Psychiatry Research: Neuroimaging 231 (2015) 269–272

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

journal homepage: www.elsevier.com/locate/psychresns

# Acute response to psychological trauma and subsequent recovery: No changes in brain structure

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ARTICLE INFO

*Article history:*
Received 29 December 2013
Received in revised form
24 December 2014
Accepted 8 January 2015
Available online 15 January 2015

*Keywords:*
Acute stress disorder
Trauma
Brain volume
Hippocampus
Amygdala
Magnetic resonance imaging (MRI)

ABSTRACT

We used magnetic resonance imaging to study brain structure in acute stress disorder (ASD) following a psychological trauma and after 4 weeks in remission. Whole-brain voxel-based morphometry and FreeSurfer analysis of the hippocampal formation and amygdala revealed no structural changes in ASD ($n=75$) compared with trauma-exposed individuals without ASD ($n=60$) and community controls ($n=60$). These results suggest that ASD, in contrast to posttraumatic stress disorder, is not characterized by structural brain alterations.



## 1. Introduction

Acute stress disorder (ASD) was introduced in DSM-IV as a new diagnostic category for immediate and temporary reaction to catastrophic stressors (American Psychiatric Association, 1994). The symptoms of ASD are similar to those of posttraumatic stress disorder (PTSD) (re-experiencing, avoidance, arousal, and dissociative symptoms), but their duration is short (a minimum of 2 days and a maximum of 4 weeks). In the DSM-5, ASD was classified as a trauma- and stressor-related disorder characterized by intrusions, negative mood, dissociative symptoms, avoidance, and hyper-arousal (duration: a minimum of 3 days and a maximum of 4 weeks) (American Psychiatric Association, 2013). However, ASD has been critically evaluated regarding its limited power to predict PTSD and its overlap with adjustment disorders (Bryant et al., 2011). In addition, in contrast to the extensive literature on the biological mechanisms of PTSD (Pitman et al., 2012), brain imaging, endocrinological, and peripheral gene expression studies are rare in ASD.

Bremner (2005) suggested that biological stress response systems, including norepinephrine and cortisol, are implicated in both acute and chronic stages of reaction to traumatic stressors. Regarding the neuronal circuits, areas involved in memory, cognitive control, and affective regulation (hippocampus, amygdala, and prefrontal cortex) are important in the effective and adaptive balancing of early responses to trauma (Bremner, 2005).

PTSD is characterized by structural brain alterations. In the first comprehensive meta-analysis, Karl et al. (2006) concluded that studies demonstrated smaller hippocampal volumes in persons with PTSD compared with control subjects with and without trauma exposure. However, trauma-exposed individuals without PTSD also showed significantly smaller bilateral hippocampi relative to non-exposed individuals. There are reports demonstrating significantly smaller amygdala and reduced anterior cingulate volume in PTSD relative to various control groups, but the results are not consistent (Karl et al., 2006; Woon and Hedges, 2009). More recently, the meta-analysis of Kühn and Gallinat, 2013 identified gray matter reductions in anterior cingulate cortex, ventromedial prefrontal cortex, left temporal pole/middle temporal gyrus, and left hippocampus in PTSD patients relative to trauma-exposed individuals without PTSD.

The reduction of the hippocampal volume is the most frequently investigated and confirmed finding in PTSD as highlighted by several meta-analyses (e.g., Smith, 2005; Karl et al., 2006; Woon et al., 2010). It is remarkable, however, that Smith (2005) noted that hippocampal volume reduction was less pronounced when researchers compared PTSD patients with trauma-exposed control subjects relative to the case when the control group

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http://dx.doi.org/10.1016/j.pscychresns.2015.01.005
0925-4927/

included individuals without trauma exposure. Woon et al. (2010) suggested that hippocampal shrinkage was associated with trauma exposure independent of the diagnosis of PTSD. Moreover, Karl et al. (2006) highlighted the issue that differences in groups were modulated by imaging methodology, PTSD severity, medication, age, and gender.

Despite these caveats and gaps in the literature, structural brain alterations have not been investigated in ASD in a prospective longitudinal follow-up study. Therefore, we first aimed to examine whether ASD is associated with structural brain alterations after trauma exposure. The second aim of the study was to address potential changes in brain structure during symptomatic recovery.

## 2. Methods

### 2.1. Participants and design

Study participants, referred by emergency medical units, were enrolled at South-Hungarian Center (Szeged and Kecskemét, Hungary) and the National Institute of Psychiatry and Addictions (Budapest, Hungary). The study was approved by the medical ethics committee and was done in accordance with the Declaration of Helsinki. Each participant was recently exposed to a single episode of traumatic event (traffic accidents, violent crime, or natural disaster of flood). No individuals living under chronic and recurrent traumatic exposure were included. There was no autobiographical evidence for multiple and severe past traumas, psychiatric co-morbidity, or positive history for mental disorders. None of the participants received psychotropic medications. A trained clinical psychologist, who was unaware of the aim of the study, administered the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV) (First et al., 1996). Among trauma-exposed individuals, 75 received the diagnosis of ASD, whereas 60 did not meet the diagnostic criteria of any Axis I disorders. Sixty community volunteers not exposed to acute trauma served as controls.

We used the Clinician-Administered PTSD Scale (CAPS) for the assessment of the symptoms during the past week (Blake et al., 1995). Table 1 presents the demographic and clinical data. At the first assessment (baseline), study volunteers underwent structural brain magnetic resonance imaging (MRI). After the baseline assessment, all participants were offered a weekly consultation with a clinical psychologist or a standard treatment following the clinical protocols. None of the participants requested psychiatric and psychological treatment beyond the consultations. The whole procedure applied at the baseline was repeated after 4 weeks, including SCID-CV, CAPS, and structural MRI. At the follow-up assessment, none of the individuals with ASD and trauma-exposed non-ASD participants developed PTSD, and none of them met the criteria of DSM-IV Axis I disorders.

