ORIGINAL ARTICLE

Amygdala Volume Changes in Posttraumatic Stress Disorder in a Large Case-Controlled Veterans Group

Rajendra A. Morey, MD, MS; Andrea L. Gold, MS; Kevin S. LaBar, PhD; Shannon K. Beall, BS; Vanessa M. Brown, BA; Courtney C. Haswell, MS; Jessica D. Nasser, BA; H. Ryan Wagner, PhD; Gregory McCarthy, PhD; for the Mid-Atlantic MIRECC Workgroup

Context: Smaller hippocampal volumes are well established in posttraumatic stress disorder (PTSD), but the relatively few studies of amygdala volume in PTSD have produced equivocal results.

Objective: To assess a large cohort of recent military veterans with PTSD and trauma-exposed control subjects, with sufficient power to perform a definitive assessment of the effect of PTSD on volumetric changes in the amygdala and hippocampus and of the contribution of illness duration, trauma load, and depressive symptoms.

Design: Case-controlled design with structural magnetic resonance imaging and clinical diagnostic assessments. We controlled statistically for the important potential confounds of alcohol use, depression, and medication use.

Setting: Durham Veterans Affairs Medical Center, which is located in proximity to major military bases.

Patients: Ambulatory patients (n = 200) recruited from a registry of military service members and veterans serving after September 11, 2001, including a group with current PTSD (n = 99) and a trauma-exposed comparison group without PTSD (n = 101).

Main Outcome Measure: Amygdala and hippocampal volumes computed from automated segmentation of high-resolution structural 3-T magnetic resonance imaging.

Results: Smaller volume was demonstrated in the PTSD group compared with the non-PTSD group for the left amygdala ($P = .002$), right amygdala ($P = .01$), and left hippocampus ($P = .02$) but not for the right hippocampus ($P = .25$). Amygdala volumes were not associated with PTSD chronicity, trauma load, or severity of depressive symptoms.

Conclusions: These results provide clear evidence of an association between a smaller amygdala volume and PTSD. The lack of correlation between trauma load or illness chronicity and amygdala volume suggests that a smaller amygdala represents a vulnerability to developing PTSD or the lack of a dose-response relationship with amygdala volume. Our results may trigger a renewed impetus for investigating structural differences in the amygdala, its genetic determinants, its environmental modulators, and the possibility that it reflects an intrinsic vulnerability to PTSD.

Arch Gen Psychiatry. 2012;69(11):1169-1178

Author Affiliations are listed at the end of this article.
Group Information: The Mid-Atlantic MIRECC (Mental Illness Research, Education, and Clinical Center) Workgroup members are listed at the end of this article.

THE AMYGDALA IS PERHAPS the most strongly implicated brain structure in the pathophysiology of posttraumatic stress disorder (PTSD). Prevalent models of anxiety have focused on an amygdalocentric neurocircuitry[1] that is critical in the fear response, conditioning, and generalization[2-4] and facilitates the response to stressful experiences.[5] Functional magnetic resonance imaging (MRI) studies[6-9] have shown that individuals with PTSD have an exaggerated amygdala response to emotional stimuli when compared with control subjects. Animal studies have demonstrated changes in amygdala morphology with chronic stress,[10] evident primarily in the growth of dendritic spines. Experimental studies of amygdala volume in mice and humans have shown an association among smaller amygdala volumes, increased levels of fear conditioning, and an exaggerated glucocorticoid response to stress.[11-13] However, efforts to find evidence of an association between amygdala volume and PTSD in humans have produced equivocal results.[14,15] Our goal was to reinvestigate amygdala volume changes in PTSD by addressing some of the potential methodological issues contributing to inconclusive findings.

The hippocampus has been the overwhelming focus of prior studies of morphological change in PTSD. These studies have demonstrated a clear association

Table 1. Structural MRI Studies of Amygdala Volume Differences in PTSD[a]

						No. of Participants				Amygdala Volume, *P* Value		ES, Cohen *d* Statistic	
Source	Field Strength, T	Slice Thickness, mm	In-Plane Resolution, mm^2	Type of Trauma	PTSD Measure	PTSD	TEC	HC[b]	Est Sample Size[c]	L	R	L	R
Adult PTSD													
Bonne et al,[17] 2001	2.0	1.5	0.94	Mixed: ED	CAPS	10	27	0	40	.16	.16	0.44	0.43
Bremner et al,[18] 1997	1.5	3.0	0.63	Child maltreatment	SADS	17	0	17	121	.08	.23	0.62	0.42
Fennema-Notestine et al,[19] 2002[d]	1.5	4.0	0.94	IPV	CAPS	11	11	17	19	.06	NS/NR	−0.56	−0.69
Gilbertson et al,[20] 2002	1.5	1.5	0.94	Combat: Vietnam	CAPS	12	23	0	67	.90	.54	−0.33	−0.07
Gurvits et al,[21] 1996[d]	1.5	1.5	0.94	Combat: Vietnam	CAPS	7	7	8	29	.53	.07	−0.57	−0.44
Lindauer et al,[22] 2004	1.5	1.0	1.00	Police officers	SCID	14	14	0	40	.25	.17	0.47	0.56
Lindauer et al,[23] 2005	1.5	1.0	1.00	Mixed	SCID	18	14	0	40	.85	.09	0.23	−0.44
Rogers et al,[24] 2009	1.5	1.5	0.94	Tokyo subway	CAPS (Japanese)	9	16	0	12	.05	.05	0.88	0.64
Wignall et al,[25] 2004	1.5	1.0	1.00	Mixed: ED	CAPS	15	0	11	14	.07	.37	0.84	0.36
Pediatric PTSD													
De Bellis et al,[26] 1999	1.5	1.5	0.94 × 1.25	Child maltreatment	K-SADS	44	0	61	40	NS/NR	NS/NR	0.44	0.40
De Bellis et al,[27] 2001	1.5	1.5	0.94 × 1.25	Child maltreatment	K-SADS	9	0	9	29	NS/NR	NS/NR	0.56	0.29
De Bellis et al,[28] 2002	1.5	1.5	0.94 × 1.25	Child maltreatment	K-SADS	28	0	66	783	.62	.73	−0.11	0.08

