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Invited Commentary

A Brain Network–Based Grading of Psychosis
Could Resting Functional Magnetic Resonance Imaging Become a Clinical Tool?

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Cognitive deficits are the major contributing factors to social and vocational deficits across many major mental illnesses such as schizophrenia, bipolar disorder, and depression. Sheffield et al[1] build on their previous investigations on the physiology of cognitive performance in psychosis to elegantly show that the generalized cognitive deficit in psychosis may result from a transdiagnostic, rather than a disorder-specific, impairment in the operation of large-scale brain networks. This is promising work that has enriched the translational potential of functional magnetic resonance imaging (fMRI) in treating psychosis.

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Sheffield et al[1] used imaging and cognitive data collected from the multisite Bipolar-Schizophrenia Network on Intermediate Phenotypes and included patients with schizophrenia, schizoaffective disorder, and psychotic bipolar disorder as well as healthy controls. General cognition was measured from a single factor explaining more than 50% of interindividual variances in cognitive ability in working memory, executive functioning, processing speed, motor speed, verbal fluency, and verbal memory. As expected, the patients with schizophrenia were the most cognitively impaired (Cohen d = 1.40) while the patients with bipolar disorder were the least impaired (Cohen d = 0.83) and the patients with schizoaffective disorder fell in between the 2 (Cohen d = 1.28). Global efficiency, a graph theoretical metric that represents the efficiency of communication within a set of connected nodes, was used as a proxy measure of network integrity. Twelve large-scale networks were studied, with a prior expectation to find anomalies in the cingulo-opercular (CON, or salience network) or frontoparietal network. The groups with schizophrenia and bipolar disorder showed significantly reduced CON global efficiency relative to the healthy controls, although no significant differences were noted among the diagnostic groups. The global efficiency of the CON and subcortical network was associated with general cognitive ability across the entire study population and mediated the relationship between psychotic status and general cognition. These results implicate the importance of the CON network in general cognition and across psychotic-spectrum disorders. They also support a role for subcortical network (thalamus/basal ganglia) integrity in the physiology of cognitive dysfunction in psychosis.

Despite the anatomical consistency of large-scale systems derived from resting state fMRI, the studies using these methods to study clinical populations are still plagued by the issue of approximate, rather than exact, replications. Major issues are not consistently using spatial localization or parcellation approaches when studying connectivity and confounding that arises during data processing. Sheffield et al[1] control for many known issues in preprocessing, including motion, site variability, and confounding related to race/ethnicity and sex. The authors treated the global average fMRI signal as a nuisance variable and discarded the negative weights when constructing networks for graph analysis, although recent studies have challenged this approach, demonstrating schizophrenia-related variations in global signals.[2] While the specificity of the brain-cognition relationship to CON and subcortical networks reduces these concerns, it is important to study the association between global signals and these networks more systematically in the future. This will also help us reconcile the inconsistencies related to other critical networks, such as the frontoparietal network, shown elsewhere to be an important subsystem with transdiagnostic abnormalities in psychosis.[3]

Since we first proposed an integrated notion of CON dysfunction in psychosis,[4] several studies have confirmed the critical role of reduced cross-network interactions between the CON and other major brain networks (especially the medial de-

fault mode and the lateral frontoparietal executive network).[5] Insula, a core hub for CON, shows significant structural deficits in psychotic disorders, suggestive of both early dysmaturation (eg, folding defects) and continued gray matter loss with illness progression.[4] Current antipsychotic treatments do not correct but may indeed worsen the structural deficits of the CON. Multiple factors, including cigarette smoking, may deleteriously alter the structure and function of the CON. To reverse the pathophysiological deficits reported by Sheffield et al,[1] it is critical that we determine the factors that lead to the reduced integrity of the CON in psychosis.

Despite its wide use, the meaning of global efficiency is still elusive for fMRI-based graph networks. High global efficiency refers to having relatively few mediating nodes (regions) in the path between a given pair of brain regions. It is somewhat farfetched to assume that the propagation of neural information will follow this path-map. Every neuronal ensemble will require a topological imprint (akin to navigational systems in cars), to calculate the shortest path for efficiently transferring information. Furthermore, fMRI signal-based correlation between 2 regions is inherently suggestive of coactivation rather than propagation of information from 1 site to another. Converging evidence from direct neuronal recordings may clarify our current interpretations of the connectomic fMRI measures.

Notwithstanding these theoretical issues, the clinical relevance of the findings of Sheffield et al[1] is immense. We recently demonstrated that among healthy individuals, using the knowledge of anterior insulaprefrontal connectivity, we can successfully modulate the physiology of the CON through neurostimulation (mediated via a change in GABA levels).[6] The observations of Sheffield et al[1] suggest that therapeutically restoring the efficiency of CON may improve cognition in psychosis. Another exciting therapeutic translation is in randomized controlled trial design. The presence of significant cognitive deficits is a poor prognostic sign in psychosis and is often associated with treatment resistance across psychiatric disorders. Sheffield et al[1] open the door to empirically grading psychoses based on a mechanistic process underpinning cognitive dysfunction. To this end, we must demonstrate the utility of network physiology in predicting clinically meaningful constructs such as treatment-resistant schizophrenia, for which alternate treatment options exist currently. Furthermore, early evidence indicates that the physiology of CON is sensitive to change with treatments that improve cognition.[7] Future randomized clinical trials of agents targeting cognition could potentially use a short resting state fMRI scan to stratify and/or monitor transdiagnostic patient samples. The success of such stratified trials will herald a remarkable scanner-to-service translation in mental health.

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