Parallel Symposia Title:

At the Crossroads of Brain, Gene, and Addiction in Bipolar Disorder: Neurophysiological and Epigenetic Mechanisms

Session Overview:

Bipolar disorder is estimated to have the highest rates of co-occurring substance use disorders (SUDs) of any neuropsychiatric diagnoses. Specifically it is estimated that up to 60% of individuals diagnosed with bipolar disorder will present with SUDs during their lifetime. The co-occurrence of SUDs and bipolar disorders is associated with worse outcomes, including greater cognitive deficits and elevated rates of suicide. Despite the importance of understanding why bipolar disorder coincides with high rates of SUD comorbidity little research has been done in this area. Research is critically needed to identify biological mechanisms that increase risk for SUDs in bipolar disorder. This symposium will present data on neurophysiological and epigenetic mechanisms that may be associated with high rates of alcohol and cannabis use disorders in bipolar disorder. Chair, Dr. Strakowski (UT Austin) will provide an overview of substance use disorder comorbidity in bipolar disorder followed by talks from Dr. Goldstein (Sunnybrook), early stage investigator Dr. Lippard (UT Austin), and Dr. Veldic (Mayo Clinic). Imaging data include structural magnetic resonance imaging (MRI), demonstrating neurostructural (cortical surface area and thickness and gray matter volume), and functional MRI correlates of cannabis and alcohol use. Study of DNA methylation of the *SLC1A2* promoter support the possibility of epigenetic biomarkers that may contribute to addiction in bipolar disorder. Data support the view that there is a bidirectional nature to understanding development of this comorbidity. Identifying risk and resilience mechanisms, and associated neurophysiological processes, may provide novel targets for early detection, prevention, and improved prognoses.

Session Chair(s)/Moderator
Full Name: **Stephen Strakowski (Chair/Moderator)**
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Full Name: **Elizabeth Lippard (Co-chair)**
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Speaker #1 Information
Presentation Title: **Neurostructural Correlates of Cannabis Use in Adolescents with Bipolar Disorder**
Presenter: **Benjamin Goldstein**
Presenter Institution: **Sunnybrook Research Institute**
Presenter Country: **United States**
Years in Field: **13**
Gender: **Male**
Presentation Abstract:

Background: Little is known regarding associations of cannabis use with brain structure in adolescents with bipolar disorder (BD). We therefore studied a well-characterized sample of adolescents with BD and healthy adolescents (HC).
Methods: Participants included 114 adolescents (n=54 BD, n=60 HC), ages14-20 years; 37 of these participants (n=29 BD, n=8 HC) reported lifetime use of cannabis. FreeSurfer-processed T1-weighted images, acquired with 3T MRI, yielded measures of cortical thickness, surface area (SA), and volume. Vertex-wise complemented region of interest analyses (ROI: amygdala, hippocampus, ventro-lateral prefrontal cortex (vlPFC), ventro-medial prefrontal cortex (vmPFC), and anterior cingulate cortex (ACC)). General linear models (GLM) analyses were performed, covaried for age, sex, and, for volume and SA analyses only, intracranial volume.

Results: ROI analysis revealed a significant diagnosis x cannabis interaction such that cannabis use was associated with decreased vlPFC SA (F=6.33, p=0.01) in BD versus HC. Vertex-wise analysis revealed a significant diagnosis x cannabis interaction such that cannabis use was associated with decreased pars orbitalis (F=12.06, p=0.001) and rostral middle frontal (F=10.46, p=0.002) SA, middle temporal volume (F=20.28, p<0.001), and banks of superior temporal sulcus thickness (F=17.40, p<0.001) in BD versus HC.
Conclusion: These preliminary findings suggest that associations between cannabis use and brain MRI phenotypes are moderated by a BD diagnosis. Adolescents with BD may be particularly sensitive to the neurostructural effects of cannabis, although further studies are necessary to determine the direction of the observed associations and to evaluate these associations in relation to neurocognitive dysfunction and symptom burden.