Abbreviations: CAPS, Clinician-Administered PTSD Scale; ED, emergency department; ES, effect size; Est, estimated; HC, healthy controls; IPV, intimate partner violence; K-SADS, Schedule for Affective Disorders and Schizophrenia for School-age Children; L, left; MRI, magnetic resonance imaging; NS/NR, nonsignificant/not reported; PTSD, posttraumatic stress disorder; R, right; SADS, Schedule for Affective Disorders and Schizophrenia; SCID, Structured Clinical Interview for *DSM-IV*; TEC, trauma-exposed control.

[a] Segmentation was performed by manual tracing for all studies.

[b] For the HC group, trauma exposure was not assessed or was determined to be absent.

[c] The per-group sample size for each study was compared with the sample size estimate based on power =0.80 and α=.05 from Morey et al.[29] A small ES (based on the meta-analysis by Woon and Hedges[14]) per group for manual tracing was used for the amygdala sample size criterion of ES=0.10 (n=783), ES=0.20 (n=199), ES=0.25 (n=121), ES=0.30 (n=90), ES=0.35 (n=67), ES=0.40 (n=51), ES=0.45 (n=40), ES=0.50 (n=34), ES=0.55 (n=29), ES=0.60 (n=24), ES=0.65 (n=22), ES=0.70 (n=19), ES=0.75 (n=17), ES=0.80 (n=15), ES=0.85 (n=14), and ES=0.90 (n=12).

[d] For studies with 3 groups, the *P* values and Cohen *d* statistic refer to the PTSD vs TEC group comparison.

between smaller hippocampal volume and PTSD.[15,16] In contrast, the relatively few studies of amygdala volume differences in PTSD have yielded mixed results (**Table 1**). Two meta-analyses[14,15] that included amygdala volumetry showed inconsistent differences between trauma-exposed participants with and without PTSD. The first meta-analysis[15] found lower volumes with small effect sizes in the left (effect size, −0.22)[30] and right amygdala (−0.18), but only after restricting the analysis to the subset of studies that produced a homogeneous sample. The second meta-analysis[14] demonstrated only a trend association (P=.06), with a small effect size (Hedges g=−0.29), between smaller left amygdala volume and PTSD in patients compared with trauma-unexposed healthy controls. The interpretation of these data is complicated by several methodological issues and limitations. For instance, the first meta-analysis[15] included a group with intrusive memories who lacked a diagnosis of PTSD. Other limitations included the use of varied manual segmentation protocols, differences in raters across studies, scanners with lower spatial resolution and field strengths than current standards, heterogeneous trauma type (eg, combat, sexual assault, intimate partner violence), and inclusion of children.[31] Although these meta-analyses offer weak support for an association of amygdala volume and PTSD, several individual studies that failed to show significant differences[17-22,25,27] suggest caution in this interpretation (Table 1). Furthermore, the number of studies reporting negative results may be an underestimation of the actual number given the disincentives for publishing negative results.

Our study had 3 main goals. The first was to assess the association of amygdala volume and PTSD in a large sample of trauma-exposed adults. The effect sizes from several prior studies that yielded marginal *P* values for amygdala differences[18,19,21,25] suggest they were underpowered to detect real effects in the population. Therefore, we hypothesized that the PTSD group would show smaller amygdala volumes than the trauma-exposed non-PTSD group when adequately powered to control for type

II error. We previously reported[29] that the sample size required to demonstrate a significant group difference in amygdala volume derived from automated segmentation using published effect sizes[15] to be at least 55 subjects per group, which is substantially larger than sample sizes used in prior published studies (Table 1).

