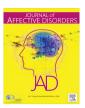
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#### Research paper

## Decreased left hippocampal volumes in parents with or without posttraumatic stress disorder who lost their only child in China



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#### ABSTRACT

Background: Limbic structural changes have been found in people with post-traumatic stress disorder (PTSD). However, the results were controversial, and no study has examined the hippocampal and amygdala volume changes in parents with or without PTSD who had lost their only child and could no longer conceive in China.

Methods: Hippocampal and amygdala volumes of 57 parents with PTSD (PTSD+), 11 trauma-exposed parents without PTSD (PTSD-) and 39 non-traumatized controls were examined using magnetic resonance imaging. Correlations of the volumes with the time since trauma, Clinician-Administered PTSD Scale (CAPS) scores, age, gender and intracranial volume (ICV) were investigated in the PTSD+ group. Results: left hippocampal volumes were significantly smaller in the PTSD+ and PTSD- groups than in the controls, but there were no significant differences between the PTSD+ and PTSD- groups. Furthermore, there was no significant difference in the right hippocampus or bilateral amygdala volumes. Additionally, the hippocampal and amygdala volumes showed no correlation with the time since trauma, CAPS score and gender, whereas the left hippocampal volumes were correlated with ICV, and the bilateral amygdala volumes were correlated with ICV and age in the PTSD+ group.

Limitations: The PTSD - group included only 11 participants.

Conclusions: left hippocampal volumes decreased in parents who lost their only child, with or without PTSD. Our results suggest a potentially unique role of the trauma of losing an only child, which is extremely painful and may induce a decrease in the left hippocampal volume independent of PTSD effects.

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#### 1. Introduction

Posttraumatic stress disorder (PTSD) is characterized by the presence of intrusion symptoms, the persistent avoidance of stimuli, and negative alterations in cognitions and mood associated with the traumatic event(s), followed by exposure to a wide range of stressors, including combat, rape, accident and bereavement according to DSM-V (Association, 2013).

Neuroimaging studies of PTSD patients have found many potential structural abnormalities in the brain associated with the pathogenesis of PTSD, including two key regions—the hippocampus and amygdala. However, the results were controversial (Pitman et al., 2012; Robinson and Shergill, 2011). Many studies and some meta-analyses (Karl et al., 2006; Kitayama et al., 2005;

Smith, 2005; Woon et al., 2010) have reported a lower hippocampal volume in PTSD relative to trauma-exposed subjects without PTSD and/or non-exposed controls. However, in the metaanalysis by Karl et al. (2006) the bilateral hippocampal volumes were significantly smaller in people with PTSD compared with trauma-exposed subjects without PTSD, and another meta-analysis found that only right hippocampus was smaller in the PTSD group than in the trauma-exposed non-PTSD group (Woon et al., 2010). Two other meta-analyses did not compare the hippocampal volumes of PTSD patients with those of trauma-exposed subjects without PTSD (Kitayama et al., 2005; Smith, 2005). Moreover, other well-controlled studies that have failed to observe any hippocampal volume difference cannot be neglected. Concerning the amygdala volume, one meta-analysis showed no significant differences between the groups (Woon and Hedges, 2009), whereas another meta-analysis found significantly smaller left amygdala volumes in adults with PTSD compared to both healthy and trauma-exposed controls (Karl et al., 2006). Moreover, a cross-

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sectional study indicated that combat-exposed individuals with PTSD exhibited larger total amygdala volumes compared with their non-PTSD counterparts (Kuo et al., 2012).

Bereavement is a serious trauma to the individual, particularly when the bereavement results from the death of a child. In modern society, children have become the major source of joy, hope, meaning and purpose in the life for most parents (Hindmarch, 2009). The loss of a child is the most traumatizing and painful bereavement experience for parents, and it can lead to a broad range of psychiatric morbidities and somatic symptoms (Chan et al., 2012). However, the impact of this trauma on parents has received limited attention relative to research on other types of loss (e.g., the death of a spouse or a parent) (Kristensen et al., 2012; O'Connor, 2010).

In mainland China, the "one couple, one child" policy enacted in the late 1970s has produced many single-child families, and the only child became the key element in ensuring family relationships and generational continuity and in providing care and support to the elderly (Lee, 1997). Unfortunately, because of such factors as traffic accidents, suicide and sudden death of unknown cause, many single-child families lose their only child. In this unique socio-cultural environment in China, parents who suffer the loss of their only child and could no longer conceive, primarily because of old age, may feel extremely desperate and are prone to develop PTSD. However, to our knowledge, there is no literature concerning the structural changes of the brain in such parents with or without PTSD.

An extensive body of literature demonstrates that glucocorticoids (GCs) secreted during stress or trauma can have deleterious effects on the hippocampus, a structure rich in corticosteroid receptors and particularly sensitive to GCs (Sapolsky, 1996, 2000). The excessive release of GCs can exert a profound effect on neurogenesis, altering the hippocampal anatomy and leading to a decrease in the rate of cell proliferation and an increase in cell death in human and animals (de Kloet et al., 2005; Nagata et al., 2009; Teicher et al., 2003; Zhao et al., 2007).

