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Archival Report

Volumetric Differences of Thalamic Nuclei Are Associated With Posttrauma Psychopathology

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ABSTRACT

BACKGROUND: Previous investigations of whole thalamus and thalamic nuclei volumes in posttrauma psychopathology have been sparse and limited in scope and have yielded inconsistent results. To address this, volumetric estimates of whole thalamus and thalamic nuclei were obtained from structural brain magnetic resonance imaging scans from 2058 participants across 20 worldwide sites in the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) Posttraumatic Stress Disorder (PTSD) working group.

METHODS: Thalamic volumes were compared in trauma-exposed participants with PTSD (n = 238), major depressive disorder (MDD) (n = 184), and comorbid PTSD+MDD (n = 618) and in trauma-exposed control participants (n = 1018). PTSD and MDD symptom severity, PTSD symptom clusters, and childhood trauma were similarly examined for associations with thalamic volume.

RESULTS: Participants with PTSD had smaller sensorimotor thalamic nuclei, while participants with MDD or comorbid PTSD+MDD had smaller mediodorsal (MD) thalamus volumes relative to control participants. Severity of PTSD and MDD symptoms negatively correlated with MD volume. A significant interaction between PTSD and MDD severity was found, such that MDD severity was positively associated with whole thalamus volume only among individuals with high PTSD severity. We observed both positive and negative volumetric associations for specific PTSD symptom clusters and childhood trauma subtypes.

CONCLUSIONS: Whole thalamus volume and volumes of the sensorimotor and limbic thalamus may play an important role in the development of PTSD and MDD in the aftermath of trauma exposure. The interaction between PTSD and MDD symptoms and contrasting effects across PTSD symptom clusters and types of childhood adversity suggest that multiple neurobiological mechanisms are involved in shaping thalamic volume posttrauma.

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More than 85% of individuals experience a traumatic event at some point in their life (1). Posttrauma psychopathology develops in a sizable minority of people exposed to trauma. For example, posttraumatic stress disorder (PTSD) has a lifetime prevalence of 6.8% in the United States (2), and in many cases, major depressive disorder (MDD) occurs independently of PTSD following a traumatic event (3,4). While the prevalence of PTSD following trauma exposure is greater than MDD in the near term, they have similar long-term prevalence rates (5). Comorbid PTSD and MDD, occurring in approximately

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50% of patients with PTSD, typically results in more severe symptomatology and more treatment-resistant illness (4,6,7). These challenges have led researchers to view these conditions not as completely independent disorders but as related aspects of a wider construct of posttrauma psychopathology (8).

Dysfunction of the hippocampus, amygdala, and ventromedial prefrontal cortex (vmPFC) resulting in altered fear learning and processing of affective information has been extensively demonstrated in posttrauma disorders (9,10). However, the thalamus has received less attention despite evidence of altered functional properties in posttrauma psychiatric groups (11–13). The thalamus is a key node in perceptual, cognitive, and affective processing circuits. It receives input from nearly every sensory organ system and reciprocally connects with virtually the entire brain, making it crucial for cortico-cortical communication, cortical arousal, modulating perceptual information, and integrating affective and memory-related information relevant to behavioral goals (14,15). Volumetric reductions or enlargements of the thalamus and thalamic nuclei have been linked to numerous psychopathologies including schizophrenia (16), obsessive-compulsive disorder (17), and bipolar disorder (18).

Thalamic volume has consistently been associated with trauma and posttrauma symptoms, but the directionality of the findings has been mixed. Individuals who develop PTSD or experience more severe PTSD symptoms following a traumatic event have lower volume of the thalamus compared with trauma-exposed individuals who do not develop PTSD (19–22). Conversely, thalamic nuclei volumes have been positively correlated with the overall severity of PTSD symptoms (21) and both positively and negatively correlated with PTSD hyperarousal and reexperiencing symptoms (21,23,24). The relationship between depressive symptoms or an MDD diagnosis and thalamic volume following trauma remains relatively unexplored. MDD diagnosis in non–trauma-exposed samples has been associated with lower whole thalamus and thalamic nuclei volumes (22,25,26). Among veterans with either MDD or PTSD, a greater number of suicidal behaviors—a sign of severe symptomatology—related to higher whole thalamus volume (27). Previous studies have also found that more severe childhood trauma is associated with lower volume of the thalamus among individuals with PTSD (19,20). Individuals with a history of childhood trauma are at a greater risk of developing psychopathology following trauma in adulthood (28). Thus, understanding the relationships between childhood trauma, posttrauma psychiatric symptoms, and thalamic volume is crucial to our overall understanding of how trauma impacts the brain.

The studies mentioned above had relatively small sample sizes, ranging from 14 to 383. Research suggests that associations between morphometric brain measures and psychiatric symptoms become robust and reproducible as sample size reaches thousands of participants (29). Smaller sample sizes result in more homogeneous samples, limiting the ability to generalize to a wider population. Small samples also lead to greater sampling variability across studies, which increases sign error and reduces reproducibility of results. A previous ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) PTSD study investigated subcortical brain volumes in PTSD with a large sample (N = 1868) and found smaller thalamic volume in PTSD, but the result did not survive adjustment for intracranial volume (ICV) or multiple comparison correction (30). However, several limitations of the study, including using meta-analysis rather than mega-analysis and only examining whole thalamus volume and not thalamic nuclei volumes, restrict the conclusions that can be drawn from the findings. To address previous limitations, we analyzed structural brain MRI scans from 2058 participants by aggregating data from 20 worldwide sites in the ENIGMA PTSD working group. Volumes of the left and right thalamus and 25 individual thalamic nuclei per hemisphere were compared in trauma-exposed control participants and participants with posttrauma psychopathology, which include PTSD-only, MDD-only, and comorbid PTSD+MDD. Based on previous findings, we hypothesized volumetric differences of the ventral motor nuclei and mediodorsal (MD) thalamus in relation to psychiatric diagnosis, symptom severity, and childhood trauma.