The second goal was to gain empirical evidence that might offer clues about factors contributing to PTSD. For example, if trauma exposure, trauma load, or illness chronicity were correlated with amygdala volume, this would be compatible with an environmental cause for the volume change or a preexisting vulnerability that interacts with environmental factors, such as trauma load and illness chronicity. Evidence of an association with PTSD in the absence of an association with trauma exposure would allow for the possibility that smaller amygdala volume may represent a vulnerability to PTSD. We hypothesized that a diagnosis of PTSD would be associated with a smaller amygdala volume but that the volume would not be correlated with trauma exposure or illness chronicity based on evidence in animals and humans that smaller amygdalae constitute a risk for heightened fear and stress responses.[11-13]

Our third and final goal was to confirm the established finding of smaller hippocampal volume[14,15] in our sample of veterans serving after September 11, 2011, using the structural neuroimaging methods we have adopted. These methods included several enhancements, such as an automated segmentation approach for better control of variability in manual segmentation protocols by human raters, improved ratio of signal to noise provided by 3-T field strength, and higher spatial resolution (1-mm isotropic voxels). For analyses of both structures, we used a multiple regression approach similar to that of Bremner and colleagues[18] to control for variables such as symptoms of depression, trauma load, duration of PTSD, intracranial volume (ICV), age, medication, and alcohol abuse.

METHODS

PARTICIPANTS

Participants (n = 200) were recruited from February 6, 2006, through October 28, 2010, from a registry[32] of military service members and veterans. All participants had served since September 11, 2001, and most (76.6%) had served in the Iraq and/or Afghanistan military conflicts. Participants underwent screening for inclusion and exclusion criteria based on information available in the registry and from subsequent telephone contact, from which 85.0% of potential subjects agreed to participate. Important exclusion criteria included a major Axis I diagnosis (other than depression), contraindication to MRI, traumatic brain injury, substance dependence, neurological disorders, and being older than 55 years. All participants provided written informed consent to participate in procedures reviewed and approved by the institutional review boards at Duke University and the Durham Veterans Affairs Medical Center. Participants completed questionnaires assessing depressive symptoms (Beck Depression Inventory–II[33]), traumatic life events (Traumatic Life Events Questionnaire[34]), combat exposure (Combat Exposure Scale[35]), alcohol abuse (Alcohol Use Disorders Identification Test [AUDIT][36]), and current medication use, and 191 participants (95.5%) were administered the Structured Clinical Interview for *DSM-IV* to assess comorbid

Table 2. Demographic and Clinical Information by Group[a]

Characteristic	PTSD Group (n=99)	Non-PTSD Group (n=102)	Group Comparison
Age, y	38.4 (9.9)	37.5 (10.6)	$t=-0.549$; $P=.58$
Female sex, No. (%)	20 (20.2)	16 (15.7)	$\chi^2=0.644$; $P=.42$
White race, No. (%)[b]	49 (49.5)	54 (52.9)	$\chi^2=0.239$; $P=.67$
BDI score	19.3 (11.0)	5.56 (5.6)	$t=-11.2$; $P<.001$
CES score	15.6 (10.1)	8.64 (9.9)	$t=-4.89$; $P<.001$
TLEQ score	14.6 (11.4)	7.41 (8.7)	$t=-5.03$; $P<.001$
AUDIT score	4.90 (5.9)	2.97 (3.3)	$t=-2.81$; $P=.006$
PTSD duration, y	8.02 (8.40)		
Serotonergic medication, No. (%)	24 (24.2)	4 (3.9)	$\chi^2=17.3$; $P<.001$
Antipsychotic medication, No. (%)	7 (7.1)	0	$\chi^2=7.40$; $P=.007$

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BDI, Beck Depression Inventory–II; CES, Combat Exposure Scale; PTSD, posttraumatic stress disorder; TLEQ, Traumatic Life Events Questionnaire.

[a] Unless otherwise indicated, data are expressed as mean (SD).

[b] Participants reported race and ethnicity information according to investigator-defined options.

Axis I diagnoses. A summary of participants' demographic and clinical features (**Table 2**) indicates that groups were matched for age, sex, and race. The PTSD group had more trauma and combat exposure, depressive symptoms, alcohol use, and psychotropic medication use. The PTSD diagnosis was ascertained with the Clinician-Administered PTSD Scale[37] (CAPS) in 149 participants (74.5%) and with the Davidson Trauma Scale[38] (DTS) in 51 participants (25.5%). The participants undergoing assessment with the DTS were assigned to a diagnostic group based on a DTS cutoff score of 40 that we have previously reported to have high positive (0.95) and negative (0.85) predictive values compared with a clinician-administered interview in a larger sample of veterans serving after September 11, 2001, from the same registry.[39] Initial study participants were administered the DTS before the study team had completed CAPS training. Major depression was diagnosed (using the Structured Clinical Interview for *DSM-IV*) in 27 PTSD participants (13.5%) and 2 controls (1.0%).

Two participants in the PTSD group and 2 in the non-PTSD group were excluded owing to use of mood stabilizers that have been reported to have conflicting effects on brain volume.[40,41] Duration of PTSD, determined from clinical assessment and defined as the time elapsed between the occurrence of criterion A trauma and the MRI scan, was available for 91 of 99 participants. For delay in the onset of symptoms (n = 4) ranging from 8 months to 1 year, PTSD duration was calculated relative to the time of symptom onset.

