• Review •

Brainnetome of schizophrenia: focus on impaired cognitive function

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Abstract: Impaired cognitive function, along with positive and negative symptoms, is a core clinical feature of schizophrenia. Earlier studies suggest that impaired cognitive functioning should be assessed from the perspective of brain networks. The recently developed brainnetome approach to evaluating brain networks—an approach that was initially developed by Chinese scientists—provides a new methodology for studying this issue. In this paper we first introduce the concept of brainnetome. We then review recent progress in developing a brainnetome of impaired cognitive function in people with schizophrenia. The models of the relevant brain networks considered were created using data obtained from functional and anatomical brain imaging technologies at different levels of analysis: networks centered on regions of interest, networks related to specific cognitive functions, whole brain networks, and the attributes of brain networks. Finally, we discuss the current challenges and potential new directions for research about brainnetome.

Key words: Brainnetome; Magnetic resonance imaging; Schizophrenia; Cognitive function

Schizophrenia is a severely disabling disease with a lifetime prevalence of 1% that mainly occurs in young and middle-aged people. The clinical symptoms are variable and range from hallucinations and delusions (positive symptoms) to flat or blunted affect and emotions (negative symptoms). Although these positive and negative symptoms are generally considered to be the characteristic features of schizophrenia, studies conducted in the last two decades have shown that impaired cognition should also be considered a core clinical symptom[1-4]. There is still disagreement about whether impaired cognition should be included in the diagnostic criteria for schizophrenia, but researchers agree that the extent of impaired cognitive function reflects the severity of the disease. For example, the American Psychiatric Association's upcoming fifth edition of the Diagnostic and Statistical Manual for mental disorders is planning to list impaired cognition as an important dimension for evaluating the severity of schizophrenia[5]. Working memory dysfunction is the most common and important type of impaired cognition in people with schizophrenia[6-10] so an understanding of the neural basis behind impaired working memory is considered essential to understanding the pathophysiology of schizophrenia[10]. The present manuscript discusses the contribution of a construct called the brainnetome in understanding impaired working memory and cognition in people with schizophrenia.

1. Brainnetome

The underlying neural mechanisms of impaired cognition, including the working memory dysfunction in people with schizophrenia, have been studied since the late 20th century. Goldman-Rakic and colleagues[10] suggested that the working memory dysfunction in individuals with schizophrenia was the result of abnormal brain networks. Based on electrophysiology results from non-human primates, he proposed that the neural activity underlying working memory is not limited to the frontal cortex but also requires interactions between the frontal cortex and other remote regions including the posterior parietal cortex, inferior temporal cortex, cingulate cortex and the hippocampus. These brain regions form fiber connections with the dorsolateral prefrontal cortex and interact via these connections. Since working memory plays a critical role in the integrity of various thought processes, abnormalities in this working memory circuit may be the neural basis of impaired cognition and, thus, be related to the psychotic symptoms observed in schizophrenia. Goldman-Rakic and colleagues proposed that impaired cognition in people with schizophrenia be

doi: 10.3969/j.issn.1002-08329.2012.01.001

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studied in terms of brain networks but they provided no specific hypothesis about the neural mechanisms underlying this impaired cognition, possibly because of a shortage of technical strategies for studying neural connections.

The creation and development of the brainnetome provides a new opportunity for studying the neural mechanisms of impaired cognition in people with schizophrenia. Brain network research is on the frontier of international science and is one of the seven important areas of research identified by the journal *Science* in 2007. The National Institute of Health in the United States launched the Human Connectome Project[11,12] that focuses on brain networks. During the past decade, a team led by the first author of this review proposed the development of an international project on the brainnetome[13], organized the 393rd Xiang-shan scientific symposium focusing on the brainnetome, and launched the brainnetome project with the support of China's National Program on Key Basic Research (the '973 program')[14].

