



Expansion of hippocampal and amygdala shape in posttraumatic stress and early life stress

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ABSTRACT

Objective: The aim of this study was to examine the effect of Posttraumatic Stress Disorder (PTSD) and childhood adversity on brain structure. We assessed hippocampal and amygdala shape in veterans with varying levels of PTSD symptom severity and exposure to early life stressors (ELS).

Methods: A total of 70 male veterans, who were deployed to a combat area during OIF/OEF/OND and who had been exposed to trauma during deployment, were included in the study. We applied a vertex-wise shape analysis of 3T MRI scans to measure indentation or expansion in hippocampal and amygdala shape.

Results: Analyses showed a positive correlation between number of ELS and vertices in the right amygdala and the right hippocampus, as well as a positive correlation between PTSD symptom severity and right hippocampal vertices. There were no significant interactions between PTSD symptoms, ELS, and brain shape.

Discussion: Results indicate a relationship between exposure to more childhood adversity and expansion in amygdala and hippocampal shape as well as between more severe PTSD symptoms and expansion in hippocampal shape. These findings may have important implications for the pathophysiology of trauma-related disorders.

1. Introduction

There is a significant number of American military veterans returning from combat zones in Iraq or Afghanistan with Post-traumatic Stress Disorder (PTSD) with a prevalence ranging between 4 and 17% (Richardson et al., 2010). PTSD is characterized by unwanted re-experiencing of the trauma, avoiding reminders of the trauma, intrusive memories, negative changes in cognition and emotion about oneself or others, and increased physiological activity such as irritability, hypervigilance, or sleep disturbance (American Psychiatric Association, 2013). It is unclear why only some individuals develop PTSD following exposure to a traumatic event; a number of potential risk factors however, including early life stressors (ELS), have been identified (Brewin et al., 2000).

A prominent neurobiological theory of PTSD posits that the constant evaluation of environmental stimuli as possible threats, and over-generalization of situations and people as potentially harmful is, in part, mediated by an abnormal interaction between the hippocampus and the amygdala (Hayes et al., 2012). The hippocampus is primarily involved in learning and recall of memories while the amygdala modulates these

processes if emotions such as threat or stress are involved (Phelps, 2004). Therefore, these two limbic regions likely play a crucial role in the etiology and maintenance of PTSD symptoms (Morey et al., 2012; O'Doherty et al., 2015).

Evidence regarding the neuropathophysiology of PTSD has been inconclusive thus far. Animal studies have shown that exposure to prolonged or acute severe stress leads to cell death and impaired neurogenesis in the hippocampus (Kim et al., 2006; Sapolsky, 2000), raising the question whether PTSD impacts hippocampal structure in humans in a similar fashion. While many studies report smaller hippocampal volumes either unilaterally (Morey et al., 2012; Woon et al., 2010) or bilaterally (Logue et al., 2018; Nelson and Tumpap, 2017; Smith, 2005), there is also research that does not confirm such structural abnormalities (Bonne et al., 2001; Eckart et al., 2012; Jatzko et al., 2006; Yehuda et al., 2007). Studies investigating structural changes in the amygdala of PTSD patients have also yielded equivocal findings as there is evidence for both decreased (Karl et al., 2006) and increased (Kuo et al., 2012) amygdala volumes of PTSD patients. Others, however, did not find any significant structural abnormalities in the amygdala of those with PTSD (Logue et al., 2018; Wignall et al., 2004;

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Woon and Hedges, 2009).

Another important consideration is that it is not clear whether structural alterations in the hippocampus or the amygdala are a consequence of chronic stress associated with PTSD symptoms or a predisposition to developing PTSD when exposed to a traumatic event. The most compelling support for the latter hypothesis comes from a twin study (Gilbertson et al., 2002). Gilbertson et al. (2002) reported smaller hippocampal volumes in subjects with severe PTSD and their identical twins (without PTSD or combat exposure), compared to both combat exposed subjects without PTSD and their identical twins. Prospective studies point to increased amygdala reactivity to negative stimuli as well as diminished hippocampal activation during response inhibition as potential biomarkers for PTSD (McLaughlin et al., 2014; Stevens et al., 2017; van Rooij et al., 2018).

In addition to a genetic predisposition, exposure to ELS increases vulnerability to the effects of stressors experienced later in life (Eckart et al., 2012; Gilbertson et al., 2002). Potential ELS include sexual and physical abuse that occurs during childhood or adolescence. Such experiences may cause structural changes in the limbic system (Logue et al., 2018), leading to an abnormal response to stress, and consequently to an increased risk for developing PTSD when exposed to additional trauma later in life (Dannowski et al., 2012; Frodl and O'Keane, 2013). However, volume loss in the hippocampus of children with PTSD may not develop until adulthood (Woon and Hedges, 2008).

