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Reduced Gray-White Matter Contrast in Chronic Posttraumatic Stress Disorder in World Trade Center Responders

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ABSTRACT

BACKGROUND: Following the collapse of the World Trade Center (WTC), many people experienced severe trauma and 23% of WTC responders developed posttraumatic stress disorder (PTSD). We hypothesized that gray-white matter contrast (GWC) would be different in participants with PTSD compared with demographically matched trauma-exposed control participants with no history of PTSD.

METHODS: T1-weighted structural images for 99 WTC responders collected on a 3T Siemen's magnetic resonance imaging scanner were retrieved and segmented to measure global, regional, and voxelwise GWC. Group-level analyses adjusted for the false discovery rate (FDR) (FDR = .05). Area under the receiver operating characteristic curve was reported. To determine correlates of PTSD, we also measured PTSD symptom severity and several putative neuroimaging measures linked to PTSD including cortical fractal dimensions, cortical free water fraction, characteristic path length, and cerebral/cerebellar cortical thickness.

RESULTS: WTC responders with PTSD exhibited reduced cerebral GWC globally (d = 0.47, SE = 0.20, p = 0.022), while vertexwise results showed focal differences (FDR $<$ .05) in the frontal, temporal, and parietal lobes. Among participants with PTSD, analyses identified correlations that passed FDR correction linking GWC with overall PTSD symptom severity ($\rho = -0.24$) that were strongest when examining re-experiencing symptom severity ($\rho = -0.28$) and when examining GWC in the pars triangularis ($\rho = -0.37$). GWC was not associated with cortical fractal dimension, cortical free water fraction, characteristic path length, or cerebral/cerebellar cortical thickness.

CONCLUSIONS: Results support emerging research suggesting that PTSD is associated with changes to intracortical health. If replicated, changes in GWC might provide novel treatment targets and could help to support diagnosis in research studies.

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Following the attacks of September 11, 2001, and the subsequent collapse of the World Trade Center (WTC) buildings, individuals who worked in search-and-rescue operations were exposed to strenuous physical and psychological conditions (1). Now, approximately 23% of WTC responders report experiencing symptoms of chronic posttraumatic stress disorder (PTSD) (2,3), a rate that is higher than that reported in the general population (prevalence estimated at 7%) (4) but similar to the rate among U.S. veterans deployed in wars in Afghanistan (4.7%–19.9%) (5), the Persian Gulf (1.9%–24%), and Vietnam (8.5%–19.3%) (6). PTSD is experienced, in part, as uncontrolled intrusive memories of the traumatic events linked to triggering events coupled with elevated stress reactivity and hyperawareness of surroundings (7).

Seeking to understand neurobiological changes underpinning PTSD symptomatology, several studies have focused on measures of gray matter (GM) structure (7,8) and changes in cerebral white matter (WM) in individuals with PTSD (9–11). Some research has reported that individuals with PTSD exhibited changes in cortical structure or dysconnectivity that were associated with PTSD symptoms (e.g., re-experiencing, avoidance, negative cognitions and mood, and arousal) (12,13). However, studies addressing the confounding effect of brain aging have reported that structural phenotypes are limited to individuals with PTSD who developed comorbid cognitive impairment but are lacking in other individuals with PTSD (14–16). The disconnect between morphological and topographical results and the relative weakness of association suggest that current measures of PTSD are inadequate for characterizing the complex neurobiology of PTSD.

One study of veterans proposed that PTSD symptom severity may be positively correlated with subcortical myelination (17). Myelin modulates the rapidity of neural impulses, potentially explaining why disruption in these circuits could help explain intrusive thoughts and their deep emotional reactions to triggering experiences (18–20). Dysregulated

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intracortical myelination could result in altered cognitive and emotional processing speeds (21–24). For example, one magnetic resonance imaging (MRI) study reported that individuals with PTSD showed widespread evidence of reduced cortical complexity, a process that may be driven by differential changes within cortical layers (25–27). Interestingly, while myelination has often been linked to WM health, myelinated and unmyelinated interneurons create the intracortical connective matrix on which many emotional and sensory functions are built (28–30). Correspondingly, several studies have noted that brain connectivity and efficiency correlated with stronger symptom severity in WTC responders with PTSD (12,27). Meanwhile, serological studies have isolated one potential source of intracortical changes when they reported evidence of interneuronal loss in individuals with PTSD (31,32). Thus, while studies of intracortical health are still in their nascence, these findings suggest that PTSD symptomatology may be influenced by differences in intracortical myelination.

