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Remodeling of the Cortical Structural Connectome in Posttraumatic Stress Disorder: Results From the ENIGMA-PGC Posttraumatic Stress Disorder Consortium

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ABSTRACT

BACKGROUND: Posttraumatic stress disorder (PTSD) is accompanied by disrupted cortical neuroanatomy. We investigated alteration in covariance of structural networks associated with PTSD in regions that demonstrate the case-control differences in cortical thickness (CT) and surface area (SA).

METHODS: Neuroimaging and clinical data were aggregated from 29 research sites in >1300 PTSD cases and >2000 trauma-exposed control subjects (ages 6.2–85.2 years) by the ENIGMA-PGC (Enhancing Neuro Imaging Genetics through Meta Analysis–Psychiatric Genomics Consortium) PTSD working group. Cortical regions in the network were rank ordered by the effect size of PTSD-related cortical differences in CT and SA. The top-*n* (*n* = 2–148) regions with the largest effect size for PTSD > non-PTSD formed hypertrophic networks, the largest effect size for PTSD < non-PTSD formed atrophic networks, and the smallest effect size of between-group differences formed stable networks. The mean structural covariance (SC) of a given *n*-region network was the average of all positive pairwise correlations and was compared with the mean SC of 5000 randomly generated *n*-region networks.

RESULTS: Patients with PTSD, relative to non-PTSD control subjects, exhibited lower mean SC in CT-based and SA-based atrophic networks. Comorbid depression, sex, and age modulated covariance differences of PTSD-related structural networks.

CONCLUSIONS: Covariance of structural networks based on CT and cortical SA are affected by PTSD and further modulated by comorbid depression, sex, and age. The SC networks that are perturbed in PTSD comport with converging evidence from resting-state functional connectivity networks and networks affected by inflammatory processes and stress hormones in PTSD.

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Posttraumatic stress disorder (PTSD) is a psychiatric condition that develops in vulnerable individuals after experiencing or witnessing a life-threatening event (1). PTSD-related changes in cortical thickness (CT) (2–5) and surface area (SA) (6,7) are found in specific cortical regions. However, relatively little is known about how PTSD affects coordinated patterns of CT and SA differences among affected cortical regions. We sought to examine PTSD effects on networks made up of cortical regions that have the greatest and the least between-group differences in CT and SA. Identifying such networks may lend support for one or more etiopathologic models of PTSD.

Structural covariance (SC) refers to the phenomenon of covarying structural brain imaging measures between cortical regions and across individuals. This covariance may be instantiated as an SC network (SCN). SCN measures are shown to be concordant with tract-based white matter connectivity, synchronous neuronal activity (e.g., functional connectivity) (8,9), and spatial patterns of gene transcription, each of which lends biological support to SCNs (10). SCNs may index mutually trophic factors between regions that covary over the course of neurodevelopment (9). Differences in SC are associated with a variety of neuropsychiatric disorders including PTSD (11–13), schizophrenia, autism, obsessive-compulsive disorder (14,15), and even trauma exposure (16).

Our investigation of structural networks with significantly different covariance was motivated by two complementary models for understanding PTSD. There is converging evidence that neurobiological mechanisms drive concerted patterns (covariance) of atrophy or hypertrophy across selected brain regions. There is generally more evidence supporting a role for CT-derived networks than SA-derived networks. Concerted processes operative in healthy neurobiological states are perturbed by disease to effect patterns of network atrophy or hypertrophy. These neurobiological perturbations may manifest as changes in network covariance. Neurobiologically deleterious processes in PTSD may instigate atrophy in a coordinated manner across many regions to reveal atrophic networks. Deleterious processes in PTSD include chronic alteration of stress hormone levels such as cortisol and norepinephrine (17,18), epigenetics mechanisms such as methylation (19,20), inflammatory processes such as oxidative stress (21) and cytokines (22), and accelerated aging through the combined effect of these and other processes (23). Alternatively, between-group differences in network SC may support one or the other prevailing neural systems model of PTSD. For instance, a dominant model of PTSD is that fear learning systems go awry in the aftermath of trauma. Behaviorally, slow or incomplete fear extinction and rapid fear reinstatement contribute to symptoms of PTSD. Effective fear learning is dependent on the healthy function of underlying brain networks. Functional connectivity networks have been found to be congruent with SCNs (24,25). Thus, between-group differences in structural networks may simply reflect the between-group differences in functional networks, and these differences pervade networks (structural and functional) involved in fear learning behavior. It is also possible that we might find hypertrophy across different networks that mediate compensatory responses to disrupted fear learning.

Wannan *et al.* (26) pioneered an innovative method to investigate the mean SC of networks constituted from regions selected by rank ordering regions most affected by the illness of interest. This method considers only the most highly ranked regions in forming networks rather than all regions as in previous SCN analyses. Their findings in schizophrenia suggest that some cortical networks connecting diverse regions may propagate cortical features from one region to another, leading to distributed cortical remodeling (9). Our approach, which modified their method, considered three classes of networks: 1) regions most affected by virtue of lower CT in PTSD formed the so-called atrophic networks; 2) regions most affected by virtue of higher CT in PTSD formed the so-called hypertrophic networks; and 3) regions least affected by PTSD formed stable networks. Rank ordering of regions was based on the effect size of between-group differences in CT or SA. The threshold for considering effect sizes (top-*n*) was initially set to the two most affected regions and was repeated for networks of up to 148 regions (top-*n* = 2, 3, 4, . . .148). Thus, networks ranging in size from 2 to 148 regions, in increments of one region, were tested. The SC of a network was calculated as the average effect size of the regions under consideration.

Even in the absence of statistically significant group differences for individual cortical regions, significant group differences in covariance were detected in networks consisting of regions with the greatest between-group differences. We examined both CT-based and SA-based networks because CT and SA index distinct features of neuronal organization (27–29). This approach enhanced sensitivity to cortical morphometry and network covariance differences associated with PTSD, given that CT- and SA-based networks may reflect different interactions between regions or distinct aspects of the same interaction between regions (30,31). Cortical volume was not examined because it is readily derived from mean CT and SA by simple multiplication of these two terms. However, CT and SA possess different biological, developmental, and genetic determinants, as we discuss later.

We hypothesized that the mean covariance of *n*-region networks would be higher than the mean covariance of randomly selected *n*-region networks in both PTSD and trauma-exposed control groups. Confirmation of this hypothesis would tell us that networks constituted from selected (top-*n*) regions are more structurally interconnected than networks of the same size composed of randomly selected regions. We further hypothesized that mean SC would be modulated by PTSD diagnosis, as well as by PTSD and comorbid depression, given that the two disorders are highly comorbid (32). We predicted greater impact of PTSD on SA-based networks than on CT-based networks because SA generally drives performance more directly for a variety of cognitive and affective processes (33,34). We also know that SA has an outsized role compared with CT in various neurobiological, neurodevelopmental, and neurogenetic processes. We predicted that because stable networks are made of regions that are least affected by PTSD, their covariance might be stronger than in non-PTSD because these networks of the least affected regions might compensate for disrupted networks composed of highly affected regions. We posited that because atrophic networks are made of regions most diminished by illness, the disease process would not necessarily affect all network regions in a systematic way, effectively lowering covariance. By contrast, we predicted that

trauma-exposed non-PTSD subjects might be protected from developing symptoms because their atrophic networks maintained their healthy level of covariance. If hypertrophic networks result from higher than normal levels of trophic factors, whereas atrophic networks result from lower than normal levels of trophic factors, then we might reason that atrophic networks and hypertrophic networks would experience the same perturbations. However, given evidence that stress hormones and inflammatory processes play a role in regional atrophy but a lack of evidence for a role in regional hypertrophic, we predicted that hypertrophic networks would demonstrate different outcomes in relation to PTSD than atrophic networks. Specifically, we hypothesized that atrophic networks, unlike hypertrophic networks, would play a central role in modulating the effects of PTSD. Finally, we explored interaction effects of sex, age, and depression on PTSD.

