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). While several studies have observed reduced hippocampal volume in PTSD, studies of amygdala volume and PTSD have been mixed.

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). 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 (*α* = .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: *β* = −0.27; *t* = 2.34; *P* = .02; Clinician-Administered PTSD Scale: *β* = −0.24; *t* = 2.10; *P* = .04). Post hoc analysis revealed that anxious arousal was independently negatively related to right amygdala volume (*β* = −0.38; *t* = 3.33; *P* = .002; no other symptom cluster was significant (*β* > −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 (*χ*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 *χ*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.
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. Right amygdala volume also 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.

Robert H. Pietrzak, PhD, MPH
Lynnette A. Averill, PhD
Chadi G. Abdallah, MD
Alexander Neumeister, MD
John H. Krystal, MD
Ifat Levy, PhD
Ilan Harpaz-Rotem, PhD

Author Affiliations: US Department of Veterans Affairs, National Center for Posttraumatic Stress Disorder, Clinical Neurosciences Division, VA Connecticut Healthcare System, West Haven (Pietrzak, Averill, Abdallah, Krystal, Levy, Harpaz-Rotem); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (Pietrzak, Averill, Abdallah, Krystal, Harpaz-Rotem); Department of Psychiatry, New York University School of Medicine, New York (Neumeister), Department of Radiology, New York University School of Medicine, New York (Neumeister); Section of Comparative Medicine, Yale University School of Medicine, New Haven, Connecticut (Levy).

Corresponding Author: Robert H. Pietrzak, PhD, MPH, US Department of Veterans Affairs National Center for Posttraumatic Stress Disorder, VA Connecticut Healthcare System, 950 Campbell Ave, 151E, West Haven, CT 06516 (robert.pietrzak@yale.edu).

uniquely associated with CM maybe a bit premature. That the GMV reductions found in the left limbic regions are has been scarce and inconsistent. However, their conclusion reported a unique association between childhood maltreatment (CM) and reduced 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. As highlighted by Dannlowski et al., 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, while the possibly mediating or moderating role of CM is rarely taken into consideration in these studies. Van Dam et al. 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.

Iris E. C. Sommer, MD, PhD

Corresponding Author: Iris E. C. Sommer, MD, PhD, Department of Psychiatry, University Medical Center Utrecht, 3584 CX Utrecht, the Netherlands (i.sommer@umcutrecht.nl).

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...