Contribution ID: **44** Type: **Poster**

Fine-grained mapping of hippocampal alterations in schizophrenia and bipolar disorder using surface-based morphometry and multiscale integration

Monday 27 October 2025 17:30 (1h 30m)

Background and Rationale: The hippocampus is a critical structure for memory, cognition, and emotional regulation, and its dysfunction is consistently implicated in major psychiatric disorders. Global hippocampal volume reduction is among the most robust neuroimaging findings in schizophrenia and bipolar disorder. However, conventional volumetric measures are inherently coarse: they collapse across distinct subfields and along the anterior–posterior axis, masking focal effects and preventing integration with molecular and functional data. This limited granularity hinders the development of mechanistic models of hippocampal pathology. To overcome these limitations, surface-based morphometry and multiscale contextualization are needed to capture the fine-grained topography of hippocampal alterations and to link them with underlying biology and function.

Methods: We will analyze large-scale 3T MRI data from individuals with schizophrenia, bipolar disorder, and matched healthy controls (e.g. B-SNIP cohort, HCP-EP). Using HippUnfold (https://github.com/khanlab/hippunfold), we will reconstruct hippocampal surfaces to quantify local thickness and gyrification across the hippocampal mantle. Case–control statistical comparisons will then be used to generate spatially detailed maps of structural alterations in schizophrenia and bipolar disorder. These alteration maps will capture subfield-specific and long-axis gradients of pathology, extending beyond global volumetric measures. To contextualize the findings, we will leverage Hippomaps (https://hippomaps.readthedocs.io), systematically compare shared and distinct multiscale associations between surface-based hippocampal alterations in schizophrenia and bipolar disorder.

Expected Results: We anticipate that surface-based analyses will reveal fine-grained alterations in hippocampal thickness and gyrification in schizophrenia and bipolar disorder that are not detectable with volume-based metrics. These patterns are expected to show spatial heterogeneity along the anterior–posterior axis and within subfields, reflecting distinct neurodevelopmental and pathophysiological mechanisms. We further hypothesize that this spatial heterogeneity will relate to cognitive symptom profiles, such that bipolar patients with more pronounced cognitive impairment resembling schizophrenia will also show more schizophrenia-like hippocampal alterations. Multiscale contextualization with Hippomaps is expected to demonstrate that structural alterations preferentially align with molecular and histological gradients, such as excitatory–inhibitory balance, synaptic density, or laminar differentiation. Furthermore, we expect altered hippocampal structure to map onto functional disruptions observed in fMRI and EEG, such as aberrant hippocampal–prefrontal connectivity and dysregulated oscillatory activity. Together, these results will provide mechanistic insights into the molecular and circuit-level underpinnings of hippocampal vulnerability in psychosis-spectrum disorders.

Conclusion: This project will deliver the first systematic surface-based characterization of hippocampal morphology in schizophrenia and bipolar disorder, integrated with histological, genetic, and functional data. By moving beyond coarse volumetric reductions, we aim to identify anatomically precise and biologically informed signatures of hippocampal pathology. This multiscale approach has the potential to refine models of disease progression, inform hypotheses about cellular and molecular mechanisms, and generate novel targets for translational research. Ultimately, these findings may help bridge the gap between structural imaging and neurobiological mechanisms, advancing our understanding of hippocampal dysfunction in psychosis-spectrum disorders.

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Session Classification: Poster Session