

A review of neuroimaging studies of anxiety disorders in China

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Background: Anxiety disorders are highly prevalent internationally, and constitute a substantial social and economic burden for patients, their families, and society. A number of neuroimaging studies have investigated the etiology of anxiety disorders in China in the last decade. We discuss the findings of these studies, and compare them with the results of neuroimaging studies of anxiety disorders outside China.

Method: A literature search was conducted using the Chinese BioMedical Literature Database, the Chinese Scientific and Technical Periodicals Database, the Chinese Journal Full-text Database, and PubMed, from 1989 to April 2009. We selected neuroimaging studies in which all participants and researchers were Chinese.

Results: Twenty-five studies fit our inclusion criteria. Nine studies examined general anxiety disorder (GAD) and/or panic disorder (PD), eight examined obsessive-compulsive disorder (OCD), and eight examined posttraumatic stress disorder (PTSD). Our literature review revealed several general findings. First, reduced regional cerebral blood flow (rCBF) was found in the frontal lobe and temporal lobe in patients with GAD and PD compared with healthy controls. Second, when viewing images with negative and positive valence, relatively increased or decreased activation was found in several brain areas in patients with GAD and PD, respectively. Third, studies with positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) imaging revealed that OCD patients exhibited hyperperfusion and hypoperfusion in some brain regions compared with healthy controls. Neuroimaging studies of PTSD indicate that the hippocampal volume and the N-acetylaspartic acid (NAA) level and the NAA/creatinine ratio in the hippocampus are decreased in patients relative to controls.

Conclusion: Neuroimaging studies within and outside China have provided evidence of specific neurobiological changes associated with anxiety disorders. However, results have not been entirely consistent across different studies of patients with the same diagnoses. International collaborative research using large samples and robust designs should be conducted in future.

Keywords: anxiety disorders, neuroimaging, GAD, PD, OCD, PTSD

Introduction

Anxiety disorders are relatively common among mental disorders, and have a prevalence of 5.6% in China, according to a recent report.¹ The *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition; DSM-IV) reports a 1-year prevalence rate in the United States for general anxiety disorder (GAD) of approximately 3%, 1%–2% for panic disorder (PD), 1.5%–2.1% for obsessive–compulsive disorder (OCD), and a lifetime prevalence for post-traumatic stress disorder (PTSD) ranging from 1%–14%.² However, the etiology of anxiety disorders remains unclear. Neuroimaging techniques enabling the evaluation of the human brain in vivo have emerged as valuable tools for

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elucidating the pathophysiological mechanisms of anxiety disorders. Neuroimaging studies have been conducted to investigate the cause of anxiety disorders for over a decade in China. In this article, we sought to present important findings of a body of neuroimaging research on anxiety disorders in China to colleagues in the international research community, to promote future collaborations in the hope of furthering our understanding of anxiety disorders.

Method

We conducted a search of the database of Chinese BioMedical Literature, the database of Chinese Scientific and Technical Periodicals, the Chinese Journal Full-text Database and PubMed from 1989 to April 2009. Our search was performed using the following keywords: “anxiety disorder”, “general anxiety disorder, GAD”, “panic disorder, PD”, “social anxiety disorder, SAD”, “posttraumatic stress disorder, PTSD”, “obsessive compulsive disorder, OCD”, “phobia”, combined one by one with “neuroimaging”, “magnetic resonance imaging, MRI”, “Positron emission tomography, PET” and “Single photon emission computed tomography, SPECT”, “functional magnetic resonance imaging, fMRI”. We selected neuroimaging studies according to the criteria that participants and researchers were Chinese. Overlapping articles were excluded.

Results

We found a total of 29 reports of neuroimaging studies of anxiety disorders. However, only 25 papers fit all of our inclusion criteria; four papers were excluded for having overlapping content and authors. No studies of social anxiety disorder (SAD) or single phobias were found. We describe the results

of these studies in the following sections, grouped according to whether they dealt with GAD/PD, OCD, or PTSD.

