•Review•

Neuroimaging studies in patients with obsessive-compulsive disorder in China

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Summary: Obsessive-compulsive disorder (OCD) is a common mental disorder of uncertain etiology. Neuroimaging studies of patients with OCD in China started to appear in the late 1990s, identifying structural abnormalities in the gray matter and white matter of the prefrontal lobe, the corpus striatum, and the thalamus. Studies using positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and magnetic resonance spectroscopy (MRS) have found increased metabolism and activation in these brain regions that are correlated with the duration, severity and cognitive symptoms of OCD. After surgery for OCD the activation in these target areas decreases. These results in China are similar to those presented in previous neuroimaging studies, including several meta-analyses from other countries.

1. Introduction

Obsessive-compulsive disorder (OCD) is a common mental disorder with a lifetime occurrence of 2 to 3% in the general population.[1] The main clinical presentations of OCD include uncontrollable obsessive thinking and compulsive behavior – which may be associated with symptoms of anxiety or depression – that cause significant impairment in social functioning and deterioration in quality of life.[2] The etiology of OCD remains unclear but studies from other countries have found abnormalities in the prefronto-striato-thalamic circuit of individuals with OCD.[3] Neuroimaging studies of OCD in China started in the late 1990s with studies using PET and single photon emission computed tomography (SPECT). These methods have now largely been replaced by MRI studies that have focused on the pathophysiological mechanisms in OCD both with and without treatment. This review will summarize the results of structural and functional imaging studies of OCD in China.

2. Structural imaging studies

2.1 Structural MRI studies

MRI provides high spatial resolution and is able to image all brain structures including gray and white matter. The three published reports by Chinese investigators of MRI studies of OCD are shown in Table 1. Using optimized voxel-based morphometry (VBM), Li and colleagues reported greater volume of gray matter in the bilateral thalamus and the left cerebellum among individuals with OCD, which suggests that these brain structures play an important role in the development of OCD.[4] Luo and colleagues[5] reported that patients with OCD had a greater volume of white matter in the right precentral gyrus, the right postcentral gyrus, the bilateral precuneus, and the left middle occipital gyrus than control subjects; they also had a smaller volume of white matter in the bilateral superior frontal gyrus, the left postcentral gyrus, the left parahippocampal gyrus/corpus callosum, and the right inferior parietal lobule.

Using surface based morphometry (SBM), Fan and colleagues[6] found that individuals with OCD had greater cortex thickness in the right inferior parietal region and increased gyrification indices in the left insula, left middle frontal gyrus, left lateral occipital region extending to the precuneus, and in the right supramarginal gyrus. They also found a positive correlation between the Yale-Brown Obsessive-Compulsive Scale (YBOCS) score and the local gyrification index of the left insular lobe. This suggests structural changes in the cortex among people with OCD and that the structural changes correlate with the severity of OCD symptoms.

2.2 Diffusion tensor imaging (DTI) studies

Diffusion tensor imaging (DTI) is a type of imaging technique that utilizes the diffusion tension of water molecules to detect detailed structural or pathological changes in organic tissues.[7] Anisotropic diffusion refers

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doi: 10.3969/j.issn.1002-0829.2013.02.004

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Table 1. Structural magnetic resonance imaging (MRI) studies of Obsessive-Compulsive Disorder (OCD) in China

Reference	# case/# controls Treatment Comorbidity Criteria	Model of the machine	Analytic method	Main results
Li F, 2011 [4]a	20/20, drug-free for 2 weeks, no comorbidity, DSM-IV	3.0T	Optimized VBM, FDR corrected, $p<0.05$	Increased volume in bilateral thalamus and left cerebellum in patients with OCD
Luo C, 2011 [5]a	23/23, never medicated, no comorbidity, DSM-IV	1.5T	Areas where there is differences between VBM, $p<0.005$; and voxel-based >200 SVC, corrected, $p<0.05$	Greater volume of white matter in right gyrus precentralis, right postcentral gyrus, bilateral precuneus, and left middle occipital gyrus; smaller volume of white matter in bilateral superior frontal gyrus, left postcentral gyrus, left corpus callosum, and right inferior parietal lobule among patients with OCD
Fan Q, 2012 [6]b	23/20 drug-free for 2 months no comorbidity, DSM-IV	1.5T	SBM, Monte Carlo simulation (1000 times), $p<0.05$,	Greater cortex thickness in the right inferior parietal gyri and an increased gyrification index in left lobus insula, left middle frontal gyrus, left lateral occipital region extending to the precuneus and the right supramarginal gyrus in patients with OCD; a positive correlation between OCD symptoms and the local gyrification index of the left insular lobe

