

investigate neurobehavioral risk markers for developing mood disorders among these youth.

Methods: Healthy boys and girls ages 8 to 17 years who were at risk for either BD (n= 34) or MDD (n=49) or were healthy comparisons (HC) (n=42) based on parental history underwent amygdala seed-based resting state functional and structural MRI, diurnal cortisol, and family environment assessments to investigate early clues of neurobehavioral dysfunction that may precede mood disorder development.

Results: Whereas HC youth showed relative negative connectivity between the amygdala and precuneus and the amygdala and superior frontal gyrus at rest ($p < 0.001$), children of parents with MDD and BD showed no such relation among these regions. We also found that youth at risk for MDD and BD had larger amygdala volumes, compared to HC offspring. HC offspring demonstrated a positive relation between amygdala volume and diurnal cortisol response that was not present in MDD risk and BD risk offspring ($p < 0.05$). MDD and BD risk youth did not distinguish themselves along these markers at a stage of health ($p > 0.05$).

Conclusions: Our findings suggest that a familial risk for mood disorders differentiates these youth from healthy comparison youth along neural and behavioral phenotypes even preceding mood disorder onset. These neurobehavioral phenotypes may potentiate susceptibility toward poor mood outcomes in youth at risk for mood disorders that may signal the need for early interventions.

Supported By: Stanford Child Health Research Institute, K23MH085919

Keywords: Risk for Mood Disorders, Amygdala, Family History, Neural Networks

59. Neural Markers of Treatment Effects and Response in First-Episode Manic Youth

Melissa DeBello¹, Wenjing Zhang², L. Rodrigo Patino³, Jeffrey Strawn¹, Jeffrey Welge¹, Christina Klein¹, Thomas Blom¹, Su Lui², and John Sweeney¹

¹University of Cincinnati, ²West China Hospital, Sichuan University, ³University of Cincinnati College of Medicine

Background: Manic youth undergo several unsuccessful medication trials prior to achieving mood stabilization. Understanding the neural effects of interventions in these youth will clarify the impact of anti-manic treatments on the neurodevelopment of bipolar disorder and may lead to identifying neurobiological response markers.

Methods: First-episode youth (FE, n=103) were randomized to blinded quetiapine (QUET) vs. lithium (Li). High-resolution MR images and fMRI during a sustained attention task were acquired from FE and healthy comparisons (HC, n=62) at baseline and Week 6. Cluster analysis and block design comparisons were performed.

Results: Response rate was greater in QUET (71%) than Li (46%, $p < 0.007$). Analysis from 68 cortical regions identified two subgroups. Group 1 with increased cortical thickness in fronto-temporo-parietal regions, consisted of 8 QUET and 8 Li. Group 2 consisted of 19 QUET and 17 Li. Group 1 (100%) had

a greater response to QUET than Group 2 (52.6%, $p < 0.02$). From baseline to Week 6, Li (n=54) exhibited increased activation in amygdala, putamen, posterior cingulate, precuneus, caudate, thalamus, and superior frontal gyrus and QUET (n=59) exhibited decreased activation in supramarginal and middle frontal gyri and increased activation in BA 10, 24, and 32. Response was associated with decreased activation in BA 40, inferior parietal lobule, supramarginal gyurs, and precuneus in Li and increased activation in anterior cingulate and BA 10 in QUET.

Conclusions: We identified two distinct patterns of gray matter abnormalities that were predictive of treatment response. We also identified differential neural effects and response predictors to lithium and quetiapine.

