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Archival Report

Structural Covariance of Early Visual Cortex Is Negatively Associated With Posttraumatic Stress Disorder Symptoms: A Mega-Analysis From the ENIGMA PTSD Working Group

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ABSTRACT

BACKGROUND: Identifying robust neural signatures of posttraumatic stress disorder (PTSD) symptoms is important to facilitate precision psychiatry and help in understanding and treatment of the disorder. Emergent research suggests that the structural covariance of early visual regions is associated with later PTSD development. However, large-scale analyses are needed in heterogeneous samples of trauma-exposed and trauma-naïve individuals to determine whether such a neural signature is a robust marker of vulnerability.

METHODS: We analyzed data from the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis)-PTSD dataset (N = 2814) and the HCP-YA (Human Connectome Project–Young Adult) dataset (N = 890) to investigate whether the structural covariance of the early visual cortex is associated with either PTSD symptoms or perceived stress. Structural covariance was derived from a multimodal pattern previously identified in recent trauma survivors, and participant loadings on the profile were included in linear mixed effects models to evaluate associations with stress.

RESULTS: Early visual cortex covariance loadings were negatively associated with PTSD symptoms in the ENIGMA-PTSD dataset. The relationship persisted when accounting for prior childhood maltreatment; supporting PTSD symptom specificity, no relationship was observed with depressive symptoms, and no association was observed between loadings and perceived stress measures in the HCP-YA dataset.

CONCLUSIONS: The structural covariance of early visual cortex was robustly associated with PTSD symptoms across an international, heterogeneous sample of trauma survivors. Future studies should aim to identify specific mechanisms that underlie structural alterations in the visual cortex to better understand posttrauma psychopathology.

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Posttraumatic stress disorder (PTSD) is a highly debilitating psychiatric condition. While trauma exposure is the principal antecedent of PTSD, not all trauma-exposed (TE) individuals develop long-term posttraumatic dysfunction.

Identification of robust signatures linked to increased risk for PTSD would help identify individuals who are most in need of resources to prevent the development of trauma-and stress-related psychopathology. Neuroimaging signatures may be valuable prognostic markers of future PTSD in TE individuals (1); however, the robustness of previously observed associations may depend on sample characteristics (2,3). Large, heterogeneous samples are needed to evaluate the potential generalizability of neural signatures of PTSD and whether such brain metrics are viable targets for future treatment research.

Structures of the ventral visual stream represent one promising neural signature for predicting the onset of PTSD. While canonical threat neurocircuitry is often involved in PTSD psychopathology, growing evidence implicates the ventral visual stream as a key component in the development and maintenance of PTSD symptoms (4). The ventral visual stream plays a critical role in object recognition and perception (5,6). Previous reviews highlight that there are reciprocal connections between canonical threat-related brain regions (e.g., amygdala and hippocampus) and regions of the ventral visual stream that support emotional function (7). PTSD has been associated with lower thickness and volume of the occipital and inferior temporal cortex (8–10). However, associations between visual circuit neurobiology and PTSD symptoms may vary with the timing of trauma exposure relative to neuroimaging. Previous research demonstrated that lower gray matter volume of the visual cortex was associated with PTSD symptoms and/or diagnosis months after trauma exposure (11). In contrast, structural covariance of the ventral visual stream, particularly early visual regions such as V1 through V3, was positively associated with PTSD symptom expression acutely (e.g., 2–4 weeks) after trauma exposure in 2 independent samples (12,13). However, a greater delay (e.g., ~6 months) revealed a negative relationship between early visual structural covariance and PTSD symptoms (12). Taken together, previous literature suggests that PTSD is associated with alterations in the structure of early visual regions that may be partially dependent on the time since trauma exposure. Identifying whether the structure of early visual regions and the ventral visual stream are associated with more enduring PTSD in large, heterogeneous samples may yield generalizable neural signatures of posttraumatic dysfunction and help clarify how such a relationship unfolds over time.

The ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis)-Psychiatric Genomics Consortium (PGC) PTSD working group is an international consortium that collaboratively analyzes one of the largest neuroimaging datasets of trauma and PTSD to date. The pooling of previously collected data across countries and samples allows for mega-analyses of neuroimaging data for high-powered confirmatory and data-driven studies. Recent ENIGMA-PTSD mega-analyses have found relationships between visual-system structures and PTSD symptoms using univariate structural covariance networks (SCNs) generated from cortical morphometry measures (14,15). SCNs represent patterns of shared interregional variability within a participant that can be correlated with psychiatric phenotypes. Lower visual system covariance, including the anterior and middle occipital cortices, was observed in individuals with PTSD. Furthermore, network properties (e.g., centrality) of regions along the ventral visual stream such as the fusiform and occipital gyrus varied as a function of PTSD status (16).

