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DTI connectometry analysis reveals white matter changes in cognitively impaired World Trade Center responders at midlife

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Abstract

Background: More than 8% of responders who participated in the search and rescue efforts at the World Trade Center (WTC) following 9/11 developed early-onset cognitive impairment (CI). Approximately 23% were also diagnosed with chronic post-traumatic stress disorder (PTSD).

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Objective: To shed light on the pathophysiology of these WTC-related conditions, we examined diffusion connectometry to identify altered white matter tracts in WTC responders with CI and/or PTSD compared to unaffected responders.

Methods: 99 WTC responders (mean age 56 years) consisting of CI-/PTSD- (n=27), CI+/PTSD- (n=25), CI-/PTSD+ (n=24), and CI+/PTSD+ (n=23) were matched on age, sex, occupation, race, and education. Cognitive status was determined using the Montreal Cognitive Assessment and PTSD status was determined using the DSM-IV SCID. Diffusion Tensor Imaging was acquired on a 3T Siemens Biograph mMR scanner. Connectometry analysis was used to examine whole-brain tract-level differences in white matter integrity as reflected by fractional anisotropy (FA) values after adjusting for confounders.

Results: Analyses identified that FA was negatively correlated with CI and PTSD status in the fornix, cingulum, forceps minor of the corpus callosum and the right uncinate fasciculus. Furthermore, FA was negatively correlated with PTSD status, regardless of CI status in the superior thalamic radiation and the cerebellum.

Conclusions: This is the first connectometry study to examine altered white matter tracts in a sample of WTC responders with CI and/or PTSD. Results from this study suggest that WTC responders with early-onset CI may be experiencing an early neurodegenerative process characterized by decreased FA in white matter tracts.

Keywords

White Matter Connectometry; Cognitive Impairment; Post-traumatic Stress Disorder; Alzheimer's disease; Diffusion Tensor Imaging; World Trade Center Responders; Midlife

1. Introduction

In the aftermath of the attacks of 9/11/2001, the men and women who responded and worked in search, rescue, and clean-up efforts at the World Trade Center (WTC) and related sites experienced a host of physical and psychological exposures, that resulted in both severe and chronic posttraumatic stress disorder (PTSD) [1, 2], and higher than expected prevalence of early-onset cognitive impairment (CI) [3], among other conditions.

CI is a critical component of the prodromal phase of Alzheimer's disease (AD) and related dementias (ADRD) [4, 5] in the presence of other signs of neuropathology [6]. The presence of neurodegeneration, particularly gray matter atrophy, is a hallmark of the pathological cascade in AD. Conceivably, one mechanism contributing to gray matter atrophy are changes occurring in white matter tracts linking cortical networks together [7]. In ADRD, white matter alterations have been linked to neural topography, deposition of β-amyloid [8, 9] as well as tau proliferation [10]. Recently, researchers have noted that interhemispheric connectivity in the posterior cortical regions is significantly worse in individuals with early-onset (aged 45–65) as compared to late-onset (aged 65 and older) ADRD [11]. Recent work has also suggested that early-onset ADRD is sometimes characterized by a parietal-dominant pattern of neurodegeneration [12] which tends to be more severe [13], and that diffusion tractography is highly sensitive to neurodegenerative diseases, noting

associations between the location of cerebral β-amyloid deposition [14], tauopathy [15], and tau spreading *via* tracts in the white matter [16].

The larger than expected group of World Trade Center (WTC) responders, 20 years after exposure, are experiencing early-onset neurocognitive dysfunction at midlife, thus representing an emerging and concerning clinical condition within this population [17]. Investigations of brain structure among WTC responders with severe CI found reduced cortical thickness consistent with parietal-dominant ADRD [18] and hippocampal atrophy with focal reductions in the presubiculum [19]. Recognizing that many neurodegenerative conditions include widespread changes to white matter, we previously conducted a small pilot study with WTC responders with mild cognitive impairment (MCI) [n=20] and identified changes to white matter tracts consistent with both increased and decreased white matter integrity [20].

To date, no studies have examined white matter differences in WTC responders with/without CI and also those with/without concurrent PTSD. We thus used diffusion imaging to study this issue in our responder population. Traditional diffusion analyses often use either tract-based or region-based analysis to compare diffusion data, by mapping macroscopic end-to-end connections between segmented grey matter regional targets, which require *a priori* tracts for analysis. However, these structural connectomic approaches rely heavily on diffusion MRI tractography to reliably quantify global end-to-end connectivity, and past studies have raised concerns that these fiber tracking algorithms exhibit limited reliability at grey-to-white matter borders [21, 22]. We therefore employed local connectometry analysis instead, to avoid this limitation by limiting tractography to consecutive fiber segments that display significant associations with the study variable, rather than mapping the entire end-to-end connectome and then analyzing tracts defined from *a priori* hypotheses [23, 24].

We hypothesized that local connectometry analysis would identify white matter tracts with altered diffusivity in WTC-CI+ when compared to cognitively unimpaired control (CI-) responders. A secondary objective was to examine whether WTC-CI+ with concurrent PTSD differed in the extent and/or distribution of white matter integrity compared to CI+ alone, since PTSD has been shown to be a risk factor for cognitive dysfunction both in the WTC cohort [25–30] and other populations [31–36], along with disrupted white matter integrity in individuals with PTSD [37–40], we hypothesized an augmented reduction of white matter integrity in WTC CI+PTSD *versus* CI alone. The study of the above two hypotheses serves to further our understanding of the neurobiological changes occurring in CI and/or PTSD at midlife in two important ways, the extent of these changes in WTC responders with CI versus those without, and whether concurrent PTSD is augmenting these changes. Furthermore, this work is important as it also informs investigations of other exposed and/or traumatized populations and how those individuals, or any future affected populations, may experience such changes.

