Archival Report

Meta-analysis of Structural Magnetic Resonance Imaging Studies in Pediatric Posttraumatic Stress Disorder and Comparison With Related Conditions

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ABSTRACT

BACKGROUND: Findings on structural brain volume associated with pediatric posttraumatic stress disorder (PTSD) have been variable, and it is unclear whether any structural differences are specific to pediatric PTSD in comparison with adult PTSD or other co-occurring pediatric psychiatric conditions.

METHODS: We tested volumetric brain differences between pediatric groups with and without PTSD in a region-of-interest meta-analysis. We conducted meta-regressions to test the effects of age and sex on heterogeneous study findings. To assess specificity, we compared pediatric PTSD with the following: adult PTSD, pediatric trauma exposure without PTSD, pediatric depression, and pediatric anxiety.

RESULTS: In 15 studies examined, pediatric PTSD was associated with smaller total gray matter and cerebral, temporal lobe (total, right, and left), total cerebellar vermis, and hippocampal (total, right, and left) volumes, compared to peers without PTSD. In the pediatric PTSD group, but not the comparison group, we found a trend toward smaller total, right, and left amygdalar volumes. In an external comparison, smaller hippocampal volume was not significantly different between adult and pediatric PTSD groups. Qualitative comparisons with a pediatric trauma exposure without PTSD group, a pediatric depression group, and a pediatric anxiety group revealed differences that may be unique to pediatric PTSD, and others that may be convergent with these related clinical conditions in youth.

CONCLUSIONS: Pediatric PTSD is associated with structural differences that parallel those associated with adult PTSD. Furthermore, pediatric PTSD appears to be distinct from other related pediatric conditions at the structural level. Future studies employing longitudinal, dimensional, and multimodal neuroimaging approaches will further elucidate the nature of neurobiological differences in pediatric PTSD.

Keywords: Brain structure, Magnetic resonance imaging, Pediatric, Posttraumatic stress, Trauma, Youth

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Exposure to traumatic events during childhood is prevalent, with more than 65% of children in the United States having experienced at least one traumatic event (criterion A) as defined by the DSM (1–4). Cross-nationally, approximately 15% of children and adolescents develop posttraumatic stress disorder (PTSD) following exposure to traumatic stress (5). Thus, childhood trauma exposure is prevalent and increases risk for PTSD, but there is also vast heterogeneity in outcome.

In the past 2 decades, structural magnetic resonance imaging (sMRI) studies have examined the association between exposure to traumatic stress (both with and without PTSD) and regional volumes in the developing brain (6–8). Volumetric differences have been identified in some structures (e.g., gray matter, cerebral, and temporal lobe volumes) (9–13), whereas no differences between groups or mixed findings have emerged for other regions (e.g., hippocampus, amygdala) (9,14–16). To better characterize the heterogeneity in findings, it is important to statistically compile existing results in a single meta-analytic study (8,17).

In this study, we aimed to collectively analyze key findings from all structural volumetric studies in pediatric PTSD using region-of-interest (ROI) meta-analyses. A comprehensive online database built for a recent meta-analysis of sMRI studies in adult PTSD (18) also included a separate database of pediatric PTSD studies. However, the pediatric findings had not been examined independently in a meta-analysis. Therefore, we updated the database of all sMRI studies using a systematic MEDLINE search in pediatric PTSD and performed a comprehensive meta-analysis across 15 studies for 13 brain regions: total gray matter; total cerebrum; total, left, and right temporal lobe; total, left, and

right hippocampus; total, left, and right amygdala; total vermis volumes; and corpus callosum structure.

We predicted that meta-analytic findings for gray matter, cerebral, and temporal lobe volumes would be consistent with results from numerous previous studies suggesting that smaller volumes are associated with pediatric PTSD, relative to persons with no PTSD (without trauma exposure) (9–13). Multiple studies have suggested no differences in hippocampal and amygdalar volumes between pediatric groups with and without PTSD (9–11,14,15,19), although smaller hippocampal, but not amygdalar, volumes have been strongly associated with adult PTSD (18). For hippocampal volume, we thus had competing hypotheses that our meta-analytic findings may show the same pattern of no difference in hippocampal volume between pediatric PTSD and no PTSD groups or that the meta-analysis may reveal a difference in hippocampal volume that had previously not been identified in individual studies. For amygdalar volume, we hypothesized that there would be no difference between pediatric PTSD and no PTSD groups. Furthermore, to determine potential sources of variation across studies included in the meta-analysis, we also conducted meta-regression analyses for key variables of interest. Specifically, given the nonlinear changes that take place across brain development (20–22) and based on prior literature highlighting structural differences in pediatric PTSD cases that are associated with factors such as age and sex (6,12), we hypothesized that age and sex might relate to potential variability in effect sizes for key ROIs, such as the hippocampus and amygdala.

To discern the extent to which structural differences in cases of pediatric PTSD were specific to pediatric PTSD versus other related conditions, we conducted 4 comparison analyses with external datasets. First, we compared pediatric PTSD with adult PTSD (effect sizes from pediatric PTSD vs. no PTSD were compared with effect sizes from adult PTSD vs. no PTSD) to investigate whether structural alterations associated with PTSD in children and adolescents differ from those associated with PTSD in adults. Adult PTSD is associated with significant volumetric differences in numerous regions, and the sensitivity analysis including children with PTSD revealed differential findings (e.g., smaller gray matter, cerebral, and amygdalar volumes in PTSD vs. those in persons with no PTSD) (18). Thus, we hypothesized that children and adolescents with PTSD would display structural patterns different from those in adults with PTSD, potentially because of dynamic developmental changes in brain architecture in which prefrontal structures undergo more protracted development than subcortical structures during typical maturation (20–22).

Second, it remains unclear whether differences that have been observed in pediatric PTSD are associated with the disorder or with trauma exposure itself (15). Given the heterogeneity in volumetric brain differences in pediatric PTSD (17) and the fact that not all children and adolescents who experience traumatic events develop PTSD (3,23), it is important to disentangle the neurobiological effects of trauma from those of PTSD itself. To this end, we compared pediatric PTSD to pediatric trauma exposure without a PTSD diagnosis.

