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Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multisite ENIGMA-PGC Study: Subcortical Volumetry Results From Posttraumatic Stress Disorder Consortia

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Abstract

BACKGROUND—Many studies report smaller hippocampal and amygdala volumes in posttraumatic stress disorder (PTSD), but findings have not always been consistent. Here, we present the results of a large-scale neuroimaging consortium study on PTSD conducted by the Psychiatric Genomics Consortium (PGC)—Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) PTSD Working Group.

METHODS—We analyzed neuroimaging and clinical data from 1868 subjects (794 PTSD patients) contributed by 16 cohorts, representing the largest neuroimaging study of PTSD to date. We assessed the volumes of eight subcortical structures (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, and lateral ventricle). We used a standardized image-analysis and quality-control pipeline established by the ENIGMA consortium.

RESULTS—In a meta-analysis of all samples, we found significantly smaller hippocampi in subjects with current PTSD compared with trauma-exposed control subjects (Cohen's $d = -0.17$, $p = .00054$), and smaller amygdalae ($d = -0.11$, $p = .025$), although the amygdala finding did not survive a significance level that was Bonferroni corrected for multiple subcortical region comparisons ($p < .0063$).

CONCLUSIONS—Our study is not subject to the biases of meta-analyses of published data, and it represents an important milestone in an ongoing collaborative effort to examine the neurobiological underpinnings of PTSD and the brain's response to trauma.

Keywords

Amygdala; Childhood trauma; Gender differences; Hippocampus; PTSD; Structural MRI

Posttraumatic stress disorder (PTSD) is a psychiatric condition that develops in about 6% to 8% of the general population following exposure to traumatic life events (1–3), with higher rates in women (8% to 10% compared with 4% to 5% of men) (1,3) and select populations such as military combat survivors (19%) (4). With the rise in global terrorism and military

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conflict, the public health impact of PTSD has attracted greater attention and fueled research on its neural and biological markers. One key goal of research on the neurobiology of PTSD has been to identify structural brain changes that are associated with PTSD, and much of this work has focused on the volume of the hippocampus and amygdala.

PTSD researchers have often focused on the hippocampus, as it plays a central role in regulating stress hormones and responses through the hypothalamic-pituitary-adrenal axis, and because it is also susceptible to the toxic effects of elevated glucocorticoids (5). Further, the hippocampus has been implicated in the contextual modulation of behavior (6,7). With its role in fear learning and suppression of fear in safe contexts, i.e., fear conditioning, extinction, and fear renewal, the hippocampus is integral to widely accepted behavioral models of PTSD (8,9). The amygdala is another subcortical region that likely plays a key role in the pathophysiology of PTSD. Animal models have established the role of the basolateral amygdala in fear learning and the centromedial amygdala in fear expression (10). The amygdala is hyperactive during various behavioral paradigms tested in PTSD (11). In addition, the amygdala is adjacent to the hippocampus, and these two highly interconnected regions have strong evidence of mutual modulatory influence, especially for emotional memory (12).

Numerous studies have examined the relationship between PTSD and the hippocampus and amygdala. Prior studies typically found smaller hippocampal volume in PTSD (13–16), but this has not been consistent (17–21). Evidence of altered amygdala volume in PTSD has been even more equivocal, with studies reporting both smaller (16) and larger (22) volumes. Meta-analyses have more consistently reported PTSD-associated reductions in hippocampal and amygdala volume (23–26). One meta-analysis found an association between PTSD and lower hippocampal volume (15 studies, $n = 562$), and smaller-sample meta-analyses found smaller volumes for the amygdala (7 studies, $n = 320$) (25). A more recent meta-analysis found smaller volumes in the hippocampus (36 studies, $n = 1623$) and the amygdala (14 studies, $n = 682$), although the association observed with the amygdala was partially due to confounding with the effects of trauma exposure (26). However, major limitations of these meta-analyses include disparate image processing steps and the “file drawer” problem, which refers to the tendency to publish only those results that confirm an initial finding, while contradictory and null results remain unpublished and relegated to the investigator’s “file drawer.” Thus, previous meta-analyses have been potentially subject to publication bias and spuriously large effect sizes because they are based solely on published results. In addition, there is limited evidence for altered volumes of other subcortical structures. Previous studies showed reduced caudate nucleus volume (27–29) and increased lateral ventricle volume (30) in PTSD patients. Furthermore, a smaller globus pallidus and thalamus were associated with more re-experiencing of symptoms (31). It is unclear if the absence of structural differences, limited sample size, or lack of interest in these structures has led to the small number of reports on subcortical structures other than hippocampus and amygdala.

Here, the Psychiatric Genomics Consortium [PGC]–Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) PTSD Working Group compared eight subcortical structure volumes (nucleus accumbens, amygdala, caudate, hippocampus, pallidum,

putamen, thalamus, and lateral ventricle) between PTSD patients and control subjects in the largest PTSD neuroimaging study to date, including data from 1868 subjects from 16 cohorts. A major advantage of the present study in comparison with previous meta-analyses examining subcortical volume in PTSD is that all 16 sites implemented a standardized image analysis and quality control pipeline developed by the ENIGMA Consortium that has also been used to identify associations between subcortical volumes and major depressive disorder (32), bipolar disorder (33), obsessive-compulsive disorder (34), and schizophrenia (35), thus avoiding potential noise introduced by varying neuroimaging processing methods across sites (36). Therefore, our study design avoids many of the serious limitations of prior meta-analyses that combined published summary statistics.