Gray-white matter contrast (GWC) is an MRI-based proxy for intracortical myelination density (33,34). This measurement examines the apparent blurriness at the WM-GM interface based on differences in signal intensity (35,36). An increase in contrast represents a sharper boundary between cortical and subcortical tissue, which is indicative of a healthy transition from GM to WM (35), while a less distinct border may suggest demyelination (36). Research suggests that individuals with autism spectrum disorder had increased GWC alongside localized reductions in GWC (37,38), while individuals with psychosis had evidence of reduced intracortical myelin (39); studies of Alzheimer's disease have shown reduced GWC and studies of Parkinson's disease have shown no association with GWC (40,41). To date, no studies have examined GWC in participants with PTSD. We hypothesized that individuals with PTSD would have evidence of increases in GWC. Because PTSD is a heterogeneous disorder with several symptom types, we also examined correlations between GWC and PTSD symptom subdomains in participants with PTSD. Because intracortical myelination can change neural network signaling rapidity, we hypothesized that GWC will be differently associated with symptom subdomains thought to be associated with neural dysfunction (e.g., re-experiencing and hyperarousal symptom severity). Because several previous studies have shown evidence of other changes to cortical structure and function, we reported correlations between GWC and cortical fractal dimension (27), weighted characteristic path length (42), cortical free water fraction (11), cerebral cortical thickness (15,43), and cerebellar cortical thickness (44). We concluded this study by examining the combined predictive power of neuroimaging-based indicators of PTSD.

METHODS AND MATERIALS

Data were retrieved for this secondary analysis from the WTC responder imaging archive. The recruitment criteria, imaging data, and demographic information for the original study has been described previously (27). Briefly, 99 WTC responders (48 with PTSD, 51 without PTSD) completed a structural neuroimaging protocol from 2016 to 2019.

Most WTC responders are fluent in English, and all reside in New York. To be eligible for the neuroimaging study, participants had to have a body mass index (BMI) $\leq$40, lack MRI-unsafe metal implants or shrapnel, be ages 44 to 65 years, and report no claustrophobia. Participants were excluded if they had a history of psychosis, diagnosed neurological conditions, head injury, or liver disease or if they currently used cognitively active medications. Participants were matched for age, gender, race/ethnicity, and education at the time of recruitment.

Image Acquisition

Participants were scanned on the same 3T Siemens Biograph mMR scanner. Three-dimensional, T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) images were acquired using the following sequencing parameters: Time until repetition/echo/inversion (TI) = 1900/2.49/900 ms, flip angle = 9°, acquisition matrix = 256 $\times$ 256, voxel resolution = 0.89 $\times$ 0.89 $\times$ 0.89 mm^3. We used FreeSurfer version 7.2.0 to process all images (45). MPRAGE scans were reconstructed, segmented into WM and GM, and parcellated into regions of interest (ROIs) from the Desikan-Killiany atlas (46).

Measures

PTSD was diagnosed using the Structured Clinical Interview for DSM-IV (SCID-IV) (47). Following previous work (12), PTSD symptom severity scores were calculated using data on symptom type and severity of functional impairment, collected as part of the SCID diagnostic survey, and split into symptom subdomains including re-experiencing symptoms, avoidance, hyperarousal, and negative thoughts or emotions. Historical data on trauma exposures and self-reported symptom histories since exposure were available to research staff during screening. Participants were only recruited if they were likely to fit diagnostic criteria, and interviews were completed in a standardized manner to help avoid subjective diagnoses due to a clinician's experience (48). Quality control was maintained throughout the research period by having other researchers observe sessions.

Image Processing

An increase in contrast represents a sharper boundary between cortical and subcortical tissue, which is indicative of a healthy transition from GM to WM (35), while a less distinct border may suggest a change to brain health (36). GWC is not static at different sampling points within GM and WM, making the depth of measurement an important question for interpretation. Thus, we examined this question directly by conducting an experiment to modify each measurement to examine the role of WM and GM in identifying signal compared with noise in this study. Overall, we anticipated that insofar as the signal may emerge from demyelination in WM, then holding GM constant but changing WM depth might result in changes to results. In contrast, if myelination in the GM was changing, then we anticipated that changing the WM would do little to change results, but changes in the GM depth would isolate stronger results. We also compared results using the boundary case as a final experiment to ensure that results were strongly isolated to either GM or WM tissues. For

each participant, GWC was extracted using the function *pctsurfcon* following equation 1:

$$GWC_{d,p} = \frac{100 \times (WS_d - GS_p)}{0.5 \times (WS_d + GS_p)} \quad (1)$$

where GS_p is the signal intensity at the pth percentile into the cortex while WS_d was the signal intensity in the WM extracted at d mm below the gray-white matter boundary. Thus, $GWC_{1,50}$ is the GWC comparing local signal intensity 1 mm into the WM with signal intensity at the 50th cortical percentile. Using this ratio, a higher $GWC_{d,p}$ indicates either a lower GM signal or a higher WM signal or vice versa for lower $GWC_{d,p}$. To further isolate the source of contrast differences, we calculated the Pearson's correlation coefficient between GWC and the cortical free water fraction to rule out water content as a contributor to GWC.

