•REVIEW•

Research Progress in Biological Studies of Schizophrenia in China in 2017

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Summary: Schizophrenia is a severe mental disorder and its etiology and pathological mechanism are unknown. This article mainly introduces the progress of biological studies of schizophrenia in China in 2017, including neuroimaging, genetics, and immunology studies. It also introduces the research progress of high-risk psychotic syndrome and physiotherapy.

Key words: schizophrenia; biological psychiatry, China

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1. Introduction

Schizophrenia is a chronic brain disease and its etiology and pathomechanism are not clear. There is a tremendous amount of research domestically and internationally conducted on the brain structure, brain function, and genetics of schizophrenia. Brain imagining studies have found that there are brain structure, function, and network abnormalities in schizophrenia.[1-5] Genome-wide association studies (GWAS) have unveiled some new risk genes loci,[6] and domestic scholars found that the Han Chinese population has some unique susceptible genes loci.[7] This article introduces Chinese research progress in brain imaging, genetics, and immunology of schizophrenia in 2017 and briefly introduces the research progress of high-risk psychosis syndrome and physiotherapy.

2. Brain imaging studies of schizophrenia

The application of neuroimaging technology in the study of schizophrenia was the most active research field in 2017. The major research teams in the country conducted a series of studies on schizophrenia. The specific research methods included: a) resting-state functional magnetic resonance imaging (rs-fMRI) and functional connectivity based on resting state, b) diffusion tensor imaging (DTI), and c) imaging genetics studies.

2.1 Resting fMRI studies

Resting-state fMRI studies require participants to lie quietly in the scanner and test their brain neural activity and its functional status by measuring the low-frequency fluctuations of the blood oxygen level dependent (BOLD) signal.[4] Li and colleagues conducted a comparative study on deficit schizophrenia (DS) (predominantly negative symptoms) and non-deficit schizophrenia (NDS). The results showed that there were abnormal spontaneous brain activities in the right fusiform gyrus, bilateral posterior lobe of cerebellum, and bilateral putamen in both types of patients. Among them the amplitude of low frequency fluctuation (ALFF) of the right insular lobe of the DS patients was

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significantly increased and was positively correlated to the S2-P50 amplitude of sensory gating P50. The ALFF of the middle temporal gyrus of the NDS patients was significantly reduced and was negatively related to the P3b latency of P300. As a result, the researchers suggested that the right insular lobe in DS and the right temporal gyrus in NDS might be correlated with the spatial information processing deficit in patients with schizophrenia.[8] Guo and colleagues innovatively combined the family-based case-control design and the traditional case-control design for study. It was found that, compared the healthy controls, there was an increase of fractional amplitude of low frequency fluctuation (fALFF) in the left posterior cingulate cortex/ precuneus of the patients with schizophrenia and their unaffected siblings. In patients with first-episode schizophrenia, the homotopic connectivity of the motor and low level sensory processing areas (including the precuneus) decreased compared with the family-based controls.[9-10]

Jingping Zhao and colleagues conducted a series of studies on patients with adolescent onset schizophrenia (AOS) and found that there was an increase of functional connectivity strength (FCS) in the left cerebellum VI and right inferior frontal gyrus / insular lobe of the first-episode, drug-naive AOS patients. There was a positive correlation between the FCS values in the right inferior frontal gyrus/ insular lobe and PANSS general psychopathology score.[11] It was concurrently found that the interaction of the bilateral cerebral hemispheric sensorimotor network of the AOS patients weakened. The result resembled the defect pattern of the patients with adult onset schizophrenia.[12] This research team further analyzed the long and short range functional connectivity of the whole brain. The results showed that the default mode network (DMN) and salience network (SN) of the AOS patients had long and short range functional connectivity abnormalities, supporting the possibility of correlation between the anomalous anatomical distance and abnormal functional connectivity of brain networks.[13] Furthermore, the research team found that there were regional connectivity abnormalities in the bilateral superior medial prefrontal lobe, left superior temporal gyrus(STG), left paracentral lobule, right precentral lobule, and right inferior parietal lobe of the AOS patients by utilizing the regional homogeneity (ReHo) analysis, proposing to use the combination of ReHo values in the medial prefrontal lobe, left superior temporal gyrus, and right inferior parietal lobe as biomarkers (sensitivity of 88.24%, specificity of 91.89% and accuracy of 90.14%) for AOS patients.[14] The above mentioned studies suggested that there were brain function and functional connectivity abnormalities in AOS patients, supporting the hypothesis of neurodevelopmental abnormalities in schizophrenia.

