transdiagnostic relationships between anticipatory and consummatory MAP scores and RSFC spatial extent.
Results: There were significant relationships between MAP and spatial extent for Salience, Ventral Attention, and Dorsal Attention networks. These relationships varied depending on diagnosis. Anticipatory and consummatory MAP was positively associated with Salience network size. In Bipolar Disorder, anticipatory MAP was negatively associated with Ventral Attention and Salience network sizes, and consummatory MAP was negatively associated with Salience network size. In Schizophrenia/Schizoaffective Disorder, consummatory MAP was negatively associated with Dorsal Attention and Salience network sizes.
Conclusions: The findings suggest associations between spatial extent metrics and MAP that differ across diagnoses. Planned additional analyses assess the relationships of RSFC and spatial extent metrics to self-report and clinician-rated MAP.
Funding Source: NIMH
Keywords: Psychosis Spectrum Symptoms, Resting-State Functional Connectivity, Negative Symptoms, EMA/ESM

546. Prefrontal Cortex and Ventral Tegmental Area (VTA) Deficits During Goal-Directed Behavior in Clinical High-Risk Psychosis

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Background: Psychotic disorders are complex disorders that are associated with deficits in motivation (e.g., anhedonia), learning, and salience detection (e.g., novelty). Animal research suggests that hippocampal novelty signals increase sustained mesolimbic engagement, while the prefrontal cortex (PFC) drives phasic mesolimbic engagement, synergistically magnifying VTA responses to goal-relevant targets. Dysregulation in this circuit has been hypothesized to underlie positive and negative symptoms associated with psychotic disorders, and prior research has documented alterations in both hippocampal and PFC integrity in psychosis-related populations. However, the dynamic relationship between these regions during behavior remains unexplored in those showing the first signs of psychosis, at clinical high-risk (CHR).
Methods: Healthy Control (n=73) and CHR participants (n=29) completed the Prodromal Questionnaire (PQ), Temporal Experience of Pleasure Scale (TEPS), and a novelty-imbued target detection task. Linear regressions examined goal-relevant VTA activation, hippocampus-VTA regulation during novelty, and PFC-VTA regulation during target detection. Associations between PFC function, PQ positive symptoms, and TEPS negative symptoms were also explored.
Results: There were no differences in HPC and VTA interactions as a function of CHR. However, CHR participants had decreased VTA ($t = 2.24$, $p < 0.05$) and PFC ($t = 2.21$, $p < 0.05$) activation during goal-relevant responding. PFC target activation was negatively associated with positive symptoms ($r = -0.23$, $p < 0.05$). No associations were found with negative symptoms.
Conclusions: Findings support models of goal-oriented behavior in which hippocampal and PFC regulatory systems invigorate VTA responsivity. Despite no differences in hippocampal-VTA interactions, the observed decrease in PFC activation correlates with positive symptom severity, highlighting a potential mechanism underlying psychosis risk.
Funding Source: NIMH R01 MH112613
Keywords: fMRI, Hippocampus, VTA, Dopamine, Psychosis Risk

547. The Dysregulation of the Glymphatic System in Patients With Psychosis Spectrum Disorders Minimally Exposed to Antipsychotics

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Background: The pathophysiological mechanisms influencing psychosis spectrum disorders (PSD) are largely unknown. The glymphatic system (GS), which is a brain waste clearance pathway, has recently been implicated in its pathophysiology and shown to be disrupted in various neurodegenerative and vascular diseases. Initial studies examining the GS in PSD have reported disruptions, but the findings have been confounded by medication effects as they included antipsychotic-treated patients. Using diffusion tensor imaging analysis along the perivascular space (DTI-ALPS), we measured the functionality of the GS in a sample of antipsychotic-minimally exposed patients with PSD and healthy controls (HC).
Methods: The study included 13 antipsychotic-minimally treated patients with PSD and 114 HC. We quantified water diffusion metrics along the x-, y-, and z-axes in both projection and association fibers to derive the DTI-ALPS index, a proxy for glymphatic activity. Between-group differences were analyzed using two-way ANCOVA controlling for age and sex.
Results: Analyses revealed that antipsychotic-minimally exposed PSD had a lower DTI-ALPS index value than HC in both hemispheres and the whole brain (all $P < 0.005$). Significant differences were also observed between the x and y projections/associations fibers between PSD and HC ($P < 0.001$). Furthermore, no significant correlations (all $P > 0.05$) were observed between the ALPS index with age, body mass index, and metabolic parameters.
Conclusions: This study shows that the GS is dysregulated in antipsychotic-minimally exposed PSD patients. Understanding the mechanisms that influence the GS may help to understand the pathophysiology of PSD as proper waste clearance is needed for normal brain functioning.