Several issues hinder the establishment of a direct link between PTSD and structural changes in the brain. For instance, high rates of comorbid disorders, including alcohol use disorders, depression, or traumatic brain injury, may confound associations (Gilbertson et al., 2002; Isaac et al., 2006). In addition, differences in subject characteristics (e.g., different trauma types, medicated versus un-medicated symptoms, long-standing versus recent PTSD, PTSD resulting from a single event versus repeated exposure to trauma, age at trauma exposure) or methodologies (e.g., different Magnetic Resonance Imaging (MRI) magnet strength, manual tracing versus automated voxel-based morphometry or vertex-based shape analyses) can lead to inconsistent findings between studies. Selection of a control cohort may also influence study findings; structural brain changes (Woon et al., 2010) have been reported in both subjects with PTSD and trauma-exposed controls without PTSD, compared to controls not exposed to trauma. This link suggests that exposure to trauma alone can have harmful effects on the brain (Johnsen and Asbjørnsen, 2008; Woon and Hedges, 2008), and highlights the need to carefully assess whether all subjects have been exposed to trauma, including both childhood and adulthood trauma.

The aim of the present study is to explore the effects of PTSD symptom severity as well as childhood adversity on brain structure. Specifically, in light of previous work suggesting that ELS, chronic stress, and PTSD are linked to abnormalities within the limbic system, we expect to find structural changes in the hippocampus and the amygdala in both subjects with more exposure to ELS and subjects with more severe PTSD symptoms. We examined structural abnormalities in bilateral hippocampi and amygdalae by applying vertex-based shape analysis MRI scans, as shape analyses are multivariate and arguably more sensitive than volume analyses. The number of PTSD studies focusing on changes in shape as opposed to volume of the hippocampus and the amygdala is extremely limited. This approach, in addition to volumetric analyses, is therefore expected to provide a more complete picture of localized abnormalities within the hippocampus and the amygdala in patients with exposure to ELS and PTSD symptoms.

2. Methods

2.1.1. Subject cohort

A total of 70 male veterans, who were deployed to a combat area during Operation Enduring Freedom (OEF), Operation Iraqi Freedom

Table 1

Demographics and characteristics of study cohort.

Variables	M (SD)/range or %	N
Demographic variables		
Age (years)	34.3 (8.4)/23–60	70
Education (years)	14.4 (1.4)/12–18	70
Ethnicity		
Caucasian	55.7%	39
Black	5.7%	4
Asian	1.4%	1
Hispanic	22.9%	16
Other or unknown	14.2%	10
Clinical variables		
PCL-M score	44.6 (16.4)/17–84	70
CAPS total severity	28.4 (19.1)/0–73	70
CAPS total symptoms	9.7 (6.0)/0–23	70
PTSD yes (CAPS)	50%	35/35
ELS yes	75.7%	53/17
ELS yes/PTSD yes	37.1%	26
ELS yes/PTSD no	38.6%	27
ELS no/PTSD yes	12.9%	9
ELS no/PTSD no	11.4%	8

Notes: M = Mean. SD = Standard deviation, N = total number. ELS = childhood physical, sexual, emotional abuse, domestic violence.

(OIF), or Operation New Dawn (OND), were included in this study. All subjects were exposed to trauma during their military deployment and met for criterion A on the Clinician-Administered PTSD Scale (CAPS-5; Weathers et al., 2015). The cohort consisted of traumatized subjects with and without PTSD and varying levels of symptom severity. Comorbidities with psychiatric disorders were assessed with the MINI Neuropsychiatric Interview (MINI 6.0; Sheehan and Lecrubier, 2010), and subjects with alcohol or substance dependence, psychotic disorders, current manic or hypomanic episode, obsessive-compulsive disorder, anorexia nervosa, or bulimia nervosa were excluded from the study. Other exclusion criteria were age above 60, history of moderate or severe traumatic brain injury (TBI), or neurological disorders that may affect cognitive functions. Exclusion criteria were assessed by means of a comprehensive phone screening. Demographics of the subject cohort are presented in Table 1. The study was approved by the Veterans Affairs San Diego Healthcare System Human Research Protection Program, and all subjects gave written informed consent.

2.1.2. Clinical variables

PTSD was diagnosed by a clinical psychologist with the CAPS-5 (Weathers et al., 2015), a structured clinical interview. PTSD symptom severity was assessed with the PTSD Checklist, military version (PCL-M; Weathers et al., 1991). Presence of ELS during childhood and adolescence was surveyed by self-report with section A of the Deployment Risk and Resiliency Inventory (DRRI; King et al., 2003). Items assessing domestic violence, as well as emotional, physical, and sexual abuse were selected from the DRRI.

2.1.3. Neuroimaging data collection and analysis

Neuroimaging scans were acquired with a Siemens 3.0 Tesla MRI scanner (Siemens Medical Solutions, Erlangen, Germany) with a 20-channel head coil. A high resolution T1-weighted scan of the whole brain was used for shape analysis of subcortical structures (160 sagittal 1.20 mm thick slices, repetition time = 2300 ms, echo time = 2.99 ms, inversion time = 1100 ms, FOV = 220 × 220 mm², matrix = 256 × 192 (interpolated to 256 × 256) flip angle = 9°; voxel size = 0.86 × 0.86 × 1.2 mm). Scans were skull stripped with Advanced Normalization Tools (ANTs) algorithms (Avants et al., 2011), and then processed using the FMRIB Software Library (FSL) FIRST (Patenaude et al., 2011). In addition, scans were N3 field inhomogeneity corrected in order to reduce MR intensity non-uniformity. The regions of interest (ROIs) included the bilateral amygdala and

