PM540
Differential changes on the white matter brain network in ultra-high risk for psychosis and first-episode psychosis
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Abstract
Background: Developmental process of connectivity disruption during transition into psychosis could appropriately be explored at the network level. However, no study has concurrently explored alterations in the white matter (WM) network of the brain among first-episode psychosis (FEP) and its prodromal stage.
Methods: Thirty-seven subjects with ultra-high risk for psychosis (UHR), 21 patients with FEP, and 37 healthy controls (HC) were recruited. 3-Tesla T1 structural and diffusion tensor images were reconstructed as weighted WM networks.
Results: At the global level, the UHR group showed a higher assortativity coefficient compared to the FEP group and a higher modularity Q compared to the HC group. At the local level, the FEP group showed a weaker left hippocampal-parahippocampal connectivity and a stronger left superior frontal-thalamic connectivity compared to the UHR and HC groups. More rightward asymmetry in the hippocampal-parahippocampal connectivity was seen in the FEP compared to the UHR and HC groups, and that asymmetry positively correlated with psychotic symptoms and negatively with level of functioning in the UHR group. Participation coefficient of the right pallidum increased in the FEP compared to the UHR and HC groups, and that measure positively correlated with nonspecific psychiatric symptoms in the FEP group.

Conclusions: UHR enhances function of WM network by increasing adaptivity and maintaining resilience without altering connection costs. Altered cortico-subcortical connectivity is characteristics of FEP. Rightward change in asymmetry in the hippocampal-parahippocampal connectivities may reflect biological mechanism underlying progression into psychosis.

PM541
Computational modeling of cognitive deficits from cortical circuit dysfunction associated with schizophrenia
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Abstract
Disruption of the balance between excitation and inhibition (E/I balance) is a leading hypothesis for pathophysiology of neuropsychiatric disorders, e.g. schizophrenia. However, it is poorly understood how synaptic-level E/I disruptions propagate upward to induce behavioral-level cognitive deficits. To link these levels, we have developed a framework for Computational Psychiatry using biophysically-based models of neural circuits to study how neural activity and cognitive behaviors are impacted by disease-related synaptic perturbations.

Here, we studied models of cortical circuits that perform cognitive computations such as working memory and decision making. Motivated by hypotheses for neuropathology associated with schizophrenia, we tested effects of hypofunction of NMDA receptors at two key sites: on inhibitory interneurons (elevating E/I ratio via disinhibition), versus on excitatory pyramidal neurons (reducing E/I ratio).

For working memory, we found disinhibition broadens the tuning of mnemonic, stimulus-selective persistent activity patterns; we tested this prediction using behavioral data from human subjects performing a spatial working memory task combined with ketamine infusion. The model further predicts increased behavioral variability degrading mnemonic precision, and impaired filtering of distractors. To test these predictions, we designed and tested behavioral tasks for patients with schizophrenia.

For decision making, we found disruption of E/I balance in either direction can impair performance as assessed by psychometric functions. Nonetheless, these two regimes make dissociable predictions for the time course of evidence accumulation. Under elevated E/I ratio, behavior is "impulsive": evidence early in time is weighted more than evidence late in time, compared to control. Under reduced E/I ratio, behavior is "indecisive": the circuit exhibits weakened integration and reduced winner-take-all competition.

Our findings highlight the importance of cortical E/I balance in cognitive functions. These models make specific predictions for behavior and neural activity that are testable in humans or animals under manipulation of E/I balance (e.g. via pharmacology) or in disease states.