MRI ACQUISITION

Images were acquired on a 3-T scanner equipped with an 8-channel head coil (Signa EXCITE; General Electric). High-resolution T1-weighted whole-brain images with 1-mm isotropic voxels were acquired axially for all participants by using an array spatial sensitivity encoding technique and fast spoiled gradient-recall. Image parameters were optimized for contrast

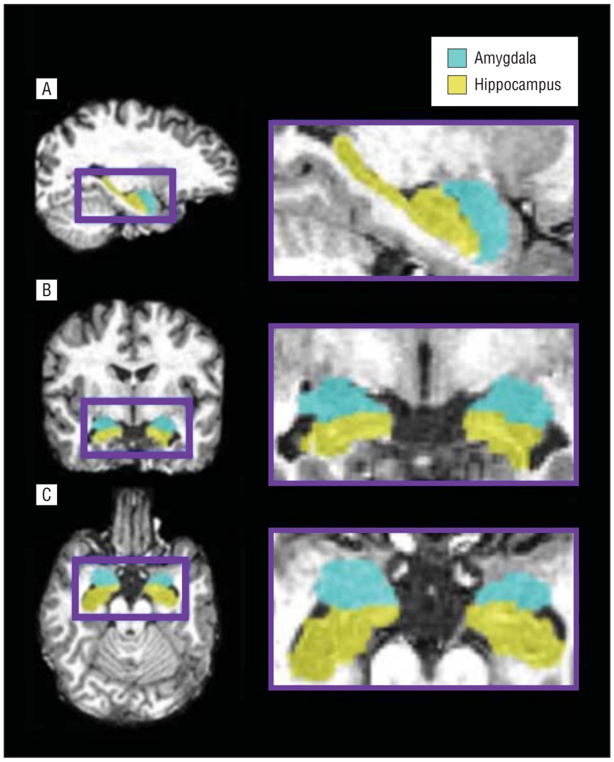

Figure. Example of automated segmentation of the amygdala and hippocampus using the FreeSurfer image analysis suite (version 5.0.0; http://surfer.nmr.mgh.harvard.edu/). The high-resolution structural magnetic resonance image of a representative subject is displayed in radiological convention with segmentation labels for the amygdala and hippocampus as shown in sagittal (A; left hemisphere), coronal (B), and axial (C) slices.

among white matter, gray matter, and cerebrospinal fluid (repetition/echo times, 7484/2984 milliseconds; flip angle, 12°; field of view, 256 mm; 1-mm slice thickness; 166 slices, 256 × 256 matrix; 1 excitation).

IMAGE ANALYSIS

All T1-weighted images were visually inspected (by C.C.H.) to ensure appropriate quality. Automated segmentation and labeling of the amygdala and hippocampus and estimation of total ICV from participants' T1-weighted images were performed using a set of image analysis tools[42] (FreeSurfer image analysis suite, version 5.0.0; http://surfer.nmr.mgh.harvard.edu/) and its library tool (recon-all). A previous study from our group[29] validated FreeSurfer automated segmentation of the amygdala and hippocampus compared with manual tracing. Spatial normalization by affine registration to Talairach space and skull stripping were performed on the T1-weighted images. Registration was checked visually for accuracy by one of us (C.C.H.). FreeSurfer segmentation and labeling of subcortical structures were based on a combination of voxel intensity, probabilistic atlas location, and the spatial relationships of voxels to the location of nearby subcortical structures. The FreeSurfer library function mri_label2vol and a transformation matrix generated by tkregister2 were used to return the segmentation labels to native space. The native-space segmentations were converted to left-anterior-superior orientation, and then the amygdala and hippocampus were extracted using the segmentation labels. The segmentation of the amygdala and hippocampus overlaid on original T1-weighted images (**Figure**) was visually inspected by several of us (A.L.G., K.S.L., and V.M.B.) slice-by-slice for correct location and shape. All participants passed this inspection process without the need for manual adjustment.

STATISTICAL ANALYSIS

We used the general linear model (GLM) to control for potential confounding variables in examining the influence of PTSD diagnosis on regional brain volume. General linear model analysis (performed by R.A.M., V.M.B., H.R.W. [biostatistician], and G.M.) on each brain region (left and right amygdala and hippocampus) included the following covariates: ICV, age, sex, combat exposure, traumatic lifetime events, depressive symptoms, alcohol abuse, duration of PTSD, and use of serotonergic (n = 28) and antipsychotic (n = 7) medications (separate covariates) based on reports of increased (associated with serotonergic agents[43]) and decreased (associated with antipsychotic agents[44]) regional volumes. The α value was .05 given our a priori hypotheses of PTSD volume differences in the amygdala and hippocampus.

Because of expected intercorrelations among the covariates, principal components analysis was performed to reduce the data dimensionality. A principal components factor analysis using varimax rotation was conducted on age, PTSD duration, and Beck Depression Inventory–II, Combat Exposure Scale, Traumatic Life Events Questionnaire, and AUDIT scores. Selection of specific components to be used in follow-up modeling was confirmed by parallel analysis,[45] which compares the eigenvalues from the principal components analysis with those from a randomly generated data set of the same size (Monte Carlo principal components analysis for parallel analysis; available at http://edpsychassociates.com/Watkins3.html). Only the components with eigenvalues higher than the randomly generated data set were retained and substituted for the individual covariates in follow-up modeling.

Finally, the disparity in trauma load between groups raised the possibility that differences in volume might be associated with the magnitude of trauma exposure rather than PTSD illness. Therefore, we repeated the GLM analysis on 2 subgroups that were matched for combat exposure and lifetime trauma.

RESULTS

DEMOGRAPHIC INFORMATION

Basic demographic and clinical information is reported by diagnostic group in Table 2.

