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Greater hippocampal volume is associated with PTSD treatment response

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ABSTRACT

Previous research associates smaller hippocampal volume with posttraumatic stress disorder (PTSD). It is unclear, however, whether treatment affects hippocampal volume or *vice versa*. Seventy-six subjects, 40 PTSD patients and 36 matched trauma-exposed healthy resilient controls, underwent clinical assessments and magnetic resonance imaging (MRI) at baseline, and 10 weeks later, during which PTSD patients completed ten weeks of Prolonged Exposure (PE) treatment. The resilient controls and treatment responders (n=23) had greater baseline hippocampal volume than treatment non-responders (n=17) (p=0.012 and p=0.050, respectively), perhaps due to more robust fear-extinction capacity in both the initial phase after exposure to trauma and during treatment.

1. Introduction

Previous studies suggest smaller hippocampal volume is a heritable vulnerability for posttraumatic stress disorder (PTSD) (Gilbertson et al., 2002). Hippocampal volume has not evinced change over the course of PTSD post onset (Bonne et al., 2001), suggesting a trait-like quality. However, current research has not clarified whether treatment affects hippocampal volume (Apfel et al., 2011), or whether hippocampal volume influences treatment response (van Rooij et al., 2015).

Although hippocampal volume increases following psychopharmacological treatment (Vermetten et al., 2003), whether psychotherapy affects hippocampal volume is unclear. Whereas both Levy-Gigi and colleagues reported increased hippocampal volume following cognitive behavioral therapy (N=39) (Levy-Gigi et al., 2013) and Eye Movement and Desentization and Reprocessing (EMDR) (N=10) (Bossini et al., 2011), other researchers failed to find any relationship between hippocampal volume changes and psychotherapy (Lindauer et al., 2005, (N=18); van Rooij et al., 2015, (N=47)).

If hippocampal volume predicts risk of developing PTSD after trauma, it may also influence treatment response. To examine this possibility, we evaluated patients with PTSD and resilient trauma-exposed healthy controls (TEHCs), matched for trauma type and demographic variables, using magnetic resonance imaging (MRI) at baseline and 10 weeks later, during which interval PTSD patients received Prolonged Exposure (PE), a first line cognitive-behavioral PTSD treatment (Foa et al., 2008). We hypothesized that larger baseline hippocampal volume would positively predict PE treatment response. We also assessed whether PE was associated with changes in hippocampal volume.

2. Methods

Seventy-six participants with adult trauma (PTSD=40, TEHC=36) received assessment by medical examination, the Structured Clinical Interview for DSM-IV Axis I Disorders (First and Gibbon, 2004), Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995), and Hamilton Depression Rating Scale (HAM-D-17). Participants answered the Life Events Checklist (LEC) to assess trauma history and determine duration and number of exposures to potentially traumatic events. PTSD group exclusion criteria included substance/alcohol dependence within the past six months, or abuse within the past two months; psychotropic medication use four weeks prior to participation; HAM-D >24, and CAPS <50. TEHC group exclusion criteria included current or past Axis I

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disorders and CAPS > 19. PTSD participants' index trauma was to have occurred after age 16. Participants in the PTSD and TEHC groups were matched on demographic variables and trauma type. Treatment response was defined *a priori* as ≥30% reduction from baseline CAPS score (Brady et al., 2000).

T1-weighted structural images were acquired on a 1.5 T GE Twin Speed MRI Scanner (TR/TE/Flip angle=7.25 ms/3 ms/7°; 1 × 1 mm in plane × 1.3 mm). After inspection for motion artifacts or gross abnormalities, volume values for both left and right hippocampus were obtained using Freesurfer 5.1 (http://surfer.nmr.mgh.harvard.edu) standard surface-based reconstruction pipeline (Dale et al., 1999). PTSD participants received 10 weekly PE sessions. The New York State Psychiatric Institute Institutional Review Board approved all procedures, and all participants provided written informed consent.

Analyses compared three groups: treatment responders (n=23), TEHCs (n=36), and non-responders (n=17). Fourteen non-responders dropped out before PE ended (five patients dropped out pre-treatment; four after completing the PE psychoeducational component; and five after the first exposure session). Within the non-responder group, completers and dropouts did not differ on any demographic, clinical, or brain volume variables. Kruskal Wallis tests, *t*-tests, and one-way analyses of variance (ANOVAs) compared baseline clinical and demographic data. Baseline hippocampal volumes were compared among the responder, non-responder, and TE-HC groups using ANCOVA with post-hoc LSD tests; a Group-by-Time repeated-measures ANCOVA compared post-treatment volume change. Both analyses controlled for age, sex, and total brain volume (TBV, included to rule out non-ROI specific trends). All tests were two-tailed with significance $\alpha < 0.05$.

