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ORIGINAL ARTICLE

Abnormal cerebellum density in victims of rape with post-traumatic stress disorder: Voxel-based analysis of magnetic resonance imaging investigation

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Keywords
cerebellum, magnetic resonance imaging, neuroimaging, post-traumatic stress disorder, victim of rape

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Abstract

Introduction: Based on early studies of non-motor function in the cerebellum and dysfunction in the cerebellum of post-traumatic stress disorder (PTSD) patients, we presumed that the cerebellum was involved in the neuropathology of cognitive and emotional processing of PTSD patients, while the density of some sub-areas of the cerebellum of PTSD patients was most likely abnormal.
Methods: Eleven female victims of rape with PTSD and 12 age-matched female normal controls received 1.5 T 3D magnetic resonance imaging (MRI) scan. The scans were then analyzed using the voxel-based morphometry 2 (VBM2) toolbox.
Results: Victims of rape with PTSD showed increased cerebellum density on the left side compared with normal controls ($P < 0.001$), especially in the pyramis ($x = -9$, $y = -72$, $z = -36$; $k = 519$; $t = 4.70$), uvula ($x = -4$, $y = -66$, $z = -35$; $k = 256$; $t = 4.02$), declive ($x = -6$, $y = -69$, $z = -30$; $k = 213$; $t = 3.84$) and nodule ($x = -4$, $y = -63$, $z = -31$; $k = 147$; $t = 3.93$). In addition, compared with normal controls, the PTSD group showed significant differences in gray matter density of other brain areas, including the frontal lobe, parietal lobe, occipital lobe ($P < 0.001$), insula, posterior cingulate, amygdala and hippocampus ($P < 0.005$).
Discussion: These finding suggest that the cerebellum may be involved in the neuropathology and functional compensation in the neurocircuitry of PTSD.

Introduction

Post-traumatic stress disorder (PTSD) is an important public health problem in the general population (Sareen *et al.*, 2007). In recent years, much research has been directed towards understanding the etiology, phenomenology, neurobiology, clinical characteristics and treatment of PTSD (Nemeroff *et al.*, 2006). However, a number of core neuropsychological processes underlying PTSD have yet to be elucidated (Shin *et al.*, 2006; Liberzon & Sripada, 2008). Over the past decade, findings from functional and structural neuroimaging studies have allowed for tremendous advances in our understanding of the dysregulation of these processes associated with PTSD. Structural magnetic resonance imaging (MRI) studies in PTSD have generally used voxel-based morphometry (VBM) to perform volumetric analysis. The most consistent structural findings have been abnormal hippocampus and medial prefrontal cortex (including anterior cingutate) volumes (Bremner, 2006). Many studies have reported decreased volume in the hippocampus (Bremner *et al.*, 1995; Lindauer *et al.*, 2004; Vythilingam *et al.*, 2005; Chen *et al.*, 2006a; Bossini *et al.*, 2008). However, some studies showed unchanged results (Golier *et al.*, 2006; Jatzko *et al.*, 2006a, b), and some findings showed increased volume (Tupler & De Bellis, 2006). Research on abnormalities in the prefrontal cortex in PTSD patients suggest decreased volume in either the prefrontal cortex (Carrion *et al.*, 2001; Bellis *et al.*, 2002; Fennema-Notestine *et al.*, 2002; Richert *et al.*, 2006; Hakamata *et al.*, 2007) or anterior cingutate cortex (Yamasue *et al.*, 2003; Villarreal *et al.*, 2004; Abe *et al.*, 2006; Chen *et al.*, 2006b; Steven *et al.*, 2006), while some findings suggested increased volume in some sub-areas of the prefrontal cortex (Richert *et al.*, 2006).

