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Commentary

Dynamic Functional Connectivity: A New Perspective on 22q11.2 Deletion Syndrome and Psychosis

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Over the last 2 decades, continued advances in magnetic resonance imaging (MRI) have improved our understanding of the neurobiological basis of most common psychiatric diseases. The relative safety of MRI coupled with its ability to examine neuroanatomy, white matter microstructure, chemical composition, perfusion, and function in vivo has established MRI as a versatile tool in the neuroscientist's armamentarium. Nevertheless, the discovery of clinically salient neuroimaging biomarkers for psychiatric diseases largely remains elusive—hindered in part by the overwhelming neuroanatomical and functional complexity of the human brain and in part by the challenges of defining psychiatric phenotypes (1).

In the current issue of *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, Zöller *et al.* (2) explore the neural substrates of psychosis and anxiety in subjects with 22q11.2 deletion syndrome (22q11DS) using resting-state functional MRI (rsMRI) and advanced analysis methods. Owing to a 1.5-Mb to 3-Mb hemizygous microdeletion, individuals with 22q11DS have an increased liability for several psychiatric disorders, including anxiety, attention-deficit/hyperactivity disorder, and autism spectrum disorder (3). However, perhaps the most remarkable feature of 22q11DS is an incidence of schizophrenia at approximately 25 times that of the general population; of all structural variants in the human genome, the 22q11.2 microdeletion conveys the highest known risk (3). Thus, examining brain connectivity in 22q11DS represents a rare opportunity to identify biomarkers for the onset of psychosis in a population with a relatively defined biological basis.

By examining correlated fluctuations in cerebral blood flow at rest, rsMRI has been established as in important research method for investigating functional brain networks. More recently, rsMRI has shown promise in identifying clinically significant disease subtypes and potentially influencing treatment decisions (4). While more traditional rsMRI analyses focus on examining patterns within MRI time series as a whole (i.e., "static" networks), newer advances in postprocessing now enable investigations of how resting-state networks change dynamically over time, providing additional insights into the spatiotemporal complexity of human brain function (5). For example, the development of innovation-driven coactivation pattern (iCAP) methodology allows for the simultaneous identification of multiple dynamic brain networks (iCAPs) that may be spatially and temporally overlapping (6). The iCAP technique also allows for quantification of the duration that each individual network is active, as well as how fundamental brain networks interact with each other.

Previous rsMRI studies on 22q11DS have shown that like schizophrenia (7), aberrant connectivity appears to play a role in the development of psychosis (8). Zöller *et al.* (2) expand on this work by using iCAP methodology in a large sample (n = 78) of individuals with 22q11DS and high-quality rsMRI data. These analyses provide the first evidence not only that the functional connectivity in 22q11DS differ from that in typically developing populations, but also that at least some differences are dynamic in nature. Individuals with 22q11DS spent relatively more time activating limbic networks and less time activating several networks involved in cognition, including a network involving the dorsal anterior cingulate and dorsolateral prefrontal cortices (dACC/dlPFC). Individuals with 22q11DS also spent longer periods of time with iCAPs in an anticoupled state, suggestive of larger-scale dynamic disruptions in internetwork connectivity.

Moreover, Zöller *et al.* (2) report that prodromal psychotic symptoms in 22q11DS are associated with longer activations within the dACC/dlPFC, frontoparietal network, and inferior temporal/fusiform (iTEMP/FUS) network. Anticoupling between dACC/dlPFC and these other implicated networks (frontoparietal and iTEMP/FUS) were also significantly associated with increases in psychotic symptoms. Symptoms of anxiety were associated with an increased length of activation within the amygdala/hippocampal and iTEMP/FUS iCAPs and a decreased length of activation of the anterior default mode network. Measures of anxiety were significantly associated with decoupling between the dACC/dlPFC and both the frontoparietal and iTEMP/FUS networks.

Many of these neuroanatomic regions not only have been implicated in the pathophysiology of anxiety and psychosis, but also have established roles in the 22q11DS endophenotype (3,9,10). For example, the cingulate, parietal lobe, fusiform gyrus, amygdala, and hippocampus have all been previously associated with aberrant structural morphometry in 22q11DS. Thus, while Zöller *et al.* (2) provide novel insights into the dynamic nature of connectivity in 22q11DS, the study also integrates well with our current understanding of functional neuroanatomy. Furthermore, by describing new functional correlates of anxiety and psychosis, Zöller *et al.* (2) provide a potential step toward clinically useful biomarkers in 22q11DS and perhaps even for idiopathic psychosis and anxiety.

The study of 22q11DS represents an invaluable opportunity to investigate the neural substrates of psychopathology while simultaneously refining our understanding of a relatively common and potentially debilitating genetic condition. However, the study of 22q11DS also exemplifies the challenges

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inherent to neuroscience research—namely the multifaceted and dynamic interplay between gene, body, brain, and behavior. Innovative methodologies that integrate multimodal data and embrace the complexity inherent to most neuroimaging datasets will likely be required to further advance our knowledge of this condition.

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Article Information

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