•Review•

Advances in neuroimaging research of schizophrenia in China

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Summary: Since Hounsfield's first report about X-ray computed tomography (CT) in 1972, there has been substantial progress in the application of neuroimaging techniques to study the structure, function, and biochemistry of the brain. This review provides a summary of recent research in structural and functional neuroimaging of schizophrenia in China and four tables describing all of the relevant studies from mainland China. The first research report using neuroimaging techniques in China dates back to 1983, a study that reported encephalatrophy in 30% of individuals with schizophrenia. Functional neuroimaging research in China emerged in the 1990s and has undergone rapid development since. Recently, structural and functional brain networks has become a hot topic among China's neuroimaging researchers.

Keywords: schizophrenia, magnetic resonance imaging, magnetic resonance spectroscopy, diffusion tensor imaging, China

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Neuroimaging studies of schizophrenia include both structural and functional techniques.[1-3] The former include X-ray computed tomography (CT) and magnetic resonance imaging (MRI); the latter include single-photon emission computed tomography (SPECT), positron emission tomography (PET), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS).[1-12] Diffusion tensor imaging (DTI) is another functional technique that measures the structure and integrity of the white matter.[13,14] This review describes the evolution of the use of these techniques in the study of schizophrenia (not including molecular neuroimaging) from the perspective of the results generated by researchers in mainland China.

1. Structural neuroimaging studies of schizophrenia

Since the end of the 19th century, researchers seeking the biological basis of schizophrenia have focused on the structure and function of the brain. The earliest study may be the 1879 report by Crichton-Browne that the brains of deceased individuals with schizophrenia were lighter than those of individuals with mood disorders but heavier than those of individuals with dementia. This was followed by a series of neurological autopsy studies and neuropathology studies.[1,2] Pneumoencephalography was the earliest form of in vivo neuroimaging. In 1927, Jacobi and colleagues used pneumoencephalography and found enlarged ventricles and hydrocephalus among individuals with schizophrenia, the first report of structural changes associated with schizophrenia.[1,2,15]

The first contemporary brain structure study of schizophrenia was conducted in 1976 by Johnstone and colleagues[16] who assessed 17 individuals with schizophrenia using CT and found enlarged lateral ventricles and cortical encephalatrophy. Additionally, they found that the enlargement of the lateral ventricles was associated with cognitive impairment but unrelated to antipsychotic treatment.[16] The earliest CT study in China by Yu and colleagues in 1983[17] found that 30% of individuals with schizophrenia had encephalatrophy. A replication study by Wang and colleagues reported in 1986[18] also documented enlarged ventricles and widened sulus. The number of CT studies on schizophrenia in China grew significantly after 1987.[19-22] A 10-year follow-up study of their original sample by Wang and colleagues[23] found that the prevalence of encephalatrophy in

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the patients had risen from 16 to 31% over the 10-year interval; they concluded that the structural abnormalities in schizophrenia were related to the duration of disease.

Table 1 lists MRI studies on schizophrenia in China. Early studies engaged relatively simple imaging sequences and low-frequency magnetic fields. The analysis and presentation of the results were relatively basic. They reported that approximately 30% of individuals with schizophrenia had encephalatrophy, which was identified as reduced volume of the brain, widened sulus, and enlarged third and lateral ventricles.[24-30] The emergence of high fields MRI (e.g., 3T) and voxel-based morphometry (VBM) in 2006 equipped researchers with improved technology that could objectively quantify the volume and density of the local gray matter. Using VBM, a series of studies in China found reductions in the gray matter in the frontal lobe, temporal lobe and its interior structures, anterior cingulate, insula, parietal lobe, and cerebellum,[31-38] results that were consistent with findings from other countries. For example, Williams reviewed MRI-VBM studies and concluded that major structural brain changes in chronic schizophrenia included decreased gray matter in the superior temporal lobe (reported by 81% of studies) and in the inferior frontal lobe, inferior frontal lobe, inferior temporal lobe, and insula (reported by 50 to 70% of studies).[39] In first-episode schizophrenia reductions of the gray matter in the anterior cingulate gyrus and in the right parietal lobe were reported by 15 to 25% of studies and reductions of the gray matter in the inferior frontal lobe and the medial prefrontal lobe were also reported.[39] After two to three years of follow-up of first-episode schizophrenia, progressive reductions of the gray matter in the prefrontal-temporal lobe were found, changes that converge with those seen among individuals with chronic schizophrenia.[39]

2. Functional neuroimaging studies of schizophrenia

2.1 Functional magnetic resonance imaging (fMRI) studies

Liu and colleagues discussed the use of MRI in psychiatric research in 2001[8] and conducted a series of studies on cognitive functioning among Chinese individuals without mental disorders.[40-42] In 2002, they reported results from a fMRI study on schizophrenia which found that treatment with antipsychotic medications (risperidone or chlorpromazine) can activate certain brain areas among patients with schizophrenia.[9]