METHODS AND MATERIALS

Sample

Clinical and demographic data on the sample from the ENIGMA PTSD working group are shown in Table 1. T1-weighted brain MRI scans were collected from 20 sites (see Table S1 for demographics by site and Table S2 for inclusion and exclusion criteria by site). After removal of statistical outliers and participants with incomplete data, 2058 participants remained in the final analysis, including 1040 participants with posttrauma psychopathology and 1018 control participants (95.8% trauma exposed). All study procedures were approved by local institutional review boards (IRBs), and all participants provided written informed consent. Secondary data analysis was deemed exempt by the Duke University Medical Center IRB.

Assessment and Harmonization of Clinical Data Across Sites

Clinical diagnosis of PTSD was determined using a specific assessment tool at each site based on DSM-IV or DSM-5 criteria, which differed by site. Test-specific cutoff scores were used to determine MDD status. Severity of psychiatric symptoms was measured using a range of questionnaires and clinical interviews across the 20 sites (see Table S1). To allow for comparison of these different measures with each other, PTSD, MDD, and symptom cluster scores were normalized between 0 and 1. This was done by subtracting the minimum possible score from each participant's score and then dividing by the maximum possible score minus the minimum possible score, resulting in a severity ranging from 0 to 1 {severity $\in$ R$|0 < x < 1$}. No harmonization was performed for childhood trauma scores because all sites used the same test (Childhood Trauma Questionnaire [CTQ]).

Image Acquisition and Processing

T1-weighted brain MRI scans were acquired from each site (see Table S3 for scanning parameters of each site) and were processed via FreeSurfer (version 7.1.1). The *SegmentThalamicNuclei* pipeline in FreeSurfer (31) was then applied to

Table 1. Demographic and Clinical Data

Measure	Control	PTSD-Only	MDD-Only	Comorbid	Statistic	Significant Pairwise
n	1018	238	184	618	–	–
Age, Years	38.83 (11.01)	38.99 (10.92)	38.38 (10.51)	38.72 (10.54)	$F_{3,2054} = 0.08$, $p = .969$	–
Age Range	18–72	18–67	19–62	18–68	–	–
Female, %	25.34%	42.02%	34.78%	40.45%	$\chi^2_3 = 50.17$, $p < .001$	Control-comorbid; control-MDD only; control-PTSD only
PTSD Severity	0.11 (0.11)	0.46 (0.13)	0.26 (0.12)	0.58 (0.14)	$F_{3,2054} = 1931.08$, $p < .001$	All pairwise comparisons significant
MDD Severity	0.11 (0.10)	0.21 (0.09)	0.45 (0.12)	0.52 (0.16)	$F_{3,2054} = 1715.71$, $p < .001$	All pairwise comparisons significant
PTSD Symptoms						
n	285	115	55	264	–	–
Reexperiencing	0.09 (0.13)	0.42 (0.18)	0.25 (0.20)	0.55 (0.19)	$F_{3,715} = 465.62$, $p < .001$	All pairwise comparisons significant
Avoidance	0.10 (0.18)	0.53 (0.22)	0.24 (0.23)	0.61 (0.22)	$F_{3,715} = 316.65$, $p < .001$	All pairwise comparisons significant
Negative mood/cognition	0.04 (0.08)	0.37 (0.15)	0.14 (0.15)	0.50 (0.19)	$F_{3,715} = 491.52$, $p < .001$	All pairwise comparisons significant
Hyperarousal	0.11 (0.14)	0.43 (0.18)	0.29 (0.19)	0.56 (0.16)	$F_{3,715} = 505.93$, $p < .001$	All pairwise comparisons significant
CTQ Severity						
n	270	75	54	156	–	–
CTQ total	37.37 (13.78)	56.49 (24.14)	40.96 (16.09)	62.77 (23.92)	$F_{3,551} = 53.15$, $p < .001$	Control-comorbid; MDD only-comorbid; PTSD only-control
Emotional abuse	7.91 (3.94)	13.21 (6.36)	8.65 (4.53)	15.35 (6.59)	$F_{3,551} = 58.77$, $p < .001$	Control-comorbid; PTSD only-control
Physical abuse	7.42 (3.59)	9.92 (5.14)	8.31 (4.32)	10.84 (5.61)	$F_{3,551} = 17.55$, $p < .001$	Control-comorbid; PTSD only-control
Sexual abuse	6.58 (3.98)	10.72 (6.96)	6.96 (4.67)	11.74 (6.95)	$F_{3,551} = 21.87$, $p < .001$	Control-comorbid; PTSD only-control
Emotional neglect	8.84 (4.24)	13.01 (6.07)	9.48 (4.38)	14.72 (5.97)	$F_{3,551} = 36.97$, $p < .001$	Control-comorbid; PTSD only-control
Physical neglect	6.62 (2.52)	9.63 (4.50)	7.56 (3.14)	10.12 (4.56)	$F_{3,551} = 33.82$, $p < .001$	Control-comorbid; MDD only-comorbid; PTSD only-control