### 2.2. Structural brain imaging

The technical aspects of MRI acquisition and FreeSurfer analysis have been described in our previous study (Levy-Gigi et al., 2013). We applied a multiecho FLASH sequence with a 1 $mm^3$ isotropic resolution (Siemens Trio 3 T scanner; 256 × 256 matrix, 176 sagittal slices with a thickness of 1 mm, repetition time (TR) 2530 ms, inversion time (TI) 1100 ms, echo time (TE) 1.64/3.5/5.36/7.22 ms, bandwidth 651 Hz, non-selective excitation at 7°). We used the FreeSurfer protocol (Martinos Center for Biomedical Imaging, Boston, MA, USA; http://surfer.nmr.mgh.harvard.edu; version: v5.1.0, Dell XPS workstation) (Fischl et al., 2002) to delineate hippocampal and amygdala volumes. The intracranial volume (ICV) was also derived from FreeSurfer. All regions of interest (ROIs) were visually inspected before data analysis. No corrections were needed. In the original analysis, we did not exclude outliers (1.5 below the first quartile or above the third quartile; $n=5$ in the ASD group, $n=9$ in the trauma-exposed non-ASD group, $n=6$ in the trauma non-exposed control group). In a secondary analysis, the outliers were excluded.

In addition to this ROI approach, we performed voxel-based morphometry (VBM) in the whole sample (Ashburner and Friston, 2000). Structural MRI analysis was performed with SPM5 (www.fil.ion.ucl.ac.uk/spm; Matlab v7.8; The MathWorks, Cambridge, UK; VBM toolbox [v5.1, http://dbm.neuro.uni-hen.de/vbm]). Brain images were segmented into gray matter, white matter and cerebrospinal fluid (no tissue priors, Hidden Markov Random Field weighting: 0.15) (Ashburner and Friston, 2000). We used DARTEL for the normalization of the images (Ashburner, 2007). We used an 8 $mm^3$ Gaussian kernel to smooth Jacobian-modulated images.

### 2.3. Data analysis

We used the PowerMap software to calculate the sample size necessary for a sufficient statistical power ( > 80%) (Joyce and Hayasaka, 2012). VBM data were analyzed with full factorial analysis of variance (ANOVA) models in SPM5. We applied repeated measures ANOVAs on hippocampal and amygdala volumes, corrected for ICV by using two methods: (i) dividing the volume of the brain structure by the ICV (Whitwell et al., 2001); (ii) the covariance method (Jack et al., 1989; Mathalon et al., 1993). The ANOVA investigated the main effects of group (ASD, trauma-exposed controls without ASD, trauma non-exposed controls), session (baseline vs. follow-up), laterality (left vs. right), and their interactions. Pearson's product-moment correlation coefficients were calculated between hippocampal/amygdala volumes and CAPS scores. Demographic data were compared with chi-square tests and two-tailed Student's $t$ tests. All analyses were corrected for gender, age, and education. The level of statistical significance was set at $\alpha < 0.05$.

## 3. Results

VBM revealed no significant differences between patients with ASD, trauma-exposed controls without ASD, and individuals without acute trauma exposition. The lack of significant differences held true at both time points of investigation ($Fs < 1$, $ps > 0.5$). VBM showed good test–retest reliability with no differences between images obtained at baseline and follow-up.

Table 2 shows the results from the FreeSurfer analysis. Similar to the VBM results, we found no significant differences among the groups (with both correction methods for ICV), and there was a sound test-retest consistency of the data ($Fs < 1$, $ps > 0.5$). The results remained the same when the outliers were excluded from the data analysis. Finally, we found no significant correlations between hippocampal/amygdala volumes and CAPS scores ($-0.1 < rs < 0.1$, $ps > 0.1$).

## 4. Discussion

The results of the present study suggest that there are no structural brain alterations in individuals exposed to acute psychological trauma. It is notable that in this population, there was

**Table 1**
Clinical and demographic characteristics of the participants.

| | Acute stress disorder ($n=75$, 27 male) | | Trauma-exposed controls ($n=60$, 15 male) | | Non-exposed controls ($n=60$, 18 male) | | $F$ | $p$ |
|---|---|---|---|---|---|---|---|---|
| | Mean | S.D. | Mean | S.D. | Mean | S.D. | | |
| Age (years) | 37.7 | 9.6 | 37.0 | 11.0 | 38.3 | 12.3 | 1.16 | 0.20 |
| Education (years) | 10.9 | 5.7 | 11.7 | 6.8 | 11.9 | 4.3 | 0.49 | 0.61 |
| Time elapsed since trauma (days) | 16.4 | 6.8 | 18.2 | 7.1 | – | – | 2.11 | 0.15 |
| Appearance of symptoms (days after the trauma) | 0.4 | 0.6 | – | | – | | | |
| Duration of symptoms (days) | 15.3 | 5.3 | – | | – | | | |
| CAPS | | | | | | | | |
| Baseline | 48.1 | 12.3 | 4.1 | 3.5 | – | | 821.2 | < 0.0001 |
| Follow-up | 3.5 | 3.2 | 4.6 | 5.1 | | | 0.62 | 0.43 |

Data are mean (standard deviation). Individuals with acute stress disorder and the control groups did not differ in age, gender distribution, and education ($ps > 0.2$). CAPS, Clinician-Administered PTSD Scale. $F$ and $p$ Values are from one-way analyses of variance comparing groups.