[a] original paper in Chinese [b] original paper in English
DSM-IV, 4th edition of Diagnostic and Statistical Manual of Mental Disorders;
VBM, voxel-based morphology; FDR, False Discovery Rate; SBM, source-based morphology; SVC, superior vena cava

to the phenomenon that it is easier for water molecules to diffuse along the direction of the white matter fiber than to move vertically in the central nervous system. DTI quantifies the anisotropic diffusion of water molecules in order to observe subtle structural changes in white matter. Since myelin sheath is an organic barrier for the diffusion of water molecules, the anisotropic diffusion of the white matter is mainly affected by axons and myelin sheath.[8] Fractional anisotropy (FA) is a parameter that describes the degree of anisotropy of a diffusion process (from 0 to 1) which is commonly assessed in DTI studies.

To date, four papers using DTI methods to assess OCD have been published by Chinese investigators (Table 2). Using the analytical method of region of interest (ROI), Wu and colleagues found lower fractional anisotropy in the rostrum of corpus callosum and the right anterior cingulum and higher fractional anisotropy in the left anterior cingulum and the right prefrontal lobe among individuals with OCD. [9]

Using the analytical method of voxel-based approaches (VBA), Fan and colleagues [10] and Li and colleagues [11] compared the whole-brain FA, mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD) between individuals with and without OCD. Li and colleagues found higher FA and AD in the truncus and genu of the corpus callosum and in the right superior frontal gyrus among individuals with OCD, but did not find any differences in the RD; furthermore, the FA value in the left middle temporal lobe was positively correlated with the severity of OCD symptoms.[11] These results suggest the existence of structural abnormalities in axons. Fan and colleagues[10] found differences in FA, MD, AD, and RD in the prefronto-striato-thalamo-cortical circuit between individuals with and without OCD. Specifically they found increased RD values in the left medial superior frontal gyrus, temporo-parietal lobe, occipital lobe, insula, striatum, and the right midbrain, but no differences in the AD values. After 12 weeks of treatment with selective serotonin reuptake inhibitors (SSRIs), the RD and MD values of patients with OCD showed a significant decrease in the left striatum. These results suggest that the structural changes in the prefronto-striato-thalamo-cortical circuit in OCD may be related to deterioration of the myelin sheath and that some of these abnormalities can be corrected with SSRI treatment.[10]

Using the DTI technique, Zhou and colleagues[12] found that after treatment of OCD with deep brain stimulation (DBS), the FA and MD increased in the bilateral frontal lobes, anterior limb of the internal capsule, upper frontal cerebellopontine angle, and anterior cingulate gyrus.[12] These findings provide insights into the mechanism via which DBS achieves its treatment effect.

2.3 Summary of structural imaging studies

Although there have been only a few structural imaging studies on OCD in China, they used standard imaging techniques and focused on issues that have been assessed in studies from other countries. The

Chines studies included both treatment-sensitive and treatment-resistant patients. Overall the findings support the hypothesis that OCD is associated with structural changes of gray and white matter in the prefrontal lobe, striatum, and thalamus. The studies have also reported structural changes in the temporo-parietal lobes, the occipital lobe, the insula lobe, the cerebellum, the anterior limb of the internal capsule, the corpus callosum, the parahippocampal gyrus, and the midbrain.

Two meta-analysis of structural imaging studies of OCD have been reported in the international literature.[13,14] Rotge and colleagues[13] summarized studies using the ROI method to analyze MRI results for patients with OCD and found decreased volume of gray matter in the left anterior cingulate and the bilateral orbitofrontal cortex and increased volume in the bilateral thalamus.[13] Radua and Mataix-Cols conducted a meta-analysis of MRI studies in patients with OCD analyzed using the VBM method and found increased volume in the bilateral caudate nucleus and decreased volume in the bilateral dorsomedial prefrontal lobe/anterior cingulum.[14] These meta-analyses support the role of the orbitofrontal-striato-thalamic circuit and the dorsomedial prefronto-striatal circuit in the pathophysiological mechanisms of OCD. In summary, studies from China also support these findings of the important role of the prefrontal-striato-thalamic circuit in OCD. Studies from China (and other countries) have also reported structural abnormalities in the temporo-parietal lobe, occipital lobe, cerebellum, and corpus callosum, but the meta-analyses of international studies do not confirm the importance of these brain regions in the pathogenesis of OCD.[15-18]

3. Functional imaging studies

Functional changes in the brain among individuals with OCD can be studied via PET, SPECT, and functional magnetic resonance imaging (fMRI). And magnetic resonance spectroscopy (MRS) studies can also assess functional changes in the brain by monitoring the concentrations of different metabolites in the corresponding regions of the brain. Functional changes can be categorized into the following groups based on the type of experiment: a) resting-state studies which compare brain functions of individuals with and without OCD while resting; b) symptom provocation studies which compare brain functions before and after OCD symptoms have been provoked (e.g., by making patients with OCD with a cleanliness obsession or compulsive washing touch something dirty); c) treatment studies which compare brain functions before and after medication treatment or psychotherapy; and d) cognitive studies which compare brain functions between patients with OCD and controls while executing cognitive tasks such as planning, mistake induction, reaction inhibition, reversal learning, and task conversion.