VOLUMETRY RESULTS

Group means, standard deviations, and the GLM results testing our hypotheses on the effects of PTSD diagnosis, combat exposure, lifetime trauma, illness chronicity, and Beck Depression Inventory–II scores are summarized in **Table 3**. The between-group results demonstrated that PTSD diagnosis was associated with a smaller volume in the left and right amygdala and the left hippocampus. Right hippocampal volume was not significantly associated with the PTSD diagnosis (Table 3). Combat exposure was not significantly related to left amygdala, right amygdala, or right hippocampal volume but showed a trend toward significance for left hippocampal volume. Lifetime trauma, illness chronicity, and depressive symptoms were not associated with volume differences in either structure for either hemisphere. Intracranial volume was significantly correlated with bilateral amygdala and hippocampal volumes ($P < .001$ for all). The other covariates, including AUDIT, medication use, age, sex, Beck Depression Inventory–II score, Combat Exposure Scale

Table 3. Volumetry Results by Diagnosis and Effect of Trauma Load and Illness Chronicity

Finding	Amygdala Left	Amygdala Right	Hippocampus Left	Hippocampus Right
Volume, mean (SD), mm^3				
Control	1810 (231)	1994 (257)	4180 (505)	4188 (469)
PTSD	1746 (233)	1894 (257)	4067 (421)	4129 (415)
PTSD group				
F value[a]	10.00	6.83	5.81	1.36
P value	.002	.01	.02	.25
CES				
F value[a]	2.26	2.54	3.60	1.23
P value	.13	.11	.06	.27
TLEQ				
F value[a]	1.22	0.59	0.14	0.01
P value	.27	.44	.71	.95
PTSD duration				
F value[a]	2.78	0.38	1.01	1.24
P value	.10	.54	.32	.27
BDI				
F value[a]	2.08	0.02	1.68	0.73
P value	.15	.89	.20	.39
PTSD effect size, Cohen *d* statistic	−0.28	−0.39	−0.22	−0.13

Abbreviations: See Table 2.
[a] *df*=1,180.

score, and PTSD duration, were not significantly related to amygdala or hippocampal volumes (data not shown; $P > .05$). Results obtained by statistically controlling for medication effects were compared with a secondary analysis that excluded participants who used antidepressants (n = 28) and antipsychotic medications (n = 7). Smaller volumes were confirmed in the left amygdala ($F_{1,154} = 8.67$ [$P = .004$]), right amygdala ($F_{1,154} = 6.60$ [$P = .01$]), and left hippocampus ($F_{1,154} = 5.74$ [$P = .02$]). Differences in the right hippocampus did not reach statistical significance ($F_{1,154} = 1.89$ [$P = .17$]).

Duration of PTSD was unavailable in 8 PTSD participants; therefore, analysis of the whole group omitted this covariate to include 99 participants with PTSD and 101 controls (**Table 4**). The differences in volume between PTSD and non-PTSD groups in the right amygdala and left hippocampus were significant but had a higher *P* value than with the inclusion of PTSD duration as a covariate, whereas the volume difference in the left amygdala was at trend level. The volume difference in the right hippocampus was not significant. Severity of PTSD in patients undergoing assessment with the CAPS, controlling for ICV, was negatively correlated with volume of the left amygdala ($r = -0.22$ [$P = .03$]) but did not reach significance in the right amygdala ($r = -0.18$ [$P = .09$]). As expected, removing ICV as a covariate resulted in a nonsignificant correlation given the established association between head size and regional brain volume.

Table 4. Effect of Diagnosis After Omitting PTSD Duration From GLM

Brain Structure	*F* Value[a]	*P* Value
Amygdala		
Left	3.55	.06
Right	5.51	.02
Hippocampus		
Left	4.78	.03
Right	.920	.40

Abbreviations: GLM, general linear model; PTSD, posttraumatic stress disorder.
[a] *df*=1,189.

DATA REDUCTION

Two components, which individually explained 30.3% and 26.9% of the variance, had eigenvalues greater than 1. Selection of these components was confirmed by parallel analysis.[45] The first component was associated with depressive symptoms, traumatic events, longer PTSD duration, older age, and combat exposure. The second component was associated with longer PTSD duration, younger age, alcohol abuse, and less combat exposure. A factor analysis that included ICV showed it had low communality (0.33), meaning the extracted components accounted for minimal ICV variance. Consequently, ICV was excluded from the final factor analysis. Results of GLM analysis using covariates of the first and second components, ICV, sex, use of serotonergic medication, and use of antipsychotic medication were similar to the original analyses conducted with all covariates. That is, PTSD diagnosis was associated with smaller left and right amygdala volume and left hippocampal volume (**Table 5**).

TRAUMA LOAD

To account for the possible nonlinear influences of trauma exposure on regional brain volume irrespective of PTSD

Table 5. Volumetry Results for PTSD Diagnosis Using Component Covariates

	Using Component Covariates		Matched for Trauma Exposure	
Brain Structure	*F* Value[a]	*P* Value	*F* Value[b]	*P* Value
Amygdala				
Left	6.27	.01	7.97	.006
Right	6.59	.01	6.54	.02
Hippocampus				
Left	6.76	.01	3.56	.07
Right	1.35	.25	1.93	.17

Abbreviation: PTSD, posttraumatic stress disorder.
[a] $df = 1,184$.
[b] $df = 1,110$.

diagnosis, follow-up analysis conducted with subgroups matched for combat exposure and lifetime trauma exposure (122 participants; 76 with PTSD and 46 non-PTSD controls) revealed group differences similar to those in the primary analytic models (Table 5). There were significant group differences in the left and right amygdala, with a trend toward significance in the left hippocampus.

