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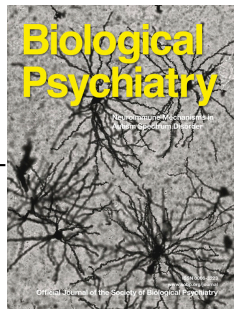

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Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multi-Site ENIGMA-PGC Study

Subcortical Volumetry Results from PTSD Consortia

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ABSTRACT

Background

Many studies report smaller hippocampal and amygdala volumes in 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 Genomic Consortium (PGC)-Enhancing Neuroimaging Genetics Through Meta-Analysis (ENIGMA) PTSD Working Group.

Methods

We analyzed neuroimaging and clinical data from 1,868 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 to trauma-exposed controls (Cohen's D=-0.17, p=0.00054), and smaller amygdalae (D=-0.11, p=0.025), although the amygdala finding did not survive a significance level that was Bonferroni corrected for multiple subcortical region comparisons ($p<0.0063$).

Conclusions

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

INTRODUCTION

Posttraumatic stress disorder (PTSD) is a psychiatric condition that develops in about 6-8% of the general population following exposure to traumatic life events,(1-3) with higher rates in women (8-10% compared to 4-5% of men),(1,3) and select populations such as military combat survivors (19%)(4). With the rise in global terrorism and military 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 (HPA 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 basolateral amygdala (BLA) in fear learning and centromedial amygdala (CeM) 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, which are two highly interconnected regions with 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 volumes(22). 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=1,623), 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 symptoms(31). It is unclear if the absence of structural differences, limited sample size, or lack of interest in these structures have led to the small number of reports on subcortical structures other than hippocampus and amygdala.

Here, we (PGC-ENIGMA-PTSD Working Group) compared eight subcortical structure volumes (nucleus accumbens, amygdala, caudate, hippocampus, pallidum, putamen, thalamus, and lateral ventricle) between PTSD patients and controls in the largest PTSD

neuroimaging study to date, including data from 1,868 subjects from 16 cohorts. A major advantage of the present study in comparison to 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 (MDD)(32), bipolar disorder(33), obsessive compulsive disorder (OCD)(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 sex effects(25), civilian vs. military samples, childhood trauma(37), and alcohol use disorder(38).

MATERIALS AND METHODS

Samples

The PGC-ENIGMA PTSD Working Group includes 16 cohorts from 5 countries, with neuroimaging and clinical data from PTSD patients and controls with varying levels of trauma exposure. Thirteen of the 16 sites exclusively used the CAPS 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 **Supplementary Table 1.** Further clinical information may be found in **Supplementary Table 2**. In total, we analyzed data from 1,868 subjects, including 794 PTSD patients and 1,074 controls. Among these, 358 PTSD patients and 478 controls came from military samples. The vast majority of participants (751 PTSD and 934 controls) were adults. Inclusion and exclusion criteria for each site may be found in **Supplementary Table 3**. Harmonized scales of childhood trauma and alcohol use disorder (AUD) were obtained from the sites (see Supplementary Materials). 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 (MRI) scans was performed using FreeSurfer(39) in conjunction with standardized ENIGMA protocols. Our primary analysis was an examination of the average volume of 8 subcortical regions adjusting for age, sex, and 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, sex, ICV, and scanner for sites with multiple scanner types.

Details on scanners and acquisition parameters are provided in **Supplementary Table 4**. 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 x 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 where significance exceeds Bonferroni correction for the number of volumes examined (0.05/8=0.0063 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 Supplementary Materials), separate analyses of males and females, and separate meta-analyses of adult (non-pediatric), 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, sex, and ICV are presented in **Figure 1** and **Table 1,** while the results of PTSD on ICV are presented in **Supplementary Table 5**. The hippocampus and amygdala were, on average, smaller in subjects with current PTSD (hippocampus: D=-0.17,*p*=0.00054; amygdala: D=-0.11,*p*=0.025). The hippocampus finding surpassed the corrected significance threshold (*p*<0.0063), 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=-.15,p=0.013), but not amygdala volume (D=-0.087,p=0.13).

A formal test of a differential effect of PTSD between hemispheres was non-significant for all of the examined regions. Our a-priori specified separate analyses of left and right subcortical volumes (after adjusting for age, sex, and ICV) are presented in **Figure 1** and **Supplementary Table 6.** Male and female effect size estimates had overlapping confidence intervals supporting this lack of differential effect by hemisphere. The association between PTSD and hippocampal volume was evident in both hemispheres (*p*<0.005, in each). For the amygdala, the association with PTSD was borderline in the right amygdala, passing *p*<0.05, but not the Bonferroni-corrected threshold (right amygdala: D=-0.12,*p*=0.017; left amygdala: D=-0.075,*p*=0.13). In addition, the volume of the left (but not

right, nor total volume) lateral ventricle was positively associated with PTSD at nominal significance levels (D=0.10,*p*=0.036).

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 **Supplementary Tables 7-10** present the results of male and female stratified meta-analyses and separate analyses of the adult (non-pediatric), military, and civilian samples. No significant difference in effect size was observed in the analysis of a sex by PTSD interaction term (*p*=0.38) on hippocampal volume or from the meta-regression of the proportion of women in each sample as predicting the effect size estimates (*p*=0.14). 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 non-significant in the male-only and military analyses. Even though the female-only analysis contained approximately 1,100 fewer subjects than the full sample, the hippocampal results were more significant in females (Table 2;*p*=0.00012), 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*=0.0032) vs. military (D=-0.11,*p*=0.11) samples. This is perhaps unsurprising given the confound between variables representing sex and military status (see Supplementary Table 1). These differences may relate more strongly to sex than military status: the effect size in military women (D=-0.23,*p*=0.34,n=88), while non-significant, was stronger (more negative) than in the overall meta-analysis estimate (D=-0.17), and the effect in civilian males (D=-

0.025,*p*=0.87) 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 sex was non-significant. 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=0.031), but the analysis of PTSD severity and amygdala volume was not (D=-0.12,p=0.20).

Potential Confounding Variables

Finally, we examined the relationship between hippocampal and amygdala volume and confounding variables including alcohol use disorder (AUD) and childhood trauma. In a linear model adjusting for age, sex, and ICV, we found AUD was not associated with hippocampal volume whether or not PTSD was included as a covariate (without PTSD: *p*=0.12; with PTSD: *p*=0.25). Childhood trauma was negatively associated with hippocampal volume in a model adjusting for age, sex, and ICV (D=-0.17,*p*=0.0031), but was not significant if PTSD was added as a covariate (D=-0.11,*p*=0.064). 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*=0.036; with PTSD: D=-0.012,*p*=0.048). Similarly, childhood trauma was associated with reduced amygdala volume whether or not PTSD was included as a covariate (without PTSD: D=-0.16,*p*=0.0044; with PTSD: D=-0.13,*p*=0.019). 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*=0.014; with CT: D=-0.14,*p*=0.015). In the subset of subjects with AUD data (n=1,443),

the association between the amygdala and PTSD was not significant whether or not AUD was included (with AUD: p=0.41; without AUD: p=0.21). Similarly, the association between PTSD and amygdala volume was not significant in the subsample with childhood trauma data (n=1,423) whether or not the adjustment for childhood trauma was included (with: p=0.33; without: p=0.11). 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 to PTSD cases with no childhood trauma (for hippocampus n=513,D=-0.17,p=0.088; for amygdala n=513,D=-0.20,p=0.053). In an analysis of female PTSD cases, effect size estimates for both hippocampus and 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=0.096; for amygdala n=102,D=-0.46,p=0.28).

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 within women (all p>0.19).

DISCUSSION

In the largest study of neuroimaging and PTSD to date, our multi-site 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 sub-cohorts. 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 non-significant or contradictory findings. We also observed associations between PTSD and the left lateral ventricle in the full meta-analysis, the volume of the accumbens in females, 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 females) and the amygdala (D=-0.11) are within the range of associations observed by other groups using the ENIGMA protocols to study MDD,(32) bipolar disorder,(33) OCD,(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 MRI 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 controls without PTSD relative to trauma-unexposed controls(46,47). In contrast, other MRI studies did not detect group differences between trauma-exposed and healthy controls(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, their 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 BLA showed a stronger conditioned fear response and corticosterone response to stress than mice strains with a large BLA(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).

