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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 of large-scale brain networks is gaining widespread acceptance. Efforts to test dysconnectivity hypotheses 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 MRI (rs-fcMRI) has profoundly affected our understanding of the functional organization of the brain, both in health and illness. The investigation by Cerliani and coauthors in this issue reports abnormal cortical-subcortical connectivity in autism¹. In this editorial, we briefly review rs-fcMRI methods, summarize several key rs-fcMRI findings in two exemplary dysconnectivity psychiatric illnesses, schizophrenia and autism, and discuss the potential usefulness of rs-fMRI in the search for biomarkers of psychiatric disorders.

Resting-state fMRI Methods

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

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task eases the cognitive demand of the fMRI environment, thereby eliminating the problem of whether or not to match groups on task performance and allowing researchers to investigate under-studied populations, including infants and cognitively impaired individuals. Finally, the relatively standard manner in which resting-state fMRI data are acquired makes it ideal for multi-site investigations and data sharing.

Resting-state Functional Connectivity Disturbances in Autism and Schizophrenia

There is considerable evidence from rs-fcMRI investigations that cortical networks and cortical-subcortical connectivity is altered in schizophrenia. A recent investigation by Baker and colleagues elegantly captured the changes in cortico-cortical connectivity hinted at in several earlier studies². Specifically, they found that cortical association networks in psychosis patients were characterized by lower functional connectivity within the fronto-parietal ‘control’ network and reduced segregation between the fronto-parietal 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 connectivity³.

Studies in 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 impact discrepancies in direction of connectivity abnormalities⁴. A recent paper notes that localized areas of both hyper- and hypo-connectivity 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 direction⁵.

The etiology of functional networks disturbances remains unclear; however, several findings point to 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: Personalized Medicine, Open Science, and Translational Neuroscience

While neuroimaging has provided abundant evidence that the brain is abnormal in many 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 it, it’s tempting to speculate that connectivity-based neuroimaging methods could one day be used to generate an individual’s unique brain connectome that 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 60–90% for schizophrenia and autism. Hyper-connectivity of the salience network may be a particularly robust classifier for autism⁶. While encouraging, more work is needed to determine if rs-fcMRI, either alone or in combination with other measures of brain connectivity (e.g. 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 (NAPLS) baseline data also suggest that abnormal thalamocortical connectivity may be useful for predicting conversion to psychosis in high-risk populations⁷. Similar studies in autism have yet to be conducted; however, the fact that rs-fcMRI data can be acquired in pediatric populations makes it a very attractive potential tool for early diagnosis.

Several factors may accelerate the discovery of connectivity-based biomarkers of psychiatric illnesses. The Research Diagnostic Criteria (RDoC) project will assist in successful characterization of connectivity disturbances in psychiatric illness by focusing attention on mapping 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 on dysfunctional connectivity in psychiatric disorders and identifying brain-behavior relationships. Indeed, Cerliani and colleagues used one such database, the Autism Brain Imaging Database Exchange (ABIDE).

Whether or not 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 it 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/genetic models may inform the etiology 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 psychopathology and advancing personalized medicine in psychiatry. Careful study design that accounts for 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. But 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.

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