METHODS AND MATERIALS

Participants

All data, aggregated by the ENIGMA-PGC (Enhancing Neuro Imaging Genetics through Meta Analysis–Psychiatric Genomics Consortium) PTSD Working Group, were shared by 29 sites located in five countries (n = 3438 for CT and 3436 for SA; ages 6.2–85.2 years). Demographic and clinical information is summarized in Table 1. Only participants with clear information of PTSD diagnosis and sex were included in the following analyses (PTSD/non-PTSD n = 1344/2073 for CT and 1348/2066 for SA). The specific psychometric instruments and magnetic resonance imaging acquisition parameters used at each study site are listed in Tables S1 and S2, respectively. For detailed information of clinical measurements, see Supplemental Methods. All study sites obtained approval from

Table 1. Demographic and Clinical Information per Site

Site	Number of Participants				Age, Years, Mean ± SD	Trauma	MDD, %	Type
	CT	SA	F/M	PTSD/non-PTSD				
ADNIDOD	194	194	1/193	80/106	69.0 ± 5.0	Y	2.5	Military
Booster (AMC)	75	75	35/40	38/37	40.0 ± 10.0	Y	31	Police
Columbia	88	88	57/31	53/35	36.0 ± 9.8	Y	24	Civilian
Duke University (De Bellis)	115	117	62/53	29/86	10.0 ± 2.6	Y/N	N/A	Civilian
Minneapolis VAMC	169	171	8/161	74/95	33.0 ± 7.9	Y	28.4	Military
Duke University/Durham VA	385	385	75/310	114/270	40.0 ± 10.0	Y	40.3	Both
Ghent	67	67	67/0	8/59	37.0 ± 12.0	N	46.3	Civilian
Groningen (Charité Berlin)	40	40	40/0	40/0	38.0 ± 10.0	Y	67.5	Civilian
University of Wisconsin (Grupe)	57	58	4/53	19/38	31.0 ± 6.4	Y	100	Military
Emory GTP	174	174	169/5	66/108	38.0 ± 13.0	Y	51.7	Civilian
INTRUST	373	373	145/220	109/262	35.0 ± 14.0	Y	21.7	Both
University of Wisconsin (Larson)	67	67	34/33	20/47	33.0 ± 11.0	Y	0	Civilian
Leiden	52	52	45/7	22/30	15.2 ± 2.0	N	19.2	Civilian
Mannheim	48	48	48/0	48/0	36.0 ± 12.0	Y	97.9	Civilian
McLean	52	52	52/0	39/13	38.0 ± 12.0	Y	75	Civilian
Muenster	47	47	42/5	21/26	27.0 ± 7.0	Y	34	Civilian
Phan	43	43	0/43	23/20	32.0 ± 8.0	Y	53.5	Military
McLean (Rosso)	106	97	57/49	21/85	34.0 ± 9.0	Y	23	Civilian
University of Toledo	76	76	34/42	15/61	35.0 ± 11.3	Y	41	Both
UCAS	70	70	38/32	34/36	50.0 ± 7.0	Y	64.3	Civilian
Cape Town	62	63	62/0	7/55	29.0 ± 8.0	Y	50	Civilian
University of Washington	255	255	130/125	53/202	14.0 ± 3.1	Y	15.3	Civilian
Waco VA	66	66	10/56	41/25	41.0 ± 11.1	N	67	Military
West Haven VA	72	71	8/63	34/40	35.0 ± 10.0	Y	75	Military
Yale	70	70	11/59	22/48	29.2 ± 9.2	Y	0	Civilian
UNSW	162	163	99/63	49/113	40.4 ± 8.0	Y	28.4	Civilian
South Dakota	123	123	24/99	78/45	29.0 ± 7.0	Y	35	Both
Stellenbosch	260	260	188/72	121/139	41.0 ± 13.0	Y	0	Civilian
Stanford	71	71	41/29	70/1	37.0 ± 11.3	Y	0	Civilian
Total	3438	3436	1586/1843	1350/2076	–	–	29.9	–

Trauma indicates whether the non-PTSD participants are trauma exposed; for type, participants are from military/police, civilian, or both units.

ADNIDOD, Alzheimer's Disease Neuroimaging Initiative–Department of Defense; AMC, academic medical center; CT, cortical thickness; F, female; GTP, Grady Trauma Project; M, male; MDD, major depressive disorder; N, no; PTSD, posttraumatic stress disorder; SA, surface area; UCAS, Universities and Colleges Admissions Service; UNSW, University of New South Wales; VA, Veterans Affairs; VAMC, VA Medical Center; Y, yes.

local institutional review boards or ethics committees. All participants provided written informed consent.

Imaging Data Preprocessing

For details of imaging data preprocessing, see Supplemental Methods.

Harmonizing Data Across Sites

ComBat was used to harmonize CT and SA values by removing the effects of study sites while preserving inherent biological associations in the data (35). For more details, see Supplemental Methods.

Adjusting for Confounding Factors

Age, age^2, sex, and mean whole-brain CT/SA estimates were regressed from the CT/SA estimates with a linear model (36). The age^2 term adjusted for possible nonlinear effects of age on CT/SA. The mean whole-brain CT/SA estimate was included as a regressor to adjust for globally higher CT/SA estimates to reflect larger regional CT/SA estimates. For more details, see Supplemental Methods.

Top-*n* Regions SC Analyses

The pipeline for the top-*n* regions SC analysis is shown in Figure 1A. The top-*n* regions SC analysis was limited to networks consisting of the top-*n* (n = 2–148) cortical regions that were selected by rank ordering PTSD-related changes in CT or SA by Cohen's *d* effect sizes (Figure 2 and Table S4). Standardized effect size estimates such as Cohen's *d* are independent of the units or magnitude of CT or SA values.

We examined three types of rank ordering of regions to generate three network types (Figure 1B): 1) regions with higher CT in PTSD than non-PTSD ordered from the largest positive to the largest negative effect size were used to construct hypertrophic networks, 2) regions with higher CT in non-PTSD than PTSD rank ordered from the largest positive to the largest negative effect size were used to construct atrophic networks, and 3) regions identified by comparing CT in PTSD to non-PTSD groups rank ordered from smallest to largest effect size were used to construct stable networks. The same approach used for CT was repeated for SA. An illustration depicting CT-based hypertrophic networks for top 3, top 10, and top 50 regions is shown in Figure 1C.

