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Published Online: February 11, 2015. doi:10.1001/jamapsychiatry.2014.2421.

Conflict of Interest Disclosures: Dr Sigmon has received research grants from the National Institute on Drug Abuse, consulting payments from Alkermes, and research support from Titan Pharmaceuticals through her university. No pharmaceutical or industry support was used in this manuscript.

Funding/Support: Preparation of this manuscript was supported in part by National Institutes of Health research grant R34DA037385 and Center of Biomedical Research Excellence award P20GM103644 from the National Institute of General Medical Sciences.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Amygdala-Hippocampal Volume and the Phenotypic Heterogeneity of Posttraumatic Stress Disorder: A Cross-Sectional Study

The amygdala and hippocampus have been implicated consistently in the pathophysiology of posttraumatic stress disorder (PTSD).[1,2] While several studies have observed reduced hippocampal volume in PTSD, studies of amygdala volume and PTSD have been mixed.[1-3]

In addition to method differences, one reason for these mixed results is that most structural magnetic resonance imaging studies in PTSD have treated PTSD as a homogeneous entity instead of considering how amygdala volume may relate to its heterogeneous phenotypic expression.

Confirmatory factor analytic studies have revealed that PTSD is best represented by 5 symptom clusters: reexperiencing, avoidance, numbing, dysphoric arousal (eg, sleep difficulties), and anxious arousal (eg, hypervigilance).[4] To our knowledge, no study has evaluated the relation between amygdala and hippocampal volume and this contemporary model of PTSD. Here, we evaluated these associations in combat veterans.

Methods | Forty-eight Iraq/Afghanistan combat veterans participated in this study. Recruitment was conducted to ensure a full dimensional range of *DSM-IV* PTSD symptoms (ie, including non/minimally symptomatic veterans and equal proportions of veterans with mild, moderate, and severe/extreme symptoms), with 23 veterans (47.9%) meeting diagnostic criteria for combat-related PTSD. Exclusion criteria included psychosis; bipolar disorder; drug abuse or dependence (current or lifetime); alcohol abuse in the past 30 days or alcohol dependence in the past 12 months; moderate and severe traumatic brain injury (ie, loss of consciousness >30 minutes); neurologic disorder (eg, stroke or seizure); learning disability or confirmed diagnosis of attention-deficit/hyperactivity disorder; use of antipsychotics, psychostimulants, or sedatives/hypnotics; antidepressant dose stable less than 30 days; and/or PTSD diagnosis prior to combat exposure. The VA Connecticut Healthcare System Human Subjects Subcommittee and Yale University Human Research Protection Program approved this study. All participants provided written informed consent.

Structural magnetic resonance imaging data were acquired on a Siemens Trio TIM 3T (MPRAGE; voxel size 1 × 1 × 1 mm; repetition time, 2.5 seconds; echo time, 2.77 milliseconds; flip angle, 7°). Blinded to the clinical status, image processing and segmentation were conducted using the fully automated Freesurfer recon-all pipeline (http://surfer.nmr.mgh.harvard.edu).

We computed partial correlations between independent variables and amygdala and hippocampal volumes adjusted for total intracranial volume and entered variables with associations at the $P < .05$ level into a multivariable linear regression analysis using total intracranial volume as a covariate. To evaluate subscales of the Clinician-Administered PTSD Scale associated with volumes, we conducted a post hoc multivariable linear regression analysis ($\alpha = .01$). Finally, to evaluate interrelationships among variables related to regional volumes, exploratory path analyses were conducted using Mplus version 7.2 (http://www.statmodel.com).

Results | The **Table** shows sample characteristics and partial correlation results. After adjustment for intracranial volume, Combat Experiences Scale and total Clinician-Administered PTSD Scale scores were independently associated with right amygdala volume. Multivariable linear regression for right amygdala volume showed adjusted $R^2 = 0.46$ (Combat Experiences Scale: $\beta = -0.27$; $t = 2.34$; $P = .02$; Clinician-Administered PTSD Scale: $\beta = -0.24$; $t = 2.10$; $P = .04$). Post hoc analysis revealed that anxious arousal was independently negatively related to right amygdala volume ($\beta = -0.38$; $t = 3.33$; $P = .002$); no other symptom cluster was significant ($\beta > -0.08$; $t < 0.53$; and $P > .59$ for all). The best-fitting model in path analyses showed right amygdala volume mediating the relationship between combat exposure and anxious arousal ($\chi^2 = 0.03$; $P = .87$; Bayesian Information Criterion = 921.38; Akaike Information Criterion = 906.41; root mean square error of approximation = 0.00 [0.00-0.20]; Comparative Fit Index = 1.00; Tucker-Lewis Index = 1.00; the other 2 models had $\chi^2 = 3.17$ or higher, $P = .07$ or lower, and higher root mean square error of approximation and lower Comparative Fit Index and Tucker-Lewis Index values, which indicate worse fit). The **Figure** shows standardized coefficients of the best-fitting model.