Although findings showed regional changes of the volume in brain areas, most of these findings were made by manual tracings of the region of interest (ROI). The brain structure area needs to be drawn artificially in advance and other important brain areas may be neglected during the process. It is difficult for a measurement of exterior volume to reflect internal changes. It cannot directly reflect whether there are changes in the internal noumenon of the brain. In recent years, technological advances have allowed us to examine the density (per unit volume in native space) of the brain directly, which could compensate these shortages. However, little relevant research has been conducted in this area. In recent years, PTSD patients have been shown to have abnormal findings in the gray matter density (GMD) of their hippocampus, anterior cingulate cortex, and insula area in succession (Fennema-Notestine *et al.*, 2002; Corbo *et al.*, 2005; Emdad *et al.*, 2006; Jatzko *et al.*, 2006a, b; Kasai *et al.*, 2008). Current studies of functional neuroimaging have shown that many brain areas are related to PTSD, including the prefrontal lobe, temporal lobe, parietal lobe, occipital lobe, and cerebellum (Bonne *et al.*, 2003; Lanius *et al.*, 2005; Bremner, 2006; Molina *et al.*, 2007; Bremner *et al.*, 2008). These functional studies indicated that there are more brain areas related to PTSD remaining to be researched, other than the hippocampus and frontal lobe, especially in the cerebellum.

The cerebellum has been considered only as a classical subcortical center for motor control (Botez, 1993). Botez *et al.* found that patients with bilateral cerebellar damage showed deficits in non-motor and behavioral functions, including execution, attention, learning and cognition (Botez, 1993; Ciesielski & Knight, 1994; Gao *et al.*, 1996). Gao *et al.* (1996) found that the lateral cerebellar output (dentate) nucleus is not activated by the control of movement per se, but is strongly engaged during passive and active sensory tasks (Gao *et al.*, 1996). Recent research of the cerebellum's contribution to cognitive processing and emotional processing have increased enormously, showing that the cerebellum is responsible for sensory perception, learning, memory, attention, linguistic, emotional control and conflict resolution processing (Mandolesi *et al.*, 2001; Bischoff-Grethe *et al.*, 2002; Vokaer *et al.*, 2002; Claeys *et al.*, 2003; Allen *et al.*, 2005; Guenther *et al.*, 2005; Konarski *et al.*, 2005; Schmahmann & Caplan, 2006; Gianaros *et al.*, 2007; Schweizer *et al.*, 2007).

Anatomical studies revealed that via the thalamus, the cerebellum interacts with multiple areas of the prefrontal cortex, subcortex limbic lobe (Middleton & Strick, 2001; Zhu *et al.*, 2006). The cerebellum influences several areas of the prefrontal cortex via the thalamus (Middleton & Strick, 2001). Gold and Buckner found a region in the right lateral cerebellum which exhibited a pattern similar to the left inferior frontal gyrus during semantic decisions on words and phonological decisions on pseudowords (Gold & Buckner, 2002). Patients with degenerative cerebellar diseases show high rates of cognitive impairment or psychiatric symptoms (Leroi *et al.*, 2002; Liszewski *et al.*, 2004), and neuroimaging studies have found that mood disorders were activated in the cerebellum (Liotti *et al.*, 2000; Phan *et al.*, 2002). A study by Gianaros *et al.* found that healthy individuals showed heightened stressor-induced neural activation in the cingulate cortex, bilateral prefrontal cortex and cerebellum while performing a standardized Stroop color-word interference task (Gianaros *et al.*, 2007). However, studies of the cerebellum in PTSD patients are very limited. In two positron emission tomography (PET) studies, abnormal activities in the cerebellum of PTSD subjects were found, including higher regional cerebral blood flow (Bonne *et al.*, 2003) and augmented glucose absorption activity (Molina *et al.*, 2007). Bellis *et al.* found that the left, right, and total cerebellum were smaller in maltreated children and adolescents with PTSD. They also found that cerebellar volume was positively correlated with the age of onset of the trauma that led to PTSD and negatively correlated with the duration of the trauma (Bellis & Kuchibhatla, 2006). However, no precise results were found in cerebellum sub-areas. Based on early studies of non-motor function in the cerebellum and dysfunction in the cerebellum of PTSD patients, we presumed that the cerebellum was involved in the neuropathology of cognitive and emotional processing of PTSD patients, while the density of some sub-areas of the cerebellum of PTSD patients was most likely abnormal.

