cue-cocaine associations, but, in the future, these findings could serve as a foundation for the development of new pharmacotherapies aimed at treating or even preventing drug relapse.

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Markedly Reduced mGluR5 Receptor Binding in Smokers and Ex-smokers Determined by [11C]ABP688 Positron Emission Tomography

Tuesday, Poster #73

Gregor Hasler, Funda Akkus, Simon M. Ametamey, Valerie Treyer, Cyrill Burger, Anass Johayem, Daniel Umbricht, Baltazar Gomez Mancilla, Judit Sovago, Alfred Buck
Psychiatric University Hospital, Bern, Switzerland

Background: Nicotine addiction is a major public health problem, resulting in primary glutamatergic dysfunction. We measured the glutamate receptor binding in the human brain and provided direct evidence for the abnormal glutamate system in smokers. Since antagonism of the metabotropic glutamate receptor 5 (mGluR5) reduced nicotine self-administration in rats and mice, mGluR5 is suggested to be involved in nicotine addiction.
Methods: We used positron emission tomography (PET) with the radiolabeled mGluR5 antagonist 3-(6-methyl-pyridin-2-ylethynyl)-cyclohex-2-enone-O-11C-methyl-oxime ([^{11}C]ABP688) (15), which binds with high selectivity to an allosteric site, to measure mGluR5 availability in 14 healthy subjects (non-smokers), 14 smokers, and 10 ex-smokers. The mean duration of nicotine abstinence in ex-smokers was 18.2 weeks (standard deviation, 14.2).
Results: We found a marked global reduction (20.6%; $p < 0.0001$) in the mGluR5 distribution volume ratio (DVR) in the gray matter in smokers. The most prominent reductions were found in the bilateral medial orbitofrontal cortex. Compared to non-smokers, ex-smokers had global reductions in the average gray matter mGluR5 DVR (12.4%; $p < 0.005$). In contrast, the differences in mGluR5 DVR in any brain region between smokers and ex-smokers did not reach statistical significance after Bonferroni correction. In smokers, age was positively correlated with mGluR5 DVR in most regions of interest, and the strongest correlations were found in the putamen. Clinical variables reflecting current nicotine consumption, dependence, and abstinence were not correlated with mGluR5 DVR.
Conclusions: These findings suggest that the reduced mGluR5 may not reflect a simple consequence of nicotine consumption but may represent a precondition

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Markedly Reduced mGluR5 Receptor Binding in Smokers and Ex-smokers Determined by [11C]ABP688 Positron Emission Tomography

Tuesday, Poster #73 (continued)

Gregor Hasler

of nicotine dependence and/or a trait-like pathogenetic or compensatory change associated with nicotine addiction. This study encourages the development and testing of drugs against addiction that directly target the glutamatergic system.

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Differentiating Neural Networks with Interleaved TMS-BOLD Imaging: Insight into Addiction

Wednesday, Poster #159

Colleen A. Hanlon, Melanie Canterberry, Joseph Taylor, Truman Brown, Mark S. George
Medical University of South Carolina

Background: Interleaved transcranial magnetic stimulation (TMS) and BOLD imaging in the MR environment provides us with a unique opportunity to probe neural circuitry. The purpose of the current study was to determine if, through the use of an optimized interleaved TMS-BOLD sequence in two cortical targets, we could differentially activate lateral and medial prefrontal cortex neural circuits.
Methods: Interleaved TMS/BOLD imaging data was acquired for a cohort of 15 healthy individuals and 15 cocaine users who received TMS in 2 runs with the coil positioned over the: 1) dorsolateral prefrontal cortex (DLPFC, EEG: F3), and 2) orbitofrontal/medial prefrontal cortex (OFC/MPFC, EEG: FP1)(Magstim MR-compatible coil). The TMS pulse started 100ms before the onset of the next TR (100% motor threshold). BOLD data was analyzed using standard parametric techniques. Additionally 5 participants were scanned twice to evaluate test-retest reliability.
Results: Among healthy controls, DLPFC TMS was associated with a significant elevation of BOLD signal in multiple dorsal cortical areas. In contrast, OFC/MPFC TMS was associated with a significant elevation of BOLD signal in multiple ventral medial cortical regions as well as limbic subcortical areas. The cocaine users demonstrated a similar pattern of activity, but had selective dysregulation in the OFC/MPFC network.
Conclusions: These novel data demonstrate that it is possible to differentially activate known cortical-subcortical networks through an optimized TMS/BOLD sequence over the DLPFC and the OFC/MPFC. Test-retest reliability is high in healthy controls and among cocaine users there is a selective deficit in OFC/MPFC circuit function. These data have important implications for both basic neuroscience research and in patient populations that may have pathology differentially affecting mesolimbic versus mesocortical circuitry.

