

Amygdala Volume in Combat-Exposed Veterans With and Without Posttraumatic Stress Disorder

A Cross-sectional Study

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Context: Data from animal models demonstrate a link between stress exposure and hypertrophic changes in the amygdala; however, studies of adults with posttraumatic stress disorder (PTSD) have failed to find analogous structural alterations.

Objectives: To compare amygdala volumes between a sample of combat veterans with and without PTSD (analysis 1) and examine whether our observation of larger amygdala volume in individuals with PTSD could be accounted for by the presence of trauma exposure in childhood and the severity of combat exposure in adulthood (analysis 2).

Design: Cross-sectional magnetic resonance imaging.

Setting: Veterans Affairs Palo Alto Health Care System Inpatient Trauma Recovery Program and Veterans Affairs New England Health Care System Outpatient PTSD program.

Participants: Ninety-nine combat-exposed veterans from the Vietnam Conflict or the Persian Gulf War who had been exposed to substantial military operational stress.

Main Outcome Measures: Amygdala volume ad-

justed for total cerebral volume, Life Events Checklist, and the Combat Exposure Scale.

Results: Analysis 1 indicated that combat-exposed individuals with PTSD exhibited larger total amygdala volume compared with their non-PTSD counterparts (99 individuals, $P = .047$). Analysis 2 indicated that greater severity of combat exposure (87 individuals, $P = .02$), as well as the interaction between the presence of early life trauma and the severity of combat exposure (87 individuals, $P = .008$), were significantly associated with smaller total amygdala volume. The PTSD diagnosis continued to explain larger amygdala volume (87 individuals, $P = .006$).

Conclusions: Posttraumatic stress disorder is associated with enlarged amygdala volume, above the variance accounted for by a history of early life trauma and severity of adult trauma exposure. The discrepancy between our and prior findings may be explained by variability in these trauma indices in previous investigations. These findings support additional study of amygdala structure in human stress disorders and further delineation of the role of early and adult trauma on associated neurologic changes.

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POSTTRAUMATIC STRESS DISORDER (PTSD) is a severe and often debilitating disorder that encompasses cognitive, emotional, and behavioral disturbances.^{1,2} Functional neuroimaging studies¹⁻³ in PTSD have consistently observed evidence of heightened amygdala reactivity among individuals with PTSD undergoing stress-reactivity paradigms with generic fear and trauma-related stimuli. In apparent harmony with these human studies, animal studies have consistently shown trophic structural alterations in the amygdala as a consequence of severe and/or prolonged stress. Vyas and colleagues^{4,5} found that rats exposed to a 10-day chronic stress paradigm exhibited increased arborization and dendritic hypertro-

phy in both the basolateral complex of the amygdala and the bed nucleus of the stria terminalis. Increased anxiety levels, as measured by the elevated plus-maze paradigm, accompanied these dendritic increases. A subsequent study⁶ explored the long-term effects of chronic stress on the basolateral complex of the amygdala in rats and found that increased arborization and dendritic hypertrophy persisted even after a considerable recovery period, as did anxiety. Building on this work, more recent studies have indicated that chronic unpredictable stress⁷ and a single prolonged stressor⁸ can result in increased volume of the bed nucleus of the stria terminalis in rats and that the increase is due, in part, to increased dendritic arborization.⁸

In light of heightened reactivity in humans with PTSD and trophic dendritic arborization in stressed animals, it would be reasonable to predict enlarged amygdala volume in PTSD. However, the results of in vivo structural neuroimaging studies have been inconclusive, with most extant data indicating no effect of diagnosis,⁹⁻¹³ although smaller amygdala volume in persons with PTSD has been reported.^{14,15} Because samples have generally been small, 2 meta-analyses aggregated the results of these studies to increase power. Karl and colleagues¹⁶ aggregated 50 magnetic resonance imaging (MRI) studies (21 hippocampus, 11 amygdala, and 18 other structural brain measures) of adults and children with PTSD and reported smaller left amygdala volume in participants with PTSD. Woon and Hedges¹⁷ examined the results of 9 MRI studies comparing amygdala volumes of adults with PTSD vs those without PTSD and found no significant group differences in total amygdala volume. It is noteworthy that these 2 meta-analyses used overlapping study samples and that the samples exhibited considerable trauma heterogeneity (eg, single- vs multiple-incident trauma).

We therefore elected to revisit the question of amygdala volume in PTSD in a relatively large and homogeneous sample of combat veterans with a chronic, severe, multiple-traumatization form of the disorder and in whom several common findings have been replicated. These included smaller hippocampal volume¹⁸ and smaller anterior cingulate cortex volume.¹⁹ In the primary analysis (analysis 1) of the present study, our comparison of individuals with and without PTSD found evidence of larger amygdala volume in the PTSD group, a finding that could not be accounted for by many possible confounders.