The previous findings summarized above suggest that the structural covariance of the early visual cortex may be a generalizable and robust marker for predicting PTSD symptoms. However, there have been limited investigations of out-of-sample, multimodal magnetic resonance imaging (MRI)-derived early visual SCNs, such as those that were identified previously (12,13) in large trauma samples. SCNs derived from multimodal fusion methods incorporate information across multiple MRI features in a manner that is not possible in typical univariate approaches (17). Such methods allow for assessment of how networks are constituted across modalities and over regions to better elucidate the potential role of visual circuitry in the pathophysiology of PTSD, in comparison to the mass univariate approaches that were used in previous ENIGMA-PTSD research. Notably, multimodal-derived early visual cortex SCNs and potential relationships with stress have not been investigated in trauma-naïve control samples. An association between a multimodal early visual SCN and general stress in typical or trauma-naïve individuals may suggest that such an SCN is not PTSD-specific. Previous experimental work supports the idea that general stress may be associated with visual neurobiology; stress is associated with both altered neural responses in visual regions, such as the lingual gyrus in humans (18), and stress-induced visual cortex atrophy in mice (19). Our previous multimodal SCN findings in recent trauma survivors suggest that early visual SCN loadings are positively associated with PTSD symptoms (12,13), and thus the SCN may be positively associated with more general stress-related measures in typical individuals. Determining whether the early visual SCN is specific to PTSD or varies with more general stress in typical samples has important implications for the translational benefit of the predictive marker of psychopathology.

Therefore, in the current study, we investigated associations between an early visual cortex SCN and (posttraumatic) stress in 2 large, independent datasets. We estimated individual participant loadings on a previously identified multimodal SCN overlapping the early visual cortex in 2 datasets: 1) one consisting of individuals who were previously exposed to trauma and 2) another, separate dataset of typical (healthy) young adults. We hypothesized that SCN loadings would be negatively associated with PTSD symptoms in the trauma sample, consistent with our previous investigations in later posttrauma phases. Furthermore, we hypothesized that SCN loadings would be positively associated with a measure of perceived stress in neurotypical controls, similar to previous work with recent trauma survivors.

METHODS AND MATERIALS

Participants

Data from TE participants were provided by the ENIGMA-PGC PTSD Working Group. Broad aspects of imaging data sharing for the dataset have been described previously (10,15,16,20,21). For the current analyses, data were available from 30 imaging sites across 9 countries from participants with and without PTSD (Table 1). Participants with available T1-weighted imaging data to reconstruct voxel/vertexwise features of interest (see below) were included in the current analysis (N = 2814). All study sites obtained local institutional review board or equivalent ethics committee approval, and all participants provided informed consent.

Typical control participants were drawn from the HCP-YA (Human Connectome Project Young Adult) dataset (S1200 release). The HCP data were all collected at a single site on a single scanner that did not undergo any hardware/software upgrades during the data collection period. Details of participant recruitment and minimal MRI preprocessing have been documented previously (22,23). For the current analyses, we selected data from individuals from an ongoing multimodal data fusion analysis (N = 890) of participants with T1-weighted, diffusion-weighted, and resting-state functional MRI data. Of the full release of participants with 3T scanner data, 223 were excluded due to missing data or quality issues (e.g., anatomical anomalies, segmentation/processing issues, head coil issues, or motion). The HCP study was approved by the Washington University in St. Louis Human Research Protection Office (Institutional Review Board #201204036, "Mapping the Human Connectome: Structure, Function, and Heritability").

Demographic Characteristics and Clinical Symptoms

In both datasets, participants reported their age and sex. Participants in the ENIGMA-PTSD dataset reported PTSD symptoms according to DSM-IV or DSM-5 criteria depending on the study, using one of several different assessments (Table S1). A harmonized measure of symptom severity was obtained by calculating the percentage of total severity score endorsed by the participant relative to the possible total severity score of the specific assessment used. For subscale scores, subscale questions were matched according to DSM-5 criterion, and subscale scores were calculated using the same percentage approach. Several sites also obtained measures of depression severity across several different questionnaires (Table S1), and a harmonized measure was calculated as above. Furthermore, several sites collected data on childhood maltreatment using the Childhood Trauma Questionnaire (CTQ) (24), and the total CTQ score was included in our analyses. The ENIGMA-PTSD dataset contained TE and trauma-naïve (NTE) participants, and our primary analyses were restricted to TE analyses in the ENIGMA-PTSD dataset given our hypotheses. Supplemental analyses involving the NTE group are described in the Supplement for completeness.

Participants in the HCP-YA dataset completed a battery of self-assessments related to mental health (17). Given that the dataset did not include typical trauma or PTSD measures (e.g., PTSD Checklist for DMS-5), we selected more general "stress" measures for comparison, focusing on perceived stress and Achenbach Adult Self-Report (ASR) scores. Perceived stress was operationalized as part of the NIH Toolbox Perceived Stress Survey using items from the Perceived Stress Scale (25). Participants were asked about the degree to which events in the past month seemed unpredictable or uncontrollable and their coping resources on a Likert scale from 0 to 4. The total score was used as a measure of perceived stress. The ASR measure was also administered as part of the NIH Toolbox (26), and we selected 3 ASR scale scores for comparison: total scores, Anxiety/Depression scores, and Intrusive scores.