Antipsychotic medication is the major treatment for schizophrenia. Nevertheless, the effect of the medication on brain function and functional connectivity of the patients with schizophrenia is still unclear. Li and colleagues found that there was improvement in the left superior temporal gyrus function and enhancement of the functional connectivity from the left STG to the dorsalateral prefrontal cortex(DLPFC) in patients with first-episode schizophrenia(FES) after taking atypical antipsychotic drugs (olanzapine, clozapine, aripiprazole, risperidone, quetiapine, or amisulpride) for a year and these changes were correlated with the improvement of negative symptoms.[15] Guo and colleagues found that the sensorimotor circuits functional connectivity of the untreated patients with reccurent schizophrenia increased after 6 weeks of olanzapine treatment, the DMN functional connectivity enhanced after 6 months of treatment, and the functional connectivity of the left STG decreased after 6 months of treatment. In addition, olanzapine can modulate the long and short range functional connectivity and homotopic connectivity of patients with schizophrenia.[16-17] Feng Chen and colleagues found that after receiving 3 months of second generation antipsychotic drug treatment, the ALFF of the bilateral cuneate of the untreated FES increased and the ALFF of the left anterior cingulate gyrus decreased.[18]

2.2 Diffusion tensor imaging (DTI) studies

Diffusion tensor imaging utilizes diffusion-weighted pulse sequences to determine the diffusion tensor of water molecules so as to show the trend of nerve conduction bundle in the white matter, determining the degree of damage and scope of the white matter fiber bundle and constructing the structural networks using DTI data.[19] In recent years, brain connectomics showed that there were densly interconnected nodes in the brain, using analysis methods such as graph theory. These nodes were connected to form the central rich-club organization. There were scholars in early years that suggested that rich-club was composed of the bilateral frontoparietal lobe, including the precuneus, superior frontal lobe, and cortex of superior parietal lobe, and the subcortical region, including the hippocampus, the thalamus, and the putamen. These brain regions were not only the central regions of the brain, but also closely interconnected. Rich-club plays a central role in the global communication, its damage impaired global efficiency is 3 times more than random damage within the network.[20] Studies have found that rich-club connectivity density declined when there was damage of the rich-club organization in patients with schizophrenia and this change was correlated with the diminished function of the whole brain in patients.[21] Rich-club connectivity of the patients with schizophrenia and their unaffected siblings declined (unaffected siblings reduced by 7.9% relative to controls, patients reduced by 19.6% compared to controls), suggesting that damage of the rich-club connectivity might be related to genetic susceptibility to schizophrenia.[22]

Domestic scholars have done relevant research in this area. Zhao and colleagues performed DTI scans to patients with schizophrenia, unaffected parents and normal controls. It was found that feeder edges

between the rich-club nodes and non-rich-club nodes were significantly decreased in patients with schizophrenia and their unaffected parents compared with the controls. Moreover, there was a positive correlation between the feeder edges and the score on the Category Fluency Test. The results supported that rich-club defects might be associated with schizophrenia susceptibility.[23]

Some scholars use DTI to examine the correlation between white matter abnormalities and cognitive deficits in patients with schizophrenia. Zhao and colleagues found that the left forceps major,inferior longitudinal fasciculus(ILF), inferior fronto-occipital fasciculus,left splenium of corpus callosum and left ILF white matter damage of the untreated patients with first-episode schizophrenia were correlated with facial emotion perception defects.[24] Jingjing Yao and colleagues found that drug-free FES had defects in the recognition of positive and negative emotions and emotion perception defect was correlated with the prefrontal lobe white matter fiber damage. [25] Yanhon Xia and colleagues also found correlation between the reduction of the FA values in the corpus callosum body, cingulum bundle, and upper left corona radiate and the cognitive function damage in research of first-episode AOS patients.[26]

2.3 Imaging genetics studies

Imaging genetics studies combine genetics and brain imaging techniques, exploring the effects of genetic mutation on brain structure, function, and behavior. A large number of imaging genetics studies have found that genetic mutation has an impact on the brain structure of schizophrenia, including gray matter volume (ACNA1C, NRGN, TCF4, and ZNF804A), ventricle volume (TCF4), cerebral cortex folds (NCAN) and thickness (ZNF804A), white matter integrity (ANK3 and ZNF804A), white matter volume (CACNA1C and ZNF804A), white matter density (ZNF804A), and so forth.[27] Some other studies have found association between schizophrenia risk genes and functional connectivity abnormalities such as the dorsal prefrontal cortex-hippocampus, prefronta - parietal, intrinsic prefrontal cortex, anterior cingulate gyrus-dorsolateral prefrontal lobe, hippocampus-parietalcortex, ventrolateral prefrontal cortex-hippocampus and amygdala-anterior cingulate cortex/ medial prefrontal cortex connectivity in the task state, and the intrinsic DMN connectivity in the resting state.[28] Jing Li and colleagues found that the polymorphism of CSMD1 rs17405197 was significantly associated with gray matter volume in the pars triangularis of right inferior frontal gyrus and verbal fluency test(VFT) scores in patients with schizophrenia, suggesting that VFT impairment in patients with schizophrenia might be associated with the impact of gene GSMD1 rs17405197 polymorphism on the patient's brain gray matter volume.[29] Zheng and colleagues found that Glu504Lys mutation of the schizophrenia susceptibility gene (ALDH2) was associated with schizophrenia and correlated with the hippocampus-prefrontal functional connectivity abnormalities.[30]