Pearson correlation coefficients were computed across subjects per group between the CT/SA estimates for each of pairs of regions with the network. All correlation coefficients were *r*-to-*z* transformed to improve normality and yielded a unique connectivity matrix for each participant group. The resulting matrix quantified SC, which was interpreted for this study as a measure of the connectivity strength between regions.

Actual Networks Versus Random Networks

The mean SC (mean of all positive SC values within a network) of an actual network of the top-*n* regions was contrasted (i.e., mathematical subtraction) with the values of mean SC from 5000 random networks consisting of *n* randomly chosen regions. This test was performed for SC measured in PTSD and non-PTSD groups, as well as between-group difference in SC. The randomly chosen regions were matched to the top-*n* regions for each value of *n*, based on the number of regions in each hemisphere and the mean Euclidean distance between all possible pairs of regions. The Euclidean distance was calculated based on the distance between the centers of cortical regions. This approach was conducted by generating 5000 randomly chosen sets of *n* regions that were matched on the number of regions per hemisphere. We then repeatedly

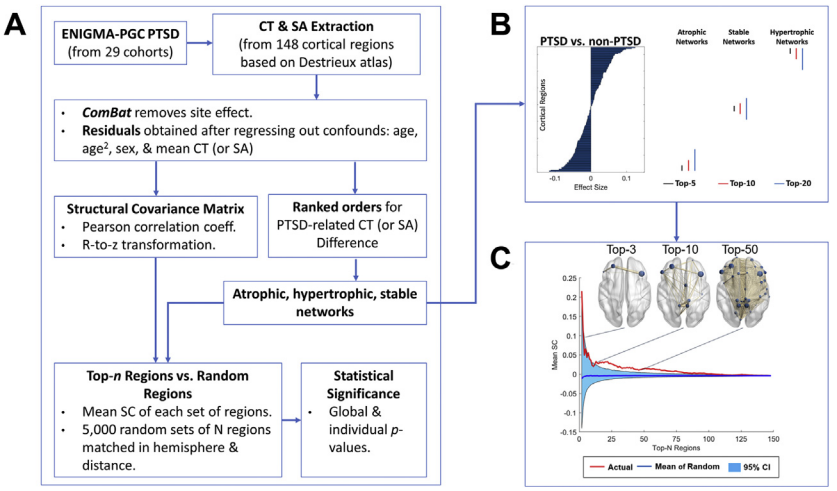

Figure 1. Analyses pipelines. **(A)** Anatomical neuroimaging data from 29 research sites were aggregated by the ENIGMA-PGC (Enhancing Neuro Imaging Genetics through Meta Analysis–Psychiatric Genomics Consortium) posttraumatic stress disorder (PTSD) working group. Regional estimates of cortical thickness (CT) and surface area (SA) extracted from 148 cortical regions based on the Destrieux atlas (64) were harmonized to remove site effects with *ComBat* approach and entered into a linear model to adjust for effects of age, age^2, sex, and whole-brain mean CT (or SA). The residuals were used to compute Pearson correlation coefficients for each pair of cortical regions across subjects within groups. The correlation coefficients were *r*-to-*z* transformed to improve normality and yielded a structural covariance (SC) matrix for each participant group. The cortical regions were rank ordered according to the magnitude of effect size when contrasting CT (or SA) between PTSD and non-PTSD groups. The top-*n* (n = 2–148) regions with the largest effect size of differences for PTSD > non-PTSD constituted atrophic networks and PTSD < non-PTSD constituted hypertrophic networks, while the smallest effect size constituted stable networks. The mean SC of a given *n*-region network measured by the mean of positive correlations between all possible pairs of regions was compared with 5000 randomly generated *n*-region networks matched for hemisphere and distance. Both global and individual tests were used to compute statistical significance based on the proportion of mean SC values from randomly chosen sets of *n* regions that exceeded or equaled the mean SC of the actual top-*n* network. **(B)** The top-*n* (n = 5, 10, and 20) regions showed the largest effect size in CT (or SA) for PTSD < non-PTSD (atrophic networks); the largest effect size of PTSD > non-PTSD (hypertrophic networks); or the smallest effect size of PTSD vs. non-PTSD (stable networks). **(C)** CT-based hypertrophic networks for top 3, top 10 and top 50 regions.

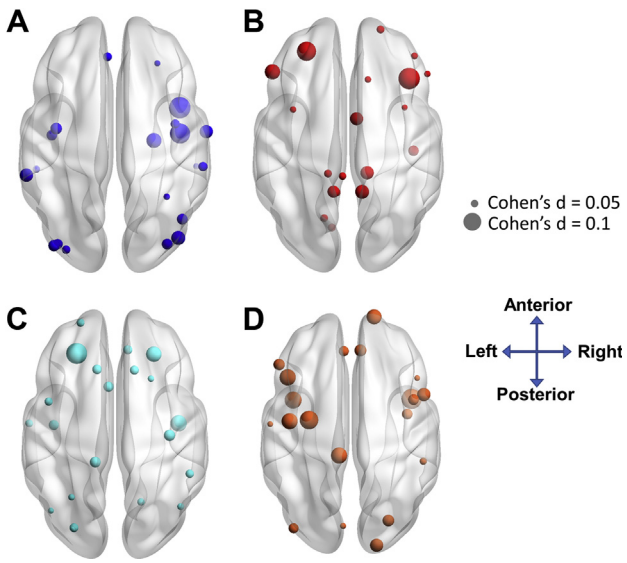

Figure 2. The top 20 regions showing posttraumatic stress disorder (PTSD)–related differences. **(A, B)** The top 20 regions where **(A)** PTSD < non-PTSD and **(B)** PTSD > non-PTSD in cortical thickness. **(C, D)** The top 20 regions where **(C)** PTSD < non-PTSD and **(D)** PTSD > non-PTSD in surface area. Node size represents the magnitude of effect size for between-group differences per region. Warm color denotes PTSD > non-PTSD, and cool color denotes PTSD < non-PTSD. Region names are listed in Table S4. Two examples are shown on the right to denote the node size and the corresponding effect size (Cohen's *d*). The directions of the brain maps (axial view) are also shown.

replaced the set of *n* regions with the largest or smallest mean distance by a randomly generated set of *n* regions until the mean distance of the actual regions was not significantly different than the mean distance from the set of randomly chosen *n* regions (one-sample *t* test thresholded at 5%) or the number of searches exceeded 3000.

We conducted replication analyses to test the reliability of our results, performed two tests of statistical significance that were complementary to each other (the global test and the individual test), and corrected for multiple comparisons using the false discovery rate method (37). For more details, see Supplemental Methods.

To test the hypothesis that brain hubs that are strongly connected with other areas (38) play a role in the spatial distribution of PTSD-related cortical changes, we investigated the association between the effect size of cortical changes for each region and the average of positive SC between the said region and all other cortical regions. For details, see Supplemental Methods, Supplemental Results, and Supplemental Discussion.

PTSD × Sex Interaction

To investigate the modulation of sex on PTSD-related SCNs, we first divided PTSD and non-PTSD groups into male and female subgroups (Table S5). Two-way interactions were calculated by first contrasting PTSD (relative to its random networks) to non-PTSD (relative to its random networks) within each sex subgroup and then calculating the difference between the two contrasts. More detailed comparisons between each pair of subgroups were conducted when there was a significant interaction effect between PTSD diagnosis and sex.

