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•Review•

Research progress in China on the assessment of cognitive function in schizophrenia

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Summary: Cognitive impairment – one of the core symptoms of schizophrenia – has become a focus of research about schizophrenia in China and elsewhere. The main reason for the interest in cognitive functioning is that the degree of cognitive impairment is associated both with the current severity of the illness and with the prognosis of the illness; cognitive functioning directly affects individuals' ability to live independently and their occupational and social functioning. The first study on cognitive function in schizophrenia in China was conducted in the late 1970s; more recently there has been a resurgence of interest in the area because of new information that has emerged as neuroimaging technologies have improved. The current review summarizes studies on cognitive impairment in schizophrenia conducted in China and proposes directions for future research in this area.

1. Major cognitive impairments in individuals with schizophrenia

Kraepelin and Bleuler were the pioneers of studying cognitive impairment in schizophrenia. Kraepelin labeled schizophrenia 'dementia praecox' and described the three main characteristics of the disorder: early onset (in adolescence or young adulthood), chronic course of illness, and declining social functioning.[1-3] Although the positive symptoms of schizophrenia have been the focus of psychiatrists since the emergence of antipsychotic drugs in the 1950s, cognitive impairment in schizophrenia regained attention in the international scientific community in the 1990s.[2,4] In China, research on the cognitive functioning of patients with schizophrenia started in 1978, when Gong[5] reported impaired short-term memory among patients with schizophrenia using the free recall paradigm. In the same year, Zhu and colleagues[6] reported that ventricular expansion in patients with schizophrenia was significantly correlated with cognitive impairment. Since then, many studies about cognitive function in schizophrenia have emerged in China, most of which have focused on attention, learning and memory, working memory, executive functioning and social cognition.

1.1 Attention

Attention is the cognitive process that involves the selective focusing of awareness and processing of information. Several studies in China highlight a familial (i.e., genetic) relationship between attention deficits and schizophrenia. Liu and colleagues[7] found deficits in active attention (assessed using the backward masking test) among healthy siblings of individuals with schizophrenia that were intermediate between the deficits identified in individuals with schizophrenia and those in community members without siblings with schizophrenia. Similarly, studies using the Continuous Performance Test found decrements in sustained attention in the siblings and parents of individuals with schizophrenia that were intermediate in severity between those of individuals with schizophrenia and those of community members without first degree relatives with schizophrenia.[8,9] Other research has found that the severity of the attention deficit in schizophrenia is not related to executive functioning, disease classification, or to the positive, negative or general pathology scores of the Positive and Negative Syndrome Scale (PANSS).[10,11]

Researchers who use the physical line bisection test report that left-sided attentional bias is observed in individuals with schizophrenia, suggesting dysfunction in the left hemisphere that results in impairment in their dextral spatial attention.[12,13] Our group has conducted a series of studies[14-18] about the mechanism underlying attention deficit using inhibition of return (testing visual attention with visual stimuli) and P50 sensory gating (testing auditory attention with auditory stimuli). We have found that (a) inhibition of return in individuals

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in their first episode of schizophrenia was better than that in individuals with chronic schizophrenia (who had delayed inhibition of return); and (b) individuals with first-episode schizophrenia and those with chronic schizophrenia had deficiencies in P50 sensory gating that were of comparable magnitude. Thus, attention deficit in individuals with schizophrenia may be related to impaired inhibition and the deficit in visual attention in these individuals may be unrelated to the deficit in auditory attention.

1.2 Learning and memory

Learning is the process of obtaining new information that is then stored in memory. Learning and memory are interrelated, but most research in individuals with schizophrenia in China has focused on memory rather than on learning. Several studies have shown that immediate memory, short-term memory and long-term memory are all impaired in individuals with schizophrenia.[5,19-21] Most of the studies focus on long-term memory which is either classified as explicit versus implicit memory (based on the degree of consciousness of the memory) or as episodic, emotional or semantic memory (based on the content of the memory). Explicit memory is more severely affected in schizophrenia than implicit memory. Explicit memory is associated with the negative (not positive) symptoms of schizophrenia while implicit memory is independent of both negative and positive symptoms.[22-24]

The impairment of episodic memory in individuals with schizophrenia can have a variety of manifestations. Previous studies have shown that source memory, item memory and emotional memory are all impaired in patients with schizophrenia.[25-27] Another type of episodic memory, prospective memory – which allows individuals to remember to perform a planned action or intention at the appropriate time – is also severely impaired among individuals with schizophrenia.[28-33] The degree of impairment in prospective memory can be an important indicator of the prognosis of schizophrenia because remembering follow-up appointments, the time and dose of medication, work schedules, and so forth is beneficial for recovery.