hippocampus as well as the brainstem. The brainstem was chosen as a control region because it is not implicated in the pathophysiology of PTSD or ELS. The ROIs were segmented using FIRST, which applies a Bayesian shape and appearance model to fit a mesh-based boundary model of a structure to a T1-weighted image. The method is trained on a set of 336 manually annotated T1-weighted images, covering a wide range of ages and pathologies (Patenaude et al., 2011). Cortical and subcortical structures were automatically segmented and registered to standard MNI space, visually inspected, and a surface mesh was generated overlaying the hippocampus and the amygdala in both hemispheres, which was used to calculate shape differences between groups based on vertex values. In particular, the deviation in shape of the hippocampus and the amygdala of the individual subject from the average shape generated for the overall group was used as the outcome measure for shape deformation. Shape deformation was used as an indication for the degree of shrinkage or expansion in the wall of the hippocampus and amygdala. The shape provides the bounds of a volume, whose total expanse is calculated from the vertex mesh.

2.1.4. Statistical analyses

Statistical analyses were performed with FSL's Randomise (Winkler et al., 2014), a tool of FSL (Woolrich et al., 2009) as well as SPSS Version 25. PTSD symptom severity (PCL-M scores) and number of types of ELS were included in the analyses as continuous variables. The effects of PTSD symptom and ELS burden on shape abnormalities of the hippocampus and the amygdala (shrinkage or expansion) as well as interaction effects between PTSD symptoms, ELS, and brain shape were examined with a multiple regression analysis. In addition, associations between volume extractions for the hippocampus and amygdala, generated by FIRST, and PTSD/ELS were analyzed by means of a regression analysis. Analyses controlled for age and intracranial volume. Randomise controls for multiple comparisons using permutation methods and applies threshold-free cluster enhancement. Only family-wise error (FWE) corrected p -values < 0.05 were considered statistically significant.

3. Results

3.1.1. Cohort

The cohort included all males with an average age of 34 years. While the number of subjects who met for a diagnosis of PTSD (50%, Table 1) was equal to the number who did not meet for PTSD (50%, Table 1), the majority of the subject cohort reported exposure to ELS (76%, Table 1). Within both categories, with and without ELS, a nearly identical distribution of PTSD diagnosis was found. The most commonly reported trauma was physical abuse (60%, Table 2). The majority of the cohort (87%, Table 3) reported a mild TBI; a chi-square test showed that TBI burden did not differ significantly between groups. However, in order to control for a potential impact of TBI on brain shape, this variable was included in the analyses as a covariate. We did not partial out covariance of depression as PHQ-9 and PCL-M scores correlated highly ($r = 0.82$, $p < 0.001$).

3.1.2. Shape analysis

Results of the multiple regression analysis revealed a main effect for number of types of ELS and vertices in the right amygdala ($p < 0.05$; Table 4) and the right hippocampus ($p < 0.05$), as well as PCL-M scores and vertices in the right hippocampus ($p < 0.05$; Table 4). In particular, analyses showed a positive correlation between ELS and vertices in the right amygdala and the right hippocampus, indicating that subjects who have been exposed to more types of ELS have a shape expansion in these regions. In addition, we found a positive correlation between PTSD symptom severity and right hippocampal vertices, suggesting an expansion in hippocampal shape in individuals with more

Table 2

Trauma types and number of trauma reported by subjects.

Trauma type	Frequency (N)	Percent
Physical abuse	42	60.0%
Domestic violence	29	41.4%
Emotional abuse	26	37.1%
Sexual abuse	11	15.7%

Number trauma types	Frequency (N)	Percent
0	17	24.3%
1	20	28.6%
2	14	20.0%
3	16	22.9%
4	3	4.3%

Notes. Trauma experienced during childhood or adolescences assessed with section A of the DRRI.

Table 3

TBI distribution per group.

Group	TBI no (%)	TBI yes (%)	Total
ELS yes/PTSD yes	1 (4%)	25 (96%)	26
ELS yes/PTSD no	4 (15%)	23 (85%)	27
ELS no/PTSD yes	2 (22%)	7 (78%)	9
ELS no/PTSD no	2 (25%)	6 (75%)	8
Total	9 (13%)	61 (87%)	70

Notes: TBI = traumatic brain injury (mild). No significant differences in distribution between groups.

Table 4

Shape abnormality in amygdala and hippocampus.

Brain region (BA)	MNI Coordinates			Volume	Statistical effect
	X	Y	Z		
Right amygdala (53)	22.9	-4.7	-18.8	517	Main effect ELS*
Right hippocampus (36)	24.4	-20.9	-14.7	127	Main effect ELS*
Right hippocampus (36)	25.9	-26.7	-12.9	490	Main effect PTSD*

Notes: Main effects represent expansion in shape. BA = Brodmann area, volume in mm^3 . * $p < 0.05$.

severe PTSD symptoms. There were no significant interactions between PTSD symptoms, ELS, and brain shape. There were no significant main or interaction effects for PTSD or ELS burden and vertices in the brain stem, which we included as a control region. Visualization of these effects is based on shape reconstructions produced by FIRST. Fig. 1 represents shape abnormalities in the amygdala and the hippocampus associated with number of ELS and PTSD symptom severity.