2. Methods

2.1 Population and Study Design

In 2002, the Centers for Disease Control and Prevention (CDC) began monitoring more than 50,000 WTC responders [41] using a comprehensive monitoring protocol that has been previously described [42]. Briefly, the Stony Brook University (SBU) program monitors law enforcement and non-law enforcement (e.g., construction, utilities, and volunteer) responders who mainly reside on Long Island, NY for a variety of health conditions, including cognitive status [3]. Participants recruited from a the SBU WTC monitoring program [42] were part of an epidemiologic study of cognitive aging involving serial administration of the Montreal Cognitive Assessment (MoCA) [28]. Responders were contacted if they had previously consented to being contacted to participate in research studies and met inclusion criteria (see below).

The study used a two-by-two matched case-control design involving CI (present/absent) and PTSD (present/absent). Inclusion criteria were ages 44 to 65, and fluency in English. Cognitive status was reconfirmed at the time of scanning. CI+ was defined as scoring less than ≤20 on the MoCA within three months prior to scanning. PTSD diagnosis was determined by the DSM-IV SCID, administered by trained clinical interviewers. To minimize the impact of confounding variables, the four groups (CI+/PTSD-, CI+/PTSD+, CI-/PTSD+, CI-/PTSD-) were matched on age, sex, race/ethnicity, occupation and education (see [18] for more details).

Exclusion criteria were history of psychosis; history of diagnosed neurological conditions including diagnosed ADRD, other dementias, major stroke, multiple sclerosis, and Parkinson's disease; any head injury during their WTC efforts or a history of military head trauma including combustive blasts; current renal or liver disease; and current use of cognitively active medications. Subjects also satisfied eligibility criteria for MRI scanning including body mass index <40, absence of claustrophobia, no known pregnancy, and no known metal implants or shrapnel that were not deemed MRI- safe. The final study sample included 99 WTC responders, of whom completed the imaging protocols described in Section 2.2.

2.2 Image acquisition

Three-dimensional T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images were acquired within three months of CI and/or PTSD diagnosis, using a 3T Siemens Biograph mMR (TR = 1900s, TE = 2.49 ms, TI = 900 ms; Flip Angle = 9°; acquisition matrix: 256 × 256; voxel resolution: 0.89 × 0.89 × 0.89 mm) at Icahn School of Medicine, Mount Sinai, NY. Scans were acquired between 2017 and 2019. For incidental pathology screening, T2-weighted anatomical scans used a turbo spin-echo pulse sequence (34 axial slices, TR = 6170s, TE = 96 ms; Flip angle = 150°; acquisition matrix = 320 × 320; voxel size = 0.36 × 0.36 × 3 mm) were acquired and read by a board-certified radiologist to determine incidental findings. Diffusion tensor imaging were also performed with the following parameters: TE/TR = 87.6/4680 ms, b value = 1200, 64 diffusion directions, in-plane resolution = 2 mm, slice thickness = 2 mm, matrix size = 128 × 128, multiband

factor = 2. After data collection, post processing incorporated standard techniques for acquisition-based artifact elimination. Specifically, subject motion and eddy corrections are were accounted for by means of eddy from the FMRIB Software Library (FSL) [43]. Total imaging time for each WTC responder participant for this study, which included T1, T2, and DTI, was no more than 18 minutes. The T1 acquisition and the diffusion acquisition were approximately 6 minutes each.

2.3 Image processing

Diffusion images were visually inspected to check for major image artifacts or significant motion during the acquisition. All images passed inspection. No radiological abnormalities were identified in the images. The diffusion data were reconstructed in the Montreal Neurological Institute (MNI) space using q-space diffeomorphic reconstruction [44] to obtain the spin distribution function (SDF; diffusion sampling length ratio = 1.25) using DSI Studio (May 4 2019 build) [45]. The FA values were used in the connectometry analysis as they can represent axonal and myelination integrity, where lower values signify increased, unrestricted permeability (isotropic) due to axonal degradation and demyelination, whereas higher values denote restricted, anisotropic diffusion that can occur in health, myelinated axons [46–48].

2.4 Connectometry

Diffusion MRI connectometry analysis [49] (DSI Studio, build 20210813) was used to identify white matter tracts with altered diffusion. A t-score threshold was assigned to select local connectomes which were significantly associated with the study variable, i.e., cognitive and/or PTSD status, while using General Linear Modelling (GLM) analysis control for age, sex, and education. Local connectomes were tracked using a deterministic fiber tracking using the quantitative anisotropy algorithm based on Euler's method, instead of traditional voxel-based index tracking methods, as these latter approaches have been shown to be less effective at selectively removing noisy fibers as they're equally anisotropic within individual voxels. Instead, deterministic fiber tracking using quantitative anisotropy can lead to improved removal of noisy fibers and definition of terminal locations (see Yeh et al., 2013 for details [50]). In all analyses, three T thresholds (2, 2.5, 3) were used to ensure the stability of the findings. All tracts generated from bootstrap resampling were included and a length threshold distance of 20 voxels was used to select tracts. The seeding number for each permutation was 10,000. To estimate the false discovery rate (FDR), a total of 2,000 randomized permutations were applied to group labels to obtain the null distribution for tract length. . The generated tracts were then segmented by using "recognize and cluster" functionality in DSI studio followed by manual corrections. Isolated tracts were excluded from the segmentation.

2.5 Cognitive impairment

Participants were considered CI+ if they had evidence of cognitive impairment as measured by the Montreal Cognitive Assessment (MoCA) [51], a widely used measure of cognitive functioning developed to objectively and reliably identify age-related CI. Consistent with NIA diagnostic criteria for dementia [52]. CI+ was present when individuals had difficulties with behavioral functioning related to cognition and if they had neuropsychological

dysfunction consistent with possible mild dementia using a conservative cutoff (MoCA ≤ 20) [53]. CI-responders had scores in the normal range (MoCA ≥ 26).

2.6 Posttraumatic stress disorder

PTSD diagnosis was assessed using the Structured Clinical Interview for the DSM-IV (SCID-IV) [54], a semi-structured interview schedule administered by trained clinical interviewers.

2.7 Demographics

Age in years, sex (male vs. female), and race (White, Black, and Hispanic) on September 11 (Law Enforcement vs Other) were included for matching purposes.