COMMENT

Our study establishes diminished amygdala volume in a large cohort of recent military veterans with PTSD compared with trauma-exposed non-PTSD veterans after controlling for depressive symptoms, alcohol use, ICV, medication use, PTSD chronicity, and trauma load. In contrast to inconclusive results from prior studies that reported marginal or nonsignificant effects for amygdala volumetry, we found a significant association between a smaller amygdala volume and PTSD. This association was not accounted for by PTSD chronicity, trauma load, severity of depressive symptoms, alcohol use, or medication status. We confirmed findings of smaller volumes in the left hippocampus for PTSD compared with trauma-exposed non-PTSD controls, which remained significant after controlling for the same variables used in the amygdala analysis. The laterality of our findings for the hippocampus was consistent with a prior meta-analysis[15] that showed significantly decreased left but not right hippocampal volume in PTSD.

COMPARISON WITH PREVIOUS FINDINGS FOR AMYGDALA VOLUMETRY

Although most previous studies reported nonsignificant findings, some studies showed a trend toward significance for smaller amygdala volumes in PTSD.[18,19,21,24,25] The investigations of PTSD and amygdala volume with the largest samples included PTSD groups with 44 participants[26] and 28 participants,[28] but these studies were conducted in children and therefore do not generalize well to adults owing to developmental changes in brain structure and connectivity.[46] All studies of adults had a sample size of fewer than 20 in the PTSD group, with most of the studies having 15 or fewer participants.[17,19-22,25] Consistent with our findings and relevant to the core symptom cluster of reexperiencing symptoms in PTSD, smaller amygdala volume was associated with the presence of cancer-related intrusive recollections in a sample of 76 breast cancer survivors.[31]

We should consider the factors that may have produced a significant association of decreased amygdala volume given the preponderance of negative findings in prior studies. The small effect sizes observed from the meta-analyses suggest that they were underpowered to detect significant differences. Assessing a large sample size is impractical with manual segmentation, and this limitation motivated our use of an automated segmentation technique. Automated segmentation also (1) facilitates future replication of these results by other investigators, (2) diminishes differences among studies owing to the use of different protocols for defining anatomical boundaries, (3) eliminates variability associated with different raters across studies and even a single rater over time, and (4) removes bias introduced by varied software interfaces that are used in manual tracing (eg, 3-plane views vs a single-plane view). Thus, replication of the present results based on automated segmentation may be achieved with greater fidelity than manual tracing methods.[42] Although we previously reported that FreeSurfer image analysis introduces additional variance compared with the criterion standard of hand tracing,[29,47] this variance would not bias volumetry measures in favor of one group over another.

Rather than matching individuals on a participant-by-participant basis to achieve the large enrollment necessary for this study in a realistic time frame, we used a statistical approach[18] to control for potentially confounding variables (eg, depressive symptoms, trauma load, duration of PTSD, ICV, age, medication use, and alcohol abuse). The effects of many of these variables have not previously been tested as covariates in PTSD amygdala investigations. Assembling a PTSD group that is free of depressive symptoms is unlikely to generalize; moreover, new evidence calls into question whether PTSD and depression are distinct entities among individuals exposed to trauma.[48] Notably, we found no significant association between depressive symptoms and amygdala or hippocampal volumes after controlling for PTSD among the other covariates. Larger amygdala volumes have been found in early depression,[49] but smaller or null findings have been found in chronic depression.[50] Nevertheless, it is important to exert statistical control for these symptoms. Exclusion of participants taking psychotropic medication has also been the accepted orthodoxy, although leaders in the field of PTSD neuroimaging have argued for their inclusion.[51] Technical concerns in previous studies include the use of older MRI technology, such as lower field strength scanners (1.5 T or 2.0 T [Table 1])[18-21,24,26-28] and lower spatial resolution (≥1.5-mm slice thickness).[17-22,24,26-28] We addressed these issues with a 3-T scanner to improve the ratio of signal to noise and 1-mm slice thickness (1-mm isometric) for superior spatial resolution. Based on our previously reported power calculation for amygdala segmentation with FreeSurfer image analysis, a sample size of at least 55 subjects per group is required for the effect sizes we observed.[29]

In addition to these methodological improvements, important demographic and trauma-related characteristics of our sample differ from those of previous studies. In contrast to some earlier studies of veterans with chronic PTSD,[20,21,52] our participants were recent military personnel who served largely in military conflicts in Iraq and Afghanistan.