In an effort to understand why our findings differed from those of prior studies, we conducted secondary analyses (analysis 2) that examined whether the observed association between PTSD and enlarged amygdala volume could be accounted for by 2 trauma-related indices that have been linked to amygdala alterations: the presence of early life trauma and severity of adult criterion A trauma. Our investigation of the former was motivated by the recent emergence of findings from the developmental literature. Mehta and colleagues²⁰ compared Romanian children who had been adopted from institutions with both noninstitutionalized and nonadopted peers. At adolescence, previously institutionalized children exhibited amygdala volumes (adjusted for cerebral tissue volumes) that were 33.5% larger than those in both control groups. Similarly, Tottenham and colleagues²¹ found, in a sample of 78 children adopted from Eastern European orphanages into socioeconomically advantaged homes, that those institutionalized for the first 15 months of life had larger amygdala volumes than did children who had been adopted at younger ages. They also found that amygdala volume was significantly associated with age at adoption and with impaired emotion regulation. Lupien et al²² recently reported increased amygdala volume in children exposed to adverse rearing conditions associated with maternal depressive symptoms. The potential relevance of our second trauma-related index, severity of adult criterion A trauma, was suggested by the results of Mollica and colleagues,²³ who

assessed structural brain volumes in Vietnamese ex-political detainees exposed to torture. The authors reported an association between smaller right amygdala volume and the number of traumatic events reported.

In combination, extant data suggest that the presence of early life trauma and severity of adult criterion A trauma might play separable roles in amygdala alterations independent of a PTSD diagnosis. Among the veterans examined in the present study, many reported criterion A events occurring during childhood. Furthermore, the age at which these events occurred was associated with systematic effects on cerebral macrodevelopment.²⁴⁻²⁶ The current study, therefore, had 2 objectives. The first was to compare the amygdala volume between our sample of combat-exposed veterans with and without PTSD. Given our observation of larger amygdala in the PTSD group, our secondary objective aimed to (1) delineate how early life trauma and severity of adult combat exposure might explain why our findings conflict with those of prior reports and (2) examine whether these 2 indices might account for variation in amygdala volume, independent of the PTSD diagnosis.

METHODS

PARTICIPANTS

Participants were recruited through a combination of advertising and word-of-mouth contacts with current and past Veterans Affairs (VA) Palo Alto Health Care System Trauma Recovery Program inpatients, VA New England Health Care System PTSD outpatients, and community-residing volunteers. Participants provided written informed consent in accordance with the procedures of the institutional review boards of Stanford University Medical School/VA Palo Alto Health Care System or Boston VA Medical Center and the McLean Hospital, Belmont, Massachusetts. Initial screening established that the participants were US military veterans of the Vietnam Conflict or the Persian Gulf War who had been exposed to substantial military operational stress. Exclusion criteria included current or past central nervous system disease, psychosis, and alcohol or substance abuse/dependence within the past 6 months. Individuals were excluded for the following reasons: negative for current military PTSD but positive for lifetime civilian PTSD (18 individuals), positive for current/recent alcohol/drug abuse (14), probable brain damage (loss of consciousness for >30 minutes or history of temperature >40°C) (6), or psychosis (2). In addition, 4 participants later withdrew because of fatigue or nicotine withdrawal, 2 missed their scanning appointments and were unreachable, and 5 withdrew because of claustrophobia. After participating, 11 additional volunteers were excluded because of imaging artifact and 2 because of previously undiagnosed brain injury. The final sample was 99 participants; approximately half were recruited at each site. Fifty-one participants (52%) met the criteria for current PTSD, and 92 (93%) were men.

ASSESSMENTS

PTSD Status and Trauma Exposure

The participants' PTSD status was determined via the Clinician-Administered PTSD Scale.²⁷ Other Axis I diagnoses were determined using the Structured Clinical Interview for the DSM-

IV.²⁸ Combat Exposure Scale (CES)²⁹ total scores were used to index an individual's cumulative degree of combat exposure. Trauma exposure was indexed using the Life Events Checklist³⁰ (LEC) component of the Clinician-Administered PTSD Scale. The LEC assesses exposure to 16 events known to potentially result in PTSD (eg, natural disaster, serious accident, and sexual or physical assault) as well as 1 item that assesses any other extraordinarily stressful event not captured. The LEC was augmented by a structured follow-up interview establishing the subcategory A1 and subcategory A2 criteria and the period of trauma occurrence.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed using two 1.5-T scanners (General Electric Signa), one located at the Diagnostic Radiology Center of the VA Palo Alto Health Care System and the other at the Brain Imaging Center of McLean Hospital. Images were acquired with a 3-dimensional volumetric pulse sequence (repetition time, 35 milliseconds; echo time, 6 milliseconds; flip angle, 45°; number of excitations, 1; matrix size, 256 × 192; field of view, 24 cm²; and section thickness, 1.5–1.7 mm, with 124 sections). Skull-stripping, positional normalization to long axis of the hippocampus orientation, re-sampling to 0.93 cubic voxels³, and tissue segmentation were performed using BrainImage.³¹ The delineation of medial temporal volumes followed the protocol detailed by Kates et al.^{32(p44)} Briefly stated, the protocol defines the following amygdala landmarks:

... [T]he anterior slice ... is identified in the coronal plane by the appearance of a globular, ovoid structure which can be differentiated ... from the cortical ribbon. The structure should have a lighter intensity than the cortical ribbon, and have a distinct superior/lateral boundary which is not contiguous with the cortical ribbon. ... The posterior slice of the amygdala coincides with a significant decrease in ... size ... and the appearance of the first slice in which the gyrus uncinatus forms a loop and turns laterally to abut the amygdala ... CSF should be present (though not continuous) between the amygdala and the hippocampus ... any portion that extends superior to the entorhinal sulcus should be excluded.

Anteriorly, "... the inferior border is marked by white matter or CSF ... from the parahippocampal gyrus." Moving caudally, "... the inferior border is defined by ... white matter ... and the temporal horn ..." and later, by the hippocampus. "The medial superior border ... can be drawn as a straight line from the inferior aspect of the entorhinal sulcus ... to the temporal stem," excluding tissue superior to the entorhinal sulcus. The lateral border is usually demarcated by a white matter tract; when the white matter is absent, a line can be drawn between the lateral aspects of the superior and inferior borders. Moving caudally, if the white matter/temporal stem cannot be visualized, a line can be extrapolated from the visible temporal stem to the inferior border of the amygdala. Delineated voxels were summed over sections to calculate left and right amygdala volumes, summing as well over gray and white matter.

STATISTICAL ANALYSIS

Analysis 1

Adjusted amygdala volume was computed by extracting standardized residual scores after regressing amygdala volume on total cerebral volume.³³ Two sets of analyses were then performed. In analysis 1, we examined whether there were differences in adjusted left and right amygdala volumes between combat veterans with and those without PTSD in the full sample

of 99 participants. A repeated-measures analysis of variance was performed to test for laterality effects in which a diagnosis of PTSD was entered as the between-subject factor and hemisphere was entered as the within-subject factor. Several possible confounders were also tested at this stage (ie, age/conflict cohort, lifetime alcohol abuse/dependence, and study site).

Analysis 2

Results of analysis 1 indicated a significant association between PTSD diagnosis and larger amygdala volume, a finding at variance with prior studies. Therefore, we performed secondary analyses (analysis 2), which examined the independent and/or interactive influence of 2 trauma-related indices on amygdala volume. The first was a dichotomous index indicating whether the age at which a participant was first exposed to a criterion A trauma of any kind was 13 years or younger (ie, presence/absence of early life trauma) based on the LEC. This cutoff was selected because it yielded reasonable cell sizes when crossed with PTSD diagnosis (yes/no, 39/48) and has been used in other studies.³⁴ The second index was the participant's total score on the CES²⁹ (ie, the severity of adult criterion A trauma). Because LEC follow-up data were not available for 12 participants, analysis 2 was performed on a subsample of 87 participants.

A hierarchical linear regression was used to give the additive or interactive influence of each index of stress equal access to variance in amygdala volume, independent of the diagnosis of PTSD. Predictors were entered in the presumptive order of their developmental effects: presence/absence of first criterion A trauma at age 13 years or younger; total CES scores; their interaction, if any; and presence/absence of a PTSD diagnosis. All predictor variables were centered in accordance with guidelines specified by Kraemer and Blasey.³⁵

RESULTS

Table 1 presents the participants' characteristics by diagnostic group, as well as tests of between-group differences. Cross-site reliability of amygdala volume estimates determined by 6 study staff and scanned in both magnets was $r_{icc}=0.92$, where icc indicates intraclass correlation coefficient. Intrarater reliability based on 16 cases drawn from both sites was $r_{icc}=0.78$. All amygdala volumes were delineated by a single rater.

ANALYSIS 1

Results indicated a significant between-groups effect, with individuals meeting the criteria for current PTSD exhibiting larger overall adjusted amygdala volumes than those not meeting the criteria ($F_{1,97} = 4.06, P = .047$). There was no within-group effect of hemisphere and no PTSD × hemisphere interaction (all F values < 1), indicating no laterality effect. There was no effect of age/conflict cohort, no effect of lifetime alcohol abuse/dependence, no age/conflict × alcohol history interaction, and no effect of study site (all F values < 1).