GWC has previously been measured at 35% cortical depth and 1 mm into the WM (49–51); however, because the source of the GWC signal may vary depending on this choice and because others have reported different results at other depths, we also quantified signal intensity for GM at 0%, 20%, 40%, 60%, 80%, and 100% cortical depth and at 0-, 1-, or 2-mm WM depths. This assessment was performed to help determine cerebral depth of GWC signal intensity and whether any changes in GWC were driven by changes in GM or WM signals. To determine how GWC changes in GM independently from WM and vice versa, we evaluated GWC at 0% GM at 1- and 2-mm WM as well as WM at 0 mm at 20% to 100% GWC; GWC at 0% GM depth and 0 mm into the WM are the same (Figure S2). GM signal was sampled along the cortical ribbon between the GM and WM boundary and cerebrospinal fluid (Figure S2A). In Figure S2B, we found that GWC signal intensity was improved by varying GM depth but could rely on WM depth at any point. Overall, these studies supported the view that GWC would be optimized at 20% into the GM and at 1-mm WM depth.

Vertexwise GWC surfaces were transformed onto a common surface brain developed by FreeSurfer and smoothed using a 20-mm Gaussian kernel—the average used in published studies (38,40,49–51).

Other Neuroimaging Measures Associated With WTC-Related PTSD

To adjust measures of vertexwise and regional GWC for cortical atrophy (49), we also examined measures of cortical thickness (in millimeters) and estimated total intracranial volume (eTIV). To contextualize effect sizes found here, we compared them with measures of cortical thickness and to other factors that have been correlated with PTSD in previous studies (11,13,27). Briefly, these include weighted characteristic path length, which uses graph theory analysis on diffusion-based imaging to reconstruct the cerebral structural connectome (52); cortical fractal dimension, which uses spherical harmonic reconstruction to reconstruct vertex alignment on the cortical surface to provide regional measures of cortical surface complexity (53); cerebellar cortical thickness using the CERES automated pipeline (54); and cortical free water fraction, which uses diffusion tensor imaging to measure the degree of extracellular free water in the cerebral parenchyma and was designed to measure the degree of neuroinflammation in the cortex (11).

Statistical Analysis

We began by showing descriptive characteristics, comparing trauma-exposed participants with PTSD to participants without PTSD. Next, we compared gross global GWC across the whole cerebrum using violin plots. To identify localized differences, we completed vertexwise analysis using a generalized linear model (GLM) fit using FreeSurfer's *mri_glmfit* tool. Minimum required inputs include contrast files, which determine the groups to be compared, and a FreeSurfer Group Descriptor File. GLM models corrected for vertexwise cortical thickness and eTIV by first regressing the GWC outcome on vertexwise cortical thickness and eTIV before estimating residual GWC. A clustering protocol used Monte-Carlo simulation with 1000 iterations with a false discovery rate (FDR) = .05 to adjust for clustering of cerebral results (55).

Then, we compared symptom domains of participants with PTSD to their gross global GWC and GWC within Desikan-Killiany regions, grouped by cerebral lobe. We used Pearson's r for unadjusted analyses because a Komogorov-Smirnov test revealed that the distribution (skew = 0.18, kurtosis = 2.81) did not differ from normality (p = .623). We used GLM to estimate standardized regression coefficients, while adjusting for BMI and eTIV, in 2 ways: 1) multiple GLMs were run for each region, and region-specific results were reported if they passed the FDR threshold (FDR = .05); and 2) a multilevel GLM to estimate the panregional association between PTSD and all regional estimates of GWC while adjusting for the intercorrelation between regional results. Finally, we defined a logistic model alongside the receiver operating characteristic curves, used leave-one-out cross-validation to estimate mean predictive curves and the estimated area under the receiver operating characteristic curve (AUROC), and reported intercorrelations between GWC and other putative neuroimaging-based bioindicators of PTSD.

RESULTS

Table 1 shows the distribution of demographic variables and assessment scores in participants with and without PTSD. Variables that were matched during recruitment, including age, gender, race/ethnicity, and education, did not differ between groups. For variables that were not addressed at the design phase, we found no statistical difference in eTIV, although BMI, cortical fractal dimension, and weighted characteristic path length differed between groups.

To visualize whether regional GWC results survived adjustment for unmatched covariation and confirmed the initial findings when accounting for BMI and eTIV (Figure 1). These results revealed that the largest differences in GWC between the groups were observed in the frontal and parietal lobes, with results in the temporal lobe showing some statistical significance.

Mean whole-brain GWC at 20% into GM and 1 mm of WM ($GWC_{1,20}$) showed a gross statistically significant difference