Third and fourth, depression and anxiety often co-occur with PTSD following trauma exposure (1,3,23), with ≤54% and ≤23% of children and adolescents with PTSD also

meeting criteria for major depressive disorder and for an anxiety disorder, respectively (23). Therefore, neurobiological differences observed in pediatric PTSD (relative to a group without PTSD or trauma exposure) may overlap with those found in pediatric depression and anxiety groups, potentially contributing to comorbidity across these conditions. It is also possible that neurobiological differences associated with pediatric PTSD are secondary to another pediatric condition and not directly related to pediatric PTSD. We addressed the specificity of structural differences in pediatric PTSD by comparing them with findings in pediatric depression and pediatric anxiety.

METHODS AND MATERIALS

Database of Imaging Studies in Pediatric PTSD

In a previously reported and publicly available online database (18) that includes studies from 1992 to 2016, 17 sMRI studies in pediatric PTSD were identified but not directly analyzed. To extend this database to the present (July 2019) and to ensure its completeness, we conducted a systematic MEDLINE search using the following terms: ("Stress Disorders, Traumatic"[MeSH] OR "PTSD" OR "post traumatic stress" OR "posttraumatic stress" OR "posttraumatic stress disorder" OR "maltreatment") AND (MRI OR "gray matter" OR "volume") AND (pediatric OR youth OR adolescent OR child) (Figure 1, Supplemental Table S1). Studies were included in the current database if they were performed in a pediatric population (i.e., included participants <18 years of age), included sMRI ROI analyses with volumetric data accessible as principal summary measures of group means and standard deviations, and included participants diagnosed with PTSD (see Table 1 for diagnostic criteria). If data were not available in the published paper or supplemental information, data were acquired through direct correspondence with the original study investigators. Studies were excluded from the entire database if only voxel-based morphometry analyses were conducted, the reported brain volumes did not include at least one ROI that was common to any study in the database, samples were overlapping with at least one other study included in the database for all ROIs, or the data of interest were not available (Figure 1, Supplemental Table S1). No studies were excluded based on type of trauma exposure (see Supplemental Table S2 for types of trauma exposures).

Statistical Analysis

Pediatric PTSD ROI Meta-analysis. ROI meta-analytic methods using the public meta-analytic Excel pipeline (www.ptsdmri.uk) are as previously described in Bromis *et al.* (18). The composite comparison group for the meta-analysis primarily included participants without PTSD and without trauma exposure. Study estimates were combined using a random-effects inverse weighted variance model (24,25). Effect sizes were calculated as Hedges' *g* (Cohen's *d* with small sample bias correction). Given that an individual meta-analysis was conducted for each brain region, we conducted Bonferroni correction for multiple comparisons and note results that survived this correction. For the corpus callosum ROI, studies that examined either volume or area were included. Finally, given

Structural MRI Meta-analysis of Pediatric PTSD
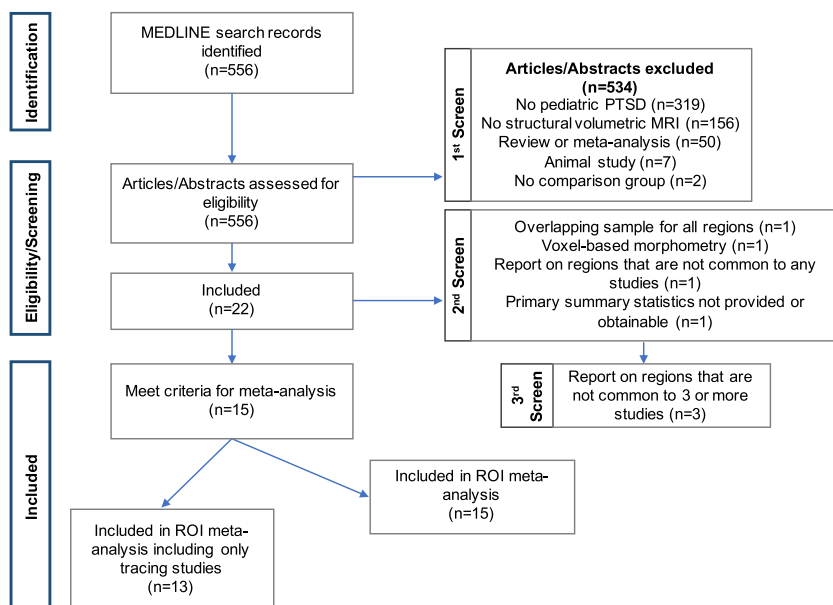
Figure 1. Flowchart indicating the number of studies excluded, reasons for exclusion, and total number of studies included in the meta-analyses. MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder; ROI, region of interest.

heterogeneity in methodological approaches used to determine ROIs in sMRI studies, which may lead to differences in study findings, especially in developmental samples (26), we conducted a separate additional analysis in which we included only studies that used manual (hand-tracing) methods (Supplemental Table S3, Supplemental Figure S1).

Pediatric PTSD ROI Meta-regression. To assess variation across studies due to heterogeneity, we calculated heterogeneity using the Cochran Q and I^2 statistics (27). We next investigated the association between potential moderator variables (age and sex) and heterogeneity in hippocampal and amygdalar effect sizes using a meta-regression analysis (28).