In addition to the main analysis of PTSD diagnosis, we performed separate analyses examining variables that have been hypothesized to influence the relationship between PTSD and subcortical volume, including gender effects (25), civilian versus military samples, childhood trauma (37), and alcohol use disorder (AUD) (38).

METHODS AND MATERIALS

Samples

The ENIGMA-PGC PTSD Working Group includes 16 cohorts from five countries, with neuroimaging and clinical data from PTSD patients and control subjects with varying levels of trauma exposure. Thirteen of the 16 sites exclusively used the Clinician-Administered PTSD Scale to diagnose PTSD, and 12 sites assessed childhood trauma. Detailed demographic information on each sample, including trauma exposure in the control samples, may be found in Supplemental Table S1. Further clinical information may be found in Supplemental Table S2. In total, we analyzed data from 1868 subjects, including 794 PTSD patients and 1074 control subjects. Among these, 358 PTSD patients and 478 control subjects came from military samples. The vast majority of participants (751 PTSD patients and 934 control subjects) were adults. Inclusion and exclusion criteria for each site may be found in Supplemental Table S3. Harmonized scales of childhood trauma and AUD were obtained from the sites (see the Supplement). All participating sites obtained approval from local institutional review boards and ethics committees. All study participants provided written informed consent.

Imaging and Statistical Analysis

Quality control and processing of structural T1-weighted magnetic resonance imaging scans was performed using FreeSurfer (39) in conjunction with standardized ENIGMA protocols. Our primary analysis was an examination of the average volume of eight subcortical regions adjusting for age, gender, and intracranial volume (ICV). Within each dataset, linear models of average subcortical volumes (mean of left and right) were fit as a function of current PTSD status, after adjusting for effects of age, gender, ICV, and scanner for sites with multiple scanner types. Details on scanners and acquisition parameters are provided in Supplemental Table S4. A random-effects meta-analysis was used to combine results across cohorts. Follow-up analyses included testing whether the difference between the right and left volumes varied as a function of case/control status (PTSD \times hemisphere interaction) and

an analysis of the left and right volumes separately. Cohen's d effect size estimates and the percentage difference in mean volume associated with PTSD are reported. Nominal (uncorrected) p values are reported throughout. Cases in which significance exceeds Bonferroni correction for the number of volumes examined ($.05/8 = .0063$ in our primary analysis) are noted. To avoid confusion, the same correction is employed in all post hoc analyses. Follow-up analyses examined potential heterogeneity with meta-regression (see the Supplement), separate analyses of men and women, and separate meta-analyses of adult (nonpediatric), military, and civilian samples. In significantly associated regions, we additionally analyzed PTSD symptom severity (normalized within site). To examine the potential impact of depression comorbidity, we performed an analysis of depression severity within PTSD cases. Furthermore, we examined the impact of AUD and childhood trauma levels, given their frequent co-occurrence with PTSD and influence on subcortical volumes (40–42). We also examined the presence/absence of childhood trauma within PTSD cases, which was used as a proxy for timing of trauma exposure.

RESULTS

Associations Between PTSD and Subcortical Volumes

The results of our primary analysis of eight mean subcortical volumes as a function of PTSD case/control status after adjusting for age, gender, and ICV are presented in Figure 1 and Table 1, while the results of PTSD on ICV are presented in Supplemental Table S5. The hippocampus and amygdala were, on average, smaller in subjects with current PTSD (hippocampus: $d = -0.17$, $p = .00054$; amygdala: $d = -0.11$, $p = .025$). The hippocampus finding surpassed the corrected significance threshold ($p < .0063$), but the amygdala did not survive this multiple-comparisons correction. I^2 and p_{het} values indicate low levels of heterogeneity across samples (Tables 1 and 2). We followed up these findings with an analysis of current PTSD severity in samples for which severity data was available. PTSD severity was significantly associated with hippocampal volume ($d = -0.15$, $p = .013$), but not amygdala volume ($d = -0.087$, $p = .13$).

A formal test of a differential effect of PTSD between hemispheres was nonsignificant for all of the examined regions. Our a priori specified separate analyses of left and right subcortical volumes (after adjusting for age, gender, and ICV) are presented in Figure 1 and Supplemental Table S6. Left and right hemisphere effect size estimates had overlapping confidence intervals supporting a lack of differential effect by hemisphere. The association between PTSD and hippocampal volume was evident in both hemispheres ($p < .005$, in each). For the amygdala, the association with PTSD was borderline in the right amygdala, passing $p < .05$, but not the Bonferroni-corrected threshold (right amygdala: $d = -0.12$, $p = .017$; left amygdala: $d = -0.075$, $p = .13$). In addition, the volume of the left lateral ventricle (but neither the volume of right lateral ventricle nor the total volume) was positively associated with PTSD at nominal significance levels ($d = 0.10$, $p = .036$).