General anxiety disorder and panic disorder

Nine studies of GAD and PD were included in our dataset. We found that GAD and PD patients were both assigned to a single group in most neuroimaging studies included. Four of the papers used SPECT, while five used fMRI (see Table 1 for an overview).

Single photon emission computed tomography

The first SPECT study of anxiety disorder (PD) in China was published in 1998.³ Another three studies (GAD and PD) were conducted in 2002 and 2005.⁴⁻⁶ One study focused on symptom provocation, using Raven’s reasoning test to elicit anxiety symptoms.⁴ Only one study used statistical parametric mapping (SPM) methods to analyze changes in regional cerebral blood flow (rCBF).⁵

All of the included studies demonstrated reduced rCBF in the frontal lobe and temporal lobe in patients with GAD and PD compared with those of healthy controls.³⁻⁶ In addition, three studies reported lower rCBF in the basal ganglia.^{3,4,6} Only one study reported an increase in rCBF in the basal ganglia in patients.⁵ Moreover, some studies found that patients exhibited decreased rCBF in the thalamus,⁴ callosal gyrus,⁵ and parts of the occipital and parietal lobes,⁴ while rCBF was higher in the frontoparietal, postcentral gyrus,⁴ precentral gyrus, and parts of the orbitofrontal cortex in patients relative to controls.⁵ Li et al reported that a reduction of rCBF was

Table 1 SPECT studies of GAD and/or PD in China

Author	Subjects	Method	Result
Li et al ³	16P (21–44, 33.9 ± 5) PD 15C (23–55, 35 ± 8)	⁹⁹ Tc ^m -ECD CCMD-2-R HAMA	Hypoperfusion especially in the frontal lobe, temporal lobe, and left basal ganglia
Wan et al ⁴	20P (25–63, 40.65 ± 10.67) 12GAD 6PD 2GAD + PD 20C (22–60, 39.25 ± 12.13)	⁹⁹ Tc ^m -ECD CCMD-2-R HAMA	Hypoperfusion in most cerebral regions at rest state, hypoperfusion at stress state, Hyperperfusion in the frontoparietal and postcentral gyrus at rest state
Jiang et al ⁵	19P (20–59, 40.8 ± 13.2) GAD + PD 23C (25–54, 38 ± 9)	⁹⁹ Tc ^m -ECD CCMD-2 ICD-10	Hypoperfusion in the bilateral temporal, superior frontal gyrus and callosal gyrus, Hyperperfusion in the precentral gyrus, frontal lob orbital part, left basal ganglia
Sun et al ⁶	65P (13–62, 37.3 ± 10.5) GAD + PD 31 use drug, 34 drug naïve 21C (21–65, 36.0 ± 11.2)	⁹⁹ Tc ^m -ECD CCMD-2-R DSM-IV HAMA	Hypoperfusion in the bilateral frontal lobes, paralimbic system, temporal lobes and basal ganglia

Abbreviations: P, patients; C, controls; PD, panic disorder; CCMD-2-R, Chinese Classification and Diagnostic Criteria of Mental Disorders, version 2 revision; HAMA, Hamilton anxiety scale; GAD, general anxiety disorder; ICD-10, International Classification of Diseases-10; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

negatively correlated with Hamilton Anxiety Scale (HAMA) scores in PD patients.³ Moreover, Sun et al found that the course of illness was negatively correlated with changes of rCBF in GAD and PD patients.⁶ They conducted a follow-up SPECT scan for seven patients, revealing that increased rCBF was related to symptom improvements. Wan et al's results also indicated that rCBF in patients was significantly increased after exposure to a stressor, opposite to the pattern of activation changes exhibited by healthy controls.⁴