Table 1. The 15 MRI Studies Included in ROI Meta-analysis Comparing Participants With PTSD and Participants Without PTSD

Study (Reference)	Participants With PTSD (n)	Comparison Participants Without PTSD (n)	Comparison Participants Without Trauma Exposure (n)	Comparison Participants With Trauma Exposure (n)	Diagnostic Criteria	Average Age, Years[a]	Method for ROI Segmentation
Ahmed et al. (14)	21	32	–	32	DSM-IV	15.3	Automated[b]
Carrion et al. (9)[c]	24	24	24	–	DSM-IV	11.0	Manual
Carrion et al. (67)[c]	24	24	24	–	DSM-IV	11.0	Manual
De Bellis et al. (10)[c]	44	61	61	–	DSM-III-R	12.1	Manual
De Bellis et al. (19)	9	9	9	–	DSM-IV	10.5	Manual
De Bellis et al. (11)[c]	28	66	66	–	DSM-IV	11.5	Manual
De Bellis et al. (68)[c]	43	61	61	–	DSM-IV	12.1	Manual
De Bellis et al. (12)[c]	61	122	122	–	DSM-IV	11.7	Manual
De Bellis et al. (69)[c]	58	98	98	–	DSM-IV	12.0	Manual
De Bellis et al. (13)	38	59	59	35	DSM-IV	10.5	Manual
Morey et al. (15)	31	57	57	32	DSM-IV	10.4	Automated[b] + manual
Mutluer et al. (70)	23	21	21	–	DSM-IV	15.4	Manual
Postel et al. (71)	15	24	24	–	DSM-IV	16.0	Manual
Weems et al. (72)[c]	24	24	24	–	DSM-IV	11.0	Manual
Weems et al. (41)[c]	28	26	26	–	DSM-IV	13.8	Automated[b]

–, not stated in the study; MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder; ROI, region of interest.

[a]The average age, in years, of all participants in a sample (PTSD and comparison groups). None of the comparison participants listed above had a PTSD diagnosis at the time of the study.

[b]The automated method used was FreeSurfer image analysis suite.

[c]Despite overlapping samples present in the overall database, none of the studies included in the individual ROI meta-analyses reported here contained overlapping samples.

We also conducted meta-regressions for the supplemental analysis including only studies that used tracing methods (Supplemental Table S4).

Comparison With Related Clinical Groups

To assess the specificity of any volumetric differences detected in pediatric PTSD, we also compared these meta-analytical results with effect sizes in 4 relevant comparison groups: adult PTSD versus no PTSD, pediatric trauma exposure without PTSD versus no trauma exposure, pediatric depression versus no depression, and pediatric anxiety versus no anxiety. First, we statistically compared pediatric PTSD with adult PTSD to test whether findings in pediatric PTSD may be developmentally specific by using the study published by Bromis *et al.* in 2018 (18), which included 66 studies of adult PTSD in an ROI meta-analysis (Supplemental Table S5). Next, we sought to compare the pediatric PTSD group to a pediatric trauma exposure without PTSD group to dissociate the extent to which structural alterations might be associated with the disorder itself versus with trauma exposure. Finally, we also aimed to compare pediatric PTSD with pediatric depression and anxiety because these disorders also arise in children and adolescents following trauma and often co-occur with pediatric PTSD (1,3,23).

To identify studies for the 3 comparisons, we conducted a MEDLINE search to identify comprehensive meta-analyses for volumetric sMRI studies using search terms "(pediatric OR child OR adolescent OR youth) AND (anxiety OR depression OR maltreatment OR stress OR trauma) AND MRI AND meta-analysis". We did not find any published meta-analytic studies of this nature. Therefore, separately for these 3 related conditions, we identified an ROI study with the largest sample size that met the following inclusion criteria: the study was performed in a pediatric population, included volumetric sMRI ROI analyses for the amygdala and hippocampus with available principal summary measures, and was related to anxiety, depression, or early-life stress and trauma (see the Supplement for full search terms). Studies selected for the comparison analyses and their respective demographic information are listed in Supplemental Table S5. Given the lack of meta-analytic studies and the use of a single study for comparison, we did not perform a formal statistical comparison between pediatric PTSD and pediatric depression, anxiety, or exposure to trauma without PTSD. Instead, we nominally compared effect sizes between pediatric PTSD and the 3 comparison conditions.

To limit the number of comparisons performed, we focused our analyses on the hippocampus and amygdala, as these were the most commonly examined regions in the studies included in the present meta-analysis (Supplemental Figure S2). For each comparison study, except for that involving adult PTSD, we calculated Hedges' *g* effect sizes using mean volumes and standard deviations for the amygdala and hippocampus. For adult PTSD, we used Hedges' *g* effect sizes and respective *p* values directly from the meta-analytic study (18). To perform the statistical comparison between pediatric and adult PTSD groups, we calculated the *z* statistics and derived the *p* value for the comparison. We also conducted statistical and qualitative comparisons for the

supplemental analysis including only studies that used tracing methods (Supplemental Tables S6–S9).

RESULTS

Database of Imaging Studies in Pediatric PTSD

Of the 17 pediatric imaging studies included in the original database, 14 met the criteria listed above (Supplemental Table S1). Our additional comprehensive MEDLINE search identified 5 eligible studies for our database per inclusion criteria (Figure 1, "1st Screen"). Of these 5 studies that were added to the database, 4 were included in the ROI meta-analysis and 1 was excluded because summary measures were not available. Thus, a total of 18 studies passed the second screen for eligibility (Figure 1).

From these 18 studies, a total of 46 brain regions were reported. Out of these 46 regions, we selected the 13 regions for the ROI meta-analysis that contained at least 3 studies (Supplemental Figure S2) with means and standard deviations for both PTSD and comparison groups to include a sufficient number of studies in each meta-analysis (18). During this third screen, 3 of the 18 studies reported only on regions that did not meet these criteria, and these 3 studies were thus not included in the meta-analyses of 13 brain regions (Figure 1). Thus, a total of 15 studies were included in the present meta-analysis (Table 1). Studies were excluded from individual ROI meta-analyses if samples were overlapping with those of other studies for the same region. Such studies were not, however, excluded from the entire database.

Of the 15 studies included in the ROI meta-analysis, 12 studies compared participants with PTSD to participants without PTSD and with no exposure to trauma. Of the remaining 3 studies, 2 studies compared participants with PTSD to participants without PTSD both with and without trauma exposure (13,15), and 1 study compared participants with PTSD to participants without PTSD with trauma exposure only (14). For the 2 studies that included 2 comparison groups (with and without trauma exposure) (13,15), we included only data for comparison participants without PTSD who did not have trauma exposure to ensure consistency with the 12 other studies and to maintain balanced sample sizes between groups with and without PTSD (Table 2), which is consistent with the approach used in the recent adult PTSD meta-analysis (18). Within the database of 15 studies, there were a total of 471 pediatric participants with a DSM diagnosis of PTSD and 676 participants without any diagnosis or trauma exposure (Table 2).