Table 2 lists task-based fMRI studies on schizophrenia from China. Tasks used in these studies included basic cognitive functioning (e.g., working memory,[10,43,45,47,48-52] verbal functioning,[9,44] and executive functioning[46]) and social cognitive functioning (e.g., face recognition[48]). These studies found that patients with schizophrenia had impairment in the memorization of active information as well as in the management and execution of active information.[10,43,45,47,48-52] The Sternberg item recognition task is one of the most widely used tests for short-term memory; studies that use this test in conjunction with fMRI report that during the maintenance stage of the task individuals with schizophrenia had increased activity levels in the left motor cortex, dorsolateral prefrontal cortex (DLPFC), ventral prefrontal cortex (VPFC), and the right precuneus – this suggests reduced efficiency of these brain regions.[10,43-45] The n-back task is a commonly used task to evaluate the ability to manage and execute working memory; based on the results of this task, individuals with schizophrenia were found to have impairment in the prefrontal cortex.[47] The Stroop task evaluates selective attention and impulse control; using this test, distracted individuals with schizophrenia were found to have deactivation in the left middle frontal gyrus and the right anterior cingulate and increased activity in the temporal lobe and right superior frontal lobe.[46] Using the facial recognition task, which evaluates social cognitive function, individuals with schizophrenia exhibited deactivation of the bilateral fusiform gyrus, occipital gyrus, cingulate gyrus, middle frontal gyrus, inferior frontal gyrus and cerebellum, left superior frontal gyrus, superior parietal lobe and the thalamus, and the right inferior parietal lobe.[48] Using the Burke dysphagia screening test, Jiang and his team found that after eight weeks of treatment with risperidone (3.8 mg/d), patients with schizophrenia showed improved brain activities in the left superior frontal gyrus and the left VPFC; this suggests that antipsychotics can ameliorate defective working memory in schizophrenia.[10]

Resting-state fMRI (as opposed to task-based fMRI) refers to fMRI conducted under a completely relaxed state. Under the resting state, certain areas of the brain are actively performing important functions.[53] Liu and colleagues found decreased regional homogeneity in individuals with schizophrenia in the bilateral frontal lobes, temporal lobes, inferior cerebellum, right parietal lobe, and the left limbic lobe.[54] Jiang and colleagues studied a sample of individuals with early-onset schizophrenia (12-19 years of age) and found lower regional homogeneity in the bilateral medial prefrontal cortex (MPFC).[55] More recently, researchers used the amplitude of low frequency fluctuations (ALFF) to evaluate resting-state brain functions and found that among individuals with schizophrenia the ALFF was elevated in the right corpus callosum, occipital lobes, left cerebellar lobe, superior frontal gyrus and precuneus, and the ALFF was decreased in the bilateral postcentral gyrus and left precuneus.[56] Huang and colleagues reported lower ALFF at the MPFC and higher ALFF at the bilateral putamina among those with drug-naïve schizophrenia.[57] The above studies provide supportive evidence about the role of a dysfunctional MPFC in the pathogenesis of schizophrenia. Lui and colleagues investigated the influence of antipsychotics on resting-state brain functions among patients with schizophrenia and found that after six weeks of treatment with atypical antipsychotic medications, patients with first-episode schizophrenia showed higher ALFF at the

