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Study concept and design: Pietrzak, Neumeister, Krystal, Harpaz-Rotem.
Acquisition, analysis, or interpretation of data: Pietrzak, Averill, Abdallah, Neumeister, Levy, Harpaz-Rotem.
Drafting of the manuscript: Pietrzak.
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Study supervision: Abdallah, Neumeister, Krystal, Levy.

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1. 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.

2. Woon FL, Hedges DW. Amygdala volume in adults with posttraumatic stress disorder: a meta-analysis. *J Neuropsychiatry Clin Neurosci*. 2009;21(1):5-12.

3. Morey RA, Gold AL, LaBar KS, et al; Mid-Atlantic MIRECC Workgroup. Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Arch Gen Psychiatry*. 2012;69(11):1169-1178.

4. Armour C, Carragher N, Elhai JD. Assessing the fit of the Dysphoric Arousal model across two nationally representative epidemiological surveys: the Australian NSMHWB and the United States NESARC. *J Anxiety Disord*. 2013;27(1):109-115.

5. Gianaros PJ, Sheu LK, Matthews KA, Jennings JR, Manuck SB, Hariri AR. Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *J Neurosci*. 2008;28(4):990-999.

6. Hartley CA, Fischl B, Phelps EA. Brain structure correlates of individual differences in the acquisition and inhibition of conditioned fear. *Cereb Cortex*. 2011;21(9):1954-1962.

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.

Marieke J. H. Begemann, MSc
Maya J. L. Schutte, MSc
Iris E. C. Sommer, MD, PhD

Author Affiliations: Department of Psychiatry, University Medical Center Utrecht and Brain Center Rudolf Magnus, Utrecht, the Netherlands.

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

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1. Van Dam NT, Rando K, Potenza MN, Tuit K, Sinha R. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry*. 2014;71(8):917-925.

2. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry*. 2012;71(4):286-293.

3. Godsil BP, Kiss JP, Spedding M, Jay TM. The hippocampal-prefrontal pathway: the weak link in psychiatric disorders? *Eur Neuropsychopharmacol*. 2013;23(10):1165-1181.

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

with large samples, such as those conducted by Dannlowski et al,[1] show that CM alone, without any history of psychiatric illnesses, is associated with lower hippocampal volume. Dannlowski et al[1] suggest that such brain limbic scars may mediate the relationship between CM, stressful life events, and psychiatric illnesses. Although this conclusion is somewhat tenuous without psychiatric illness present, these findings would seem to suggest a common theme related to CM and alterations to the hippocampal complex.

Begemann et al point out that, in our study, 24% of the control individuals with CM (n = 25) also exhibited a psychiatric diagnosis (ie, anxiety, depression, or posttraumatic stress disorder) compared with only 5.5% in the control individuals without CM (n = 73). In our study, as shown in eFigure 1A in the Supplement, although control individuals with CM showed smaller left hippocampal complex volume relative to control individuals without CM, this difference was not significant within the control group.[2] Additionally, we examined all individuals who were CM positive (including those in the substance-dependent group). This analysis revealed no significant difference in the CM-identified volume between those with vs without psychiatric diagnoses (eFigure 1A). It would seem likely that those with CM, who go on to develop a psychiatric diagnosis, are potentially more susceptible and/or exhibit particular predispositions likely not present in those with CM who do not go on to develop a psychiatric diagnosis. In our study,[2] this link was most notable in relation to substance dependence (although this may be owing to underrepresentation of other psychiatric conditions).

There are several issues with the subsequent, requested analyses. It is true that we cannot completely rule out the potential confounding effect of psychiatric history; however, with our limited sample sizes (CM-positive control group, n = 25; n = 19 after exclusion of psychiatric history), one cannot argue for the null hypothesis from this lack of significant difference among control individuals. In contrast to the point by Begemann et al, difficulty identifying those who experienced CM and failed to develop psychiatric problems is consistent with the observed positive relationship between childhood adversity and later psychiatric problems.[3,4] Further, while observing pure cases of CM (ie, homogenous samples and lacking psychiatric comorbidity) can provide a certain type of insight into the retrospective impact of CM, it fails to provide insights on the heterogeneous nature of psychiatric populations in the clinical setting.[5] In lieu of well-conducted longitudinal studies, we cannot entirely resolve such issues; however, we highlight the work of Dannlowski et al.[1] Given our bias toward pure samples, it may benefit us as a field to embrace heterogeneity as a part of our work. While we could not entirely disentangle psychiatric effects from CM in our study, they often go hand in hand in the real world. Indeed, CM is likely to increase distress and greater maladaptive coping, resulting in greater risk for psychiatric symptoms. Thus, we are not any less convinced of the potentially additive neurobiological effects of childhood trauma, maladaptive coping, and subsequent psychiatric symptoms.

Nicholas T. Van Dam, PhD
Rajita Sinha, PhD

Author Affiliations: Department of Psychiatry, New York University School of Medicine, New York (Van Dam); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (Sinha).

Corresponding Author: Rajita Sinha, PhD, Yale University, Department of Psychiatry, 2 Church St South, Ste 209, New Haven, CT 06519 (rajita.sinha@yale.edu).

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1. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry*. 2012;71(4):286-293.

2. Van Dam NT, Rando K, Potenza MN, Tuit K, Sinha R. Childhood maltreatment, altered limbic neurobiology, and substance use relapse severity via trauma-specific reductions in limbic gray matter volume. *JAMA Psychiatry*. 2014;71(8):917-925.

3. Kessler RC, McLaughlin KA, Green JG, et al. Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *Br J Psychiatry*. 2010;197(5):378-385.

4. Dube SR, Felitti VJ, Dong M, Chapman DP, Giles WH, Anda RF. Childhood abuse, neglect, and household dysfunction and the risk of illicit drug use: the adverse childhood experiences study. *Pediatrics*. 2003;111(3):564-572.

5. Kapur S, Phillips AG, Insel TR. Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Mol Psychiatry*. 2012;17(12):1174-1179.