ASSOCIATIONS WITH FUNCTIONAL NEUROIMAGING OF AMYGDALA

Functional differences of the amygdala, particularly in the left hemisphere, during emotion processing were supported by a meta-analysis showing ventral anterior hyperactivation and a dorsal posterior hypoactivation in PTSD.[9] Amygdala engagement during fear conditioning is well established in healthy adults. Thus, amygdala hyperactivity in PTSD may reflect an exaggerated response of fear circuitry and may explain PTSD symptoms, such as hypervigilance and hyperarousal. Despite concerns with statistical power, heterogeneity of task design, patient characteristics, imaging modality, and analytic approaches in functional neuroimaging studies of PTSD, these results have been more consistent than results from volumetric studies of the amygdala. Overall, there are numerous reports of greater amygdala activation in PTSD,[6,7,53-56] whereas some others failed to show increased amygdala activation,[57-59] further obfuscating a coherent hypothesis for amygdala volume differences in PTSD. Indeed, a decrease in amygdala volume appears to correspond with increased functional MRI activation in PTSD.[60] The ventral hyperactive cluster reported by Etkin and Wager[9] may relate to the basolateral amygdala complex (BLA; described in the next section) and may be relevant to acquired fear responses in PTSD given the role of this region in forming emotional memories.[61,62]

PATHOBIOLOGY OF PTSD

The amygdala plays a key role in a wide variety of behaviors and mnemonic functions, most critically in modulating negative affect and emotion.[3,63,64] Changes in fear, stress, and anxiety in rats are induced by lesions to subnuclei of the amygdala, notably the BLA, which is needed to form and later express associative fear memories. Evidence primarily from rodent work has led to a model in which the lateral nucleus in the BLA receives aversive and sensory signals that are passed on to the basal nucleus and central nucleus. Fear-associated behaviors are governed by the central nucleus, which provides the major outputs of the amygdala.[65,66] This model is consistent with the observation that prior to fear conditioning, rats with lesions to the lateral nucleus did not form fear memories, unlike lesions to the basal nucleus.[67,68] However, following fear conditioning, lesions to the basal nucleus blocked the expression of fear memories, but not the ability to encode those memories.[69] Thus, fear-related plasticity in the amygdala is essential for fear learning and accompanying fear behaviors.[11,66]

The effect of persistent and chronic threat-induced hyperexcitation of the amygdala on its volume in humans is yet unclear. Much of our knowledge on the pathobiology of threat and stress effects on the brain, and on the medial temporal lobe in particular, comes from animal models using acute stressors that are qualitatively different from the chronic and/or extreme stressors typically experienced by humans with PTSD. One of several competing theories is based on established findings that the amygdala and hippocampus undergo stress-induced structural remodeling, albeit in very different ways.[10] Most of the research on stress effects has focused on the hippocampus, with very few studies investigating the amygdala directly.

SMALLER AMYGDALA VOLUME: VULNERABILITY OR CONSEQUENCE?

The second goal of this study was to gain insight into whether the smaller amygdala volume is a preexisting vulnerability factor for developing PTSD or a consequence of having PTSD. Our data failed to show a correlation of trauma load or PTSD chronicity with lower amygdala volume, suggesting the lack of a dose-response effect for trauma and amygdala volume or that smaller amygdalae might be a risk factor for developing PTSD.

Evidence from prior work in humans and animals demonstrates an association between smaller amygdalae and stronger fear conditioning and stress reactivity, which are considered risk factors for PTSD. Prior work in animals by Yang and colleagues[11] used recombinant inbred strains of mice that exhibit up to a 2-fold difference in BLA size.[11] Mice were categorized into groups with small, medium, and large BLA volume and underwent a pavlovian fear-conditioning procedure. The small-BLA mice showed stronger fear conditioning than the medium- and large-BLA mice, and freezing to the conditioned stimulus was significantly correlated with volume of the BLA but not of comparison regions, including the hippocampus, striatum, or cerebellum. Mice were also subjected to a stress condition (forced swim), which was associated with elevated corticosterone level in the small-BLA but not the medium- or large-BLA groups. Nonstressed mice did not differ by corticosterone level. The BLA is a critical site through which corticosterone enhances associative fear memories.

The BLA volume association raises a fundamental question whether a small BLA is the consequence or the cause of stronger fear conditioning. A smaller BLA is unlikely to be a consequence given that chronic threat and stress lead to corticosterone-mediated spinogenesis and dendritic arborization in mice.[10,70-72] In clear contradistinction, the hippocampus shows loss of neurons and synaptic connectivity in response to elevated adrenal hormone levels associated with chronic threat and stress.[73-75] Thus, the smaller volume of the BLA, which constitutes the largest of the amygdalar nuclei, is linked to stronger fear conditioning, chronic threat, and vigilance, leading to a potential increase in BLA volume.[5] Although the effects of chronic threat and stress in rodents may differ in humans, the neural systems for fear processing are highly conserved across phylogeny. The evidence of counteracting influences on amygdala volume found in rodents is likely to cloud any association of amygdala volumetry and PTSD and may explain the inconsistent and sometimes conflicting reports of amygdala volumes in PTSD.[14,15]

Evidence from 2 studies in humans builds on the work of Yang and colleagues[11] in mice. Studies in humans not exposed to trauma or chronic threat and stress are especially informative because trauma-induced structural changes in the amygdala are unlikely to have occurred. First, Hartley et al[13] paired colored squares (conditioned stimuli) with mild electrical shock (unconditioned stimuli) and measured the strength of fear acquisition via skin conductance response. The magnitude of the conditioned fear response was correlated with the smaller amygdala volume. Second, Gianaros et al[12] measured mean arterial pressure in response to a stressor (performance-titrated Stroop Color-Word Interference task) and found that a smaller amygdala volume was correlated with stressor-evoked blood pressure reactivity.