Functional magnetic resonance imaging

In two experiments, Li et al examined patients (7GAD, 2PD, 1GAD + PD) and healthy controls (n = 10) with fMRI while they were presented with emotionally neutral or threat-related words.⁷ By presenting neutral words alternating with rest periods, their first experiment revealed that the superior temporal gyrus, middle temporal gyrus, middle frontal gyrus, superior frontal gyrus, and parietal lobe were activated in patients, while only the superior temporal gyrus and transverse temporal gyrus were activated in healthy controls. In the second experiment, neutral words were presented, alternating with threat-related words. Activation in the superior temporal gyrus, middle temporal gyrus, middle frontal gyrus, inferior frontal gyrus, cingulate gyrus, and inferior parietal lobule was observed only in patients. However, in the second experiment of a study by Zhao et al, patients exhibited deactivation in several regions, including the medial prefrontal cortex (MPFC) and bilateral inferior parietal cortex.⁸ In addition, their first experiment revealed stronger deactivation in the posterior cingulate cortex (PCC) of patients compared to controls. In another study by Zhao et al, the same method was used to examine patients with GAD (n = 10).⁹ The results of their first experiment revealed that patients exhibited greater activation in the bilateral superior temporal gyrus, dorsal lateral prefrontal cortex, and bilateral inferior parietal lobules compared with those of controls (n = 10). In their second experiment, patients, but not controls, exhibited significant activation in several brain areas, including the bilateral superior temporal gyrus, middle temporal gyrus, inferior prefrontal gyrus, inferior parietal lobules, anterior motor areas, supplemental motor areas, anterior cingulate gyrus, and left dorsal lateral prefrontal cortex.

Li et al reported that patients (five with GAD and three with PD) exhibited greater activation in the right inferior frontal gyrus, right middle temporal gyrus and weaker activation in the right inferior parietal lobule, right lingual gyrus, and right precuneus when viewing negatively valenced images.

In addition, when positively valenced images were presented, patients exhibited stronger activation in the right paracentral lobule, bilateral middle frontal gyri, left cerebellar declive, and right cingulate gyrus, while controls (n = 8) exhibited greater activation in the left middle and superior frontal gyrus, left postcentral gyrus, left lentiform nucleus, left putamen, and left anterior cingulate gyrus.¹⁰ The same experiment was later conducted in GAD patients (n = 9).¹¹ Patients exhibited stronger activation in the right precentral gyrus, right hippocampus, right lingual gyrus, and weaker activation in the right frontal gyrus, left paracentral gyrus, right middle temporal gyrus, right fusiform gyrus, left middle occipital gyrus, and the right tonsil of the cerebellum compared with those of controls (n = 9) when negative or positive pictures were viewed.

Obsessive-compulsive disorder

To date, there have been few neuroimaging studies in China examining OCD. At the time of our literature search, we found only eight studies that used SPECT or other functional neuroimaging techniques to examine OCD.

Single photon emission computed tomography

The first SPECT study of OCD in China was published in 1997, and did not include healthy controls.¹² In this study, 18 of 22 unmedicated OCD patients exhibited a reduction of rCBF in some brain regions, including the parietal lobe (12/22), frontal lobe (7/22), temporal lobe (5/22), and occipital lobe (3/22). Five patients were scanned when symptoms were provoked, and the rCBF of the parietal lobe and frontal lobe in four patients was found to be increased compared with the resting state. Moreover, of three patients who received effective treatment, rCBF was found to return to normal in two. Other studies have reported hyperperfusion in the thalamus, parietal lobes, basal ganglia,¹³ prefrontal lobes, anterior temporal lobes,¹⁴ and hypoperfusion in the temporo-occipital lobe,¹⁵ right temporal lobe¹³ in OCD patients compared with healthy controls. One study reported that rCBF in the left hemisphere was significantly lower than that in the right hemisphere in patients (see in Table 2).¹⁵ Lin et al examined patients exhibiting washing and avoidant phobic behavior, revealing that scores on the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) were correlated positively with rCBF in the right basal ganglia.¹³

Li et al found that rCBF results varied with different analysis methods.¹⁶ Reduced rCBF was found in the right anterior temporal, temporo-parietal, and left temporo-occipital lobes