Sex Differences

PTSD is more prevalent in females than in males(55). Our results show that the PTSD association with smaller hippocampal volume was primarily due to a strong negative association in females. However, we were unable to conclusively demonstrate a larger effect size in females compared to males, because the PTSD by sex interaction term was not

significant. There are several potential reasons for the observed strong effect in women apart from a true differential effect by sex. 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 males and females may play a role in the observed differential effect. Information on mean age, PTSD severity, depression severity, alcohol use disorders, and childhood trauma broken down by site and sex are presented in **Supplementary Tables 12-18**. Future studies should include both males and females when possible to better assess sex 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 Alcohol Use Disorder (AUD)

AUD was not associated with hippocampal volume, and hippocampal results remained significant after controlling for alcohol. Our finding supports other studies that show hippocampal differences persist(13,48) or show bilateral effects(50) after controlling for lifetime alcohol (ab)use, 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 may 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 multi-site consortium study and the largest meta-analysis of subcortical structures in PTSD to date, the inclusion of additional cohorts with specific characteristics more detailed clinical information across cohorts will be needed to evaluate the role of stratifying factors such as age, sex, and type of trauma. For example, we only had one non-adult (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 non-adult 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 non-military 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

even potentially 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 most powerful study of subcortical volumes in PTSD to date.

Conclusion

The PGC-ENIGMA 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 and colleagues 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 alcohol use disorder. 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 PGC-ENIGMA 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.

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FIGURES

Figure 1: Cohen's D estimate of the association between PTSD and subcortical brain volumes and confidence intervals on effect size.

Included is a primary analysis adjusted for age, sex, and ICV and follow-up analyses with left and right volumes analyzed separately. A "+" indicates that the comparison of PTSD cases – controls was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

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 PTSD.

For detailed descriptions and full names of participating sites see Supplementary Tables 1-3. Adult meta-analysis includes all sites but U of Washington. Military meta-analysis includes DoD ADNI, Duke/Durham VA, TRACTS, UMC Utrecht, and West Haven VA. The Civilian meta-analyses includes AMC Amsterdam, Cape Town, Emory GTP, McLean, UNSW, U of Sydney, U Michigan, VUMC Amsterdam, Western Ontario, and Yale studies.

Figure 3: Cohen's D estimate of the association between PTSD and subcortical brain volumes and confidence intervals on effect size for subsets of the data.

Included are analyses of males and females analyzed separately, as well as all adult samples (non-pediatric), military, and civilian datasets meta-analyzed separately. A "+" indicates that the comparison of PTSD cases – controls was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

TABLES

Table 1: Meta-analysis of the effect of PTSD (PTSD-Control) on subcortical region volumes across 16 datasets adjusting for age, sex, and ICV.

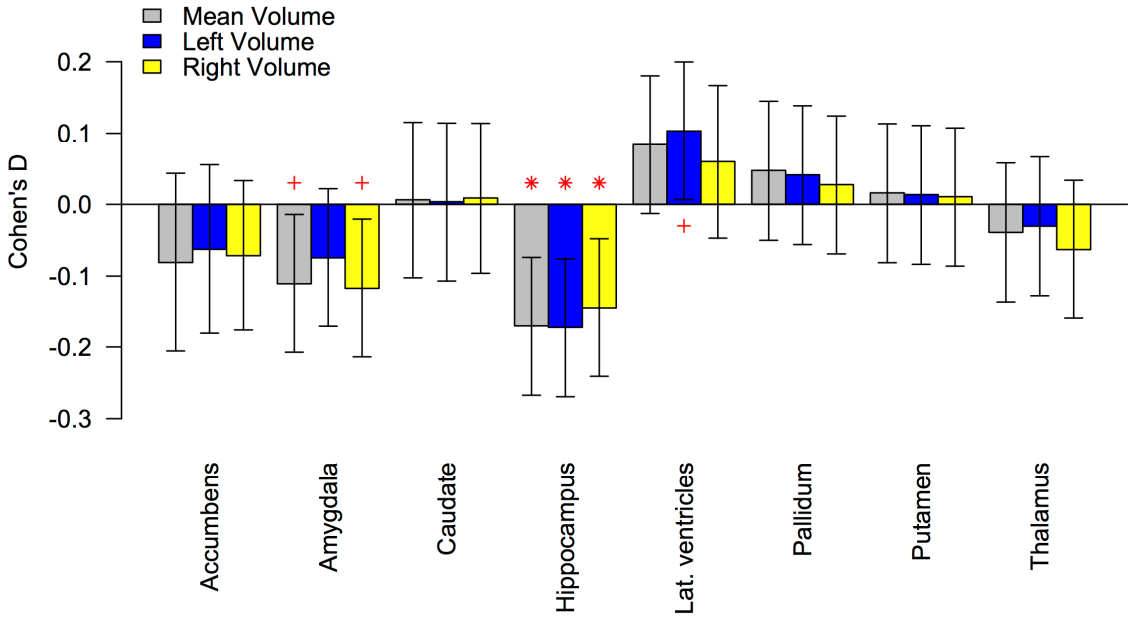
Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls	n Males/ Females	n Military/ Civilian	n Pediatric/ Adult
Accumbens	-0.081 (-0.206,0.043)	0.064	0.20	-1.21%	33.13	0.080	778	1,061	1,105/ 734	836/ 1,003	161/ 1,678
Amygdala	-0.11 (-0.207,-0.014)	0.049	**0.025 +**	-1.11%	0.00	0.36	780	1,061	1,105/ 736	836/ 1,005	161/ 1,680
Caudate	0.0064 (-0.102,0.115)	0.056	0.91	0.13%	16.38	0.28	780	1,063	1,105/ 738	836/ 1,007	161/ 1,682
Hippocampus	-0.17 (-0.267,-0.074)	0.049	**0.00054***	-1.50%	0.00	0.74	780	1,062	1,104/ 738	835/ 1,007	161/ 1,681
Lat ventricle	0.084 (-0.013,0.180)	0.049	0.089	3.75%	0.00	0.48	781	1,064	1,105/ 740	836/ 1,009	161/ 1,684
Pallidum	0.047 (-0.050,0.145)	0.050	0.34	0.82%	0.00	0.10	766	1,048	1,105/ 709	836/ 978	161/ 1,653
Putamen	0.016 (-0.081,0.113)	0.050	0.75	0.18%	0.00	0.76	764	1,050	1,105/ 709	836/ 978	161/ 1,653
Thalamus	-0.039 (-0.136,0.058)	0.050	0.43	-0.33%	0.00	0.56	772	1,053	1,105/ 720	836/ 989	161/ 1,664

Abbreviations: lat, lateral.. CI, Confidence intervals; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; I^2, the estimated proportion of variance due to sample heterogeneity; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$). The n military and civilian represents the number of subjects from military and civilian cohorts. Civilian cohort members were not screened for military service.

Table 2: Female-only meta-analysis the effect of PTSD (PTSD-Control) on subcortical-region volumes adjusting for age and ICV.

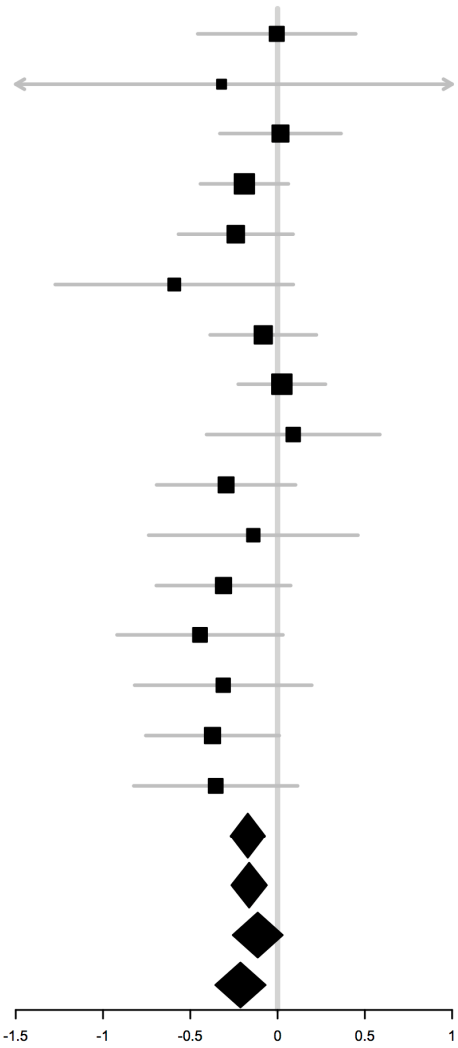
Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
Accumbens	-0.22 (-0.39,-0.061)	0.083	**0.0071+**	-2.32%	1.50	0.16	305	427
Amygdala	-0.14 (-0.30,0.015)	0.081	0.075	-1.46%	0.0047	0.18	307	427
Caudate	0.008 (-0.15,0.17)	0.081	0.92	0.19%	0.00	0.67	307	429
Hippocampus	-0.31 (-0.47,-0.15)	0.081	**0.00012***	-2.42%	0.00	0.90	308	428
Lat ventricle	0.081 (-0.077,0.24)	0.081	0.32	3.49%	0.00	0.87	308	430
Pallidum	0.10 (-0.12,0.32)	0.11	0.39	1.13%	35.30	0.068	293	414
Putamen	-0.051 (-0.21,0.11)	0.083	0.54	-0.49%	0.0064	0.60	291	416
Thalamus	-0.13 (-0.32,0.073)	0.10	0.22	-0.84%	23.74	0.12	299	419