Examining Heterogeneity

Figure 2 presents a forest plot of the effect size estimates and 95% confidence intervals of the 16 participating sites and meta-analyses for the association between mean hippocampal

volume and PTSD. Figure 3, Table 2, and Supplemental Tables S7 to S10 present the results of male and female stratified meta-analyses and separate analyses of the adult (nonpediatric), military, and civilian samples. No significant difference in effect size was observed in the analysis of a gender by PTSD interaction term ($p = .38$) on hippocampal volume or from the meta-regression of the proportion of women in each sample as predicting the effect size estimates ($p = .14$). However, as these tests can have low power, we examined the associations observed in each subgroup. The negative association between hippocampal volume and PTSD was significant in the female-only, adult-only, and civilian analyses. The association was nonsignificant in the male-only and military analyses. Even though the female-only analysis contained approximately 1100 fewer subjects than the full sample, the hippocampal results were more significant in women (Table 2; $p = .00012$), and Cohen's d estimates indicated a stronger effect than in the full sample ($d = -0.31$ vs. $d = -0.17$). Similarly, effect size estimates indicated a higher impact in the civilian ($d = -0.21$, $p = .0032$) versus military ($d = -0.11$, $p = .11$) samples. This is perhaps unsurprising given the confound between variables representing gender and military status (see Supplemental Table S1). These differences may relate more strongly to gender than military status: the effect size in military women ($d = -0.23$, $p = .34$, $n = 88$), while nonsignificant, was stronger (more negative) than in the overall meta-analysis estimate ($d = -0.17$), and the effect in civilian men ($d = -0.025$, $p = .87$) is smaller than the overall meta-analysis. However, it should be noted again that the confidence intervals in effect size for men and women overlapped, and the formal test of heterogeneity by gender was nonsignificant. The nominal association with the amygdala in the full dataset was not significant in the subgroup meta-analyses, potentially due to sample size. An analysis of PTSD severity and hippocampal volume in women was nominally significant ($d = -0.22$, $p = .031$), but the analysis of PTSD severity and amygdala volume was not ($d = -0.12$, $p = .20$).

Potential Confounding Variables

Finally, we examined the relationship between hippocampal and amygdala volume and confounding variables including AUD and childhood trauma. In a linear model adjusting for age, gender, and ICV, we found AUD was not associated with hippocampal volume whether or not PTSD was included as a covariate (without PTSD: $p = .12$; with PTSD: $p = .25$). Childhood trauma was negatively associated with hippocampal volume in a model adjusting for age, gender, and ICV ($d = -0.17$, $p = .0031$) but was not significant if PTSD was added as a covariate ($d = -0.11$, $p = .064$). AUD was associated with smaller amygdala volume whether or not PTSD was included as a covariate (without PTSD as a covariate: $d = -0.012$, $p = .036$; with PTSD: $d = -0.012$, $p = .048$). Similarly, childhood trauma was associated with reduced amygdala volume whether or not PTSD was included as a covariate (without PTSD: $d = -0.16$, $p = .0044$; with PTSD: $d = -0.13$, $p = .019$). We then examined the effects of PTSD on hippocampal and amygdala volume, adjusting for these potential confounding variables in datasets where this covariate data was available. The association between hippocampal volume and PTSD was attenuated but remained significant when AUD or childhood trauma were added as covariates (with AUD: $d = -0.14$, $p = .014$; with CT: $d = -0.14$, $p = .015$). In the subset of subjects with AUD data ($n = 1443$), the association between the amygdala and PTSD was not significant whether or not AUD was included (with AUD: $p = .41$; without AUD: $p = .21$). Similarly, the association between PTSD and

amygdala volume was not significant in the subsample with childhood trauma data ($n = 1423$) whether or not the adjustment for childhood trauma was included (with: $p = .33$; without: $p = .11$). We additionally examined the presence/absence of childhood trauma within PTSD cases as a proxy for chronicity of trauma exposure (childhood vs. adult). In both the hippocampus and the amygdala, there was a trend toward smaller volumes for PTSD cases with the presence of childhood trauma compared with PTSD cases with no childhood trauma (for hippocampus: $n = 513$, $d = -0.17$, $p = .088$; for amygdala: $n = 513$, $d = -0.20$, $p = .053$). In an analysis of female PTSD cases, effect size estimates for both the hippocampus and the amygdala were larger (more negative), but the p value for the test of association in the amygdala was no longer close to significant, potentially due to the great reduction in sample size (for hippocampus: $n = 103$, $d = -0.51$, $p = .096$; for amygdala: $n = 102$, $d = -0.46$, $p = .28$).

Finally, to examine the effect of comorbidity between depression and PTSD, we examined depression severity within PTSD cases. Depression severity was not significantly associated with either hippocampus or amygdala volume either in the overall sample or in women (all $p > .19$).