2.8 Statistical analyses

Descriptive characteristics for the present sample were provided using mean and standard deviations, or frequencies and percentages as noted. In this study, confounding from central variables including age was completed using matching in the study design phase. One-way analysis of variance and $\chi 2$ tabulations were used to examine differences in matching and diagnostic variables across diagnostic groups. A two-tailed $\alpha = 0.05$ was used to determine nominal statistical significance and results from repeated testing analyses were adjusted to avoid Type I errors using the false discovery rate (FDR = 0.05) [55].

2.9 Ethics

The Institutional Review Boards at both Stony Brook University and the Icahn School of Medicine at Mount Sinai approved study procedures; participants provided informed written consent.

3. Results

3.1 Sample Characteristics

The descriptive characteristics of the sample (n = 99) are shown in Table 1. The study sample is all WTC responders. Groups did not differ on matching criteria, such as age, sex, or race; however, CI-/PTSD- group had significantly higher education (in years) than the CI+/PTSD- and CI+/PTSD- group, which was then adjusted for in subsequent analyses.

3.2 WTC Connectometry

We conducted a series of four pairwise comparisons examining changes in tractography across the four groups of WTC responders in this sample using three T-thresholds (T=2, 2.5, 3) while adjusting for multiple comparisons using FDR. Non-significant findings were inferior longitudinal fasciculus omitted. As shown in Figure 2, analysis of all responders with CI+ when compared to all CI- responders, regardless of PTSD status, identified that FA was negatively associated with CI across several cortical tract bundles and subcortical tract bundles (FDR = 0.0128). No tracts were found to have significant FA values positively associated with CI status for all three T-thresholds.

As shown in Figure 3, analysis of all responders with PTSD when compared to all responders without PTSD, regardless of cognitive status, identified that FA was negatively associated with PTSD across several cortical and subcortical tract bundles. No tracts were found to have significant FA values positively associated with PTSD status.

As shown in Figure 4, connectometry comparisons between CI+/PTSD- (n=25) compared to CI-/PTSD- responders (n=27) identified that FA was negatively associated in some cortical and subcortical tracts in the former group. No tracts were found to have significant FA values positively associated with CI status for all three T thresholds.

As shown in Figure 5, subgroup analysis between CI+/PTSD+ (n=23) and CI+/PTSD- (n=25) WTC responders, found negative associations of FA in some cortical and subcortical tracts in responders with CI+/PTSD+. No tracts were found to have FA values positively significantly associated with PTSD diagnosis for all three T thresholds between the two groups.

An ROI summary table of results for the four findings above identifying associations with reduced white matter FA is shown in Table 2.

4. Discussion

This is the first study to examine white matter alterations using connectometry analysis in a sample of WTC responders at midlife with and without CI as well as with and without concurrent PTSD. The goal of this study was to examine and elucidate the extent to which white matter tract integrity might be impaired in WTC responders with CI and/or PTSD. We previously reported changes in white matter diffusivity in a sample of 20 WTC responders with MCI, using diffusion spectrum imaging (DSI) measures in regions characteristic of early AD [20]. Results from the present study extend our previous finding of white matter changes in WTC responders with MCI, as we now identified bundles of decreased white matter integrity in responders with CI and PTSD, or both. Specifically, we hypothesized that local connectometry analysis would identify white matter tracts with altered diffusivity in WTC-CI+ when compared to cognitively unimpaired control (CI-) responders, and our results identified reduced white matter integrity in responders with CI+ across occipitotemporal (inferior and longitudinal fasciculus, thalamocortical (posterior and superior thalamic radiations), frontal lobe (forceps minor), and cerebellar tracts (middle cerebellar peduncle. A secondary objective was to examine whether WTC-CI+ with concurrent PTSD differed in the extent and/or distribution of white matter integrity compared to CI+ alone, and our results identified decreased connectivity in limbic regions in responders with WTC-CI+ and concurrent PTSD.

White Matter Integrity in WTC responders with cognitive impairment and PTSD.

Our most significant finding might be that white matter tracts identified here might suggest that the fornix, in the forceps minor of the corpus callosum, and the cingulum bundle may act as a convergent mechanism to link conditions affecting discussed here. The fornix, whose development peaks during late adolescence and serves to connect the hippocampus to other limbic structures, has been implicated in episodic memory recall

and processing speed, where damage to this area and functions have been implicated in AD and can serve as a marker for neurodegeneration [56–61]. The forceps minor is situated in the anterior portion and serves to connect regions of the frontal cortices [62], while the inferior segment of the cingulum is an intersectional region connecting the hippocampus and parahippocampal gyrus [63], whose function serves as a compound measure of cognitive skills such as reasoning, problem solving and behavioral flexibility [64]. It has been previously demonstrated that FA in the cingulum is reduced in MCI and AD [65–69], whereby microstructural changes in this region have been shown to be predictive of decline in cognitive controls [70]. Lesions to the cingulum have also been associated with transient confusion, disorientation, disrupted verbal working memory, and memory loss [63, 71]. However, changes in this region are also implicated in PTSD (for review, see [63]). Considering that PTSD is a risk factor for CI [26, 28–30, 33–36], this result suggests that the fornix, forceps minor and cingulum bundle may serve as a shared neural correlate that is affected by either CI alone, PTSD alone, or both comorbidly. Future studies with affected WTC responders or similar populations may benefit from monitoring changes in the fornix.

Reduced FA was also identified in the right arcuate fasciculus of responders with CI, regardless of PTSD status, but not in our subgroup analyses. The arcuate fasciculus is a large axonal tract connecting the temporal and inferior parietal cortices to the inferior frontal cortex, bridging key language regions such as Broca's and Wernicke's areas serves as an important neural correlate implicated in language disruption and aphasia [72]. White matter disruptions and demyelination in the arcuate fasciculus have been previously demonstrated in MCI and AD [73], including conditions with are high CI risk such as schizophrenia [74] and traumatic brain injury [75]. Interestingly, we did not observe reduced FA in the right arcuate fasciculus in our subgroup analyses, such as responders with CI+/PTSD- or responders with CI+/PTSD+, suggesting a statistical power limitation that was only surpassed when we grouped them together. Therefore, future studies with sufficient sample sizes should monitor this white matter tract to establish whether PTSD contributes to our present observation, as prior studies with PTSD populations have implicated white matter abnormalities within the arcuate fasciculus [76–78].