Values are reported mean (SD), *n*, or %. Symptom severity scores have been normalized between 0 and 1. MDD data are not available for ∼20% of CTQ subset.
CTQ, Childhood Trauma Questionnaire; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

segment the thalamus into 25 distinct nuclei in each hemisphere. Volumetric estimates were obtained for the left and right whole thalamus and for each of the 50 thalamic nuclei (Figure 1). The thalamus can be broadly divided into 6 subregions: the posterior, ventral, anterior, lateral, medial, and intralaminar regions. An alternative classification scheme divides the thalamus by nuclei function and recognizes sensorimotor nuclei, limbic nuclei, and association nuclei involved in both sensorimotor and limbic processes (32).

Nuclei in the segmentation include sensorimotor nuclei in the posterior subregion (lateral geniculate nucleus; medial geniculate nucleus; limitans-suprageniculate; and anterior pulvinar [PuA], inferior pulvinar [PuI], lateral pulvinar [PuL] and medial pulvinar [PuM]) and ventral subregion (ventral posterolateral [VPL], ventromedial, ventral lateral anterior, ventral lateral posterior, ventral anterior [VA], and ventral anterior magnocellular [VAmc]); limbic nuclei in the medial subregion (mediodorsal medial [MDm], mediodorsal lateral [MDl], paratenial, and reuniens [Re]), intralaminar subregion (central medial [CeM]), and anterior subregion (anteroventral [AV]); and association nuclei in the intralaminar subregion (central lateral [CL], paracentral, centromedian [CM], parafascicular [Pf]) and lateral subregion (lateral posterior [LP] and lateral dorsal [LD]).

To address the problem of potential missegmentations, statistical outliers were removed following standard ENIGMA quality control procedures for structural segmentations. Segmentations with any thalamic hemisphere or nuclei that exceeded ±2.698 SDs (33) from the sample mean for that region were removed completely from statistical analysis (control *n* = 234, PTSD-only *n* = 60, MDD-only *n* = 31, comorbid PTSD+MDD *n* = 111).

Volume Harmonization Across Sites

To adjust for the effects of site on thalamic volume, the *neuroHarmonize* package in Python (version 3.9.19) was used to adjust for variability related to site while preserving variability related to the variables of interest (34). The *neuroHarmonize* package implements the *ComBat-GAM* algorithm based on an empirical Bayes framework. For sites that collected data from multiple MRI scanners, each scanner was treated as a separate site to adjust for scanner-related variability in thalamic

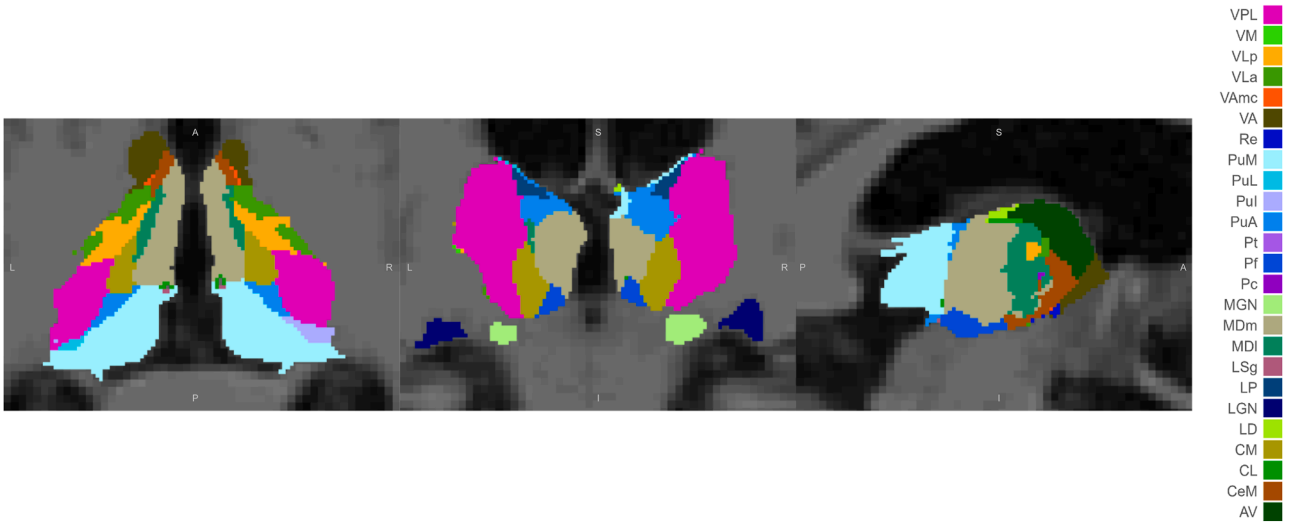

Figure 1. Thalamic segmentation. Axial (left), coronal (middle), and sagittal (right) views of an example thalamic segmentation in participant space with thalamic nuclei color coded. A, anterior; AV, anteroventral; CeM, central medial; CL, central lateral; CM, central medial; I, inferior; LD, laterodorsal; LGN, lateral geniculate nucleus; LP, lateral posterior; LSg, limitans-suprageniculate; MDl, mediodorsal lateral; MDm, mediodorsal medial; MGN, medial geniculate nucleus; P, posterior; Pc, paracentral; Pf, parafascicular; Pt, paratenial; PuA, anterior pulvinar; PuL, lateral pulvinar; PuM, medial pulvinar; Pul, pulvinar; Re, reuniens; S, superior; VA, ventral anterior; VAmc, ventral anterior magnocellular; VLa, ventrolateral anterior; VLp, ventrolateral posterior; VM, ventromedial; VPL, ventral posterolateral.

volume. All harmonization models included sex, age, and ICV as covariates, with age being set as a smooth term to account for nonlinear effects, in addition to the clinical variables of interest. The site-harmonized thalamic volumes were then entered into linear models to test for significant associations between thalamic volume and the clinical variables of interest.