PTSD × Age Interaction

To investigate the modulation effect of depression on PTSD-related SCNs, we first divided PTSD and non-PTSD groups into eight decadal subgroups based on age: <10 years, 10 ≤ age < 15 years, 15 ≤ age < 20 years, 20 ≤ age < 30 years, 30 ≤ age < 40 years, 40 ≤ age < 50 years, 50 ≤ age < 60 years, and ≥60 years (Table S6). Two-way interactions were calculated by first contrasting PTSD (relative to its random networks) to non-PTSD (relative to its random networks) within each age subgroup and then calculating the difference between the two contrasts. More detailed comparisons between each pair of subgroups were conducted when there was a significant interaction effect between PTSD diagnosis and age.

PTSD × Depression Interaction

To investigate the modulation effect of depression on PTSD-related SCNs, we first divided PTSD and non-PTSD groups into subgroups based on depression diagnosis consisting of two subgroups: depressed and nondepressed (Table S7). Two-way interactions were calculated by first contrasting PTSD (relative to its random networks) to non-PTSD (relative to its random networks) within each depression subgroup and then calculating the difference between the two contrasts. More detailed comparisons between each pair of subgroups were conducted when there was a significant interaction effect between PTSD diagnosis and depression.

RESULTS

Effect Size of CT and SA Differences

Effect sizes for between-group differences in CT and SA are shown in Figure 2 and reported in Table S4. Effect sizes ranged from −0.103 (atrophic) to +0.112 (hypertrophic) for CT and from −0.110 (atrophic) to +0.083 (hypertrophic) for SA.

Top-*n* Regions SC Analyses

More detailed results of actual networks versus random networks in PTSD (Figure 3 and Table 2) and in non-PTSD (Figure 4 and Table 2) are listed in Supplemental Results for the methodologic confirmation.

PTSD Versus Non-PTSD. As displayed in Figure 5 and Table 2, global tests showed that PTSD versus non-PTSD participants had lower mean SC in both CT-based (p = .014) and SA-based (p = .024) atrophic networks.

No significant differences were found in CT-based (p = .098) and SA-based ($p > .5$) hypertrophic networks or CT-based ($p > .5$) and SA-based ($p > .5$) stable networks. No individual test results survived correction (p values > .05).

Replication Analyses Results. As shown in Figure 6, the global test results displayed in Figures 3–5 and Table 2 are reliable because the area under the curve of mean SC for the results based on all 29 sites was always located within the

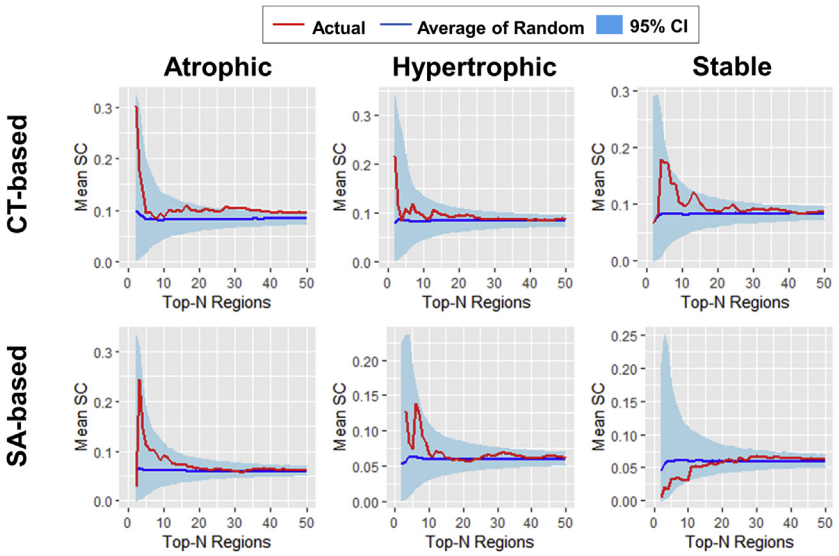

Figure 3. Mean structural covariance (SC) of patients with posttraumatic stress disorder. Global tests showed that patients with posttraumatic stress disorder have higher mean SC in both cortical thickness (CT)–based ($p < .001$) and surface area (SA)–based ($p = .017$) atrophic networks, both CT-based ($p = .029$) and SA-based ($p = .017$) hypertrophic networks, and CT-based ($p < .001$) but not SA-based ($p > .5$) stable networks than the corresponding random networks. The curves of networks with up to 50 nodes are shown for illustrative purposes, given that the mean SC of actual networks and the mean SC of the average of random networks were very similar for large network sizes. Red curve indicates mean SC of the actual networks. Blue curve indicates mean SC of the average of 5000 random networks. Light blue ribbon indicates 95% CI of the 5000 random networks.

95% confidence interval of the area under the curve of mean SC from 5000 iterations, leaving out three different sites with each iteration of the analysis across all types of networks.

Only a very small number of the individual test results were beyond their 95% confidence intervals. These include the CT-based stable network with top 24 regions in the non-PTSD group, the SA-based atrophic network with top 11 regions for the PTSD versus non-PTSD comparison, and the SA-based hypertrophic networks with top 32, 33, 34, or 35 regions for the PTSD versus non-PTSD comparison.

PTSD × Depression Interaction. As listed in Figure 7, global tests showed a significant interaction effect in CT-based atrophic networks ($p = .029$) (Figure 7A). Further analyses showed that participants with depression alone had greater mean SC than the participants with PTSD and comorbid depression ($p < .001$), participants with PTSD alone ($p < .001$), and healthy control subjects ($p < .001$).

There was a significant interaction effect in SA-based atrophic networks ($p = .001$) (Figure 7B). Further analyses showed that participants with PTSD alone had greater mean SC than participants with PTSD and comorbid depression ($p < .001$) and healthy control subjects ($p = .014$). Participants with depression alone also had greater mean SC than participants with PTSD and comorbid depression ($p < .001$) and healthy control subjects ($p < .001$).

Table 2. AUC of Mean SC for the Actual Network and the Average of 5000 Random Networks

	CT-Based Networks				SA-Based Networks			
Network Type	Actual	Random	95% CI	Global *p*	Actual	Random	95% CI	Global *p*
PTSD								
Atrophic	13.975	12.195	11.918 to 12.572	<.001[a]	9.480	8.725	8.494 to 9.126	.017[b]
Hypertrophic	12.846	12.104	11.839 to 12.512	.029[b]	9.356	8.692	8.483 to 9.061	.017[b]
Stable	13.211	12.193	11.938 to 12.567	<.001[a]	8.652	8.689	8.473 to 9.049	>.500
Non-PTSD								
Atrophic	14.483	12.397	12.112 to 12.785	<.001[a]	9.616	8.511	8.286 to 8.918	<.001[a]
Hypertrophic	12.832	12.317	12.049 to 12.729	.139	9.050	8.450	8.242 to 8.804	.014[b]
Stable	11.977	12.260	11.983 to 12.642	.264	8.798	8.566	8.363 to 8.890	.732
PTSD vs. non-PTSD								
Atrophic	−0.507	−0.205	−0.382 to −0.037	.014[b]	−0.136	0.211	0.052 to 0.372	.024[b]
Hypertrophic	0.015	−0.212	−0.390 to −0.037	.098	0.332	0.240	0.079 to 0.403	>.500
Stable	−0.155	−0.141	−0.312 to 0.033	>.500	0.172	0.215	0.062 to 0.376	>.500

Actual: the mean SC of the actual network; random: the average of the mean SC of 5000 random networks; 95% CI of the mean SC of 5000 random networks; global *p* value (Bonferroni corrected) for the actual-vs.-random comparison.