ANALYSIS 2

Table 2 presents the zero-order Pearson correlations among the model factors: total adjusted amygdala vol-

ume, presence/absence of criterion A trauma at age 13 years or younger (yes/no), total CES scores, and presence/absence of PTSD diagnosis (yes/no). Expected correlations were observed between PTSD and amygdala volume (based on analysis 1) and between PTSD and total CES scores. A diagnosis of PTSD was also associated with the presence of criterion A trauma at age 13 years or younger ($\chi^2 = 9.58, P = .002$). All other associations were nonsignificant. Notably, there was no zero-order relationship between the presence of criterion A trauma at age 13 or younger and CES total scores.

Table 3 presents the results of analysis 2. One case was identified as an outlier; however, examination of standardized residuals, the Cook distance, and leverage values indicated that this case was not an influential data point and was therefore retained in the analysis. Model 1 suggested a trend level association between the presence of criterion A trauma at age 13 years or younger and larger amygdala. In model 2, the addition of CES total scores failed to account for additional variance in total adjusted amygdala volume. However, in model 3, the presence of criterion A trauma at age 13 or younger predicted larger amygdala volume ($\beta = 0.24, P = .03$), and the interaction of presence/absence of criterion A trauma at age 13 or younger and CES total scores predicted smaller amygdala volume ($\beta = -0.29, P = .007$). In model 4, the addition of PTSD diagnosis as a predictor modified the findings from model 3 such that the presence of criterion A trauma at age 13 or younger no longer accounted for significant unique variance in amygdala volume; CES total scores became associated with smaller amygdala volume ($\beta = -0.25, P = .02$). The interaction of the presence/absence of criterion A trauma at age 13 or younger and CES total scores continued to predict smaller amygdala volume ($\beta = -0.28, P = .008$). Finally, a PTSD diagnosis accounted for additional variance in amygdala volume in a manner consistent with the results of analysis 1 ($\beta = 0.32, P = .006$).

We also tested for a possible laterality effect by performing the same multiple regression on paired differences between left and right amygdala volume. There were no significant associations ($P > .10$ for all comparisons), indicating no effect of laterality.

The interaction between criterion A trauma at age 13 years or younger and CES total scores on total amygdala volume is shown in the **Figure**, in which the bivariate relationship between CES total scores and total adjusted amygdala volume is plotted. The observed pattern indicated that, among individuals reporting criterion A trauma at 13 or younger, there was a negative association between combat exposure and adjusted amygdala volume ($r = -0.38, P = .02$), whereas among individuals not reporting criterion A trauma at age 13 or younger, no association was observed ($r = 0.19, P = .21$).

COMMENT

Our study found that amygdala volume, adjusted for total cerebral tissue volume, is systematically associated with PTSD as well as with indices of traumatic stress. Given our relatively large and homogeneous sample, in-

Table 1. Characteristics by PTSD Diagnosis in 87 Participants

Characteristic	PTSD+ (n = 42)	PTSD- (n = 45)	Test Statistic ^a
Age, mean (SD), y	49.5 (8.6)	46.6 (10.5)	$t = -1.40$
White race, %	67	80	$\chi^2 = 1.99$
Current psychiatric disorder, %			
MDD	74	2	$\chi^2 = 47.88^b$
Panic disorder	7	0	$\chi^2 = 3.33$
Social anxiety disorder	5	0	$\chi^2 = 2.19$
Criterion A trauma at age ≤ 13 y, % ^c	62	29	$\chi^2 = 9.58^d$
Educational level, mean (SD), y	14.3 (1.5)	15.3 (2.0)	$t = 2.42^d$
Total score, mean (SD)			
CES	26.8 (11.2)	16.5 (10.3)	$t = -4.48^b$
CAPS	76.1 (19.4)	8.4 (9.2)	$t = -20.56^b$
LEC	3.9 (2.8)	5.2 (3.3)	$t = 2.05^c$

Abbreviations: CAPS, Clinician-Administered PTSD Scale; CES, Combat Exposure Scale; LEC, Life Events Checklist; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

^a Unpaired 2-tailed t tests were used.

^b $P < .001$.

^c $P < .05$.

