

Research Status and Strategies for Cognitive Function in Schizophrenia

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Cognition is divided into neurocognition and social cognition, both of which are interconnected with each other and yet are mutually independent. Neurocognition, which is based on neuroanatomical structures, function connections, neuroelectrophysiology and molecular biology, is the basis of the human brain and the reflection of advanced integrative neural function in behavioral science. Social cognition is the cognitive process of perceiving others' emotions or intentions and making responses. It took almost a century from 1893 when Kraepelin first described the cognitive impairment of schizophrenia as "Dementia praecox" to the last two decades when the research on cognition recaptured people's attention. It is commonly accepted that cognitive impairment is one of the symptoms of schizophrenia that is characterized by cognitive impairment in learning, memory, attention, speed of information processing, executive function and social cognition, and the severity of cognitive impairment in schizophrenia is often worse than that of healthy controls.^[1] Studies found that neurocognition had an impact on the variance of functional outcome in schizophrenia patients with an effect size of 20%-60%.^[2] According to a meta-analysis, 8 out of 9 studies showed that social cognition was also related to the functional outcome in schizophrenia patients.^[3] Although the research on cognitive impairment of schizophrenia has made great progress in recent years, there are still many deficiencies to be solved, including a lack of depth and undesirable results that we need to work together to solve.

Studies have revealed that patients with schizophrenia experienced structural changes in the brain such as the decrease of whole brain volume, whole brain gray matter, prefrontal cortex, white matter volume, parietal white matter and temporal lobe white matter, and the increase of the third ventricle

volume;^[4-5] moreover, compared with healthy controls, the patients showed abnormal function connections in the brain with decreased activation in some brain areas, including the right prefrontal cortex, right middle frontal gyrus, frontal gyrus, superior frontal gyrus, left anterior cingulate gyrus, right parietal cortex, right putamen and right thalamus.^[6] In addition to the abnormalities of activation and connections in a single nucleus, there were abnormal connections within or between the networks (default mode network, DMN; dorsal attention network, DAN; salience network, SN; executive control network, ECN) in patients with schizophrenia. The neurotransmitters involved in schizophrenia mainly include choline, dopamine, glutamic acid and γ -aminobutyric acid, on which many researchers currently focus.^[7] However, current research on the pathogenesis of schizophrenia shows some disadvantages such as limitations and lack of specificity, also studies fail to reveal the brain connection loops and signal transduction pathways underlying the symptoms of schizophrenia, including hallucinations, delusions, looseness of thought, all of which require more systematic and in-depth investigations.

There are a number of tools that have been developed to assess the cognitive function of schizophrenia. They differ in length, operability, test-retest reliability, fields of assessment, and sensitivity to treatment. In earlier studies, some scholars used the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (WMS) to evaluate cognitive function for patients. The MATRICS Consensus Cognitive Battery (MCCB) is the most classical and globally recognized cognitive test^[8] that has been translated into dozens of languages and has been established as a norm in many countries. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), the Brief Assessment of Cognition in Schizophrenia

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(BACS), and the Brief Cognitive Assessment (BCA) were three of the widely-used short cognitive tests^[9-11], which are all objective cognitive tests based on operation. Schizophrenia Cognition Rating Scale (SCoRS) is an interview-based assessment tool whose information sources are from patients, inside informants and assessors.^[12] As regards social cognition, the tools related to Theory of Mind (TOM) were the most common assessment tools, including false belief test, lie test, story test, gaffe test, suggestive test, social speculation, cognitive test and eye emotional task. With respect to the assessment tools used for cognitive function, the existing measurement tools focus on the assessment of the whole or several major cognitive dimensions, and are not accurate enough when evaluating the process of some specific cognition such as registering, consolidating and extracting the information in the process of memory, whereas the assessment of cognitive process generating paranoia in schizophrenia is hardly mentioned. Consequently, these deficiencies need to be taken into account in future studies.

As for the antipsychotic medications for cognitive improvement, a study by CATIE showed that the effect value of overall efficacy was between 0.12 and 0.26, showing no difference between the first and second generation antipsychotics.^[13] Studies suggested that first and second generation antipsychotics improved cognition with a standard deviation between 0.32 and 0.69.^[14] These studies argued that the first generation antipsychotics had a detrimental effect on cognitive function, which subverted the traditional notions.^[15] Meanwhile, along with the progress on other therapies, relevant studies indicated that repetitive transcranial magnetic stimulation (rTMS) could promote cognitive function, especially in the area of working memory,^[16] and cognitive improvement training was also good for cognition with the value of overall effect at 0.45.^[17] Aerobic exercise and yoga training also had definite improvements on attention and working memory.^[18] Newly developed cognitive enhancers such as $\alpha 7$ -nicotinic cholinergic receptor agonists, glycine-converting enzyme inhibitors, cholinesterase inhibitors, and dopamine-1 agonists, were still under development, whereas the roles of these drugs in improving cognitive function were inconclusive.^[19] For example, in a phase II clinical trial evaluating the efficacy and safety of ABT-126 ($\alpha 7$ -nicotinic receptor partial agonist),^[20] the researchers, using a double-blind, parallel-controlled trial, divided patients from 22 centers into three groups (the low-dose group treated with ABT-126 10 mg/d, the high-dose group treated with ABT-126 25 mg/d and the control group treated with placebo), who were

treated for 12 weeks and then were assessed by MCCB at baseline and 12th week, respectively. The results indicated that the final MCCB score of non-smoking subjects in the low-dose group that was compared with the control group was 2.9, the MCCB score of the high-dose group was 5.2, whereas there were no differences in smoking subjects. Meanwhile, it was also observed that subjects receiving treatment with ABT-126 25 mg/d in non-smokers had significant improvements in speech learning, working memory and attention/alertness compared with the control group. The MCCB scores of other drugs such as AL-108, Armodafinil, MK0777 and Pregnenolone showed no significant differences between the drug-treated group and the control group. Although a large number of studies had shown that both drugs and physical or psychological behavioral therapies were effective in improving the cognitive impairment of schizophrenia to some extent, these therapies lacked sufficient data support to the improvements of long-term cognitive function, social function, as well as long-term life satisfaction in the future. Moreover, studies on the efficacy of these therapies for different clinical types of patients were relatively deficient.

Our subsequent research should focus on the long-term follow-up of treated patients with schizophrenia, comprehensively evaluate the overall improvement of social life that the treatments exert on patients, and compare the therapeutic efficacy of the treatments by classifying the patients according to different clinical types, providing theoretical basis for more accurate clinical treatments. In addition, new therapies such as transcranial direct current stimulation (tDCS), virtual reality (VR) and minocycline, which are used to improve cognitive function in schizophrenia, need to be explored. Thus, these improvements will help patients return to society and will improve their life satisfaction.

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

Authors' contributions

Ke Ma: literature search and manuscript writing

Chuan Shi: paper drafting, draft revision, related content supplement, editorial revisions.

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