AUC, area under the curve; CT, cortical thickness; PTSD, posttraumatic stress disorder; SA, surface area; SC, structural covariance.

[a]$p < .001$.

[b]$p < .05$.

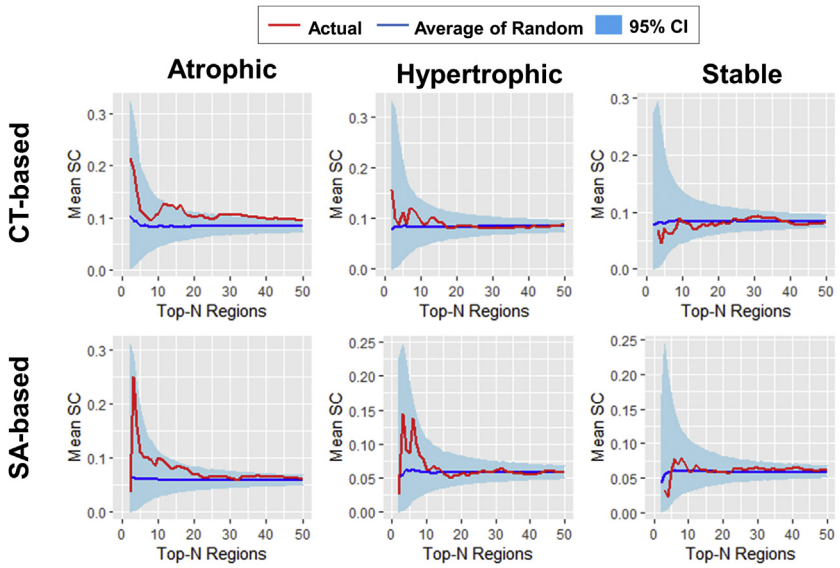

Figure 4. Mean structural covariance (SC) of trauma-exposed participants without posttraumatic stress disorder. Global tests showed that participants without posttraumatic stress disorder had higher mean SC in both cortical thickness (CT)–based ($p < .001$) and surface area (SA)–based ($p < .001$) atrophic networks, SA-based ($p = .014$) but not CT-based ($p = .139$) hypertrophic networks, and neither CT-based ($p = .264$) nor SA-based ($p = .732$) stable networks than in corresponding random networks. The curves for networks with up to 50 nodes are shown for illustrative purpose, given that the mean SC of actual networks and the mean SC of the average of random networks were very similar for large network sizes. Red curve indicates mean SC of the actual networks. Blue curve indicates mean SC of the average of 5000 random networks. Light blue ribbon indicates 95% CI of the 5000 random networks.

There was a significant interaction effect in SA-based hypertrophic networks ($p = .014$) (Figure 7D). Further analyses showed that patients with PTSD and comorbid depression ($p = .029$) and healthy control subjects ($p < .001$) had greater mean SC than patients with depression alone. No other global tests (p values $> .2$) and no individual tests (p values $> .05$) survived correction.

Effects of PTSD × Sex Interaction. Global tests showed that females with PTSD ($p = .029$) and males without PTSD ($p = .014$) had greater mean SC in CT-based atrophic networks than females without PTSD. Males without PTSD had greater mean SC in CT-based stable networks than males with PTSD ($p = .014$) and females without PTSD ($p < .001$). No significant PTSD × sex interaction effect (global p values $> .1$) was found in the other types of networks.

Effects of PTSD × Age Interaction. An inverted-U relationship between decadal age and mean SC was observed in CT-based atrophic networks in both non-PTSD participants, peaking in the third decade, and patients with PTSD, peaking in the second decade, and SA-based hypertrophic networks in patients with PTSD and non-PTSD patients, both peaking in the second decade. PTSD-related differences in mean SC

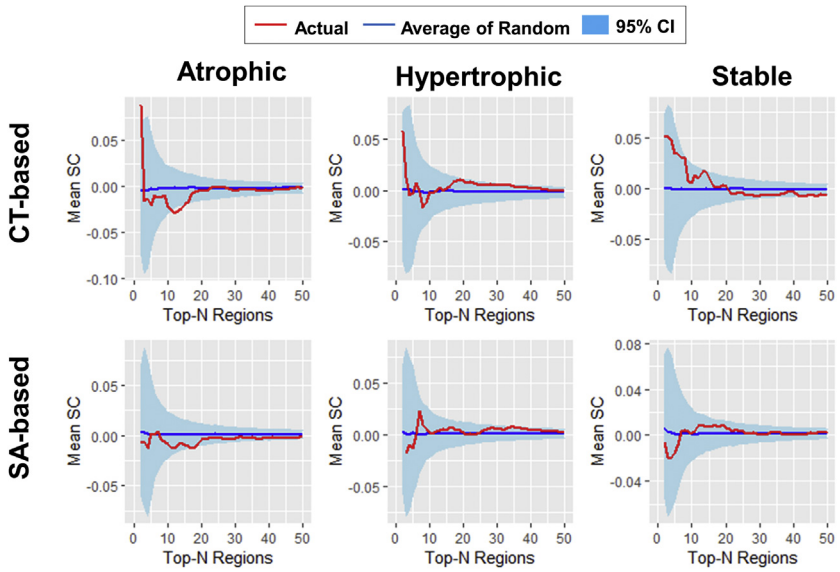

Figure 5. Mean structural covariance (SC) of posttraumatic stress disorder (PTSD) vs. non-PTSD. Global tests showed that patients with PTSD vs. non-PTSD participants had lower mean SC in both cortical thickness (CT)–based ($p = .014$) and surface area (SA)–based ($p = .024$) atrophic networks, but no significant difference in CT-based ($p = .098$) and SA-based ($p > .5$) hypertrophic networks or CT-based ($p > .5$) and SA-based ($p > .5$) stable networks. The curves of networks with up to 50 nodes are shown for illustrative purpose, given that the mean SC of actual networks and the mean SC of the average of random networks were very similar for large network sizes. Red curve indicates mean SC of the actual networks. Blue curve indicates mean SC of the average of 5000 random networks. Light blue ribbon indicates 95% CI of the 5000 random networks.