Similarly, we identified reduced FA in the uncinate fasciculus in responders with both CI+ and PTSD+. The uncinate fasciculus is a tract that connects the limbic and temporal lobes to the inferior frontal lobe and has been implicated in several psychiatric disorders and frontotemporal dementias, where it is in involved in higher memory associations, such as assigning a name and voice with a face in addition to being involved in reward behaviors (for review, see [79]).

Reduced FA was identified in the left and right inferior longitudinal fasciculus in both responders with PTSD alone but also with CI+/PTSD-. The inferior longitudinal fasciculus is a white matter tract that connects the occipital to the temporal lobes, whereby atrophy has been associated with visuospatial, semantic, object recognition, face processing and language dysfunction in dementia populations [80–84] and has been reported to be disrupted in AD, semantic dementia, and Lewy-body dementia [85–88]. Considering the extensive cortical connective bundles that this tract serves in the brain, this result can be considered as a widespread disruption in white matter connectivity presenting in responders that is shared

with both those who present with CI alone and PTSD alone. Interestngly, our responder group with both CI+/PTSD+ did not show that FA was significantly associated with the comorbid condition, suggesting that that smaller sample size of this group may have not been sufficiently large to power this result. Nevertheless, this observation was absent in responders with CI+, regardless of PTSD status, which confounds the above interpration and requires future interrogation to clarify whether reduced FA is associated by CI, PTSD, or both.

Lastly, we identified reduced FA in the middle cerebellar peduncle, which is a tract that connects the pons to the cerebellum, conveying information to the cerebrum. This tract has been reported to be implicated demyelinating diseases such as multiple sclerosis, vascular and toxic encephalopathies, and other neurodegenerative disorders [89]. In addition, we also identified reduced FA in the left and right cerebellum of responders with PTSD+, regardless of CI status, and also in our subgroup analyses of both CI+/PTSD- and CI+/PTSD+. However, and rather perplexingly, we did not observe reduced white matter FA in the group of responders with CI+, regardless of PTSD status, as we have previously reported reduced cerebellar thickness in responders with CI+, regardless of PTSD status [90]. This discrepancy may be due to the pooling of responders with/without PTSD, because as previously mentioned, we observe reduced FA in the cerebellum in our subgroup analyses. Nevertheless, the cerebellum, which is a critical structure for cognition, emotion, and coordination, has long been associated with alterations in trauma-exposed populations (for review, see [91]), but has largely been absent in dementia conditions [92]. However, taken together with our prior findings, we definitively identify that both cerebellum grey and white matter are affected in WTC responders with CI with/without PTSD.

White Matter Integrity in WTC responders with PTSD, regardless of CI status.

Here, we focus our discussion on results that demonstrated reduced FA in responders with PTSD with a T value of 2.5, regardless of CI status. We identified reduced FA in the superior thalamic radiation, where thalamocortical radiations are the primary relay tracts of the brain that connect the thalamus to the cerebral cortex, relaying sensorimotor activity throughout the cortex and back. Specifically, the superior thalamic radiations bridge the ventral nuclear group of the thalamus to the precentral and postcentral gyri [93]. While the thalamic radiations serve multiple functions, reductions in white matter integrity in the superior portion have been associated with reduced global cognition and processing speed [94, 95]. This result is in line with a prior study examining cortical thickness in WTC responders with CI [18], who show reduced cortical thickness in both the precentral and postcentral gyri, suggesting a possible mechanistic explanation to how reduced white matter integrity in the connecting superior thalamic radiation may have lead to reduced thickness in these cortical regions.

Taken together, we identified a large array of ROIs that display reduced white matter integrity in responders with CI and/or PTSD in a topographical manner that overlap with a variety of dementia-like conditions rather than a single neurological condition per se. While challenging to amalgamate and generalize these results, nevertheless, identifying these tracts is an important step toward better characterizing the etiology of the emerging

neurological changes in affected WTC responders at midlife. As research efforts continue to identify the etiology for this emerging WTC neurological condition in efforts to determine which dementia subgroup these responders may present as, or if it is a unique WTC condition, it is important that we continue to interrogate underlying neurophysiological correlates. Results from the present study suggest a more widespread pattern of reduced white matter integrity, which does not necessarily ascribe to a single known neurological disorder, such as AD. Nevertheless, WTC responders with CI and/or PTSD, now at midlife, continue to demonstrate cognitive impairment and PTSD are coupled with neuropathological phenomena, as shown in prior research and this study. Ongoing research with cognitively impaired and PTSD endorsing WTC responders will be paramount to uncovering and elucidating the neural correlates for these observations.

5. Limitations

This is the first DTI study of WTC responders with CI and/or PTSD nested in a prospective cohort study of individuals at midlife. While being novel in several ways, this study also has several limitations including the small sample size and the lack of an external control group. Additionally, despite over-sampling minorities and women, the study's sample size resulted in subgroup samples that were too small to examine separately. Additionally, this study relied on DTI imaging though studies are increasingly using DSI because of its improved capabilities to track crossing fibers and map axonal trajectories via the use of probabilistic density functions instead of single tensor analysis [96, 97]. Another limitation is that data in this study were cross-sectional, hence we cannot rule out whether the observed results emerged with aging and exposure to the WTC disaster, or were present and unchanged for the two decades prior. Finally, though meeting the criteria commonly used to diagnose dementia, the lack of certainty regarding the etiology of CI in this population has caused us to be conservative with nomenclature utilized in all of our studies.

6. Conclusions

This study examined, for the first time, white matter integrity in WTC responders with CI and/or PTSD at midlife. Results are supportive of reduced white matter integrity in responders with CI+ across occipitotemporal (inferior and longitudinal fasciculus, thalamocortical (posterior and superior thalamic radiations), frontal lobe (forceps minor), and cerebellar tracts (middle cerebellar peduncle), possibly accounting for neuropathology arising in certain regions. We also identified decreased connectivity in limbic regions in responders with PTSD, suggesting that mechanisms of depotentiated synaptic plasticity may be at work, due to the debilitating nature of chronic PTSD and CI. To date, it remains unclear how WTC exposures might have resulted in changes to white matter integrity. These results support ongoing work suggesting that WTC responders with CI and/or PTSD are experiencing neurological changes, perhaps with the involvement of neuroinflammation as the etiological substrate. This warrants future investigations of neuroinflammation, such as free water DTI techniques, as WTC responders are aging and the risk of CI increases substantially. Our results herein and in future studies, might therefore serve to inform policymakers and to direct clinical intervention strategies for WTC responders and for other trauma-exposed populations.