3.1.3. Volume analysis

There were no significant correlations between hippocampal and amygdala volumes and PTSD symptoms and number of ELS. Volumes per group are presented in Table 5 for interpretive purposes.

4. Discussion

The aim of the present study was to investigate the effects of PTSD symptoms and ELS on structural abnormalities in the hippocampus and the amygdala. Both PTSD symptom severity and number of ELS were found to be associated with structural abnormalities in these limbic regions. In particular, PTSD symptom severity was associated with an expansion of the right hippocampus. Number of different types of ELS (i.e., sexual, physical, emotional abuse, and domestic violence) was linked to an expansion of the right amygdala and the right hippocampus. There were no significant effects of PTSD symptoms and/or

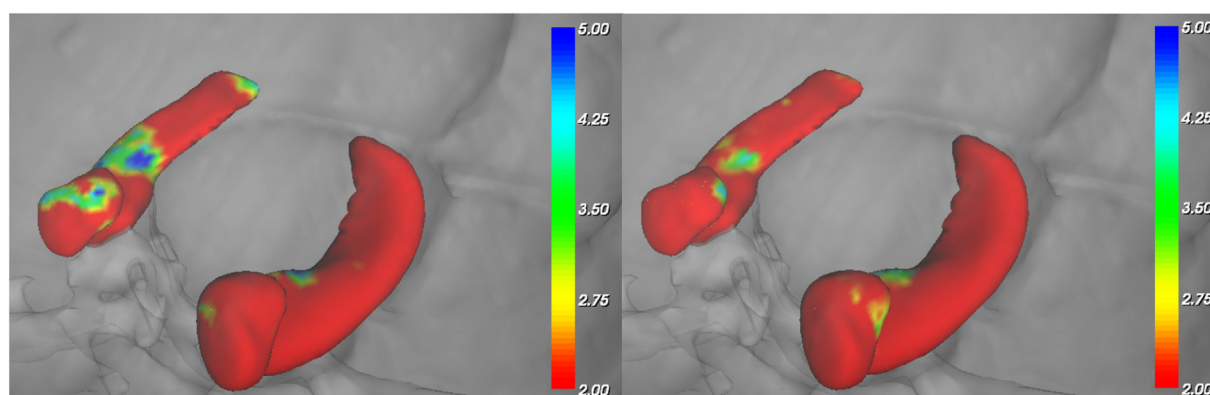


Fig. 1. Superolateral view of the hippocampus and the amygdala showing shape expansion in subjects with more exposure to ELS (left) and more severe PTSD symptoms (right). Figures represent main effects and are not residualized for covariates (age, ICV). Color bar represents *t* statistic.

Table 5

Mean volumes hippocampus and amygdala per group.

Group	R amyg.	L amyg.	R hippoc.	L hippoc.	N
ELS yes/PTSD yes	1374	1311	4071	3864	26
ELS yes/PTSD no	1431	1311	3833	3845	27
ELS no/PTSD yes	1349	1365	4045	3744	9
ELS no/PTSD no	1391	1435	3703	3649	8

Notes: Volumes in mm³, R = right hemisphere, L = left hemisphere, N = total number. Categorization of outcome variables is for interpretive purposes; analyses were based on continuous variables.

ELS on hippocampal or amygdala volume.

To our knowledge, this is the first study to report a link between both ELS burden and PTSD symptoms and hippocampal expansion. There are several considerations that may shed some light on these unexpected findings. For instance, a thorough search of the relevant literature yielded only one other study assessing shape abnormalities as opposed to volume changes in the hippocampus and amygdala of individuals with PTSD (Akiki et al., 2017). Assessing shape involves different methodologies than assessing volume, i.e. measuring vertex-based shape versus voxel-based volume. Although data derived from these two approaches is related, they provide distinct types of information with regards to morphometry. The vertex-based approach runs more localized calculations of both expansion and indentation, allowing opposite directionalities to be captured. It is possible that such opposite directionalities are nullified when calculating overall volume in voxel-based morphometry analyses. Although the present research showed associations contrasting a recent, very similar study with regards to shape abnormalities (Akiki et al., 2017), it is speculative, yet plausible, that studies reporting no volumetric changes would have found opposite directionalities within the hippocampus or amygdala had they measured shape abnormalities.

Shape expansion in the amygdala may be explained by increased reactivity of this brain region in patients with stress-related disorders. Support for this theory comes from animal studies, which have shown that chronic and severe acute stress leads to increased dendritic arborization in the basolateral amygdala and overall neuronal growth (Cui et al., 2008; Popoli et al., 2012; Vyas et al., 2002). In humans, poor maternal care and childhood adversity have been linked to larger amygdala volumes as well as poorer emotion regulation and increased glucocorticoid levels in children (Lupien et al., 2011; Mehta et al., 2009; Tottenham et al., 2010). Further support comes from functional MRI studies, which have reported increased activation in the amygdala during processing of threatening or emotional faces in adults reporting childhood maltreatment (Dannowski et al., 2012; van Harmelen et al., 2012). In addition to heightened reactivity of the amygdala, childhood maltreatment has also been linked to increased connectivity between

the amygdala and the hippocampus (Jedd et al., 2015). Perhaps our findings reflect more subtle alterations in amygdala morphology due to ELS that fall short of volumetric abnormalities.