Table 2. Diffusion tensor imaging studies of Obsessive-Compulsive Disorder (OCD) in China

Reference	# case/# controls Treatment Comorbidity Criteria	Model of the machine	Analytic method	Main results
Zhou Y, 2006 [12]a	7 persons with OCD, all taking medications, unknown comorbidity, DSM-IV	3.0T	VBA and ROI, non-corrected, $t>2.5$, voxel >30	Increased FA and MD in bilateral frontal temporal lobes, anterior limb of the internal capsule , upper frontal cerebellopontine angle, and frontal cingulate gyrus among Patients with OCD after deep brain stimulation
Wu W, 2012 [9]a	15/15, drug-free for 2 weeks, no comorbidity, DSM-IV and CCMD-3	3.0T	ROI, $P<0.05$	Lower fraction anisotropy in the rostrum of corpus callosum and right anterior cingutate and higher fraction anisotropy in the left anterior cingutate and right prefrontal lobe among individuals with OCD
Li F, 2012 [11]b	23/23, 13 were taking medication, unknown comorbidity, DSM-IV	3.0T	VBA, FDR corrected, $p<0.05$, voxel >50	Higher FA and AD in the trunk and genu of corpus callosum and in the right superior frontal gyrus in patients with OCD; the FA value in the left middle temporal lobe positively correlates with OCD symptoms
Fan Q, 2012 [10]b	27/23, drug-free to two weeks, no comorbidity, DSM-IV	1.5T	VBA, Uncorrected, $p<0.001$, voxel>10	Increased FA, MD, AD, and RD in prefrontal-striatum-thalamus-cortex circuit in patients with OCD; after 12 weeks of treatment with SSRI, the RD and MD values decrease in the left striatum.

[a] original paper in Chinese [b] original paper in English DSM-IV, 4th edition of Diagnostic and Statistical Manual of Mental Disorders;
CCMD-3, 3rd edition of the Chinese Classification of Mental Disorders;
VBA, voxel-based approaches; ROI, region of interest; FDR, False Discovery Rate;
FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity; SSRI, selective serotonin reuptake inhibitor

Table 3. Positron emission tomography (PET) studies of Obsessive-Compulsive Disorder (OCD) in China

Reference	# case/# controls Treatment Comorbidity Criteria	Analytic method	Main results
Guan Y, 2001 [19]a	9/9, unknown medication status, unknown comorbidity, CCMD-2-R	ROI, p<0.05	Decreased FDG metabolism in the frontal lobe, cingulate gyrus, gyri orbitales, the head of basal ganglia caudate nucleus, and thalamus after bilateral anterior capsulotomy
Zuo C, 2003 [20]a	6/6, unknown medication status, unknown comorbidity, CCMD-2-R	Voxel-based, Uncorrected, p<0.01	Increased glucose metabolism in the left cingulate gyrus, gray matter in the superior frontal gyrus, gray and white matter in middle frontal gyrus, white matter in the inferior frontal gyrus, white matter outside the putamen, white matter in the anterior commissure of the limbic lobe, parahippocampal gyrus, dorsomedial nucleus of the thalamus, and amygdale
Zuo C, 2003 [21]a	8 cases, self-control before v. after surgery, at least 2 years of treatment, unknown comorbidity, DSM-IV	Voxel-based, uncorrected, p<0.01	Decreased glucose metabolism in the cingulate gyrus, gray matter in the limbic lobe, caudate nucleus, dorsomedial nucleus of the thalamus, white matter of the middle frontal gyrus and the inferior frontal gyrus, and white matter outside of the right putamen after capsulotomy
Qiu C, 2011 [22]a	8/8, drug-free in last week, unknown comorbidity, DSM-IV	Voxel-based, uncorrected, p<0.01	Decreased glucose metabolism in the bilateral cortex of eloquent areas; glucose metabolism in the anterior cingulate correlates with OCD symptoms

[a] original paper is in Chinese
CCMD-2-R, seconded revised edition of the Chinese Classification of Mental Disorders;
DSM-IV, 4th edition of Diagnostic and Statistical Manual of Mental Disorders;
ROI, region of interest; FDG, fludeoxyglucose