Table 1. Sample Characteristics Stratified by the Presence of PTSD

Characteristics	PTSD−, n = 51	PTSD+, n = 48	p
Female/Male	12/39	9/39	.56
Cognitively Impaired/Unimpaired	25/26	23/25	.91
Age, Years	56.43 (5.37)	55.29 (5.04)	.28
Body Mass Index	28.06 (3.65)	30.45 (4.08)	.003
Race			
Black	11.54%	8.51%	.87
White	75.00%	78.72%	
Other	13.46%	12.77%	
Hispanic, Yes	15.71%	15.28%	.30
Education, School Years	15.71 (1.96)	15.28 (2.47)	.34
Domain-Specific PTSD Symptom Severity			
Re-experiencing	12.22 (3.14)	23.08 (4.66)	<.001
Avoidance	16.31 (3.25)	32.31 (6.64)	<.001
Hyperarousal	12.18 (2.94)	23.69 (3.96)	<.001
Negative affect	9.06 (1.67)	15.60 (4.29)	<.001
Additional Imaging Parameters			
Cortical free water fraction	0.33 (0.04)	0.34 (0.05)	.206
Cortical fractal dimension	26.10 (0.03)	25.95 (0.03)	.002
Weighted characteristic path length	47.50 (2.37)	59.09 (4.36)	.02
Estimated total intracranial volume	1586.12 (21.56)	1573.26 (20.28)	.67

Values for descriptive characteristics are presented as n, mean (SD), or %. These criteria were confirmed using a Welsh's t test for continuous quantities and a χ^2 test for categorical variables. There was no statistical difference between matching groups.

PTSD, posttraumatic stress disorder.

(Cohen's d = 0.47, p = .022) between participants with versus without PTSD (Figure S2), which was stronger in a multivariable-adjusted panregional multilevel GLM (Cohen's d = 0.86, p < .001). Subsequent vertexwise analysis revealed significantly lower GWC in WTC responders with chronic PTSD (Figure 1), which showed areas with reduced GWC across the whole brain even upon addressing cluster-wide multiple comparison–corrected statistical testing (Q = 0.0001) (Figure 2).

Unadjusted correlations between regional GWC and PTSD symptom subdomains among those with PTSD, parcellated into cortical ROIs (Table 2), revealed significantly lower GWC in frontal, parietal, and temporal lobes but not in the occipital lobe or cingulate. Interestingly, GWC in the pars triangularis, the subregion with the strongest signal, was associated with increases in all subdomains of PTSD even after accounting for the FDR (FDR = .05).

Finally, we considered the potential benefit of using any single or multiple cortical contrast parameters to identify the presence of PTSD and developed a classification model using logistic regression (Figure 3). These results show that whole-brain GWC was weakly associated with other measures of cortical structure in participants with and without PTSD. When relying on all 3 imaging parameters we found that a logistic model had moderate accuracy (AUROC = 0.77; 95% CI, 0.67–0.86).

DISCUSSION

After being exposed to traumatic events, many individuals develop chronic PTSD. To date, the importance of cortical structure and the role of cortical myelination are not well understood. In this first study of GWC in PTSD, we found that PTSD was associated with lower GWC bilaterally with focal results in the frontal, parietal, and temporal lobes. Furthermore, we found that differences in bilateral GWC were evident across ROIs in the frontal, parietal, and temporal lobes. Vertexwise analyses supported regional analyses but also provided some evidence for mild left-right asymmetry, with clusters in the right hemisphere being larger and encompassing more of the cortical structures. Symptom-specific analyses revealed that GWC was significantly associated with re-experiencing symptoms after FDR adjustment. However, analyses comparing GWC with other putative markers of cortical changes in PTSD revealed no statistically significant associations between GWC and any other imaging-based markers linked to PTSD that were available to this study. Overall, these results suggest that GWC may be an important and domain-sensitive method for helping to characterize the presence and severity of PTSD in trauma-exposed individuals.

The source of GWC differences is still widely debated, as signal intensity can also be affected by extracellular free water content or iron deposition in WM (33,56–58). However, we replicated previous results showing that there was no association between water content and PTSD (11) and also found that cortical free water fraction was not correlated with GWC in this study. We determined that cortical thickness was not associated with PTSD in this cohort and, consistent with previous work, we found no statistically significant associations between GWC and cortical thickness or cerebellar cortical thickness (15,59). To determine whether iron deposition was a concern, we recognized that iron deposition would have the most intense impact in the WM (60) and showed that the WM contrast remained unchanged, and signal intensity was primarily driven by changes to GM signal intensity. Together, these results could imply that changes in GWC signal intensity may emerge due to differences in the ratio of myelin content in the GM.

GWC is best known as an indicator of myelin health in WM when studying cognitive aging (61), Parkinson's disease (40), and mild cognitive impairment (49). However, studies of neurodegenerative conditions have reported alterations in increased GWC, with results primarily driven by reductions in WM signal intensity. However, several studies of psychiatric conditions including autism spectrum disorder (37,38) and psychosis (39) report increased GWC resulting from changes in the GM signal, where myelin is less abundant. When emerging from the GM, changes in GWC could indicate differences in the ratio of myelinated interneurons to other cortical material (35). Interneurons make up one-fifth of all cortical material and are considered of central importance to several psychiatric conditions, in part because they express GABA (gamma-aminobutyric acid) (62), a neurotransmitter that is responsible for myelin regulation (63) that appears dysregulated in people with PTSD (64). Therefore, these results may help to contextualize findings from proteomic