As mentioned previously, it is still a matter of debate whether hippocampal abnormalities present a predisposing risk factor or a consequence of PTSD. Support for the former theory comes from a recent study reporting a positive correlation between right hippocampal volume prior to trauma exposure and PTSD symptom severity (Koch et al., 2018). The notion that structural changes in the hippocampus can occur in response to cognitive or environmental demands lends support for the latter theory. For instance, Maguire et al. (2000) famously demonstrated that London taxi drivers, compared to normal controls, have larger posterior hippocampi, a structure involved in spatial memory and spatial navigation (Maguire et al., 2000). Other activities such as meditation (Kurth et al., 2014), video gaming (Kühn et al., 2014) and extensive learning of semantic information (Koch et al., 2016) have also been associated with volume increases in the hippocampus.

It is therefore possible that the present findings with regards to shape expansion are due to excessive activation of the hippocampus, as well as overactive interactions between the hippocampus and the amygdala. PTSD is characterized by a number of memory-related symptoms, such as flashbacks, nightmares, as well as intrusive and recurrent memories of the trauma. The hippocampus plays a key role in these behaviors and thought patterns. Functional neuroimaging studies show that patients with PTSD show increased activation in the hippocampus during encoding and recall of negative words (Brohawn et al., 2010; Thomas et al., 2009). A tendency towards paying more attention to potentially threatening stimuli may consequently lead to more engagement of both the hippocampus and the amygdala during encoding of emotional or negative information (Hayes et al., 2012). Animal research suggests that stressful experiences during early life may prepare for adverse events during adulthood, enhancing learning if exposed to a stressful event again later in life (Oomen et al., 2010). Another consideration is therefore that for some the experience of ELS may have been effectively overcome and led to greater resilience towards stress experienced during adulthood, obfuscating a relationship between PTSD and ELS.

Our analyses did not confirm an association between hippocampal or amygdala volume and PTSD or ELS. While ample data suggests that decreased hippocampal volume is a feature of PTSD (Logue et al., 2018; Morey et al., 2012; Nelson and Tumpap, 2017; Smith, 2005; Woon et al., 2010) and ELS (Calem et al., 2017), there is also a large number of studies that did not confirm volumetric changes (Bonne et al., 2001; Eckart et al., 2012; Jatzko et al., 2006; Yehuda et al., 2007). Likewise, research investigating the effect of PTSD and ELS on amygdala volume has been inconsistent thus far as both increased (Kuo et al., 2012) and decreased (Karl et al., 2006) volumes as well as no structural

abnormalities (Woon and Hedges, 2009) have been reported. Moreover, as mentioned previously, shape analysis may pick up more subtle structural changes that may not be detected by volume measurements.

Several methodological differences with regards to subject characteristics should be taken into consideration when discussing study findings. One factor that is often overlooked is trauma exposure in healthy control subjects or additional trauma exposure in subjects with PTSD. Decreased hippocampal volume has been reported in subjects who experienced trauma but who did not meet for PTSD (Woon et al., 2010). Likewise, volume loss in both the amygdala and the hippocampus were found in children who were exposed to ELS, possibly putting them at greater risk for psychopathologies later in life (Hanson et al., 2015). Accounting for trauma exposure therefore provides important information about a potential effect of trauma itself on brain structure.

Other variables that may account for differences within as well as between studies are trauma types and patient characteristics. Inclusion of subjects with mixed trauma types and demographics may introduce uncaptured variance. For instance, trauma due to sexual or physical abuse may influence the brain slightly differently than motor vehicle accidents or combat. Moreover, there may be sex differences in brain changes following a traumatic experience. Time since trauma exposure, age at trauma exposure, repeated or additional trauma, as well as age at and time since onset of PTSD symptoms, may be other factors causing varying study results.

The present study included a homogeneous subject cohort (i.e., male OEF/OIF/OND veterans whose primary trauma was experienced during deployment to a combat area). In addition, four groups of stressors were selected to assess exposure to ELS during childhood or adolescence (i.e., sexual, physical, emotional abuse, and domestic violence). Other potentially confounding variables that should be included in future studies are health status, sleep problems, and sedentary lifestyles (Germain et al., 2017; Head et al., 2012; Mao and Yang, 2015). Lastly, it is important to point out that a high proportion of the sample reported having sustained one or multiple mild TBIs. Although including TBI in the analyses as a covariate did not change findings, a potential impact of TBI on brain shape should be taken into consideration. While a homogenous sample minimizes the impact of potential confounders, our findings may not generalize beyond these characteristics.

The present study provides novel data regarding structural abnormalities in the hippocampus and the amygdala in PTSD and ELS; nevertheless, results need to be interpreted with caution. Because the majority of the cohort reported exposure to ELS and the study did not include a control cohort that was not trauma exposed, it is unclear whether structural changes are due to repeated trauma exposure or developmental abnormalities caused by childhood adversity. However, the distribution of PTSD between groups reporting exposure to ELS versus no ELS suggests that the likelihood for developing PTSD following trauma exposure during adulthood was not influenced by the presence of prior stressors. The modest sample size and variability in type and frequency of ELS in our sample should be taken into consideration when interpreting these associations. Although we did not find a significant interaction effect between PTSD and ELS, it is important to point out that the number of subjects with PTSD but no exposure to ELS was small. Therefore, the power to detect such a relationship may be limited.