3.1 PET studies

In PET the fludeoxyglucose (FDG) marker is used to monitor changes in brain functions.[18] Since 2001, PET has been used in China to compare glucose metabolism in the brain between Patients with OCD and healthy controls, and between Patients with OCD who do and do not receive surgery for OCD. The four studies by Chinese investigators using PET to assess patients with OCD are shown in Table 3. Using the ROI method in patients with intractable OCD, Guan and colleagues reported high FDG intake in the frontal lobe, the cingulate gyrus, the head of the basal ganglia caudate nucleus, and the thalamus. They also found that after bilateral anterior capsulotomy using a Radionis radiofrequency generator FDG metabolism decreased in the frontal lobe, cingulate gyrus, gyri orbitales, head of basal ganglia caudate nucleus, and thalamus. These findings were used as evidence for the existence of an abnormal circuit in OCD, helped locate abnormal brain regions prior to surgery for OCD, and identified outcome measures that could be used to assess the effectiveness of surgery.[19] In a subsequent study,[21] the same research team assessed a sample of patients with intractable OCD and found increased glucose metabolism in several brain regions: left cingulate gyrus, gray matter in the superior frontal gyrus, gray and white matter in the middle frontal gyrus, white matter in the inferior frontal gyrus, white matter outside the putamen, white matter in the anterior commissure of the limbic lobe, parahippocampal gyrus, dorsomedial nucleus of the thalamus, and amygdale.[20] They also found decreased glucose metabolism after capsulotomy in several brain regions: cingulate gyrus, gray matter in the limbic lobe, caudate nucleus, dorsomedial nucleus of the thalamus, white matter of the middle frontal gyrus and the inferior frontal gyrus, and white matter outside of the right putamen.[21] Recently, this research team also found decreased glucose metabolism in the bilateral motor areas of the frontal and parietal lobes; moreover, glucose metabolism in the anterior cingulum was correlated with the severity of OCD symptoms.[22] Based on these findings, the authors suggest that the glucose metabolism in the anterior cingulate could be used as a marker of OCD severity. [22]

3.2 SPECT studies

SPECT uses a radionuclide tracer to monitor changes in the blood flow of different brain regions as a method of assessing functional changes in the brain. Four research teams in China have published a total of 11 papers (the main papers are shown in Table 4) that use the 99mTc-ECD tracer with SPECT to evaluate patients with OCD. Earlier studies[23] using the statistical parametric mapping (SPM) software for data analysis found that compared to the cerebellum (the reference), patients with OCD showed changes in blood flow in the precuneus, left superior temporal gyrus, right superior gyri orbitales, bilateral superior frontal gyrus, and left superior parietal lobule; when compared to the whole brain region, these patients showed changes in blood perfusion in the bilateral precuneus, right cuneus, right

Table 4. Single photon emission computed tomography (SPECT) studies of Obsessive-Compulsive Disorder (OCD) in China

Reference	# case/# controls Treatment Comorbidity Criteria	Analytic method	Main results
Guo W, 2001 [23][a]	13/23, drug-free for 3 weeks, no comorbid depression, DSM-II-R or ICD-10	Voxel-based method with the cerebellum and whole brain as reference, $Z>2.33$	Compared to the cerebellum (the reference), changes in blood flow were found in the precuneus, left superior temporal gyrus, right superior gyri orbitales, bilateral superior frontal gyrus, and left superior parietal lobule in patients with OCD; when compared to the whole brain region, changes in blood perfusion were found in the bilateral precuneus, right neus, right temporal gyrus, left superior temporal gyrus, bilateral superior fontal gyrus, superior gyri orbitales, left superior parietal lobule, left frontal cingulate, bilateral putamina, right angular gyrus, and right cerebellum
Li P, 2002 [24][a]	14/23, drug-free for 3 weeks, no comorbid depression, DSM-II-R or ICD-10	Voxel-based method with the whole brain as reference, uncorrected, $p<0.01$; and ROI, $p<0.05$	Decreased blood flow was found in the bilateral putamen, superior temporal lobe, precuneus, right gyri orbitales, right superior frontal gyrus, right middle frontal gyrus, left temporal and occipital lobe, superior parietal lobule, and the cauda cerebella in patients with OCD
Chen Y, 2004 [26][a]	13/19, drug-free for 1 week, no comorbidity, CCMD-2-R	ROI with the optical region as reference, $p<0.05$	Lower blood flow in the left prefrontal lobe, temporal lobe, and the occipital lobe when compared to the right side; difference in blood flow between mild and severe OCD cases in the bilateral caudate nucleus
Lin X, 2005 [28][a]	28/15, no medication, unknown comorbidity, ICD-10	ROI, $p<0.05$	Increased blood flow in the bilateral thalamus, parietal lobe, and the basal ganglia; decreased blood flow in the right temporal lobe; a positive correlation between the blood flow in the right basal ganglia and the obsessive-compulsive behavior score in the intrusive fears/excessive washing and avoidance group
Guo W, 2006 [25][a]	13/24, drug-free for 3 weeks, no comorbid depression, unknown diagnostic criteria	Automated extraction with the whole brain as reference, $p<0.05$	Decreased blood flow in the left inferior temporal lobe, supramarginal gyrus, transverse temporal gyri, outer dorsal nuclei, outer posterior nucleus, and the intercalated nucleus; increased blood flow in the left superior parietal lobule, and the dorsal thalamus in patients with OCD
Li Y, 2009 [29][a]	39/39, drug-free for 1 month, no comorbidity, ICD-10	ROI with the cerebellum as reference, $p<0.05$	Increased blood flow in bilateral prefrontal lobe and the anterior temporal lobe; assessment with the WCST found a negative correlation between blood flow in the right prefrontal lobe and the number of correct answers, a positive correlation between blood flow in the right anterior temporal lobe and the number of wrong answers, a positive correlation between the blood flow in the right prefrontal lobe and the number of consecutive wrong answers, and a positive correlation between blood flow in bilateral prefrontal lobes and right temporal lobe and intrusive thoughts

