

NEUROIMAGING

Reduced cortical thickness in World Trade Center responders with cognitive impairment

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Abstract

Introduction: This study examined cortical thickness (CTX) in World Trade Center (WTC) responders with cognitive impairment (CI).

Methods: WTC responders (N = 99) with/without CI, recruited from an epidemiologic study, completed a T1-MPRAGE protocol. CTX was automatically computed in 34 regions of interest. Region-based and surface-based morphometry examined CTX in CI versus unimpaired responders. CTX was automatically computed in 34 regions of interest. Region-based measures were also compared to published norms.

Results: Participants were 55.8 (SD = 0.52) years old; 48 had CI. Compared to unimpaired responders, global mean CTX was reduced in CI and across 21/34 cortical subregions. Surface-based analyses revealed reduced CTX across frontal, temporal, and parietal lobes when adjusting for multiple comparisons. Both CI and unimpaired WTC groups had reduced CTX in the entorhinal and temporal cortices compared to published normative data.

Discussion: Results from the first structural magnetic resonance imaging study in WTC responders identified reduced CTX consistent with a neurodegenerative disease of unknown etiology.

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KEYWORDS

cognitive impairment, cortical thickness, World Trade Center responders

1 | INTRODUCTION

Studies have documented the extreme exposures and concomitant high burden of psychiatric illness among the men and women (currently aged 45 to 65) who responded to the World Trade Center (WTC) attacks on September 11, 2001.¹ Despite their relative youth, currently available data suggest that this population is also at an increased risk for age-related cognitive impairment (CI).² Age-related CI with dysfunction in episodic memory is most commonly attributed to neurodegenerative diseases including Alzheimer's disease and related dementias (ADRD). Earlier reports indicate that post-traumatic stress disorder (PTSD) among veterans of the Vietnam, Iraq, and Afghanistan wars was associated with cortical atrophy.^{3,4} Studies have also increasingly suggested that severe and/or chronic exposure to inhaled fine particulate matter (PM < 2.5 μ m) as was experienced on-site at the WTC disaster,⁵ may also cause neurodegeneration in the temporal lobe.⁶ To date, no studies have used neuroimaging in CI in WTC responders. Yet, risk of CI in WTC responders is more common than in the general population and is associated with risk factors for ADRD including aging, apolipoprotein- ϵ 4 allele possession, and is also associated with WTC exposures and PTSD.^{2,7-12}

Cortical thickness (CTX) measurement from magnetic resonance imaging (MRI) provides a powerful non-invasive method for quantifying neurodegenerative disease risk including for AD.¹³ For example, prior studies have shown that individuals with AD experience reductions in CTX in the medial temporal and posterior cingulate/retro-splenial cortices,¹⁴ with reductions in mean CTX estimated at -0.04 mm in mild CI (regional range: [0.00 to -0.16]),¹⁵ and -0.13 mm in AD (regional range: [0.00 to -0.48]),¹⁶ with effects concentrated in the temporal lobe. The objective of the current study was to determine whether CI in WTC responders was potentially attributable to reduced CTX, and whether the pattern of CTX reductions matched known disease profiles. A secondary objective was to examine whether CI among responders with PTSD differed in extent and/or distribution compared to CI alone. Finally, because many cognitively unimpaired WTC responders also spent significant amounts of time near the WTC site, a final objective was to examine the potential for population-wide differences in comparison to population norms.

2 | METHODS

Participants were recruited from a single clinic-based monitoring program in the WTC Health Program¹⁷ who participated in an epidemiologic study of cognitive aging involving serial administration of the Montreal Cognitive Assessment (MoCA).¹⁸ Responders were contacted if they had previously consented to being contacted to participate in research studies and met inclusion criteria.

RESEARCH IN CONTEXT

1. To date, little is known about the reasons for cognitive impairment in World Trade Center (WTC) responders.
2. In this study of WTC responders aged 55.8 years, whole-brain and regional cortical thickness was reduced in cognitively impaired responders with and without posttraumatic stress disorder.
3. Compared to published norms, cognitively unimpaired and impaired responders had reduced cortical thickness throughout the temporal lobe.