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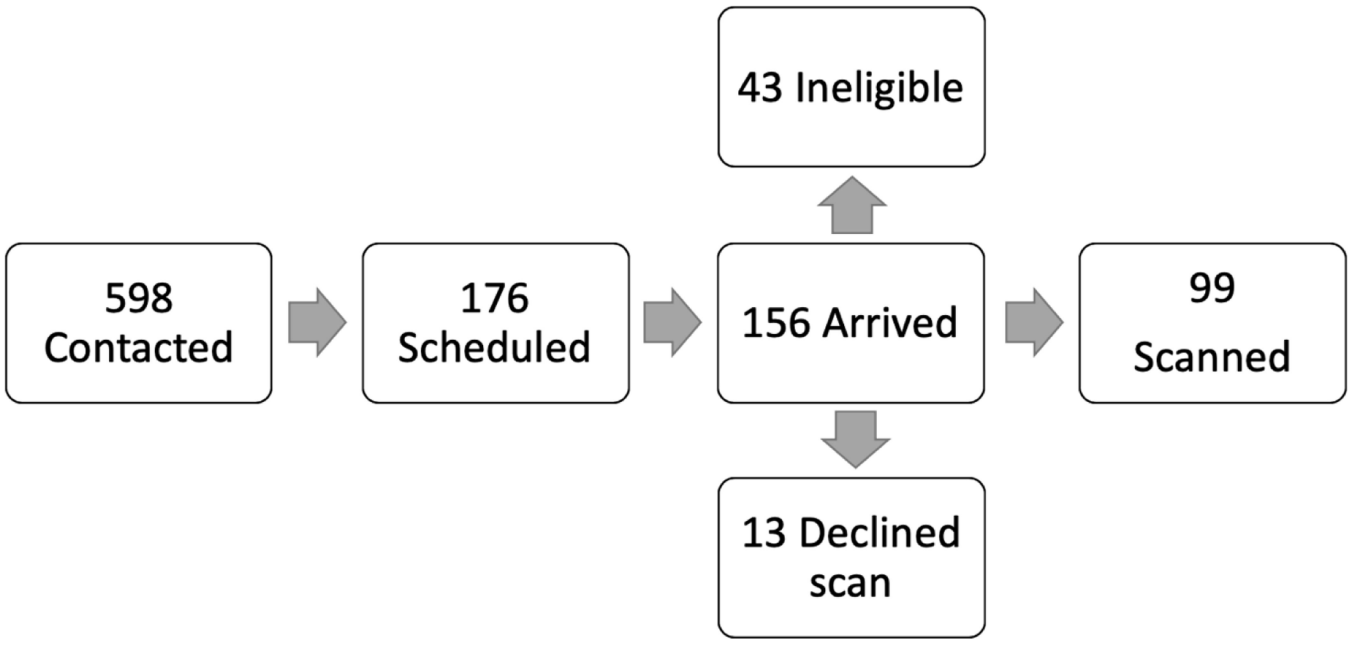

Figure 1.
Flow Chart illustrating subject enrollment into study.