We utilized a research-dedicated 3D MRI and VBM2 to investigate differences in brain structure between rape victims with PTSD and normal controls.

Methods

Human subjects

PTSD group

Samples were recruited from psychological consulting clinics and a non-government organization which specializes in providing assistance to sexual assault victims. Subjects who met the following criteria were included: female; victim of rape; 18 years or older; right-handed; educational attainment above secondary school level; and met Diagnostic and Statistical Manual of Mental Disorders, IV Edition (DSM-IV) (American Psychiatric Association, 1994) diagnostic criteria for current PTSD. Exclusion criteria were previous or current psychiatric diagnosis; history of neurological or brain trauma; and alcohol or drug use.

Controls

Age-matched female subjects were recruited from healthy female volunteers who were right-handed with an educational attainment above secondary school level. Each was screened to exclude a history of rape or other significant trauma, previous or current psychiatric diagnosis, history of neurological or brain trauma, and alcohol or drug use.

Participants were native Chinese speakers from mainland China. From an initial interview, 13 victims of rape with PTSD (mean age = 24.46 years, range = 18–32 years, SD = 5.77) and 13 controls (mean age = 26.00 years, range = 21–31 years, SD = 3.39) met the inclusion criteria and agreed to participate in the study. Each psychiatrist was trained to expertly use the Post-traumatic Stress Disorder Checklist Civilian Version (PCL-C) (Weathers *et al.*, 1991) to screen PTSD, and use the DSM-IV and the Clinician-Administered PTSD Scale (CAPS) (Blake *et al.*, 1995) to diagnose PTSD. The groups did not differ significantly in age ($P > 0.2$). However, the PTSD group differed significantly with the control group on scores of PTSD symptomatology ($P < 0.001$). The average interval between the rape trauma and data acquisition was 54.31 months (SD = 59.79). Participants in both groups were enrolled into the study in parallel.

Procedures

Following a detailed description of the study protocol, written informed consent was obtained from all participants prior to the initial interview. The study protocol was approved by the Ethics Committee of Second Xiangya Hospital, Central South University, China.

Following the primary interview, participants selected for the study were immediately scanned with MRI. Following the MRI scans, the participants in the trauma group were offered psychological counseling and medical therapy. Three participants (two patients and one control) made head movements during MRI scanning. Thus, these imaging data were removed from analysis. The final analysis consisted of 11 patients and 12 controls.

MRI data acquisition

Measurements were performed using a research-dedicated Siemens Avanto 1.5 T MRI scanner (Siemens AG, Erlangen, Germany). T1-weighted anatomical images were acquired using a 3D gradient-echo sequence, with TR = 11 ms, TE = 4.94 ms, number of averages = 1, matrix = 256 × 224 pixels, field of view = 256 mm × 224 mm, with a flip angle of 15°. One-hundred and seventy-six sagittal slices at 1-mm slice thickness were acquired with no interslice gap. There was a voxel resolution of $1 \times 1 \times 1\ \text{mm}^3$. Total the acquisition time was 5 minutes 34 seconds.

MRI data analysis

VBM analyses are commonly performed using parametric tests with Statistical Parametric Mapping (SPM) software. (Wellcome Department of Imaging Neuroscience, London, UK) The present analysis was performed with optimized VBM using the VBM2 toolbox (http://dbm.neuro.uni-jena.de/vbm), an extension of the SPM2 (Wellcome Department of Imaging Neuroscience, London, England; http://www.fil.ion.ucl.ac.uk). The T1-weighted images were transformed into standard Montreal Neurological Institute (MNI) (average 152 T1 brain) space using an automated spatial normalization algorithm (Ashburner & Friston, 1999), and segmented into gray matter, white matter, and cerebrospinal fluid component images. Prior to analysis, each normalized parametric image was smoothed using a 12-mm full-width at half-maximum isotropic Gaussian kernel and transformed with a logit function (Ashburner & Friston, 2000).