DISCUSSION

In the largest study of neuroimaging and PTSD to date, our multisite consortium found evidence of lower hippocampal volume in subjects with current PTSD. Robust hippocampal findings remained significant after controlling for multiple comparisons, AUD, and childhood trauma, and within smaller subcohorts. We additionally report smaller amygdala volume in PTSD, but this result did not survive the Bonferroni correction for multiple comparisons and must therefore be interpreted with caution. Similar effects have been observed in retrospective meta-analyses of published data, but these studies had smaller sample sizes and may be biased by the file drawer problem. Our meta-analysis was prospective and performed with harmonized analysis of original data. Therefore, it is unlikely that our effect size estimates are inflated by excluding studies with nonsignificant or contradictory findings. We also observed associations between PTSD and the left lateral ventricle in the full meta-analysis, the volume of the nucleus accumbens in women, and the pallidum in civilians, but these did not survive multiple testing correction, thus requiring replication. The strength of the associations observed with the hippocampus ($d = -0.17$, $d = -0.31$ in women) and the amygdala ($d = -0.11$) are within the range of associations observed by other groups using the ENIGMA protocols to study major depressive disorder (32), bipolar disorder (33), obsessive-compulsive disorder (34), and schizophrenia (35) (absolute value of d from 0.11 to 0.46 across subcortical structures and disorders).

Although we found an association between PTSD and hippocampus volume, there are still many unanswered questions about underlying causation. High levels of glucocorticoid receptors in the hippocampus make it particularly prone to effects of the elevated levels of glucocorticoids released in response to stress (43–45). Some magnetic resonance imaging studies in PTSD patients also concluded that reduced hippocampal volume is a result of stress exposure. This conclusion is based on observations of reduced hippocampal volume in trauma-exposed control subjects without PTSD relative to trauma-unexposed control

subjects (46,47). In contrast, other magnetic resonance imaging studies did not detect group differences between trauma-exposed and healthy control subjects (48–50), suggesting that lower hippocampal volume is specifically related to the presence of a psychiatric disorder rather than exposure to trauma. These studies are consistent with the hypothesis that lower hippocampal volume is a heritable risk factor for developing PTSD as demonstrated in twin studies. In these studies, one twin was exposed to military combat, and one was not. Of the combat-exposed individuals who developed PTSD, the unexposed twin (without PTSD) also had reduced hippocampal volume (51).

There is also evidence that amygdala volume may be negatively associated with stress and stress-response mechanisms. Exposure to high levels of chronic stress in rodents produces corticosterone-mediated spinogenesis, dendritic arborization, and hypertrophy of the amygdala (52). One study has found that inbred recombinant mice strains with a relatively small basolateral amygdala showed a stronger conditioned fear response and corticosterone response to stress than mice strains with a large basolateral amygdala (53). A recent study that showed reduced amygdala volume following childhood trauma suggested that severe adversity during childhood may at first enhance amygdala sensitivity through dendritic growth and synaptic connectivity, as shown in rodents (52), but repetitive activation induces “wear and tear,” eventually resulting in a smaller amygdala in adulthood (54). However, our amygdala results did not survive multiple comparisons corrections, and any speculations regarding the molecular mechanisms involved in reduced amygdala volume must be interpreted with caution. Further, potential confounding remains a plausible alternative explanation for the observed association (see below).

Gender Differences

PTSD is more prevalent in women than in men (55). Our results show that the PTSD association with smaller hippocampal volume was primarily due to a strong negative association in women. However, we were unable to conclusively demonstrate a larger effect size in women compared with men, because the PTSD by gender interaction term was not significant. There are several potential reasons for the observed strong effect in women apart from a true differential effect by gender. Demographic differences between samples may have inflated the strength of the association in samples that are primarily female. Differences in the type of trauma experienced by men and women may play a role in the observed differential effect. Information on mean age, PTSD severity, depression severity, AUD, and childhood trauma broken down by site and gender are presented in Supplemental Tables S12 to S18. Future studies should include both males and females when possible to better assess gender differences in the negative association between PTSD and hippocampal volume.

Childhood Trauma Exposure

In the current study, childhood trauma was negatively associated with hippocampal volume, but not when PTSD was included as a covariate. Controlling for childhood trauma attenuated our hippocampal results, but hippocampal volume was still significantly smaller in PTSD patients. These findings suggest that reduced hippocampal is associated with PTSD and not with childhood trauma itself.

Lower amygdala volume, on the other hand, was significantly associated with more childhood trauma, both with and without PTSD as a covariate. This is in line with prior studies showing a negative correlation between childhood trauma and amygdala volume (54,56,57). However, the relationship between PTSD and amygdala volume was not even nominally significant in the subsample with available childhood trauma information, so we could not evaluate childhood trauma effects on the negative association between amygdala volume and PTSD.

Role of AUD

AUD was not associated with hippocampal volume, and hippocampal results remained significant after controlling for alcohol. Our finding supports other studies that show that hippocampal differences persist (13,48) or show bilateral effects (50) after controlling for lifetime alcohol use or abuse, suggesting that reduced hippocampal volume in PTSD is not due to a confound with AUD.

In contrast, we observed a significant association between AUD and smaller amygdala volume, irrespective of PTSD. This finding is in line with prior studies showing smaller amygdala volumes in alcohol-dependent perpetrators of intimate partner violence (58), individuals with a family history of alcoholism (59), and alcohol-dependent individuals, who also showed an association with increased alcohol craving and intake (60). The negative association between the amygdala and PTSD in the subsample possessing alcohol information was not significant; hence, we were not able to determine the degree to which our observed nominally significant association with the amygdala was due to confounding between PTSD and AUD.