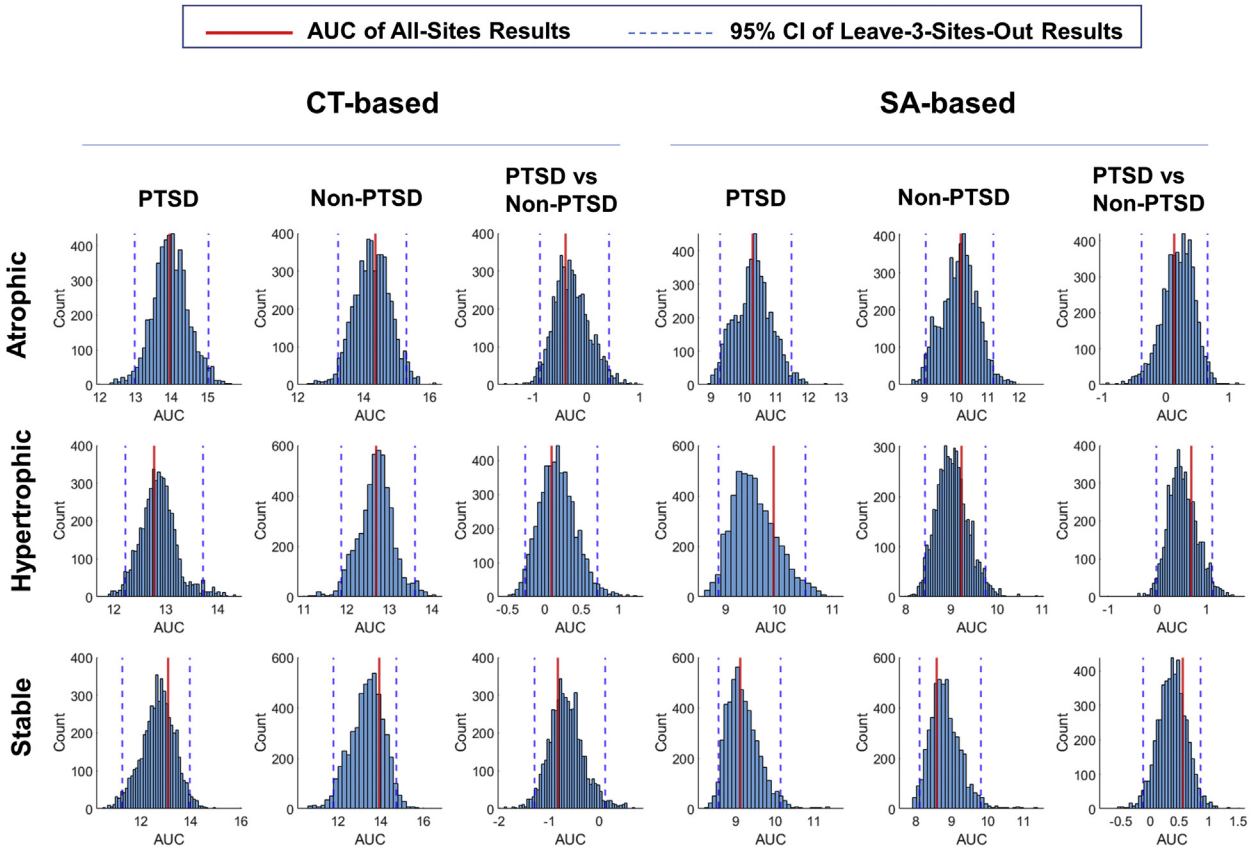

Figure 6. Replication analyses results. The global test results shown in Figures 3–5 are reliable, as underscored by the fact that the area under the curve (AUC) of mean structural covariance for the results based on all 29 sites (represented by the red vertical line) was always located within the 95% CI (represented by two blue vertical dashed lines) of the AUC of mean structural covariance from 5000 iterations, leaving out three sites at each iteration, across all types of networks. CT, cortical thickness; PTSD, posttraumatic stress disorder; SA, surface area.

were observed in different age groups, especially in the first decade, represented by lower mean SC in CT-based atrophic networks ($p < .001$) and SA-based hypertrophic networks ($p = .019$), as well as higher mean SC in CT-based hypertrophic ($p < .001$) and stable ($p < .001$) networks, in patients with PTSD compared with non-PTSD participants.

DISCUSSION

We investigated CT-based and SA-based SCNs composed of regions with the most atrophic, most hypertrophic, and most stable relationships to PTSD relative to trauma-exposed control subjects. Three network classes were composed of regions selected based on the effect size of PTSD-related differences in regional CT and SA. We compared the mean SC of these networks to random networks in PTSD and non-PTSD groups, respectively. We also investigated the role of PTSD diagnosis and PTSD severity on SC and interaction effects of PTSD with age, sex, and depression. We performed methodologic confirmation by demonstrating that PTSD and non-PTSD groups had higher SC in CT-based atrophic networks, SA-based atrophic networks, and SA-based hypertrophic networks than corresponding random networks (Table 2 and Figures 3 and 4). Methodologic confirmation also showed that the PTSD group had higher SC in CT-based hypertrophic networks and CT-based stable networks than corresponding random networks. Of particular interest and consistent with a priori hypotheses, we discovered that participants with PTSD had lower SC than trauma-exposed non-PTSD participants in CT- and SA-based atrophic networks (Table 2 and Figure 5). Furthermore, depression alone had higher SC in both CT- and SA-based atrophic networks and lower SC in SA-based hypertrophic networks compared with patients with PTSD and comorbid depression and with healthy control subjects (Figure 7A, B, D). Patients with PTSD alone showed lower SC in CT-based atrophic networks than patients with depression alone (Figure 7A) and higher SC in SA-based atrophic networks compared with patients with PTSD and comorbid depression and with healthy control subjects (Figure 7B).

Our main finding shows that the networks composed of regions having the greatest PTSD-related atrophy have significantly lower network covariance in the PTSD group than in the trauma-exposed control group. This finding was present for networks derived from both CT and SA. A number of interpretations of this finding are tenable. First, we note a degree of consistency between CT- and SA-based networks in our