^d $P < .01$.

creased statistical power and the severity and chronicity of the disorder together may account for the observation of a positive association between PTSD and amygdala volume, a finding in contradiction with earlier studies. Indeed, 8 of the 9 studies included in the Woon and Hedges¹⁷ meta-analysis comparing amygdala volumes among PTSD vs non-PTSD trauma-exposed controls or healthy controls without trauma exposure indicated no significant differences in amygdala volume. These studies had considerable sample heterogeneity regarding the type of trauma (eg, sexual abuse, combat exposure, police work, and motor vehicle accidents), age at onset of the trauma, and chronicity of the trauma. Variability among any of these factors may account for the discordant findings. Notably, 2 of these studies^{13,36} compared combat-exposed Vietnam veterans with PTSD with combat-exposed³⁷ and non-combat-exposed controls¹³ and reported no significant differences in amygdala volume. The mean age of the participants from these studies, as well as the exclusion criteria implemented by Gurvits and colleagues³⁶ (exclusion criteria were not reported by Gilbertson et al¹³), were similar to those of the current study. However, samples from both studies were significantly smaller than ours (PTSD, 7-24 participants; non-PTSD, 8-23); thus, it is likely these 2 studies were underpowered to detect group differences. That being said, invoking inadequate power does not reconcile our findings with reports of smaller amygdala volume in PTSD.¹⁵ Our secondary analyses offer potential insight into this conflict.

Results from our secondary analyses suggest that specific trauma-related indices (ie, a history of early life trauma and severity of adult criterion A trauma) may independently as well as interactively explain unique variance in amygdala volume in adults, above the variance explained by a PTSD diagnosis. Moreover, the observed

Table 2. Pearson Correlations Among Model Factors in 87 Participants

Characteristic	Total Amygdala Volume	Criterion A Trauma, Age ≤13 y	CES Total Scores	PTSD Diagnosis
Total amygdala volume
Criterion A trauma at age ≤13 y	0.18
CES total scores	-0.07	0.14
PTSD diagnosis	0.27 ^a	0.33 ^b	0.44 ^c	...

Abbreviations: CES, Combat Exposure Scale; PTSD, posttraumatic stress disorder.

^a*P* = .01.

^b*P* = .002.

^c*P* < .001.

Table 3. Hierarchical Multiple Regression Examining Early Life Trauma, Severity of Adult Criterion A Trauma, Their Interaction, and PTSD Predicting Total Adjusted Amygdala Volume in 87 Participants^a

Model	B	SE	β	<i>t</i> ^b	<i>P</i> Value ^c	Δ <i>R</i> ^{2d}	Δ <i>F</i> ^d	<i>P</i> Value ^d
1								
Constant	0.02	0.11		0.17	.86	0.03	2.77	.10
Criterion A trauma at age ≤13 y	0.35	0.21	0.18	1.67	.10			
2								
Constant	0.03	0.11		0.29	.77	0.009	0.76	.39
Criterion A trauma at age ≤13 y	0.38	0.22	0.19	1.77	.08			
CES	-0.008	0.009	-0.09	-0.87	.39			
3								
Constant	0.08	0.10		0.73	.47	0.08	7.74	.007
Criterion A trauma at age ≤13 y	0.47	0.21	0.24	2.25	.03			
CES	-0.01	0.009	-0.13	-1.21	.23			
CES × criterion A trauma at age ≤13 y	-0.05	0.02	-0.29	-2.78	.007			
4								
Constant	0.09	0.10		0.92	.36	0.08	7.83	.006
Criterion A trauma at age ≤13 y	0.29	0.21	0.15	1.36	.18			
CES	-0.02	0.009	-0.25	-2.30	.02			
CES × criterion A trauma at age ≤13 y	-0.05	0.02	-0.28	-2.74	.008			
PTSD diagnosis	0.64	0.23	0.32	2.80	.006			

Abbreviations: B, unstandardized beta coefficient; CES, Combat Exposure Scale; PTSD, posttraumatic stress disorder.

^aSignificant differences are bold.

^bUnpaired *t* tests were used.

^cValues represent comparisons within the model.

^dValues represent comparisons between the models.

associations between these indices and amygdala volume are not straightforward. Three key findings emerged in our final model, model 4. First, severity of adult criterion A trauma (ie, combat exposure) was significantly negatively associated with amygdala volume, a finding in broad agreement with a study by Mollica and colleagues,²³ who observed a negative association between the number of traumatic events and right amygdala volume among Vietnamese ex-political detainees. Second, the interaction of early life trauma and severity of adult criterion A trauma uniquely predicted smaller amygdala volume. Third, a PTSD diagnosis was associated with larger amygdala volume, consistent with our primary analysis.

The complexity of influences involving early life and adult trauma on amygdala structure can be adduced by the significant interaction between early life trauma and severity of criterion A trauma in adults. Inspection of this interaction indicated a negative relationship between severity of combat exposure and amygdala volume but only among the subgroup reporting early life trauma. It may be that trauma exposure in childhood initiates a devel-

opmental trajectory that places the individual at risk for structural alterations when re-exposed to traumatic events in adulthood. Longitudinal studies in at-risk populations are necessary to disentangle these influences.