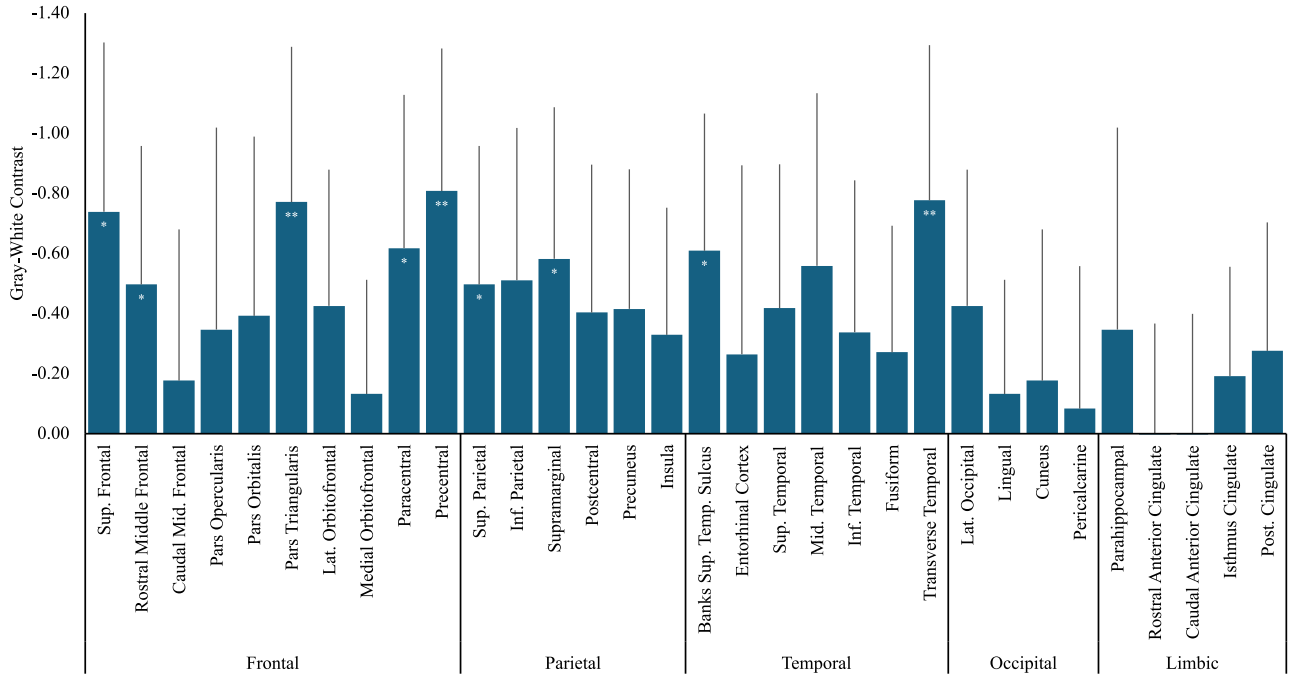


Figure 1. Bar chart showing differences in $GWC_{1,20}$ across regions of interest in responders with posttraumatic stress disorder compared with trauma-exposed control participants. Results are from multivariable generalized linear models, adjusting for body mass index and intracranial volume. Results from a panregional multilevel generalized linear model support these results (Cohen's $d = 0.86$, $p < .001$). *$p < .05$, **$p < .01$. GWC, gray-white matter contrast; Inf, inferior; Lat, lateral; Mid, middle; Post, posterior; Sup, superior; Temp, temporal.