[a] original paper is in Chinese

DSM-II-R, second revised edition of the Diagnostic and Statistical Manual of Mental Disorders;

ICD-10, 10th edition of the International Classification of Diseases;

CCMD-2-R, second revised edition of the Chinese Classification of Mental Disorders;

ROI, region of interest; WCST, Wisconsin Card Sorting Test

temporal gyrus, left superior temporal gyrus, bilateral superior fontal gyrus, superior gyri orbitales, left superior parietal lobule, left frontal cingulate, bilateral putamina, right angular gyrus, and right cerebellum. These findings suggest blood flow changes in the cerebellum among patients with OCD; thus, changes of blood flow in the cerebellum itself or other brain regions related to the cerebellum may be missed when using the cerebellum as the reference region.[23] Later, this research team[24] found that compared to the whole brain region, patients with OCD have decreased blood flow in the bilateral putamen, superior temporal lobe, precuneus, right gyri orbitales, right superior frontal gyrus, right middle frontal gyrus, left temporal and occipital lobe, superior parietal lobule, and the cerebellar vermis. These findings support the hypothesized changes in the prefronto-striatal circuit among individuals with OCD.[24] Recently, this research team[25] used an automated extraction method (which is more efficient that the ROI method) in patients with OCD and found decreased blood flow in the left inferior temporal lobe, supramarginal gyrus, transverse temporal gyrus, outer dorsal nuclei, outer posterior nucleus, intercalated nucleus, and increased blood flow in the left superior parietal lobule, and the dorsal thalamus. Overall these results indicate that Patients with OCD have decreased blood flow in multiple regions in the bilateral temporal lobes and increased blood flow in the dorsal thalamus.

Using the ROI method and employing the optic region as the reference, Chen and colleagues[26] found that blood flow in patients with OCD was lower in the left temporal and occipital lobes than in controls. Among patients with OCD, blood flow was lower in the left prefrontal, temporal and occipital lobes than in the corresponding lobes on the right. Differences in the rates of blood flow in the bilateral caudate between mild and severe OCD support suggestions about the role for the temporal lobe and the caudate nucleus in the pathophysiology of OCD.[26] The same research team compared patients with OCD, anxiety disorders, and depressive disorders using SPECT [27] and found significant differences in the blood flow of Patients with OCD compared to that in patients with anxiety disorders but no significant differences between Patients with OCD and patients with depressive disorders.

Using the ROI method, Lin and colleagues[28] compared Patients with OCD with healthy controls and subdivided the OCD group into those whose symptoms were limited to intrusive thoughts (*n*=8), those with intrusive suspicion and repetitive behavior (*n*=8), and those with intrusive fears, excessive hand washing and avoidance (*n*=12). They found increased blood flow in the bilateral thalamus, parietal lobe, and basal ganglia and decreased blood flow in the right temporal lobe. There was a positive correlation between the blood flow in the right basal ganglia and the obsessive-compulsive behavior score among patients in the intrusive fears, excessive hand washing and avoidance group. These results suggest that patients with OCD have hyper-functioning of the bilateral thalamus, parietal lobes, and basal ganglia and hypo-functioning of the right temporal lobe. Obsessive-compulsive behavior in Patients with OCD with intrusive fears, excessive washing and avoidance is related to hyper-functioning of the basal ganglia.[28]