Table 1. Magnetic resonance imaging (MRI) studies of schizophrenia in China

Author [reference number] (year, magnetic field)	Main findings
Shi[24] (1996, unspecified)	Abnormal brain structures were found in 32% of patients with schizophrenia. Main abnormalities reported included encephalatrophy and enlarged ventricles.
Chen[25] (1997, 0.15T)	Reduced length and area of the callosum was found among patients with schizophrenia, more pronounced among those with Type II schizophrenia.
Wang[26] (1998, 0.2T)	Abnormal brain structures were found in 32.5% of patients with schizophrenia. Main abnormalities included encephalatrophy of the frontal and temporal lobes as well as enlarged lateral and 3rd ventricles. Encephalatrophy was more pronounced among those with dominant negative symptoms.
Gan[27] (2000, unspecified)	Encephalatrophy was found in 31.7% of patients with schizophrenia. Significant differences were found for the encephalatrophy score and the width of the 3rd ventricle.
Sui[28] (2001, unspecified)	Enlarged 3rd ventricle, caudatum, and hippocampus were found among patients with schizophrenia.
Kang[29] (2004, 1.5T)	Reduced volume of the right inferior temporal gyrus was found among individuals with first-episode schizophrenia. Level of delusions was negatively correlated with the length of the left temporal lobe and the area of the left inferior temporal gyrus.
Sui[30] (2005, unspecified)	Patients with schizophrenia had shorter callosum. Reduced width of the splenium of corpus callosum was found among those with a positive family history of mental illness. Age of onset correlated with the length and width of the callosum.
Wu[31] (2006, 1.5T)	Patients with schizophrenia had reduced gray matter in the bilateral anterior cingulate, prefrontal cortex, and right superior temporal gyrus. Asymmetry was found in the gray matter. Asymmetry index was +0.19 and -0.50 for the prefrontal and temporal areas, respectively. Increased volume of gray matter was found in the right precentral gyrus, right occipital region, and left inferior parietal lobule. Asymmetry was found in these regions as well.
Lv[32] (2007, 3T)	Drug naïve patients with first-episode schizophrenia had reduced volume and density of the bilateral temporal lobes and frontal lobes. Lower density of the gray matter was also found in the parietal lobe, occipital lobe, and cerebellum.
Zou[33] (2008, 3T)	Asymmetrical changes were found among drug naïve patients with first-episode schizophrenia. In specific, reduced asymmetry was found in the left brain (e.g., the superior frontal gyrus, middle temporal gyrus, cingulate gyrus, orbital gyrus, head of the thalamus and the caudate nucleus). Reversed asymmetry was found for the postcentral gyrus. Increased asymmetry was found for the hippocampus and the parahippocampal gyrus.
Lui[34] (2009, 3T)	Reduced density of the gray matter was found among patients with schizophrenia in the bilateral insula, right temporal lobe, occipital lobe and cerebellum, and the left putamen. Patients with a positive family history of mental illness and their parents had a lower density of gray matter in the thalamus compared to patients without a family history of mental illness.
Cui[35] (2011, 3T)	Similar changes were found for patients with schizophrenia (paranoid type) and patients with bipolar disorder (with psychotic symptoms) including reduced volume of gray matter in the superior temporal lobe (BA22 area), inferior parietal lobule, and enlarged putamen.
Lai[36] (2012, 3T)	Structural abnormality was found in the left crus of fornix among patients with first-episode schizophrenia.
Sheng[37] (2013, 1.5T)	Reduced volume of gray matter was found among patients with first-episode schizophrenia in the prefrontal cortex, anterior cingulate, temporal lobe, parahippocampal gyrus, fusiform gyrus, and insula. These patients had greater volume in the cerebellum than controls. The right asymmetry of the temporal lobe was more prominent in cases than controls and it was correlated with the severity of symptoms and social dysfunction.
Hu[38] (2013, 3T)	Compared to sex- and age-matched controls, reduced volume was found among patients with first-episode schizophrenia in the bilateral hippocampus, parahippocampal gyrus, middle temporal gyrus, and superior temporal gyrus. Their gray matter volume was also smaller in the right hippocampus and parahippocampal gyrus compared to their unaffected siblings. Compared to controls, unaffected siblings had reduced gray matter in the left middle temporal gyrus.

Table 2. Task-based functional magnetic resonance imaging (fMRI) studies of schizophrenia in China