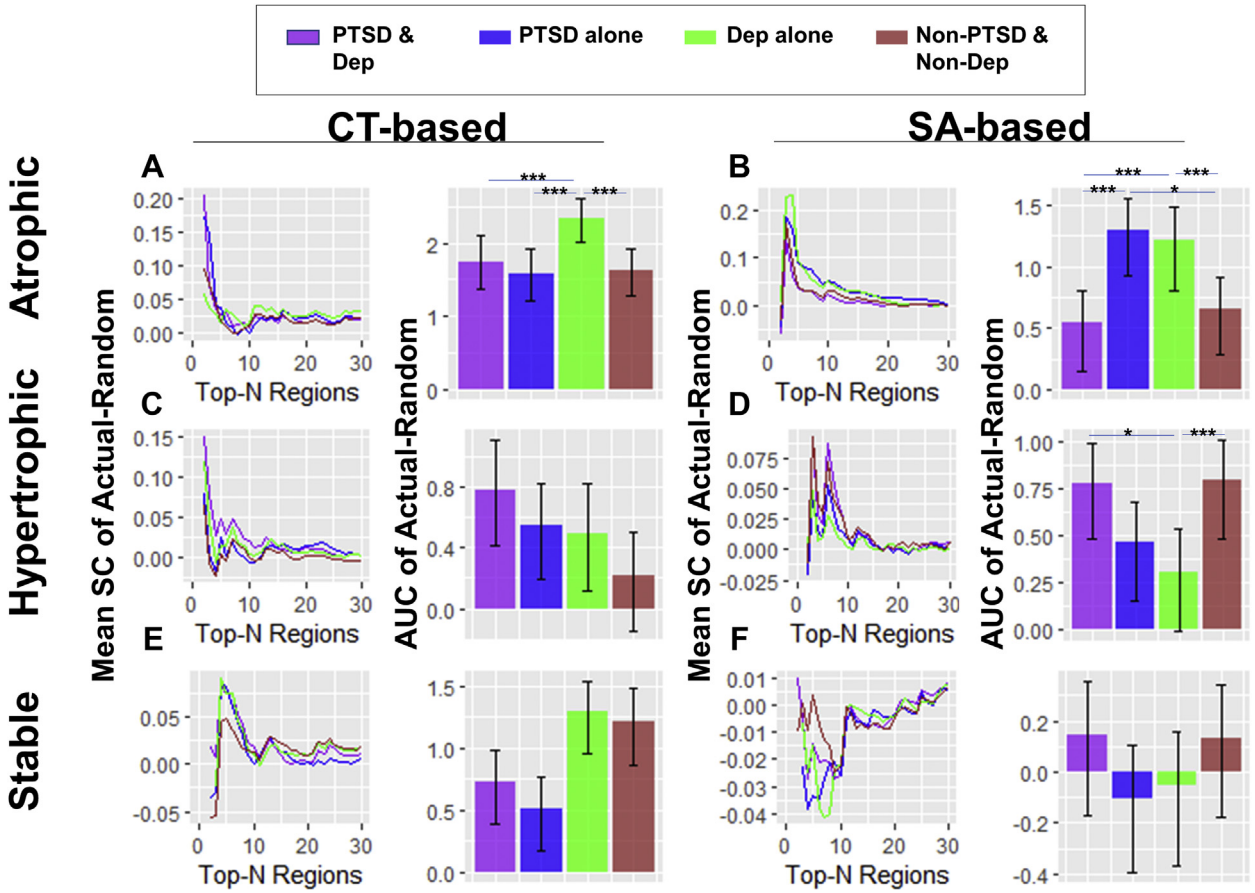

Figure 7. Interaction effects of posttraumatic stress disorder (PTSD) and depression (dep). Global tests showed that patients with depression alone had higher mean structural covariance (SC) in **(A)** cortical thickness (CT)–based ($p < .001$) and **(B)** surface area (SA)–based ($p < .001$) atrophic networks and lower mean SC in **(D)** SA-based hypertrophic networks ($p = .029$) than patients with both PTSD and depression. Patients with depression alone also showed higher mean SC in both **(A)** CT-based ($p < .001$) and **(B)** SA-based ($p < .001$) atrophic networks and lower mean SC in **(D)** SA-based hypertrophic networks ($p < .001$) than patients with neither PTSD nor depression. Patients with PTSD alone showed lower mean SC in **(A)** CT-based atrophic networks than patients with depression alone ($p < .001$) and higher mean SC in **(B)** SA-based atrophic networks than patients with both PTSD and depression ($p < .001$) and participants with neither PTSD nor depression ($p = .014$). No significant PTSD × depression interaction effect (global p values $> .2$) was found in the other types of networks shown in **(C)**, **(E)**, and **(F)**. The curves of networks with up to 30 nodes are shown for illustrative purposes. Error bar denotes 95% confidence interval of 5000 random networks. *$p < .05$; ***$p < .001$.

results concerned with PTSD diagnosis. Many cortical regions within networks that are affected by PTSD are strongly implicated (by definition) in PTSD—such as the insula, orbitofrontal cortex, anterior cingulate cortex, and subcallosal gyrus. However, our study is not focused on the status of individual regions but rather in network perturbations associated with PTSD. Of particular note, the functional networks previously implicated in PTSD comport with the present structural network findings such as in low-level perceptual networks (39), salience network (40), default mode network (41), and central executive network (42), also referred to as the frontoparietal network (43). Another finding of our study was that structural networks involving the medial prefrontal cortex, posterior cingulate cortex (SA-based only), and angular gyrus are canonical regions of the default mode network, which is also strongly implicated in PTSD. Our finding of structural networks involving the anterior cingulate cortex, and insular cortex recapitulated salience network differences that have been reported in PTSD. However, our structural network findings did not recapitulate prior reports of central executive network involvement in PTSD, and the largest meta-analysis of network differences in PTSD did not find central executive network involvement (40) either. Unfortunately, there is a profound dearth of published findings on SCN differences in PTSD for purposes of comparison. It is possible that the cortical networks or network mechanisms that propagate PTSD-related structural atrophy are dampened by the disease itself or dampened unevenly across brain topography. Alternatively, individuals with weaker connections in atrophic networks may be more vulnerable to PTSD. Unfortunately, our cross-sectional study design is unable to discern causal factors that contribute to PTSD.

In addition to functional networks, there is converging evidence that inflammatory processes, which contribute to PTSD,

preferentially affect the same regions that constitute atrophic networks that we identified. The medial prefrontal cortex, insula, and anterior cingulate cortex are all preferentially affected by inflammatory processes that plague PTSD and other fear- and anxiety-based conditions (44). While the amygdala and hippocampus are also affected by inflammatory processes, we included only cortical structures, which have a uniquely measurable CT and SA. Stress hormones pose pronounced deleterious effects to the medial prefrontal cortex (45) and orbitofrontal cortex (46), which also featured prominently in the atrophic networks we linked to PTSD. Evidence of stress hormone effects on the brain are strongly informed by animal models. In humans, frontoparietal connectivity is disrupted after exposure to 1 month of intense academic stress (47). Thus, stress-induced changes to the medial prefrontal cortex, orbitofrontal cortex, and frontoparietal regions were present in atrophic networks we linked to PTSD. Epigenetic effects on the brain have been linked to intergenerational trauma and its effects, particularly on the medial prefrontal cortex (48,49). Epigenetic regulation of the *FKBP5* gene in response to early trauma is implicated in PTSD pathogenesis (50). The methylation of *FKBP5* CpG1 of intron 7 is associated with lower gray matter in the bilateral orbitofrontal gyrus (51). Epigenetic regulation at the stress-responsive genes that encode ADCYAP1 and CpG island methylation levels of its receptor ADCYAP1R1 predict PTSD symptom severity (50). Thus, inflammation, stress hormones, and epigenetics all appear to play a role in SC network difference linked to PTSD.

This study extends several facets of earlier SC reports in PTSD. Broadly, this study has three major methodological differences compared with published reports:

1. While we focused only on regions at the extremes of between-group differences in constructing networks, prior studies have considered all regions in such covariance networks, which compromises power compared with the feature reduction strategy we implemented.
2. Our sample size (N = 3400) is 10-fold larger than any previous study (11).
3. Two prior studies were focused on children and adolescents (n = 88 and n = 120, respectively) (12,13) and a third study focused on remitted PTSD in adults (n = 317) (11). Thus, this study is uniquely situated with respect to statistical power, a target population from a broad age-range, and illness chronicity.