Using the ROI method and the cerebellum as the reference region, Li and colleagues studied the brain blood flow among patients with OCD and correlated the results with scores on the Modified version of Wisconsin Card Sorting Test (WCST) and with clinical severity. They found increased blood flow in bilateral prefrontal lobes and in the anterior temporal lobe. There was also a negative correlation between blood flow in the right prefrontal lobe and the number of correct answers on the WCST, a positive correlation between blood flow in the right anterior temporal lobe and the number of wrong answers, a positive correlation between the blood flow in the right prefrontal lobe and the number of consecutive wrong answers, and a positive correlation between blood flow in bilateral prefrontal lobes and right temporal lobe and intrusive thoughts. These results suggest a correlation between cognitive impairment and blood flow in the right prefrontal lobe and in the left thalamus; the results also suggest that abnormal functioning of the prefrontal lobe and of the right anterior temporal lobe may be the biological origin of intrusive thoughts among patients with OCD.[29] This research team also compared the SPECT results of Patients with OCD with those of patients with depressive disorders;[30] but in contrast to the findings of Chen's group[26] they found increased blood flow in the prefrontal lobe and anterior temporal lobe among patients with OCD, and decreased blood flow in these regions among patients with depressive disorders.

3.3 fMRI studies

The fMRI technique uses blood oxygen level dependent (BOLD) signals to reflect changes of brain function. Statistical methods to analyze resting state fMRI data include regional homogeneity (ReHo), amplitude of low frequency fluctuation (ALFF), functional connectivity, and independent component analysis (ICA).[31] The 5 fMRI studies on OCD conducted in China are presented in Table 5.

Tian and colleagues[32] reported increased ReHo in patients with OCD in the right frontal cortex, right parietal cortex, right insular, left cingulum and left parietal lobe. Yang and colleagues[33,34] assessed never-medicated Patients with OCD and found increased ReHo and ALFF in the left anterior cingulum, increased ALFF in the left middle cingulate gyrus, and lower ReHo in the left inferior temporal gyrus. Zhang and colleagues[35] found abnormal functional connectivity in the neural control networks of patients with OCD, including decreased functional connectivity in the posterior temporal area; increased functional binding in the cingulum, precuneus, thalamus and cerebellum; and a significantly higher level of local clustering (compared to the small-world architecture of health control subjects).

Hou and colleagues[36] conducted fMRI while Patients with OCD and control subjects completed the Chinese version of the Stroop task and a block design test. They found that several brain regions of Patients with OCD showed above normal levels of activation during the relatively easy non-interference section of the color and word matching task (including the left parahippocampal gyrus, paracentral lobule, thalamus, and calcarine gyrus) and only a few regions showed lower levels of activation than controls (the anterior cingulate and left caudate nucleus); however, during the more difficult matching task when interference was present there were no brain regions in Patients with OCD with higher than normal activation and some

Table 5. Functional magnetic resonance imaging (fMRI) studies of Obsessive-Compulsive Disorder (OCD) in China

Reference	# case/# controls Treatment Comorbidity Criteria	Model of the machine	Analytic method	Main results
Tian F, 2010 [32]a	13/14, drug-free for 6 months, no comorbid schizophrenia, DSM-IV	3.0T	ReHo, two-sample t-test, uncorrected, $p<0.0002$, voxel >10	ReHo enhancement in the right frontal cortex, right parietal cortex, right insular, left cingulate and left parietal in patients with OCD
Yang T, 2010 [33]b	22/22, no medication, no comorbidity, DSM-IV	1.5T	ReHo, two-sample t-test, FDR corrected, $p<0.05$	Increased ReHo and ALFF in the left anterior cingulate; decreased ReHo in the left inferior temporal gyrus in patient with OCD
Yang T, 2011 [34]a	22/22, no medication, no comorbidity, DSM-IV	1.5T	ALFF, two-sample t-test, Monte Carlo simulation $p<0.001$, voxel ≥33	Increased ALFF in the left anterior and middle cingulate gyrus in patients with OCD
Zhang T, 2011 [35]b	18/16, unknown medication status, no comorbidity, DSM-IV	3.0T	two-sample t-test, FDR corrected, $p<0.05$	Decreased functional connectivity in the posterior temporal area, enhancement of the functional binding in cingulate, precuneus, thalamus and cerebellum; higher local clustering of the control networks
Hou J, 2011 [36]a	13/15, unknown medication status, unknown comorbidity, CCMD-3 and DSM-IV	3.0T	voxel-based methods, FDR corrected, $p<0.05$, voxel >10	Increased brain activation in the left parahippocampal gyrus, paracentral lobule, thalamus, and calcarine gyri; reduced activation in the anterior cingulate and left caudate nucleus; when asked to complete the relatively complex color words tasks with interference, patients with OCD show reduced activation in the bilateral orbital prefrontal cortex, left anterior cingulate and left caudate nucleus .