There are a number of suggestions for future research that result from the present findings. Considering the prevalence of ELS in those with PTSD, especially combat veterans (Cabrera et al., 2007), it is crucial to continue to carefully investigate the effect of childhood adversity on the development and course of PTSD. Furthermore, although we did not observe a relationship between volumetric abnormalities and shrinkage or expansion in shape in this group of participants, it may prove valuable to examine the relationship across other individuals. Another aspect that warrants further research is the question

of whether hippocampal and amygdala shape expansion are linked to symptom specific functional correlates in trauma-related disorders.

Lastly, the present findings raise the question of whether smaller hippocampal volume is a consequence of chronic, long-standing PTSD as opposed to recent onset PTSD. If that were to hold true, it is possible that in our sample, the neurotoxic effects of stress have yet to significantly damage the hippocampus. These questions exemplify how methodological differences between studies can lead to contrasting findings, and highlight the need for more prospective, longitudinal research. In addition, longitudinal studies with larger samples are needed to fully understand both risk factors for structural abnormalities in hippocampal and amygdala shape as well as resiliency factors.

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References

- Akiki, T.J., Averill, C.L., Wrocklage, K.M., Schweinsburg, B., Scott, J.C., Martini, B., ... Abdallah, C.G., 2017. The association of PTSD symptom severity with localized hippocampus and amygdala abnormalities. *Chronic Stress* 1, 1–10.
- American Psychiatric Association, 2013. *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (Washington, DC).
- Avants, B.B., Tustison, N.J., Song, G., Cook, P.A., Klein, A., Gee, J.C., 2011. A reproducible evaluation of ANTs similarity metric performance in brain image registration. *Neuroimage* 54 (3), 2033–2044.
- Bonne, O., Brandes, D., Gilboa, A., Gomori, J.M., Shenton, M.E., Pitman, R.K., Shalev, A.Y., 2001. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am. J. Psychiatr.* 158 (8), 1248–1251.
- Brewin, C.R., Andrews, B., Valentine, J.D., 2000. Meta-analysis of risk factors for post-traumatic stress disorder in trauma-exposed adults. *J. Consult. Clin. Psychol.* 68 (5), 748.
- Brohawn, K.H., Offringa, R., Pfaff, D.L., Hughes, K.C., Shin, L.M., 2010. The neural correlates of emotional memory in posttraumatic stress disorder. *Biol. Psychiatry* 68 (11), 1023–1030.
- Cabrera, O.A., Hoge, C.W., Bliese, P.D., Castro, C.A., Messer, S.C., 2007. Childhood adversity and combat as predictors of depression and post-traumatic stress in deployed troops. *Am. J. Prev. Med.* 33 (2), 77–82.
- Calem, M., Bromis, K., McGuire, P., Morgan, C., Kempton, M.J., 2017. Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples. *NeuroImage* 14, 471–479.
- Cui, H., Sakamoto, H., Higashi, S., Kawata, M., 2008. Effects of single-prolonged stress on neurons and their afferent inputs in the amygdala. *Neuroscience* 152 (3), 703–712.
- Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D., ... Bauer, J., 2012. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol. Psychiatry* 71 (4), 286–293.
- Eckart, C., Kaufmann, J., Kanowski, M., Tempelmann, C., Hinrichs, H., Elbert, T., ... Kolassa, I.T., 2012. Magnetic resonance volumetry and spectroscopy of hippocampus and insula in relation to severe exposure of traumatic stress. *Psychophysiology* 49 (2), 261–270.
- Frodl, T., O'Keane, V., 2013. How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiol. Dis.* 52, 24–37.
- Germain, A., McKeon, A.B., Campbell, R.L., 2017. Sleep in PTSD: conceptual model and novel directions in brain-based research and interventions. *Curr. Opin. Psychol.* 14, 84–89.
- Gilbertson, M.W., Shenton, M.E., Ciszewski, A., Kasai, K., Lasko, N.B., Orr, S.P., Pitman, R.K., 2002. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat. Neurosci.* 5 (11), 1242.
- Hanson, J.L., Nacewicz, B.M., Sutterer, M.J., Cayo, A.A., Schaefer, S.M., Rudolph, K.D., ... Davidson, R.J., 2015. Behavioral problems after early life stress: contributions of the hippocampus and amygdala. *Biol. Psychiatry* 77 (4), 314–323.
- Hayes, J.P., Van Elzakker, M.B., Shin, L.M., 2012. Emotion and cognition interactions in PTSD: a review of neurocognitive and neuroimaging studies. *Front. Integr. Neurosci.* 6, 89.
- Head, D., Singh, T., Bugg, J.M., 2012. The moderating role of exercise on stress-related effects on the hippocampus and memory in later adulthood. *Neuropsychology* 26 (2), 133–143.
- Isaac, C.L., Cushman, D., Jones, G.V., 2006. Is posttraumatic stress disorder associated with specific deficits in episodic memory? *Clin. Psychol. Rev.* 26 (8), 939–955.
- Jatzko, A., Rothenhöfer, S., Schmitt, A., Gaser, C., Demirkaya, T., Weber-Fahr, W., ... Braus, D., 2006. Hippocampal volume in chronic posttraumatic stress disorder (PTSD): MRI study using two different evaluation methods. *J. Affect. Disord.* 94 (1–3), 121–126.