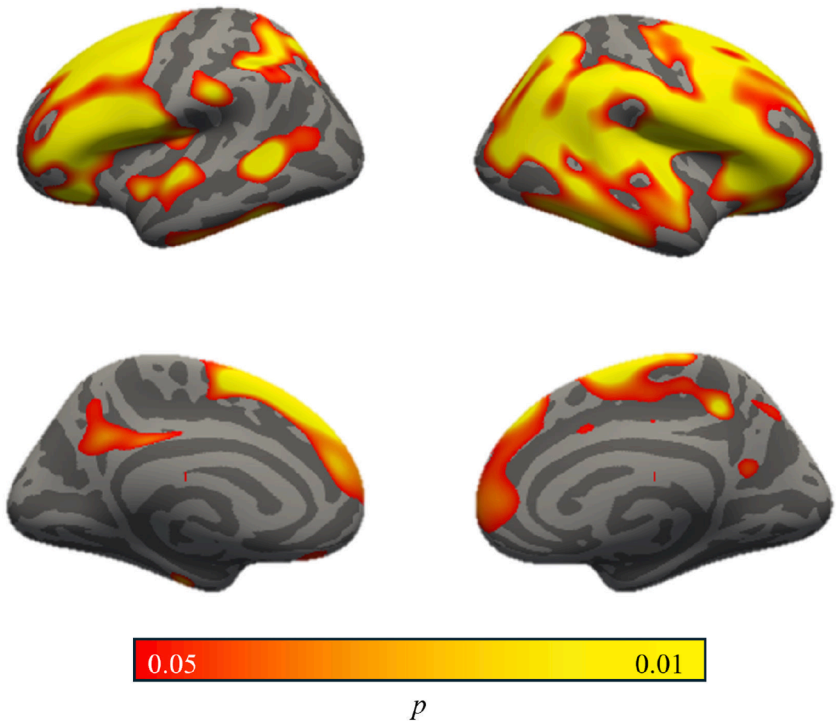


Figure 2. World Trade Center responders with chronic posttraumatic stress disorder (PTSD) exhibited widespread decreased gray-white matter contrast (GWC) relative to trauma-exposed control participants with no diagnosis or history of clinically significant PTSD. Mapping the strength of potential differences in GWC in PTSD using overall nominal *p* values to show areas of differences in GWC, noting that all results showed reduced GWC at 20% gray matter and 1-mm white matter depths using cluster forming thresholds. All clusters survived correction for multiple comparisons (false discovery rate–adjusted $p < .05$).

Table 2. Associations Between Domains of PTSD Symptoms and $GWC_{1,20}$ Stratified by Bilateral Desikan-Killiany Cortical Regions of Interest in Responders Diagnosed With PTSD (n = 48)

		Overall Symptoms	Re-experiencing	Avoidance	Hyperarousal	Negative Affect
Gross Measures						
Average Cortical GWC, Correlation Coefficient		−0.24*	−0.28**	−0.19*	−0.22*	−0.26*
Multivariable-Adjusted Pan-Region GWC, Cohen's *d*		−0.59**	−1.24**	0.16*	−0.22*	−0.74**
Regional Measures, Correlation Coefficient						
Lobe	Region					
Frontal	Superior frontal	−0.27**	−0.21*	−0.29**	−0.27*	−0.27*
	Rostral middle frontal	−0.23*	−0.19*	−0.22*	−0.25*	−0.26*
	Caudal middle frontal	−0.07	0.00	−0.06	−0.08	−0.12
	Pars opercularis	−0.14	−0.11	−0.15	−0.19*	−0.12
	Pars orbitalis	−0.25*	−0.17	−0.26*	−0.23*	−0.27**
	Pars triangularis	−0.36**	−0.29**	−0.36**	−0.37**	−0.30**
	Lateral orbitofrontal	−0.15	−0.11	−0.11	−0.14	−0.27*
	Medial orbitofrontal	0.00	0.03	0.03	0.01	−0.11
	Paracentral	−0.20*	−0.20*	−0.16	−0.24*	−0.19*
	Precentral	−0.27*	−0.24*	−0.28**	−0.29**	−0.23*
Parietal	Superior parietal	−0.23*	−0.19*	−0.22*	−0.25*	−0.26*
	Inferior parietal	−0.20*	−0.16	−0.17*	−0.21*	−0.24*
	Supramarginal	−0.23*	−0.19*	−0.22*	−0.25*	−0.20*
	Postcentral	−0.15	−0.13	−0.16	−0.18*	−0.16
	Precuneus	−0.20*	−0.15	−0.18*	−0.20*	−0.24*
	Insula	−0.11	−0.13	−0.09	−0.14	−0.09
Temporal	Banks of the superior temporal sulcus	−0.28**	−0.23*	−0.28**	−0.26*	−0.24*
	Entorhinal cortex	−0.14	−0.10	−0.14	−0.19*	−0.17
	Superior temporal	−0.23*	−0.15	−0.24*	−0.27*	−0.19*
	Middle temporal	−0.27**	−0.16	−0.27**	−0.27**	−0.29**
	Inferior temporal	−0.18*	−0.12	−0.16	−0.20*	−0.23*
	Fusiform	−0.15	−0.12	−0.12	−0.15	−0.18*
	Transverse temporal	−0.21*	−0.15	−0.22*	−0.26*	−0.18*
Occipital	Lateral occipital	−0.15	−0.11	−0.11	−0.14	−0.27*
	Lingual	0.00	0.03	0.03	0.01	−0.11
	Cuneus	−0.07	0.00	−0.06	−0.08	−0.12
	Pericalcarine	0.11	0.10	0.11	0.12	0.02
Limbic	Parahippocampal	−0.14	−0.11	−0.15	−0.19*	−0.12
	Rostral anterior cingulate	−0.06	−0.01	−0.04	−0.10	−0.02
	Caudal anterior cingulate	0.00	0.04	−0.03	−0.02	0.02
	Isthmus cingulate	−0.10	−0.03	−0.12	−0.09	−0.13
	Posterior cingulate	−0.09	−0.04	−0.10	−0.13	−0.09