Author [reference number] (year, magnetic field)	Task	Findings
Liu[9] (2002, 1.5T)	verbal fluency	Activation of the prefrontal cortex and the parietal lobe was observed among patients with schizophrenia. After antipsychotic treatment for 8 weeks, enhanced activation of the bilateral frontal gyri was observed in 7 out of 9 patients. Significant changes were observed in the left dorsolateral prefrontal lobe, which suggests that antipsychotics can improve cognitive functioning.
Liu[43] (2004, 1.5T)	backward digit span	Deactivation in the lower part of the left dorsolateral prefrontal lobe and right posterior parietal lobe was found among patients with schizophrenia, which suggests deficiency of working memory in corresponding brain areas.
Liu[10] (2004, 1.5T)	backward digit span	Extensive activation of brain regions among patients with first-episode schizophrenia was found. After 8 weeks of treatment with risperidone (mean[sd] dose=3.8[0.9]mg/d), improvement was seen in the left superior frontal lobe and the left ventral lateral prefrontal lobe.
Liu[44] (2005, 1.5T)	verbal fluency	Deactivation was found in the bilateral frontal gyrus, inferior frontal gyrus, anterior cingulate, and right precentral gyrus among patients with first-episode schizophrenia. These findings suggest dysfunctional verbal fluency among early-stage schizophrenia.
Wu[45] (2007, 1.5T)	double working memory tasks	Extensive activation of brain regions among patients with schizophrenia and impaired executive functioning. Increased activation was found in the bilateral dorsolateral prefrontal lobe, lateral ventral prefrontal cortex, medial frontal gyrus, insula, and right orbitofrontal gyrus. Reduced activation was found in the left superior frontal lobe. These findings suggest abnormal activities of the prefrontal lobe during cognitive tasks in schizophrenia.
Liu[46] (2007, 1.5T)	Stroop	Deactivation was seen in the left middle frontal lobe and the right anterior cingulate among patients with schizophrenia (paranoid type). Heightened activation was found in the temporal lobe and the right superior frontal lobe. No differences under the two Stroop conditions were found in the schizophrenia group; in the control group, significant differences under the two conditions were observed in the right inferior frontal lobe and the left middle frontal lobe. These findings suggest deficiency of selective attention in schizophrenia; the left middle frontal lobe, right anterior cingulate, and the temporal lobe may be the brain areas that are responsible for this deficiency.
Wang[47] (2007, 1.5T)	n-back (n=0,1,2,3)	Reduced activation was observed among patients with schizophrenia in the prefrontal cortex. Among patients with non-deficit schizophrenia, heightened activation was observed in the bilateral prefrontal cortex. Among patients with deficit schizophrenia, the opposite was observed. These results suggest dysfunction of the prefrontal cortex that varies depending on the subtype of schizophrenia.
Zou[48] (2007, 1.5T)	facial working memory	Among drug naïve patients with schizophrenia (paranoid type), deactivation was found in the bilateral fusiform gyrus, occipital gyrus, cingulate gyrus, middle frontal gyrus, inferior frontal gyrus and cerebellum, left superior frontal gyrus, thalamus, and right inferior parietal lobe. This finding suggests that the fusiform gyrus is the main brain area that is responsible for the dysfunctional facial recognition in schizophrenia, and the deactivation of the bilateral prefrontal cortex, cingulate, cerebellum, and the left thalamus underlies this deficiency in information processing.
Yang[49] (2009, 1.5T)	n-back (n=0,3)	Among patients with schizophrenia, deactivation was found in the bilateral dorsolateral and ventrolateral prefrontal cortex, left premotor area, posterior parietal cortex, rostral prefrontal cortex (Brodmann area 10), and the left supplementary motor area. Heightened activation was found in the bilateral medial prefrontal cortex, temporal lobe, and cingulate.
Yang[50] (2009, 1.5T)	Sternberg	Among patients with schizophrenia, heightened activation was found in the right precuneus during the coding stage; the left premotor area, dorsolateral and ventrolateral prefrontal cortex, and right precuneus during the maintenance stage; and the left pre-motor area during the extraction stage. Heightened activation was also observed in some sub-cortex structures, in the primary motor cortex, and in the left temporal lobe related to linguistic functions. These findings suggest lower efficiency in brain areas involved in the coding, maintaining, and extraction of the working memory in schizophrenia.
Gu[51] (2009, 1.5T)	n-back (n=0,2)	Among patients with schizophrenia task-induced deactivation of brain areas included the prefrontal cortex, cingulate, and precuneus. Changes in task-induced deactivation in the medial prefrontal cortex and the posteromedial cortex correlated with the negative mood score. Task-induced deactivation in the medial prefrontal cortex negatively correlated with negative mood. These findings suggest dysfunctional attention transmission during cognitive-emotional tasks among patients with schizophrenia.
Zhang[52] (2013, 3.0T)	n-back (n=0,2)	Reduced task-related inhibition was found in the left posterior cingulate and the prefrontal cortex among patients with schizophrenia (both high- and low-suicide risk). An enhanced connection was found between the left posterior cingulate and the left prefrontal cortex. Reduced connection was found between the posteromedial cortex and the posterior cingulate among those with high suicide risk.

bilateral prefrontal cortex, parietal lobe, left superior temporal lobe, and the right caudate; moreover, this increase of ALFF was correlated with improvement of clinical symptoms.[58]

2.2. Magnetic resonance spectroscopy (MRS) studies

Dopamine (DA) hyperfunction is an important hypothesis in the etiology of schizophrenia. It has been challenged in recent years due to the limited effectiveness of antipsychotic medications on negative symptoms and impaired cognition.[59] In its place the glutamate hypothesis has gained in popularity because it not only accounts for psychotic symptoms but it can provide a sensible explanation for the defective cognition in schizophrenia. This hypothesis postulates that individuals with schizophrenia have deactivated N-methyl-D-aspartic acid (NMDA) receptors, which results in a deficiency of gamma-aminobutyric acid (GABA) and disinhibition of glutamic acid. Some scholars consider the hyperfunction of DA a result of the deficiency of GABA.[59,60] Assessment of the glutamate hypothesis requires accurate measurement of GABA in the brains of individuals with schizophrenia. Magnetic resonance spectroscopy (1H-MRS) is the most common technique for measuring the level of GABA in combination with high-frequency (≥3T) MRI.[61,62]

Table 3 lists MRS studies in China which have been used to assess levels of N-acetylaspartic acid (NAA), creatine (Cr), and choline (Cho) in individuals with schizophrenia.[63-68] They have found a decreased NAA/Cr ratio in the prefrontal cortex among patients with schizophrenia.[64-67] Most studies found no significant changes in the Cho/Cr ratio,[64-66] but Gao and colleagues reported a decreased Cho/Cr ratio in the bilateral frontal cortex.[67] These findings support hypotheses about the early damage of neurons in the frontal cortex of individuals with schizophrenia. There have been contradictory results from MRS studies of the hippocampus: Wang and colleagues[63] found an increased Cho/Cr ratio but no changes in the NAA/Cr ratio among male patients with schizophrenia while Peng and colleagues[65] found a decreased NAA/Cr ratio among patients with first-episode schizophrenia. Chen and colleagues[64] explored the effect of antipsychotics on brain metabolism but found no changes in the NAA/Cr or CHO/Cr ratios at the bilateral frontal cortex with treatment, suggesting that short-term treatment with atypical antipsychotic medications may not affect metabolism in the frontal cortex.