Limitations

Our study has some limitations. The uneven availability of covariates across sites precluded an examination of important factors such as PTSD duration, comorbidity (apart from depression), trauma chronicity, and treatment. Inclusion of information on PTSD duration, chronicity, and treatment in particular might have altered findings, and their absence limits interpretation of the findings. The presence or absence of childhood trauma was our only available proxy for chronicity of trauma exposure, as detailed information of chronicity of trauma exposure was unavailable from the majority of sites. We did not control for psychotherapy or medication, and all patients included in our analysis had current PTSD, and some were recent-onset PTSD patients. Recent treatment studies suggest that smaller hippocampal volume may be specifically related to persistence of PTSD after treatment (50,61) and smaller hippocampal volume was not observed in (recent-onset) patients who recovered from PTSD (50,61–63). Follow-up data on the chronicity of PTSD symptoms and treatment could help strengthen the current findings.

While this is the largest multisite consortium study and the largest meta-analysis of subcortical structures in PTSD to date, the inclusion of additional cohorts with specific characteristics and more detailed clinical information across cohorts will be needed to evaluate the role of stratifying factors such as age, gender, and type of trauma. For example, we only had one nonadult (pediatric) cohort. Our adult-only analyses were sufficient to

demonstrate that the inclusion of this cohort did not unduly bias results, but additional pediatric samples are needed demonstrate if results are consistent across adult and nonadult samples. We also lack sufficient data to assess the overall impact of adult trauma load or to assess specific types of adult and childhood trauma. We distinguished military and civilian samples. However, individuals in the military samples have also been exposed to nonmilitary trauma, and vice versa, civilians were not excluded for deployment. Therefore, the military-civilian distinction is not synonymous with different types of trauma exposure. Much larger sample sizes will be needed to robustly evaluate the role genetic variants play in the observed associations.

An additional limitation is the absence of cross-site standardization of raters performing clinical assessment and absence of standardization of scanners or acquisition sequences, operating system, and hardware platform running FreeSurfer. Similarly, there were differences in the instruments used to assess PTSD, trauma, and AUD across sites, and potentially even differences in how the instruments were applied and interpreted. However, these weaknesses and many others not present in the current research would be faced by every literature-based meta-analysis of PTSD. A major strength of our study is the standardization of segmentation technique, and running a harmonized analysis protocol across all sites. Methodological consistency was promoted by using the same statistical models across all samples, making this the most powerful study of subcortical volumes in PTSD to date.

Conclusions

The ENIGMA-PGC PTSD Working Group has demonstrated that PTSD is associated with smaller hippocampus and possibly amygdala volume. Both structures have ample a priori evidence implicating their role in PTSD starting with the report of reduced hippocampal volume in PTSD by Bremner *et al.* in 1995 (64). Our study confirms this finding across a large number of demographically and clinically heterogeneous cohorts analyzed with standardized segmentation technique, and running a harmonized analysis protocol across all sites. Methodological consistency was promoted by using the same statistical models across all samples, making this the largest and most powerful study of subcortical volumes in PTSD to date. Reduced hippocampal volume was the most robust finding and survived a conservative correction for childhood trauma and AUD. Although we had nearly equal sample sizes across eight subcortical structures, only the hippocampus was unequivocally associated with PTSD. Therefore, the outsized role of the hippocampus in the literature is not attributable solely to greater attention paid to this structure. The hippocampus is crucial for fear processing, episodic and contextual learning, and memory processes related to PTSD symptomatology. This meta-analysis firmly establishes the importance of the hippocampus in PTSD, which by itself represents a substantial step forward in the neurobiology of PTSD. Nevertheless, many questions remain unanswered, and this study is part of an ongoing extensive investigation into the neurobiological underpinnings of PTSD. The ENIGMA-PGC PTSD Working Group has several studies underway, including the association between PTSD and white matter integrity, cortical thickness, regional cortical volumes, hippocampal subfield volumes, and subcortical shape. Forthcoming cross-disorder analyses are planned to study the effects of childhood trauma on the brain. An investigation

of the impact of genetic variation on PTSD risk and response to stress is also planned, which will leverage the work of the PGC-PTSD workgroup—a large-scale genomics consortium to study PTSD genomics (65). Taken together, these future investigations will advance our understanding of PTSD neurobiology and potentially yield new targets for treatment, improve personalized medicine with existing treatments, and identify new targets to ameliorate the negative effects of trauma exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Novartis Pharma AG, Otsuka America Pharmaceutical, Inc., Sage Therapeutics, Inc., Sunovion Pharmaceuticals, Inc., and Takeda Industries; is on the Scientific Advisory Board for Lohocla Research Corporation, Mnemosyne Pharmaceuticals, Inc., Naurex, Inc., and Pfizer; is a stockholder in Biohaven Medical Sciences; holds stock options in Mnemosyne Pharmaceuticals, Inc.; holds patents for Dopamine and Noradrenergic Reuptake Inhibitors in Treatment of Schizophrenia, U.S. Patent No. 5,447,948 (issued Sep 5, 1995), and Glutamate Modulating Agents in the Treatment of Mental Disorders, U.S. Patent No. 8,778,979 (issued Jul 15, 2014); and filed a patent for Intranasal Administration of Ketamine to Treat Depression. U.S. Application No. 14/197,767 (filed on Mar 5, 2014); U.S. application or Patent Cooperation Treaty international application No. 14/306,382 (filed on Jun 17, 2014).