Table. Sample Characteristics and Results of Total Intracranial Volume-Adjusted Partial Correlations[a]

Characteristic	No. (%)	Amygdala		Hippocampus	
		Right	Left	Right	Left
Age, mean (SD), y	33.1 (7.8)	0.00	0.05	−0.05	0.17
Male	41 (85.4)	−0.02	0.20	0.05	0.08
White race/ethnicity	32 (66.7)	−0.07	−0.20	−0.17	−0.11
College or higher education	13 (27.1)	0.22	0.10	0.17	0.26
Married/living with partner	20 (41.7)	0.01	−0.04	0.08	0.17
Lifetime traumatic events (TLEQ score), mean (SD)	12.3 (6.1)	−0.27	0.08	0.09	0.00
Childhood trauma (CTQ total score), mean (SD)	42.6 (15.1)	−0.02	−0.13	−0.12	−0.06
Time in service, mean (SD), y	10.4 (6.8)	0.06	0.01	0.03	0.15
No. of deployments, mean (SD)	2.0 (1.3)	−0.05	−0.10	−0.03	−0.01
Combat exposure severity (CES score), mean (SD)	5.6 (4.4)	−0.36[b]	−0.14	−0.23	−0.32[c]
CAPS total score, mean (SD)	25.5 (27.0)	−0.39[b]	−0.16	−0.26	−0.20
Reexperiencing	6.5 (8.1)	−0.35[c]	−0.15	−0.27	−0.24
Avoidance	2.5 (3.9)	−0.35[c]	−0.18	−0.27	−0.24
Numbing	5.8 (7.2)	−0.31[c]	−0.17	−0.26	−0.15
Dysphoric arousal	7.0 (6.9)	−0.33[c]	−0.07	−0.14	−0.08
Anxious arousal	3.6 (4.0)	−0.45[b]	−0.16	−0.25	−0.20
Chronic PTSD symptoms (≥3 mo)	4 (8.3)	0.01	0.09	0.14	0.08
Depressive symptom severity (BDI-II score), mean (SD)	14.1 (12.7)	−0.11	−0.06	0.03	−0.02
Psychotropic medication	12 (25.0)	0.19	−0.05	−0.05	0.00
Lifetime dependence					
Alcohol	3 (6.3)	−0.17	−0.09	−0.18	−0.21
Nicotine	5 (10.4)	−0.27	−0.11	−0.18	−0.12

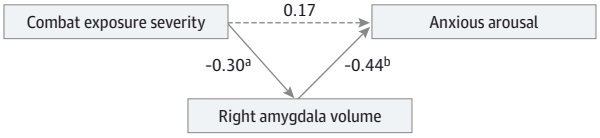
Abbreviations: BDI-II, Beck Depression Inventory–II; CAPS, Clinician-Administered PTSD Scale; CES, Combat Experiences Scale; CTQ, Childhood Trauma Questionnaire; PTSD, posttraumatic stress disorder; TLEQ, Traumatic Life Events Questionnaire

[a] A total of 3 multivariable linear regression analyses were conducted: one with main effects of intracranial volume, combat exposure severity, and CAPS scores, and combat exposure severity by CAPS score interaction term; a second with only intracranial volume, combat exposure severity, and CAPS scores; and a third post hoc analysis to evaluate how the 5 PTSD symptom clusters were related to amygdala volume (results reported in the Results section). In the multivariable linear regression analysis, the combat exposure severity by CAPS interaction was not significant (β = −0.01; t = 0.02; P = .98); thus, the final model contained only main effects of total intracranial volume, combat exposure, and CAPS scores.

[b] P < .01.

[c] P < .05.

Figure. Path Model of Right Amygdala Volume as a Mediator of the Relation Between Combat Exposure and Anxious Arousal Symptoms



The values represent standardized β coefficients. The solid lines represent significant associations; dotted line, nonsignificant association. Right amygdala volume was additionally regressed on total intracranial volume in all path models. Association between combat exposure severity and anxious arousal was significant when right amygdala volume was excluded from the model (β = 0.31; t = 2.22; P = .03). The 95% CI for the association between combat exposure severity and anxious arousal when right amygdala volume was excluded from the model was −0.16 to 0.43; for combat exposure severity and right amygdala volume, −0.10 to −0.52; and for right amygdala volume and anxious arousal, −0.17 to −0.67.