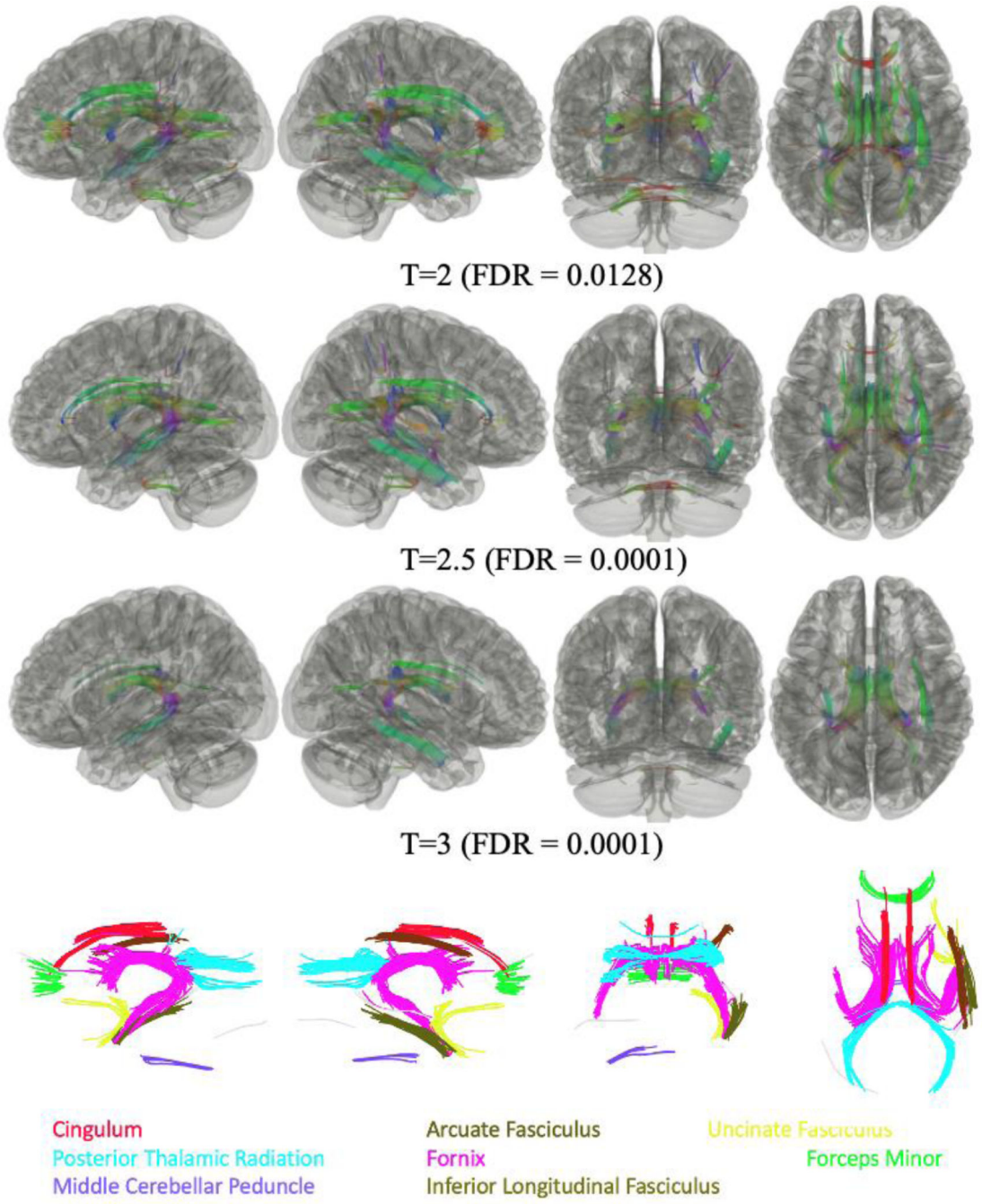

Figure 2.

Connectometry comparisons between WTC responders with Cognitively Impairment (CI+) [n=48] and those who were Cognitively Unimpaired (CI-) [n=51] responders, regardless of PTSD status, using three T-thresholds (T=2, 2.5, 3), identified that FA values were lower in responders with CI+ compared to CI- responders. Significantly different tracts included the left and right fornix, the right posterior thalamic radiation, and the middle cerebellar peduncle for all three T thresholds; and the forceps minor, the left posterior thalamic

radiation, the right arcuate fasciculus, the left and right cingulum, and the right uncinate fasciculus for T<=2.5.

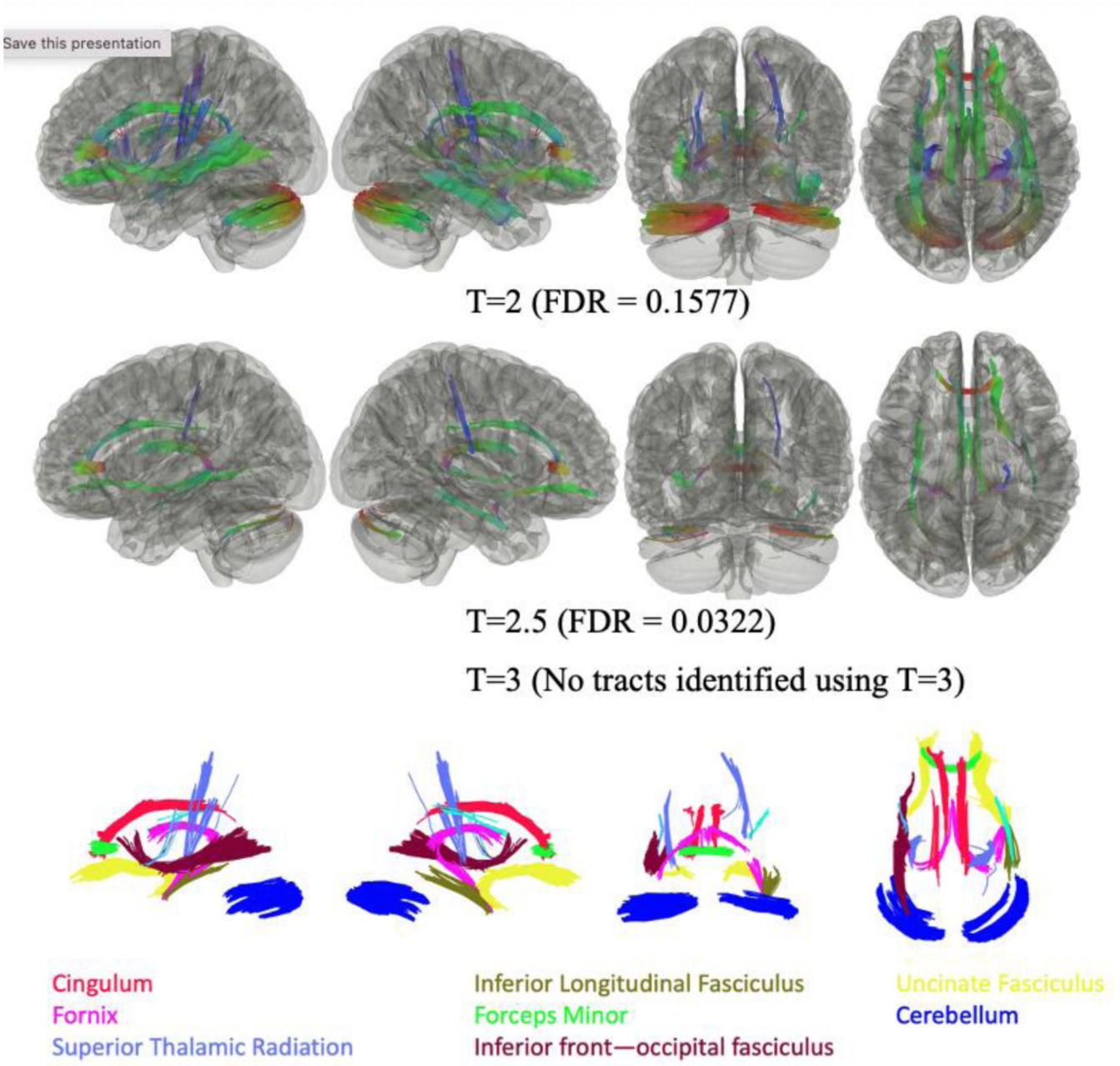

Figure 3.