1.3 Working memory

Working memory, which is similar to but distinct from short-term memory, consists of a central executive system and two subsystems – the visuospatial sketch pad and the phonological loop. Working memory is a platform for the storage and executive control of information used to direct activities and other advanced cognitive functions such as learning, understanding and reasoning. Working memory can be categorized as verbal working memory or visuospatial working memory.[34]

Using digit span performance and space span perfor-mance, Wang and colleagues[35] found that there were impairments in verbal and visuospatial working memory in individuals with schizophrenia both before and after the age of 45. To evaluate patients' information storage capacity, the revised Sternberg item recognition task has been widely used in China; the results of these studies suggest that the capacity for storing spatial information and information of objects is decreased in individuals with schizophrenia[36,37] while their capacity for storing language-coded information still remains normal.[38,39] However, using the alphabet edition and digital edition of the n-back task, Chinese researchers found that executive control of language-coded information used to direct activities is decreased in individuals with schizophrenia.[40,41]

1.4 Executive function

Executive function is the self-monitoring and self-control of consciousness and behavior. It includes self-regulation, cognitive flexibility, planning, reaction inhibition, and so forth. Due to the complexity of executive function, there is no standard evaluation tool for it. The evaluation tools commonly used in China are the Wisconsin Card Sorting Test (WCST), the Stroop color words test and the Tower of London task. WCST, the most commonly used test in China for executive function, is considered a measure of prefrontal functions.

Significant impairments in executive function have been found in individuals with first-episode schizophrenia and in those with chronic schizophrenia, both when taking antipsychotic medication and when not taking medication.[10,42-44] Furthermore, parents and siblings of individuals with schizophrenia have also been found to have impairments in executive function.[44,45] Results of the Stroop color words test and the Tower of London task indicated impaired conflict suppression and problem solving in individuals with schizophrenia.[46-48]

Other researchers have assessed the relationship between psychiatric symptoms and executive functioning. Zhao and colleagues[49] compared the WCST results of individuals with schizophrenia who do and do not experienced auditory hallucinations; they found no significant difference except in the number of WCST categories completed (i.e., the CC index). Two studies explored the relationship of homicidal or aggressive behaviors and executive function: Wang[50] found that individuals with schizophrenia who had homicidal behaviors did worse in abstract conceptualization than those without homicidal behaviors; and Wang[51] found that among males with schizophrenia those with a history of aggressive behavior had worse executive function than those without a history of aggressive behavior.

1.5 Social cognition

Social cognition is an advanced cognitive process which involves many components that help inform an individual's social actions: interpreting facial expressions, understanding psychological states and personalities, interpreting gestures and facial expressions, evaluating

behaviors in social interactions and comprehending the characteristics of interpersonal relationships. Studies conducted by researchers in other countries show that individuals with schizophrenia have impairments in social cognition. Chinese researchers are just starting to pay attention to this topic. Zhu and colleagues[52] explored social cue recognition in individuals with schizophrenia using the eye gaze discrimination task, eye basic emotion discrimination task and faux pas recognition task; they found that individuals with schizophrenia had impairments in social cue recognition, some of which led to impairments in their social functioning. Using the Chinese facial emotion test, Xia and colleagues[53] found that individuals with schizophrenia had pervasive impairments in facial emotion recognition which were associated with their deficits in executive function.