While different brain connectomes address the structural connections between different neurons (nuclei) or brain regions, brainnetome not only focuses on structural connections between neurons and brain regions but also emphasizes the dynamic characteristics of fully constructed brain networks and the relationship between brain network changes and neuropsychological disease. Specifically, the Brainnetome research project[13] focuses on the study of the topological structure, dynamics, and functions of brain networks as well as the superficial characteristics and genetic contents of dysfunctional brain networks from different temporospatial scales. By combining imaging techniques that have high temporospatial resolution with modern computational techniques, these programs can be used to develop models of the interactions between different brain regions and the dynamic evolution of brain networks. These models will facilitate systematic study of the structure and function of the brain on different temporospatial dimensions, help in the analysis of transmission mechanisms of internal signals using different brain indices, identity pathways for studying complicated information interactions and high-efficacy tissue structures within the brain, and explore new pathways for understanding information processing and the higher functions of the human brain. The study of brain networks has become a key research focus for information science, neuroscience, clinical medicine and other fields. The investigation of abnormal models and the specificity of these abnormal models in disease with respect to brain networks is not only helpful for promoting the understanding of normal and abnormal brain functions, but can also aid in the identification of specific imaging characteristics of diseases at the brain network level. This will be helpful in improving current diagnostic standards and, thus, is important both for theory and in the clinic. Currently, the brainnetome represents a new direction for studying the pathophysiological mechanisms of impaired cognition in schizophrenia.

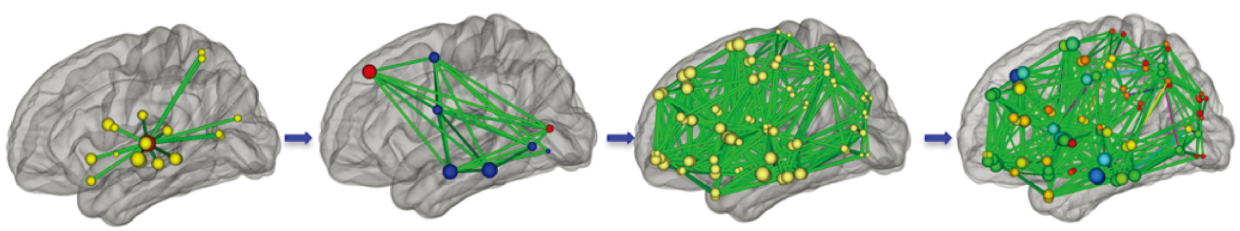
2. Brain network study of impaired cognition in schizophrenia

The human brain integrates and merges information from multiple regions to perform high-level cognitive functions. The human brain is a system with multiple levels and therefore needs to be studied at different levels. Brain network research can be divided into functional or anatomic approaches based on modes of imaging. Alternatively, this research can be divided into brain network analysis based on single region-of-interest, specific brain network analysis, whole brain network analysis, and brain network attributive analysis (Figure 1). By choosing investigative strategies based on different levels of analysis and imaging modes, we have generated some primary information about the mechanisms of impaired cognition and abnormal working memory in people with schizophrenia.

2.1 Functional brain network during task

Single-unit recordings from non-human primates and imaging studies of the normal human brain have contributed to the recognition of the dorsolateral prefrontal cortex (DLPFC) as a core region of the working memory network. The majority of fMRI studies

Figure 1. Schematic of brain networks



Research on brain networks can focus on 1) networks centered in regions of interest, 2) networks related to specific cognitive functions, 3) whole brain networks and 4) brain network attributive analysis

on working memory in patients with schizophrenia are focused on the DLPFC[15-19]. Using region-of-interest functional connectivity analyses, it was found that the task load of working memory can modulate the functional connectivity between the hippocampus and DLPFC in normal humans. However, in patients with schizophrenia, the correlation between the left hippocampus and the right DLPFC was not modulated by the task load[20]. By analyzing subcomponents of working memory, it was found that in patients with schizophrenia the connectivities between the prefrontal cortex and the hippocampus and intraparietal cortex were reduced during the non-articulatory maintenance of phonological information[21]. Moreover, connectivity between the DLPFC and the cerebellum was increased during the high-load state, and this was correlated with improvement of working memory in patients with schizophrenia[22].

The lateral frontoparietal network is considered the core network underlying adaptive cognition control[23,24] so this was also a focus of study for the brainnetome investigation of impaired cognition in people with schizophrenia. By using independent components analyses methods, it was found that the connectivity in the bilateral DLPFC and the left inferior parietal lobe was increased during a verbal working memory task[25]. Furthermore, accuracy during the working memory task was positively correlated with the strength of functional connectivity in the left DLPFC[25]. The abnormal enhancement of fronto-parietal connections suggested the presence of a compensatory process in patients, that is, the DLPFC needs more involvement and interaction with the parietal cortex to satisfy the task requirement. However, when separating the encoding stage from the recognition stage during working memory, it was found that during the encoding stage the integration function of the bilateral fronto-parietal network in patient with schizophrenia was reduced and that the left fronto-parietal network displayed abnormal activity with a load-dependent functional response[26].