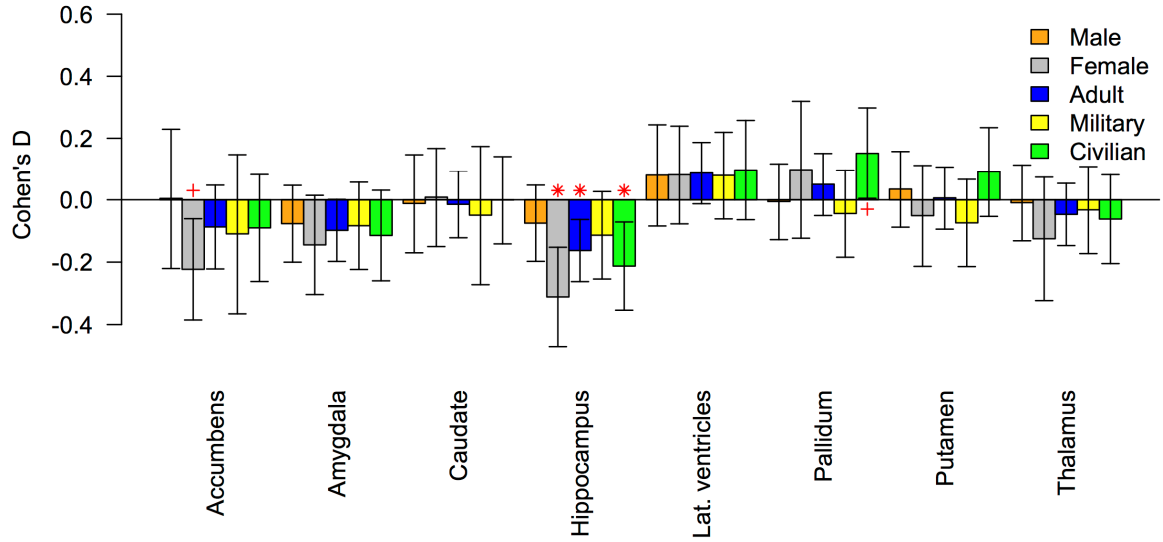
Abbreviations: Lat, lateral; CI, Confidence intervals; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; I^2, the estimated proportion of variance due to sample heterogeneity; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).



Hippocampus

Study	D	SE
AMC Amsterdam	0	0.23
Cape Town	-0.32	1.01
DoD ADNI	0.02	0.18
Duke/Durham VA	-0.19	0.13
Emory GTP	-0.24	0.17
McLean	-0.59	0.35
UNSW	-0.08	0.16
TRACTS	0.02	0.13
U of Sydney	0.09	0.25
U of Washington	-0.29	0.2
U Michigan	-0.14	0.31
UMC Utrecht	-0.31	0.2
VUMC Amsterdam	-0.44	0.24
West Haven VA	-0.31	0.26
Western Ontario	-0.37	0.19
Yale	-0.35	0.24
All	**-0.17**	**0.05**
Adult	**-0.16**	**0.05**
Military	**-0.11**	**0.07**
Civilian	**-0.21**	**0.07**





Smaller Hippocampal Volume in Posttraumatic Stress Disorder: A Multi-Site ENIGMA-PGC Study

Supplemental Information

Supplementary Methods

Harmonization of Childhood Trauma and Alcohol Use Disorder Variables

Each site recoded childhood trauma information obtained from a variety of instruments, as specified in Supplemental Table S2, according to the number of categories of childhood trauma experienced by each participant rather than the number of events, which is the same harmonization method used by the PGC-PTSD. The recoding process assigned a childhood trauma score of 0 (no childhood trauma exposure), 1 (exposure to a single category of child trauma), or 2 (exposure to two or more categories of childhood trauma). Each site recoded alcohol use disorder information obtained from a variety of instruments, as specified in Supplemental Table S2, according to the coding system implemented in the SCID of 0 (no symptoms), 2 (subthreshold symptoms), or 3 (meets diagnostic criteria).

Image Processing and Analysis

Each site acquired structural T1-weighted MRI scans. Scans were analyzed locally using a uniform processing pipeline established by the ENIGMA consortium (http://enigma.ini.usc.edu/protocols/imaging-protocols/) that is based on subcortical segmentation by FreeSurfer (1). Image acquisition parameters and software descriptions for each sample are given in Supplementary Table S4. The segmentation of seven subcortical gray matter regions, lateral ventricles and total ICV were visually inspected for accuracy following ENIGMA protocols. These protocols enabled quality control and image analysis procedures that are consistent and uniform across sites and have been successfully implemented in published reports by working groups for other psychiatric disorders (2-5) and

throughout the ENIGMA consortium to find genetic variants associated with subcortical volume (6).

Image QC

Image segmentation was examined by a neuroimaging expert at each site by overlaying the segmentation label of each structure on the T1-weighted brain scan. Furthermore, we collected study-wide statistics (means and standard deviations) as well as histogram plots in order to identify non-normally distributed data and major outliers defined statistically as volume > 2.698 standard deviations from the global mean. For each subject that was marked as a statistical outlier, individual sites were asked to re-inspect the subject's segmentation to verify that the structure was properly segmented. Statistical outliers that were deemed to be properly segmented were kept in the analysis. Otherwise the subject was removed.

Statistical Methods

Analyses were performed using the R statistical computing package (7). Within each dataset, linear models of average subcortical volumes were fit as a function of current PTSD status adjusting for age, sex, and ICV using the *lm* function in R. For sites with multiple scanners, analyses included a categorical scanner covariate as well (dummy coded for n-1 scanners). An additional model was run for ICV as a response adjusting for age and sex. Follow-up analyses also included an examination of L/R volumes separately. Cohen's D and the SEs for Cohen's D were computed from the t-statistics for individual coefficients using the methods described in Nakagawa and Cuthill 2007 (8). The adjusted Cohen's D (sometimes called Hedge's G), which includes a correction for small sample size was used. The effect-size estimates from each site were meta-analyzed using an inverse-variance weighted random-effects method using the *rma* function from the R *metafor* package (9). In addition to effect sizes, we report the percentage difference ($\%_{diff}$), which is 100 times the estimated volume difference (PTSD cases – controls) divided by the meta-analysis estimated mean volume in controls. For each meta-analysis we also report the p-value of a test

for heterogeneity (p_{het}) and the estimated percentage of variance due to sample heterogeneity (I^2). We explored the possibility of heterogeneity of effect using meta-regression. Meta-regression tests whether effect size estimates across samples vary as a function of a dataset-level summary statistic. We tested for heterogeneity of effect for PTSD as a function of the average age of the sample, proportion of females in the sample, mean level of childhood trauma exposure in the sample, average level of alcohol use/abuse in the sample, scanner strength, and the FreeSurfer version. Follow-up analyses included separate meta-analyses of adult (non-pediatric) samples, military only meta-analyses, and civilian (non-pediatric) meta-analyses. Because this is a prospective rather than a retrospective analysis of published summary statistics, we had access to the individual-level summary data. Hence, we were able to perform meta-analyses of men and women separately and test the significance of a PTSD X sex interaction computed via a meta-analysis of the interaction terms estimated in datasets containing both men and women. The potential role of alcohol use and childhood trauma as confounders were examined in two ways, first by estimating the effects of PTSD in a model which included them as covariates. Second, we performed meta-analyses of the effects of childhood trauma and alcohol as predictors both with and without PTSD as a covariate. Plots were generated using the *boxplot* function in R and the *forestplot* package (10).

Supplementary Results

Meta-regression

We examined potential heterogeneity in a meta-regression including average age, alcohol, proportion of women, field-strength of scanner, FreeSurfer version, and military or civilian status of the sample. The results are presented in Supplementary Table S11. Alcohol was associated with the effect size estimates for the caudate (p=0.011). No other meta-regression moderator analyses were significant.