Pediatric PTSD ROI Meta-analysis

Significantly smaller total gray matter, total cerebral, temporal lobe (total, right, and left), total cerebellar vermis, and hippocampal (total, right, and left) volumes were associated with pediatric PTSD compared with no PTSD and no trauma exposure. There were trend-level differences in total (*p* = .052), right (*p* = .060), and left (*p* = .073) amygdalar volumes between pediatric PTSD and no PTSD groups such that smaller amygdalar volume was associated with pediatric PTSD (relative to the comparison group of pediatric participants without PTSD). In contrast, there were no significant differences in

Table 2. Demographic and Clinical Data From Participants in the Database of 15 MRI Studies Included in the 13-Brain-Region Meta-analysis Comparing Participants With PTSD and Participants Without PTSD

Variable	Pooled Participants in Database, *n*	Studies Reporting the Variable, *n*	Mean Value or Percentage per Study	Between-Study SD
Participants With PTSD, *n*	471	15	33	15
Comparison Participants Without Trauma Exposure, *n*	676	14	48	33
Comparison Participants With Trauma Exposure, *n*	99	3	33	2
Age, Years				
Participants with PTSD, mean		15	12.3	2.0
Participants with PTSD, SD		12	2.2	0.5
Comparison participants (no trauma), mean		15	12.3	1.9
Comparison participants (no trauma), SD		12	2.2	0.5
Comparison participants (with trauma), mean		3	11.4	2.6
Comparison participants (with trauma), SD		3	2.5	0.2
Medication-free Status		9	100%	0
Sex of Participants With PTSD, Female/Male	239/232	15	53%/47%	4.4
Sex of Comparison Participants Without Trauma, Female/Male	339/337	14	51%/49%	6.2
Sex of Comparison Participants With Trauma, Female/Male	51/48	3	52%/48%	2.6

MRI, magnetic resonance imaging; PTSD, posttraumatic stress disorder.

corpus callosum structure between children and adolescents with and without pediatric PTSD (Table 3, Figure 2). Importantly, there was a significant publication bias for total cerebral volume (*p* = .04) but not for any of the other regions.

Meta-regression Analyses

There was significant heterogeneity across studies for total, right, and left hippocampal as well as total and left amygdalar volume meta-analyses (Table 3). Meta-regression results revealed that age was a significant moderator of heterogeneity for total, right,

and left hippocampal regions, accounting for >30% of the heterogeneity across effect sizes from studies included in the regional meta-analysis (Table 4). Specifically, older age was associated with larger negative effect sizes for total hippocampal volume (relative to studies with younger participants) (Supplemental Figure S3). Age was not a significant moderator for total or left amygdalar regions. Sex was a significant moderator of heterogeneity for all hippocampal and amygdalar regions, accounting for >50% of heterogeneity across studies' effect sizes (Table 4). Specifically, a higher percentage of female participants was associated with larger negative effect sizes (relative to those of

Table 3. Meta-analysis Results of Comparison Between Pediatric Participants With PTSD and All Participants Without PTSD

| Brain Region	Studies, *n*	Sample Size		Comparison of Participants With and Without PTSD			Heterogeneity		Small-Study Bias
		PTSD Group, *n*	Comparison Group, *n*	Effect Size[a]	95% CI	*p*	*I²*, %	*p*	
Gray Matter (Total)[b]	3	123	205	−0.56	−0.83, −0.28	<.001[c]	25.24	.26	0.28
Cerebral Volume (Total)[b]	3	123	205	−0.56	−0.79, −0.33	<.001[c]	0.00	.59	0.04
Temporal Lobe (Total)[b]	4	105	160	−0.6	−0.86, −0.35	<.001[c]	0.00	.79	0.57
Temporal Lobe (Right)[b]	3	96	151	−0.58	−0.85, −0.32	<.001[c]	0.00	.60	0.43
Temporal Lobe (Left)[b]	3	96	151	−0.54	−0.80, −0.27	<.001[c]	0.00	.50	0.75
Hippocampus (Total)[b]	8	195	294	−0.51	−0.88, −0.13	.007	72.68	.00	0.24
Hippocampus (Right)[b]	7	171	270	−0.51	−0.93, −0.09	.016	75.28	.00	0.25
Hippocampus (Left)[b]	7	171	270	−0.46	−0.87, −0.04	.030	74.69	.00	0.34
Amygdala (Total)	8	208	296	−0.28	−0.56, 0.00	.052	54.31	.03	0.48
Amygdala (Right)	8	208	296	−0.23	−0.47, 0.01	.060	39.69	.11	0.50
Amygdala (Left)	8	208	296	−0.29	−0.61, 0.03	.073	64.29	.01	0.46
Vermis (Total)[b]	3	120	181	−0.46	−0.88, −0.04	.033	64.51	.06	0.18
Corpus Callosum (Total)	3	106	178	−0.30	−0.87, 0.27	.307	76.74	.01	0.63

CI, confidence interval; PTSD, posttraumatic stress disorder.

[a]Effect sizes are reported as Hedges' *g* values. Negative effect sizes indicate that the region is smaller in pediatric participants with PTSD, whereas positive effect sizes indicate that the region is larger in pediatric participants with PTSD compared to that of participants without PTSD.

[b]For the meta-analytic comparison between participants with and without PTSD, these regions showed significant differences.

