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More vulnerability of left than right hippocampal damage in right-handed patients with post-traumatic stress disorder

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ABSTRACT

Previous studies have shown hippocampal abnormalities in people with post-traumatic stress disorder (PTSD), but findings of diminished volume in shortages in the hippocampus have been inconsistent. In this study, we investigated changes in hippocampal volume and neuronal metabolites in right-handed PTSD patients to determine their possible relationship(s) with PTSD severity. We performed a case-control study of 11 right-handed PTSD patients and 11 healthy controls using magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopy (^{1}H MRS). Hippocampal volume and metabolite ratios of *N*-acetylaspartate (NAA) to creatine (Cr) (NAA/Cr) and choline compounds (Cho) to Cr (Cho/Cr) were calculated. The severity of PTSD was evaluated by the Clinician-Administered PTSD Scale (CAPS). Significantly decreased left and total normalized hippocampal volumes were found in PTSD patients compared with controls (6.6% for the left hippocampus, 5.5% for total hippocampus). Also, the bilateral hippocampal NAA/Cr ratio of PTSD patients was significantly reduced compared with controls. The volume of the left hippocampus was negatively correlated to the CAPS total and CPAS-C scores. The left hippocampal NAA/Cr ratio was negatively correlated to the CAPS-total, CAPS-B, CAPS-C, and CAPS-D scores. The CAPS total and the CAPS-B scores were positively correlated to the Cho/Cr ratio of the right hippocampus. Our results indicate that hippocampal dysfunction is asymmetric in right-handed PTSD patients, with the left side affected more than the right.

1. Introduction

Post-traumatic stress disorder (PTSD) is a highly disabling condition observed in people exposed to severe emotional or physically life-threatening traumatic events such as war, sexual abuse, and natural disasters. It is characterized by three distinct types of symptoms: reexperiencing the event, avoidance of clues associated with the trauma, and hyperarousal.

It has been suggested that the structural brain abnormalities associated with PTSD mainly involve the amygdala, hippocampus, and medial prefrontal cortex. The hippocampus, in particular, is thought to be involved because of its critical role in learning and memory as well as stress regulation. Neuroendocrinological investigations in animals indicate that glucocorticoids secreted by the adrenal glands during stress can damage the hippocampus, inducing hippocampal cell apoptosis (Zhao et al., 2007) and CA3 dendritic retraction (Magarinos et al., 1996), and inhibiting cell proliferation (Fuchs et al., 2001; Lucassen et al., 2001; Zhao et al., 2007). Furthermore, we previously found that hippocampal volume and the level of certain metabolites were reduced in chronically stressed animals (Liu et al., 2011).

Neuroimaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) are effective in exploring the pathogenesis and pathophysiology of PTSD. Structural abnormalities in PTSD found with MRI include nonspecific white-matter lesions and decreased hippocampal volume (Pitman et al., 2001). However, results from neuroimaging research are controversial (Jelicic and Merckelbach, 2004). Several studies have reported diminished hippocampal volume in subjects with PTSD as compared to controls, e.g., in men with combat exposure (Gilbertson et al., 2002; Hayes et al., 2011; Pavic et al., 2007), in female adult survivors of childhood sexual abuse (Bremner et al., 1997; Stein et al., 1997), and in adults with mixed adversities (Villarreal et al., 2002). Moreover, some studies found hemispheric asymmetries in PTSD, with significantly greater reductions in the right (Bremner et al., 1995; Pavic et al., 2007; Wignall et al., 2004) or left (Lindauer et al., 2004; Nakano et al., 2002; Stein et al., 1997) hemispheres, and bilaterally in other studies (Bonne et al., 2008;

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Bremner et al., 2003; Villarreal et al., 2002). Other investigators failed to find any differences in hippocampal volume between traumatized subjects and controls (Bonne et al., 2001; Fennema-Notestine et al., 2002; Pederson et al., 2004). However, some of these studies included patients with alcoholism and/or depression, which might be partly responsible for hippocampal atrophy (Karl et al., 2006). Although these studies failed to show consistent changes in hippocampal volume in PTSD patients, others have demonstrated that hippocampal volume differences vary with PTSD severity (Mahmutyazicioglu et al., 2005). Bremner et al. (1997) reported that decreased hippocampal volume was significantly associated with PTSD severity in women who experienced childhood sexual abuse. Astur et al. (2006) also reported reduced hippocampal activity was associated with more severe PTSD symptoms.