Table 2 SPECT studies of OCD in China

Author	Subjects	Method	Result
Yang et al ¹²	22P (20–60, 30 ± 10) 7F 15M	DSM-III-R CCMD-2 Y-BOCS	Hypoperfusion
Li et al ¹⁶	14P (30.8 ± 12.38) 23C	CCMD-2 ICD-10 Y-BOCS	Hypoperfusion
Chen et al ¹⁵	13P (35 ± 14) 6F 7M 19C (38 ± 10) 4F 15M	CCMD-2-R Y-BOCS	Hypoperfusion Asymmetry: L < R
Lin et al ¹³	28P (14–45, 25.25 ± 8.41) 12F 16M 15C (14–45, 24.87 ± 6.7) 7F 8M	ICD-10 Y-BOCS	Hyperperfusion in the thalamus, parietal lobes and basal ganglia, Hypoperfusion in right temporal lobe
Li et al ¹⁴	22 (16–46, 24.1 ± 7.8) 10F 12M 19C (19–41, 29.2 ± 9.7) 10F 9M	ICD-10 Y-BOCS	Hyperperfusion

Abbreviations: P, patients; F, female; M, male; CCMD-2, Chinese Classification and Diagnostic Criteria of Mental Disorders 2nd version; DSM-III, *Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition Revised; Y-BOCS, Yale-Brown Obsessive Compulsive Scale; C, controls; ICD-10, International Classification of Diseases-10; L, left; R, right.

in OCD patients using a region of interest (ROI) method, but lower in the bilateral putamen, superior temporal gyrus, precuneus, right orbital gyrus, superior and middle frontal gyrus, left temporo-occipital lobes, and superior parietal gyrus when SPM analysis was used.

Other functional neuroimaging studies of obsessive-compulsive disorder

Zuo et al used ¹⁸F-FDG PET to examine six patients who were resistant to medication and psychotherapy treatment and six age- and –gender-matched healthy controls.¹⁷ Compared with healthy controls, OCD patients exhibited elevated glucose metabolism was found in the left cingulate gyrus, left superior frontal lobe, bilateral middle frontal lobes, left inferior frontal lobe, bilateral extra-putaminal white matter, left anterior commissure, left parahippocampus, bilateral thalamic nucleus dorsalis medialis, and left tonsilla cerebelli.

Chen et al investigated regional relative cerebral blood flow (rCBF) of 10 patients using magnetic resonance perfusion-weighted images.¹⁸ It was found that rCBF was increased in the left inferior frontal cortex, anterior cingulate cortex, the head of the right caudate nucleus, the putamen, bilateral orbitofrontal cortex, thalamus, and amygdala when patients were in the provoked state. However, rCBF within the left inferior frontal cortex and right putamen were negatively correlated with scores on the OCD analogue scale. It should be noted that this study did not include a healthy control group.

A magnetic resonance spectroscopy (MRS) imaging study of 10 patients and 10 healthy controls revealed that N-acetylaspartic acid (NAA)/creatinine (Cr) ratios in the right prefrontal region, choline (Cho)/Cr ratios in the hippocampus, and Cho levels in the right hippocampus were higher in patients with OCD compared with those of controls.¹⁹

Posttraumatic stress disorder

Though many imaging studies investigating PTSD have been conducted internationally, only eight imaging studies of PTSD have been conducted in China, similar to the case for OCD.

Single photon emission computed tomography

Only one study using SPECT to examine PTSD in China has been published to date. This semi-quantitative study did not include normal controls,²⁰ and involved SPECT scanning of 30 patients. The conditions of half of these patients were related to sexual abuse. The results showed that after exposure to traumatic stimuli, rCBF was increased in the right amygdala, thalamus, and bilateral occipital lobes, but was decreased in the medial temporal lobes, hippocampus, and left middle frontal gyrus. The rCBF reduction in the left hippocampus was more significant than that in the right.