Supported By: MH077138, MH083924, MH080973

Keywords: Bipolar Disorder, Multimodal Neuroimaging, Treatment Predictions

60. Predicting Future Affective Lability From Neural Circuitry Function and Gray Matter in Youth at Risk for Bipolar Disorder

Michele Bertocci¹, Lindsay Hanford¹, Amelia Versace¹, Kelly Monk¹, Lisa Bonar¹, Satish Iyengar¹, Danella Hafeman¹, Genna Bebkow¹, Cecile Ladouceur¹, Rasim Somer Diler², Boris Birmaher¹, and Mary Phillips¹

¹University of Pittsburgh, ²University of Pittsburgh Medical Center

Background: Biomarkers of bipolar disorder are needed; identifying neural markers of known prodromal behaviors is a step toward that goal. Factors within affective lability scales are recognized as prodromal to the development of bipolar disorder. We identified neural and behavioral markers of future affective lability in at-risk youth from the Pittsburgh bipolar offspring study (BIOS) and validated these in an independent sample from the Longitudinal assessment of manic symptoms (LAMS) study.

Methods: Factors of mania/mixed, irritability, and anxiety/depression derived from affective lability scales 29-months' post fMRI scanning in 41 youth aged 14.0 (sd=2.30), 19 female were predicted from clinical, demographic, and neural measures (whole brain BOLD activity during reward and emotion processing and cortical thickness) using Regularized regression analyses. Linear regression analyses were then completed in LAMS youth (n=55) using the identified variables (24-months' follow-up).

Results: Depression severity, affective lability, and left ventrolateral prefrontal, bilateral parietal, and right auditory cortices thicknesses predicted the mania/mixed factor 29 months in the future (BIOS sample adjusted $r^2=55.3%$, $p < .001$, LAMS: $r^2=33.5%$, $p=.006$). The irritability factor was predicted by depression severity, depression diagnosis, bilateral parietal, right entorhinal cortical thicknesses, and emotion processing activity in right fusiform gyrus (BIOS sample adjusted $r^2=44.1%$, $p < .001$, LAMS: $r^2=29.3%$, $p=.004$). The anxiety/depression factor was predicted by depression severity (BIOS sample adjusted $r^2=26.8%$, $p < .001$, LAMS: $r^2=11.8%$, $p=.011$).

Conclusions: Distinct combinations of clinical and neural markers predict affective lability factors in the future in two independent samples of at-risk youth suggesting the utility of these variables as objective markers of future risk and potential targets for intervention

Supported By: R01MH060952 2R01 MH73953-06A1 2R01 MH73816-06A1 2R01 MH73967-06A1 2R01 MH73801-06A1

Keywords: Outcome Prediction, Bipolar Disorder, At-Risk Youth, Cortical Thickness, BOLD fMRI

SYMPOSIUM

Mitochondrial Stress and Psychiatric Disorders

3:00 p.m. - 5:00 p.m.

Chair: Josine Verhoeven

Co-Chair: Daniel Lindqvist

61. Developing Sensitive Measurements of Mitochondrial Responses to Acute and Chronic Stress

Martin Picard¹, Caroline Trumpff¹, Anna Marsland², Aric Prather³, Brett Kauffman², Eli Puterman⁴, Kirstin Aschbacher³, Gabriel Sturm¹, James Martin², Judith Caroli⁵, Bruce McEwen⁶, Yan Burelle⁷, and Elissa Epel³

¹Columbia University Medical Center, ²University of Pittsburgh, ³University of California, San Francisco, ⁴University of British Columbia, ⁵University of California, Los Angeles, ⁶The Rockefeller University, ⁷University of Ottawa

Background: Mitochondria are complex organelles with their own genome that generate the energy required for life and produce signals that enable stress adaptation. A systematic review of animal studies suggests that acute and chronic psychological stress can damage and impair specific aspects of mitochondrial function and health. However, evaluating this possibility in humans has been difficult due to the lack of scalable measures that accurately reflect mitochondrial health.

Methods: In one study of caregivers experiencing chronic life stress, we developed an index of mitochondrial health (MHI) by measuring and integrating the activity of three mitochondrial enzymes and mtDNA copy number from frozen leukocytes. In another study where participants were exposed to acute socioevaluative stress on two separate visits, we measured pre- and post-stress circulating cell-free levels of the mitochondrial and nuclear genomes, putative signals of intracellular stress.