The study used a two-by-two design including CI (present/absent) and PTSD (present/absent). Inclusion criteria were ages 44 to 65, fluent in English, current cognitive assessment indicative of unimpaired (MoCA \geq 26) or CI (MoCA \leq 20), and a diagnostic assessment of WTC-PTSD. While not an inclusion/exclusion criterion, all but one responder with CI had functional limitations consistent with mild dementia. Cognitive status was re-assessed at the screening visit to ensure case status, and only responders who maintained cognitive status were invited to complete imaging. Responders whose case status was not confirmed were excluded from the neuroimaging study. Eligible responders also had to have diagnoses of either non-PTSD or PTSD at screening. To account for differences in design across these four general categories, responders' status was matched across groups based on age, sex, and race/ethnicity as well as occupation and education.

Exclusion criteria: 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 the WTC or a history of military head trauma including combative blasts; current liver disease; and current use of cognitively active medications. Subjects also satisfied eligibility criteria for MRI scanning including body mass index \geq 40, no known claustrophobia, and no known metal implants or shrapnel that was not deemed MRI-safe. Upon enrollment, eligible responders were screened to provide more detailed information about functioning and also to ensure case status.

In total, 598 responders were contacted because they fit preliminary inclusion criteria. After screening to determine interest in study participation, 176 were scheduled for screening visits. Of those who were scheduled, 88.6% (n = 156) completed screening visits of whom 27.6% (n = 43) were deemed ineligible, and 7.7% declined participation. The most frequent reason for screened participants being deemed ineligible was failure to screen into appropriate study groups; for example,

34.9% ($n = 15$) of responders who had previously been diagnosed with PTSD failed to endorse PTSD at screening interviews. Finally, 100 WTC responders commenced neuroimaging; however, only 99 responders completed the imaging used herein. On average, 26.2 (standard deviation [SD] = 17.2) days (inter-quartile range = 14 to 35 days) elapsed between screening and neuroimaging.

2.1 | Image acquisition

Three-dimensional T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images were acquired 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). 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.

2.2 | Image processing

Image processing was completed in two steps. Region-based analysis was completed using FreeSurfer (version 5.3) to process T1-weighted images, because it provides the best regional estimate of CTX both compared to other quantification programs,¹⁹ and compared to histological data.²⁰ Regional CTX was computed automatically using the standard, automated cortical reconstruction pipeline of FreeSurfer, as described in previous publications.^{21,22} Mean CTX was measured as the average distance between gray and white matter bounds and the outer surface of the cortex of the brain for a given region. CTX values were extracted for 34 regions of interest (ROIs) in each hemisphere based on the "Desikan-Killiany" atlas.²³ ROI measures of CTX across the two hemispheres were averaged to compute bilateral mean CTX values for each of the 34 ROIs included in the analyses. Visual inspection was performed during quality control efforts. All scans passed global visual inspection in both FreeSurfer and Computational Anatomy Toolbox (CAT12) for severe motion artifacts and low gray-white matter contrast, which can undermine segmentation accuracy.

Surface-based morphometry (SBM) was conducted using the CAT12.²⁴ CAT12 provides better signal to noise calculation in SBM compared to FreeSurfer,¹⁶ and also facilitates threshold-free cluster analysis. A fully automated projection-based thickness estimation method incorporating partial volume correction was used to measure CTX.²⁵ Topological defects were repaired using spherical harmonics as part of CAT12.²⁶ Analyses followed standard guidelines for pre-processing including cortical segmentation and Dartel registration prior to CTX being bilaterally merged and smoothed (at 15 mm). For descriptive purposes, total intracranial volume, gray and white matter volume, and white matter hypointensity volume were also extracted using CAT12 automated volumetrics.