Statistical Analysis

The effects of psychopathology on whole thalamus and thalamic nuclei volume were examined. All models included sex, age, age^2, and ICV as covariates of no interest. Age^2 was included due to the large age range of our sample and the known nonlinear effects of age on brain volume (35,36).

An analysis of covariance (ANCOVA) was used to test for group differences between 4 diagnostic groups including participants with 1) PTSD-only, 2) MDD-only, and 3) comorbid PTSD+MDD and 4) control participants without PTSD or MDD (95.8% trauma exposed) (equation 1). Post hoc pairwise comparisons were performed on significant ANCOVA results. Cohen's *d* was used as a measure of effect size. Tests for the 50 thalamic nuclei were corrected for multiple comparisons using the Benjamini-Hochberg procedure with a false discovery rate (FDR) of $q = .05$ (37), and p values of post hoc pairwise comparisons were corrected for the 6 group comparisons using the Tukey honestly significant difference method.

$$\text{Volume} \sim \text{Group} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (1)$$

PTSD and MDD symptom severity were tested for associations with thalamic volume (equations 2 and 3). The interaction between PTSD and MDD severity was also examined (equation 4).

$$\text{Volume} \sim \text{PTSD severity} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (2)$$

$$\text{Volume} \sim \text{MDD severity} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (3)$$

$$\text{Volume} \sim \text{PTSD severity} \times \text{MDD severity} + \text{PTSD severity} + \text{MDD severity} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (4)$$

Specific psychiatric symptoms were examined by testing the association between DSM-5 symptom clusters for PTSD (criteria B, C, D, and E) and thalamic volume (equation 5). These symptom clusters refer to reexperiencing, avoidance, negative mood/cognition, and hyperarousal symptoms, respectively. Each symptom cluster was analyzed while controlling for the other symptoms to better understand the unique contributions of each symptom cluster.

$$\text{Volume} \sim \text{Cluster B} + \text{Cluster C} + \text{Cluster D} + \text{Cluster E} + \text{MDD severity} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (5)$$

Finally, childhood trauma was measured via the CTQ (38). Total CTQ scores and CTQ subscores—emotional abuse (EA), physical abuse (PA), sexual abuse (SA), emotional neglect (EN), and physical neglect (PN)—were tested for associations with thalamic volume (equations 6 and 7).

$$\text{Volume} \sim \text{CTQ total} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (6)$$

$$\text{Volume} \sim \text{EA} + \text{PA} + \text{SA} + \text{EN} + \text{PN} + \text{Sex} + \text{Age} + \text{Age}^2 + \text{ICV} \quad (7)$$

Dominance analysis was used to determine which model terms contributed the most to predicting thalamic volume using the *domir* package in R (39). Model terms of interest were ranked according to which term was assigned the highest proportion of model fit.

RESULTS

Psychiatric Diagnosis and Thalamic Volume

Statistically significant ANCOVA (equation 1) results are available in Table 2, and full statistical results are available in Table S4. Several thalamic nuclei showed significant volumetric differences between diagnostic groups (Figure S1).

Among participants with PTSD-only, smaller volume was found in the right PuA, right PuM, left VAmc, and right Pf nuclei compared with control participants. Among participants with MDD only, smaller volumes were found in the right MDl and right MDm nuclei compared with control participants.

Participants with comorbid PTSD+MDD displayed smaller volumes of the right MDl and the right MDm nuclei compared with control participants. Additionally, comorbidity was associated with larger volume of the left Re nucleus compared with participants with PTSD-only.

Symptom Severity and Thalamic Volume

Symptom severity was tested for associations with thalamic volume (equations 2–4) across the entire sample (N = 2058). PTSD symptom severity was significantly negatively correlated with left thalamus (b = −98.0, p = .022) and right thalamus (b = −114.91, p = .014) volumes. Volumes of the right PuA (b = −5.85, p_{FDR} = 0.038), right MDl (b = −0.967, p_{FDR} = 0.004), and right MDm (b = −25.45, p_{FDR} = 0.003) nuclei were also significantly negatively correlated with PTSD severity.

MDD symptom severity was not significantly correlated with left or right thalamus volume ($p > .05$). However, volume of the right MDl (b = −11.24, p_{FDR} = .002) and right MDm (b = −24.25, p_{FDR} = 0.012) nuclei were significantly negatively correlated with MDD severity.

A significant interaction between PTSD severity and MDD severity was found (equation 4), displaying a positive beta value for the right thalamus (b = 502.47, p = .008). Simple slopes analysis revealed that PTSD severity significantly negatively correlated with right thalamus volume only when MDD severity was <0.30 (Figure 2A). A significant positive relationship between MDD severity and right thalamus volume was observed only when PTSD severity was >0.66 (Figure 2B).