Recently, Kelley et al. reported that the clinical presentation of PTSD symptoms varied by trauma type and that each trauma type would produce a unique pattern of psychopathology (Kelley et al., 2009). A meta-analysis showed that PTSD patients who experienced accidental or non-accidental trauma presented anatomical changes in different brain regions, suggesting that PTSD patients with different types of trauma may have different cerebral deficits (Meng et al., 2014). Additionally, adult PTSD may be associated with decreased hippocampal volumes, whereas pediatric maltreatment-related PTSD often fails to result in a smaller hippocampus and amygdala (De Bellis et al., 2001; Pitman et al., 2012).

Therefore, in the present study, we aimed to investigate alterations in the hippocampal and amygdala volumes using magnetic resonance imaging (MRI) and to determine the correlations of structural abnormalities with patient gender and age, time since trauma and symptom severity to explore whether the parents who had lost their only child and could no longer conceive would exhibit a unique pattern of neuropathology in the brain.

#### 2. Methods

#### 2.1. Subjects

Fifty-seven current or lifetime unmedicated PTSD patients (the PTSD+ group) who had lost their only child and could no longer conceive were recruited from The Affiliated Yixing Hospital of Jiangsu University. Eleven participants who had also lost their only child but were free of current or lifetime PTSD were enrolled as the PTSD- group. Thirty-nine healthy individuals matched for age

and gender were recruited as the control group. The diagnosis and the severity of PTSD were established using the Structured Clinical Interview for the DSM-IV (SCID) (First et al., 1998) and the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). All diagnoses were made by two trained clinical psychologists (XZ and YY). The inter-rater reliability was evaluated using the intra-class correlation, which was high in our study (r=0.82).

The inclusion criteria for all subjects were right-handedness, an IQ > 80 assessed with the Wechsler Intelligence Scale, and a Mini-Mental State Examination score > 24. The trauma-exposed subiects (PTSD+ and PTSD-) had no history of other Axis I psychiatric diagnoses according to the SCID for DSM-IV Axis I Disorders (First et al., 1998). To assure that the subjects (PTSD+ and PTSD-) had only suffered the trauma being studied (the loss of their only child and an inability to conceive), the Life Stressor Checklist-Revised (Wolfe et al., 1996) was used to ensure that the subjects did not experience childhood trauma or other stress exposures. The exclusion criteria for all groups were contraindications for MRI and other neuropsychiatric disorders, such as depression, schizophrenia, mental retardation, epilepsy, Alzheimer's disease, substance abuse and head injury with loss of consciousness. None of the PTSD patients had ever taken psychotropic medication.

The local ethics committee approved the study, and the participants gave their written informed consent to participate, in keeping with the Declaration of Helsinki. Table 1 lists the demographic and neuropsychological data for the groups.

#### 2.2. Image acquisition and processing

MRI examinations were performed at 3.0 T using an eight-channel phased-array coil (Achieva 3.0 T TX; Philips, Amsterdam, the Netherlands). Foam padding was used to minimize head motion in all subjects. Three-dimensional high-resolution sagittal T1 weighted images with turbo fast echo (3D-T1 TFE) acquisition was applied to measure the volumes of the studied brain regions, and the parameters were set as follows: repetition time (TR)=9.7 ms, echo time (TE)=4.6 ms, inversion time (TI)=900 ms, flip angle=8°, field of view (FOV)=256 × 256, voxel size=1 mm × 1 mm × 1 mm, and 160 slices. The total scan time was 5 min and 34 s.

#### 2.3. Image processing

The volumes of the hippocampus and amygdala were estimated using FreeSurfer v5.1.0 (http://www.nmr.mgh.harvard.edu/freesurfer/). The overall process and analysis pipeline have been described elsewhere (http://surfer.nmr.mgh.harvard.edu). Briefly, this process includes the motion correction and averaging of

**Table 1**Demographic and neuropsychological data for the groups.

Items	PTSD+ (N=57)	PTSD- (N=11)	Control (N=39)	$F/X^2$ , $P$ value
Ages (years)	$57.10 \pm 5.99$	$58.09 \pm 6.46$	$55.70 \pm 5.74$	1.121, 0.330
Education (years)	$8.11\pm2.19$	$\textbf{8.55} \pm \textbf{2.87}$	$9.31 \pm 3.11$	2.418, 0.094
Gender (male: female)	20:37	6:5	19:20	2.550, 0.279
CAPS score	$40.14 \pm 7.81$	$8.73\pm10.42$	-	133.3, 0.00 <sup>a</sup>
Time since trauma (month)	$81.88 \pm 56.36$	$105.73 \pm 65.53$	-	1.567, 0.215 <sup>a</sup>

PTSD: Posttraumatic stress disorder; CAPS: Clinician-Administered PTSD Scale.

<sup>&</sup>lt;sup>a</sup> P: comparison between the PTSD+ and PTSD-.

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