Although these studies found abnormal activity in the brain networks of patients while performing working memory tasks, these abnormal patterns were not consistent. This may be explained by the complexity of working memory tasks. Working memory tasks involve several different cognitive processes, including the initial information encoding stage, the subsequent maintenance stage (which includes updating and managing information) and the final selecting and responding stage. Each stage has a different neurobiological basis[27]. Additional study is necessary to further investigate the characteristics of brain networks of patients with schizophrenia by distinguishing the different cognitive stages or processes of working memory.

2.2 Functional brain network during rest

Resting fMRI studies have recently become popular because of various advantages, including the ease of working with subjects with neuropsychiatric disorders (without task design or subject training) and their comparability across different studies. At rest, blood-oxygen-level-dependent (BOLD) signals show spontaneous low-frequency fluctuations (SLFF) (<0.1 Hz), which have been verified as physiologically meaningful signals[28]. Through studies of the temporal correlation of the SLFF between different brain regions (via functional connectivities), it was found that functional connectivities during the resting state were not derived from respiration or heartbeats. In addition, the functional connectivities had anatomical foundations and existed at different resting conditions (e.g., eye-opening, eye-closing, visual fixation, and anesthesia), suggesting that resting-state functional connectivities reflect intrinsic brain activities[28]. The default-mode network is always the focus of studies of brain function in resting conditions[29,30]. The default-mode network refers to the brain regions that are negatively activated in goal-directed tasks but are active in resting conditions. Regions involved in this network include the posterior cingulate cortex, the medial frontal cortex, and the lateral parietal cortex, among others. These brain regions have significant functional connectivities in resting conditions, and may reflect the active state of brain function at the “baseline” stage. Therefore, these were defined as the default-mode network[31,32].

The functional activities of the brain default-mode network are modulated by working memory tasks and can predict individual variations in cognitive capability. Previous studies in normal humans investigated the functional connectivity between the core node in the default-mode network (i.e., the posterior cingulate cortex) and the core node in the medial prefrontal cortex[33], and assessed functional connectivities between the posterior cingulate cortex and other brain regions[34] during working memory tasks and during the resting state. The results indicated that during working memory tasks the functional connectivities between the two default-mode brain regions were weaker than during the resting state. However, the functional connectivities between the default-mode brain network and the working memory-related brain regions were enhanced, including those between the posterior cingulate cortex and the bilateral inferior parietal gyri, the medial prefrontal cortex, the left inferior frontal gyrus, and the superior parietal lobule[33,34]. Using functional connectivity/network analysis methods based on graph theory, it was determined that the topological structure of core brain regions in the default-mode network during a working memory

task was similar to that during rest, but the degree of connectivity between the brain regions related to task execution increased. This supports the notion of the increased importance of these brain regions during task performance[35]. Although the topological structure of networks in normal humans does not change, tasks do have modulating effects on the default-mode network. The scores on the working memory task are not only positively correlated with the functional connectivity strength of the default-mode network under different task conditions, but also positively correlated with the connectivity strength under the resting condition. This suggests that the strength of functional connectivities of the default-mode network during rest can predict individual differences in the cognitive ability required to complete the working memory task[33].

Researchers currently attribute abnormal cognitive function and impaired working memory in patients with schizophrenia to interference of the default-mode network[36], that is, the patient cannot transfer the necessary attention from intrinsic thoughts and emotions to the exterior stimulus, resulting in low cognitive scores. Studies have repeatedly found that the extent of deactivation of default-mode networks during working memory tasks is reduced in schizophrenia patients[37-40]. Previous investigations found that the functional connectivities between the bilateral DLPFC and the posterior cingulate gyrus in patients with first-episodic schizophrenia are reduced during rest[41]. However, the resting-state functional connectivities in the regions constituting the default-mode brain network, the connectivities in the regions constituting the task-positive brain network, and the connectivities between these two brain networks are increased in patients with paranoid schizophrenia[42]. Additionally, the abnormally enhanced functional connectivities in the default-mode brain network are also found in healthy siblings of people with schizophrenia, suggesting that the abnormal functional connectivities of the default-mode brain network may be important characteristics of the disease[43]. An investigation of the modulating effect of working memory task state on functional connectivities of the default-mode network in patients with schizophrenia revealed that the functional connectivities of the default-mode network are found both while performing working memory tasks and during rest, similar to findings in normal controls. However, these connectivities were significantly stronger in people with schizophrenia than in normal individuals and were correlated with the severity of positive symptoms[39].