Proton magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive method that can detect in vivo levels of various neurotransmitters and metabolites in the brain, including *N*-acetylaspartate (NAA), creatine (Cr), and choline compounds (Cho), within a certain volume or voxel. Thus, ^{1}H MRS may provide biochemical evidence of underlying neural processes, even in the absence of cerebral anatomical changes. Lower NAA concentrations have been found in neurological diseases associated with neuronal damage and death (Brooks et al., 1997), so reduced levels of NAA have been considered symptomatic of decreased neuronal density and impaired neuronal health (Brooks et al., 1999). Previous ^{1}H MRS studies of PTSD patients have detected a low NAA/Cr ratio in the medial temporal lobe and hippocampus or decreased hippocampal NAA concentration (Freeman et al., 1998; Schuff et al., 2001). In addition, hippocampal NAA measures strongly correlated with PTSD symptoms in prisoners of war in one study (Brown et al., 2003), but these results could not be replicated in a second study of a similar population (Freeman et al., 2006). Other studies suggested that the NAA/Cr ratio was significantly lower in the left hippocampus of patients with PTSD compared to control subjects (Li et al., 2006; Villarreal et al., 2002), which is consistent with the idea that hippocampal dysfunction in PTSD is lateralized, with greater impairment seen on the left side (Mohanakrishnan Menon et al., 2003). The reasons for laterality findings being inconsistent across the studies are unclear but may stem from differences in handedness of subjects, because several studies showed that right-handed healthy participants have greater volume asymmetry on the right amygdala and hippocampus (Szabo et al., 2001). Nevertheless, handedness has been taken into consideration in only a few studies (Pederson et al., 2004). Whether and how these factors are associated with PTSD severity remains unclear. Detection of changes in metabolite ratios is expected to be a more sensitive technique than determining changes in brain volumetric measurements in PTSD.

From results of previous studies, we hypothesized that right-handed subjects with PTSD would have smaller hippocampal volumes and decreased NAA/Cr ratios than those without PTSD. Therefore, in this study, we examined right-handed PTSD subjects to determine hippocampal volume and metabolite level (NAA/Cr ratio) in vivo using MRI and ^{1}H MRS. We also evaluated the PTSD severity by the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995), and measured serum levels of cortisol and free triiodothyronine (FT3). We aimed to explore the neurochemical and neuroendocrinological mechanism of hippocampal damage in PTSD patients and the relations among PTSD severity, hippocampal volume and metabolite level to establish a multiple factor model of PTSD symptom severity.

2. Materials and methods

2.1. Subjects

We performed a case-control study. The sample consisted of case group (PTSD patients) and control group (healthy subjects). The case group comprised 11 patients with PTSD referred to the Mental Health Center of Wuhan University People Hospital over the period between April 2006 and July 2007. All the participants were strongly right-handed as judged by the Lateral Dominance Test.

The patients were diagnosed according DSM-IV criteria for PTSD by two principal psychiatrists through clinical interviews. Exclusion criteria included (1) current or past history of bipolar disorder, schizophrenia, or other psychotic disorder; (2) alcohol or substance abuse or dependence in the past 5 years; (3) physical or sexual abuse during childhood; (4) current or past history of neurological disease; (5) other physical diseases identified by EEG or MRI examinations. Meanwhile, symptomatology and symptom severity for the last month were assessed with the Clinician-Administered PTSD scale (CAPS). The CAPS consists of 17 items that are evaluated by interviewers. These items include core symptoms of PTSD determined by DSM-IV criteria; the CAPS also includes five additional scales to evaluate social and vocational functioning, general severity, changes in the severity of the symptoms, and validity of patient feedback.

