Psychiatry Research: Neuroimaging 222 (2014) 119–123

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Hippocampal volume is inversely related to PTSD duration

Linda L. Chao [a,b,e,*], Kristine Yaffe [b,c,d,f], Kristin Samuelson [f,g], Thomas C. Neylan [b,f]

[a] Department of Radiology and Biomedical Imaging, University of California at San Francisco, San Francisco, CA, USA
[b] Department of Psychiatry, University of California at San Francisco, San Francisco, CA, USA
[c] Department of Neurology, University of California at San Francisco, San Francisco, CA, USA
[d] Department of Epidemiology and Biostatistics, University of California at San Francisco, San Francisco, CA, USA
[e] Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, 4150 Clement Street, 114M, San Francisco, CA 94121, USA
[f] Mental Health Service, Department of Veterans Affairs Medical Center, San Francisco, CA, USA
[g] California School of Professional Psychology, Alliant International University, San Francisco, CA, USA

ARTICLE INFO

Article history:
Received 17 December 2013
Received in revised form
7 March 2014
Accepted 11 March 2014
Available online 19 March 2014

Keywords:
Posttraumatic stress disorder
Hippocampus
Structural magnetic resonance imaging
Volumetry
Combat veterans

ABSTRACT

Numerous imaging studies have reported smaller hippocampal volumes in patients with PTSD. To investigate whether decreased hippocampal volume is associated with PTSD chronicity, independent of age, we used hierarchical linear regression to examine the relationship between PTSD duration (estimated from the amount of time that had elapsed since the traumatic event; mean=17 years; range=6–36 years) and hippocampal volume, adjusting for age and other factors. Freesurfer version 4.5 was used to quantify the volumes of the hippocampus and the caudate nucleus, which served as a "control" region, from the 1.5 T Magnetic Resonance Images (MRI) of 55 combat veterans (mean age 45 ± 9 years) with chronic and current PTSD. PTSD duration was significantly associated with right hippocampal volume ($\beta = -0.34$, $t = -2.40$, $P = 0.02$) after accounting for intracranial volume, age, gender (entered in the first step) and comorbidities (e.g., early life trauma, current major depression, history of substance abuse/dependence, psychotropic medication use, entered in the second step). This finding provides support for the potential neurotoxic effects of PTSD on hippocampal volume.

Published by Elsevier Ireland Ltd.

1. Introduction

Posttraumatic Stress Disorder (PTSD) is a psychiatric illness that can affect individuals who have been exposed to a life-threatening event or trauma. Numerous structural magnetic resonance imaging (MRI) studies of PTSD have reported reduced hippocampal volume in patients with PTSD relative to controls (Bremner et al., 1995; Gilbertson et al., 2002; Gurvits et al., 1996; Hedges et al., 2003; Lindauer et al., 2004; Pavic et al., 2007; Stein et al., 1997; Villarreal et al., 2002; Vythilingam et al., 2005; Wang et al., 2010; Woodward et al., 2006). However, there is controversy about whether this volume reduction represents a pre-existing vulnerability factor for developing PTSD following exposure to trauma (Gilbertson et al., 2002), an acquired sign of PTSD due to the traumatic stress that caused PTSD, or the chronic effects of having PTSD (Bremner, 1999, 2001).

Animal research has provided compelling evidence that exposure to severe and chronic stress can cause brain damage, particularly in the hippocampus, via the neurotoxic effect of elevated corticosteroids levels and excitotoxins (McEwen and Sapolsky, 1995; Sapolsky et al., 1990). It has been proposed that psychological trauma may cause neurological damage by a similar mechanism in humans (Bremner, 1999, 2001). Even if a small hippocampus confers vulnerability for developing PTSD, it does not necessarily exclude the additional neurotoxic effects of repeated stress-responses to trauma cues once an individual acquires PTSD. Because Felmingham et al. (2009) previously reported a significant negative correlation between right hippocampal volume and PTSD duration in 21 civilians with PTSD but no history of substance dependence, we sought to test the hypothesis that increasing duration of PTSD would be independently associated with reduced hippocampal volume but not with the volume of a "control" subcortical brain structure (i.e., caudate nucleus).