Magnetic Resonance Imaging

Three-dimensional volumetric T1-weighted brain MRI data collected by participating sites were used to derive structural features for calculation of early visual structural covariance in both datasets, similar to our previous reports (12,15,16). The previously observed SCN was predominantly composed of pial surface area (PSA) and gray matter volume derived from voxel-based morphometry (VBM); therefore, we focused our derivation of the SCN on these metrics. For the ENIGMA-PTSD dataset, anatomical brain images were preprocessed at Duke University using the standardized ENIGMA 3.0 pipeline (https://enigma.ini.usc.edu/protocols/imaging-protocols/) and FreeSurfer (27). Standard FreeSurfer reconstruction (recon-all) was completed to generate vertexwise maps of PSA across the cortex. Whole-brain PSA maps were then smoothed using a 10-mm full width at half maximum (FWHM) Gaussian kernel for subsequent analyses. Gray matter volume was calculated using standard steps in FSLVBM (28) to derive whole-brain maps of gray matter volume (i.e., VBM maps); VBM data were smoothed using a 3-mm FWHM Gaussian kernel for subsequent analysis. The HCP-YA data were processed using the HCP minimal preprocessing pipeline, which has been described previously (23). Cortical surface maps were reconstructed in FreeSurfer as part of the pipeline. As with the ENIGMA-PGC dataset, PSA maps were smoothed with a 10-mm FWHM Gaussian kernel; VBM maps were calculated with FSLVBM and smoothed using a 3-mm FWHM Gaussian kernel.

Early visual structural covariance was calculated using previously applied approaches to back-project precomputed multimodal maps onto participant data (12,29). Briefly, 4-dimensional image files of participants' VBM and PSA data (i.e., voxel/vertexwise feature maps concatenated across participants) were created and used as inputs in FSL's dual regression. We used our previously identified early visual covariance maps from our previous report, which were originally identified using linked independent component analysis (12,30), as spatial maps to project onto participant data (Figure 1A). Individual participant feature loadings for VBM and PSA were obtained for each component (i.e., stage 1 of dual regression). Feature loadings from the first stage of dual