2. Factors associated with cognitive function in schizophrenia

2.1 Age

Generally speaking, cognitive function improves as children develop and reaches a peak during early adulthood, after which it declines. It is still uncertain whether or not cognitive function in individuals with schizophrenia declines with age more quickly than in the general population. Most studies in China find that the cognitive function of elderly individuals is more impaired in persons with schizophrenia than in age-matched controls.[54-56] Several follow-up studies and a study comparing elderly individuals with schizophrenia to those with Alzheimer's disease found that the pattern of cognitive decline with age in schizophrenia started at a somewhat earlier age and was, unlike the decline in Alzheimer's disease, largely limited to the types of cognitive functions that had been most affected by their schizophrenic illness at an earlier age.[57-59]

2.2 Course of the disorder

There is much debate about whether or not the course of schizophrenia affects individuals' cognitive function and, if it is related, how the trajectory of the illness is related to changes in cognitive function. In some long-term follow-up studies, individuals with schizophrenia were found to suffer from aggravated cognitive impairments (particularly in immediate memory and language function) if they had more frequent acute episodes of illness, a relationship that was more evident among individuals with an earlier age of onset of schizophrenia.[60-63] In contrast, other studies have reported that the cognitive function of individuals with schizophrenia is not affected by the course of the disorder.[64,65]

2.3 Psychiatric symptoms

Most studies concur that cognitive impairment in individuals with schizophrenia is associated with psychiatric symptoms, especially negative symptoms.[47,48,66-68] Niu and colleagues[69] followed a group of individuals with first-episode schizophrenia for three years and found that at the end of the first and second years of treatment patients' cognitive impairment was strongly associated with the severity of both positive and negative symptoms; even at the end of the third year of treatment most of their cognitive function indicators were still related to some of the positive and negative symptoms. Their findings support the association between cognitive impairments and psychiatric symptoms in schizophrenia.

2.4 Other factors

Shang and colleagues[70] reported that cognitive function was less impaired in males with schizophrenia than in their female counterparts. However, later studies failed to confirm this gender effect.[71,72] Other investigators have reported that hospitalization,[73,74] the metabolic syndrome, diabetes,[75-78] tardive dyskinesia[79,80] and smoking[81,82] may also affect cognitive function in persons with schizophrenia.

3. Biological basis of cognitive impairment in individuals with schizophrenia

3.1 Neurotransmitter and genetic research

Cognitive impairment in individuals with schizophrenia is associated with abnormalities of neurotransmitters, for instance the dysfunction of the serotonin system, degeneration of Y-gaba neurons, norepinephrine deficiency, hyperfunction of the dopamine system and hypofunction of excitatory amino acids.[83] In addition, oxidative stress,[84, 85] interleukin[86] and 4-hydroxy-3-methoxyphenylacetic[87] have also been associated with the cognitive impairment of individuals with schizophrenia.

In recent years genetic studies have identified some genotypes that are correlated with cognitive function in individuals with schizophrenia, including dopamine genes, 5-HT genes, apolipoprotein E (ApoE), brain derived neurotrophic factor (BDNF) genes, and so forth.[88-93] One study[94] found that the severity of the cognitive impairment in individuals with schizophrenia and in their relatives increased as the degree of genetic loading increased, suggesting that cognitive impairment could be a potential endophenotype to detect generic vulnerability to schizophrenia.[94] However, none of these findings were successfully replicated in different populations, so further studies are needed.

3.2 Electrophysiological and eye movement research

3.2.1 Evoked potentials and event-related potentials (ERP)

The sensory gating of the brain is usually viewed as an automatic pre-attentional suppression mechanism that reduces responses to meaningless stimuli. The P50 auditory-evoked potential sensory gating is widely used to identify deficits in schizophrenia. Some

studies reported P50 deficits in both first-episode individuals with schizophrenia and in those with chronic schizophrenia,[95-99] deficits that do not improve with the use of antipsychotic medications.[96] Surprisingly, the sensory gating malfunction identified as a reduction in P50 suppression was not correlated with the results of other neuropsychological indicators; this suggests that P50 sensory gating is the result of different cognitive processes than the other types of cognitive deficits seen in schizophrenia, but further studies are needed to explore this possibility.[97-99]