Speaker #2 Information
Presentation Title: **Alcohol Use Patterns in Young Adults with Bipolar Disorder and Correlated Activity of Prefrontal-Paralimbic Systems.**
Presenter: **Elizabeth Lippard**
Presenter Institution: **Dell Medical School, University of Texas at Austin**
Presenter Country: **United States**
Years in Field: **5**
Gender: **Female**
Presentation Abstract:

Background: Alcohol Use Disorders (AUDs) occur at a higher rate in bipolar disorder compared to the general population. There is a paucity of study on biological mechanisms underlying development of this comorbidity. Previous research suggests lower gray matter prefrontal-paralimbic regional volumes may predate and be associated with risk for alcohol use problems in adolescents with bipolar disorder. Functional consequences of neuroanatomical differences that may translate into risk is unknown.
Methods: To date, 33 young adults (19 with bipolar disorder and 14 healthy participants; 82% female, $mean_{age} \pm stdev = 21 \pm 2$ years) have completed a Continuous Performance fMRI Task with Emotional and Neutral Distractors and a battery of alcohol-related measures, including the Daily Drinking and Drinking Motives Questionnaires. In this preliminary analysis, we investigated group differences in drinking patterns and relationships between drinking patterns and function of prefrontal-paralimbic systems within bipolar disorder.
Results: Individuals with bipolar disorder did not report drinking more frequently or greater quantities compared to healthy participants. When viewing targets, individuals with bipolar disorder who drink more frequently showed lower activity in the right insula and dorsomedial prefrontal cortex. When viewing emotional distractors, those who consume greater quantities of alcohol showed lower activity in the right insula and bilateral inferior frontal gyrus ($p<0.005$, ≥ 20 voxels). Lower activity in the insula was associated with greater coping motives for drinking ($p<0.05$).
Conclusion: Preliminary results from this ongoing study suggest variation in prefrontal-paralimbic function during attentional and emotional processing may increase risk of developing AUDs in bipolar disorder. Longitudinal study of outcomes is needed.

Speaker #3 Information
Presentation Title: **DNA Methylation in Bipolar Disorder: Can it be used as a biomarker?**
Presenter: **Marin Veldic**
Presenter Institution: **Mayo Clinic**
Presenter Country: **United States**
Years in Field: **17**
Gender: **Male**
Presentation Abstract:

Background: Addiction associated with bipolar disorder (BD) may be an acquired comorbidity for some patients. The primary vs. secondary distinction of substance use

disorders in dual diagnosis may be further refined by investigating epigenetic modifications of disease risk genes.
Methods: We examined methylation of the *SLC1A2* promoter, encoding for excitatory amino acid transporter 2, in DNA from the blood of patients with BD with and without addiction (n=150) and healthy subjects (n=32). In postmortem human brains (Brodmann's area 9 and 38) we assessed the impact of addiction on genome-wide methylation in subjects with BD (n=20), unipolar depression (n=10), and healthy individuals (n=10).
Results: High resolution melting PCR (HRM-PCR), in DNA from the blood, showed hypermethylation of the SLC1A2 promoter in BD without addiction ($p<0.0001$), while in BD with addictions SLC1A2 promoter was associated with hypomethylation [alcohol ($p=0.002$), nicotine ($p<0.0001$)]. HRM-PCR findings were validated by direct sequencing. In postmortem brains global DNA-methylomic study, utilizing the 850K Illumina MethylationEPIC BeadChip, unsupervised hierarchical clustering analysis did not detect significant associations between clusters and the history of smoking and alcohol abuse.
Conclusion: These results suggest that individual point methylation within the SLC1A2 promoter may be modified by alcohol and nicotine addiction. Currently, it is unclear whether findings from peripheral tissues reflect neuronal DNA methylation status. However, assessment of the peripheral DNA methylation may still have a potential for developing clinically valuable epigenetic biomarkers for BD diagnosis and monitoring. Future studies should be designed to elucidate correlations between DNA methylation in brain and peripheral tissues.