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Treatment of Depression with Botulinum Toxin A: A Randomized, Double-Blind, Placebo Controlled Trial

Wednesday, Poster #5

Eric Finzi, Norman Rosenthal
Chevy Chase Cosmetic Center

Background: In spite of advances in our understanding and treatment of major depressive disorder(MDD) , many patients fail to achieve remission . Recently, it has been proposed that inhibition of frowning could be used as a treatment for MDD(Finzi et al., 2006). Preliminary studies have suggested that botulinum toxin treatment of frown muscles may help depression (Finzi et al. 2006, Wollmer et al., 2012). The corrugator (frown) muscle plays an essential role in the facial expressions of anger and sadness. Charles Darwin first suggested that muscle contractions involved in the formation of facial expressions contribute to emotional states and mood; William James elaborated on this concept, which has been confirmed experimentally, and is now known as the facial feedback hypothesis. Darwin also recognized that severely depressed individuals show corrugator muscle overactivity, which may result in the "omega sign." Botulinum toxin (BT) reversibly inhibits muscle contraction. When injected into the glabellar region, BT reversibly inhibits frowning for about three months. We have conducted a randomized, double-blind, placebo controlled trial of BT injection into the glabellar region as a treatment for MDD.
Methods: The study was IRB approved, and informed consent was given by all subjects. Male or female outpatients aged 18 to 65 years, with MDD, as diagnosed by the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID), were eligible. Subjects were required to have a Montgomery-Asberg (MADRS) score $\geq$ 26 and a Clinical Global Impression – Severity (CGI) score $\geq$ 4 at screening Eligible subjects were randomly assigned at screening to receive either onabotulinumtoxinA(OBA) (Botox Cosmetic, Allergan) or placebo(PLB) (0.9%NaCl) injections in the glabellar region(Finzi et al.,2006). Women received 29 U of OBA and men, 40 U. All patients were assessed at randomization and after 3 and 6 weeks with the MADRS, Beck Depression Inventory II (BDI) and CGI. The primary outcome measure was response to treatment, as defined as a

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Treatment of Depression with Botulinum Toxin A: A Randomized, Double-Blind, Placebo Controlled Trial

Wednesday, Poster #5 (continued)