2.3 | Norms

For external comparisons of region-based analyses generated by FreeSurfer, we extracted CTX norms derived from 2799 MRI images of cognitively unimpaired (CU) controls aged 18 to 94.²⁷ Published norms were matched to our protocol using norms adjusted for age, sex, scanner type, and scanner resolution demographic characteristics.

2.4 | Measures

2.4.1 | Cortical thickness

CTX is a consistent measure of brain atrophy that is commonly used in studies of AD and other related dementias.²⁸ CTX compares favorably with gray matter volume, whole-brain volume, and hippocampal volumes because, while all of these measures can be indicators of neurodegeneration, CTX can be quantified across multiple brain regions, and is unrelated to intracranial volume, or sex.

2.4.2 | Cognitive impairment

The MoCA is a widely used measure of cognitive functioning developed to objectively and reliably identify age-related CI. A conservative cutoff (MoCA ≤ 20) was used to identify CI, at a level consistent with possible mild dementia.²⁹ CU controls had scores in the normal range (MoCA > 26).

2.4.3 | Cognitive functioning

A validated computer assisted battery consisted of repeated game-like tasks.^{30,31} A total of five tasks were used to measure cognitive dysfunction across domains of episodic memory (accuracy), visuospatial functioning and recall (total number of errors), working memory (accuracy), throughput (accurate responses per second), intra-individual item-response variability (measured in standard deviations), processing speed (responses per millisecond), response speed (answers per millisecond), and attention (accuracy). Each task includes 30 to 88 independent trials with an overall score being averaged across valid trials within each task.

2.4.4 | Posttraumatic stress disorder

Diagnosis was assessed using the Structured Clinical Interview for the DSM-IV (SCID-IV)³², a semi-structured interview schedule administered by trained clinical interviewers. Symptom subdomains were measured using subscales calculated using reported symptom severity in the SCID for the following symptom domains: re-experiencing symptoms, avoidance, hyperarousal, and negative life experiences.

2.4.5 | WTC exposure severity

An interviewer-administered exposure assessment questionnaire (EAQ) was administered to all responders upon enrollment into the epidemiologic study, that is, at baseline, to record exposures to harmful physical and psychological conditions during work on the WTC recovery effort.¹⁷ In this study, we examined time spent on site among individuals who worked at the WTC pile.^{10,33} High exposure was defined as the top quintile of exposure duration (≥ 15 weeks).

2.4.6 | Demographics

Age in years, sex (male vs female), race (white, black, and Hispanic), educational attainment (high school or less, some college, and university degree), and occupation on September 11 (New York Police vs Other) were included for matching purposes.

2.5 | Statistical analyses

Descriptive characteristics were provided using mean and standard deviations, or frequencies and percentages where noted. In this study, confounding from central variables including age was completed by the use of matching in the design phase. One-way analysis of variance and χ^2 tabulations were used to examine differences in matching and diagnostic variables across diagnostic groups.

The analytic plan focused on studying first global mean CTX, then examining CTX in subregions, before finally examining whole-brain SBM. In each section, the study compared WTC responders to CI versus unimpaired responders, and then compared PTSD to non-PTSD responders. Analyses then sought to compare subgroups, PTSD-CI to CI alone, as well as PTSD-CI and CI alone compared to unimpaired responders without PTSD. Regional differences in CTX in CI were examined using generalized linear modeling. Because main covariates were included in matching efforts, analyses did not include additional adjustments for matched variables. Additionally, because both CI and PTSD were independent effects, generalized linear modeling was additionally used to examine associations between CTX and both PTSD and CI status; however, because CI emerged as the predominant predictor while PTSD was consistently non-significant, associations with PTSD were described as sensitivity analyses. A similar approach was used in other sensitivity analyses examining stability in the predictive value of CI while adjusting for potential confounders. Analyses initially included total intracranial volume as a confounder; however, since it was not associated with the outcome in any analyses and made no substantial changes to interpretation presented, it was not included in final reported analyses.