2. Methods

2.1. Sample and clinical assessment

We conducted secondary analysis of structural MRI data of 55 combat veterans with chronic and current PTSD. The imaging data was acquired from previous cross sectional imaging studies that examined the effects of service in the Persian Gulf War (Weiner et al., 2010) and the effects of PTSD and alcohol abuse on brain function and structure (Schuff et al., 2008). Only data from subjects without

* Corresponding author at: Center for Imaging of Neurodegenerative Diseases, Department of Veterans Affairs Medical Center, 4150 Clement Street, 114M, San Francisco, CA 94121, USA. Tel.: +1 415 221 4810x4386; fax: +1 415 668 2864.
E-mail address: linda.chao@ucsf.edu (L.L. Chao).

http://dx.doi.org/10.1016/j.pscychresns.2014.03.005
0925-4927/Published by Elsevier Ireland Ltd.

a diagnosis of alcohol abuse or dependence in the past 5 years were included for analysis in the present study.

PTSD was diagnosed using the Clinician Administered PTSD Scale (CAPS; Blake et al., 1995). Interviewers assessed time since the Criterion A event, which served as an estimate of the duration of PTSD. The Structured Clinical Interview for DSM-IV Diagnosis (SCID; Spitzer et al., 1992) was used to diagnose psychiatric disorders other than PTSD, including the exclusionary diagnoses of lifetime psychotic disorders, bipolar disorder, and diagnosis of alcohol abuse or dependence in the past 5 years. All diagnoses were made by trained clinical interviewers, who calibrated their assessments at weekly case consensus meetings, under the supervision of a Ph.D.-level clinical psychologist. Depressive symptoms were assessed with the Hamilton Depression Scale (HAMD, Hamilton, 1967). Exposure to severe childhood trauma before age 14 was assessed by five items from an interview version of the Life Stressor Checklist (Wolfe et al., 1996). Participants were asked whether they had been exposed to any of the following experiences to the extent that they felt that they could die or be physically harmed: physical neglect, family violence, physical abuse, forced sexual touch, or forced sexual intercourse (O'Donovan et al., 2011; Otte et al., 2005; Pole et al., 2007).

Because a majority of the veterans in this secondary analysis were Gulf War (GW) veterans, we accounted for Gulf War Illness as defined by the Center for Disease Control and Prevention's criteria (Fukuda et al., 1998). Because we previously found reduced hippocampal volumes in GW veterans with suspected low-level sarin exposure from the destruction of a munitions storage pit in Khamisiyah, Iraq compared to non-exposed GW veterans (Chao et al., 2010), we also accounted for possible sarin exposure in our analyses. We used information obtained from the office of the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness to dichotomously account for the presence or absence of suspected sarin exposure.

2.2. Image acquisition and processing

All subjects were scanned on a 1.5 T Vision, Siemens MRI scanner (Siemens Medical Systems, Iselin, New Jersey). A T1-weighted 3D volumetric Magnetization-Prepared Rapid Gradient Echo (MPRAGE) sequence was acquired the following parameters: repetition time/spin-echo time/inversion time = 10/4/300 ms, 1×1 mm^2 in-plane resolution, and 1.5-mm slab thickness, angulated perpendicular to the long axis of the hippocampus. We used the publically available Freesurfer version 4.5 (http://surfer.nmr.mgh.harvard.edu/) to estimate each subjects' right and left hippocampal and Intracranial Volume (ICV, Buckner et al., 2004). We also examined the volume of the caudate nucleus as a "control" brain structure. All regional volumes were visually inspected for errors.

2.3. Statistical methods

We used normal probability plots and the Shaprio–Wilks test to examine the distribution of the imaging and continuous independent variables. The imaging variables, total CAPS, and HAMD scores were normally distributed. However, PTSD duration had a positive skew of 1.4. Therefore, subsequent analyses were conducted on log-transformed PTSD duration data. Next, we used hierarchical linear regressions to examine the relationship between PTSD duration (i.e., time since the Criterion A event), PTSD symptom severity (i.e., total CAPS score), hippocampal, and caudate volume. The models accounted for ICV, age, and gender (entered in the first step of the regression), as well as the potential confounding effects of early life trauma (determined by five items from an interview version of the Life Stressor Checklist), current depressive symptoms (determined by HAMD scores), history of drug/alcohol abuse/dependence (determined from the SCID), Gulf War Illness and suspected low-level sarin exposure. PTSD duration or PTSD severity were entered in the final step of the models.

In post-hoc analyses, we excluded the three GW veterans with suspected sarin exposure to examine whether they unduly influenced the relationship between PTSD duration, PTSD severity, and hippocampal volume.