Two-sample *t*-tests were performed in a voxel-by-voxel manner. Statistical significance was determined at a *P*-value of 0.001 using a cluster size of 50 voxels. To visualize regions that were significantly different, significant regions were superimposed onto SPM2's spatially normalized T1-weighted template brain images.

Based on previous research, we hypothesized that compared with normal healthy controls, victims of rape with PTSD would show abnormal density in the cerebellum and other brain regions, including the frontal lobe, parietal lobe, occipital lobe and temporal lobe. We used the small volume correction

(SVC) tool in the SPM2 package with the specific purpose of restricting comparisons to specific voxels located in these regions. This approach permits the implementation of hypothesis-driven analyses with corrections for the pre-specified ROI rather than corrections for the whole brain.

Results

The PTSD group showed increased cerebellum density compared with controls in the left side, specifically in the pyramis, uvula, declive, and nodule (see Figure 1). Other brain areas with increased GMD included the postcentral gyrus (BA2). Brain areas with decreased GMD in the PTSD group compared to controls existed within the left middle frontal gyrus (BA10), superior frontal gyrus (BA10), fusiform gyrus (BA19), middle occipital gyrus (BA18) and inferior occipital gyrus (BA18) (see Table 1).

Significant differences of GMD in some important brain areas were seen at $P < 0.005$ between groups. Compared with the controls, the PTSD group had reduced GMD in the right amygdala ($x = 31$, $y = -8$, $z = -11$; $k = 33$, $t = 3.21$) and hippocampus ($x = 32$, $y = -11$, $z = -11$; $k = 18$, $t = 3.12$). The areas with increased GMD included the left insula ($x = -39$, $y = 5$, $z = 7$; $k = 36$, $t = 3.3$) and right posterior cingulate ($x = 4$, $y = -64$, $z = 7$; $k = 449$, $t = 3.57$).

Discussion

In the present study, decreased GMD was observed in the frontal cortex in PTSD patients. This agrees with volumetric imaging findings that showed abnormal frontal lobes in PTSD patients (Carrion *et al.*, 2001; Bellis *et al.*, 2002; Fennema-Notestine *et al.*, 2002; Richert *et al.*, 2006; Hakamata *et al.*, 2007), smaller prefrontal lobe volumes in pediatric PTSD patients (Carrion *et al.*, 2001; Bellis *et al.*, 2002; Richert *et al.*, 2006), female victims of intimate partner violence with PTSD (Fennema-Notestine *et al.*, 2002), and cancer-related PTSD patients (Hakamata *et al.*, 2007). All these findings suggest that decreased GMD in the frontal cortex of PTSD patients implies brain lesion due to serious trauma.

We found that the density of the cerebellum, which plays an important role in motor and cognition (Mandolesi *et al.*, 2001; Bischoff-Grethe *et al.*, 2002; Vokaer *et al.*, 2002; Claeys *et al.*, 2003; Allen *et al.*, 2005; Guenther *et al.*, 2005; Konarski *et al.*, 2005; Schmahmann & Caplan, 2006; Gianaros *et al.*, 2007; Schweizer *et al.*, 2007), was increased in patients with PTSD. Combined with early studies of structural (Leroi *et al.*, 2002; Liszewski *et al.*, 2004; Bellis & Kuchibhatla, 2006) and functional (Liotti *et al.*, 2000; Phan *et al.*, 2002; Bonne *et al.*, 2003; Gianaros *et al.*, 2007; Molina *et al.*, 2007) abnormal in the cerebellum in PTSD patients, this finding is consistent with our hypothesis that the cerebellum was involved in the neuropathology of cognitive processing and emotional processing in PTSD patients. Further, density increased in the cerebellum, while density decreased in the prefrontal cortex. According to anatomical studies which found that the cerebellum interacts with the prefrontal cortex via the thalamus (Middleton & Strick, 2001; Zhu *et al.*, 2006), and functional studies which found that the cerebellum influences several areas of the prefrontal cortex via the thalamus (Middleton & Strick, 2001) and exhibited a pattern similar to the frontal cortex during semantic decisions (Gold & Buckner, 2002), these findings suggest that the cerebellum may be involved in the functional compensation for the pathological changes in the neuro-circuitry of PTSD.