Supplementary Tables

Supplementary Table S1: Sample characteristics

Country	Site	N	PTSD/control	Age (average, SD, range)	M/F	Population type	Sites
Netherlands	AMC Amsterdam	75	38/37	39.99, 9.90, 22-59	40/35	Police officers	1
South Africa	Cape Town	49	1/48	28.21, 5.78, 20-42	0/48	Civilian	1
USA	DoD ADNI	129	60/69	69.12, 4.66, 61-83	128/1	Military	20
USA	Duke/Durham VA	284	88/196	39.58, 10.18, 21-67	232/52	Military	3
USA	Emory GTP	153	58/95	39.84, 12.58, 18-62	4/149	Civilian	1
USA	McLean	42	30/12	37.38, 12.96, 19-62	0/42	Civilian	1
Australia	UNSW	165	82/84	40.23, 12.63, 18-69	65/101	Civilian	1
USA	TRACTS	248	135/113	31.87, 8.43, 19-58	223/25	Military	1
Australia	U of Sydney	64	27/37	36.25, 8.79, 17-49	34/30	Civilian	1
USA	U of Washington	161	30/131	14.94, 2.78, 8-20	74/87	Civilian	3
USA	U of Michigan	46	17/29	26.76, 4.93, 19-41	46/0	Military and civilian	3
Netherlands	UMC Utrecht	106	53/53	36.32, 9.88, 21-57	105/1	Military	1
Netherlands	VUMC Amsterdam	72	37/35	35.32, 10.38, 17-57	0/72	Civilian	1
USA	West Haven VA	73	23/50	30.17, 7.86, 20-52	59/11	Military	1
Canada	Western Ontario	111	66/45	35.89, 12.52, 18-60	33/78	Civilian	1
USA	Yale	71	37/34	34.49, 9.46, 21-60	63/8	Military	1

Supplementary Table S2: Clinical measures

Site	% reporting childhood trauma	Childhood Trauma scale used	Control Type	PTSD scale used	Severity	% reporting Alcohol Use Disorders	Alcohol scale used
AMC Amsterdam	94.7%	Early Trauma Inventory	Trauma-exposed	CAPS		5.3%	AUDIT
Cape Town	62.8%	CTQ	Trauma-exposed	CAPS		17.0%	ASSIST
DoD ADNI	NA	none	Trauma-exposed	CAPS		39.8%	SCID
Duke/Durham VA	37.3%	CTQ	Trauma-exposed	CAPS/SCID		12.3%	AUDIT
Emory GTP	52.3%	CTQ	Trauma-exposed	CAPS/PSS		32.0%	AUDIT
McLean	78.6%	CTQ/TEI	Both trauma-exposed and non-exposed	CAPS		20.0%	SCID
UNSW	66.1%	CTQ	Trauma-exposed	CAPS		23.0%	MINI
TRACTS	32.1%	TLEQ	Trauma-exposed				
U of Sydney	NA	none	Trauma-exposed	CAPS		NA	none
U of Washington	37.3%	CTQ	Non-exposed	DISC, CAPS, UCLA PTSD Index		NA (pediatric)	none
U of Michigan	NA	none	Both trauma-exposed and non-exposed	CAPS		NA	none
UMC Utrecht	39.5%	Early Trauma Inventory	Both trauma-exposed and non-exposed	CAPS		3.8%	SCID
VUMC Amsterdam	51.4%	STI	Non-exposed	CAPS		11.8%	SCID
West Haven VA	NA	CTQ	Trauma-exposed	CAPS		NA	none
Western Ontario	61.3%	CTQ	Non-exposed	CAPS		NA	none
Yale	NA	none	Trauma-exposed	CAPS		NA	none

Abbreviations: CTQ, Childhood Trauma Questionnaire; TEI, Traumatic Events Inventory; TLEQ, Traumatic Life Events Questionnaire; STI, Structure Trauma Interview; CAPS, Clinician Administered PTSD Scale; DISC, Diagnostic Interview Schedule for Children; AUDIT, Alcohol Use Disorders Identification Test; SCID, Structured Clinical Interview for DSM; MINI, Mini International Neuropsychiatric Interview.

Supplementary Table S3: Inclusion and exclusion criteria

Site	Inclusion criteria	Exclusion criteria
AMC Amsterdam	All: 18-65 years of age, police officers, eligible for MRI. PTSD: current PTSD diagnosis, with CAPS ≥ 45. Controls: exposure to at least one traumatic event (according to DSM-IV A1 criterion), with CAPS < 15	All: history of neurological disorders, any severe or chronic systemic disease or unstable medical condition (including endocrinological disorders), use of psychotropic medications. Females: pregnancy or breastfeeding. PTSD: current psychotic disorder, substance-related disorder, severe personality disorder, severe major depressive disorder (MDD) (i.e., involving high suicidal risk and/or psychotic symptoms) or current suicidal risk. Controls: any current Axis-1 disorder and lifetime history of PTSD or MDD
Cape Town	Between 18 and 65 years, speak English, Afrikaans or Xhosa	Mental retardation, critical medical condition, current psychotic episode/disorder, contraindications for MRI (e.g. metal objects in body, pace makers)
DoD ADNI	*PTSD*: Subjects must be Veterans of the Vietnam War, 50-90 years of age. Subjects who meet the SCID-I (for DSM-IV-TR) criteria for current/chronic PTSD (identified by records, and verified by our telephone assessments). In addition to meeting DSM-IV-TR criteria for current/chronic PTSD, subjects must have a minimum current CAPS score of 50 as determined by telephone assessment. The PTSD symptoms contributing to the PTSD Diagnosis and Current CAPS score must be related to a Vietnam War related trauma. Must live within 150 miles of the closest ADNI clinic in subject's area. *Control:* Subjects must be Veterans of the Vietnam War, 50-90 years of age. Comparable in age, gender, and education with TBI and PTSD groups May be receiving VA disability payments for something other than TBI or PTSD – or no disability at all. Must live within 150 miles of the closest ADNI clinic in subject's area	*PTSD*: Mild Cognitive Impairment/Dementia Documented or self report history of mild/moderate severe TBI Any history of head trauma associated with injury onset cognitive complaints, or Loss of consciousness for >5minutes. Control: MCI/Dementia Presence of PTSD by SCID-I for DSM-IV-TR criteria, or a CAPS score of >30 (Both current and/or a history of PTSD will be excluded). Documented or self report history of mild/moderate severe TBI Any history of head trauma associated with injury onset cognitive complaints, or Loss of Consciousness for >5 minutes History of PTSD or current PTSD Exclusionary criteria applied to TBI/PTSD will be applied to controls. ALL: MCI/dementia History of psychosis or bipolar affective disorder; History of alcohol or substance abuse/dependence within the past 5 years (by DSM IV – TR criteria); MRI-related exclusions: aneurysm clips, metal implants that are determined to be unsafe for MRI; and/or claustrophobia; Contraindications for lumbar puncture, PET scan, or other procedures in this study; Any major medical condition must be stable for at least 4 months prior to enrollment. These include but are not limited to clinically significant hepatic, renal, pulmonary, metabolic or endocrine disease, cancer, HIV infection and AIDS, as well as cardiovascular disease. Seizure disorder or any systemic illness affecting brain function during the past 5 years will be exclusionary Clinical evidence of stroke. Have a history of relevant severe drug allergy or hypersensitivity. Subjects with current clinically significant unstable medical comorbidities, as indicated by history or physical exam, that pose a potential safety risk to the subject.
Duke/Durham VA	18-65, OEF/OIF veterans, fluent in English, free of implanted metal objects or metal shards in eyes, antidepressant, sleep, and anti-anxiety medication permitted	Axis I other than PTSD or MDD, current substance abuse or lifetime substance dependence (other than nicotine), high risk for suicide, claustrophobia, neurological disorders, learning disability or developmental delay, major medical conditions
Emory GTP	18-65 years of age, endorsed at least 1 criterion A trauma, English-speaking	Current psychotic symptoms or bipolar disorder, current substance or alcohol dependence, history of head trauma, taking any psychoactive medication, current illegal drug use (verified with urine drug screen within 24 hours of scan)
McLean	History of childhood maltreatment; Legal and mental competency of the patient; Female; All ethnic backgrounds; Age between 18 and 60; Fluent English speakers; Normal or Corrected Vision	Male; Under 18 or over 60; Delirium secondary to medical illness; History of neurological conditions that may cause significant psychiatric symptomatology (e.g., dementia); Any contraindication to MR scans, including claustrophobia, pregnancy, metal implants, etc.; Current alcohol or substance use disorder (within the last month); A history of schizophrenia or