Eric Finzi

≥ 50% decrease in MADRS score. Remission was defined as a MADRS score of 10 or lower along with a ≥50% decrease in score. Secondary outcomes were response to treatment in scores on BDI and CGI. Subjects at rest and maximal frowns, were assessed photographically at the beginning and end of the study.
Results: 121 subjects were screened, of whom 84 subjects were randomized: 41 to OBA and 43 to placebo. Eight patients were excluded (4 patients in the OBA group for withdrawal of consent, and two in each group for protocol violations.) One OBA subject was lost to follow-up after injection. 33 subjects in the OBA group and 41 in the placebo group completed all three visits. The two groups did not differ significantly on any of the demographic or clinical baseline variables. 91% of the OBA, and 80% of the PLB subjects suffered from recurrent depression. The average number of antidepressants tried during subject lifetimes, were 2.2 for OBA, and 1.8 for PLB, and the mean duration of the current depressive episode was 27.9 months. As for the primary end point, MADRS scores at the six week visit versus baseline, there was a significant improvement in the OBA group compared to the PLB group; there was a 47.0% reduction in MADRS scores for OBA subjects, versus a 20.6% reduction for PLB(student's t test, $p < 0.0004$). The OBA group showed a significant clinical improvement in depression, compared to the PLB group, over time, as measured by MADRS score, (ANOVA, $f=9.7$, $p < 0.0028$, two-tailed);BDI-II score, (ANOVA, $f=5.7$, $p< 0.019$,two-tailed.); and CGI score(ANOVA, $f=15.3$, $p< 0.0002$,two-tailed.).The response rate for MADRS was 51.5 % vs. 14.6 %; $p < 0.0009$ Fisher's exact test. The remission rate, as judged by MADRS, was significantly higher in the OBA group, 27.3%, than in the PLB group, 7.3%, $p< 0.027$, Fisher's exact test. A decrease in the maximal ability to frown at 6 weeks(among all subjects) was correlated with MADRS response; $p< 0.01$; Spearman coefficient. In the OBA group, there was a trend towards greater response (≥ 50% decrease in MADRS score) with increasing baseline frown(N.S.,$p<0.07$).

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Treatment of Depression with Botulinum Toxin A: A Randomized, Double-Blind, Placebo Controlled Trial

Wednesday, Poster #5 (continued)

Eric Finzi

Conclusions: This is the first randomized, double-blind and placebo -controlled clinical trial to show that a single treatment of the glabellar region with OBA induces a strong and sustained alleviation of symptoms in a broadly defined group of people with MDD. The results are consistent with those of our earlier pilot study (Finzi et al.) and the prior smaller controlled study of BT in patients with refractory depression. Our study is also the first to show that subjects treated with OBA went into remission at a significantly higher rate than placebo subjects. The mechanism of action of OBA in helping depression is unknown, but our results support the facial feedback hypothesis and suggest that it can be utilized therapeutically. The results also support the concept of *emotional proprioception* (Finzi, 2013) whereby the brain continuously monitors the relative valence of salient facial expressions, which may be an important influence on mood.

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A Randomized Controlled Crossover Trial of Ketamine in Obsessive-Compulsive Disorder

Wednesday, Poster #7

Carolyn I. Rodriguez, Lawrence S. Kegeles, Amanda Levinson, Sue Marcus, Helen Blair Simpson
Columbia University

Background: Obsessive-compulsive disorder (OCD) is a leading cause of illness-related disability (1). First-line OCD pharmacological treatments lead to limited symptom relief and typically have a lag time of 6-10 weeks before clinically meaningful improvement(2). Identifying more effective pharmacological treatments with faster onset of action would be a major advance. Medications thought to modulate the glutamate system are a promising new class of pharmacological agents for the treatment of OCD (3-8). Ketamine, a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, modulates glutamate and has been shown to have rapid anti-depressant effects in multiple studies (9-15). A recent case study of a unmedicated individual with OCD without comorbid depression who was given ketamine (0.5mg/kg IV over 40 minutes) showed rapid anti-obsessional effects that persisted from 1 to 7 days post-infusion, long after the drug had cleared (16). A subsequent open trial of ketamine in ten individuals showed modest but significant improvement in OCD symptoms over days 1 to 3 following ketamine infusion compared to baseline; the majority of individuals with OCD in this study were taking multiple medications and had moderate to severe current comorbid depression (17). We investigated the effects of ketamine on individuals with OCD who were not currently on medications and did not have moderate to severe comorbid depression.
Methods: In a randomized, double-blind, placebo-controlled, crossover design, unmedicated adults (N=10) with OCD received two intravenous infusions: one of saline and one of ketamine (0.5mg/kg) over 40 minutes. These infusions were spaced at least 1 week apart; the order of each pair of infusions was randomized. To be eligible, participants were required to have at least moderate to severe OCD (Yale-Brown Obsessive-Compulsive Scale [YBOCS] score > 16) with no or mild depression (Hamilton Depression Rating Scale [HDRS-17] < 25), and endorse