Connectometry comparisons between WTC responders with PTSD+ (n=47) and PTSD- (n=52), regardless of cognitive status, using three T-thresholds (T=2, 2.5, 3) identified lower FA values in responders with PTSD when compared to responders without PTSD. Significantly different tracts included the left and right fornix, the right uncinate fasciculus, the forceps minor, the left and right cingulum, the left and right cerebellum, the right superior thalamic radiation, and the right inferior longitudinal fasciculus for T<=2.5; and the left superior thalamic radiation, the left inferior fronto-occipital fasciculus, and the left uncinate fasciculus, for T=2.

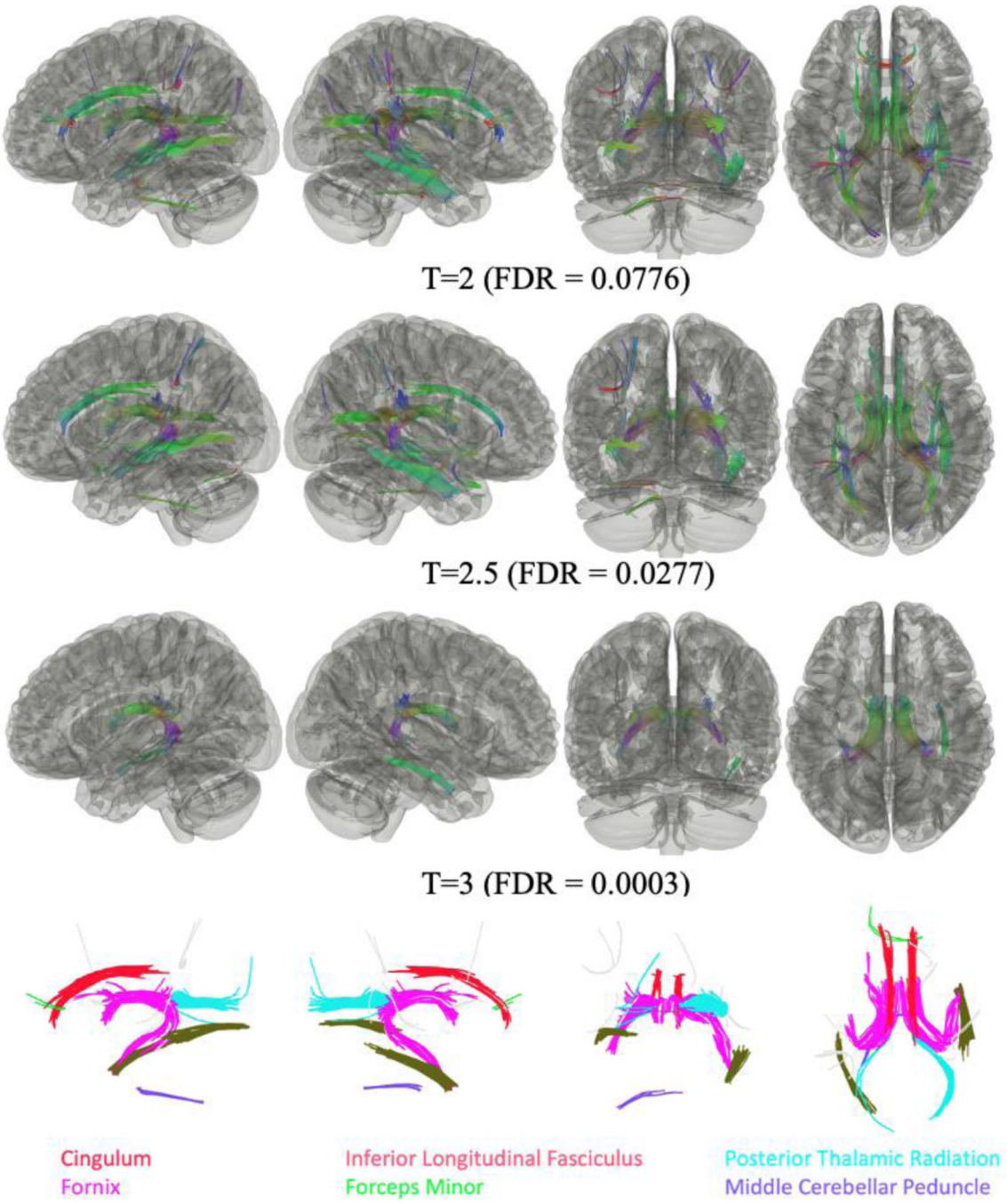

Figure 4.

Connectometry comparisons between WTC responders with Cognitive Impairment but no PTSD (CI+/PTSD-) [n=25] and no cognitive impairment or PTSD (CI-/PTSD-) [n=27] using three T-thresholds (T=2, 2.5, 3), identified that FA values were negatively associated with CI.

Significantly different tracts included the left and right fornix, the right cingulum, and the right inferior longitudinal fasciculus for all three thresholds; and the left cingulum, the left cerebellum, the left inferior longitudinal fasciculus, the right posterior thalamic radiation,

and the middle cerebellar peduncle for T≤2.5; with the forceps minor, and the left posterior thalamic radiation for T=2.