To investigate directly whether our finding of decreased amygdala volume in PTSD represents a preexisting vulnerability factor or an acquired sign of the disorder, research studies using prospective, longitudinal design and twin-discordance models are needed.[76] Vulnerability related to genetic or epigenetic effects has been hotly debated, but little empirical evidence is available. Altered serotonin binding in the left amygdala[8] and increased left amygdala activation modulation by the *5HTTLPR* serotonin transporter gene[77] have been observed in PTSD. However, evidence showing specific genetic modulation of amygdala volume in PTSD is lacking.

LIMITATIONS

We used covariates to control for variables such as depressive symptoms, alcohol abuse, and age. This approach is adequate unless a nonlinear association is present. For instance, trauma exposure may not follow a linear dose response but instead may require a specific threshold beyond which a marked effect on amygdala volume is produced. Secondary analyses that matched groups for trauma exposure were performed to rule out this possibility. Also, our sample consisted of veterans from the Iraq and Afghanistan conflicts, who were mostly men; therefore, owing to these and other sources of selection bias, we urge caution when generalizing these results to other demographic groups. Our sample also showed high levels of combat trauma relative to other trauma types, and it remains unclear whether the type of trauma predicts the magnitude of volume loss in the amygdala. Approximately one-fourth of the sample was diagnosed using the DTS, a self-report measure that has high predictive power compared with the CAPS but may misclassify some subjects. Finally, based on the effect sizes we obtained for the hippocampus, the present sample size may have been insufficient to detect volume differences in the right hippocampus; however, this effect size was consistent with a large meta-analysis.[15]

CONCLUSIONS

These results provide robust evidence of an association between a smaller amygdala volume and PTSD. We did not observe correlation between trauma load or illness chronicity with amygdala volume. When considered in the context of previous translational research linking smaller amygdala volume with stronger fear conditioning and stress response, our results are consistent with the theory that a smaller amygdala represents a vulnerability to developing PTSD rather than an outcome of the disorder. The story for amygdala volumetry might be more elusive than that of the hippocampus. For instance, counteracting influences show that, on one hand, smaller amygdala size may be consistent with a vulnerability to PTSD but that elevated corticosterone levels lead to increased amygdala volume on the other hand. Our results may trigger a renewed impetus for investigating structural changes in the amygdala, its genetic determinants, environmental modulators, and the possibility that lower amygdala volume represents an intrinsic vulnerability to PTSD.

Submitted for Publication: October 4, 2011; final revision received January 3, 2012; accepted January 11, 2012.
Author Affiliations: Duke-UNC (University of North Carolina) Brain Imaging and Analysis Center (Drs Morey and LaBar and Mss Beall, Brown, Haswell, and Nasser), Department of Psychiatry and Behavioral Sciences (Drs Morey, LaBar, and Wagner), and Center for Cognitive Neuroscience (Drs Morey and LaBar), Duke University, and Mental Illness Research Education and Clinical Center for Post Deployment Mental Health, Durham Veterans Affairs Medical Center (Drs Morey, Wagner, and McCarthy and Mss Beall, Brown, Haswell, and Nasser), Durham, North Carolina; and Department of Psychology, Yale University, New Haven, Connecticut (Ms Gold and Dr McCarthy).
Correspondence: Rajendra A. Morey, MD, MS, Duke-UNC Brain Imaging and Analysis Center, Box 2737, Hock Plaza, Durham, NC 27710 (rajendra.morey@duke.edu).
Author Contributions: Dr Morey had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Mid-Atlantic MIRECC Workgroup: Elizabeth S. Selgrade, BS; Jasmeet Pannu Hayes, PhD; Christine E. Marx, MD; Jean C. Beckham, PhD; Patrick S. Calhoun, PhD; John A. Fairbank, PhD; Kimberly T. Green, MS; Larry A. Tupler, PhD; Richard D. Weiner, MD, PhD; Mira Brancu, PhD; Jeffrey M. Hoerle, MS; Mary Pender, PhD; Jennifer L. Strauss, PhD; Harold Kudler, MD; Angela M. Eggleston, PhD; Vito S. Guerra, PhD; Jason A. Nieuwsma, PhD;

Victoria Payne, MD; Jennifer J. Runnals, PhD; Nagy A. Youssef, MD; Scott D. McDonald, PhD; Elizabeth Van Voorhees, PhD; Rita Davison, BA; Katherine H. Taber, PhD; and Robin Hurley, MD.
Conflict of Interest Disclosures: None reported.
Funding/Support: This study was supported by grant K23 MH073091 from the National Institutes of Health (Dr Morey), by grants 00507153 and 10490938 from the Department of Veterans Health Affairs, and by the MIRECC Grant for PostDeployment Mental Health.
Disclaimer: The sponsors had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.
Previous Presentation: This paper was presented at the 66th Annual Meeting of the Society of Biological Psychiatry; May 13, 2011; San Francisco, California.

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