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A Randomized Controlled Crossover Trial of Ketamine in Obsessive-Compulsive Disorder

Wednesday, Poster #7 (continued)

Carolyn I. Rodriguez

near-constant intrusive obsessions (>8 hours per day) (18, 19). To assess rapid changes in obsessions, the OCD visual analogue scale (OCD-VAS) was used at baseline, at 26, 90, 110, and 230 minutes and daily for 7 days post-infusion (16). To assess both obsessive and compulsive symptoms, the YBOCS scale, designed to be used to assess OCD symptoms at 1 week intervals, was used at baseline and 7 days post-infusion. To monitor depressive symptoms, the HDRS-17 was used at baseline and 1 and 3 days post-infusion. Response rate of obsessions was defined as a minimum of 35% improvement in obsessions (as measured by the OCD-VAS), and response rate for OCD symptoms was defined as a minimum of 35% reduction in OCD symptoms (as measured by the YBOCS).

Results: All ten participants completed the study. At baseline, participants had moderate to severe OCD symptoms (mean YBOCS 27.1+/-3.4 SD, range: 22-34). On average, there was a significant rapid decrease in obsessions (as measured by OCD-VAS) which decayed over time and then reached a plateau. Responder rate (n=10) of obsessions (as measured by OCD-VAS) at post-infusion time points were as follows: 90% at 3 hours, 80% at 1 day, 60% at 2 days, 50% at 3 days, and 50% until day 7. Responder rate (n=10) for OCD symptoms (as measured by YBOCS) was 50% at day 7. Responder rate for OCD symptoms among the subset of patients (n=5) who got the ketamine infusion first (and thus the effects of ketamine could be evaluated at both day 7 and day 14), was 40% at day 14. At baseline, participants had minimal depressive symptoms (mean HDRS 4.2+/-5.6, range: 0-16). The average depressive symptoms of the 10 patients did decrease somewhat after the ketamine infusion (4.2 +/- 5.6 to 1.8 +/- 1.9, $F(2,17) = 3.38$, $p = 0.058$).

Conclusions: These data suggest that ketamine can rapidly relieve symptoms of OCD, and this effect can persist for at least one week in 50% of OCD patients with constant intrusive thoughts. A subset of individuals had relief for up to two weeks. Future research is needed to better understand the mechanism of ketamine's rapid

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A Randomized Controlled Crossover Trial of Ketamine in Obsessive-Compulsive Disorder

Wednesday, Poster #7 (continued)

Carolyn I. Rodriguez

anti-obsessional effect and persistent reduction in OCD symptoms, long after the drug has cleared. These insights will help inform the development of new treatment strategies for individuals suffering with OCD.

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Effects of Oxytocin on Social Cognition and Olfaction in Adults with Schizophrenia and Healthy Subjects

Monday, Poster #30

Josh Woolley, Brandon Chuang, Olivia Lam, Kate Rankin, Daniel H. Mathalon, Sophia Vinogradov
University of California, San Francisco

Background: Patients with schizophrenia (SCHZ) have multiple social cognitive deficits, including difficulty in recognizing facial emotion, interpreting paralinguistic cues (e.g. sarcasm) and understanding other's mental states (i.e., theory of mind). Patients also have impaired olfaction, which is associated with worse negative symptoms and decreased social motivation. Social cognitive and olfactory deficits are correlated with worse functional outcome and quality of life and currently there are few available treatments for these deficits in SCHZ. The neuropeptide oxytocin (OT) has multiple prosocial effects when administered intranasally in humans and offers a potential remedy for these social deficits. OT has been implicated in bonding and has shown promise in enhancing social cognition in SCHZ. Further, OT signaling has been implicated in socially relevant olfaction in animals. Therefore, we investigated the effects of intranasal oxytocin on social cognition and olfaction in patients with SCHZ and healthy subjects (HS).
Methods: We administered OT (40IU) and placebo (PL) intranasally to 22 male adult patients with SCHZ and 20 HS of similar age and educational level in a randomized, double-blind, cross-over, within-subject study, with the two days of testing separated by one week. We measured performance on The Awareness of Social Inference Test (TASIT), which uses short video clips of actors to assess subjects' ability to comprehend counterfactual statements from paralinguistic cues signaling white lies (*White Lie items*), sarcasm (*Sarcasm Items*), and to make judgments about the actors' thoughts (*Theory of Mind Items)*. Olfactory thresholds were measured for lyral, clove, and anise oils using a modified Munich Olfaction Test. Subjects identified the bottle with the testing compound from amongst two mineral oil containing distracter bottles in an upward step procedure