PTSD Symptom Clusters and Thalamic Volume

Reexperiencing, avoidance, negative mood/cognition, and hyperarousal PTSD symptoms (DSM-5 criteria B, C, D, and E symptom clusters) were tested for associations with thalamic volume (equation 5) across the entire sample with symptom-level data (n = 719). The variance inflation factor (VIF) was calculated for each term to assess the impact of multicollinearity on model fit and stability (reexperiencing VIF = 3.74, avoidance VIF = 3.02, negative mood/cognition VIF = 3.18, hyperarousal VIF = 3.49, and MDD severity VIF = 2.10). Further evaluation of multicollinearity was unwarranted because all VIF values were <5 (40).

Table 2. Significant Results From Pairwise Comparisons Between Diagnostic Groups

Region	ANCOVA			PTSD > Control			MDD > Control			Comorbid > Control			Comorbid > PTSD			Comorbid > MDD			MDD > PTSD		
	t	p	p_{FDR}	b	p	d	b	p_{HSD}	d	b	p_{HSD}	d	b	p_{HSD}	d	b	p_{HSD}	d	b	p_{HSD}	d
Right PuA	17.840	1.98×10^{-11}	4.94×10^{-10}	−4.335[a]	.022[a]	−0.208[a]	−2.880	.314	−0.138	−2.037	.232	−0.098	2.298	.473	0.110	0.842	.964	0.040	1.456	.894	0.070
Right PuM	15.955	2.96×10^{-10}	2.47×10^{-9}	−21.208[a]	.029[a]	−0.201[a]	−8.195	.769	−0.078	−7.264	.543	−0.069	13.944	.309	0.132	0.931	1.000	0.009	13.013	.594	0.123
Left VAmc	13.228	1.49×10^{-8}	6.77×10^{-8}	−0.550[a]	.045[a]	−0.190[a]	−0.053	.996	−0.018	0.011	1.000	0.004	0.560	.055	0.193	0.064	.994	0.022	0.496	.303	0.171
Right Pf	13.797	6.58×10^{-9}	3.65×10^{-8}	−1.341[a]	.037[a]	−0.195[a]	−0.892	.371	−0.130	−0.499	.497	−0.073	0.842	.378	0.122	0.393	.905	0.057	0.449	.911	0.065
Right MDl	13.342	1.26×10^{-8}	6.32×10^{-8}	−4.803	.084	−0.172	−6.766[a]	.014[a]	−0.242[a]	−5.256[a]	.002[a]	−0.188[a]	−0.452	.997	−0.016	1.510	.918	0.054	−1.963	.892	−0.070
Right MDm	13.125	1.73×10^{-8}	7.20×10^{-8}	−9.896	.205	−0.142	−16.158[a]	.020[a]	−0.232[a]	−12.987[a]	.002[a]	−0.186[a]	−3.090	.938	−0.044	3.172	.949	0.045	−6.262	.798	−0.090
Left Re	3.439	1.60×10^{-2}	1.90 × 10^{-2}	−0.405	.102	−0.166	−0.104	.952	−0.043	0.080	.920	0.033	0.485[a]	.046[a]	0.199[a]	0.184	.806	0.075	0.301	.593	0.123

The p values for ANCOVA results have been FDR corrected for the 50 thalamic nuclei, while p values for pairwise comparisons have been corrected using the Tukey HSD method for the 6 group comparisons.
ANCOVA, analysis of covariance; FDR, false discovery rate; HSD, honestly significant difference; MDl, mediodorsal lateral; MDm, mediodorsal medial; Pf, parafascicular; PuA, anterior pulvinar; PuM, medial pulvinar; Re, reuniens; VAmc, ventral anterior magnocellular.
[a]Significant pairwise results.

