EDITORIAL

Resting-State Functional Connectivity in Psychiatric Disorders

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The idea that serious mental illnesses, such as autism and schizophrenia, result from abnormal connectivity among large-scale brain networks is gaining widespread acceptance. Efforts to test hypotheses of dysconnectivity have historically been hindered by tools with insufficient spatial resolution to investigate human brain connectivity in vivo and an incomplete understanding of the large-scale organization of the brain, the so-called *connectome*. The development of resting-state functional connectivity magnetic resonance imaging (rs-fcMRI) has profoundly affected our understanding of the functional organization of the brain, both in health and illness. The investigation by Cerliani and colleagues[1] in this issue describes abnormal cortical-subcortical connectivity in the brains of individuals with autism. In this Editorial, we briefly review rs-fcMRI methods; summarize several key rs-fcMRI findings in 2 exemplary dysconnectivity-associated psychiatric illnesses, schizophrenia and autism; and discuss the potential uses for rs-fcMRI in the search for biomarkers of psychiatric disorders.

Related article

Resting-State Functional Magnetic Resonance Imaging Methods

Resting-state functional connectivity measures the temporal correlation of the spontaneous blood-oxygen-level-dependent signal among spatially distributed brain regions, with the assumption that regions with correlated activity form functional networks. There are 2 broad methods used to examine functional connectivity: seed-based approaches and independent-components analysis. In seed-based approaches, activity is extracted from a defined brain region and correlated with the rest of the brain. In contrast, independent-components analysis does not begin with predefined brain regions. It is a multivariate data-driven approach that deconstructs functional magnetic resonance imaging (fMRI) time-series data throughout the brain into separate spatially independent components. The components are usually then sorted into nuisance components (ie, noise or motion related) and components of interest that correspond to well-known networks, such as the default-mode network. Cerliani and colleagues[1] used the independent-components analysis approach.

In addition to producing reliable and reproducible results, there are several features of resting-state fMRI that make it a particularly attractive method for investigating the neural correlates of psychiatric and neurological disorders. First, compared with modular representations of traditional fMRI, functional connectivity provides a broader network representation of the functional architecture of the brain. Second, the absence of an explicit task eases the cognitive demand of the fMRI environment, thereby eliminating the problem of whether to match groups on task performance and allowing researchers to investigate understudied populations, including infants and cognitively impaired individuals. Finally, the relatively standard manner in which resting-state fMRI data are acquired makes it ideal for multisite investigations and data sharing.

Resting-State Functional Connectivity Disturbances in Autism and Schizophrenia

There is considerable evidence from investigations that used rs-fcMRI that cortical networks and cortical-subcortical connectivity are altered in individuals with schizophrenia. A recent investigation by Baker and colleagues[2] captured the changes in corticocortical connectivity hinted at in several earlier studies. Specifically, they found that cortical association networks in patients with psychosis were characterized by lower functional connectivity in the frontoparietal control network and reduced segregation between the frontoparietal control and default-mode networks. With respect to cortical-subcortical connectivity, several studies have found altered thalamocortical connectivity, characterized by reduced prefrontal-thalamic and increased somatomotor-thalamic connectivity.[3]

Studies of individuals with autism are less consistent and include reports of both widespread decreased and increased connectivity in intrinsic networks, such as the default-mode network. Different methodological approaches have been shown to affect discrepancies in the direction of connectivity abnormalities.[4] A recent article noted that localized areas of hyperconnectivity and hypoconnectivity characterize autism, suggesting that what may truly distinguish individuals with this heterogeneous disorder is the absolute degree of departure from the prototypical connectivity pattern, regardless of direction.[5]

The etiologic features of functional network disturbances remain unclear; however, several findings implicate atypical brain development. One of the key principles of brain development uncovered by rs-fcMRI is that cortical networks develop through the processes of integration and segregation; within-network connectivity increases and between-network connectivity decreases with development. As such, diminished cortical network integration and segregation is consistent with neurodevelopment hypotheses of schizophrenia. In the case of autism, the significant changes in brain connectivity that occur with typical development may partially explain the discrepant results.

Resting-State fMRI and the Search for Biomarkers

While neuroimaging has provided abundant evidence that the brain's features are abnormal in many patients with psychiatric illnesses, biomarkers linked to disease risk, differential diagnosis, and treatment response remain elusive. Given the richness of the data and the relative ease of acquiring them, it is tempting to speculate that connectivity-based neuroimaging methods could one day be used to generate an individual's unique brain connectome, which could inform diagnosis and treatment selection and perhaps even predict conversion to full-blown illness in high-risk individuals. It is too early to say if these goals are realistic. As a diagnostic tool, classification rates based on rs-fcMRI alone range from 60% to 90% for schizophrenia and autism. Hyperconnectivity of the salience network may be a particularly robust classifier for autism.[6] While encouraging, more study is needed to determine if rs-fcMRI, either alone or combined with other measures of brain connectivity (eg, structural connectivity), meets biomarker standards for diagnosis. Evidence linking rs-fcMRI to the effectiveness of brain stimulation targets for a variety of psychiatric illnesses suggests that an individual's unique connectome could be used to guide target selection for brain stimulation and possibly other interventions. Recent findings from the North American Prodromal Longitudinal Study baseline data also suggest that abnormal thalamocortical connectivity may be useful for predicting conversion to psychosis in high-risk populations.[7] Similar studies of autism have yet to be conducted; however, the fact that rs-fcMRI data can be acquired in pediatric populations makes it an attractive potential tool for early diagnosis.

Several factors may accelerate the discovery of connectivity-based biomarkers of psychiatric illnesses. The Research Diagnostic Criteria project will assist in successful characterization of connectivity disturbances in psychiatric illness by focusing attention on the mapping of disease phenotypes to neural networks. This approach will be aided by incorporating findings from the Human Connectome Project. Finally, data-sharing initiatives will be critical for establishing reliable reproducible information regarding dysfunctional connectivity in psychiatric disorders and identifying brain-behavior relationships. Cerliani and colleagues[1] used one such database, the Autism Brain Imaging Database Exchange.

Whether rs-fcMRI and other connectivity-based neuroimaging methods can inform mechanistic models of psychiatric disorders is an open question. Resting-state networks are conserved across species, making them a potentially powerful tool for exploring the neuropharmacological and genetic underpinnings of functional brain networks. For example, extending connectivity disturbances detected in clinical studies to rodent pharmacological and genetic models may inform the causes of mental illnesses and help identify molecular targets for new therapeutic approaches. An additional translational opportunity afforded by rs-fcMRI is the elucidation of experience-dependent plasticity at the level of large-scale neural networks, which may have important implications for behavioral therapeutic approaches to psychiatric conditions.

Conclusions

Resting-state fMRI is a promising method for uncovering the neural correlates of mental disorders and advancing personalized medicine in psychiatry. Careful study design that accounts for the specific clinical characteristics and developmental course of the disorder in question will facilitate progress. A limitation for rs-fcMRI in the effort to identify brain-behavior relationships is that it is a measure of fluctuation in neural activity in the absence of a specific externally prescribed behavior. As such, rs-fcMRI will likely remain a complement to task-based imaging. However, because of its task-free nature, rs-fcMRI can span human clinical populations and animal models to achieve a level of translational continuity that has eluded functional neuroimaging thus far.

ARTICLE INFORMATION

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