Site	Inclusion criteria	Exclusion criteria
		other psychotic disorder; History of head injury or loss of consciousness for longer than 5 min (including concussion); Positive pregnancy test
UNSW	18-60 years	Neurological disorders, under 18; over 60; traumatic brain injury; psychosis
TRACTS	1. Veteran of OEF/OIF/OND (deployed at least one time to either Afghanistan or Iraq) or 2. Active duty Service Member (SM) not yet deployed to OEF/OIF/OND. Age 18-65 years.	History of neurological illness (Huntington's, Parkinson's, dementia, MS, etc). History of Seizure Disorders, unrelated to head injury(ies). Current diagnosis of schizophrenia spectrum or other psychotic disorders (not related to PTSD). Current diagnosis of bipolar or related disorders (not related to PTSD). Current active homicidal and/or suicidal ideation with intent requiring crisis intervention. Cognitive disorder due to general medical condition other than TBI. Unstable psychological diagnosis that would interfere with accurate data collection, determined by consensus of at least two doctorate-level psychologists. Also, MRI contra-indications for MRI including metallic implants or foreign objects deemed unsafe by the MRI technician (such as but not limited to pace-maker, shrapnel, metallic screws). Surgery in the past 2 months except as approved by the MRI technician (such as but not limited to dental work, colonoscopy). Weight exceeding the capacity of the scanner table.
U of Sydney	18-65 years of age, endorsed at least 1 criterion A trauma, English-speaking	History of neurological illness (Huntington's, Parkinson's, dementia, MS, etc). History of Seizure Disorders, unrelated to head injury(ies). Current diagnosis of schizophrenia spectrum or other psychotic disorders (not related to PTSD). Current diagnosis of bipolar or related disorders (not related to PTSD). Current active homicidal and/or suicidal ideation with intent requiring crisis intervention. Cognitive disorder due to general medical condition other than TBI. Unstable psychological diagnosis that would interfere with accurate data collection, determined by consensus of at least two doctorate-level psychologists. Also, MRI contra-indications for MRI including metallic implants or foreign objects deemed unsafe by the MRI technician (such as but not limited to pace-maker, shrapnel, metallic screws). Surgery in the past 2 months except as approved by the MRI technician (such as but not limited to dental work, colonoscopy). Weight exceeding the capacity of the scanner table.
U of Washington	Aged 8-20	Psychiatric medication use (excepting stimulant meds for ADHD), braces, claustrophobia, active substance dependence, pervasive developmental disorder, non-english speaking, active safety concerns.
U of Michigan	All: 18-55 years of age, combat veterans and civilians, eligible for MRI. PTSD: current PTSD diagnosis, with CAPS ≥ 50. Trauma controls: exposure to at least one traumatic event (according to DSM-IV A1 criterion), with CAPS < 15, Community Controls, CAPS < 15	All: history of neurological disorders, any severe or chronic disorder, alcohol or drug abuse and/or dependence during course of the study.
UMC Utrecht	All: 18-60 years of age, eligible for MRI. PTSD: current PTSD diagnosis, with CAPS ≥ 45, military deployment >4 months. Trauma controls: exposure to at least one traumatic event (according to DSM-IV A1 criterion), with CAPS < 15, no current psychiatric disorder, military deployment >4 months; healthy controls: no current psychiatric disorder according to DSM-IV.	All: history of neurological disorders, any severe or chronic disorder, alcohol or drug abuse and/or dependence during course of the study.

Site	Inclusion criteria	Exclusion criteria
VUMC Amsterdam	18-65	Antisoc. pers. disorder, DID, recurrent psychoses, current drug abuse or dependence, medication other than stable SSRIs or infrequent benzodiazepine use
West Haven VA	Combat-exposed Veterans with PTSD and 21 age-matched male combat-exposed healthy controls (combat controls; CC). All participants had been deployed on one or more tours to Iraq and/or Afghanistan and reported exposure to combat-related experiences. All participants were 18 to 50 years of age.	Participants were excluded based on moderate and severe TBI, neurological disorder, and MRI contraindications. Participants with PTSD were also excluded on the basis of a diagnosis of current drug/alcohol abuse, recent change in antidepressant medications (stable dose for 4-weeks required).
Western Ontario	Primary diagnosis PTSD	Psychotic disorder, bipolar disorder, traumatic brain injury, narcotic use, active substance use disorder within 3 months of study entry
Yale	Participants ranged in age from 21 to 60, and had been deployed on one or more combat tours.	Individuals were excluded from the study if they met any of the following criteria: a diagnosis of bipolar disorder or psychotic disorder, as assessed by the SCID-IV (First, Spitzer, Gibbon, & Williams, 2002); current benzodiazepine use; a history of ADHD, learning disorder, moderate or severe traumatic brain injury (TBI), brain tumor, epilepsy, or a neurological disorder; current inpatient status; or an MRI contraindication.

Supplementary Table S4: Scanner characteristics and parameters

site	scanner manufacturer	scanner model/series	number of channels in head coil	acquisition sequence	voxel size (mm)	FOV (mm)	acquisition orientation	TR (ms)	TE (ms)	flip angle	slice thickness	FreeSurfer version
AMC Amsterdam	Philips	Achieva	32-channel	FAST MPRage sequence	1x1x1	240x188	Axial	8200	3.8	8	1	5
Cape Town	Siemens	Magnetom Allegra	4-channel	MPRAGE	1x1x1.5	256x256	Sagittal	2000	1.53x3.21x4.89x6.57	20	1.5	5.3
DoD ADNI	GE	Signa HDxt; Discovery MR750; Discovery MR750w	8-channel (mostly); 24; 50	SPGR; FSPGR	1x1x1.2	256x256	Sagittal	6.98; 7.34; 7.65	2.8; 3.0; 3.1	11	1.2	5.3
Duke/Durham VA	GE; Philips; Siemens	EXCITE; MR750; Ingenia	8-channel quadrature	FSPGR; sT1W_3D_TFE	1x1x1; 0.9375x0.9375x1	256x256	Axial; Oblique Axial	7484; 8173	2.984; 3.739	12; 8	1; 1	5.3
Emory GTP	Siemens	Tim Trio	12-channel	MPRAGE	1x1x1	224x256	Sagittal	2600	3.02	8	1	5.3
McLean	Siemens	TIM Trio	12-channel	MEMPRAGE	1x1x1	256x256	Sagittal	2530	1.64; 3.5; 5.36; 7.22	7	1	5.3
UNSW	GE	Signa HDx	8-channel	3D SPGR	1x1x1mm	256x256	Sagittal	8.3	3.2	11	1	4.3
TRACTS	Siemens	Tim Trio	12-channel	3D MPRAGE	1x1x1	256x256	Sagittal	2530	3.32	7	1	5.1
U of Sydney	GE	MR750	8-channel	3D	0.9x.0.9x0.9	256x256	Sagittal	7256	2.776	12	0.9	5.1
U of Washington	Siemens; Philips	Tim Trio; Achieva	32-channel	MEMPRAGE; MPRAGE	1x1x1	220x220; 256x256	Sagittal	2530; 7.6	1.6-7; 3.5	7	1	5.3
U of Michigan	Philips	Achieva 3.0T X-series	8-channel sensitivity-encoding (SENSE) parallel-imaging head coil	SPGR	1x1x1mm	256x256	Sagittal	9800	4.6	8	1	5.1

site	scanner manufacturer	scanner model/series	number of channels in head coil	acquisition sequence	voxel size (mm)	FOV (mm)	acquisition orientation	TR (ms)	TE (ms)	flip angle	slice thickness	FreeSurfer version
UMC Utrecht	Philips	Achieva	8-channel sensitivity-encoding (SENSE) parallel-imaging head coil	3D FAST Echo Field sequence	0.8x0.748 0.748	240x240	Sagittal	10	3.8	8	0.748	5.1
VUMC Amsterdam	Siemens	1.5 T Sonata MR System	8-channel	MPRAGE	1x1x1.5	256x256	Coronal	2700	4.0	8	1.5	5.3
West Haven VA	Siemens	Tim Trio	12-channel	MPRAGE	1x1x1	256x256	Sagittal	2500	2.77	7	1	5.3
Western Ontario	Siemens	Magnetom Allegra	32-channel phased array	MPRAGE	1x1x1	256x240	Sagittal	2300	2.98	9	1	5.3
Yale	Siemens	Tim Trio	32-channel	MPRAGE	1x1x1	256x256	Sagittal	2530	2.71	7	1	5.2

Supplementary Table S5: Meta-analysis of the effect of PTSD (PTSD-Control) on the ICV and 8 subcortical-region volumes adjusting for age and sex

Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
ICV	-0.15 (-0.27,-0.03)	0.061	**0.013**	-1.51%	28.71	0.14	781	1,065
Accumbens	-0.11 (-0.22, 0.010)	0.059	0.075	-1.64%	24.07	0.14	778	1,061
Amygdala	-0.16 (-0.28,-0.047)	0.059	**0.0058***	-1.84%	23.66	0.055	780	1,061
Caudate	-0.067 (-0.19,0.051)	0.060	0.27	-0.72%	27.36	0.16	780	1,063
Hippocampus	-0.22 (-0.33,-0.12)	0.055	**0.000048***	-2.16%	13.66	0.35	780	1,062
Lat ventricle	0.026 (-0.070,0.12)	0.049	0.59	1.68%	0.00	0.64	781	1,064
Pallidum	-0.0017 (-0.099,0.096)	0.050	0.97	0.11%	0.0084	0.28	766	1,048
Putamen	-0.038 (-0.14,0.059)	0.050	0.44	-0.36%	0.00	0.69	764	1,050
Thalamus	-0.11 (-0.23,-0.00012)	0.058	**0.0498+**	-1.14%	20.15	0.11	772	1,053

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S6: Meta-analysis of the effect of PTSD (PTSD-Control) on the left and right volumes of 8 subcortical regions adjusted for age, sex, and ICV

	Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
Left	**Accumbens**	-0.063 (-0.18,0.055)	0.060	0.30	-1.15%	26.70	0.12	778	1,061
	Amygdala	-0.075 (-0.17,0.022)	0.049	0.13	-0.77%	0.0085	0.42	781	1,064
	Caudate	0.004 (-0.11,0.11)	0.056	0.95	0.081%	18.53	0.28	781	1,063
	Hippocampus	-0.17 (-0.27,-0.076)	0.049	**0.00046***	-1.64%	0.00	0.60	780	1,062
	Lat ventricle	0.10 (0.0068,0.20)	0.049	**0.036+**	4.87%	0.00	0.82	781	1,065
	Pallidum	0.041 (-0.056,0.14)	0.050	0.41	0.53%	0.023	0.11	768	1,052
	Putamen	0.014 (-0.084,0.11)	0.050	0.78	0.15%	0.00	0.86	766	1,051
	Thalamus	-0.030 (-0.13,0.067)	0.049	0.54	-0.20%	0.00	0.58	772	1,055
Right	**Accumbens**	-0.072 (-0.18,0.033)	0.053	0.18	-1.16%	11.23	0.35	781	1,064
	Amygdala	-0.12 (-0.21,-0.021)	0.049	**0.017+**	-1.30%	0.00025	0.56	780	1,062
	Caudate	0.0089 (-0.10,0.11)	0.054	0.87	0.17%	11.65	0.32	780	1,065
	Hippocampus	-0.14 (-0.24,-0.048)	0.049	**0.0033***	-1.33%	0.00	0.91	781	1,065
	Lat ventricle	0.060 (-0.047,0.17)	0.055	0.27	2.90%	13.95	0.20	781	1,064
	Pallidum	0.028 (-0.069,0.12)	0.049	0.58	0.40%	0.00	0.57	779	1,059
	Putamen	0.011 (-0.086,0.11)	0.049	0.83	0.12%	0.00	0.62	775	1,059
	Thalamus	-0.063 (-0.16,0.034)	0.049	0.20	-0.55%	0.00	0.66	779	1,058

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S7: Male-only meta-analysis of the effect of PTSD (PTSD-Control) on subcortical-region volumes for PTSD adjusting for age and ICV

Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
Accumbens	0.0043 (-0.22,0.23)	0.11	0.97	0.09%	65.59	**0.0023***	472	629
Amygdala	-0.077 (-0.20, 0.047)	0.063	0.22	-0.82%	1.06	0.45	472	629
Caudate	-0.012 (-0.17,0.15)	0.081	0.88	-0.11%	32.37	0.15	472	629
Hippocampus	-0.075 (-0.20,0.047)	0.062	0.23	-0.66%	0.000069	0.46	471	629
Lat ventricle	0.080 (-0.084,0.24)	0.084	0.34	3.47%	36.06	0.062	472	629
Pallidum	-0.0056 (-0.13,0.12)	0.062	0.93	-0.020%	0.008	0.62	472	629
Putamen	0.034 (-0.088,0.16)	0.062	0.58	0.41%	0.012	0.39	472	629
Thalamus	-0.0093 (-0.13,0.11)	0.062	0.88	-0.060%	0.00	0.60	472	629

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S8: Adult-only dataset meta-analysis the effect of PTSD (PTSD-Control) on subcortical-region volumes adjusting for age, sex, and ICV

Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
Accumbens	-0.09 (-0.22,0.047)	0.069	0.20	-1.28%	38.16	0.058	748	930
Amygdala	-0.10 (-0.20,0.0014)	0.051	0.053	-0.99%	0.0039	0.36	750	930
Caudate	-0.015 (-0.12,0.093)	0.055	0.79	-0.065%	10.17	0.38	750	932
Hippocampus	-0.16 (-0.26,-0.063)	0.051	**0.0014***	-1.45%	0.00	0.70	750	931
Lat ventricle	0.087 (-0.013,0.19)	0.051	0.087	3.92%	0.00	0.41	751	933
Pallidum	0.050 (-0.051,0.15)	0.051	0.33	0.89%	0.0018	0.076	736	917
Putamen	0.0061 (-0.094,0.11)	0.051	0.91	0.10%	0.00	0.75	734	919
Thalamus	-0.047 (-0.15,0.053)	0.051	0.36	-0.36%	0.00	0.51	742	922

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S9: Military sample meta-analysis of the effect of PTSD (PTSD-Control) on subcortical-region volumes adjusting for age, sex, and ICV

Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
Accumbens	-0.11 (-0.37,0.15)	0.13	0.40	-1.65%	66.71	**0.027+**	358	478
Amygdala	-0.083 (-0.22,0.057)	0.072	0.24	-0.78%	0.00	0.72	358	478
Caudate	-0.049 (-0.27,0.17)	0.11	0.66	-0.57%	56.22	0.060	358	478
Hippocampus	-0.11 (-0.25,0.027)	0.072	0.11	-1.04%	0.00	0.46	357	478
Lat ventricle	0.079 (-0.061,0.22)	0.072	0.27	3.58%	0.00	0.48	358	478
Pallidum	-0.044 (-0.18,0.10)	0.072	0.54	-0.51%	0.010	0.39	358	478
Putamen	-0.074 (-0.21,0.066)	0.072	0.30	-0.73%	0.00	0.87	358	478
Thalamus	-0.032 (-0.17,0.11)	0.072	0.65	-0.22%	0.011	0.26	358	478

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S10: Civilian sample meta-analysis the effect of PTSD (PTSD-Control) on subcortical-region volumes adjusting for age, sex, and ICV

Region	Cohen's D (95% CI)	SE	P-value	$\%_{diff}$	I^2	P_{het}	n Cases	n Controls
Accumbens	-0.090 (-0.26,0.082)	0.088	0.30	-1.50%	25.98	0.23	390	452
Amygdala	-0.11 (-0.26,0.031)	0.074	0.12	-1.14%	3.78	0.16	392	452
Caudate	-0.00052 (-0.14,0.14)	0.072	0.99	0.017%	0.00	0.76	392	454
Hippocampus	-0.21 (-0.35,-0.071)	0.072	**0.0032***	-1.79%	0.00	0.72	393	453
Lat ventricle	0.10 (-0.064,0.26)	0.082	0.24	4.27%	17.79	0.27	393	455
Pallidum	0.15 (0.0047,0.30)	0.075	**0.043+**	2.13%	2.09	0.11	378	439
Putamen	0.090 (-0.053,0.23)	0.073	0.22	0.83%	0.00	0.70	376	441
Thalamus	-0.062 (-0.20,0.081)	0.073	0.40	-0.49%	0.00	0.56	384	444

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S11: P-values from meta-regression analyses of potential moderators of the PTSD effect size

Region	Mean age	Childhood trauma	% Female	Mean Alcohol	Mean ICV	Military/ Civ	FreeSurfer Version	Scanner Strength
Accumbens	0.72	0.73	0.17	0.26	0.28	0.95	0.91	0.22
Amygdala	0.45	0.10	0.89	0.18	0.64	0.60	0.67	0.49
Caudate	0.082	0.53	0.51	**0.011+**	0.66	0.52	0.28	0.23
Hippocampus	0.28	0.58	0.14	0.077	0.21	0.27	0.46	0.25
Lat ventricle	0.76	0.11	0.71	0.71	0.39	0.93	0.93	0.57
Pallidum	0.80	0.53	0.051	0.76	0.72	0.076	0.33	0.89
Putamen	0.72	0.23	0.64	0.39	0.77	0.080	1.00	0.92
Thalamus	0.59	0.21	0.87	0.88	0.65	0.90	0.39	0.82

Abbreviations: CI, Confidence intervals; Lat, lateral; SE, standard error; % diff, the percentage difference in cases vs. mean volume in controls; P_{het}, p-value from a test of heterogeneity; n number. A "+" indicates that the comparison was significant at the $p<0.05$ level. A "*" indicates that the comparison was significant after a Bonferroni correction for 8 subcortical regions examined ($p<0.0063$).