2.3 Diffusion tensor imaging (DTI) studies

DTI, which produces images of brain white matter and fiber tracts, highlights structural and functional asymmetry in different parts of the brain. Normally both grey matter and white matter are asymmetric,[1,2] but several researchers have found that in schizophrenia the asymmetry is reduced or reversed. Wang and colleagues[70] found that the asymmetry of the anterior cingulate tract was reduced in patients with schizophrenia. Su and colleagues[80] found that the asymmetry of the bilateral frontal lobe disappeared in

Table 3. Magnetic resonance spectroscopy (MRS) studies on schizophrenia in China

Author [reference number] (year, magnetic field)	Findings
Wang[63] (2004, 1.5T)	A higher choline/creatine ratio was found in the hippocampus of male patients with schizophrenia compared to controls. No differences in the N-acetylaspartic/creatine ratio was found. This suggests disrupted membrane metabolism of phospholipids in the hippocampus among male patients with schizophrenia.
Chen[64] (2006, 1.5T)	A lower N-acetylaspartic/creatine ratio was found in the bilateral frontal lobes of first-episode male patients with schizophrenia, but no differences were found in the choline/creatine ratio. Treatment with atypical antipsychotics did not induce changes in the N-acetylaspartic/creatine ratio or the choline/creatine ratio. There may be dysfunctional neurons in the frontal cortex in schizophrenia that are not responsive to short-term treatment with atypical antipsychotics.
Peng[65] (2006, unspecified)	The N-acetylaspartic/creatine ratio was lower in the left prefrontal cortex and hippocampus of patients with first-episode schizophrenia, but there were no differences in the choline/creatine ratio, myoinositol/creatine ratio, or (glutamate + glutamine)/creatine ratio in these brain regions. None of the metabolite ratios were different between cases and controls in the left thalamus, transverse temporal gyri, or occipital lobe.
Ma[66] (2006, 1.5T)	The N-acetylaspartic/creatine ratio was lower in the prefrontal cortex of patients with first-episode schizophrenia compared to controls; no such differences were found for choline/creatine ratio
Gao[67] (2010, 1.5T)	The N-acetylaspartic/creatine and choline/creatine ratios were lower in the bilateral frontal cortex among patients with schizophrenia (paranoid type). They also had a higher N-acetylaspartic/creatine ratio in the left frontal lobe, a lower choline/creatine ratio in the right cerebellum, and a higher choline/creatine ratio in the right caudatum.
Li[68] (2011, 3T)	No differences in N-acetylaspartic acid, choline, or creatine were found in the left prefrontal lobe, thalamus, hippocampus, or pons between first-degree relatives of individuals with schizophrenia and controls.

patients with schizophrenia and that the laterality of the genu and the posterior limb of the internal capsule was reversed.

DTI research has found structural abnormalities in the corpus callosum of patients with both first-episode and chronic schizophrenia. Most research on the corpus callosum of patients with schizophrenia reports decreased fractional anisotropy (FA) in the genu,[79,80,83,86] and some studies report abnormalities in the splenium[73,76,86] and the truncus[74,86] of the corpus callosum. Kong and colleagues[83] found a reduced FA value in the genu of chronic patients but not in first-episode patients, suggesting that the abnormality in that area reflects progression of the disease. Li and colleagues[86] compared five areas of the corpus callosum (splenium, truncus, anterior genu, mid genu, and posterior genu) in patients with schizophrenia, patients with bipolar disorder, and healthy controls; they found that both patient groups had lower FA values in all areas than those of healthy controls but they did not differ significantly from each other—which suggests that abnormalities in the corpus callosum are a shared component in the pathogenesis of schizophrenia and bipolar disorder.

The internal capsule has also been extensively studied. The first study in China by Zhao and colleagues[72] did not find any abnormalities in the internal capsule of patients with schizophrenia but subsequent studies reported reduced FA in the anterior limb of the bilateral internal capsule,[75,80] anterior limb of the left internal capsule,[77] genu of the left internal capsule,[80] and genu of the right internal capsule.[84]

Other studies report changes in the white matter and fiber tracts in other brain regions including the cerebellar peduncle, cingulate tract, cerebral peduncle, corona radiate, frontal lobe, temporal lobe, parietal lobe, insula, hippocampus, frontotemporal junction, parieto-occipital fasciculus, longitudinal fasciculus, and external capsule.[69-73,76,78,80-82,84-85] The results of DTI studies about schizophrenia conducted in China are summarized in Table 4.