Magnetic resonance imaging

Three studies reported that the volume of the hippocampus in patients with PTSD was significantly reduced.^{21–23} Chen et al

also reported a reduction of volume in the anterior cingulate cortex and bilateral insula (see Table 3).²¹

Three MRS imaging studies of PTSD in China (see Table 3) have been published at present. All three of these studies reported a reduction in NAA levels or NAA/Cr ratio in the hippocampus of patients with PTSD compared to controls.^{22,24,25}

Chen et al conducted an fMRI investigation in 12 patients who developed PTSD after a fire, six victims of the same fire that did not suffer PTSD, and six healthy volunteers.^{26,27} Compared with the control group, the PTSD group was found to exhibit significantly less activation in the frontal lobe, anterior cingulate cortex, and parahippocampal gyrus while performing a Stroop task.²⁶ In addition, during an encoding task, patients exhibited significantly less activation in the left insula.²⁷

Discussion

Although neuroimaging research on anxiety disorders has been conducted in China for the last decade, the number of studies remains small compared with the number of studies in the international research community. Of the studies that have been conducted in China, several SPECT experiments have reported decreased rCBF in the frontal and temporal lobes of patients with PD.^{28–30} Others have reported abnormalities in the hippocampus and parahippocampus.^{28,31–35} One study of PD in China reported that rCBF was lower in the frontal and temporal lobes, and in the left basal ganglia.³

A number of MRI studies have reported volume decreases in the temporal lobe,^{36–38} amygdala,³⁹ and anterior

cingulate cortex in subjects with PD.^{40,41} However, Uchida et al reported a PD-related volume increase in the left insula.⁴⁰

Hyperactivity has been found in the frontal orbitofrontal cortex, hippocampus, cingulate, and amygdala of patients with PD in some fMRI studies.^{42–45} In addition, the results of Pfeleiderer et al implicate the amygdala in the pathogenesis of PD.⁴⁶

The results of two fMRI studies of patients with GAD in China indicated a dysfunction of the superior temporal lobe and dorsal prefrontal cortex,⁹ the right middle frontal gyrus, the tonsil of the cerebellum, hippocampus, and occipital lobe.¹¹ However, De Bellis et al reported that the volumes of the temporal lobe and amygdala were increased in patients with GAD.^{47,48} Studies of fMRI in patients with GAD in other countries have reported increased activity in the ventral prefrontal, cingulate, and orbitofrontal cortices, and the amygdala.^{49–52}

Chen, Yang and Xiong reported that the volumes of the hippocampus, anterior cingulate cortex, and insula were decreased in patients with PTSD.^{21–23} Overall, the results of structural neuroimaging studies in China are similar to those reported by several meta-analyses of research in other countries.^{53–57}

fMRI studies of patients with PTSD in China while performing cognitive tasks have reported decreased reactivity in the frontal lobe, anterior cingulate cortex, parahippocampal gyrus and left insula, relative to controls.^{26,27} Using resting-state paradigms to measure cerebral perfusion, researchers

Table 3 Structure MRI and magnetic resonance spectroscopy imaging studies of posttraumatic stress disorder (PTSD) in China

Author	Subjects	Method	Result
Chen et al ²¹	12P (26–52, 34 ± 5) 8F 4M 12 NP (27–50, 33 ± 5) 8F 4M	DSM-IV SCID MRI VBM	Gray matter density in the left hippocampus, left anterior cingulate cortex, and bilateral insulars↓
Xiong et al ²³	30P (18–50, 28.33 ± 10.79) 20F 10M 30C (18–50, 35.4) 18F 12M	CCMD-3 MRI ROI	Volume of the bilateral hippocampus↓
Yang et al ²²	17P (13–62, 37.2) 10F 7M 17C (14–62, 38.5)	DSM-IV MRI MRS	Volume of the left hippocampus↓ NAA and Cr level in the bilateral hippocampus↓
Chen et al ²⁴	12P (26–47, 34) 8F 4M 12C 6NP (26–45) 4F 2M 6HC (28–47) 4F 2M	DSM-IV SCID MRS	NAA/Cr ratio in the left hippocampus↓
Xia et al ²⁵	19P (31.2 ± 7.4) 13F 6M 19C (34.4 ± 8.1) 14F 5M	CCMD-3 MRS	NAA and NAA/Cr in the bilateral hippocampus↓