[a] original paper in Chinese [b] original paper in English

DSM-IV, 4th edition of Diagnostic and Statistical Manual of Mental Disorders;

CCMD-3, 3rd edition of the Chinese Classification of Mental Disorders;

ReHo, regional homogeneity; FDR, false discovery rate; ALFF, amplitude of low frequency fluctuation

brain regions showed lower than normal activation (e.g., bilateral orbital prefrontal cortex, left anterior cingulum and left caudate nucleus). Taken together, these results suggest that functional abnormalities in the orbital frontal cortex, anterior cingulate cortex, caudate nucleus and other brain regions play important roles in the pathogenesis of OCD.[36]

3.4 MRS studies

MRS is a functional imaging technique that quantitatively measures the chemical composition of specific nuclei. It uses nuclear magnetic resonance to assess chemical shifts in order to detect the concentrations of neurometabolities in different regions of the brain. The neurometabolites frequently studied include N-acetylaspartate (NAA), creatine (Cr), choline-containing compound (Cho), myoinositol (mI) and glutamine and glutamate complex (Glx). Five papers from China that used the hydrogen proton magnetic resonance spectroscopy (^{1}H-MRS) method for studying OCD are described in Table 6.

Lu and colleagues[37] reported that NAA/Cr ratios in the prefrontal cortex and left hippocampus of patients with OCD were higher than in normal controls and that the concentration of NAA in the right prefrontal cortex of patients was higher than in controls. These results suggest increased neuronal vitality in the prefrontal cortex and left hippocampus of patients with OCD and abnormal membrane metabolism in the hippocampus of patients with OCD.[37]

Fan and colleagues[38] found that the NAA/Cr ratio was significantly higher in the medial prefrontal cortex of patients with OCD than in healthy controls. This research team subsequently reported that the peak ratios of ml/Cr and NAA/Cr in the bilateral thalamus were significantly lower in Patients with OCD than in controls and that the NAA/Cr ratio in the right thalamus of patients was negatively correlated with the duration of OCD.[39] These findings support the hypothesized role of the prefronto- striato-thalamic loop in OCD. This team also found that the concentration of NAA metabolites was significantly higher in Patients with OCD with a family history OCD than in normal controls or in Patients with OCD without a family history.[40] This result suggests that further study about the pathophysiologcial mechanisms of NAA may help identify susceptible genes for OCD, especially in those with a family history of the condition.

Zhao and colleagues[41] reported several findings about the NAA/Cr and Cho/Cr ratios: (a) compared with normal controls, the NAA/Cr ratio in patients with OCD was higher in the right caudate nuclei and the left hippocampus but lower in the genu of the corpus callosum; (b) compared to normal controls the Cho/Cr ratio in Patients with OCD was higher in the right caudate nucleus and the left temporal lobe; (c) among Patients with OCD the duration of illness was negatively

Table 6. Magnetic resonance spectroscopy (MRS) studies of Obsessive-Compulsive Disorder (OCD) in China

Reference	# case/# controls Treatment Comorbidity Criteria	Model of the machine	Single or multiple voxel	Analytic method	Main results
Lu Y, 2007 [37][a]	10/10, unknown medication status, no comorbidity, CCMD-3	1.5T	single	One-sample t-test, $p<0.05$	Increased NAA/Cr ratios in prefrontal cortex and left hippocampus in patients with OCD; higher NAA in right prefrontal cortex
Fan Q, 2010 [38][b]	21/19, drug-free for 2 months, no comorbidity, DSM-IV	1.5T	single	ANCOVA with age as the covariate, $p<0.05$	Increased NAA/Cr ratio in the inner prefrontal lobe in OCD
Fan Q, 2010 [40][a]	24[c] /12 drug-free for 2 months, no comorbidity, CCMD-3	1.5T	single	ANOVA, LSD corrected, $p<0.05$	Higher levels of metabolites of NAA in medial prefrontal cortex in OCD.
You C, 2011 [39][a]	13/14, drug-free for 2 months, unknown comorbidity, CCMD-3	1.5T	single	One sample t-test, $p<0.05$	Lower ml/Cr and NAA/Cr in bilateral thalamus in patient with OCD; the NAA/Cr ratio in right thalamus was negatively associated with the duration of OCD
Zhao X, 2011 [41][a]	19/22, unknown medication status, no comorbidity, DSM-IV and CCMD-3	1.5T	multiple	One sample t-test, $p<0.05$	Higher NAA/Cr ratios in right caudate nuclei and left hippocampus in patient with OCD; higher Cho/Cr ratios in right caudate nucleus and left temporal lobe; duration of OCD was negatively correlated with NAA/Cr ratios in right prefrontal lobe