2.4 Brain network

Brain network is currently a popular field in brain imaging research of schizophrenia in China.[87,88] Structural brain network research employs MRI to assess complex structural human brain networks and DTI to assess the white matter fiber tracts that connect these networks. Functional brain network research employs resting-state fMRI, task-state fMRI, electroencephalography (EEG), and magnetoencephalography (MEG) to assess complex functional human brain networks.[87-91]

2.4.1 Structural brain network

In 2012, Zhang and colleagues[92] used structural MRI to collect morphological data of the brain, and used the Automated Anatomical Labeling atlas (ALL) template to divide the brain into 78 areas (nodes). They used the graph theory analytical method for complex networks to analyze the brain network based on the thickness of the cortices. They found that the 'small world' property of the brain network of patients with schizophrenia was abnormal: (a) compared to normal brains the characteristic path length and the clustering coefficient increased; (b) the nodes in some brain areas had decreased centrality and thinner cortices (especially the left parahippocampal gyrus, inferior temporal gyrus, angular gyrus, and right superior frontal gyrus, which are part of the default network); and (c) the nodes in other brain areas had increased centrality, including nodes in the primary cortex (bilateral precuneous, left precentral gyrus, postcentral gyrus, and right Heschl gyrus) and the paralymbic system (bilateral orbital frontal gyrus, temporal pole, right cingulate tract, and inferior parietal gyrus). These findings indicated that the characteristics of the topology of the brain network changed in patients with schizophrenia. In 2014, Zhang and colleagues[93] reported that patients with schizophrenia had decreased connectivity between the thalamus and the bilateral inferior frontal gyrus, left superior temporal gyrus, and right parieto-occipital regions. These findings indicated that schizophrenia is associated with the loss of brain connectivity.

Wang and colleagues[94] used the ALL template along with white matter fiber tracts data collected using DTI to map the brain into 90 areas, and analyzed the white matter fiber tracts network using fiber tracking technology and graph-theory-based complex network analysis. They found that the normal characteristics of the topography of the brain network changed in patients with schizophrenia, resulting in a significant decrease in global efficiency that was correlated with scores on the Positive and Negative Syndrome Scale (PANSS). They also found decreased regional efficiency of some hubs, including the joint frontal cortex, paralimbic system, limbic system, and left lentiform nucleus.

2.4.2 Functional brain network

Functional brain networks are constructed using time series data of functional brain activities. Brain networks are differentiated into brain networks based on regions of interest, brain networks with specific functions, and whole brain networks. Examples of brain networks based on regions of interest are the dorsal lateral prefrontal lobe network and the medial prefrontal lobe network. Examples of specific brain networks are the default mode network (DMN) and the fronto-parietal network (FPN).[91]

Zhou and colleagues[95] studied the functional connection of the bilateral dorsal lateral prefrontal cortex (DLPFC); they found that patients with schizophrenia had reduced functional connection between the DLPFC and the parietal lobe, post cingulate gyrus, thalamus and striatum, but increased functional connection between the left DLPFC and the left mid-anterior temporal lobe and paralimbic regions. Fan and colleagues[96] studied the functional connection of the vetromedial prefrontal cortex (vMPFC) in patients with schizophrenia; they found (a) decreased functional