All the patients were receiving antidepressant medications or antipsychotic medications during the assessment, while control subjects were free of all psychiatric medication. The study was approved by the ethical committee of Sun Yat-Sen University. After a comprehensive description of the study was given to the subjects, written informed consent was obtained.

2.2. Neuroendocrine evaluation

Venous blood samples were collected at 8:00 h, and were spun at 4000 rpm for 10 min to separate serum and the serum was then stored at −80 °C until assay. A radioimmunoassay was used to measure the serum cortisol and FT3 concentration (Chemclin Biotech, Beijing, China).

2.3. MRI and ^{1}H MRS acquisition

The subjects were scanned on a 1.5 T GE Signa Twinspeed magnetic resonance (MR) system, equipped with a standard head coil. Subjects were stretched back about 20–30° by a sponge pad, so that sections were parallel to the long axis of the hippocampus. The fast gradient echo (FGRE) sequence was run first for three-dimensional positioning. The FGRE sequence is as follows: the repetition time (TR) 115.5 ms; echo time (TE) 1.6 ms, and six echoes, slice thickness 5 mm, with no interval, field of view (FOV)=24×24 cm^2, matrix=256×256. A series of T2-weighted axial view images was acquired with a fast recovery fast spin echo (frFSE) sequence with following parameters: TR=2500.0 ms, TE=80.8 ms, slice thickness=5 mm, with no interval. A three-dimensional sagittal gradient echo (3D SPGR) was used for hippocampal volume and intracranial volume measurement. 3DSPGR scan parameters are as follows: Preptime=500 ms, TR=16.0 ms, TE=4.0 ms, flip angle=15°, FOV=24×24 cm^2, slice thickness=1.2 mm, spacing=0, number of excitations (NEXs)=2. Volumetric analysis of the hippocampus was done by using three-dimensional software (CURRY) that allows simultaneous analysis of sagittal, coronal, and horizontal images. The hippocampal boundaries were as follows: posterior, the section with the greatest length of continuous fornix; medial, the open-end of the hippocampal fissure posteriorly, the uncal fissure in the hippocampal body, and the medial aspect of the ambient gyrus anteriorly; lateral, the temporal horn of the lateral ventricle; inferior, the white matter inferior to the hippocampus; and superior, the superior border of the hippocampus. Anteriorly, the alveus was used to differentiate the hippocampal head from the amygdala. The anterior border was the most difficult to identify consistently and was aided by moving between sections before and after the index section. All analyses were done by a single rater who was blind to the subjects' diagnostic information. In order to compensate for head and brain volume differences among the subjects, we normalized the raw hippocampus volumes using Jack's formula (Jack et al., 1989): Volume (adjusted)=Volume (observed) − B (TCVi − TCVm), where Volume (adjusted)=normalized hippocampus volume, Volume (observed)=absolute hippocampus volume, B=regression coefficient, TCVi=intracranial volume of the subject, and TCVm=mean intracranial volume of the group.

Parameters of point resolved spectroscopy (PRESS-CSI) used for acquiring the multivoxel spectroscopy data are as follows: TR/TE=1000/144 ms, voxel thickness=10 mm, FOV=24×24 mm^2, number of excitations (NEX) =2; phase =18, frequency = 18 (see Fig. 1), voxel voxel analyzed was $7.5\times7.5\times10$ mm^3; acquisition time was 5 min 28 s. Shimming with full width at half-maximum (FWHM) < 8, the water suppression > 96%. Multi-voxel data were transported to a workstation (Advantage Windows 4.0∼02, GE) for phase calibration, baseline correction and the ppm conversion. The PRESS series consisted of three major peaks: NAA peak at 2.0 ppm, Cr peak at 3.0 ppm, Cho peak at 3.2 ppm. The peak area of NAA, Cho and Cr (include creatine and creatine phosphate) were automatically measured by spectral analysis software (GE ADW Functool). Cr is used as internal standard. NAA/Cr and Cho/Cr rates were used in the statistics (Fig. 1 B1, B2, C1 and C2).

2.4. Statistical analysis

Volume measures and metabolite ratios between the case group and the control group, left and right hippocampus, were compared with a two-tailed