Abbreviations: P, patients; F, female; M, male; NP, victims of the same fire without PTSD; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition; SCID, Structured Clinical Interview for DSM-IV; MRI, magnetic resonance imaging; VBM, voxel-based morphometry; C, controls; CCMD-3, Chinese Classification and Diagnostic Criteria of Mental Disorders 3rd version; ROI, region of interest; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartic acid; Cr, creatine.

outside of China have also reported abnormalities in the frontal, temporal and parietal lobes, thalamus, caudate, and cerebellum of patients with PTSD.^{58–62}

International symptom provocation studies have generally reported heightened amygdala responses^{63–67} and decreased activation in medial frontal, temporal and parietal cortices, hippocampus, and thalamus in individuals with PTSD, compared with non-PTSD controls.^{67–78}

Task activation studies outside of China have demonstrated greater amygdala activation, but lower anterior cingulate cortex, mesial and dorsolateral prefrontal cortex, and hippocampus reactivity in PTSD patients.^{78–87} A recent international meta-analysis confirmed an association between PTSD and hypoactivation in ventromedial prefrontal cortex, and rostral and dorsal anterior cingulate cortices.⁸⁸

A number of neuroimaging studies have implicated activity increases in prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, striatum, thalamus, hippocampus and parahippocampus.^{17,18,89–92} The orbitofrontal-striatal circuit is thought to be involved in the pathophysiology of OCD.^{93,94} Some studies have reported increased amygdala activation in patients with OCD relative to controls.^{18,95} This suggests that limbic structures might be associated with the pathology of OCD.⁹⁴

Our literature search did not reveal any neuroimaging studies of social anxiety disorder (SAD) in China. Some international studies suggested that the anterior paralimbic and sensory cortical regions were involved in specific phobia (SP).^{96–103} However, the amygdala and hippocampus have been related to the pathophysiology of SAD.^{104–106} Some studies also found evidence of dysfunction in the insula, cingulate cortex, frontal cortex, and temporal cortex of patients with SAD.^{107–109}

The results of studies inside and outside China are not entirely consistent in terms of the brain areas implicated in anxiety disorders. We propose that the differences in the results of these studies have arisen from several factors, including small sample sizes, different demographic characteristics (including age, gender, symptom severity, course, comorbidity disorders, medication), and differences in experimental neuroimaging paradigms and analysis methodology.

Despite the limitations of the research discussed above, these neuroimaging studies have provided valuable evidence of dysfunction in some brain regions of patients with anxiety disorders. On the basis of the data included in the present analysis, we hypothesize that different subtypes of anxiety disorders may involve abnormalities in different neural circuits, but similar core areas (see Table 4). It appears that the amygdala, cingulate cortex and frontal cortex underlie anxiety disorders in general, because they have been implicated in

Table 4 Dysfunction of brain regions of anxiety

	PD	GAD	OCD	PTSD	SP	SAD
Amygdala	+	+	±	+	±	+
Hippocampus/parahippocampus	+		+	+	+	+
Cingulate cortex	+	+	+	+	+	+
Thalamus			+	+	+	
Insula	+			+		+
Striatum			+			
Frontal cortex	+	+	+	+	+	+
Orbitofrontal cortex	+	+	+	+		
Temporal cortex	+	+			+	+
Occipital cortex				+	+	
Parietal cortex					+	

Abbreviations: PD, panic disorder; GAD, general anxiety disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SP, specific phobia; SAD, social anxiety disorder.

all of the anxiety disorders included in the selected studies. The hippocampus appears to be related to specific anxiety disorders, but not to GAD. The thalamus appears to be primarily associated with OCD, PTSD and SP, whereas the insula is related to PD, SAD and PTSD. The striatum has been implicated only in OCD, while the parietal cortex has been implicated only in SP. The orbitofrontal cortex is related to PD, GAD, OCD and PTSD, while temporal cortex dysfunction has been associated with PD, GAD, SAD and SP. The occipital lobe appears to be involved in PTSD and SP.

In conclusion, future research involving larger and more homogenous samples, and international collaboration is required to shed further light on the details of the mechanisms underlying anxiety disorders.

Disclosure

The authors report no conflicts of interest for this work.

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