3. Genetic studies of schizophrenia

Schizophrenia is known as a disease with genetic predisposition and high heritability. Zhiqiang Li and colleagues carried out a schizophrenia genome-wide association analysis (GWAS) and conducted a transancestry meta-analysis combining the latest data from the Psychiatric Genome Wide Association Study Consortium (PGC2). The results showed that schizophrenic risk alleles with significant difference demonstrated consistency in the direction between different races. The transancestry meta-analysis found that there were 113 GWAS loci, of which 30 loci were newly discovered and 4 loci (rs2073499, rs7757969, rs4479915, and rs11534004) existed only in the Chinese sample. In addition, there was a significant genetic correlation between schizophrenia and major depressive disorder in the Chinese population (rg= 0.43, p= 5.87 x 10^{-8}).[7]

Many scholars have carried out cross-race analysis. Weihua Yue and colleagues performed meta-analysis on the GWAS in the Han population and found that MIR137, ZNF804A, VRK2, and AS3MT were schizophrenia susceptibility genes shared by European and East Asian populations.[31] Li and colleagues performed meta-analysis on the rs10503253 gene locus of the schizophrenia risk gene CSMD1 in the European population and found that rs10503253-A allele was also associated with schizophrenia in the Asian population (p=0.0093, OR= 1.062, 95% confidence interval= 1.015-1.111).[32] Wang and colleagues conducted a study on the schizophrenia risk gene NDST3 in the Caucasian population. However, the results did not show correlation between the gene and schizophrenia in the Han population.[33]

Furthermore, some scholars in China have studied genes of cytochrome oxidase and complement factor and found that the CYP2D6 gene, CYP1A2 gene, and CFH gene were not associated with schizophrenia susceptibility.[34-36] Due to the reduction of risk of cancer in patients with schizophrenia, researchers have explored the correlation between tumor suppressor genes and schizophrenia and found that the interaction between TXNIP and AF1q gene polymorphisms (TXNIP-rs2236566, TXNIP-rs7211, and AF1q-rs2769605) was associated with schizophrenia susceptibility.[37]

4. Immunological studies of schizophrenia

The inflammatory hypothesis of schizophrenia has attracted wide attention in recent years. Cytokine studies found that the schizophrenia pathomechanism was correlated with the IL-6,TNF-α,INF-γ, IL-2, IL-8, IL-1RA, IL-1β, IL-18, and IL-10 cytokine levels of

schizophrenia, TNF-α rs1800629, IL-6 rs1800795, IL-1β rs16944 gene polymorphisms, and IL-6, TNFR1, TNFR2, IL-1βmRNAs expressions.[37] Zhang and colleagues found abnormalities in hsCRP and IL-10 levels and hsCRP/IL-10, and suggested hsCRP/IL-10 to serve as the biomarker of schizophrenia (p-value= 0.783, $p< 0.01$; sensitivity= 85.4%; accuracy= 67.5%).[39] Yayan Luo and colleagues found that the IL-2 level of the patients with chronic schizophrenia was higher than healthy controls.[40]

The meta-analysis by Müller and colleagues showed that the levels of IL-6, IFN- γ and TNF-α of the first-episode untreated patients and patients with acute relapse elevated; the levels of IL-6, IL-1 β, and IFN-γ of the patients who took medication regularly reduced,and the IL-12 and soluble IL-2 receptor levels elevated;[41] the results revealed that antipsychotics might affect the immune function of the patients. Lin and colleagues found that the baseline MCP-1 level of the first-episode untreated patients increased and the level of MCP-1 before treatment was significantly negatively correlated with the reduction of general psychopathology score in the PANSS scale after 4 weeks of risperidone monotherapy. The authors suggest that the serum MCP-1 level before treatment was the biomarker for risperidone efficacy prediction.[42]