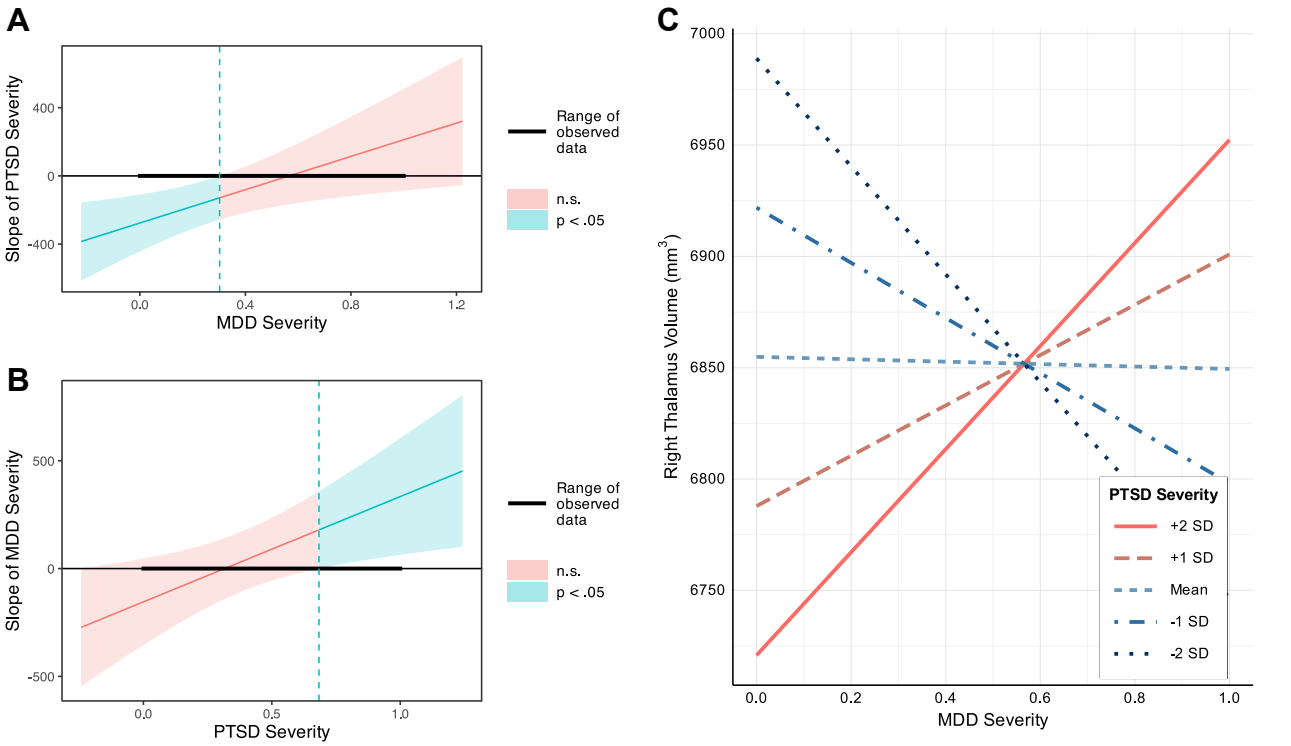

Figure 2. Interaction between posttraumatic stress disorder (PTSD) and major depressive disorder (MDD) severity. **(A)** PTSD severity is significantly negatively associated with right thalamus volume only when MDD severity is below 0.30. **(B)** MDD severity is significantly positively associated with right thalamus volume only when PTSD severity is above 0.66. **(C)** Right thalamus volume vs. MDD symptom severity with PTSD severity standard deviations plotted. Among individuals with high PTSD symptoms, MDD severity is positively associated with right thalamus volume. n.s., not significant.

Reexperiencing symptoms were significantly negatively correlated with left thalamus ($b = -258.6$, $p = .043$) and right thalamus ($b = -315.4$, $p = .015$) volumes. Negative mood/cognition symptoms were significantly negatively correlated with left thalamus volume ($b = -287.4$, $p = .019$). Conversely, avoidance symptoms were positively correlated with left thalamus volume ($b = 207.4$, $p = .033$).

Regarding individual thalamic nuclei, reexperiencing symptoms were negatively correlated with volume in the right LP nucleus ($b = -16.36$, $p_{FDR} = .044$). Hyperarousal symptoms were positively correlated with the right CL ($b = 6.52$, $p_{FDR} = .033$), right LP ($b = 16.03$, $p_{FDR} = 0.033$), and bilateral LD (left: $b = 6.86$, $p_{FDR} = .033$; right: $b = 7.05$, $p_{FDR} = .033$) nuclei.

For the left thalamus, dominance analysis revealed the largest proportion of model fit to be attributed to negative mood/cognition symptoms (3.52%), followed by reexperiencing (2.38%), avoidance (1.35%), hyperarousal (0.84%), and MDD severity (0.63%). For the right thalamus, negative mood/cognition symptoms accounted for 2.72% of model fit, followed by reexperiencing (2.70%), avoidance (1.29%), hyperarousal (0.90%), and MDD severity (0.57%).

Childhood Trauma and Thalamic Volume

Childhood trauma was assessed using the CTQ. Total CTQ scores (equation 6) and CTQ subscores (equation 7)—EA, PA, SA, EN, and PN—were tested for associations with thalamic volume across the entire sample with CTQ data ($n = 694$). To ensure that multicollinearity was not leading to an unstable model fit, the VIF was calculated for each model term (EA VIF = 4.30, PA VIF = 2.08, SA VIF = 1.76, EN VIF = 3.95, and PN VIF = 2.50). Further evaluation of multicollinearity was unwarranted because all VIF values were <5 (40).

Total CTQ scores were not significantly associated with thalamic volume or thalamic nuclei volume (all $ps > .05$). Regarding the 5 CTQ subscores, PA was positively correlated with the left thalamus volume ($b = 13.49$, $p = .001$), while EA was negatively correlated with left thalamus volume ($b = -12.27$, $p = .044$).

The left CeM ($b = -0.40$, $p_{FDR} = .024$), left Re ($b = -0.10$, $p_{FDR} = .026$), and left AV ($b = -0.72$, $p_{FDR} = .004$) nuclei were significantly negatively correlated with EA scores. Volumetric analyses were rerun with PTSD and MDD diagnoses included in the model, with consistent results. A summary of significant findings from all analyses can be seen in Figure 3.

Dominance analysis revealed that the greatest proportion of model fit for predicting left thalamus volume was explained by EA (1.40%), followed by PA (0.85%), SA (0.65%), EN (0.37%), and PN (0.26%). For the right thalamus, SA ranked highest (1.04%), followed by PN (0.69%), EA (0.54%), PA (0.47%), and EN (0.30%).