Table 1. ENIGMA-PGC Demographic Data

	No. of Participants	Age, Years	Sex		PTSD Severity, % Total	Depression Severity, % Total	CTQ Total Score	Exposure/Diagnosis			Race			
			Female	Male				NTE	TE/PTSD	TE/No PTSD	Asian	Black	Other	White
Total Dataset	2814	37.89 (15.69)	1425 (50.6%)	1384 (49.2%)	0.26 (0.23)	0.26 (0.21)	47.14 (22.05)	323 (11.5%)	1127 (44.0%)	1076 (38.2%)	249 (8.8%)	418 (14.9%)	190 (6.8%)	1383 (49.1%)
Site														
ADNI	112	68.71 (4.65)	0 (0.0%)	112 (100.0%)	0.22 (0.21)	–	–	1 (0.9%)	51 (45.5%)	60 (53.6%)	2 (1.8%)	11 (9.8%)	3 (2.7%)	95 (84.8%)
Amsterdam	73	39.67 (9.80)	34 (46.6%)	39 (53.4%)	0.27 (0.25)	0.28 (0.29)	–	0 (0.0%)	37 (50.7%)	36 (49.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	73 (100.0%)
Beijing	82	47.72 (10.22)	49 (59.8%)	33 (40.2%)	0.35 (0.20)	0.33 (0.17)	–	0 (0.0%)	36 (43.9%)	46 (56.1%)	82 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
CapeTown1	57	25.95 (6.61)	57 (100.0%)	0 (0.0%)	–	0.23 (0.15)	37.92 (13.38)	43 (75.4%)	0 (0.0%)	14 (24.6%)	0 (0.0%)	33 (57.9%)	24 (42.1%)	0 (0.0%)
CapeTown2	110	26.93 (6.54)	110 (100.0%)	0 (0.0%)	–	0.23 (0.17)	39.17 (14.14)	92 (83.6%)	1 (0.9%)	17 (15.5%)	0 (0.0%)	45 (40.9%)	65 (59.1%)	0 (0.0%)
Columbia	3	40.33 (10.50)	2 (66.7%)	1 (33.3%)	0.15 (0.27)	0.11 (0.15)	62.50 (41.72)	0 (0.0%)	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	1 (33.3%)	2 (66.7%)
Duke	176	40.31 (10.32)	36 (20.5%)	140 (79.5%)	0.19 (0.24)	0.16 (0.19)	43.69 (19.18)	0 (0.0%)	40 (22.7%)	121 (68.8%)	0 (0.0%)	73 (41.5%)	9 (5.1%)	78 (44.3%)
EmoryGTP	95	38.15 (10.79)	95 (100.0%)	0 (0.0%)	0.25 (0.20)	0.24 (0.19)	43.44 (18.83)	0 (0.0%)	10 (10.5%)	43 (45.3%)	0 (0.0%)	93 (97.9%)	1 (1.1%)	0 (0.0%)
Ghent	61	36.94 (11.67)	61 (100.0%)	0 (0.0%)	–	0.16 (0.15)	–	0 (0.0%)	7 (11.5%)	0 (0.0%)	–	–	–	–
Groningen	38	38.45 (9.87)	38 (100.0%)	0 (0.0%)	0.50 (0.09)	0.36 (0.22)	76.65 (20.70)	0 (0.0%)	38 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	38 (100.0%)
Leiden	19	15.00 (1.94)	17 (89.5%)	2 (10.5%)	–	0.16 (0.16)	–	13 (68.4%)	6 (31.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (5.3%)	18 (94.7%)
Masaryk	281	52.21 (19.02)	169 (60.1%)	112 (39.9%)	0.18 (0.15)	–	–	0 (0.0%)	115 (40.9%)	10 (3.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	281 (100.0%)
McLeanKaufman	79	34.39 (12.51)	79 (100.0%)	0 (0.0%)	0.43 (0.32)	–	60.39 (29.30)	0 (0.0%)	52 (65.8%)	27 (34.2%)	5 (6.3%)	4 (5.1%)	2 (2.5%)	68 (86.1%)
Michigan	62	30.73 (7.67)	0 (0.0%)	62 (100.0%)	0.36 (0.24)	0.37 (0.30)	–	12 (19.4%)	40 (64.5%)	10 (16.1%)	2 (3.2%)	4 (6.5%)	3 (4.8%)	53 (85.5%)
MinnVA	242	32.75 (7.93)	14 (5.8%)	226 (93.4%)	0.30 (0.19)	0.18 (0.13)	–	0 (0.0%)	90 (37.2%)	151 (62.4%)	11 (4.5%)	4 (1.7%)	9 (3.7%)	215 (88.8%)
Munster	21	24.10 (2.88)	15 (71.4%)	6 (28.6%)	–	0.03 (0.03)	–	21 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	21 (100.0%)
Nanjing	127	57.34 (5.92)	71 (55.9%)	56 (44.1%)	–	–	–	0 (0.0%)	49 (38.6%)	78 (61.4%)	127 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stanford	182	34.66 (10.99)	78 (42.9%)	102 (56.0%)	0.27 (0.24)	0.24 (0.21)	53.02 (25.01)	6 (3.3%)	92 (50.5%)	84 (46.2%)	–	–	–	–
Toledo	78	35.46 (11.44)	35 (44.9%)	43 (55.1%)	0.17 (0.18)	0.29 (0.26)	51.58 (15.93)	0 (0.0%)	14 (17.9%)	64 (82.1%)	0 (0.0%)	14 (17.9%)	1 (1.3%)	41 (52.6%)
Tours	42	27.98 (9.63)	42 (100.0%)	0 (0.0%)	0.29 (0.15)	0.12 (0.16)	–	20 (47.6%)	10 (23.8%)	12 (28.6)	–	–	–	–
UMN	72	42.39 (9.23)	6 (8.3%)	66 (91.7%)	0.14 (0.15)	0.18 (0.16)	–	0 (0.0%)	15 (20.8%)	57 (79.2%)	1 (1.4%)	1 (1.4%)	2 (2.8%)	68 (94.4%)
UMSL	66	31.89 (9.60)	66 (100.0%)	0 (0.0%)	–	–	–	0 (0.0%)	59 (89.4%)	7 (10.6%)	0 (0.0%)	24 (36.4%)	4 (6.1%)	36 (54.5%)
Uwash	149	12.82 (2.65)	74 (49.7%)	75 (50.3%)	0.05 (0.08)	0.48 (0.04)	36.80 (14.69)	56 (37.6%)	33 (22.1%)	60 (40.3%)	17 (11.4%)	36 (24.2%)	31 (20.8%)	65 (43.6%)
UWMadison_Cisler	99	32.49 (8.18)	99 (100.0%)	0 (0.0%)	0.43 (0.27)	0.29 (0.22)	56.33 (25.82)	0 (0.0%)	78 (78.8%)	21 (21.2%)	1 (1.0%)	14 (14.1%)	3 (3.0%)	81 (81.8%)
UWMadison_Grupe	57	30.47 (6.32)	4 (7.0%)	53 (93.0%)	0.26 (0.20)	0.20 (0.21)	–	0 (0.0%)	19 (33.3%)	18 (31.6%)	0 (0.0%)	1 (1.8%)	1 (1.8%)	54 (94.7%)
UWMilwaukee	76	33.36 (10.45)	39 (51.3%)	37 (48.7%)	0.18 (0.14)	0.21 (0.21)	43.61 (17.41)	0 (0.0%)	20 (26.3%)	56 (73.7%)	1 (1.3%)	44 (57.9%)	6 (7.9%)	19 (25.0%)
Vanderbilt	50	31.34 (4.63)	9 (18.0%)	41 (82.05%)	0.12 (0.15)	0.10 (0.13)	33.72 (9.61)	15 (30.0%)	15 (30.0%)	20 (40.0%)	0 (0.0%)	5 (10.0%)	6 (12.0%)	39 (78.0%)
WacoVA	70	39.13 (10.25)	6 (8.6%)	63 (90.0%)	0.54 (0.28)	0.31 (0.20)	44.38 (19.85)	0 (0.0%)	48 (68.6%)	22 (31.4%)	0 (0.0%)	12 (17.1%)	18 (25.7%)	38 (54.3%)
WestHavenVA	65	34.78 (9.66)	7 (10.8%)	58 (89.2%)	0.32 (0.22)	0.30 (0.19)	–	0 (0.0%)	35 (53.8%)	30 (46.2%)	–	–	–	–
WestOntario	170	37.93 (12.68)	113 (66.5%)	57 (33.5%)	0.35 (0.26)	0.30 (0.24)	51.54 (22.89)	44 (25.9%)	116 (68.2%)	10 (5.9%)	–	–	–	–