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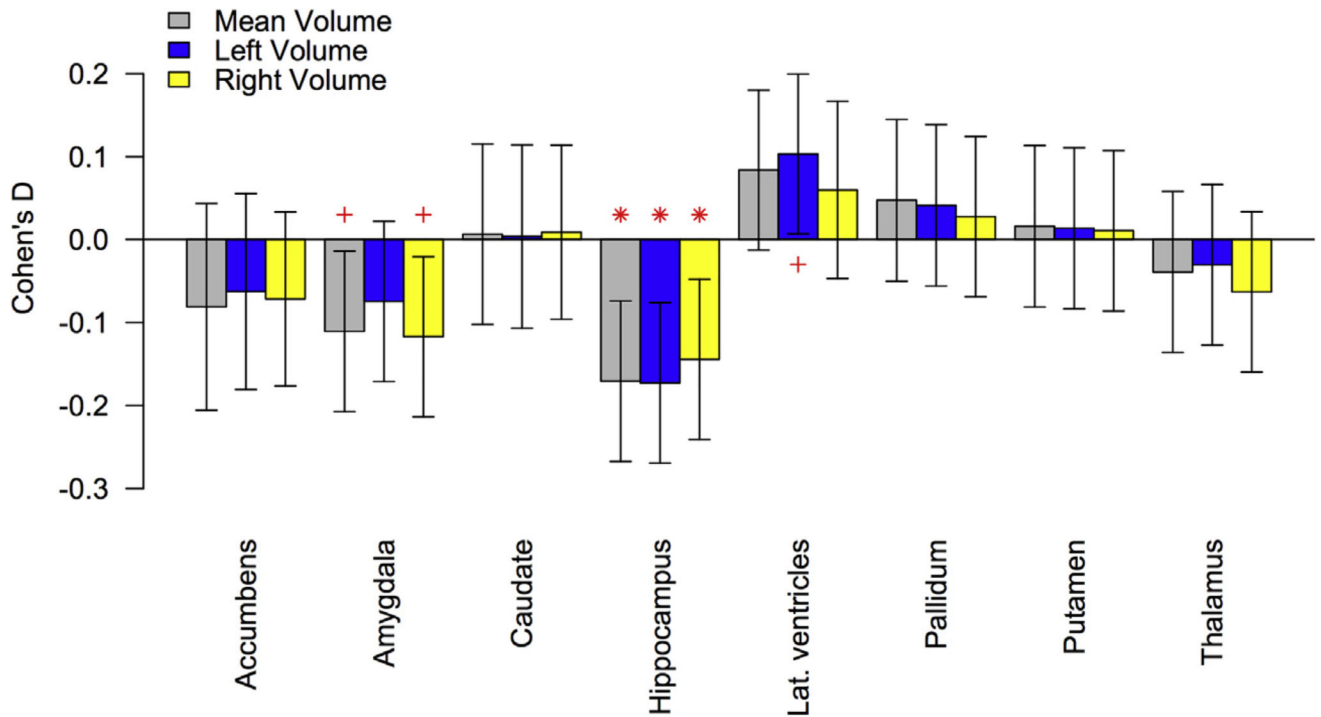


Figure 1.

Cohen's d estimate of the association between posttraumatic stress disorder and subcortical brain volumes as well as confidence intervals on effect size. Included is a primary analysis adjusted for age, gender, and intracranial volume and followup analyses with left and right volumes analyzed separately. A plus sign (+) indicates that the comparison of posttraumatic stress disorder cases and control subjects was significant at the $p < .05$ level. An asterisk (*) indicates that the comparison was significant after a Bonferroni correction for the eight subcortical regions examined ($p < .0063$). Lat., lateral.