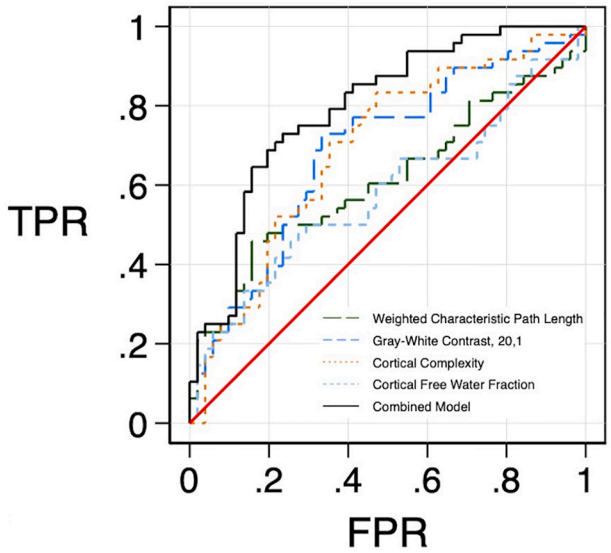
Pearson correlations or Cohen's *d* from multivariable-adjusted generalized linear models with *statistically significant *p* values (2-tailed $p < .05$) and **statistically significant values after adjusting for the false discovery rate.

GWC, gray-white matter contrast; PTSD, posttraumatic stress disorder.

studies reporting that PTSD symptom severity is associated with dysregulation of several proteins (e.g., neurocan and brevican) that support perineuronal nets surrounding inhibitory interneurons (31,32). Therefore, future work should evaluate whether indicators of interneuronal health help to explain the association between GWC and PTSD.

When compared with other indicators of intracortical health disrupted in PTSD including cortical complexity (27) and characteristic path length in WTC responders with PTSD (13), the results from this study show independent changes in GWC that are not collocated with previous results in WTC responders with PTSD. While not strongly associated across the cerebrum, clusterwise distributions appear similar in that this study also reported changes that are most severe in the frontal and parietal lobes in the right hemisphere (27). Overall, these results carry at least 2 implications. First, it may be that several different cortical changes, when combined, are associated with symptoms consistent with PTSD. Second, there may be neurobiological subtypes of PTSD that could be associated with different forms of cortical dysfunction. These observations inform future multimodal neuroimaging studies of both WTC responders with chronic PTSD and other

A



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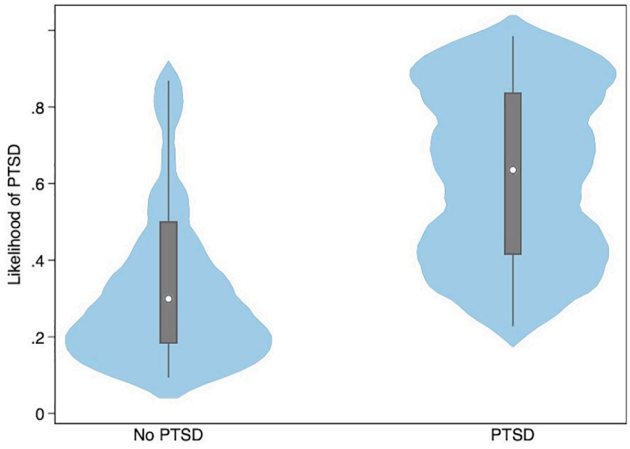

C

Cerebral Characteristic	AUC (95% C.I.)
Gray-White Contrast ($GWC_{1,20}$)	0.65 (0.54-0.76)
Cortical Free Water Fraction (CFWF)	0.58 (0.46-0.70)
Weighted Cerebral Path Length (wCPL)	0.61 (0.50-0.72)
Cortical Fractal Dimension (CFD)	0.69 (0.59-0.80)
Cortical Thickness (CTX)	0.56 (0.45-0.68)
Cerebellar Cortical Thickness (cCTX)	0.52 (0.40-0.64)
Combined Model	0.77 (0.67-0.86)

D

Metric	Median in No PTSD Group	Optimal Cutoff	Median Value in PTSD Group
Cutoff	0.295	0.388	0.620
Sensitivity	91.67%	81.25%	54.17%
Specificity	52.94%	68.63%	84.31%
Positive Predictive Value	64.71%	70.91%	0.00%
Negative Predictive Value	87.10%	79.55%	66.15%
Correctly Classified	71.72%	74.75%	69.70%

E

Cerebral Characteristic	GWC	CFWF	wCPL	CFD	CTX	cCTX
Gray-White Contrast ($GWC_{1,20}$)	1.00	0.10	-0.04	-0.05	0.00	0.08
Cortical Free Water Fraction (CFWF)	-0.01	1.00	-0.15	0.08	-0.19	0.30*
Weighted Cerebral Path Length (wCPL)	0.01	-0.32*	1.00	-0.24	-0.06	0.00
Cortical Fractal Dimension (CFD)	-0.15	-0.15	0.06	1.00	-0.15	0.00
Cortical Thickness (CTX)	0.19	-0.10	-0.23	0.14	1.00	-0.17
Cerebellar Cortical Thickness (cCTX)	0.11	0.19	0.07	0.30*	0.00	1.00

