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Neuroanatomical deficits in drug-naïve adult patients with generalized social anxiety disorder: A voxel-based morphometry study

Yajing Meng [a], Su Lui [b,**], Changjian Qiu [a], Lihua Qiu [b], Sunima Lama [b], Xiaoqi Huang [b], Yuan Feng [a], Chunyan Zhu [a], Qiyong Gong [b], Wei Zhang [a,*]

[a] Mental Health Center, West China Hospital of Sichuan University, 37 Guoxue Lane, 610041 Chengdu, Sichuan Province, PR China
[b] Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital of Sichuan University, 37 Guoxue Lane, 610041 Chengdu, Sichuan Province, PR China

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ABSTRACT

Little is known, so far, about the cerebral structural deficits in drug-naïve adult social anxiety disorder (SAD) patients. The present study aimed to explore the cerebral anatomic deficits in drug-naïve adult generalized SAD patients using voxel-based morphometric analysis with DARTEL. High-resolution T1-weighted images were acquired from 20 drug-naïve adult SAD patients and 19 age-, sex- and education-matched controls. The volumes of gray matter, white matter, cerebrospinal fluid, and total intracranial volume were compared between groups using two-sample *t*-tests with age and gender as covariates. Gray matter density (GMD) was compared between groups using voxel-wise two-sample *t*-test analysis. Correlation analysis was used to identify any associations between regional GMD and clinical symptoms. Compared with healthy controls, SAD patients showed significantly lower GMD in the bilateral thalami, right amygdala, and right precuneus. Furthermore, the GMD in the right amygdala was negatively related to the disease duration, but positively correlated with age of onset. Our findings demonstrated that cerebral anatomic deficits could be found within limbic and thalamic areas in drug-naïve SAD patients, which provides structural information to complement the functional alterations observed in the same regions.

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1. Introduction

Social anxiety disorder (SAD), often referred to as social phobia, is thought to involve fear and avoidance of the scrutiny of others. As the most common anxiety disorder, it is also a risk factor for subsequent depressive illness and substance abuse (Mather et al., 2010). Besides its serious impact on human health, little is known about the pathogenesis of this disorder. Previous studies using functional magnetic resonance imaging (fMRI) found altered brain function in SAD within the medial prefrontal cortex and the limbic regions, including the amygdala, hippocampus, and insula (Tillfors et al., 2001; Furmark et al., 2002; Stein et al., 2002; Straube et al., 2004; Etkin and Wager, 2007; Sareen et al., 2007; Gentili et al., 2008; Engel et al., 2009; Damsa et al., 2009). However, a better understanding of the neurobiology of SAD would require investigations at the morphological level, especially in patients not yet exposed to psychotherapy or psychiatric medications. To date, the very few morphological studies of drug-naïve SAD patients yet conducted have revealed results showing no significant difference in respect to total cerebral, caudate, putamen, and thalamic volumes (Potts et al., 1994); lower gray matter (GM) volume of amygdala, hippocampus (Irle, 2010), bilateral temporal poles and left lateral orbitofrontal cortex (Talati et al., 2013); greater GM in the left middle occipital, bilateral supramarginal, angular cortices, and the left cerebellum (Talati et al., 2013); and bilateral cortical thinning in fusiform and post-central regions (Syal et al., 2012) in SAD relative to controls. In view of the inconsistent findings from previous studies, it is necessary to explore the GM deficits within the whole brain in SAD patients, especially for patients who are free of treatment/medication and also free of other psychiatric comorbidity including other anxiety disorders.

Voxel-based morphometry (VBM), an automated tool to assess the cerebral anatomical changes in vivo based on MRI scans (Ashburner and Friston, 2000), has been successfully applied in exploring the alterations of brain structures in patients with psychiatric disorders (Ferrari et al., 2008; Lui et al., 2009; Zou et al., 2010). Diffeomorphic Anatomic Registration Through Exponentiated Lie Algebra (DARTEL) is a relatively new method that was used for VBM analysis (Ashburner, 2007). Gray matter density

* Corresponding author. Tel.: +86 28 85422005; fax: +86 28 85582944.
** Corresponding author. Tel.: +86 28 85423960; fax: +86 28 85423503.
E-mail addresses: lusuwcums@hotmail.com (S. Lui), weizhanghx@163.com, weizhang27@163.com (W. Zhang).

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(GMD) is one of the useful parameters that reflect the amount of regional gray matter (Ashburner and Friston, 2001). GMD has been used to locate regional GM deficits in schizophrenic brains and has proved to be a more sensitive and easy to use approach than more labor-intensive region of interest (ROI) analyses (Giuliani et al., 2005; Tapp et al., 2006).

Thus, the primary aim of the present work was to explore the GMD deficits in drug-naïve adult SAD patients using VBM–DARTEL analysis. The following two questions were addressed: (1) whether and where GMD differences would be observed between drug-naïve patients with SAD and controls; and (2) whether there would be any relationship between the clinical features and morphological deficits.

2. Methods

2.1. Subjects

Twenty right-handed patients (mean age = 21.80 ± 3.68 years) were consecutively recruited using two approaches: 10 of them were recruited by our advertisement posters presented in the outpatient department of West China Mental Health Centre; and the others were recruited from the psychological counseling office in Sichuan University. Diagnosis of SAD was determined by consensus in the presence of two attending psychiatrists using the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) Patient Version (SCID). Exclusion criteria included: history of neurological and psychiatric disease and diagnosis of other mental disorders except SAD; existence of organic brain disorder; alcohol or drug abuse; and pregnancy or any physical illness such as hepatitis, brain tumor, and epilepsy as assessed based on the medical records. No gross abnormalities were observed in brain MRI scans (i.e., T1-weighted and T2-weighted images) for any of the subjects; MRI was performed under the supervision of an experienced neuroradiologist. None of the patients received any psychotherapy or anti-psychiatric medications before MR scanning.