3. Anatomical brain network

Diffusion Tensor Imaging (DTI) is a recent advance in MRI technology that can provide diffusion information about hydrogen molecules in brain tissue and thus indirectly reflect the physical and functional characteristics of white matter in the brain[44]. DTI represents a departure from the traditional in vitro fiber tracing methods of white matter and makes it possible to study white matter fibers in vivo. Based on anatomical knowledge, all white matter fibers originate from gray matter structures and end in other gray matter structures. Therefore, DTI is a powerful technique for directly describing the anatomical networks of brain.

Previous studies have indicated that the superior frontal-intraparietal network, which comprises the superior longitudinal fasciculus connecting the frontal and parietal cortices and the adjacent gray matter, is an important component of the working memory brain network[45]. The integrity of the superior longitudinal fasciculus is decreased in people with recent-onset schizophrenia, and performance on a linguistic working memory task is correlated with disrupted fiber integrity. This structural change may be one reason for the difficulty in recovery of cognitive abilities in people with schizophrenia[46]. It has also been demonstrated that the anatomical connectivity between the DLPFC and the anterior cingulate cortex is reduced in patients with schizophrenia and that this structural abnormality is related to working memory task performance[47,48]. By combining DTI and fMRI findings on working memory tasks, Schlosser and colleagues[49] found that the fractional anisotropy (FA) in the right medial parietal and frontal lobes was reduced in people with schizophrenia, and that the activation of prefrontal, superior parietal, and occipital lobes during a working memory task was weakened. More importantly, the abnormal white matter in the prefrontal lobes of patients with schizophrenia was directly correlated with the extent of activation of the prefrontal and occipital lobes. These results suggest that the integrity of the anatomical connectivities underlying the working memory network are related to behavioral test scores, and that abnormal anatomical connectivities can result in changes of brain activation during working memory tasks. However, these studies are only the starting point—the etiological role of abnormal anatomical connectivities between the core brain regions in the working memory network as a cause of the impaired working memory in people with schizophrenia needs to be verified in future studies.

4. Topological properties of the brain network

Brain network analysis based on graph theory is a new method for studying the pathophysiological mechanisms of neuropsychological diseases. A variety of imaging studies have indicated that the human brain is a complicated network with small-world topology[50,51]. This efficient topological structure changes with aging[52,53] and state[54], and has a genetic basis[55]. Using this analysis method, we found that abnormal resting-state functional connectivities were widely distributed within the entire brain in people with schizophrenia[56].

Furthermore, we found that the topological properties of the brain functional network are changed in people with schizophrenia. These differences are demonstrated by a decreased cluster coefficient, prolonged minimal path length, and reduced information transmission efficiency, all of which suggest abnormal information exchange of the brain functional network[57]. Additionally, the topological structural characteristics of the brain functional network were significantly correlated with clinical indices; the longer the duration of illness the lower the efficiency of information transmission[57] and the extent of the abnormal brain anatomical characteristics was correlated with clinical severity[58]. Similar results were obtained by constructing brain networks using EEG[59, 60] and structural MRI[61]. All of these studies of brain networks revealed abnormal connectivity patterns in people with schizophrenia. The integrated information obtained by brain network analysis provides a new strategy for understanding the pathophysiological mechanisms of schizophrenia, potentially aiding early diagnosis and improving the efficacy of clinical evaluations.

Cognitive functions like working memory cannot be independently executed by one neuron or one single brain region but are accomplished by interactions between multiple brain regions. The study of local brain regions and the interactions among these brain regions is the core focus of brainnetome studies. The dynamic interaction mode between brain regions is the basis of human cognitive processes and operations[62]. Understanding how the human brain generates cognition depends on knowledge of large-scale brain organization[63]. It is known that the characteristics of the brain structural network are significantly correlated with intelligence[64]. A team lead by Professor Bullmore at the University of Cambridge[65] found that behavioral performance on a verbal fluency task was positively correlated with functional connectivities and with the topological characteristics of the functional network during rest. Specifically, better behavioral performance was positively correlated with greater functional connectivity strength and integration, higher small-world-like characteristics and clustering coefficiency, and a more hub-dominated degree of distribution during rest. The team found that this relationship also existed in patients with schizophrenia, among whom there was reduced clustering and small-world-like characteristics, a reduced probability of high-degree hubs, and increased robustness. Relatively intact global properties of network topology in the brain functional network were found in people with first-episode schizophrenia while performing a cognitive control task, but there were widespread abnormalities in the connectivities, particularly in cognitive control-related brain regions[66]. Using magnetoencephalography, this team also compared brain networks in people with schizophrenia and normal controls while performing a working memory task. The results indicated that working memory performance was positively correlated with the global cost efficiency of the beta-band network and with the cost efficiency of nodes in the left lateral, parietal and frontal areas in both groups[67].