[c]Result remained significant after Bonferroni correction for multiple comparisons of 13 brain structures.
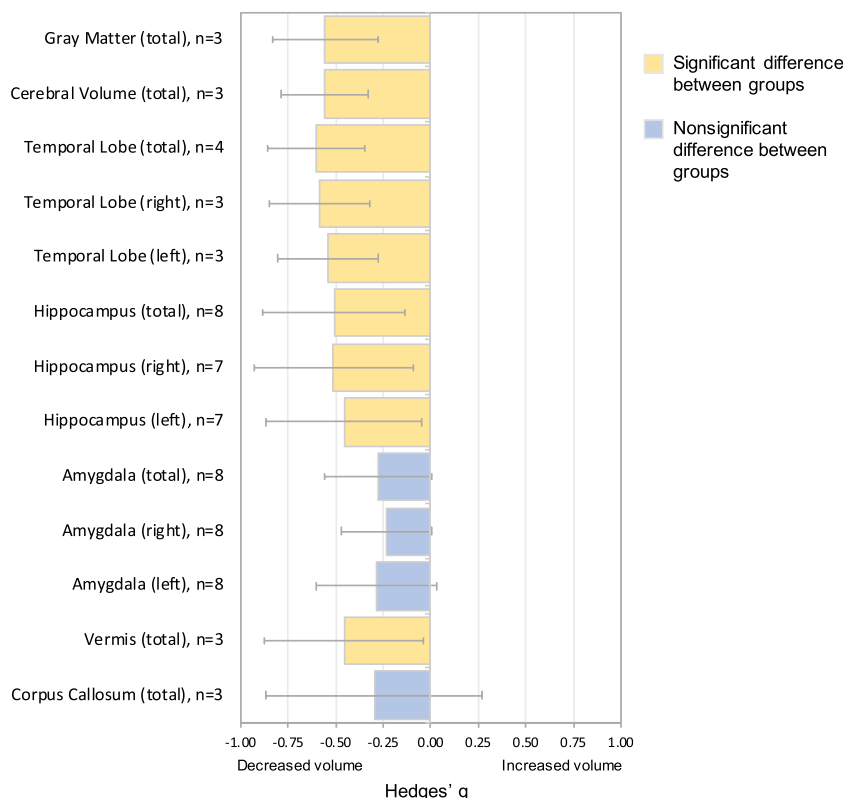
Figure 2. Meta-analysis comparing the pediatric posttraumatic stress disorder (PTSD) group and the pediatric group with no PTSD. For each of the 13 regions of interest in the meta-analysis, Hedges' *g* values are reported with 95% confidence intervals. Positive Hedges' *g* values indicate increased structural volume in pediatric participants diagnosed with PTSD. Negative Hedges' *g* values indicate smaller structural volumes in participants with pediatric PTSD. The number of studies included in the meta-analysis (*n*) that report on the relevant region is listed for each region. Error bars represent the width of the 95% confidence interval.

studies with equal numbers of male and female participants) (Supplemental Figure S5).

Comparison With Related Clinical Groups

To assess the specificity of the meta-analytic findings, we compared volumetric differences in the hippocampus and amygdala in the pediatric PTSD group with differences in key clinical groups.

Pediatric PTSD Versus Adult PTSD. To statistically compare meta-analytic results between pediatric PTSD and adult PTSD groups, we used the recently published meta-analysis in adult PTSD (18) (Supplemental Table S5). There were no significant differences between effect sizes in

pediatric versus adult PTSD for any hippocampal or amygdalar regions (Figure 3, Supplemental Table S10).

**Pediatric PTSD Versus Pediatric Exposure to Trauma Without PTSD Diagnosis.** Given that a meta-analysis of pediatric exposure to trauma without PTSD was not available, we selected the study obtained from our MEDLINE search that had the largest sample size and included hippocampal and amygdalar volumetric findings so we could conduct an indicative qualitative comparison, as using a single study for comparison precluded the use of formal statistical analyses (15) (see Supplemental Table S5 for demographic characteristics of comparison studies). Our qualitative comparison revealed a difference between

Table 4. Meta-regression Results for Age and Sex Moderators for Primary Database

Brain Region	I^2, %	*p* Value	Moderator: Age			Moderator: Sex		
			R^2, %	Test of Moderator, QM	*p* Value	R^2, %	Test of Moderator, QM	*p* Value
Hippocampus (Total)	72.68	.00	34.86	5.23	.022	84.79	13.49	.0002
Hippocampus (Right)	75.28	.00	41.92	5.63	.018	79.59	11.32	.0008
Hippocampus (Left)	74.69	.00	33.37	4.73	.030	100.00	19.60	.0001
Amygdala (Total)	54.31	.03	0.00	0.69	.407	63.70	5.82	.016
Amygdala (Right)	39.69	.11	12.77	1.46	.226	77.61	4.51	.034
Amygdala (Left)	64.29	.01	0.00	0.30	.581	51.57	5.99	.015

I^2, meta-analysis heterogeneity; QM, Q-statistic for model fit; R^2, amount of heterogeneity accounted for by moderator.

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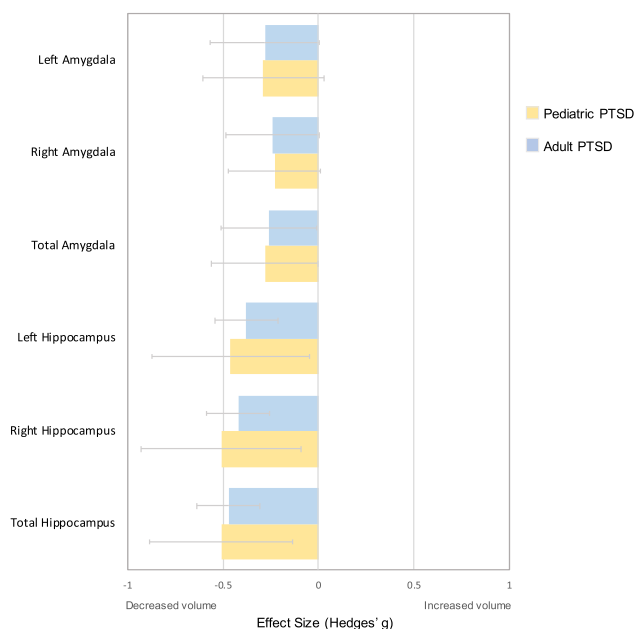
Figure 3. Comparison analysis of hippocampal and amygdalar volumes between pediatric PTSD and adult PTSD groups. The comparison adult PTSD study is a meta-analysis of 89 adult structural magnetic resonance imaging (MRI) studies (18). Positive Hedges' *g* values indicate increased structural volume in pediatric participants, with the condition indicated in the legend. Negative Hedges' *g* values indicate smaller structural volumes in participants with the condition indicated in the legend. Error bars represent the width of the 95% confidence interval.