Twenty right-handed healthy controls (HC) (mean age = 21.58 ± 3.72 years) were recruited from the local area by poster advertisement and screened using the SCID-I/P Version to rule out the presence of psychiatric or neurological illness. All of them were interviewed to confirm that there was no history of psychiatric illness among their first-degree relatives. One of these subjects was removed from the study during MR scanning due to hypertension. Thus, imaging data were acquired from 19 subjects.

All participants of the two groups were evaluated with the Liebowitz Social Anxiety Scale (LSAS), the Hamilton Anxiety Rating Scale (HAMA), and the Hamilton Depression Rating Scale (HAMD). The present study was approved by the local Ethics Committee, and written informed consent was obtained from each subject.

2.2. Image acquisition

High-resolution T1-weighted images were acquired on a 3.0-Tesla MRI scanner (GE Medical Systems, Milwaukee, WI, USA), producing 156 contiguous coronal slices with slice thickness of 1.0 mm. The other acquisition parameters included: repetition time (TR) = 8.5 ms and echo time (TE) = 3.4 ms. The final matrix of T1-weighted images was automatically interpolated in-plane to 512 × 512 pixels, which yielded an in-plane resolution of 0.47 × 0.47 mm^2.

2.3. VBM–DARTEL algorithm

Voxel-based morphometry with DARTEL was performed using Statistical Parametric Mapping (SPM)-8 (Welcome Trust Center for Neuroimaging, London, UK, ⟨http://www.filion.ucl.ac.uk/spm/software/spm8/⟩). The procedure included the following five steps (Bergouignan et al., 2009): (1) checking for scanner artifacts and gross anatomical abnormalities for each subject; (2) setting the image origin to the anterior commissure; (3) segmenting the images into GM and white matter (WM) images in SPM8 toolbox; (4) using the DARTEL toolbox on SPM8 to produce a high-dimensional normalization protocol, following John Ashburner's chapter in its standard version including the Montreal Neurological Institute (MNI) space transformation (Ashburner, 2007); and (5) checking for homogeneity across the sample and using standard smoothing by a Gaussian kernel (full width at half-maximum = 12 mm). After the preprocessing, images of GMD were acquired for all subjects and compared between SAD subjects and controls, which is similar to the previous studies (Gong et al., 2005; Good et al., 2001; Wilke et al., 2004).

2.4. Statistical analysis

Data analysis was conducted in three steps. First, the absolute GM, WM, and cerebrospinal fluid (CSF) volumes were obtained after the automatic brain segmentation procedure in VBM8. The total intracranial volume (TIV) was calculated as the sum of the volumes of GM, WM, and CSF. The differences of GM, WM, and TIV between patients and controls were compared using the two-sample *t*-test in the Statistical Package for the Social Sciences (SPSS Windows version 16). The statistical threshold was set at $p < 0.05$.

Secondly, for the GMD analysis, GMD images in each group were entered into a voxel-wise two-sample *t*-test analysis in SPM8 with covariation for age, gender, and TIV (Good et al., 2001). The statistical threshold was set at $p < 0.05$ corrected by AlphaSim (per-voxel *p* value was less than 0.001 with cluster size more than 33 voxels) (⟨http://afni.nimh.nih.gov/pub/dist/doc/program_help/AlphaSim.html⟩).

Finally, to identify the association between structural abnormalities and clinical symptom severity, we conducted voxel of interest (VOI) analyses on cerebral tissues

Table 1
Demographic data, rating scale scores and volumetric data.

	SAD (n=20)	HC (n=19)	SAD vs. HC (d.f.=37)	
	MD ± S.D.	MD ± S.D.	*t* or *F* value	*p* Value
Gender (*n*; male/female)	14 M/6 F	13 M/6 F	5.769*	0.873
Age (years)	21.80 ± 3.68	21.58 ± 3.72	0.187	0.853
Education (years)	14.00 ± 1.49	14.11 ± 2.00	0.187	0.852
Age of onset below 18 (years)	13.31 ± 3.11(9 patients)	–	–	–
Age of onset after 18 (years)	20.94 ± 4.71(11 patients)	–	–	–
Duration (months)	50.50 ± 45.82	–	–	–
LSAS				
Total scale	52.75 ± 11.67	21.53 ± 8.66	9.451	< 0.0001
Fear factor	27.85 ± 6.81	9.00 ± 4.71	10.635	< 0.0001
Avoidance factor	24.55 ± 7.75	12.53 ± 6.47	5.271	< 0.0001
HAMD	9.55 ± 8.91	1.68 ± 3.67	3.608	< 0.001
HAMA	5.85 ± 5.03	1.16 ± 2.09	3.768	< 0.001
Volumetric data				
GM	602.76 ± 42.24	621.46 ± 58.96	−1.143	0.260
WM	512.24 ± 43.43	536.98 ± 40.53	−1.838	0.074
Cerebrospinal fluid	277.98 ± 52.60	284.36 ± 28.16	−0.469	0.642
Total intracranial volume	1393.00 ± 110.94	1442.80 ± 96.47	−1.498	0.143

Data from questionnaires are presented in terms of mean score (*M*) and standard deviation (S.D.) in SAD and HC groups. The *p* values were obtained by two-sample two-tailed *t*-test,
SAD, social anxiety disorder; HC, healthy controls; LSAS, Liebowitz Social Anxiety Scale; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale. GM, gray matter; WM, white matter.

* Indicates *F* values for chi-square test.

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