5. Current situation of brainnetome study in China

Brainnetome is a field of study that was originally proposed by Chinese scientists and is gradually being accepted by more and more researchers. Chinese researchers have made important contributions in this area. Through several years of investigations, the team led by the first author of this review (Professor Jiang) progressed from study of the functional connection of areas of interest, to the study of functional connection analysis of brain sub-systems, and finally to the study of the functional connection modes of the whole brain and the characteristic analysis of brain networks. Through these studies they systemically established a new framework for data analysis of the brain functional network in the resting state and applied it to the study of multiple brain diseases, including schizophrenia[41-43,56,57]. Their models of the functioning of brain networks in various diseases established a methodological basis for completely and correctly understanding the mechanisms of information management in the brain and the changes in brain function that accompany disease conditions. There method of studying the brain structural network of normal subjects and neuropsychological patients by measuring cortical thickness using structural MRI and cortical reflection techniques resulted in the generation of important structural evidence for understanding the pathophysiological mechanisms of “connection loss” seen in people with Alzheimer’s disease[68]. Extension of this method for constructing brain anatomic networks using fiber tracing, successfully identified the weighted and non-weighted whole-brain anatomic network of young participants and verified the significant correlation between individual intelligence and brain network characteristics[64]. This research group also used these methods to study brain anatomic networks based on diffused MRI to compare the normal population to patient populations and found that the information transmission efficacy of the brain network in people with schizophrenia was significantly decreased and, moreover, was significantly correlated with clinical scores reflecting disease severity (that is, greater disease severity was related to lower information transmission efficacy) which provided new imaging evidence for schizophrenia research[58].

Domestic researchers in China have their own areas of specialization. For example, Yong He and colleagues in Beijing Normal University have a unique contribution to the study of brain structural networks based on morphological data from structural MRI. For the first time, this team established the brain structural network in a normal population using morphological data about

brain white matter from structural MRI images and applied these to the study of Alzheimer's disease[69] and multiple sclerosis[70]. The team led by De-zhong Yao from the institute of Electronic Science and Technology established a brain network using EEG techniques[71] and proposed the spatial fusion method of EEG and fMRI for researching brain networks[72-74].

Compared to foreign research teams, Chinese researchers take advantage of the large number of available subjects with different diseases. Combining the large samples makes it possible to adjust for the variability in findings caused by patient heterogeneity and long-term medication use, thus providing a clearer picture of the pathophysiological mechanisms of schizophrenia. Currently, with the support of China's 973 National Natural Science Foundation Key program, a consortium of 10 specialized centers in China is establishing a multiple-center imaging database of people with schizophrenia. On the basis of this collaboration, new methods and techniques of brainnetome research are being developed that will generate an improved brain map with clearer functional significance and more detailed anatomical classifications. It is hoped that this work will lead to important breakthroughs in the study of cognitive disorders in people with schizophrenia.

6. Prospects

The study of schizophrenia from the perspective of the brainnetome is just beginning. Despite exciting new findings in the brainnetome study of cognitive dysfunction in people with schizophrenia, there are many issues that remain unresolved. There is no clear answer to core scientific questions regarding which core brain regions and key abnormal connectivities are related to abnormal cognition in people with schizophrenia. Currently, knowledge about the brain mechanisms of cognitive disorders is mainly derived from functional imaging studies; there is very little understanding of the related anatomical networks. Brain anatomical networks are the basis of functional networks and provide anatomical constructs for functional interactions so it is essential to combine studies of anatomical and functional networks to fully explain the brain network mechanisms of cognitive disorders in schizophrenia. In summary, the brainnetome brings a new and exciting perspective to the study of psychological diseases that has the potential of increasing our understanding of the basic mechanisms that result in schizophrenia.

Funding

Supported by the National Key Basic Research Program of China (2011CB707800), the Young Program from the National Natural Science Foundation of China (30900487) and the Open Project of National Laboratory of Pattern Recognition.

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