- Jedd, K., Hunt, R.H., Cicchetti, D., Hunt, E., Cowell, R.A., Rogosch, F.A., ... Thomas, K.M., 2015. Long-term consequences of childhood maltreatment: altered amygdala functional connectivity. *Dev. Psychopathol.* 27 (4pt2), 1577–1589.
- Johnsen, G.E., Asbjørnsen, A.E., 2008. Consistent impaired verbal memory in PTSD: a meta-analysis. *J. Affect. Disord.* 111 (1), 74–82.
- Karl, A., Schaefer, M., Malta, L.S., Dörfel, D., Rohleder, N., Werner, A., 2006. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci. Biobehav. Rev.* 30 (7), 1004–1031.
- Kim, J.J., Song, E.Y., Kim, J.J., Song, E.Y., Kosten, T.A., 2006. Stress effects in the hippocampus: synaptic plasticity and memory. *Stress* 9 (1), 1–11.
- King, D., King, L., Vogt, D., 2003. *Manual for the Deployment Risk and Resilience Inventory (DRRI): A Collection of Measures for Studying Deployment-Related Experiences of Military Veterans*. National Center for PTSD, Boston, MA.
- Koch, K., Reess, T.J., Rus, O.G., Zimmer, C., 2016. Extensive learning is associated with gray matter changes in the right hippocampus. *NeuroImage* 125, 627–632.
- Koch, S., Kaldewaij, R., Zhang, W., Hashemi, M., Klumpers, F., Roelofs, K., 2018. T29. Hippocampus volume as predisposing risk factor for posttraumatic stress disorder. *Biol. Psychiatry* 83 (9), S139–S140.
- Kühn, S., Gleich, T., Lorenz, R.C., Lindenberger, U., Gallinat, J., 2014. Playing super Mario induces structural brain plasticity: gray matter changes resulting from training with a commercial video game. *Mol. Psychiatry* 19 (2), 265.
- Kuo, J.R., Kaloupek, D.G., Woodward, S.H., 2012. Amygdala volume in combat-exposed veterans with and without posttraumatic stress disorder: a cross-sectional study. *Arch. Gen. Psychiatry* 69 (10), 1080–1086.
- Kurth, F., Luders, E., Wu, B., Black, D.S., 2014. Brain gray matter changes associated with mindfulness meditation in older adults: an exploratory pilot study using voxel-based morphometry. *NeuroImage* 1 (1), 23.
- Logue, M.W., van Rooij, S.J., Dennis, E.L., Davis, S.L., Hayes, J.P., Stevens, J.S., ... Koch, S.B., 2018. Smaller hippocampal volume in posttraumatic stress disorder: a multisite ENIGMA-PGC study: subcortical volumetry results from posttraumatic stress disorder consortia. *Biol. Psychiatry* 83 (3), 244–253.
- Lupien, S.J., Parent, S., Evans, A.C., Tremblay, R.E., Zelazo, P.D., Corbo, V., ... Séguin, J.R., 2011. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proc. Natl. Acad. Sci.* 108 (34), 14324–14329.
- Maguire, E.A., Gadian, D.G., Johnsrude, I.S., Good, C.D., Ashburner, J., Frackowiak, R.S., Frith, C.D., 2000. Navigation-related structural change in the hippocampi of taxi drivers. *Proc. Natl. Acad. Sci.* 97 (8), 4398–4403.
- Mao, C.P., Yang, H.J., 2015. Smaller amygdala volumes in patients with chronic low back pain compared with healthy control individuals. *J. Pain* 16 (12), 1366–1376.
- McLaughlin, K.A., Busso, D.S., Duys, A., Green, J.G., Alves, S., Way, M., Sheridan, M.A., 2014. Amygdala response to negative stimuli predicts PTSD symptom onset following a terrorist attack. *Depress. Anxiety* 31 (10), 834–842.
- Mehta, M.A., Golemb, N.I., Nosarti, C., Colvert, E., Mota, A., Williams, S.C., ... Sonuga-Barke, E.J., 2009. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian adoptees study pilot. *J. Child Psychol. Psychiatry* 50 (8), 943–951.
- Morey, R.A., Gold, A.L., LaBar, K.S., Beall, S.K., Brown, V.M., Haswell, C.C., ... McCarthy, G., 2012. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Arch. Gen. Psychiatry* 69 (11), 1169–1178.
- Nelson, M.D., Tumpap, A.M., 2017. Posttraumatic stress disorder symptom severity is associated with left hippocampal volume reduction: a meta-analytic study. *CNS Spectrums* 22 (4), 363–372.
- O'Doherty, D.C., Chitty, K.M., Saddiqui, S., Bennett, M.R., Lagopoulos, J., 2015. A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Res. Neuroimaging* 232 (1), 1–33.
- Oomen, C.A., Soeters, H., Audureau, N., Vermunt, L., van Hasselt, F.N., Manders, E.M., ... Krugers, H., 2010. Severe early life stress hampers spatial learning and neurogenesis, but improves hippocampal synaptic plasticity and emotional learning under high-stress conditions in adulthood. *J. Neurosci.* 30 (19), 6635–6645.