Table 4. Diffusion tensor imaging (DTI) studies on schizophrenia in China

Author [reference number] (year, magnetic field)	Findings
Wang[69] (2003, 1.5T)	There were no differences between individuals with schizophrenia and controls in fractional anisotropy and apparent diffusion coefficient of the superior cerebellar peduncle.
Wang[70] (2004, 1.5T)	Lower FA in the bilateral anterior cingulate bundle as well as reduced level of asymmetry was found for schizophrenia.
Hao[71] (2006, 1.5T)	Lower fractional anisotropy was found in individuals with schizophrenia in the cerebral peduncle, frontal regions, inferior temporal gyrus, medial parietal lobes, hippocampal gyrus, insula, right anterior cingulum bundle, and right corona radiata.
Zhao[72] (2006, 1.5T)	Comparing individuals with first-episode schizophrenia and controls, no differences in fractional anisotropy and apparent diffusion coefficient were found in the white matter of the front temporal junction and internal capsule, or in the gray matter of the temporal gyrus, anterior medial gyrus, or posterior medial gyrus.
Wu[73] (2006, 1.5T)	Lower fractional anisotropy in the bilateral frontal lobes and splenium corporis callosi among patients with schizophrenia. Fractional anisotropy positively correlated to score on Positive and Negative Syndrome Scale.
Li[74] (2008, 1.5T)	Lower fractional anisotropy in the splenium corporis callosi among patients with first-episode schizophrenia. Fractional anisotropy correlated to negative symptom score on Positive and Negative Syndrome Scale.
Zou[75] (2008, 1.5T)	Lower fractional anisotropy in the bilateral anterior limb of internal capsule among patients with schizophrenia. No differences in the apparent diffusion coefficient were found.
Li[76] (2008, 3.0T)	Lower density of the white matter was found in the left lateral parieto-occipital bundle, superior longitudinal fasciculus, and right posterior cingulate among first-episode, drug-naïve patients with schizophrenia. Lower fractional anisotropy was found in the right fasciculus occipitofrontalis, splenium corporis callosi, and posterior cingulate.
Zou[77] (2009, 1.5T)	Lower fractional anisotropy was found in the left anterior limb of the internal capsule among male patients with schizophrenia. No change was found in the fractional anisotropy of the right anterior limb of internal capsule or in the apparent diffusion coefficient of the bilateral anterior limb of the internal capsule.
Hao[78] (2009, 1.5T)	Lower fractional anisotropy was found in the left prefrontal cortex and hippocampus among patients with schizophrenia and their siblings without schizophrenia. Compared to the siblings without schizophrenia, patients had lower fractional anisotropy in the left anterior cingulate.
Su[79] (2009, 1.5T)	Lower fractional anisotropy and higher apparent diffusion coefficient were found in the genu of the corpus callosum among patients with first-episode schizophrenia (paranoid type).
Su[80] (2010, 1.5T)	Lower fractional anisotropy was found in the bilateral frontal cortex, anterior limb of the internal capsule, exterior capsule, left temporal lobe, genu of the internal capsule, and genu of corpus callosum among patients with first-episode schizophrenia (paranoid type). In the control group the left frontal cortex had higher fractional anisotropy compared to the right cortex while no such differences were found in the schizophrenia group. In the control group higher fractional anisotropy was found in the left versus right genu and posterior limb of the internal capsule while the opposite was found for the schizophrenia group.
Li[81] (2011, 3T)	Lower fractional anisotropy was found in the left superior cerebellar peduncle among patients with schizophrenia.
Cui[82] (2011, 3T)	Lower fractional anisotropy was found in the left posterior corona in patients with schizophrenia (paranoid type) and in patients with bipolar disorder who had psychotic symptoms. The fractional anisotropy value of the left frontoparietal fibers was negatively correlated with the positive symptom score of the Positive and Negative Syndrome Scale. There were no significant differences in the fractional anisotropy values between patients with schizophrenia and those with bipolar disorder.
Kong[83] (2011, 1.5T)	Lower fractional anisotropy was found in the genu of corpus callosum among patients with chronic schizophrenia while no such change was found among patients with first-episode schizophrenia.
Guo[84] (2012, 1.5T)	Lower fractional anisotropy was found in the right superior longitudinal fasciculus, fornix, internal capsule, and external capsule among drug naïve patients with first-episode schizophrenia (paranoid type).
Chen[85] (2013, 1.5T)	Lower fractional anisotropy was found in the left parietal lobe and the right posterior cingulate among patients with late-onset schizophrenia.
Li[86] (2014, 3T)	Lower fractional anisotropy was found in five different areas of the corpus callosum among patients with schizophrenia. No differences were found between patients with schizophrenia and those with bipolar disorder.

connection between the vMPFC and the medial frontal lobe, right middle temporal gyrus, right hippocampus, parahippocampal gyrus and amygdale, (b) decreased strength of the negative correlation between the vMPFC and the bilateral DLPFC and anterior supplementary motor area, and (c) a positive correlation between the reduction in the vMPFC-DLPFC connection and the positive symptoms of schizophrenia.

Tang and colleagues[97] studied the default mode network (DMN) in patients with early-onset schizophrenia (12 to 19 years old); they found increased functional connection between the ventromedial prefrontal lobe and the right inferior temporal gyrus, left angular gyrus, and dorsomedial prefrontal lobe, but decreased functional connection between the right angular gyrus and the cerebellar tonsil, left superior frontal gyrus and right inferior semilunar lobule. Chang and colleagues[98] studied the anterior and posterior DMN as well as the left lateral and right lateral fronto-pariental networks (FPN); they found (a) abnormal intra-network connections in the anterior DMN and bilateral FPN in both patients with schizophrenia and their healthy siblings, (b) normal intra-network connection of the posterior DMN, (c) a positive association between the two networks in patients with schizophrenia, their healthy siblings, and healthy controls, and (d) a stronger functional connection between the right FPN and the anterior DMN in patients with schizophrenia than in healthy controls.

Other researchers studied schizophrenia from the perspective of inherent networks, and proposed that the inherent networks include a task-positive network (TPN) and a task-negative network (TNN). Kong and colleagues[99] found increased functional connection in the bilateral inferior temporal gyrus of the TNN among individuals with schizophrenia and their healthy siblings; they also found increased functional connection between the left DLPFC and the right inferior temporal gyrus of the TPN among individuals with schizophrenia. Zhou and colleagues[100] assessed the TNN and TPN in patients with paranoid schizophrenia and found abnormal TNN functional connections with the bilateral dorsomedial prefrontal cortex, lateral parietal lobe, and inferior temporal gyrus, and abnormal TPN functional connections with the DLPFC and the right dorsal premotor cortex.

Liang and colleagues[101] used the ALL template to divide the brain into 116 areas, and analyzed the whole brain network using a complex network analysis method based on graph theory. They found that the functional brain connection of patients with schizophrenia during the resting state showed a wide-spread decline. Ke and colleagues[102] compared the properties of the brain network of patients with schizophrenia who primarily have positive symptoms with that of patients who primarily have negative symptoms; they found that the decline in the 'small-world' network was more pronounced in the patients with negative symptoms.