Although the associations found in our secondary analyses are, at this juncture, poorly understood, what can be concluded is that different trauma-related indices appear to have independent and potentially opposing influences on the amygdala. Indeed, given the substantial variability across prior studies in sample characteristics, trauma type, and trauma histories, it is possible that the countervailing effects of different trauma types “washed out” the ability of previous studies to detect group differences.

Finally, it is noteworthy that our final model did not find evidence of a unique relationship between early life trauma and amygdala volume. This is in apparent contrast to studies by Tottenham et al²¹ and Mehta et al²⁰ suggesting that extended orphanage stay is associated with larger amygdala volume. It is clear that our index of early adversity does not replicate the sharp contrasts in very early adversity/deprivation tested by Tottenham et al and

Mehta et al. Indeed, animal models and developmental human studies suggest that stress-induced changes in the amygdala may be apparent earlier in life (reviewed by Tottenham and Sheridan³⁷). Thus, it may be that our index of early life trauma (ie, any criterion A trauma occurring at age 13 years or younger) was too broad to effectively capture amygdala alterations that might have occurred after very early trauma. It bears mentioning, however, that we observed a significant positive association between early life trauma and amygdala volume in model 3. However, when we added PTSD to model 4, this association was lost and a significant association between PTSD and larger amygdala volume was observed. Therefore, it appears that, in this sample, the association between early life trauma and amygdala volume found in model 3 was better accounted for by a diagnosis of PTSD.

An alternative explanation for the conflict between our findings and those from the developmental studies is differences in the timing of measurement. In a comprehensive review of data from animal and developmental studies, Tottenham and Sheridan³⁷ presented an integrative developmental model proposing that exposure to trauma may result in an initial enlargement of the amygdala, followed by eventual reduction in volume. Within this framework, amygdala morphology may vary as a function of the timing of measurement. The mean age at the time of measurement for the children observed by Tottenham and Sheridan was 8 years, whereas the mean age of institutionalization and adoption was 2½ months and 1½ years, respectively. Thus, participants in their sample were measured approximately 7 to 8 years after the onset of stress/trauma. In our sample, the mean age at the time of measurement was 48 years, and our index of early life trauma was anchored to criterion A events occurring at age 13 years or younger. Given that the discrepancy between the onset of trauma and the time of measurement in our sample was substantially longer than those reported in the developmental literature, it may be that our minimum 35-year gap between the onset of early trauma and time of measurement was too large to capture increases in amygdala volume that may have occurred earlier.

This study has important limitations. First, more than 75% of the study sample met criteria for current major depressive disorder, a group in which amygdala alterations have been reported.³⁸⁻⁴⁰ However, we tested for the effects of depression in our primary and secondary analyses and found no significant effects. In addition, our predominantly male veteran sample limits the generalizability of these findings to females and to subsamples exposed to single-incident traumas. It is also noteworthy that we did not include a control group that had not been exposed to trauma. Thus, this study was not equipped to determine whether trauma exposure alone (independent of the PTSD diagnosis) is associated with structural amygdala alterations compared with clinically healthy controls. The lack of a clinically healthy control group also precluded analysis of the potentially cumulative effects of trauma exposure concurrent with a PTSD diagnosis. However, the primary aim of this study was to examine the effects of PTSD, rather than trauma exposure alone, on damage to the amygdala. Given that

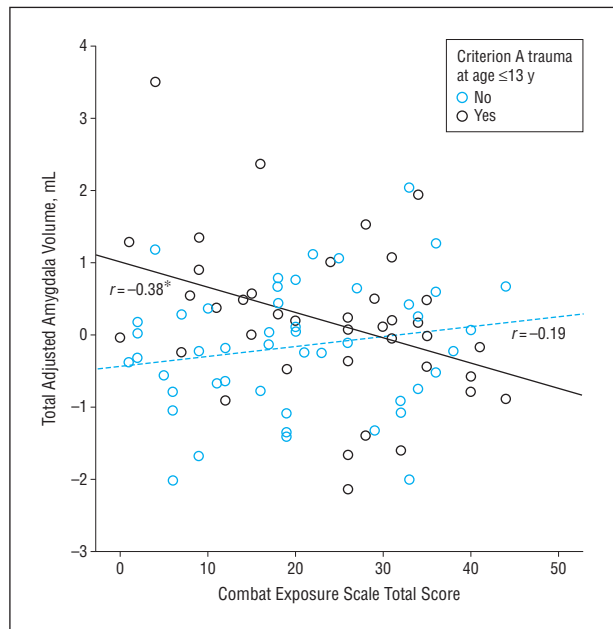


Figure. Interactive effect of presence or absence of criterion A trauma at age 13 years or younger and severity of combat exposure on total adjusted amygdala volume. * $P = .02$.

trauma exposure is a necessary component of the PTSD diagnosis, an initial yet critical step is to disentangle the relative effect of trauma exposure vs a PTSD diagnosis on amygdala damage. Indeed, it is imperative that future studies include a clinically healthy control group to further delineate the effects of trauma exposure alone on structural changes.

