Measures of Human Functional Connectome as Intermediate Phenotypes for Schizophrenia: Optimization for Methods and Application in Imaging Genetics

Autor:	Hengyi Cao
Institut / Klinik:	Zentralinstitut für Seelische Gesundheit Mannheim (ZI)
Doktorvater:	Prof. Dr. A. Meyer-Lindenberg

The search for quantifiable biological traits mediated by genetic predisposition, or "intermediate phenotypes", is a key strategy for understanding underlying genetic mechanisms of highly heritable mental disorders such as schizophrenia. From a systems neuroscience viewpoint, schizophrenia is characterized by a wide range of abnormal neural connectivity which leads to severe impairments in multiple functional domains such as memory, executive function, and emotion. As a result, the study of large-scale network organizations of the whole brain system, or the connectome, has been used as an important tool for schizophrenia research. However, it remains unclear whether human functional connectomic measures can be used as intermediate phenotypes for schizophrenia. This work covers two interrelated topics regarding this question. In the first study, I aimed to probe for optimal data processing methods and graph theory based connectomic measures for imaging genetics research, particularly in an functional magnetic resonance (fMRI) setting with active tasks that are commonly used in schizophrenia studies. Here, I used test-retest reliability as selection criterion and examined the reliability measures of connectomic measures derived from different signal processing methods, experimental tasks and node definitions. In the second study, using the optimal method derived from the first study, I aimed to explore if any functional connectomic measures fulfilled the basic characteristics of a potential intermediate phenotype for schizophrenia in the emotional domain. Specifically, I investigated functional connectomic differences between unaffected first-degree relatives of schizophrenia patients and healthy controls during an emotional face-matching task. For the identified connectomic alteration linked to genetic risk, I subsequently tested the presence of the same alteration in patients with schizophrenia. I also performed several follow-up analyses to substantiate the finding as a potential functional intermediate phenotype, including the examination of task specificity, test-retest reliability and potential structural confounds. Furthermore, I examined the main and interactive effects between two well-identified dopaminergic risk variants (*COMT* Val^{158}Met and *DRD2* rs2514218) on the identified intermediate phenotype.

The results in the first study showed a superior reliability for task-regression method with condition-specific regressors and a superior reliability for connectivity- and global network properties, suggesting that task-regression method and connectivity- and global network properties are preferred for task-based functional connectomic analysis in imaging genetics. The results in the second study identified a significantly altered visual-limbic subnetwork in first-degree relatives of schizophrenia patients compared to healthy controls. This subnetwork alteration was also manifest in patients with schizophrenia, was test-retest reliable, was task specific, and was primarily functional. In addition, it could be modulated by the epistasis between dopaminergic risk genes *COMT* and *DRD2.* These results suggest a potential emotion-related connectomic intermediate phenotype for schizophrenia, and imply a potential neural mechanism of dopaminergic genes for increasing the risk of schizophrenia. Collectively, my doctoral work provides direct evidence for an underlying neural mechanism of genetic risk for schizophrenia in the emotion domain, highlights the possibility and importance of searching for connectome-based intermediate phenotypes for schizophrenia, and informs an optimal method for graph theory based analysis of the human functional connectome, particularly during active tasks that are commonly implemented in psychiatric neuroscience and imaging genetics.