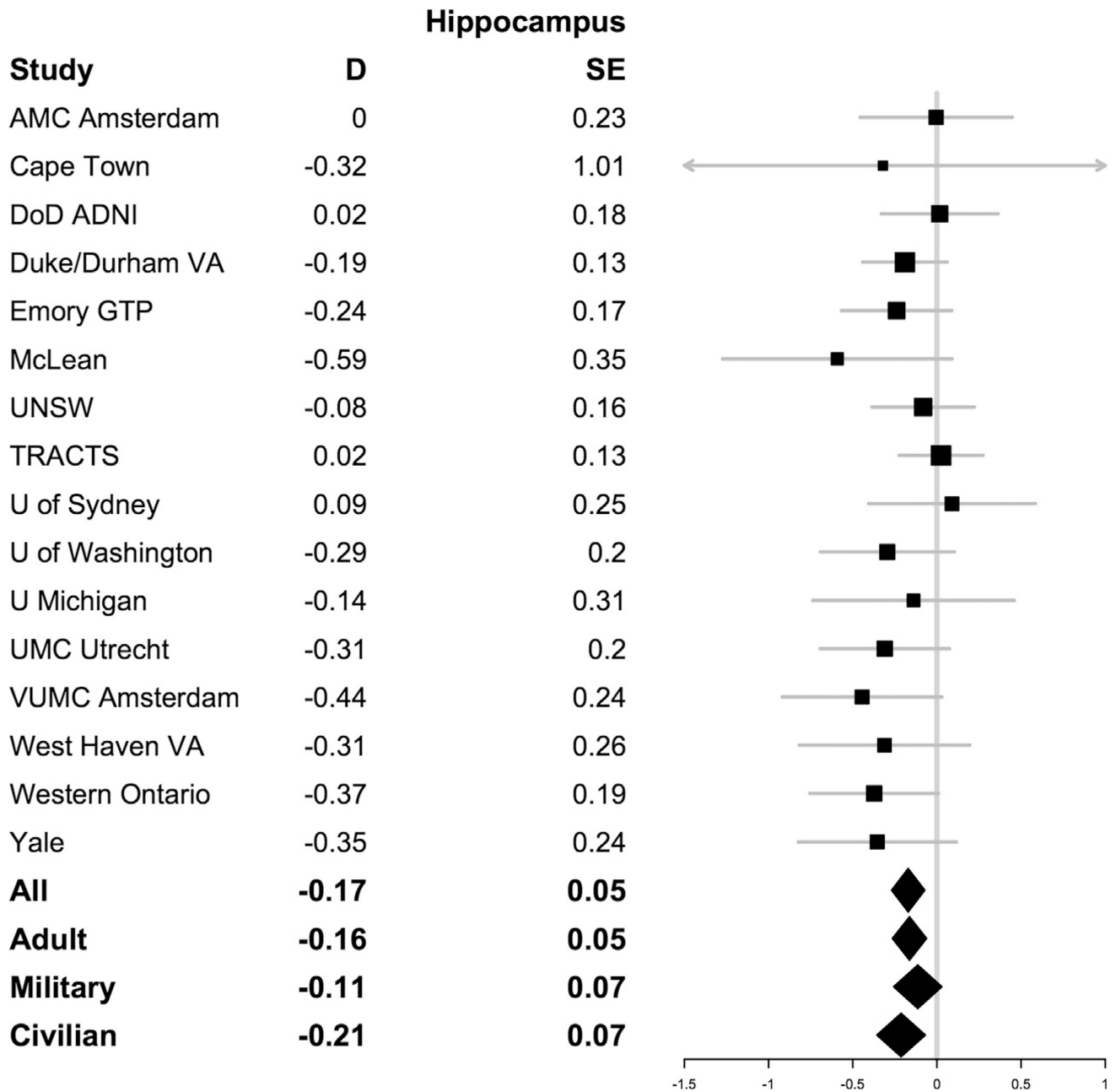


Figure 2.

Forest plot of the effect size estimates and 95% confidence intervals of 16 participating sites and meta-analyses for the association between mean hippocampal volume and posttraumatic stress disorder. For detailed descriptions and full names of participating sites see Supplemental Tables S1–S3. Adult meta-analysis includes all sites but University of Washington. The military meta-analysis includes Department of Defense (DoD) Alzheimer’s Disease Neuroimaging Initiative (ADNI), Duke/Durham Veterans Administration (VA), the VA Translational Center for Traumatic Brain Injury and Stress Disorders (TRACTS), University Medical Center (UMC) Utrecht, and West Haven VA. The civilian meta-analysis includes the Academic Medical Center (AMC) Amsterdam, Cape Town, Emory Grady

Trauma Project (GTP), McLean, University of New South Wales (UNSW), University of Sydney (U of Sydney), University of Michigan (U Michigan), VU University Medical Center (VUMC) Amsterdam, Western Ontario, and Yale studies.

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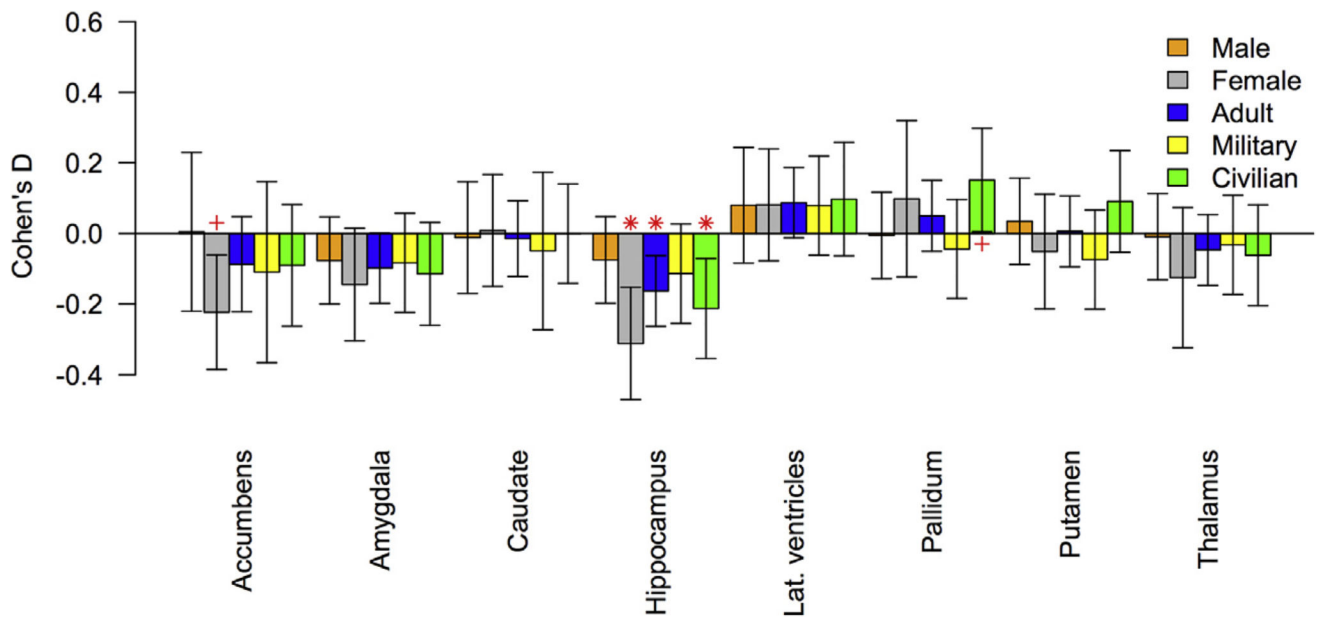