[a] P < .01.

[b] P < .001.

Discussion | This study suggests that reduced right amygdala volume is most strongly associated with anxious arousal symptoms in combat veterans. This finding is consistent with experimental studies linking reduced amygdala volume to stress-evoked hyperresponsiveness.[5,6] Right amygdala volume also fully mediated the relation between combat exposure severity and anxious arousal, suggesting that increased combat exposure may contribute to reduced amygdala volume, which in turn is associated with increased anxious arousal.

While this study was limited by the cross-sectional design and relatively small and predominantly male sample, the results underscore the potential utility of a dimensional approach to evaluating neurobiological factors associated with PTSD. Such an approach may be useful in informing etiologic models, as well as prevention and treatment approaches for this debilitating disorder.

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Published Online: February 18, 2015. doi:10.1001/jamapsychiatry.2014.2470.

Author Contributions: Dr Pietrzak had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Pietrzak and Averill contributed equally.
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Acquisition, analysis, or interpretation of data: Pietrzak, Averill, Abdallah, Neumeister, Levy, Harpaz-Rotem.
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Obtained funding: Neumeister, Krystal, Harpaz-Rotem.
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Conflict of Interest Disclosures: Dr Pietrzak is a scientific consultant to Cogstate Ltd. Dr Abdallah has received consultation fees from Genentech. Dr Krystal consults for several pharmaceutical and biotechnology companies. No other disclosures were reported.

Funding/Support: Preparation of this study was supported in part by the Clinical Neurosciences Division of the US Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, grant K23 MH-101498 from the National Institutes of Health (Dr Abdallah), and a private donation.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views and opinions expressed in this report are those of the authors and should not be construed to represent the views of sponsoring organizations, agencies, or the US government.

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COMMENT & RESPONSE

Childhood Trauma–Specific Reductions in Limbic Gray Matter Volume: Still in the Dark

To the Editor In their article, Van Dam and colleagues[1] reported a unique association between childhood maltreatment (CM) and decreased gray matter volumes (GMVs) in the left limbic regions, both in individuals with substance use disorder and in healthy control individuals. By disentangling the separate influences of CM and psychopathology on GMV, the authors make an important contribution as literature on the specific effects of CM in the absence of psychopathology has been scarce and inconsistent. However, their conclusion that the GMV reductions found in the left limbic regions are uniquely associated with CM may be a bit premature.

Most studies conducted on GMV alterations associated with childhood adversities investigated participants with a concurrent diagnosis such as major depressive disorder or posttraumatic stress disorder.[2] As highlighted by Dannlowski et al,[2] it is therefore difficult to infer whether limbic abnormalities related to CM are only evident in individuals who develop psychopathology later in life or if these alterations are detectable consequences of CM in persons without any psychiatric history.

Limbic abnormalities have repeatedly been reported for various psychiatric conditions,[3] while the possibly mediating or moderating role of CM is rarely taken into consideration in these studies. Van Dam et al[1] investigated this association using an elegant design—their results indeed suggest that previous findings on GMV reductions in patients with substance use disorder may actually relate to CM. When evaluating their results for CM, 24% of the control individuals with CM were also affected by a psychiatric disorder compared with only 5.5% of control individuals without CM, marking a significant difference. As such, we wonder if psychiatric history really was no confounding factor as the authors suggested. Therefore, we would like to know whether the association between CM and reduced GMV in the left limbic regions can be replicated in their group of healthy control individuals only when patients with concurrent psychiatric history are excluded from analysis.

The specific association between CM and limbic regional volumes is as yet still in the dark and in fact (sub)clinical psychiatric symptoms may have contributed to previous reports on structural abnormalities. It is important to study individuals without concurrent psychiatric disorders because only a minority of children exposed to traumatic experiences will develop a psychiatric disorder later in life. To further understand the influence of traumatic experiences during childhood, future studies need to determine the specific effects of traumatic childhood experiences on brain abnormalities with as little bias as possible.

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Conflict of Interest Disclosures: None reported.

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In Reply We agree with Begemann et al that psychiatric illness is often a confound in retrospective characterization of the potential neuroanatomical changes associated with childhood maltreatment (CM). One approach to address this confound is to conduct longitudinal studies. On the other hand, studies