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·Research Highlight·

Altered topological properties in the heritable schizophrenic brain

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It is well established that complex networks are responsible for the high-level information processing in the human brain. The topology of complex networks allows efficient dynamic interactions between spatially distinct brain areas, which may be studied by analyzing the topological properties of the network. Nowadays, one of the powerful ways to study the brain from the perspectives of graphs is to model the structural and/or functional connectome, with emphasis on testing the widely recognized dysconnectivity theory of schizophrenia[1]. Along with these exciting exploratory studies in this field, two questions appear to be fundamental and need to be addressed. First, how do the topological properties of the brain network change in patients with schizophrenia? Second, are the altered topological properties of schizophrenia heritable?

In a paper published in Neuroscience Bulletin in June[2], Yan and colleagues confirmed that the schizophrenic brain exhibits the small-world properties of global and local efficiency by establishing a white matter connectivity network with diffusion tensor imaging using graph theoretical analysis. They found lower global and local efficiency, especially with reduced regional efficiency in hubs in the bilateral frontal cortices, bilateral anterior cingulate, and left precuneus. Overall, their findings were partly in line with previous studies that explored the topological characteristics of the brain network by analyzing cortical thickness and brain volumes, as well as functional connectivity, which also found decreased clustering, reduced modularity, reduced local efficiency and hierarchy, excess long-distance connections, and increased topological integration and robustness of structure or functional brain networks in patients with schizophrenia[3]. Furthermore, Yan's work provided new evidence for the conserved primary small-world network with altered topological properties, especially impaired "hubs", in schizophrenia. This work also suggested less efficiency in interactions between interconnected brain regions that lead to an anomalous equilibrium between local processing and the global integration of information in patients with schizophrenia.

Another outstanding advantage of Yan's work was that they further studied the topological characters of a brain structure network in the unaffected parents of schizophrenic patients. This work is excellent because it may lead to an answer to the critical question that researchers in this field always ask, i.e. are the altered topological properties of schizophrenia independent of the disease state? Furthermore, can these altered topological properties be regarded as endophenotypes for further genetic analysis? As expected, they found a trend of lower global efficiency and reduced regional efficiency in the hubs of the right temporal cortex, left thalamus, and left supplementary motor area in the unaffected parents of patients with schizophrenia. The results indicated that a similar pattern of lower connectivity and reduced regional efficiency of rich hubs is present in patients with schizophrenia and their unaffected first relatives, and the latter showed milder abnormalities than the former. This pattern was also confirmed by another work performed by Collin and colleagues[4]. Using diffusion-weighted images, Collin *et al*. found that the connectivity between rich club hubs constructed by white matter tracts is lowest in patients with schizophrenia (19.6% lower than healthy controls), intermediate in unaffected siblings (7.9% lower

than healthy controls), and highest in healthy controls. And the rich club regions with abnormal connectivity were also located in the bilateral superior frontal and rostral anterior cingulate gyri, left medial orbitofrontal and inferior temporal gyri, and right precentral and insular gyri in schizophrenic patients[4]. These two studies collectively provided convincing evidence to support the concept that the aberrant functional connectivity of frontal and cingulate cortexes is not only associated with schizophrenia, but is heritable and more frequent in unaffected relatives with an increased genetic risk of the illness, which might be a valuable endophenotype for schizophrenia.

Previous studies have indicated that the topological properties of brain graphs are genetically mediated and highly heritable[5, 6], and modulate cognitive ability and behavioral performance[7]. These studies imply that graph theoretical analysis of structural and functional brain networks by magnetic resonance imaging would shed light on the pathophysiology of schizophrenia, which might be due to developmentally perturbed formation of the brain connectome. So far, only Yan and Collin, both using diffusion-weighted images, have explored topological characters of the brain networks in probands with schizophrenia and their unaffected first-degree relatives. Other than the fractional anisotropy of white matter or fiber tracking, cross-correlational cortical thickness (defined as edges), cortical surface area or volume, and bivariate or partial correlations (edges) of blood-oxygenation level-dependent time series between regions (nodes) also could be used to construct structural and functional networks. Furthermore, apart from 'small-worldness and efficiency' and 'the distribution of network hubs', other characteristics describing the topological properties of complex brain networks such as 'degree and degree distribution', 'modularity', 'centrality', and 'hierarchy' also need to be analyzed in schizophrenia.

The incredible complexity of the human brain impedes our understanding of the pathophysiology of schizophrenia. It should be noted that, other than analyses of the topological properties of complex networks in patients with schizophrenia as performed by Yan *et al*.[2], analysis of either specific candidate neuronal circuits or unbiased connectome-wide approaches is important for exploring the different levels of the anomalous connectomic brain in schizophrenia[8]. And investigations using the "brainnetome" concept, which integrates multi-level network features, could open a new window on comprehending the brain of patients with schizophrenia[9]. Furthermore, given the high heritability of schizophrenia, it is feasible and effective to approach the genetic mechanism of schizophrenia by studying the endophenotype (also named the intermediate phenotype) simultaneously in patients and individuals at high genetic risk, such as unaffected first-degree relatives of patients[10]. In conclusion, combining the brainnetome concept with the notion of endophenotype could confer advantages in providing useful biomarkers for diagnosis and etiological studies of schizophrenia, as well as of other highly-heritable psychiatric disorders such as bipolar disorder.

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