Values are presented as mean (SD) or *n* (%). Percentages may not equal 100% due to unreported answers from participants within site. Blank cells reflect uncollected/unreported data.

ADNI, Alzheimer's Disease Neuroimaging Initiative; CTQ, Childhood Trauma Questionnaire; EmoryGTP, Emory Grady Trauma Project; MinnVA, Minneapolis VA Health Care System; NTE, non–trauma-exposed; PTSD, posttraumatic stress disorder; TE, trauma-exposed; UMN, University of Minnesota; UMSL, University of Missouri-St. Louis; UW, University of Wisconsin; Uwash, University of Washington; UWMadison, University of Wisconsin-Madison; VA, Veterans Administration.

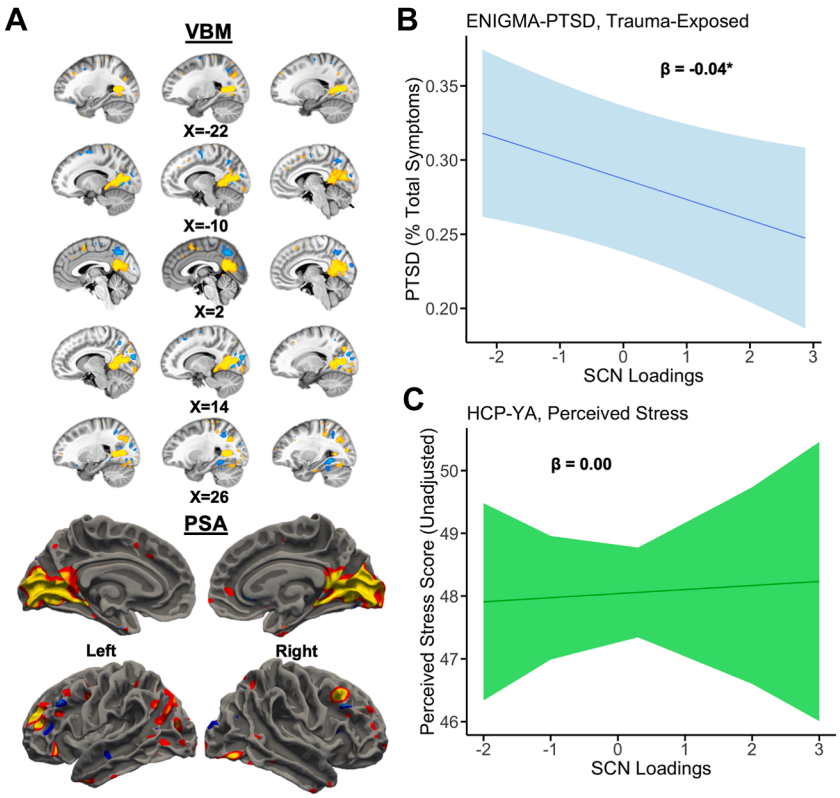

Figure 1. Early visual structural covariance is associated with posttraumatic stress disorder (PTSD) symptoms in the ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis)-PGC (Psychiatric Genomics Consortium) cohort. Voxel-based morphometry (VBM) and pial surface area (PSA) features of a previously identified multimodal structural covariance network (SCN) (12) were projected onto data from the ENIGMA-PTSD and HCP-YA (Human Connectome Project–Young Adult) **(A)**. Within the ENIGMA-PTSD dataset, individual participant loadings for the SCN were negatively correlated with PTSD symptoms **(B)**; however, no relationship was observed between loadings and perceived stress in the HCP-YA dataset **(C)**. Warmer and cooler colors in panel **(A)** reflect positive and negative relationship strength of each modality with spatial covariance loadings across regions, respectively. Graphs represent the partial plots from linear mixed effects models. Solid lines represent the unique association from the model, and the shaded bars represent the confidence intervals.

regression were then averaged together across the modalities and *z*-standardized to index individual participant component loadings for the early visual cortex SCN. The dual regression steps were applied separately for the ENIGMA-PTSD and HCP-YA datasets.