Guo and colleagues[103] assessed first order symmetry (the strength of the functional connection between the same brain regions from opposite hemispheres) and second order symmetry (the functional connection between the same pairs of brain regions from opposite hemispheres). They found that patients with schizophrenia had significantly decreased first and second order symmetry: the decrease in the first order symmetry indicated a reduced synchronicity between the two hemispheres; the decrease in the second order symmetry indicated a pronounced difference between the functional networks in the two hemispheres. They then compared the brain areas that were connected by the corpus callosum (CC) and the anterior commissure (AC) in patients with schizophrenia, and found that first and second order symmetry decreased in brain areas connected by the CC, but only first order symmetry decreased in brain areas connected by AC.

Liu and colleagues[104] assessed the diagnostic distinctiveness of the resting-state whole brain network. They found an 80.4% accuracy in distinguishing patients with schizophrenia from healthy controls, a 77.6% accuracy in distinguishing patients with schizophrenia from their healthy siblings, and a 78.7% accuracy in distinguishing schizophrenia patients' healthy siblings and healthy controls without relatives with schizophrenia. These results suggest that the resting-state brain network of the patients' siblings without schizophrenia is also changed in ways that distinguish it both from the brain network of their ill siblings and from that of healthy controls without a family history of mental illness.

3. Conclusions and future directions

In the past 30 years, advances in imaging technology and data analysis techniques have transformed neuroimaging into an exciting field that is rapidly advancing our understanding of the normal and abnormal functioning of the brain. These methods have identified structural and functional abnormalities in the brains of individuals with schizophrenia that confirm the biological basis of the disorder. However, much more multi-disciplinary work will be needed to integrate these findings into a comprehensive model of the etiology of this complex disorder. Chinese investigators have been and will continue to be enthusiastic participants in this global effort to understand, treat, and, hopefully, prevent this devastating condition.

Future neuroimaging research needs to overcome several central problems.

(a) Schizophrenia is highly heterogeneous, so dividing individuals with the clinical diagnosis into relatively homogeneous subgroups is essential to identifying distinct biological markers using neuroimaging techniques. The traditional methods of categorizing subtypes (paranoid, adolescent-onset, catatonic, simple, etc.) are obviously insufficient for research purposes. The dimensional approach based on rating the severity of 8 core symptoms of psychosis suggested in DSM-5[105] may be an improvement, but the utility of this method has not yet been assessed.

(b) There are some basic limitations to neuro-imaging that need to be overcome. Re-construction of images of white matter fiber tracts using DTI still has many methodological problems, including the false connections that can appear when reconstructing crossing fibers or longer fibers.[88] At present neuroimaging can only use MRI morphological data based on the population to construct a collective brain structural network; it cannot use data from a single participant to build an individualized brain structural network.

(c) Current brain network research is focused on the macro-level (whole brain or brain region) and relies on brain atlases (e.g., dividing the brain into 90 regions/nodes). Micro-level brain network research (neuron-level or voxel-level) may be more helpful for revealing the pathological mechanisms of a disorder, but such voxel-level studies will require much longer image processing time and more complex image analysis techniques.[87,88] Moreover, present brain network research describes associations *not* cause and effect relationships, so we do not know how the related brain areas work together to function effectively. Future research must construct directional networks that specify the directionality of the fiber connection between different brain regions and the causal relationship between neural activities.[87,88]

(d) More research in multi-modal imaging is needed to explore the potential benefits of combining methods. Many possible combinations are possible: structural MRI and resting-state fMRI;[106] resting-state fMRI and DTI;[107] neural imaging techniques based on MRI and EEG or MEG;[88] task-state fMRI and event-related potentials (ERP) or resting-state fMRI; and so forth. These multi-modal imaging methods can attain better results than single-mode methods by combining the complementary strengths of the different methods. For example, MRI has higher spatial resolution and EEG has better time resolution so combining the two methods provides a more multi-dimensional assessment.

(e) A parallel effort needs to be made in combining neuroimaging with genetics research[108,109] and with cognitive-behavioral research. Such a multi-disciplinary approach could reduce the necessary sample size of genetics research, help identify the genetic basis of the abnormal structure and function of the brain in schizophrenia, and clarify the link between altered genes, dysfunctional brains, and abnormal behavior.

Conflict of interest

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

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中国精神分裂症的神经影像学研究进展

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概述：自 Hounsfield 于 1972 年首次报道 X 线计算机断层扫描（CT）后，神经影像学技术应用持续发展，用于研究大脑结构、功能和生物化学等方面。本文就中国近年来对精神分裂症结构性和功能性神经影像学的研究做了一个概述并且用 4 个表格来描述中国大陆所有相关研究。国内在精神科领域使用神经影像学技术的首个研究报告可追溯至 1983 年，研究发现 30%精神分裂症患者存在脑萎缩。上世纪 90 年代国内逐渐出现功能神经影像学研究，并且快速发展。近年来，脑结构网络和脑功能网络研究已成为中国神经影像学研究的一个热门话题。

关键词：精神分裂症，磁共振成像，磁共振波谱，弥散张量成像，中国

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