Our study extends the methodology developed by Wannan *et al.* (26) by investigating CT and SA of hypertrophic, atrophic, and stable networks separately rather than considering only the CT of atrophic networks. We show that some brain networks, independent of disease, mirror the spatial distribution of disease-related changes in cortical morphometry, thus confirming the work of Wannan *et al.* (26). Our results demonstrate for the first time that the SC of three different network classes are each uniquely associated with PTSD. We explicitly investigated stable networks, which could be summarily dismissed as negative findings because the contributing regions have minimal between-group differences. However, negative findings do not necessarily indicate that group differences in SC are absent. Negative findings may indicate insufficient statistical power. The sample size of this study provides sufficient power to detect extremely small effect sizes, which we may confidently interpret as negative findings that reflect networks of stable regions.

It is important to contrast the interpretation of CT- with SA-based networks. The relationship between CT and SA is complex, involving myriad factors including brain hemisphere, brain region, age, IQ, disease, genetics, and many other factors (33,52). The large size of the human cortex, in comparison to other animals, is driven primarily by expansion of SA, not increased CT (53), and achieved through gyral folding. Individual differences in cortical volume are largely attributable to variability in SA as opposed to CT (54). While CT and SA are highly heritable (r_g = 0.81 and 0.89, respectively), the genetic correlation between CT and SA is exceedingly low (r_g = 0.08). The influence of environment on CT and SA is also relatively low, accounting for 20% of their variance (55). Findings from structural magnetic resonance imaging of 51,665 genotyped individuals show that common genetic variants explain greater phenotypic variance in SA (8%–31%) than in CT (1%–13%). Strikingly, 175 unique genetic loci were associated with SA, but only 10 unique loci were associated with CT (56). Understanding the functional roles of these genetic loci will contribute to interpretation of CT- and SA-based structural connectivity, which will help us to understand the genetic contribution of remodeling of cortical topography in PTSD. Perhaps identifying common genetic variants that explain CT- and SA-based structural connectivity between regions and within networks will provide insights into the genetic architecture of the structural connectome (10).

Patients with depression alone showed higher mean SC in both CT- and SA-based atrophic networks and lower mean SC in SA-based hypertrophic networks than healthy control subjects. These results suggest that depression is associated with more coordinated propagation of CT and SA reductions and less coordinated SA increases. Our result is consistent with previous reports that depression is associated with widely distributed CT reductions (57). Patients with PTSD alone showed lower mean SC in CT-based atrophic networks than patients with depression alone, suggesting that PTSD is associated with more coordinated decline throughout CT-based networks than depression. We also found that PTSD with comorbid depression was associated with lower mean SC in CT-based atrophic networks than depression alone, lower mean SC in SA-based atrophic networks compared with PTSD alone and depression alone, and higher mean SC in SA-based hypertrophic networks relative to depression alone. Previous studies have documented greater volume reductions in cortical structures including the anterior/middle cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex in PTSD with comorbid depression that are absent in either disorder alone (58). Behaviorally, higher levels of distress (59), impaired neurocognitive function (60), and greater risk for suicide (61) are present in comorbid PTSD and depression compared with PTSD alone. PTSD with comorbid depression, relative to either disorder alone, may be associated with larger disruptions of individual cortical regions and their network SC, which may explain greater symptom severity.

We explored the modulation of PTSD-related differences in SCNs by sex and age and modulation of SCNs by PTSD

symptom severity. We found that females with PTSD and males without PTSD had greater SC in CT-based atrophic networks than females without PTSD (Figure S1). Males without PTSD had greater mean SC in CT-based stable networks than males with PTSD and females without PTSD. Diffusion-based structural connectome studies in youth show that males have stronger connections between regions for perception and coordinated action, whereas females have stronger connections between analytic and intuitive processing modes (62), demonstrating the sex-related differences in brain connections. We also found an inverted U–shaped relationship between age and SC in CT-based atrophic networks that peaked at 20 to 30 years in non-PTSD and 15 to 20 years in PTSD, whereas SA-based hypertrophic networks peaked at 10 to 15 years in both groups (Figure S2). We found significant PTSD-related SC differences in some age groups, particularly $<$10 years, as demonstrated by higher SC in CT-based hypertrophic and stable networks, lower SC in CT-based atrophic networks, and lower SC in SA-based hypertrophic networks. Our results suggest that multiple networks undergo transformation in a coordinated fashion to support the development of the brain as well as PTSD symptoms, particularly during early childhood. A previous longitudinal study in healthy young people (9) showed that similar global and nodal topological properties and mesoscopic features are shared by SC networks and maturation networks, which are based on each region's slope of maturation with age and pairwise correlations in the rate of maturation across subjects.

Strengths and Limitations

A major strength of our study is a large cohort of more than 3400 participants who represent diverse geography, demography (sex, age, race), trauma type (military, sexual violence, natural disasters), and clinical comorbidity. This sample heterogeneity enhances the generalizability and reproducibility of our findings. Harmonization of CT and SA measures sourced from 29 international sites with different magnetic resonance imaging scanners was addressed with *ComBat* (35). A major strength of our methodology is empirical confirmation that the most atrophic regions, or most hypertrophic regions, constitute the networks with the greatest change in SC. The possibility that SC might be most affected by PTSD in networks formed of random regions, i.e., where PTSD-associated changes of individual regions are completely unremarkable, has been robustly addressed.

The following limitations warrant consideration when interpreting our results. First, our study is based on cross-sectional data, which lacks longitudinal information to inform neurodevelopmental processes. Combining neuroimaging data from multiple longitudinal scans on each subject over several years of follow-up, preferably with pretrauma and post-trauma observations, may help us to better understand the developmental changes in SC networks among trauma-exposed subjects and subjects with PTSD. Second, image quality reflected by the Euler number was not significantly different between PTSD and non-PTSD groups in most sites except for Duke University (De Bellis) and INTRUST. Higher image quality is associated with greater CT in the dorsolateral prefrontal cortex, superior parietal cortex, and lateral temporal cortex, as well as smaller CT in the occipital and posterior cingulate cortex (63). Cortical morphometry and therefore SC may be biased by the PTSD-related differences in image quality at two sites. However, our leave-three-sites-out analyses indicated that our results are reliable. Future studies on cortical morphometry and corticocortical SCNs should consider including image quality as a covariate in statistical models. Finally, information on illness chronicity, developmental timing of trauma, childhood maltreatment, and other comorbidities such as anxiety were unavailable in the datasets shared with us by our Consortium partners. Future research comparing trauma-exposed individuals without PTSD to trauma-unexposed individuals could offer evidence supporting a hypothetical resilience network. Similarly, differences in patients with remitted PTSD compared with chronic PTSD could support the existence of a hypothetical recovery network. Future research could also compare patient groups exhibiting specific symptom clusters of PTSD.

Conclusions

Corticocortical connections shape the topography of PTSD-related differences in cortical morphometry. Thus, regional cortical morphometry associated with PTSD does not occur in isolated brain regions and independent of differences seen in other cortical regions. Rather, the regions whose morphometry are most affected by PTSD, albeit not significantly, form networks whose covariance structure is significantly affected by PTSD diagnosis and symptom severity. This finding fundamentally and significantly extends our understanding about the effects of PTSD on brain structure. Namely, cortical regions must be viewed from a holistic standpoint as acting within the context of networks that are affected in a coordinated manner by PTSD and further modulated by comorbid depression, sex, and age. The SCNs that are perturbed in PTSD comport with converging evidence from resting-state functional connectivity networks and networks affected by stress hormones, inflammation, and epigenetics.

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