[a] original paper in Chinese [b] original paper in English [c] of the 24 OCD cases, 10 had a positive family history and 12 did not

CCMD-3, 3rd edition of the Chinese Classification of Mental Disorders;

DSM-IV, 4th edition of Diagnostic and Statistical Manual of Mental Disorders;

ANCOVA, analysis of covariance; ANOVA, analysis of variance; LSD, least significant difference;

NAA, N-acetylaspartate; Cr, creatine; ml, myoinositol, Cho, choline-containing compound

correlated with the NAA/Cr ratio in the right prefrontal lobe; and (d) among Patients with OCD the NAA/Cr ratio in the genu of the corpus callosum and the Cho/Cr ratio in the left temporal lobe were negatively correlated with the total score of YBOCS. Taken together, these results suggest that increased function of neurons in the right caudate nucleus and left hippocampus and decreased function of neurons in the genu of the corpus callosum may play an important role in the development of OCD.[41]

3.5 Summary of functional neuroimaging studies

There are more functional neuroimaging studies of OCD in China than structural neuroimaging studies. SPECT studies were conducted during the early stage of neuroimaging research about OCD in China but recently fMRI and MRS studies have become more popular. Studies have now started to focus on subgroups of Patients with OCD, including those with a positive family history or those who are treatment refractory. Most PET, fMRI and MRS studies have consistent results: the cerebral metabolism and activation in the prefrontal cortex, striatum and thalamencephalon are increased in patients with OCD and are correlated with patients' cognitive functioning, with the severity of their symptoms, and with the duration of their illness. These studies have also reported that the elevated cerebral metabolism in these brain regions of Patients with OCD decreases after surgical treatments for OCD.

These findings parallel those reported in studies from other countries. A summary of English-language publications of functional neuroimaging studies of OCD by Kwon and colleagues[3] reported that the orbitofrontal cortex, anterior cingulate cortex and basal ganglia in patients with OCD showed a high metabolic rate or excessive excitability during the resting state and when obsessive-compulsive symptoms were active, but the metabolic rate and level of blood perfusion in these regions decreased with pharmacological or cognitive behavioral treatment. Whiteside and colleagues[42] conducted a meta–analysis of PET studies and SPECT studies which concluded that radiotracer uptake in patients with OCD was abnormal in the orbital gyrus and the head of the caudate nucleus. Another meta-analysis by Rotge and colleagues[43] of fMRI and PET studies based on the symptom provocation paradigm concluded that the excitability of the bilateral orbitofrontal cortex, the bilateral anterior cingulate cortex and the left dorsolateral prefrontal cortex were higher in patients with OCD than in controls.

Functional neuroimaging studies of OCD from China confirm the centrality of the prefrontol-striato-thalamic circuit in the pathophysiology of OCD. However, SPECT studies of OCD from China also report abnormal functioning in several other regions of the brain including the parietal lobe, temporal lobe, insular cortex, hippocampus, parahippocampal gyrus, cerebellar tonsils and corpus callosum. But findings about the increased or decreased blood perfusion of these regions in patients with OCD are inconsistent.

4. Future directions

The technology and design of imaging studies of OCD in China need to be updated and improved. None of the published DTI studies of OCD in China have yet used fiber tractography and the published MRS studies have not assessed the absolute concentrations of neural metabolites. fMRI studies of brain networks and task-related fMRI studies among Patients with OCD are quite limited. Clinical neuroimaging studies in China have almost all used a case-control design; prospective cohort studies and before-after treatment studies are needed to understand the neurodevelopmental process underlying OCD and the underlying mechanisms for achieving a positive treatment effect. And stratified analysis by age of onset, pattern of symptoms and other variables may help identified biologically or genetically homogenous subgroups of Patients with OCD.

Conflict of interest

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

Funding

This review is funded by National Key Clinical Disciplines at Shanghai Mental Health Center (Office of Medical Affairs, Ministry of Health, 2011-873; OMA-MH, 2011-873), the Shanghai Science and Technology Committee Medical Science Guidance Project (No.124119a8200) and the Shanghai Jiao Tong University 'Medicine and Engineering collaboration foundation' project (No.YG2012MS59).

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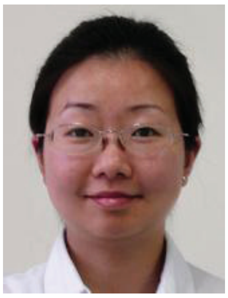

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