Reverse Postulation for "Disruption of Brain Networks" Hypothesis of Schizophrenia

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To the Editor: In the previous two decades, increasing numbers of studies have used magnetic resonance imaging (MRI) techniques to investigate the brain characteristics of schizophrenia. These studies have produced important and useful achievements and enhanced our understanding of the mechanisms of schizophrenia from neural perspectives. We hope that in the future, researchers will discover additional milestone findings in this field to relieve the current bottleneck with respect to accurately determining the mechanisms of schizophrenia and identifying precise treatment targets for this disease, which is associated with high disability and mortality.

However, the current difficulty which we face is that brain alterations of schizophrenia found by MRI cannot be tested from the opposite direction; as a result, the "reversal postulation is unfounded."[1] For example, if I received treatment after being in a traffic accident that caused a fracture in my leg, a clinical expert would determine a recovery prognosis based on my clinical symptoms and signs, and a radiology expert could also assess my recovery based on the features of X-ray images obtained during follow-up. This relationship is bilateral and reciprocally supported. However, in schizophrenia, an MRI expert cannot determine a diagnosis based on brain features, and MRI features also cannot reciprocally support a clinical diagnosis. For example, if I was recovering from a cerebral hemorrhage, I believe that there might be an overlap between my disrupted brain structure and the altered brain networks found in schizophrenia but that I might manifest the psychotic symptoms of craniocerebral injury; remission of these psychotic symptoms may occur after treatment. However, MRI experts could not diagnose my recovery from this disease based on follow-up MRI examinations. Although this example is not completely accurate, it has potential significance.

With the objective of enhancing the strength of our evidence, we reviewed several papers published in high-quality psychiatry journals with a 5-year impact factor >8 points. A stark contrast we observed was that nearly one thousand studies focused on investigating various brain features of schizophrenia, ranging from local spontaneous neural activity to functional and structural connectivity and the topological features of brain functional and structural networks. However, few studies focused on brain features on MRI after treatment. A study by Crossley *et al*.[2] has indicated that there were no specific brain connectomic changes related to responses after antipsychotic treatment, while other reports have found that impairments in dorsal cortical attention networks can be alleviated using antipsychotics; gray matter volume increased in the left hippocampal region and the precuneus after repetitive transcranial magnetic stimulation; and cognitive remediation therapy can increase interhemispheric information transfer between the bilateral prefrontal cortices through the corpus callosum in schizophrenia patients. Given the inconsistent results and few studies for a systematic review and meta-analysis on brain network alterations after treatment to be carried out, it is important to strengthen summaries of this knowledge. We draw conclusions about alterations in brain structural and functional networks after treatment to investigate which network has been generally acknowledged with high accuracy and high repeatability.

Of course, we also read approximately 80 articles obtained from a search of the PubMed database. Similarly, extremely few studies focused on investigating alterations (repairs) in functional and structural features in the brain after treatment. Certain reports have indicated that the default mode network, frontal–temporal circuit, and/or other components of the brain might be targets of treatment. Unfortunately, inconsistent findings have been obtained.

The bottleneck associated with such research must be relieved in the upcoming years. The first key factor related to this bottleneck is that most of the aforementioned studies involved comparisons between two or more groups rather than comparisons at the individual level. Only at the individual level, we can observe individual alterations and establish precise treatment stages to detect the detailed mechanisms of treatment effects. Although many studies have focused on individual investigations, most of these studies primarily sought to investigate disease-related individual brain features, with the objective of establishing classifiers to enhance disease

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Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.235871

Received: 11-03-2018 **Edited by:** Yuan-Yuan Ji
How to cite this article: Guo XY, Li S, Tian HJ, Li J, Zhuo CJ. Reverse Postulation for "Disruption of Brain Networks" Hypothesis of Schizophrenia. Chin Med J 2018;131:1748-9.

diagnosis. At present, due to limitations imposed by the barrel of available techniques or other factors, few studies have sought to investigate brain alterations after treatment. In the future, with the development of machine learning or deep learning techniques, technical problems may be solved, which may help advance research at the individual level.

Another key factor of the aforementioned bottleneck is the lack of large-sample, long-term follow-up studies that dynamically characterize the trajectory of structural and functional alterations in the brain. Thus, a large-sample, long-term follow-up investigation should be conducted in which first-episode schizophrenia patients are enrolled, and MRI and clinical data are acquired at several time points, such as the treatment inflection point and the final treatment outcome point (at 3 years). Such a study could fully characterize the trajectory of brain alterations that accompany treatment at the individual level, which could help us more deeply understand the neural mechanisms of schizophrenia and develop "clear" antipsychotics to treat this disorder.[3]

Financial support and sponsorship

This work was supported by grants from the Key Project of Science Fund of Tianjin Science Committee (No. 17JCZDJC35700) and the Key Project of Tianjin Health Bureau (No. 2014KR02).

Conflicts of interest

There are no conflicts of interest.

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