3. Results

The treatment responders, non-responders and TEHCs did not differ on demographics or number of traumatic events. In addition, there were no statistically significant baseline differences in total brain volume pre- $F(2, 74)=0.070$; $p > 0.25$, or post-treatment $F(2, 50)=0.93$; $p > 0.25$. Expected clinical symptom differences and treatment effects appeared pre- ($F(2, 74)=337$; $p < 0.001$), and post- treatment ($F(2, 46)=27.0$; $p < 0.001$) (see Table 1).

Baseline hippocampal volume showed a significant main effect of group $F(2, 71)=3.42$, $p=0.038$, $\eta^2=0.088$. *Post hoc* analyses indicated treatment responders had larger hippocampal volumes at trend level than non-responders ($p=0.050$), and TE-HCs had

Table 1
Demographic, clinical, and MRI characteristics.

Characteristic	PTSD treatment responders (n=23)	PTSD non treatment responders (n=17)	Trauma exposed healthy controls (n=36)	Group comparison
Age, mean (SD), y	34.4 (8.5)	37.5 (10.7)	34.4 (10.8)	F(2, 75)=0.61; p > 0.250
Gender, female, %	78	59	69	H(2)=1.73; P > 0.250
Ethnicity				H(2)=0.07; P > 0.250
White, n	4	6	11	
African American, n	3	7	12	
Hispanic, n	13	4	12	
Other, n	3	0	1	
Recency of trauma, mean (SD), y	15.8 (14.4)	12.4 (9.3)	11.4 (12.5)	F(2, 75)=0.87; p > 0.250
Age at primary trauma, mean (SD), y	27.9 (8.8)	32.1 (12.6)	25.9 (10.2)	F(2, 75)=2.09; p=0.130
Total number of Traumatic events, mean (SD)	3.7 (3.6)	3.8 (3.4)	2.4 (2.4)	H(2)=2.91; P =0.220
Trauma type				
Natural disaster, n	10	4	9	
Fire/explosion, n	4	3	2	
Accident, n	14	6	12	
Toxic exposure, n	2	0	1	
Physical assault, n	8	8	14	
Assault w/ =Weapon, n	9	7	6	
Sexual assault, n	11	7	5	
Other sexual contact, n	4	3	5	
Combat, n	4	2	2	
Captivity, n	5	1	1	
Illness or injury, n	2	0	4	
Severe suffering, n	0	2	1	
Violent death, n	6	8	3	
Unexpected death, n	7	5	17	
Terrorism, n	6	0	5	
Other, n	8	2	5	
Baseline CAPS total score, mean (SD)	81.3 (16.4)	81.0 (14.5)	3.2 (3.6)	F (2, 70)=337; p < 0.001
Followup CAPS total score, mean (SD)	23.0 (20.4)	68.0 (10.8)	3.3 (6.1)	F (2, 46)=27.0; p < 0.001
Baseline HAM-D total score, mean (SD)	16.2 (5.7)	16.5 (5.7)	2.2 (2.4)	F (2, 70)=90.1; p= < 0.001
Followup HAM-D total score, mean (SD)	8.2 (6.9)	16.3 (5.7)	2.9 (3.3)	F (2, 46)=8.6; p=0.001
Lifetime alcohol dependence, n	2	1	0	
Right hippocampus, mean (SD)	4164.8 (405.8)	3912.2 (491.2)	4221.1 (443.4)	F (2, 71)=3.26; p=0.04[a]
Left hippocampus, mean (SD)	4032.9 (412.5)	3848.1 (569.8)	4093.3 (339.5)	F (2, 71)=2.84; p=0.06[a]
Total hippocampal volume, mean (SD)	8197.7 (792.9)	7760.2 (1042.1)	8315.2 (758.3)	F (2, 71)=3.42; p=0.038[a], η^2 =0.088

Abbreviation: TEHC, Trauma Exposed Healthy Controls; CAPS, Clinician Administered PTSD Scale; HAM-D, Hamilton Rating Scale for Depression.
[b]Analysis controlled for sage and sex.

[a] Analysis controlled for age, sex, and total brain volume.