The P300 component of the event-related potential (ERP) is associated with the cognitive process involved in selective attention and the mismatch negativity (MMN) component of ERP is associated with the automatic detection of deviated stimuli when not attending to the stimuli. Studies have shown that P300 and MMN could be used as objective indicators of cognitive impairment in individuals with schizophrenia, especially memory.[100-102] The N400 component of ERP is an indicator of the ability to comprehend verbal material; studies finding positive effects of antipsychotic treatment on N400 suggest that N400 could be used as a state marker for schizophrenia.[103-105] Error-related negativity (ERN) provides an opportunity to objectively observe how the brain processes the perception of errors; the latent period and amplitude of ERN are abnormal in individuals with first-episode schizophrenia, suggesting that they have defects in the functioning of the cognitive mechanism that monitors errors.[106]

3.2.2 Eye movement

Studies in China have confirmed previous findings that impairments in executive functioning and other cognitive functions in persons with schizophrenia are associated with abnormal eye movements.[107-109] It was also found that eye movements in individuals with schizophrenia can be affected by the course of the illness and by pharmacological treatment of the illness. Hence, detailed assessment of eye movement abnormalities could be a potential auxiliary diagnostic method for schizophrenia.

3.3 Functional neuroimaging research

Single Photon Emission Computerized Tomography (SPECT), Positron Emission Tomography (PET) and functional Magnetic Resonance Imaging (fMRI) are the commonly used functional neuroimaging technologies. Functional neuroimaging research of individuals with schizophrenia started in the 1990s in China and fMRI technology became widely available in the early 2000s. To localize the encephalic region or neural network related to specific cognitive deficits, functional neuroimaging research compares the activation of certain brain regions when performing particular cognitive tasks to the resting-states of these regions. SPECT studies have detected regional cerebral blood flow (rCBF) abnormalities in the frontal and temporal lobes among patients with schizophrenia; for example, while performing the WCST task, the rCBF of the left frontal lobe increases among healthy controls but not among individuals with schizophrenia (one study found that the rCBF *decreased* during the WCST task among individuals with schizophrenia who had predominantly negative symptoms).[110-111] PET has been less used in research about schizophrenia in China due to its high cost.

fMRI studies on schizophrenia in China[112-115] have reported that: (a) during verbal fluency (VF) tasks the bilateral frontal gyrus, inferior frontal gyrus and anterior cingulate cortex are relatively inactive; (b) during the backward digit span tasks (BDST) the left frontal gyrus, left inferior frontal gyrus and bilateral posterior inferior parietal lobe are relatively inactive; and (c) the activity of some of the relatively inactive regions is increased after treatment with risperidone (for example, significantly improved activation of the left frontal gyrus and left inferior frontal gyrus during the BDST).

Other fMRI studies have focused on working memory. Yang and colleagues[39] adopted the Sternberg's Memory Scanning Test (MST) to investigate the neural mechanism of the encoding, maintenance and retrieval components of working memory (WM) and found that the executive brain regions of individuals with schizophrenia do not efficiently execute these core WM processes. Using n-back tasks, Wang and colleagues[116] discovered that compared to healthy controls, in individuals with schizophrenia the volume of the prefrontal lobe being activated was smaller and the regions involved were more subcortical; moreover, the number of activated brain regions during the task were fewer and the size of the activated region was smaller in individuals with schizophrenia who performed poorly on the task than in individuals with schizophrenia who did not perform poorly. Zou and colleagues[37] used facial recognition tasks to study WM and found that individuals with schizophrenia showed low activity in several cortical areas, particularly the fusiform gyrus.

4. Treatment of cognitive impairment in individuals with schizophrenia

4.1 Pharmacotherapy

4.1.1 Atypical Antipsychotics

The clinical use of the new types of antipsychotic medications once inspired hope. Studies in China and elsewhere reported that almost all of the new atypical antipsychotic drugs could significantly alleviate cognitive dysfunction in individuals with schizophrenia.[3,117-119] However, in recent years – after the results of the influential Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study were published – both international and Chinese researchers have re-evaluated the effects of atypical antipsychotics on cognitive function and concluded that they have little to no effect

on these core symptoms of the disorder. Subsequently the Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) trial has been funded by the NIMH with the specific purpose of developing two types of drugs for improving cognitive function in schizophrenia.[120]

4.1.2 Nootropics

Jie and colleagues[121] reported that the combination of risperidone and huperzine A could improve cognitive function in individuals with schizophrenia and suggested that the mechanism of action of huperzine A was via its ability to increase acetylcholine concentration in the central nervous system (CNS); the increased acetylcholine concentration enhances neuronal excitability and, thus, improves the learning and memory functions of the brain. Bai and colleagues[122] found that combining antipsychotics and aniracetam could mitigate the cognitive impairment of individuals with schizophrenia, especially their problems in memory processing.