Statistical Analyses

We completed linear mixed effect models to identify associations between early visual covariance loadings and PTSD symptoms. Participant age and sex were included as fixed-effect covariates in all models while participant site and scanner (ENIGMA-PTSD dataset) or family ID (HCP-YA, to account for siblings/twins in the dataset) were included as random effects for the intercept; we also completed supplemental analyses with the HCP-YA dataset in which we removed siblings in sensitivity analyses (see Supplement).

Our primary models tested 1) the association between SCN loadings and PTSD symptoms in TE participants separately within the ENIGMA-PGC dataset and 2) the association between SCN loadings and perceived stress within the HCP-YA dataset. For each model, SCN loading was used as the independent variable, and either PTSD symptoms or perceived stress was the dependent variable. Given our directional hypotheses (i.e., negative association between SCN loadings and PTSD symptoms for TE individuals but positive for NTE controls), for our primary analyses we used 1-tailed hypothesis testing with a nominal $p < .05$ as a significance threshold. The standardized betas for the linear mixed models were calculated using the *effectsize* package in R, and 90% CIs were calculated corresponding to our 1-tailed tests (specified in the Results).

We completed several follow-up and sensitivity analyses to understand the robustness of observed effects using separate linear mixed effects models. For the ENIGMA-PGC dataset, we completed follow-up analyses to first investigate associations between SCN loadings and PTSD subscale severity (e.g., percentage severity for intrusion, avoidance). We completed additional analyses within the ENIGMA-PTSD dataset by removing participants with "0" PTSD symptoms (i.e., symptoms assessed but reported as 0) to control for potential zero-inflation of results. To test the specificity of our putative findings, we also investigated the association between SCN loadings and depression severity. We completed an additional linear mixed model to investigate whether SCN loadings differed as a function of group (NTE, TE without PTSD, TE with PTSD), comparing NTE to TE groups. Finally, additional sensitivity analyses were used to determine whether SCN loadings were associated with PTSD symptoms when we covaried for CTQ scores in the subset of individuals with complete data.

We also completed several follow-up analyses for the HCP-YA dataset. Sensitivity analyses with the HCP-YA data were recompleted with monozygotic and dizygotic twins removed as an alternative approach to counteract genetic confounding in the model. We also tested associations between SCN loadings and the total, Anxiety/Depression, and

Intrusive scores from the ASR measure using alternative linear mixed models to determine whether associations were tied to more DSM-like measures of stress.

RESULTS

ENIGMA-PGC Dataset

Demographic information is presented in Table 1. We observed a negative relationship between SCN loadings and PTSD symptoms in TE individuals with and without PTSD ($\beta = -0.04$, 90% CI = −0.08 to −0.01, $p = .014$, 1-tailed, $n = 2027$) (Figure 1B). Raw scatterplots between the independent and dependent variables are provided in the Supplement (Figure S1A).

Subscale analyses within the trauma-exposed group revealed that SCN loadings were negatively associated with alterations in cognition and mood subscale scores ($\beta = -0.06$, 95% CI = −0.11 to −0.01, $p = .029$, $n = 1139$). However, a significant relationship was not observed with intrusive ($\beta = -0.02$, 95% CI = −0.07 to 0.03, $p = .422$, $n = 1479$), avoidance ($\beta = -0.04$, 95% CI = −0.10 to 0.02, $p = .156$, $n = 1140$), or hyperarousal subscale scores ($\beta = -0.04$, 95% CI = −0.09 to 0.01, $p = .110$, $n = 1479$).

The relationship between PTSD symptoms and SCN loadings remained significant ($\beta = -0.04$, 90% CI = −0.07 to 0.00, $p = .043$, 1-tailed, $n = 1754$) when we removed individuals who reported no PTSD symptoms ($n = 273$) (Figure S1B). Linear mixed models did not show a significant association between SCN loadings and depression symptoms, although the effect size was similar ($\beta = -0.04$, 95% CI = −0.08 to 0.01, $p = .156$, $n = 1386$); an alternative model in which depression severity was included as a covariate in models for PTSD severity revealed an effect similar to that of our main model ($\beta = -0.03$, 90% CI = −0.06 to 0.00, $p = .038$, 1-tailed, $n = 1336$). An additional sensitivity analysis revealed that SCN loadings remained associated with PTSD severity while covarying for CTQ total scores in a subset ($n = 780$) of participants ($\beta = -0.07$, 95% CI = −0.13 to −0.02, $p = .005$).