In conclusion, to our knowledge, this study is the first to report an association between PTSD and an enlarged amygdala volume. Moreover, our secondary analyses suggest that much remains to be explained in the relationships among early life trauma, adult trauma, and adult psychopathologic features. Cross-sectional studies of amygdala structure in PTSD might benefit from more refined measurement of trauma history. Furthermore, longitudinal studies are necessary to provide greater clarity into the interplay between different trauma factors and their relative influence on amygdala structural plasticity across human development.

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REFERENCES

- Lanius RA, Bluhm R, Lanius U, Pain C. A review of neuroimaging studies in PTSD: heterogeneity of response to symptom provocation. *J Psychiatr Res.* 2006; 40(8):709-729.
- Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry.* 2007;164(10):1476-1488.
- Bremner JD. Functional neuroanatomical correlates of traumatic stress revisited 7 years later, this time with data. *Psychopharmacol Bull.* 2003;37(2):6-25.
- Vyas A, Bernal S, Chattarji S. Effects of chronic stress on dendritic arborization in the central and extended amygdala. *Brain Res.* 2003;965(1-2):290-294.
- Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S. Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci.* 2002;22(15):6810-6818.
- Vyas A, Pillai AG, Chattarji S. Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience.* 2004;128(4):667-673.
- Pêgo JM, Morgado P, Pinto LG, Cerqueira JJ, Almeida OFX, Sousa N. Dissociation of the morphological correlates of stress-induced anxiety and fear. *Eur J Neurosci.* 2008;27(6):1503-1516.
- Cui H, Sakamoto H, Higashi S, Kawata M. Effects of single-prolonged stress on neurons and their afferent inputs in the amygdala. *Neuroscience.* 2008;152(3):703-712.
- Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK, Shalev AY. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. *Am J Psychiatry.* 2001;158(8):1248-1251.
- Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse—a preliminary report. *Biol Psychiatry.* 1997; 41(1):23-32.
- Lindauer RJ, Vlieger EJ, Jalink M, Olff M, Carlier IV, Majoie CB, Den Heeten GJ, Gersons BP. Effects of psychotherapy on hippocampal volume in out-patients with post-traumatic stress disorder: a MRI investigation. *Psychol Med.* 2005; 35(10):1421-1431.
- Wignall EL, Dickson JM, Vaughan P, Farrow TF, Wilkinson ID, Hunter MD, Woodruff PW. Smaller hippocampal volume in patients with recent-onset posttraumatic stress disorder. *Biol Psychiatry.* 2004;56(11):832-836.
- Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. *Nat Neurosci.* 2002;5(11):1242-1247.
- Pavliisa G, Papa J, Pavić L, Pavliisa G. Bilateral MR volumetry of the amygdala in chronic PTSD patients. *Coll Antropol.* 2006;30(3):565-568.
- Rogers MA, Yamasue H, Abe O, Yamada H, Ohtani T, Iwanami A, Aoki S, Kato N, Kasai K. Smaller amygdala volume and reduced anterior cingulate gray matter density associated with history of post-traumatic stress disorder. *Psychiatry Res.* 2009;174(3):210-216.
- Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev.* 2006;30(7):1004-1031.
- Woon FL, Hedges DW. Amygdala volume in adults with posttraumatic stress disorder: a meta-analysis. *J Neuropsychiatry Clin Neurosci.* 2009;21(1):5-12.
- Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, Wald LL, Renshaw PF, Frederick BB, Lane B, Sheikh JI, Stegman WK, Kutter CJ, Stewart LP, Prestel RS, Arsenault NJ. Hippocampal volume, PTSD, and alcoholism in combat veterans. *Am J Psychiatry.* 2006;163(4):674-681.
- Woodward SH, Kaloupek DG, Streeter CC, Martinez C, Schaefer M, Eliez S. Decreased anterior cingulate volume in combat-related PTSD. *Biol Psychiatry.* 2006; 59(7):582-587.
- Mehta MA, Golemboski NI, Nosarti C, Colvert E, Mota A, Williams SCR, Rutter M, Sonuga-Barke EJS. Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *J Child Psychol Psychiatry.* 2009;50(8):943-951.