pediatric PTSD and pediatric exposure to trauma without PTSD. Specifically, whereas there was a medium negative effect size and small negative effective size for total hippocampal (Hedges' $g = -0.51$) and amygdalar (Hedges' $g = -0.28$) volumes in pediatric PTSD, respectively, there was a small positive effect size for total hippocampal (Hedges' $g = 0.24$) and small to medium positive effect sizes for total (Hedges' $g = 0.42$) and left (Hedges' $g = 0.46$) amygdalar volumes, respectively, in pediatric trauma exposure without PTSD (Figure 4, Supplemental Table S11).

Pediatric PTSD Versus Pediatric Depression. Because a meta-analysis of structural volumetric studies in pediatric depression was not available, we selected the largest study obtained from our MEDLINE search that included hippocampal and amygdalar volumetric findings in pediatric depression (29) (Supplemental Table S5). Our qualitative comparison showed that while pediatric PTSD was associated with medium and small negative effect sizes for total hippocampal (Hedges' $g = -0.51$) and amygdala (Hedges' $g = -0.28$) volumes, respectively, pediatric depression was associated with only small positive effect sizes for both total hippocampal (Hedges' $g = 0.20$) and amygdalar (Hedges' $g = 0.20$) volumes (Figure 5, Supplemental Table S12).

Pediatric PTSD Versus Pediatric Anxiety. A meta-analysis of structural volumetric studies in pediatric anxiety was not available; thus, we selected the largest study obtained

from our MEDLINE search that included hippocampal and amygdalar volumetric findings in pediatric anxiety (30) (Supplemental Table S5). Our qualitative comparison revealed that both pediatric PTSD (Hedges' $g = -0.51$) and pediatric anxiety (Hedges' $g = -0.38$) were associated with negative effect sizes for total hippocampal volume (Figure S7, Supplemental Table S13). Pediatric anxiety (Hedges' $g = -0.38$) and PTSD (Hedges' $g = -0.51$) were both also associated with smaller right hippocampal volume. Finally, whereas pediatric PTSD was associated with small negative effect size for total amygdalar volume (Hedges' $g = -0.28$), smaller total amygdalar volume was not associated with pediatric anxiety (Hedges' $g = -0.17$) (Figure S7, Supplemental Table S13).

DISCUSSION

Our meta-analysis of 15 ROI volumetric sMRI studies showed significantly smaller total gray matter, total cerebral, temporal lobe (total, right, and left), total vermis, and hippocampal (total, right, and left) volumes in the pediatric PTSD group when compared to volumes in a group of pediatric participants with no PTSD. Additionally, a trend toward smaller amygdalar volume (total, right, and left) was associated with pediatric PTSD relative to no PTSD. However, we found no significant differences in corpus callosum structure between pediatric PTSD and no PTSD groups. Importantly, there was a notable qualitative difference between pediatric PTSD and pediatric exposure to trauma without PTSD such that the former was
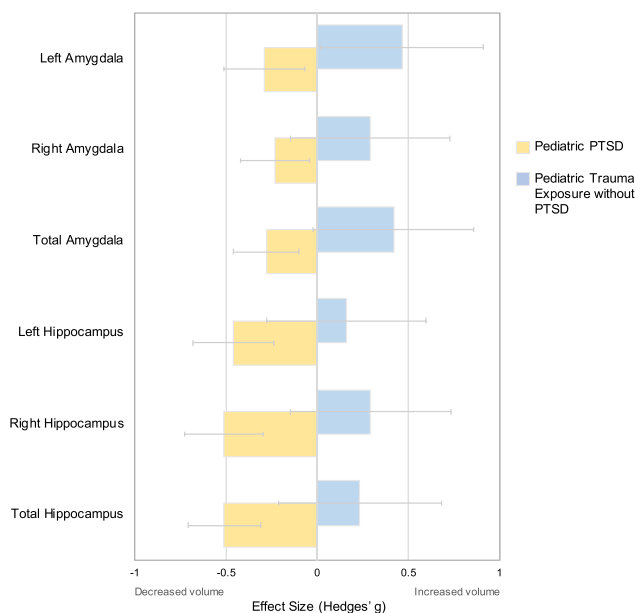
Figure 4. Comparison analysis of hippocampal and amygdalar volumes between the pediatric posttraumatic stress disorder (PTSD) group and the group of pediatric participants with exposure to trauma without PTSD. The comparison study is one in which a group of pediatric participants with exposure to trauma without PTSD (*n* = 32) was compared to a group of age-matched participants with no trauma exposure (*n* = 57) (15). Positive Hedges' *g* values indicate increased structural volume in pediatric participants with the condition indicated in the legend. Negative Hedges' *g* values indicate smaller structural volumes in participants with the condition indicated in the legend. Error bars represent the width of the 95% confidence interval.
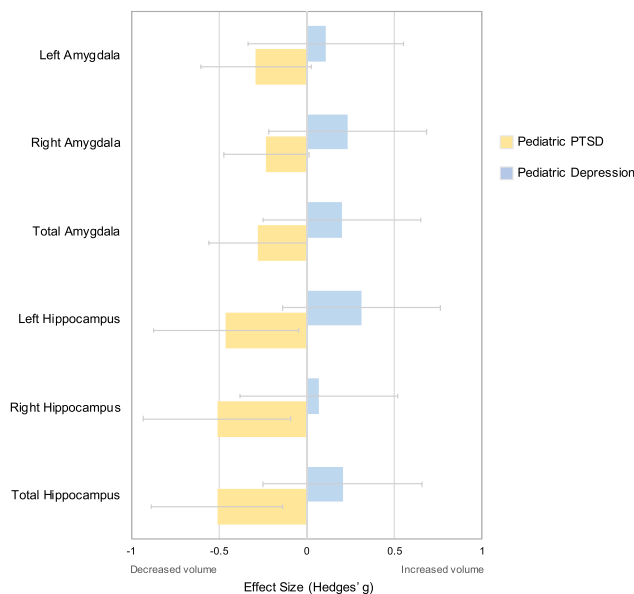
Figure 5. Comparison analysis of hippocampal and amygdalar volumes between the pediatric posttraumatic stress disorder (PTSD) group and the pediatric depression group. The comparison study is one in which a group of pediatric participants with depression ($n = 30$) was compared to a pediatric group without depression ($n = 56$) at the second time point in a longitudinal study by Whittle *et al.* (29). Positive Hedges' *g* values indicate increased structural volume in pediatric participants with the condition indicated in the legend. Negative Hedges' *g* values indicate smaller structural volumes in participants with the condition indicated in the legend. Error bars represent the width of the 95% confidence interval.