DISCUSSION

In the current investigation, we found lower volume among several nuclei spanning the ventral (VAmc), posterior (PuA, PuM),

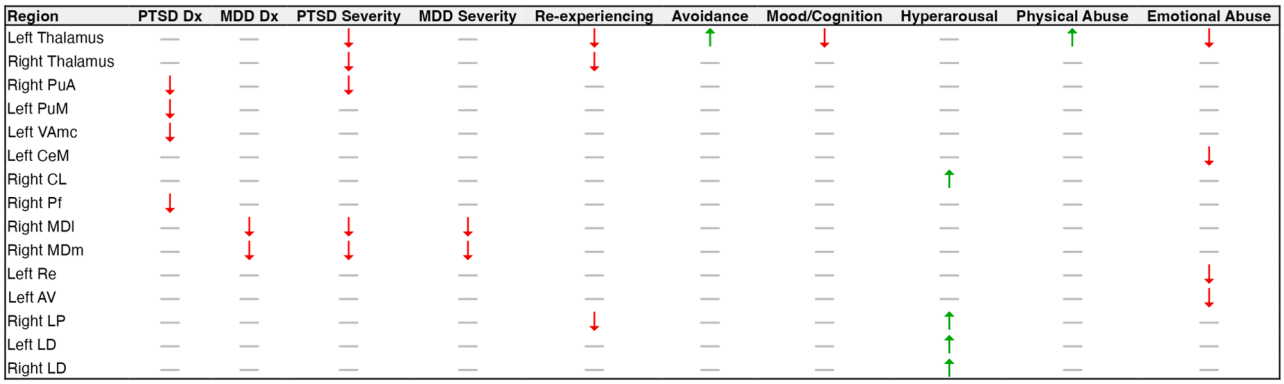

Figure 3. Summary of results. Green up arrows represent findings of larger volume, and red down arrows represent findings of smaller volume. Comparisons of comorbid posttraumatic stress disorder (PTSD) + major depressive disorder (MDD) diagnosis and the interaction term between PTSD and MDD severity are not shown. AV, anteroventral; CeM, central medial; CL, central lateral; Dx, diagnosis; LD, laterodorsal; LP, lateral posterior; MDl, mediodorsal lateral; MDm, mediodorsal medial; PuA, anterior pulvinar; PuM, medial pulvinar; Re, reuniens; VAmc, ventral anterior magnocellular.

intralaminar (Pf), and medial (MDm, MDl) subregions of the thalamus in relation to PTSD or MDD diagnostic status. Severity of PTSD symptoms negatively correlated with left and right whole thalamus volumes, while both PTSD and MDD severity negatively correlated with MD thalamus volume. We found a significant negative correlation of PTSD reexperiencing and negative mood/cognition symptoms with thalamic volume, but there was a positive association between avoidance and hyperarousal symptoms with thalamic volume. Finally, childhood PA positively correlated with left thalamus volume, while childhood EA negatively correlated with left thalamus and thalamic nuclei volume.

Differences in Thalamic Volume in Posttrauma Psychopathology

Smaller thalamic nuclei volumes were observed in the PTSD-only, MDD-only, and comorbid PTSD+MDD groups compared with the control group, and greater severity of PTSD and MDD symptoms were associated with smaller thalamus volume. However, we identified a significant interaction between PTSD and MDD severity, wherein high comorbidity was linked to larger thalamic volume, and the right Re nucleus displayed higher volume in the comorbid group compared with the PTSD-only group. These findings suggest that while mild to moderate posttrauma psychopathology is associated with lower thalamic volume, severe symptomatology and comorbidity is associated with higher thalamic volume. Thus, our results offer a nuanced explanation that partially reconciles previous findings of both smaller (19,21) and larger (24,27) thalamic volumes in trauma-related psychopathology. Previous investigations have reported reduced thalamic and thalamic subregion volumes in PTSD cases relative to trauma-exposed control participants, but patients with more severe symptoms exhibited greater thalamic volumes compared with patients with mild symptoms (21). Aspects of severe symptomatology, such as suicidal behaviors, have also been associated with larger thalamic volumes (27). Together, these published results support our finding that severe symptomatology and comorbidity may be related to greater thalamic volume.

Severity of specific PTSD symptom clusters improved model fit to a greater extent than overall PTSD severity and MDD severity. Negative mood/cognition and reexperiencing symptoms contributed the most to model fit for predicting whole thalamus volume and were negatively associated with thalamic volume, while avoidance and hyperarousal symptoms were positively associated with thalamic volume. This evidence points to distinct neurobiological mechanisms acting on the thalamus leading to differential relationships between distinct components of current symptomatology. Clinician assessment of patients with posttrauma psychiatric conditions and the development of individualized treatments may be improved by considering the degree of comorbidity and the severity of specific symptom profiles.

Childhood Trauma and Thalamic Volume

Previous research reported an inverse association between childhood trauma and thalamic volume in PTSD (19). We found no significant association with total CTQ scores and thalamic volume but significant effects regarding CTQ subscores. Childhood abuse was significantly related to thalamic volume while childhood neglect was not. Moreover, childhood PA had a positive association with thalamic volume while childhood EA had a negative association. These findings are consistent with evidence in the literature that different types of childhood adversity can lead to differential alterations in neurodevelopmental processes (41). Our results expand upon these ideas by demonstrating that the neurodevelopmental alterations implicated in distinct types of threat may be explained by specific brain changes to the thalamus.