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Regency Ballroom 1 & 2

Effects of Oxytocin on Social Cognition and Olfaction in Adults with Schizophrenia and Healthy Subjects

Monday, Poster #30 (continued)

Josh Woolley

with increasing geometric dilutions (12.5 X 10^{-6}% to 20% m^3/m^3). Paired t-tests were used for all comparisons and data are expressed as Mean ± (S.E).
Results: OT administration to SCHZ patients (Age: 44.0 (10.0), Education: 13.5 (2.2)) improved overall performance on TASIT (74% ± 2% vs. 70% ± 2%, p=0.02), on *White Lie Items* (77% ± 2% vs. 71% ± 2%, p=0.02), *Sarcasm Items* (70% ± 3% vs. 65% ± 3%, p=0.05) and *Theory of Mind Items* (77% ± 2% vs. 72% ± 3%, p=0.05). In HS (Age: 36.0 (13.1), Education: 15.3 (1.9)), OT administration-induced changes on these scales did not reach significance. In SCHZ patients, OT led to enhanced detection of Lyral (but not Anise or Clove) at lower concentrations (3 X 10^{-5}% ± 1 X 10^{-7}% m^3/m^3 vs. 2 X 10^{-4}% ± 1 X 10^{-7}% m^3/m^3, p=0.03). In HS, OT effects on olfactory thresholds did not reach significance. For TASIT, we divided subjects on a median split based on performance on the placebo day. The group of patients who scored poorly on the placebo day had greater OT-induced improvements on multiple measures (*Overall Items*: (OT-PL) 9% ± 2% vs. -1% ± 2% p=0.001; *Sarcasm Items*: 16% ± 3% vs. -4% ± 2% p=0.0001; *Theory of Mind Items*: 12% ± 3% vs. -3% ± 2% p=0.0001). However, in HS this relationship did not reach significance (*Overall Items*: 4% ± 4% vs. -2% ± 1% p=0.2; *Sarcasm Items*: 7% ± 5% vs. -6% ± 3% p=0.06; *Theory of Mind Items*: 5% ± 5% vs. -2% ± 2% p=0.21).
Conclusions: Our findings indicate that OT significantly improves SCHZ patients' ability to 1) interpret paralinguistic cues (e.g., white lies and sarcasm), and understand other's mental states (i.e., theory of mind), and 2) detect lyral at lower concentrations. The OT-induced improvement in social cognition is clinically significant because deficits in these domains are strong predictors of functional outcome in SCHZ and are currently difficult to treat. The OT-induced improvement in detection of lyral demonstrates that OT may be the first pharmacological agent to remediate the olfactory deficits in SCHZ. Furthermore, the selectivity of this effect for lyral fits with previous data indicating that

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Hot Topics
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patients with SCHZ are selectively impaired at detecting lyral possibly due to cAMP signaling dysfunction and that OT can increase cAMP signaling *in vitro*. Finally, it appears that OT has differential effects depending on an individual's baseline ability in that subjects who score poorly on the placebo day have large significant improvements on performance when administered OT. The underlying mechanisms for this differential effect remain unknown, however, OT may be improving basic, early sensory processing, such as gaze to the eye region, which helps individuals with poor baseline social cognition. In sum, our data provide support for using OT as a pharmacological agent to remediate multiple social deficits in SCHZ. Larger studies focused on patients with SCHZ who have significant baseline deficits in social cognition are needed to confirm and extend our findings.