Supplemental analyses with the NTE group revealed a positive association between SCN loadings and PTSD severity that was not significant when we removed individuals with no PTSD symptoms (Figure S2). SCN loadings did not differ between the NTE group and TE individuals either with or without PTSD (Figure S3).

HCP-YA Dataset

Demographic information on the sample is presented in Table 2. Our linear mixed effects models did not reveal a significant association between SCN loadings and perceived stress ($\beta = 0.00$, 90% CI = −0.05 to 0.06, $p = .429$, 1-tailed, $n = 889$) (Figure 1C). Follow-up analyses using the ASR did not show a relationship with ASR total scores ($\beta = 0.05$, 90% CI = −0.01 to 0.10, $p = .092$, 1-tailed, $n = 887$) (Figure S4). Subsequent analyses with ASR Anxiety/Depression ($\beta = -0.01$, 90% CI = −0.07 to 0.04, $p = .369$, 1-tailed, $n = 887$) and ASR Intrusive scores ($\beta = 0.03$, 90% CI = −0.03 to 0.08, $p = .208$, 1-tailed, $n = 887$) did not show significant relationships with SCN loadings. Removal of twins/siblings from the HCP-YA dataset did not impact the results (see the Supplement). The findings suggest that the structural covariance of early visual regions is not associated with perceived stress in a typical control sample.

Table 2. HCP-YA Demographic Data ($N = 890$)

Characteristic	Mean (SD) or *n* (%)
Age, Years	28.71 (3.73)
Sex	
Female	491 (55.2%)
Male	399 (44.8%)
Race	
Asian/Hawaiian/Pacific Islander	57 (6.4%)
Black	122 (13.7%)
Other	23 (2.6%)
White	672 (75.5%)
Unknown	16 (1.8%)
Perceived Stress	48.03 (9.04)
ASR	
Total	36.25 (22.18)
Anxious/depressed	5.75 (5.31)
Intrusive	2.39 (2.15)

ASR, Adult Self-Report; HCP-YA, Human Connectome Project–Young Adult.

DISCUSSION

Identifying robust and generalizable neuroimaging signatures of PTSD is essential for the development of neuroscience-informed predictive models and, ultimately, early interventions. Multimodal MRI-based indices of specific neural circuits, such as the ventral visual stream, may help in developing reproducible markers for PTSD symptoms. Here, we analyzed data from the ENIGMA-PGC PTSD Neuroimaging Working Group to investigate individual variability in a multimodal SCN overlapping early visual brain regions that was related to PTSD symptom severity. TE individuals with and without PTSD showed a negative relationship between loadings on the network and PTSD symptoms. In a separate sample, the HCP-YA cohort, there was no relationship between network loadings and more general measures of perceived stress. Taken together, our findings suggest that the decreased covariance of early visual regions may be associated with chronic PTSD symptom development.

The current findings partially replicate our previous reports of divergent associations between ventral visual stream network loadings and PTSD symptoms in acute versus chronic posttrauma samples (12,13). In our previous work, trauma survivors—with imaging data collected beyond the acute posttrauma period—showed a negative relationship between participant loadings on an SCN of early visual regions in the ventral visual stream and PTSD symptoms. Similarly, in the current heterogenous international sample, loadings of the same SCN were negatively associated with PTSD symptoms and in particular with negative alterations in cognition and mood. A growing body of research suggests that trauma exposure is related to altered function and structure along the ventral visual stream, which in turn is related to posttraumatic dysfunction (9,15,31). Furthermore, the current finding of chronic PTSD symptom severity being associated with early visual cortex covariance mirrors our

previous work from the AURORA (Advancing Understanding of RecOvery afteR traumA) study (12). The current results suggest that weakened covariance of the ventral visual stream, during the chronic post-trauma phase, may partially underlie the development of affective trauma-related cognitions, potentially through disruption of connections with canonical emotion regulation regions, although additional research is needed.

A speculative mechanism underlying visual pathway alterations in PTSD is that the stress of trauma exposure or PTSD itself induces excitotoxic mechanisms that contribute to overall weakening of stimulus processing pathways. For example, traumatic stress or PTSD-related stressors may increase excitatory neurotransmitter release and/or potentiate activity in circuits that are important for emotional processing (e.g., threat/visual regions). Previous reviews have highlighted that across both preclinical and human studies, traumatic stress may lead to increased glutamate and decreased GABA (gamma-aminobutyric acid) in threat and sensorial regions (32). For example, previous work with trauma survivors observed that greater glutamate/glutamine within the prefrontal cortex was associated with greater acute PTSD symptoms (33). Disrupted glutamatergic/GABAergic processes or sustained activation of visual/threat circuitry (e.g., heightened attention processes) may in turn contribute to degradation of the underlying structural connections between regions. Consistent with such reasoning, we found that lower SCN loadings were associated with greater PTSD symptoms, which may reflect degradation of structural integrity of the ventral visual stream across VBM and PSA features. Furthermore, while childhood maltreatment and exposure to traumatic events are known to be related to diminished integrity and volume of visual pathways (34–36), our findings persisted when we covaried for childhood maltreatment. Taken together, our findings suggest that the structure of the ventral visual stream plays a potentially important role in the maintenance and severity of PTSD symptoms after trauma exposure.