Volumetric Changes to the Sensorimotor Thalamus in PTSD

The PTSD-only group exhibited lower volumes of the PuA, PuM, VAmc, and Pf nuclei compared with the control group. While the severity of both PTSD and MDD symptoms were associated with MD thalamus volume, only PTSD severity related to PuA volume. Moreover, the LD, LP, and CL nuclei were positively associated with hyperarousal symptoms, and the LP nucleus was also negatively associated with reexperiencing symptoms. These nuclei are predominantly implicated in sensorimotor functions and have strong connections to sensory and/or motor cortices. VAmc and Pf nuclei contain strong projections with motor cortices, while the LD, LP, PuA,

and PuM are considered visual association regions involved in visual or multisensory processing (42–44).

Volumetric differences in these regions may suggest a reduced ability to respond appropriately to incoming sensory information and properly integrate information from various motor regions for adaptive motor responses. PTSD is characterized in part by somatomotor complaints and hyper- or hyporesponding to stimuli across sensory modalities, leading to combinations of sensory sensitivity, low sensory registration, sensory avoidance, and sensation seeking (45). Altered sensory processing and multisensory integration have been theorized as prominent components of the emotion dysregulation experienced in PTSD (46). Clusters of symptoms related to sensorimotor responding, such as hyperarousal and avoidance symptoms (45), may explain volumetric changes to nuclei involved in sensory processing and the generation of motor responses.

Volumetric Changes to the Limbic Thalamus in MDD and Childhood EA

We observed volumetric differences in the MDm, MDl, Re, CeM, and AV nuclei, which corroborates previous research (19,21). Both MDm and MDl nuclei volumes were found to be lower in participants with MDD and participants with comorbid PTSD+MDD and negatively correlated with both PTSD and MDD symptom severity. The Re, CeM, and AV nuclei were negatively associated with childhood EA, and the Re nucleus also displayed larger volume in the comorbid PTSD+MDD group compared with the PTSD-only group. These regions are considered limbic nuclei due to their strong connectivity to subcortical and cortical limbic structures. The MDm, Re, and AV nuclei have the strongest connectivity to the hippocampus of any thalamic nuclei (47,48). Dense cortical connections are found with prefrontal and retrosplenial regions, making these nuclei crucial for learning and memory, spatial processing, and goal-directed behavior (47–49). Given the dense connectivity of these nuclei to the hippocampus and vmPFC, in addition to the strong evidence of hippocampal and vmPFC dysfunction in posttrauma psychopathology (10), we hypothesize that volumetric alterations to the limbic thalamus may play a role in impaired hippocampal-vmPFC communication posttrauma.

Limitations and Strengths

This study has several important limitations, including a lack of information on comorbid conditions beyond PTSD and MDD, history of alcohol and substance use, and psychotropic medication usage. Nevertheless, the exclusion criteria used by participating study sites likely reduced the impact of these confounding factors. Of the 20 contributing sites, 16 sites excluded individuals with a history of substance abuse, 17 sites excluded individuals with either any Axis I psychiatric disorder or a history of psychotic or manic symptoms, and 13 sites excluded individuals currently using any, or certain classes of, psychotropic medications. The exclusion of these individuals likely mitigated the influence of these potential confounds on our results. The sizable difference in the number of participants in each of the diagnostic groups is a limitation as well. Finally, a limitation of this study is the lack of standardized trauma load measures across all participating sites. While our control group is well matched for binary trauma exposure (95.8% trauma exposed), we cannot rule out the possibility that differences in trauma severity, chronicity, or type between diagnostic groups might have contributed to the observed thalamic volume differences.

Strengths of the current study are an order-of-magnitude larger sample size than any published study of thalamic nuclei volumes in posttrauma psychopathology. We examined volumetric differences in greater detail, with 25 thalamic nuclei as compared with 5 or 6 regions used in previous studies. Using a mega-analysis in a large multicohort consortium dataset enabled us to observe small effect sizes on thalamic nuclei. The clinical demography of our sample was diverse with respect to age, sex, clinical status, trauma type, race, and ancestry. Therefore, our findings are likely to generalize better than findings of previous studies with much smaller and homogeneous samples and trauma types. Another strength is using *ComBat-GAM* harmonization to adjust for site and scanner effects. *ComBat-GAM* is currently recognized as one of the best methods for removing site- or scanner-related variability from neuroimaging datasets (50).

Conclusions

Altered structure of the limbic and sensorimotor thalamus are linked to the onset and severity posttrauma psychiatric disorders. Smaller MD thalamus volume may contribute to dysregulated fear learning and extinction, affect, and mood, whereas alterations of sensorimotor nuclei could underlie hypervigilance and heightened sensory reactivity. Differential effects of PTSD symptom clusters and types of childhood adversity suggest that multiple neurobiological mechanisms are involved in shaping the thalamus posttrauma. Future research examining diagnostic status and changes in symptom severity over time is needed to understand whether altered thalamic volume constitutes a risk factor for or a consequence of psychiatric symptoms. The thalamus and some of its associated networks deserve consideration in future research on new interventions for posttrauma psychiatric conditions.

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RJD is the founder and president of and serves on the board of directors for the nonprofit organization Healthy Minds Innovations, Inc. CGA has served as a consultant, speaker, and/or on advisory boards for FSV7, Lundbeck, Psilocybin Labs, Genentech, and Janssen; served as an editor of *Chronic Stress* for Sage Publications, Inc.; and filed a patent for using mTOR (mechanistic target of rapamycin) inhibitors to augment the effects of antidepressants (filed on August 20, 2018). All other authors report no biomedical financial interests or potential conflicts of interest.

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