Supplementary Table S12: Mean age by site and sex

Site	N	Mean	SD	N Males	Mean Males	SD Males	N Females	Mean Females	SD Females	P
AMC Amsterdam	75	39.99	9.90	40	41.73	10.22	35	38.00	9.27	0.10
Cape Town	49	28.21	5.78	0	NA	NA	49	28.21	5.78	NA
DoD ADNI	129	69.12	4.66	128	69.14	4.67	1	66.00	NA	NA
Duke/Durham VA	284	39.58	10.18	232	39.55	10.10	52	39.71	10.61	0.921
Emory GTP	153	39.84	12.58	4	46.00	17.47	149	39.68	12.46	0.523
McLean	42	37.38	12.96	0	NA	NA	42	37.38	12.96	NA
UNSW	166	40.23	12.63	65	42.78	12.18	101	38.59	12.70	0.035
TRACTS	248	31.87	8.43	223	31.58	8.18	25	34.40	10.24	0.19
U Sydney	64	36.25	8.79	34	38.03	9.53	30	34.23	7.54	0.081
U of Washington	161	14.94	2.78	74	14.52	2.84	87	15.30	2.69	0.078
U of Michigan	46	26.76	4.93	46	26.76	4.93	0	NA	NA	NA
UMC Utrecht	106	36.32	9.88	105	36.41	9.88	1	27.00	NA	NA
VUMC Amsterdam	72	35.32	10.38	0	NA	NA	72	35.32	10.38	NA
West Haven VA	70	30.17	7.86	59	31.05	8.10	11	25.45	4.01	0.002
Western Ontario	111	35.89	12.52	33	39.21	11.78	78	34.49	12.63	0.063
Yale	71	34.49	9.46	63	34.76	9.67	8	32.38	7.80	0.45
ALL	1846	36.63	14.79	1105	38.35	15.64	741	34.06	13.02	2.20E-10

Supplementary Table S13: Mean childhood trauma by site and sex

Site	N	Mean	SD	N Males	Mean Males	SD Males	N Females	Mean Females	SD Females	P
AMC Amsterdam	75	1.72	0.56	40	1.78	0.53	35	1.66	0.59	0.37
Cape Town	43	1.12	0.93	0	NA	NA	43	1.12	0.93	NA
DoD ADNI	0	NA	NA	0	NA	NA	0	NA	NA	NA
Duke/Durham VA	284	0.55	0.78	232	0.47	0.73	52	0.92	0.86	0.00068
Emory GTP	153	0.74	0.79	4	0.25	0.50	149	0.75	0.80	0.136
McLean	42	1.57	0.83	0	NA	NA	42	1.57	0.83	NA
UNSW	165	1.16	0.91	65	1.00	0.94	100	1.27	0.87	0.065
TRACTS	246	0.48	0.75	222	0.44	0.73	24	0.83	0.92	0.053
U of Sydney	0	NA	NA	0	NA	NA	0	NA	NA	NA
U of Washington	161	0.58	0.81	74	0.55	0.80	87	0.60	0.83	0.73
U of Michigan	0	NA	NA	0	NA	NA	0	NA	NA	NA
UMC Utrecht	81	0.62	0.83	80	0.63	0.83	1	0.00	NA	NA
VUMC Amsterdam	72	0.86	0.91	0	NA	NA	72	0.86	0.91	NA
West Haven VA	0	NA	NA	0	NA	NA	0	NA	NA	NA
Western Ontario	111	0.00	0.00	33	0.00	0.00	78	0.00	0.00	NA
Yale	0	NA	NA	0	NA	NA	0	NA	NA	NA
ALL	1433	0.72	0.87	750	0.58	0.81	683	0.87	0.90	2.55E-10

Supplementary Table S14: Mean depression severity score by site and sex

Site	N	Mean	SD	N Males	Mean Males	SD Males	N Females	Mean Females	SD Females	P
AMC Amsterdam	73	5.78	5.97	39	6.13	6.23	34	5.38	5.71	0.60
Cape Town	0	NA	NA	0	NA	NA	0	NA	NA	NA
DoD ADNI	128	2.24	2.62	127	2.22	2.62	1	5.00	NA	NA
Duke/Durham VA	282	11.24	11.57	230	11.04	11.09	52	12.15	13.58	0.58
Emory GTP	151	11.79	10.49	4	3.50	3.11	147	12.02	10.53	0.005
McLean	42	22.93	16.28	0	NA	NA	42	22.93	16.28	NA
UNSW	154	6.11	9.30	57	6.02	9.78	97	6.16	9.06	0.93
TRACTS	237	1.60	1.04	215	1.60	1.04	22	1.64	1.09	0.87
U of Sydney	64	31.70	34.86	34	29.15	34.40	30	34.60	35.74	0.54
U of Washington	161	9.66	7.87	74	9.30	8.54	87	9.98	7.28	0.59
U of Michigan	44	8.39	10.95	44	8.39	10.95	0	NA	NA	NA
UMC Utrecht	97	22.27	10.30	96	22.23	10.35	1	26.00	NA	NA
VUMC Amsterdam	71	16.93	15.94	0	NA	NA	71	16.93	15.94	NA
West Haven VA	68	10.24	12.09	58	10.62	12.35	10	8.00	10.73	0.50
Western Ontario	103	15.68	14.63	31	15.13	15.08	72	15.92	14.53	0.81
Yale	71	19.13	12.37	63	18.52	12.36	8	23.88	12.21	0.27

Total scores not computed as sites varied by instrument and scale.

Supplementary Table S15: Descriptive statistics of depression severity by site and case/control status

	In PTSD Cases					In Controls					
Site	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**P**
AMC Amsterdam	37	10.78	4.24	3	20	36	0.64	1.02	0	5	3.42E-17
Cape Town*	47	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DOD ADNI	60	3.82	2.94	0	13	68	0.85	1.11	0	5	2.19E-10
Duke/Durham VA	87	21.36	11.35	0	52	195	6.73	8.40	0	58	1.03E-19
Emory GTP	57	18.77	10.54	2	54	94	7.56	7.91	0	42	5.15E-10
McLean	30	31.37	10.67	17	54	12	1.83	2.82	0	10	2.33E-16
UNSW	72	9.92	10.74	0	35	82	2.77	6.17	0	26	2.45E-06
TRACTS	127	2.01	1.24	1	5	110	1.13	0.41	1	3	3.23E-12
U of Sydney	27	56.70	34.32	0	124	37	13.46	21.56	0	98	9.43E-07
U of Washington	30	13.30	7.33	1	29	131	8.83	7.78	0	43	0.0046
U of Michigan	15	21.67	8.33	0	32	29	1.52	2.49	0	10	1.33E-07
UMC Utrecht	47	29.36	8.57	15	54	50	15.60	6.73	12	42	1.40E-13
VUMC Amsterdam	36	30.89	9.78	10	54	35	2.57	2.50	0	9	1.19E-19
West Haven VA	22	11.14	12.97	0	37	46	9.80	11.77	0	39	0.69
Western Ontario	60	13.83	14.40	0	52	43	18.26	14.72	0	52	0.13
Yale	37	26.16	10.49	3	46	34	11.47	9.43	0	32	3.39E-08