5. Other important progress

'Clinical high risk' (CHR)for psychosis or 'psychosis risk syndrome' is one of the hot research topics in recent years. The Shanghai at risk for Psychosis project (SHARP) for the first time reported the research progress of the population at high risk of psychosis in mainland China and proposed that approximately 5% of the patients in the first consultation of psychological counseling met the diagnostic criteria for high-risk psychiatric syndrome. The 2-year conversion rate of psychosis in the high-risk group was 29.1% in the follow-ups. The average time was about 4 months from attenuated symptom onset to seeking professional help and 12 months from symptom onset to fully psychotic transformation.[43-44] The duration of untreated prodromal symptoms (DUPrS) had an important impact on the clinical outcome of the high-risk population. DUPrS shorter than 2 months or longer than 6 months exibits a lower risk for conversion to psychosis. At the same time, it was found that the demographics and clinical and functional characteristics of the high risk group of psychosis were associated with longer DUPrS.[45] The team especially studied the changes in cognitive function (basic cognition and social cognition) in the process of transforming from the high-risk group to mental illness. The results showed that the association of neurocognition and theory of mind (ToM) were stronger in the converters group, revealing that the link between neurocognition and social cognition might be enhanced as the disease progressed (especially for individuals who convert to psychosis quickly).[46] Furthermore, it was found that individuals at ultra-high risk for psychosis exibit limited eye movement pattern in free visual exploration compared with healthy people. However, further studies are needed to examine the underlying pathophysiological mechanism.[47]

In the American Psychiatric Association Annual Meeting in 2016, a study showed that electroconvulsive therapy (ECT) was still an important treatment for schizophrenia, with the total effective rate up to 76.7%. However, it has adverse effect on the cognitive function of some patients.[48] Huang and colleagues explored the impact of various treatment methods (antipsychotics treatment group, antipsychotics treatment+MECT group) on the global functional connectivity density (gFCD). The results indicated that the gFCD of the dorsomedial prefrontal cortex, the ventromedial prefrontal cortex, and the left anterior precuneus increased only in the antipsychotics +MECT treatment group, suggesting MECT might play a therapeutic role by enhancing the functional connectivity strength in the default mode network.[49]

6. Conclusion and prospect

For the past 100 years, scholars in China and abroad have shifted their understanding of schizophrenia from from a "functional disease" to a "chronic brain disease" and attempted to apply different research techniques and methods to explore the organic brain basis of schizophrenia. Unfortunately, the current understanding of schizophrenia remains on a basis of phenomenology. The application of genetic technology in the study of schizophrenia is an important research direction for schizophrenia, especially GWAS research which has found more schizophrenia susceptibility loci in recent years. Nevertheless, there rarely are genetic loci that can be repeatedly verified and confirmed. In addition, genetics research has hit bottlenecks as well in need for support of a huge sample size and more research funding. In the past 30 years, neuroimaging technology (including imaging technology and data analysis technology) has entered a stage of rapid development and has been an important weapon for us to understand the normal physiological functions and pathological phenomena of the brain. Studies found that there were abnormalities in the brain structure and function in schizophrenia; revealed abnormal changes in the brain network properties of schizophrenia and the decline of information processing ability regardless of brain structure network or brain function network; supported schizophrenia was a kind of brain disease.

Domestic scholars stand at the front of the world and have carried out a series of studies on the biological factors of schizophrenia. The human brain, however, is an efficient and complex system. The etiology of schizophrenia is complicated and requires multidisciplinary and multi-level research. Brain imaging is still an important development direction for schizophrenia in the future. However, the shortcomings and limitations of brain imaging technology should be fully understood. For instance, MRI morphological

data can only get a brain structure network based on the population and cannot establish individual brain structure network for a single subject. Brain network research is based on large scale which is the brain level. However, brain network research based on microscale (neuron level) or voxel level requires longer imaging time and more complex image analysis techniques. Brain network describes a correlation rather than a causal relationship or an effective connection. Imaging genetics studies can combine brain imaging with genetic information for analysis. On the one hand, it can reduce the sample size needed for genetic research. On the other hand, it can reveal the genetic basis of both the structural and functional abnormalities in the brain of schizophrenia. In the end, the heterogeneity issue of schizophrenia should be adequately understood. The method of sample collection and purification is a crucial and fundamental issue. Traditional classifications (such as paranoid type, hebephrenic type, catatonic type, and simple type) have apparently failed to meet the needs of scientific research. Further observation is needed to determine whether the dimension assessment brought up by the DSM-5 and ICD-11 can improve the quality of research.

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Conflict of interest statement

The authors declare no conflict of interest related to this manuscript.

Authors' contributions

Dengtang Liu and Haixin Cen were responsible for the literature search, drafting, and revising the main contents of the paper.

Yifeng Xu, Kaida Jiang, and Dengtang Liu took part in the selection of the thesis and made core revisions according to the requirements of the editorial department, and made the final agreement on publishing the article.

2017 年中国精神分裂症生物学研究进展

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概述：精神分裂症是一种严重的精神疾病，其病因及病理机制未明。本文主要介绍了 2017 年中国精神分裂症的生物学研究进展，包括神经影像学、遗传学及免疫学等方面研究，同时介绍了精神病高危综合征及物理治疗研究进展。

关键词：精神分裂症；生物精神病学；中国

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