Results: The MHI was sensitive to previous day mood and showed superior effect size ($n=85$, $d=0.63$, $p<0.01$) comparing groups, compared to individual enzymatic and molecular measures (all $d=0.11-0.36$, n.s.). In healthy men and women, acute psychological stress triggered robust increases in circulating cell-free mtDNA (ccf-mtDNA, $n=36$, $n_2=0.57$, $p<0.0001$), but not circulating nuclear DNA.

Conclusions: We describe a new integrative index of mitochondrial health that can be applied to frozen blood leukocytes, and an approach to quantify the selective release of ccf-mtDNA. Building from these examples, this presentation

will also review and discuss currently available methodologies to assess mitochondrial health and mitochondrial allostatic load (MAL) in human samples.

Supported By: NIA, NIGMS, Wharton fund

Keywords: Mitochondria, Chronic Stress, Mood, Laboratory Measurements, Systematic Review

62. Circulating Cell-Free Mitochondrial DNA – a Novel Marker of Mitochondrial Stress Associated With Suicidality and Major Depressive Disorder

Daniel Lindqvist¹, Owen Wolkowitz², Martin Picard³, Lars Ohlsson⁴, Francesco Saverio Bersani⁵, Johan Fernström⁶, Åsa Westrin⁶, Christina Hough², Jue Lin², Cécile Grudet⁶, Lennart Ljunggren⁴, Lil Träskman-Bendz⁶, Victor Reus², Elissa Epel², and Synthia H. Mellon²

¹Lund University/UCSF, ²University of California, San Francisco, ³Columbia University, ⁴Malmö University, ⁵Sapienza University of Rome, ⁶Lund University

Background: Mitochondrial DNA copy number (mtDNA-cn), which represents the number of mitochondrial genomes per cell, can be quantified in peripheral blood mononuclear cells (PBMC) and is thought to reflect variations in mitochondrial biogenesis. Additionally, mtDNA may be released at low levels into the circulation from mitochondria under cellular stress, resulting in circulating cell-free mtDNA (ccf-mtDNA) detectable in plasma. The source or physiological significance of ccf-mtDNA in psychiatric illness is unknown but may reflect cell damage, cell death, or bioenergetic compromise.

Methods: We enrolled suicide attempters (across diagnoses), non-suicidal subjects with Major Depressive Disorder (MDD), and healthy controls (all medication-free) in two independent cohorts ($n=110$ & $n=74$). MtDNA was quantified in cell-free plasma and in PBMCs.

Results: Ccf-mtDNA was elevated in suicide attempters and in non-suicidal MDD subjects, compared to healthy controls. These group effects were very large (Cohen's d ranging from 0.9 to 4.0, all $p<0.00001$). Ccf-mtDNA and cellular PBMC mtDNA-cn were not significantly correlated with each other ($r=0.02$, $p=0.87$), suggesting they reflect different processes. Ccf-mtDNA correlated with post-dexamethasone cortisol ($r=0.5$, $p<0.001$), suggesting that HPA-axis hyperactivity may be associated with cellular damage and release of ccf-mtDNA into the blood. Ccf-mtDNA also directly correlated with the antioxidant enzyme glutathione peroxidase ($r=0.32$, $p=0.001$), possibly reflecting a compensatory attempt to upregulate antioxidant defence mechanisms due to cellular stress.

Conclusions: Ccf-mtDNA may represent a novel marker of cellular stress, which is increased in certain psychiatric conditions. These results call for replication in larger cohorts and in longitudinal studies.

Supported By: This study was funded by grants from the National Institute of Mental Health (NIMH) (Grant Number R01-MH083784), the O'Shaughnessy Foundation, the Tinberg family, and grants from the UCSF Academic Senate, the UCSF Research Evaluation and Allocation Committee (REAC), and the Bernard and Barbro Foundation. This project was also