Commentary

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Individually Specific Topography Maps Derived From Resting-State Functional Magnetic Resonance Imaging to Understand the Neurobiology of Psychosis

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Since the landmark study by Biswal *et al.* (1) demonstrating temporal correlations of low-frequency fluctuations in sensorimotor regions associated with hand movement, there has been an exponential increase in the use of resting-state functional magnetic resonance imaging (rs-fMRI) to understand the neurobiology of both healthy and disease processes. In contrast to other neuroimaging modalities such as structural MRI and positron emission tomography, however, the data obtained from rs-fMRI have had less clinical utility at the individual level. Although rs-fMRI acquisitions can reliably identify standard functional networks, there is significant individual variability in this topography, thus potentially limiting both clinical and research applications. The ability to identify individually unique patterns of functional organization using rs-fMRI, which might not otherwise be available except through invasive procedures, has been a promising area in healthy human research studies but remains largely unexplored in the neuropsychiatric literature. The longer acquisitions of rs-fMRI data that are required to capture individual variation in functional networks that could increase their utility are typically not feasible, however, due to time and/or financial constraints.

The study by Mamah *et al.* (2) recently published in *Biological Psychiatry: Global Open Science* is timely and novel because it leverages the acquisition of 60 minutes of rs-fMRI data acquired on the Connectom MRI scanner to better understand the pathophysiology of psychotic experiences. This goal has particular relevance for identifying individuals who are at elevated risk for developing psychosis and/or those who may derive benefit from specific treatment interventions. Their main study goal was to investigate the size and functional topography of individual network maps in relationship to psychotic experiences in the HCP-YA (Human Connectome Project Young Adult) cohort (N = 1003). In addition, previous studies that have investigated rs-fMRI measures in schizophrenia and bipolar disorder have been inconsistent regarding the direction of findings (i.e., hyper- and/or hypoconnectivity) and which networks are involved. Therefore, they also investigated network size in cohorts of individuals with schizophrenia (n = 27) and bipolar disorder (n = 35) using the same rs-fMRI parameters as the HCP-YA cohort, which represents the longest acquisition of such data in these psychiatric groups to date.

Previous empirical studies have demonstrated that individually specific patterns of data or functional connectivity "fingerprints" can be obtained from approximately 25 minutes of rs-fMRI data to reliably distinguish an individual from a group average (3). Even greater improvements were observed with 90 minutes of scan time, at which point an asymptotic value was achieved (4). Particularly noteworthy is that the use of these longer acquisitions revealed reliable individual features in the resting-state data that were not observed in group-level averages and could be replicated across independent datasets (5). The presence of these unique features raises the empirical question of whether individual variability in these network patterns has functional significance and whether these patterns can be identified in case-control studies.

The methodologic approach in the study by Mamah *et al.* (2) also addresses the limitations of assigning brain regions to functional networks on the basis of population-averaged rs-fMRI networks that may not account for individual functional topography. Current analytic approaches can incorrectly assign some brain regions to functional networks due to misalignment, thus increasing error variance and reducing power in the investigation of within- and between-network effects that, for example, examine the neurobiology of psychiatric disorders or assess change in longitudinal studies. To overcome this problem, Mamah *et al.* (2) utilized an individually specific template-matching approach to investigate the network topography of 8 well-known rs-fMRI networks that have been widely used in previous studies including default mode, dorsal attention, language, frontoparietal, cingulo-opercular, somatosensory-body and somatosensory-face, and visual.

One main finding from their study was that the default mode network was largest in size of the networks (a pattern present in all groups) and represented approximately 18% of the cortical area in the HCP-YA cohort. The default mode network is one of the most well-known, identifiable, and stable brain networks (6) believed to play a role in daydreaming and envisioning the future-self. Mamah *et al.* (2) acknowledge that although network size does not provide direct information regarding connectivity strength either within or between networks, it could be informative regarding how much of a given network is utilized and its relative importance. The finding that the default mode network exists in nonhominoid primate species, although it displays differential engagement among nodes in humans, supports its potential importance in the cortical hierarchy from an evolutionary perspective (7). Given the complex nature of the relationship between general cognitive ability and cortical surface area and thickness (8),

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brain-behavior relationships that involve rs-fMRI network size are likely to be as complex. Understanding individual variability in size and functional topography in the anterior (e.g., medial prefrontal cortex) versus posterior (e.g., posterior cingulate cortex) parts of the default mode network could also shed light on the neurobiology of psychotic experiences given that they appear to have different functions.