Figure 3.

Cohen's d estimate of the association between posttraumatic stress disorder and subcortical brain volumes as well as confidence intervals on effect size for subsets of the data. Included are analyses of men and women analyzed separately, as well as all adult samples (nonpediatric), military, and civilian datasets meta-analyzed separately. A plus sign (+) indicates that the comparison of PTSD cases and control subjects was significant at the $p < .05$ level. An asterisk (*) indicates that the comparison was significant after a Bonferroni correction for the eight subcortical regions examined ($p < .0063$). Lat., lateral.

Table 1
 Meta-analysis of the Effect of Posttraumatic Stress Disorder on Subcortical Region Volumes Across 16 Datasets Adjusting for Age, Gender, and Intracranial Volume

Region	Cohen's <i>d</i> (95% CI)	SE	<i>p</i> Value	% _{airr}	<i>r</i> ²	<i>p</i> _{het}	Cases	Control Subjects	Men/ Women	Military/Civilian Cohort	Pediatric/ Adult Cohort
Nucleus Accumbens	-0.081 (-0.206 to 0.043)	0.064	.20	-1.21	33.13	.080	778	1061	1105/734	836/1003	161/1678
Amygdala	-0.11 (-0.207 to -0.014)	0.049	.025 ^a	-1.11	0.00	.36	780	1061	1105/736	836/1005	161/1680
Caudate	0.0064 (-0.102 to 0.115)	0.056	.91	0.13	16.38	.28	780	1063	1105/738	836/1007	161/1682
Hippocampus	-0.17 (-0.267 to -0.074)	0.049	.00054 ^b	-1.50	0.00	.74	780	1062	1104/738	835/1007	161/1681
Lateral Ventricle	0.084 (-0.013 to 0.180)	0.049	.089	3.75	0.00	.48	781	1064	1105/740	836/1009	161/1684
Pallidum	0.047 (-0.050 to 0.145)	0.050	.34	0.82	0.00	.10	766	1048	1105/709	836/978	161/1653
Putamen	0.016 (-0.081 to 0.113)	0.050	.75	0.18	0.00	.76	764	1050	1105/709	836/978	161/1653
Thalamus	-0.039 (-0.136 to 0.058)	0.050	.43	-0.33	0.00	.56	772	1053	1105/720	836/989	161/1664

CI, confidence interval.

^aComparison was significant at the $p < .05$ level.

^bComparison was significant after a Bonferroni correction for eight subcortical regions examined ($p < .0063$).

Female-Only Meta-analysis of the Effect of Posttraumatic Stress Disorder on Subcortical Region Volumes Adjusting for Age and Intracranial Volume

Table 2

Region	Cohen's <i>d</i> (95% CI)	SE	<i>p</i> Value	%airr	<i>I</i> ²	<i>p</i> _{het}	Cases	Control Subjects
Nucleus Accumbens	-0.22 (-0.39 to -0.061)	0.083	.0071 ^a	-2.32	1.50	.16	305	427
Amygdala	-0.14 (-0.30 to 0.015)	0.081	.075	-1.46	0.0047	.18	307	427
Caudate	0.008 (-0.15 to 0.17)	0.081	.92	0.19	0.00	.67	307	429
Hippocampus	-0.31 (-0.47 to -0.15)	0.081	.00012 ^b	-2.42	0.00	.90	308	428
Lateral Ventricle	0.081 (-0.077 to 0.24)	0.081	.32	3.49	0.00	.87	308	430
Pallidum	0.10 (-0.12 to 0.32)	0.11	.39	1.13	35.30	.068	293	414
Putamen	-0.051 (-0.21 to 0.11)	0.083	.54	-0.49	0.0064	.60	291	416
Thalamus	-0.13 (-0.32 to 0.073)	0.10	.22	-0.84	23.74	.12	299	419

CI, confidence interval.

^aComparison was significant at the $p < .05$ level.

^bComparison was significant after a Bonferroni correction for eight subcortical regions examined ($p < .0063$).