following trauma exposure (34). However, another study shows that hippocampal volume is not associated with increased risk for PTSD following trauma exposure (35). In addition, neurobiological differences associated with trauma and PTSD might reflect preexisting vulnerabilities rather than consequences of trauma exposure (36). The current meta-analysis suggests developmental differences that warrant future investigations on the temporal relationship between structural changes, trauma exposure, and disorder onset.

Regarding the amygdala, which plays a central role in fear learning and threat reactivity (37), our meta-analytic findings show trend-level volumetric differences between children and adolescents with and without PTSD. Although there was a trend-level decrease in amygdalar volumes in pediatric PTSD, the supplemental meta-analysis that included only studies using tracing methods revealed that pediatric PTSD is associated with significantly smaller amygdalar volumes. Previous reviews of this literature (6,17) have proposed that a lack of significant findings regarding amygdalar volume in pediatric PTSD (9–11,15,19) may stem from developmental changes in limbic structures (38–40) that have not been taken into consideration. That is, the association between amygdalar volume and PTSD may vary depending on age, such that an effect could be obscured in studies that do not examine age-related changes (17,41). Although we find that age is a significant moderator of variability for hippocampal but not amygdalar regions in our primary analysis, age does emerge as a significant moderator for amygdalar regions when only tracing studies are included in the meta-analysis. This finding may be explained by the fact that there is greater variability in ROI delineation using automated approaches for smaller subcortical regions (26), and thus developmental effects may have been less likely to be detected in our analysis that included studies using automated methods. Taken together, these findings indicate the need to employ a developmental approach to understand the relationship between PTSD and brain structure, in addition to traditional reliance on comparisons between age-matched clinical and control groups. Although we focus here on the amygdala and hippocampus, the current meta-analysis also shows differences in the temporal lobe and cerebellar vermis (a finding that did not survive correction for multiple comparisons of 13 brain regions) in pediatric PTSD. Little is known about structural changes in these regions following trauma exposure, and thus interpretation of these findings will depend on future research.

In addition to performing an analysis of regional brain structure in cases of pediatric PTSD, we aimed to assess the degree to which these findings were specific to pediatric PTSD. First, we compared a pediatric PTSD group with an adult PTSD group. The hippocampus and amygdala undergo dynamic changes with neurodevelopment (20–22,42,43), suggesting that they may be differentially influenced by trauma or involved in PTSD-related symptoms depending on developmental stage. Our analysis revealed that both adult and pediatric PTSD are associated with significantly smaller hippocampal volumes (relative to no PTSD) and that there is no significant difference between adult and pediatric PTSD for this finding. This pattern could be because, although adults may have experienced more traumatic stress (e.g., greater cumulative exposure to trauma over more years of life) than children

associated with smaller amygdalar volume (trend-level), while the latter with larger total amygdalar volume.

The finding of smaller total hippocampal volume in pediatric PTSD in the present meta-analysis highlights volumetric differences in a region commonly involved in emotional memory and learning, both of which are disrupted in PTSD (31,32). This finding is particularly important as prior meta-analyses of neuroimaging studies in pediatric PTSD have not shown significantly smaller hippocampal volume to be associated with pediatric PTSD (8,33). The inconsistency in meta-analytic findings may be attributed to the specific studies included in each regional meta-analysis. For example, the meta-analysis conducted by Woon and Hedges in 2008 (33) included only 4 studies, whereas Milani *et al.* (8) included 4 studies ($N = 343$), one of which (16) was excluded from our database because of an overlapping sample. Our meta-analysis of total hippocampal volume included a total of 8 studies ($N = 489$) with nonoverlapping samples. Thus, the examination of different studies likely accounts for the disparate findings regarding hippocampal volume in pediatric PTSD across these meta-analyses. It is also important to note that the finding of differences in hippocampal volume did not survive correction for multiple comparisons of 13 brain regions.

Whether smaller hippocampal volume is a risk factor for PTSD versus a consequence of trauma or PTSD remains an open question. Evidence from monozygotic twins discordant for trauma exposure suggests that smaller hippocampal volume may predispose some individuals to developing PTSD

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and adolescents, the hippocampus has been shown to be especially vulnerable earlier in life (44–46). There were also no significant differences in amygdalar volumes between pediatric and adult PTSD groups.

Second, we compared ROI volumes in a pediatric PTSD group and volumes in a group of pediatric participants who experienced trauma but did not develop PTSD. Given that most studies in pediatric PTSD to date, and thus also the current ROI meta-analysis, have focused on pediatric groups with PTSD compared to pediatric groups without any exposure to trauma, much remains unknown about the extent to which volumetric differences observed in PTSD cases relate to the disorder versus trauma exposure. A qualitative comparison between the present meta-analysis and a study of pediatric exposure to maltreatment without PTSD (15) revealed a notable difference between effect sizes for hippocampal and amygdalar volumes in a pediatric PTSD group versus effect sizes in a group with pediatric exposure to trauma with no PTSD. Specifically, regional volumes were smaller in the pediatric PTSD group than in a group with no PTSD (the present meta-analysis), but regional volumes were larger in the group with trauma exposure without PTSD versus those in the group of participants with no trauma exposure (15). Notably, within the individual study used in the comparison analysis (15), left amygdalar volume was significantly larger in the group with trauma exposure relative to the volume in the group of participants with no trauma exposure. These results suggest that exposure to trauma itself may be associated with amygdalar differences, with a general trend toward larger volume. In contrast, we observed a trend toward smaller amygdalar volume in groups with pediatric PTSD. Taken together, amygdalar and hippocampal volumetric differences found in pediatric PTSD are unlikely to be explained solely by exposure to trauma. Although this study compares pediatric trauma exposure with and without PTSD in a qualitative manner, a meta-analysis of studies including groups with trauma exposure but without PTSD was not conducted, as only a limited number of studies with a trauma exposure without PTSD group have been reported.