- Tottenham N, Hare TA, Quinn BT, McCarty TW, Nurse M, Gilhooly T, Millner A, Galvan A, Davidson MC, Eigsti IM, Thomas KM, Freed PJ, Booma ES, Gunnar MR, Altemus M, Aronson J, Casey BJ. Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci.* 2010;13(1):46-61.
- Lupien SJ, Parent S, Evans AC, Tremblay RE, Zelazo PD, Corbo V, Pruessner JC, Séguin JR. Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proc Natl Acad Sci U S A.* 2011;108(34):14324-14329.
- Mollica RF, Lyoo IK, Chernoff MC, Bui HX, Lavelle J, Yoon SJ, Kim JE, Renshaw PF. Brain structural abnormalities and mental health sequelae in South Vietnamese ex-political detainees who survived traumatic head injury and torture. *Arch Gen Psychiatry.* 2009;66(11):1221-1232.
- Woodward SH, Kaloupek DG, Streeter CC, Kimble MO, Reiss AL, Eliez S, Wald LL, Renshaw PF, Frederick BB, Lane B, Sheikh JI, Stegman WK, Kutter CJ, Stewart LP, Prestel RS, Arsenault NJ. Brain, skull, and cerebrospinal fluid volumes in adult posttraumatic stress disorder. *J Trauma Stress.* 2007;20(5):763-774.
- De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. A. E. Bennett Research Award: developmental traumatology, part II: brain development. *Biol Psychiatry.* 1999;45(10):1271-1284.
- De Bellis MD, Keshavan MS, Shifflett H, Iyengar S, Beers SR, Hall J, Moritz G. Brain structures in pediatric maltreatment-related posttraumatic stress disorder: a sociodemographically matched study. *Biol Psychiatry.* 2002;52(11): 1066-1078.
- Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, Keane TM. The development of a clinician-administered PTSD scale. *J Trauma Stress.* 1995;8(1):75-90.
- First MB, Spitzer RL, Gibbon M, Williams JBW. *Structured Clinical Interview for Axis I/DSM-IV Disorders—Patient Edition (SCID-I/P)*. New York: Biometrics Research Dept, New York State Psychiatric Institute; 1995.
- Keane TM, Fairbank JA, Caddell JM, Zimering RT, Taylor KL, Mora CA. Clinical evaluation of a measure to assess combat exposure. *Psychol Assess.* 1989; 1(1):53-55.
- Gray MJ, Litz BT, Hsu JL, Lombardo TW. Psychometric properties of the Life Events Checklist. *Assessment.* 2004;11(4):330-341.
- Reiss AL, Hennessey JG, Rubin M, Beach L, Abrams MT, Warsosky IS, Liu AM, Links JM. Reliability and validity of an algorithm for fuzzy tissue segmentation of MRI. *J Comput Assist Tomogr.* 1998;22(3):471-479.
- Kates WR, Abrams MT, Kaufmann WE, Breiter SN, Reiss AL. Reliability and validity of MRI measurement of the amygdala and hippocampus in children with fragile X syndrome. *Psychiatry Res.* 1997;75(1):31-48.
- Sanfilippo MP, Benedict RH, Zivadinov R, Bakshi R. Correction for intracranial volume in analysis of whole brain atrophy in multiple sclerosis: the proportion vs. residual method. *Neuroimage.* 2004;22(4):1732-1743.
- Mauder RG, Peladeau N, Savage D, Lancee WJ. The prevalence of childhood adversity among healthcare workers and its relationship to adult life events, distress and impairment. *Child Abuse Negl.* 2010;34(2):114-123.
- Kraemer HC, Blasey CM. Centring in regression analyses: a strategy to prevent errors in statistical inference. *Int J Methods Psychiatr Res.* 2004;13(3):141-151.
- Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolesz FA, McCarty RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry.* 1996;40(11):1091-1099.
- Tottenham N, Sheridan MA. A review of adversity, the amygdala and the hippocampus: a consideration of developmental timing. *Front Hum Neurosci.* 2010; 3:68. doi:10.3389/fnhum.09.068.2009.
- Hamilton JP, Siemer M, Gotlib IH. Amygdala volume in major depressive disorder: a meta-analysis of magnetic resonance imaging studies. *Mol Psychiatry.* 2008; 13(11):993-1000.
- Lorenzetti V, Allen NB, Whittle S, Yücel M. Amygdala volumes in a sample of current depressed and remitted depressed patients and healthy controls. *J Affect Disord.* 2010;120(1-3):112-119.
- Sheline YI. 3D MRI studies of neuroanatomic changes in unipolar major depression: the role of stress and medical comorbidity. *Biol Psychiatry.* 2000;48(8): 791-800.