Supplementary Table S16: Mean alcohol use disorder by sex and site

Site	N	Mean	SD	N Males	Mean Males	SD Males	N Females	Mean Females	SD Females	P
AMC Amsterdam	75	0.05	0.23	40	0.05	0.22	35	0.057	0.24	0.89
Cape Town	47	0.26	0.64	0	NA	NA	47	0.26	0.64	NA
DoD ADNI	127	0.62	0.83	126	0.63	0.83	1	0.00	NA	NA
Duke/Durham VA	284	0.14	0.38	232	0.15	0.40	52	0.077	0.27	0.11
Emory GTP	128	0.41	0.65	2	0.50	0.71	126	0.40	0.65	0.88
McLean	40	0.35	0.74	0	NA	NA	40	0.35	0.74	NA
NSW	160	0.44	0.82	61	0.46	0.83	99	0.43	0.82	0.85
TRACTS	248	0.62	0.49	223	0.63	0.48	25	0.48	0.51	0.17
U of Sydney	0	NA	NA	0	NA	NA	0	NA	NA	NA
U of Washington	161	0.00	0.00	74	0.00	0.00	87	0.00	0.00	NA
U of Michigan	0	NA	NA	0	NA	NA	0	NA	NA	NA
UMC Utrecht	106	0.06	0.30	105	0.06	0.30	1	0.00	NA	NA
VUMC Amsterdam	72	0.21	0.58	0	NA	NA	72	0.21	0.58	NA
West Haven VA	0	NA	NA	0	NA	NA	0	NA	NA	NA
Western Ontario	0	NA	NA	0	NA	NA	0	NA	NA	NA
Yale	0	NA	NA	0	NA	NA	0	NA	NA	NA
ALL	1448	0.31	0.59	863	0.34	0.58	585	0.26	0.60	0.015

Supplementary Table S17: Mean PTSD severity by sex and site

Site	N	Mean	SD	N Males	Mean Males	SD Males	N Females	Mean Females	SD Females	P
AMC Amsterdam	75	36.67	33.32	40	37.90	34.15	35	35.26	32.78	0.73
Cape Town*	47	NA	NA	0	NA	NA	47	NA	NA	NA
DoD ADNI	127	27.87	27.89	126	28.09	27.89	1	0.00	NA	NA
DUKE_CAPS4	208	31.67	31.96	170	31.83	31.08	38	30.95	36.08	0.89
DUKE_CAPS5	39	10.87	15.50	35	10.49	15.99	4	14.25	11.44	0.58
Emory GTP	106	28.58	23.20	3	25.67	8.62	103	28.67	23.51	0.62
McLean	41	36.54	24.85	0	NA	NA	41	36.54	24.85	NA
UNSW	155	39.95	31.82	63	37.63	33.31	92	41.54	30.85	0.46
TRACTS	248	45.67	28.67	223	44.45	28.36	25	56.48	29.76	0.06
U of Sydney	64	27.61	32.31	34	25.00	31.23	30	30.57	33.78	0.50
U of Washington*	161	NA	NA	74	NA	NA	87	NA	NA	NA
U of Michigan	30	41.80	35.08	30	41.80	35.08	0	NA	NA	NA
UMC Utrecht	106	38.10	34.56	105	37.61	34.34	1	90.00	NA	NA
VUMC Amsterdam	72	45.33	46.58	0	NA	NA	72	45.33	46.58	NA
West Haven VA	47	26.49	28.32	40	28.20	29.35	7	16.71	20.43	0.23
Western Ontario	103	43.23	36.50	33	37.94	35.65	70	45.73	36.88	0.31
Yale	71	44.63	30.84	63	44.62	30.57	8	44.75	35.14	0.99

Total scores not computed as sites varied by instrument and scale.
*PTSD symptom severity scores not available.

Supplementary Table S18: Descriptive Statistics for PTSD severity by site and case/control status

	In PTSD Cases					In Controls					
Site	**N**	**Mean**	**SD**	**Min**	**Max**	**N**	**Mean**	**SD**	**Min**	**Max**	**P**
AMC Amsterdam	38	67.74	13.75	46	101	37	4.76	4.72	0	14	1.55E-29
DoD ADNI	60	54.68	14.40	16	92	67	3.85	7.76	0	41	5.62E-41
DUKE_CAPS4	73	68.49	22.10	8	120	135	11.76	13.32	0	53	5.51E-37
DUKE_CAPS5	8	36.50	10.27	23	53	31	4.26	7.72	0	26	1.50E-05
Emory GTP	42	45.26	22.85	0	94	64	17.64	15.83	0	69	3.09E-09
McLean	29	51.38	10.06	29	69	12	0.67	1.72	0	6	4.53E-23
NSW	81	64.47	22.37	19	110	74	13.12	13.84	0	51	3.59E-36
TRACTS	135	66.74	18.85	29	117	113	20.49	14.58	0	63	3.65E-59
U Sydney	27	56.26	29.01	0	101	37	6.70	12.43	0	44	1.25E-09
U of Michigan	17	67.24	25.00	17	104	13	8.54	5.03	3	21	2.56E-08
UMC Utrecht	53	71.08	13.20	45	107	53	5.13	4.58	0	15	4.13E-43
VUMC Amsterdam	37	87.97	20.84	28	120	35	0.26	1.20	0	7	8.80E-25
West Haven VA	22	50.05	24.13	11	100	25	5.76	8.43	0	31	1.35E-08
Western Ontario	62	71.40	13.98	50	100	41	0.63	2.97	0	17	1.76E-48
Yale	37	69.11	18.35	31	115	34	18.00	15.76	0	57	1.45E-19

Supplementary Table S19: Disclosures and Conflicts of Interest

Site	Author	Funding	Conflicts of Interest
AMC Amsterdam	Miranda Olff*	The Netherlands organization for health research and development (ZonMw, grant no 40-00812-98-10041), Academic Medical Center Research Council (grant no 110614)	None
	Saskia B. Koch	None	None
	Jessie L. Frijling	None	None
	Laura Nawijn	None	None
	Mirjam van Zuiden	None	None
Cape Town	Dan J. Stein*	MRC Unit on Anxiety & Stress Disorders, Bill and Melinda Gates Foundation [OPP 1017641]	None
	Jonathan Ipser	None	None
	Sheri Koopowitz	None	None
DoD ADNI	Paul M. Thompson*	DoD: W81XWH-12-2-0012	None
	Emily L. Dennis	None	None
	Neda Jahanshad	None	None
Duke/Durham VA	Rajendra A. Morey*	VISN6 MIRECC, VA Merit: 1I01RX000389-01, NINDS: 5R01NS086885-02, K23 MH073091-01, VA Merit: 1I01CX000748-01A1	None
	Sarah L. Davis	None	None
	Courtney C. Haswell	None	None
Emory GTP	Kerry J. Ressler	NIMH: MH071537, NCRR: M01RR00039	None
	Tanja Jovanovic	NIMH: MH098212	None
	Jennifer S. Stevens	NIMH: F32 MH101976 NCATS: UL1TR000454.	None
	Sanne J.H. van Rooij	None	None
McLean	Milissa L. Kaufman	Anonymous Women's Health Fund McLean Hospital; Frazier Foundation Grant for Mood and Anxiety Research McLean Hospital; O'Keefe Family Foundation; Trauma Scholars Fund McLean Hospital	

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	Kerry J. Ressler	NIMH: R21MH112956-01	None
	Lauren A.M. Lebois	None	None
	Justin T. Baker	None	None
	Staci A. Gruber	None	None
	Sherry R. Winternitz	None	None
	Jonathan D. Wolff	None	None
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	Mayuresh Korgaonkar	None	None
Boston VA	Mark Miller	R21MH102834	None
	Mark Logue	VA BLR&D I01BX003477	None
	William P. Milberg	TBI National Network Research Center (B9254-C).	None
	Regina E. McGlinchey		None
	Jasmeet P. Hayes	None	None
	David H. Salat	None	None
	Jeffrey Spielberg	None	None
	Erika Wolf	None	None
U of Sydney	Jim Lagopoulos	None	None
	Mayuresh Korgaonkar	None	None
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	Matthew Peverill	None	None
U of Michigan	Anthony P. King	Telecommunication and Advanced Technology Research Center (TATRC) W81XWH-08-2-0208; Center for Computation in Medicine and Biology (CCMB)	None
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	Dick Veltman	None	None
	Premika Boedhoe	None	None
West Haven VA	Kristen Wrocklage	VA NCPTSD	None
	Chadi G. Abdallah	VA NCPTSD	None
	John H. Krystal	VA NCPTSD	None
	Ilan Harpaz-Rotem	None	None
Western Ontario	Maria Densmore	Canadian Institutes of Health Research (CIHR), Canadian Institute for Military and Veteran Health Research (CIMVHR)	None
	Ruth Lanius	Canadian Institute for Military and Veteran Health Research (CIMVHR)	None
Yale	Ifat Levy	None	None
	Margaret A. Sheridan	None	None
	Chadi G. Abdallah	None	None
	John H. Krystal	None	Dr. Krystal is a consultant for AbbVie, Inc., Amgen, Astellas Pharma Global Development, Inc., AstraZeneca Pharmaceuticals, Biomedisyn Corporation, Bristol-Myers Squibb, Eli Lilly and Company, Euthymics Bioscience, Inc., Neurovance, Inc., FORUM Pharmaceuticals, Janssen Research & Development, Lundbeck Research USA, 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).

* denotes PI

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