- Patenaude, B., Smith, S.M., Kennedy, D.N., Jenkinson, M., 2011. A Bayesian model of shape and appearance for subcortical brain segmentation. *NeuroImage* 56 (3), 907–922.
- Pelphs, E.A., 2004. Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.* 14 (2), 198–202.
- Popoli, M., Yan, Z., McEwen, B.S., Sanacora, G., 2012. The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nat. Rev. Neurosci.* 13 (1), 22.
- Richardson, L.K., Frueh, B.C., Acierno, R., 2010. Prevalence estimates of combat-related post-traumatic stress disorder: critical review. *Aust. N. Z. J. Psychiatr.* 44 (1), 4–19.
- Sapolsky, R.M., 2000. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch. Gen. Psychiatry* 57 (10), 925–935.
- Sheehan, D.V., Lecrubier, Y., 2010. *The Mini International Neuropsychiatric Interview Version 6.0 (MINI 6.0)*. Medical Outcomes System Inc, Jacksonville, FL.
- Smith, M.E., 2005. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: a meta-analysis of structural MRI studies. *Hippocampus* 15 (6), 798–807.
- Stevens, J.S., Kim, Y.J., Galatzer-Levy, I.R., Reddy, R., Ely, T.D., Nemeroff, C.B., Hudak, L.A., Jovanovic, T., Rothbaum, B.O., Ressler, K.J., 2017. Amygdala reactivity and anterior cingulate habituation predict posttraumatic stress disorder symptom maintenance after acute civilian trauma. *Biol. Psychiatry* 81 (12), 1023–1029.
- Thomaes, K., Dorrepaal, E., Draijer, N.P., de Ruiter, M.B., Elzinga, B.M., van Balkom, A.J., ... Veltman, D.J., 2009. Increased activation of the left hippocampus region in complex PTSD during encoding and recognition of emotional words: a pilot study. *Psychiatry Res. Neuroimaging* 171 (1), 44–53.
- Tottenham, N., Hare, T.A., Quinn, B.T., McCarry, T.W., Nurse, M., Gilhooly, T., ... Eigsti, I.M., 2010. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev. Sci.* 13 (1), 46–61.
- van Harmelen, A.-L., van Tol, M.-J., Domes, L.R., van der Wee, N.J., Veltman, D.J., Aleman, A., ... Elzinga, B.M., 2012. Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Soc. Cogn. Affect. Neurosci.* 8 (4), 362–369.
- van Rooij, S.J., Stevens, J.S., Ely, T.D., Hinrichs, R., Michopoulos, V., Winters, S.J., Ogbonmwan, Y.E., Shin, J., Nugent, N.R., Hudak, L.A., Rothbaum, B.O., Ressler, K.J., Jovanovic, T., 2018. The role of the hippocampus in predicting future posttraumatic stress disorder symptoms in recently traumatized civilians. *Biol. Psychiatry* 84 (2), 106–115.
- Vyas, A., Mitra, R., Rao, B.S., Chattarji, S., 2002. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J. Neurosci.* 22 (15), 6810–6818.
- Weathers, F., Huska, J., Keane, T., 1991. *The PTSD checklist military version (PCL-M)*. US Department of Veterans Affairs. National Center for PTSD, Boston, MA.
- Weathers, F.W., Blake, D.D., Schnurr, P.P., 2015. *Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)*. US Department of Veterans Affairs. National Center for PTSD, Boston, MA.
- Wignall, E.L., Dickson, J.M., Vaughan, P., Farrow, T.F., Wilkinson, I.D., Hunter, M.D., Woodruff, P.W., 2004. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. *Biol. Psychiatry* 56 (11), 832–836.
- Winkler, A.M., Ridgway, G.R., Webster, M.A., Smith, S.M., Nichols, T.E., 2014. Permutation inference for the general linear model. *NeuroImage* 92, 381–397.
- Woolrich, M.W., Jbabdi, S., Patenaude, B., Chappell, M., Makni, S., Behrens, T., ... Smith, S.M., 2009. Bayesian analysis of neuroimaging data in FSL. *NeuroImage* 45 (1), S173–S186.
- Woon, F.L., Hedges, D.W., 2008. Hippocampal and amygdala volumes in children and adults with childhood maltreatment-related posttraumatic stress disorder: a meta-analysis. *Hippocampus* 18 (8), 729–736.
- Woon, F.L., Hedges, D.W., 2009. Amygdala volume in adults with posttraumatic stress disorder: a meta-analysis. *J. Neuropsychiatr. Clin. Neurosci.* 21 (1), 5–12.
- Woon, F.L., Sood, S., Hedges, D.W., 2010. Hippocampal volume deficits associated with exposure to psychological trauma and posttraumatic stress disorder in adults: a meta-analysis. *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* 34 (7), 1181–1188.
- Yehuda, R., Golier, J.A., Tischler, L., Harvey, P.D., Newmark, R., Yang, R.K., Buchsbaum, M.S., 2007. Hippocampal volume in aging combat veterans with and without post-traumatic stress disorder: relation to risk and resilience factors. *J. Psychiatr. Res.* 41 (5), 435–445.