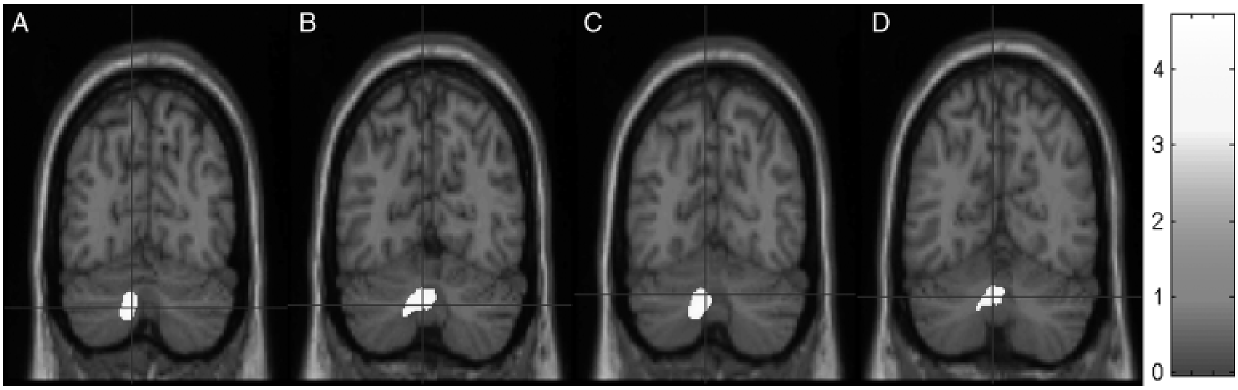

Figure 1 Significantly increased cerebellum density in 11 PTSD patients compared with 12 normal controls. (A) Pyramis ($x = -9$, $y = -72$, $z = -36$; $k = 519$, $t = 4.70$); (B) uvula ($x = -4$, $y = -66$, $z = -35$; $k = 256$, $t = 4.02$); (C) declive ($x = -6$, $y = -69$, $z = -30$; $k = 213$, $t = 3.84$); and (D) nodule ($x = -4$, $y = -63$, $z = -31$; $k = 147$, $t = 3.93$) (right = right, left = left) (coordinates presented are in Montreal Neurological Institute space).

Table 1. Gray matter density in post-traumatic stress disorder group versus controls

k	Voxel *t*-value	MNI coordinates (*x*, *y*, *z*)	Region	Brodmann area
Greater reduction				
135	4.67	−31, 54, 2	Middle frontal gyrus (L)	10
56	4.09	−10, 68, 12	Superior frontal gyrus (L)	10
268	4.73	−30, −83, −18	Fusiform gyrus (L)	19
222	4.48	−30, −83, −16	Middle occipital gyrus (L)	18
138	4.40	−33, −83, −18	Inferior occipital Gyrus (L)	18
Greater increase				
79	4.17	55, −28, 35	Postcentral gyrus (R)	2

k, cluster size; regions displayed are for $P < 0.001$, $k > 50$.

However, findings from the present study need to be confirmed in future studies and in different subgroups of PTSD patients. In addition, the small sample size in the present study (11 PTSD subjects) is a limitation.

Earlier studies in the cerebellum of PTSD patients found correlations with abnormal blood flow and glucose absorption (Bonne *et al.*, 2003; Molina *et al.*, 2007), and abnormal volume (Bellis & Kuchibhatla, 2006) in the cerebellum. This study adds to the literature on cerebellum structure involvement in PTSD. This finding, if replicated in larger patient samples, may serve as a marker of brain dysfunction in PTSD, and thus allow for the study of cerebellum pathophysiology before and throughout the course and treatment of PTSD.

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Written consent was obtained from the participants or their relatives for the publication of the study.

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