Figure 3. Classifier models were developed for 4 cortical measures of posttraumatic stress disorder (PTSD) and a combined model. **(A)** Receiver operating characteristic curve for 4 cortical measures of PTSD and the combined model. **(B)** Violin plots for model estimates of the probability of PTSD stratified by clinical group. **(C)** Area under the receiver operating characteristic curve (AUC) for each parameter and the combined model are listed. **(D)** Fit statistics for the combined model [$\ln(Pr(Y)/(1 - Pr(Y))) = -0.344 \times GWC_{1,20} - 5.073 \times CFWF + 0.013 \times wCPL + 5.681 \times CFD + 1.812 \times CTX + 0.534 \times cCTX + 44.68$] at multiple potential cutoffs. **(E)** Correlation table for participants with PTSD (below the diagonal) and participants without PTSD (above the diagonal). *$p < .05$. FPR, false positive rate; TPR, true positive rate.

similarly afflicted cohorts to evaluate both measures of surface complexity, WM integrity, GM connectivity, and GWC. These cortical differences may serve as surrogate biomarkers for compromised cortical health in populations experiencing chronic PTSD, as well as potentially informing early screening strategies.

PTSD is evidenced by the presence of several different emotional and behavioral symptom types (65). We interrogated the association between symptom types and GWC among WTC responders with PTSD to find the strongest negative associations between GWC primarily in the frontal, parietal, and temporal regions. These findings are consistent

with studies reporting that symptom severity was positively correlated with increased regional top-down processing (66) and disrupted frontal lobe circuitry (18). Similarly, neurodegeneration of the middle frontal, superior frontal, and orbitofrontal cortices (67,68) have been linked to hyperarousal symptoms, such as alertness and vigilance. Interestingly, although reduced GM volumes in the precuneus and insula have been linked to re-experiencing symptoms (20,69), cortical thickness was not associated with PTSD or GWC in this study.

In this study, GWC in the pars triangularis was consistently associated with symptom severity across all symptom domains. The pars triangularis is involved with several cognitive linguistic processes, such as verbal working memory (70), language and sentence processing (71), and language switching (72). In a conversation, these functions may present themselves as the complexity of sentence structure or words, longer sentences, the use of first-person singular or plural pronouns, or attention to specific themes (73). Using shorter words has been associated with PTSD due to a higher cognitive load resulting from intrusive thoughts and thought suppression (74), attention to trauma (75), and increased use of negative emotion words and first-person singular pronouns (76). In a study comparing language with PTSD symptom severity, first-person singular pronouns were positively associated with PTSD symptom severity (77). Future work should determine whether the GWC in the pars triangularis is associated with linguistic indicators of PTSD.

Limitations

First, this study was limited by its relatively small sample size and by the specific traumatic exposures. However, for a neuroimaging study, it is moderately sized. Additionally, previous work has found that the source of PTSD may impact the severity and chronicity of symptoms but that PTSD in different populations tends to have similar overall symptom presentations.

Second, participants were predominantly male in this study, despite efforts to oversample women. However, while we did not find that gender was associated with GWC, and we matched PTSD status on gender, this imbalance may reduce the generalizability of our findings.

Third, while we believe that the results imply a change in myelin health in the cortex, we lacked a direct measure of myelin content. The source of GWC differences is still widely debated, as signal intensity may also be affected by extracellular free water content or iron deposition in WM (33,56). Additionally, image resolution and submillimeter effects along the cortex could be confounded by partial volume effects in the cerebrospinal fluid (78), although trimming results above 50% to 60% into the GM allows us to reduce this bias (39,51). Nonetheless, head motion (79) and wraparound (80) could affect the GM and WM signals due to blurring. We did not find substantively important motion or warping in this study during quality control. However, it may be that observed differences indicate undiscovered neurobiological differences influencing GWC.

Finally, out of interest we reported results from a simple logistic model to see whether combining GWC with previously identified neuroimaging correlates of PTSD would improve model fit over GWC alone. Improved AUROCs were expected because cortical fractal dimension and characteristic path length were associated with PTSD but not GWC, suggesting the potential for improved accuracy when used in combination. The purpose of this analysis was only to demonstrate potential, so the accuracy reported here was evaluated only in the training set and was not independently validated. Future research should develop machine learning methods to verify, validate, and extend this work.

Conclusions

WTC responders with chronic PTSD have previously been shown to display reductions in cortical complexity and reduced WM integrity but not cortical thinning. In the current study, we hypothesized that quantifying GWC from T1-weighted MR images could help us better identify WTC responders with chronic PTSD compared with their healthy counterparts. Our results suggest that decreased GWC was associated with chronic PTSD. Furthermore, while GWC alone was moderately associated with PTSD in WTC responders, a multimodal logistic model comprised of several imaging surrogate markers appeared more precise. Intriguingly, the different quantifications used here were not intercorrelated, implying that the presence of one cerebral dysfunction does little to help us understand the others. Taken together, these results may imply that neuroimaging may help identify clinical PTSD but may also imply that PTSD may be made up of several etiologic subtypes. More research is warranted to better understand the neurobiology of GWC in individuals with PTSD.

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