Finally, we aimed to dissociate volumetric effects in pediatric PTSD from those of other psychiatric disorders that commonly co-occur following trauma (3,23). We found that while pediatric PTSD was associated with smaller hippocampal volume and a trend toward smaller total amygdalar volume, pediatric depression was not associated with any notable volumetric differences (relative to individuals without depression). Notably, for the qualitative comparison with pediatric anxiety, we observed that both pediatric PTSD and pediatric anxiety were associated with smaller total hippocampal volumes. Only pediatric PTSD was associated with smaller total amygdalar volume (trend-level). Investigation of pediatric PTSD co-presenting with depression and with anxiety in the same sample, and inclusion of psychiatric comparison groups with depression or anxiety only, will further clarify the specificity of structural differences in pediatric PTSD. This approach will provide a foundation for future investigations that aim to enhance risk identification using neuroimaging correlates or to elucidate mechanisms that may inform clinical practice.

Three considerations are important to contextualize our findings and their interpretation within the broader literature on PTSD and on structural imaging. First, the use of categorical

DSM-defined PTSD diagnoses and the definition of criterion A trauma exposure remain debated in the field (47–52), and differences in trauma exposure or clinical presentation across individuals included in different studies may be due in part to this substantial heterogeneity in classification (53). Although clinicians and researchers use the PTSD diagnosis to maintain consistency in clinical and scientific practices, this categorical approach may obscure meaningful complexity in traumatic experiences or symptom presentations. Although we were able to investigate the association between age and sex as moderators of hippocampal and amygdalar findings, we were underpowered to investigate the role of a number of other key variables, such as age at PTSD onset, age during traumatic exposures, duration of trauma exposures, and duration of PTSD. It is possible, however, that age at PTSD diagnosis may relate to key neurobiological changes associated with pediatric PTSD (6). Thus, it is important that future studies investigate the complex contributions of these elements to neurobiological changes following trauma exposure and PTSD development. Finally, recent work has suggested the use of a network approach to identify related symptom subgroups that may share ontological origins (49,51,52), which could allow for more direct mapping to neurobiological correlates.

Second, the functional and mechanistic relevance of identifying volumetric differences using structural neuroimaging in humans remains unclear. Cross-species studies suggest potential mechanisms underlying hippocampal and amygdalar volumetric differences. For example, chronic stress in rodents can lead to smaller hippocampal dendritic spine density, dendritic remodeling, and neurogenesis (54–58). Evidence also shows that stress activates inflammatory and anti-inflammatory responses (59) and that early-life stress in mice is associated with increased density and morphological differences in hippocampal microglia (60,61). Finally, in primates, direct cortisol administration to the hippocampus results in dendritic atrophy and shrinkage of the soma (62). In the amygdala, by contrast, chronic stress in rodents is associated with increased dendritic remodeling, growth, and spine density (63). These lines of evidence from animal studies illustrate mechanisms by which structural volumetric changes may occur.

While the etiology underlying volumetric differences in human neuroimaging is unknown, a recent study aimed to probe this very question (64). The authors showed that increased axonal myelination in the human visual cortex underlies the developmental decrease in cortical thickness that had previously been interpreted as cortical thinning (64). These processes can be regionally dependent, however; thus, it is unclear whether increased myelination underlying decreased cortical thickness generalizes beyond the human visual cortex to other cortical or subcortical structures. Therefore, investigating volumetric differences in humans does not currently provide conclusive evidence of the mechanisms underlying neurodevelopmental differences following trauma. Future investigations using multimodal structural and functional approaches within the same samples and longitudinal design will provide further insight into observed structural differences.

A final consideration surrounding the current findings is the nature of structural differences regarding behavior and adaptation following stress. Though volumetric differences following trauma exposure are often characterized as

pathologic, they may also reflect ways in which the brain has adapted to meet the needs of an adverse environment (6,65). For instance, some evidence suggests that neurobiological differences in children and adolescents exposed to early adversity are ontogenetic adaptations that confer some functional benefit, at least in the short term (66), though long-term consequences remain to be explored. To better inform whether specific neurobiological differences are adaptive, research investigating structural brain differences in PTSD will benefit from examining behavioral correlates and mechanistic processes, as well as longitudinal designs to evaluate potential adaptations in the context of development and changing environmental circumstances.

The present meta-analysis leverages prior research to delineate differences in brain structure in pediatric PTSD and investigates the extent to which structural differences are specific to cases of pediatric PTSD relative to those with trauma exposure, commonly comorbid pediatric affective disorders, and PTSD in adults. Furthermore, it highlights the relative paucity of research investigating regional differences in pediatric PTSD, as we identified only 22 studies conducted since 1992 that met the criteria for this study. There remains an important need in the field for future studies to better elucidate neurobiological changes following exposure to trauma, including multimodal investigations of structural and functional connectivity to examine circuit-based differences in pediatric PTSD. Future work will benefit from considering the complex and co-occurring psychiatric presentations following trauma that are the reality in clinical settings, dimensional approaches to better capture heterogeneous symptoms, and developmental designs to elucidate age-dependent effects of trauma and PTSD. Taken together, the current study identifies key structural brain differences in pediatric PTSD and provides concrete directions for future research that will further elucidate the nature of brain development following trauma exposure and in children and adolescents with PTSD.

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