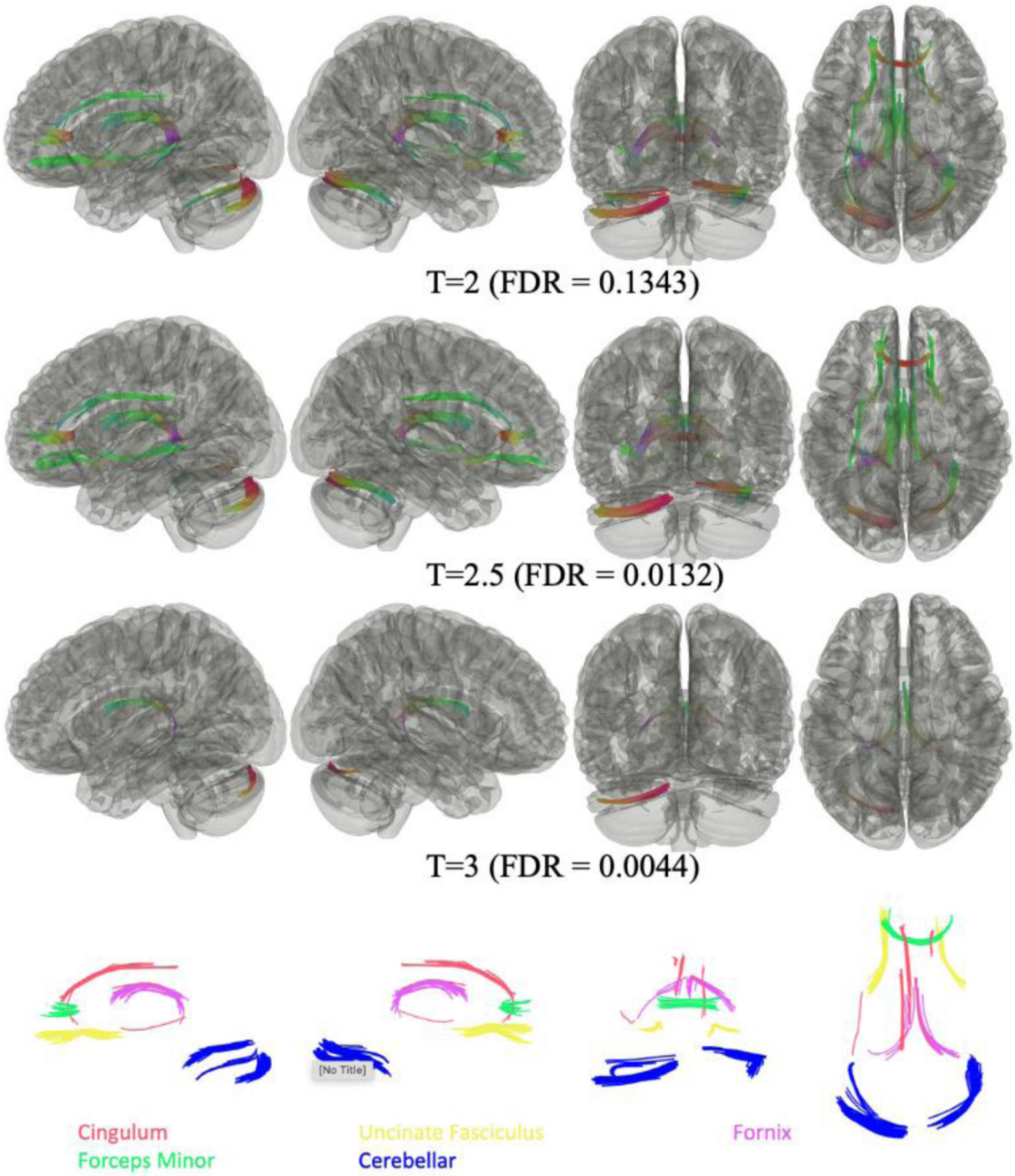

Figure 5.

Connectometry analysis of between WTC responders with Cognitive Impairment but no PTSD (CI+/PTSD-) [n=25] and those with both Cognitive Impairment and PTSD (CI+/PTSD+) [n=23], suggested that FA negatively correlated with responders with both CI+ and PTSD+ status. Significantly different tracts included the left and right fornix and the left cerebellum for all three thresholds: and the forceps minor, the right cerebellum, the left and right uncinate fasciculus and the left cingulum for T≤2.5. x

Table 1.

Sample Characteristics.

Characteristic	CI−/PTSD− (n = 27)	CI+/PTSD− (n = 25)	CI−/PTSD+ (n = 24)	CI+/PTSD+ (n = 23)	F/χ^2	P
Age	57.07 (4.36)	55.60 (6.24)	54.58 (4.69)	56.13 (5.45)	1.007	0.393
Sex						0.933
Male	77.78%	76.00%	83.33%	78.26%		
Female	22.22%	24.00%	16.67%	21.74%		
Education (years)	16.52 (1.87)	14.84 (1.7)	15.75 (2.61)	14.78 (2.28)	3.842	0.012
Minority status					10.312	0.112
Black	11.11%	12.00%	0.00%	17.39%		
White	81.48%	68.00%	95.83%	60.87%		
Other	7.41%	12.00%	4.17%	21.74%		
Hispanic					2.927	0.403
Yes	11.11%	20.00%	4.17%	13.04%		
No	88.89%	80.00%	95.83%	86.96%		
WTC exposure (months)	3.42 (3.39)	3.63 (3.61)	4.11 (2.98)	3.75 (3.44)	0.19	0.903

Note: Means (standard deviations) or percentages (%) reported. P-values examine the extent to which noted characteristics differ across groups and were derived using $\chi 2$ tests for categorical variables, and one-way ANOVA for continuous variables. Abbreviations: WTC = World Trade Center; CI = Cognitive Impairment; PTSD = Posttraumatic stress disorder.

Table 2:

Summary table of results showing regions of interest where white matter FA displayed significant negative associations with: cognitive impairment (CI+), regardless of posttraumatic stress disorder (PTSD) status; PTSD+, regardless of CI status; CI+/PTSD− versus CI−/PTSD−; CI+/PTSD+ versus CI+/PTSD−.

Region of interest	CI+ (n = 48)	PTSD+ (n = 47)	CI+/PTSD− (n = 25)	CI+/PTSD+ (n = 23)
L Fornix	xxx	xx	xxx	xxx
R Fornix	xxx	xx	xxx	xxx
L Posterior Thalamic Radiation	xx		x	
R Posterior Thalamic Radiation	xxx		xx	
L Superior Thalamic Radiation		x		
R Superior Thalamic Radiation		xx		
L Inferior Longitudinal Fasciculus			xx	
R Inferior Longitudinal Fasciculus		xx	xxx	
Forceps Minor	xx	xx	x	xx
R Arcuate Fasciculus	xx			
Middle Cerebellar Peduncle	xxx		xx	
L Cingulum	xx	xx	xx	xx
R Cingulum	xx	xx	xxx	
L Uncinate Fasciculus		x		xx
R Uncinate Fasciculus	xx	xx		xx
L Cerebellum		xx	xx	xxx
R Cerebellum		xx		xx
L Inferior Fronto-Occipital Fasciculus		x		

Note: x: T=2; xx: T=2.5; xxx: T=3; L: Left; R: Right.