3. Results

Table 1 summarizes the demographic and clinical data for the 55 combat veterans with chronic, current PTSD. Mean PTSD duration was 17 years (range: 6–36).

3.1. Relationship between regional brain volume, PTSD duration, and PTSD severity

After accounting for ICV, age, gender, and comorbidities (entered in the first two steps of the model), PTSD duration significantly predicted right hippocampal volume ($\beta = -0.34$, $t = -2.40$, $P = 0.02$; see Table 2).

Table 1
Demographic and clinical characteristics of veterans with PTSD.

	Mean (SD) or *N* (%)	Range
Age (years)	44.9 (8.9)	31–59
No. (%) Female	10 (18%)	
No. (%) Caucasian	31 (56%)	
Education (years)	14.4 (2.2)	9–20
Total CAPS[a]	65.3 (15.9)	40–108
Re-experiencing	15.8 (7.1)	4–37
Avoidance	26.0 (7.8)	12–44
Hyperarousal	23.5 (5.7)	9–34
Time since trauma (years)[b]	16.7 (8.7)	6–36
Traumatic event		
Gulf War related	38 (69%)	
Vietnam War related	12 (22%)	
Other military related	3 (6%)	
Non-military related	2 (3%)	
Hippocampal volume/ICV[c]	5.5 (0.5)	4.5–6.7
No. (%) with early life trauma[d]	28 (51%)	
No. (%) with current MDD[e]	22 (40%)	
Hamilton Depression Scale	13.6 (6.3)	3–28
No. (%) on psychotropic medication	21 (38%)	
No. (%) with history alcohol abuse/dependence[f]	35 (64%)	
No. (%) with history drug abuse/dependence[f]	14 (25%)	
No. (%) with Gulf War Illness[g]	24 (44%)	
No. (%) with suspected sarin exposure[h]	3 (5%)	

[a] Clinician Administered PTSD Scale.
[b] Used as proxy measure for PTSD duration.
[c] Intracranial volume, units = mm^3/cm^3.
[d] Assessed by five items from an interview version of the Life Stressor Checklist (Wolfe et al., 1996) as previously described in O'Donovan et al. (2011), Pole et al. (2007), and Otte et al. (2005).
[e] Major depressive disorder, determined by the Structured Clinical Interview for DSM IV.
[f] Determined by the Structured Clinical Interview for DSM IV.
[g] Defined using the Center for Disease Control and Prevention's criteria (Fukuda et al., 1998).
[h] Defined using information obtained from the office of the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness.

There was no significant relationship between PTSD duration and left hippocampal volume ($\beta = -0.18$, $t = -1.12$, $P = 0.27$).

Although log-transformation reduced the positive skew of PTSD duration, there were still three cases with large Cook's Distance values (i.e., $> 4/N$). Excluding these cases from the analysis improved the association between PTSD duration and volumes of the right ($\beta = -0.35$, $t = -2.86$, $P = 0.007$) and left ($\beta = -0.22$, $t = -1.38$, $P = 0.18$) hippocampus. When we re-analyzed the entire data set using robust regression, the unstandardized coefficient for the right hippocampus changed from −809.8 (std err: 342.8) to −855.8 (std err: 350.6) and the *t*-value increased from $t = 2.36$ to $t = 2.44$. This suggests that the inverse relationship between PTSD duration and right hippocampal volume is not driven by outliers.

There was no significant relationship between PTSD duration and the volume of our control brain structure (right caudate: $\beta = -0.23$, $t = -1.35$; left caudate: $\beta = -0.30$, $t = -1.76$). There was also no significant relationship between PTSD symptom severity and hippocampal (right: $\beta = -0.10$, $t = -0.77$; left: $\beta = -0.13$, $t = -0.88$) or caudate (right: $\beta = 0.13$, $t = 0.87$; left: $\beta = 0.12$, $t = 0.76$) volumes.

3.2. Post-hoc analyses excluding three GW veterans with suspected sarin exposure

Excluding the three GW veterans with suspected sarin exposure (different subjects than the ones with large Cook's Distance values) did not alter the relationship between PTSD duration and right hippocampal ($\beta = -0.32$, $t = -2.08$, $P < 0.05$) volume. There was still no significant relationship between PTSD duration and left hippocampal, right, or left caudate volume ($\beta = -0.16$ to -0.30, $t \leq 1.66$, $P \geq 0.11$). There was also no significant relationship between PTSD severity