4.2 Non-pharmacological treatments

4.2.1 Cognitive therapy

Several types of cognitive therapy have been used in the treatment of schizophrenia, including cognitive remediation therapy, cognitive rehabilitation therapy, and cognitive-behavioral therapy. These approaches combine cognitive restructuring and social skills training with the goal of improving patients' cognitive function by teaching them information processing strategies for problem solving. One study reported that cognitive remediation therapy was able to improve memory, executive function and psychomotor speed in individuals with schizophrenia.[123] In another study that compared the effectiveness of antipsychotic medication alone to that of combined treatment with medication and cognitive rehabilitation therapy, the latter intervention proved to have better outcomes.[124] Other reports suggest that cognitive-behavioral therapy improves the quality of life of individuals with schizophrenia.[125] In addition, Naikan therapy and Morita therapy – which have some cognitive components – were also found to be effective in improving the social functioning, attention and a range of symptoms of interests in patients with schizophrenia.[126,127]

4.2.2 Repetitive transcranial magnetic stimulation (rTMS)

Transcranial magnetic stimulation (TMS) is a non-invasive method of brain stimulation that uses magnetic fields to stimulate nerve cells. Repetitive transcranial magnetic stimulation (rTMS), a variant of TMS, has been developed as an intervention for various psychiatric conditions that has been shown to be both safe and tolerable in routine clinical practice settings. rTMS helps to temporarily reinforce the functions of the cerebral cortex and neural networks by stimulating the brain regions that affect specific functions.

Liu and colleagues[128] found that rTMS could positively affect some aspects of cognitive impairment in patients with schizophrenia. Zheng and colleagues[129] found that compared to sham stimulation, 20 Hz rTMS could improve visuospatial working memory, 10 Hz rTMS could decrease negative symptoms, and that both 10 and 20 Hz rTMS could lessen general psychopathology symptoms. This suggests that different types of rTMS may have differential effects on cognitive function and psychotic symptoms in schizophrenia; the hope is that eventually it will be possible to individualize the rTMS stimulation parameters to meet the treatment goals of specific patients.

5. Summary and future directions

Research in China focusing on the cognitive function of individuals with schizophrenia began in the 1970s and has recently grown rapidly due to the development of functional imaging technologies in the mid and late 1990s. Several potential avenues for further research in China remain: (a) previous studies have demonstrated deterioration in overall cognitive functioning but more detailed studies are needed on specific cognitive functions such as information processing, selective attention, and working memory; (b) interdisciplinary research that combines the approaches of psychiatry, psychology and functional imaging are needed to clarify the underlying mechanisms of cognitive impairments in schizophrenia; (c) innovative treatment strategies including cognitive therapy, rTMS and so forth need to be developed and rigorously assessed; and (d) long-term panel studies of first-onset patients are needed to assess the natural history of cognitive functioning during the course of illness and the prognostic utility of cognitive tests.

Conflict of interest

All authors declare that they have no conflict of interest.

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•综述•

中国精神分裂症认知功能的研究进展

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摘要

认知功能障碍－精神分裂症的核心症状之一－已经成为国内外研究精神分裂症的热点。它不仅反映了疾病的严重程度，而且是精神分裂症功能预后的重要影响因素，因为认知功能损害的程度对患者的独立生活能力以及他们的就业和社会功能都会有影响。国内最早的精神分裂症认知功能研究可以追溯到上个世纪七十年代晚期。近年来，由于新的信息的出现，例如神经影像技术的进步，国内涌现了大量研究。本文在对国内既往研究进行综述的基础上提出了精神分裂症认知功能的未来研究方向。