The findings from their study also indicated that the language network was larger among individuals with schizophrenia than in individuals in the HCP-YA cohort and that these effects were most pronounced in the posterior part of the left superior temporal cortex. Consistent with these findings, the authors also found that the larger language network area was associated with a greater likelihood of hearing "sounds or voices that other people think aren't there" in the HCP-YA cohort. Taken together, these findings are consistent with the hypothesis that this network may overprocess language and/or is more sensitive to auditory speech. Their results converge with previous studies that reported left hemisphere temporal lobe structural and functional abnormalities in the neurobiology of schizophrenia that were associated with speech/language abnormalities and auditory hallucinations. Individual functional topography maps of the language network focused on more circumscribed regions of the temporal lobe, including Wernicke's area, could be integrated with natural language processing approaches to guide empirical studies that determine the neurobiological basis of deficits in the ability to comprehend spoken language and auditory hallucinations in schizophrenia.

The dorsal attention network, comprising the intraparietal sulcus and frontal eye fields, was larger among individuals with schizophrenia and bipolar disorder than among individuals in the HCP-YA cohort. Abnormalities in dorsal attention network size could contribute to deficits in the ability to exert attentional control for maintaining task demands and processing external stimuli in the face of competing demands, thus leading to cognitive distortions. The finding of comparable dorsal attention network size in schizophrenia and bipolar disorder suggests that these abnormalities could be transdiagnostic and reflect a more general aspect of psychopathology. This possibility was supported by the finding in their study of an association between dorsal attention network size and thought disorganization in the HCP-YA cohort that was largely driven by the nonpsychotic items, including items assessing repetitive behavior, self-injurious behavior, and difficulty with peer relationships.

Smaller cingulo-opercular network size in schizophrenia (although not statistically significant after correction for multiple comparisons) was inversely correlated with strange thoughts and strange actions from the Thought Problems Scale, thus implicating a potential role for this network in delusional thinking and behavioral disorganization, respectively. The observed correlations in their study highlight the importance of this network, which interacts with the default mode and dorsal attention networks, in monitoring mismatch between internally versus externally guided stimuli to focus attention when required. Their findings converge broadly with neurobiological models of schizophrenia that posit that tonic arousal (possibly reflecting aberrant dopamine modulation via striatal networks) could partially explain misattribution of external events and/or subjective internal experiences, which lead to paranoid ideation and psychosis (9).

The work from Mamah *et al.* (2) provides several interesting directions for future research studies that investigate individual variability in functional network size using rs-fMRI data. Given that schizophrenia has been conceptualized as a neurodevelopmental disorder, it would be of interest to investigate age-associated changes in network size and how deviations in a healthy trajectory may coincide with the onset of psychosis. Similarly, asymmetry in network size could provide novel information regarding the failure of left hemisphere lateralization and deficits in associated functions in schizophrenia. Better understanding how intraindividual differences in network size and associated functional metrics (e.g., amplitude of low-frequency fluctuations) relate to each other and neurocognitive functioning in both health and disease are particularly important areas for future studies. The identification and mapping of unique patterns of rs-fMRI networks at the individual level could lead to the construction of an atlas that describes these variations, similar to ones that describe variations in the cerebral sulci. Investigating whether variations in network topography are associated with constructs of psychopathology that cut across traditional diagnostic categories could facilitate identification of network biotypes to potentially guide more personalized intervention approaches (10).

In sum, the results from the study by Mamah *et al.* (2) highlight the importance of identifying individual functional networks that may not be evident from population-averaged data and provide new information regarding the contribution of network size to the phenomenology of schizophrenia and bipolar disorder.

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