Contrary to our hypothesis, we did not observe an association between SCN loadings and perceived stress among participants in the HCP-YA dataset. Previous research with healthy participants suggests that visual cortex and the ventral visual stream are involved in responses to stressors, although the majority of such work assessed brain function. For example, recent work demonstrated that neuromodulation of the visual cortex reduced the intensity of experimentally induced intrusive memories in healthy controls (37). Previous work has also demonstrated that levels of social fearfulness in healthy participants is associated with slower habituation of neural responses to facial stimuli within the visual cortex (38). The findings may suggest that function of the visual cortex may play a more significant role in response to stress. However, there are limited data on brain structural associations with perceived stress in healthy samples. Evidence from animal models suggests that severe stress can contribute to atrophy within the visual cortex and related regions (19), and recent work with humans suggests that stress can induce rapid changes in gray matter volume (39). However, there is limited comparative or longitudinal work with TE individuals showing that traumatic stress may acutely alter visual cortex structure. Thus, it is unclear from the current findings whether the current SCN is an actionable pretrauma marker of PTSD susceptibility. The lack of association in the HCP-YA dataset may suggest that exposure to traumatic events is a necessary condition for the predictive utility of the network. Alternatively, it may suggest that the association is specific to PTSD symptoms and that measures of perceived stress do not capture the same process that underlies visual stream associations with trauma exposure. Our supplementary analyses of the NTE group may grant limited support for such an interpretation given the positive relationship between "PTSD" symptoms and SCN loadings. However, very few NTE participants reported experiencing PTSD symptoms (n = 12), and no significant association was observed in the reduced sample. There is also a lack of clarity about what endorsement of PTSD symptoms means when individuals do not have a history of trauma exposure. It also remains unclear why this relationship could be related to PTSD as opposed to perceived stress. The current results suggest that additional work is needed to understand interrelationships among the SCN loadings and different domains of stress to understand whether this SCN may be a useful marker for future posttraumatic stress susceptibility. One potential approach is to leverage naturalistic longitudinal datasets such as the UK Biobank (40) to select a subset of individuals who experience trauma during the study period and determine whether the SCN is associated with later PTSD symptoms.

Several limitations should be considered when interpreting the current results. While the ENIGMA-PGC is the largest consortium sample of trauma-related MRI to date, there is significant heterogeneity in the assessment of PTSD symptoms, collection of data, inclusion of pretraumatic factors, and demographic data availability that may moderate the current findings. Furthermore, there is evidence to suggest that additional stressors that were experienced before the index trauma, such as childhood maltreatment, have observable associations with sensorial neurobiology in adult trauma survivors (35,41). Although the early visual SCN was associated with PTSD symptoms while covarying for childhood maltreatment, the follow-up sample with complete CTQ data was limited, and more consideration of potential associations with pretraumatic stressors is needed. In addition, although samples were largely from samples of chronic PTSD, it is also likely that there was variability in the time between trauma and MRI assessments across studies that could not be included in the current analysis; future work would benefit from additional consideration of time delay in SCN loading associations. In addition, although we had directional a priori hypotheses based on previous work, our observed effect sizes are small. Small effects may reflect some of the heterogeneity in the current sample or suggest that the relative influence of visual circuit covariance on PTSD is weak. However, the replication of our previous work—including subscale specificity in the association—suggests that early visual cortex covariance may still be a promising neural signature for PTSD. Furthermore, such small effects may still be clinically meaningful if a robust neural signature can be translated to effective therapeutics. Another consideration is the relatively limited availability of data from other modalities (e.g., diffusion imaging) to reconstruct the SCN for each participant. While using an out-of-sample template may help to establish robustness of the network associations, precluded MRI

features can contribute to reduced statistical power or removal of sample-idiosyncratic noise. Additional research that includes other modalities in similarly large samples may be helpful for better understanding ventral visual stream covariance in PTSD.

Conclusions

The current analyses revealed that the structural covariance of early visual brain regions is negatively associated with PTSD symptoms in an international sample of TE individuals. Critically, the structural covariance of the network is not associated with individual variability in general stress in a typical control sample. Therefore, trauma exposure may be a prerequisite for structural disruption of the visual pathway that contributes to PTSD, which may be due to the unique stress of trauma. The findings highlight an important role for the structure of visual processing pathways in understanding the neuroetiology of trauma and stress-related disorders.

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