Whole-brain SBM relied on threshold-free cluster enhancement (TFCE; $E = 0.5$, $H = 2.0$) using Draper-Stoneman (10,000 permutations) to detect vertex clusters; TFCE-calculated t-values were reported (t_{TFCE}).³⁴ Cluster-based analyses were reported mapped onto central surface maps; cluster locations were reported in Montreal Neurolog-

ical Institute (MNI) coordinates and mapped onto Desikan-Killiany ROIs.

One-sample t-tests were used to determine differences between WTC responders and published norms. In ROI-based analyses, standardized mean differences between groups were calculated and both nominal differences ($\alpha = 0.05$), and differences that were statistically significant after accounting for the false discovery rate (FDR = 0.05) were reported.³⁵ Generalized linear modeling was used to estimate effect sizes while adjusting for PTSD status in dimensional analyses. Sensitivity analyses further examined results when controlling for matching criteria including age; however, because the design ensured that similar results would be evident the results of these analyses were not reported. Statistical analyses of whole-brain mean CTX and ROI-based differences in CTX were implemented using Stata 15/SE (StataCorp).

2.6 | Power analysis

CTX is reduced by 0.50 to 1.50 SDs in mild CI and ADRD.³⁶ This study was created to detect differences in mean CTX with a signal intensity of 0.57 SDs between two groups, and 0.82 SD in 34 subregions.

2.7 | 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

Responders who completed T1-weighted imaging in this study (Table 1) were in their mid-50s at the time of the scan (max age was 65 years), and most were male. By design, sample subgroups were matched in terms of age at scan, sex, race/ethnicity, occupation, educational attainment (Table S1 in supporting information for subgroup table).

Not shown in Table 1, when comparing WTC-CI to unimpaired responders, total intracranial volume (1528.05 [SD = 132.50] cm^3 vs 1498.72 [173.88] cm^3 ; $P = .286$), white matter volume (551.37 [62.00] cm^3 vs 547.51 [10.67] cm^3 ; $P = .778$), and white matter hypointensity volume (1.92 [1.09] cm^3 vs 2.12 [2.14] cm^3 ; $P = .554$) were similar across groups, while gray matter volume (629.22 cm^3 vs 603.20 cm^3 ; $P = .030$) and mean whole-brain mean CTX (2.48 [0.08] mm vs 2.41 [0.08] mm; $P = .0003$) were significantly reduced in CI.

While mean CTX was reduced in CI, PTSD status did not predict reduced CTX across groups (Figure 1). For example, no differences were evident in mean CTX when comparing PTSD to non-PTSD groups ($P = .261$), or in analyses comparing PTSD-CI to CI alone ($P = .521$), justifying combining PTSD with non-PTSD groups in further analyses. In addition, multivariable analyses controlling for cognitive status showed PTSD was not associated with mean CTX ($P = .216$) further

TABLE 1 Sample characteristics

Characteristic	Overall (N = 99)	Cognitively unimpaired (N = 51)	Cognitively impaired (N = 48)	P
Age	56.38 (0.52)	56.42 (0.63)	56.32 (0.86)	.926
Intracranial volume	1516.23 (15.51)	1532.05 (18.58)	1498.72 (25.36)	.292
Cognitive domains				
Response speed	0.08 (0.01)	0.08 (0.01)	0.07 (0.01)	8.61E-05
Processing speed	0.06 (0.01)	0.07 (0.00)	0.06 (0.01)	2.32E-04
Episodic memory	0.64 (0.17)	0.72 (0.19)	0.56 (0.10)	2.68E-06
Intra-individual response variability	0.10 (0.04)	0.09 (0.03)	0.12 (0.04)	2.34E-05
Visuospatial function	75.08 (47.36)	57.08 (15.42)	95.04 (61.21)	4.40E-05
Visuospatial memory	13.28 (9.09)	9.47 (4.33)	17.5 (10.99)	5.42E-06
Throughput	0.32 (0.04)	0.33 (0.04)	0.30 (0.03)	3.74E-05
Working memory	0.95 (0.12)	0.99 (0.12)	0.91 (0.10)	3.39E-04
Posttraumatic stress disorder				
No	52.5%	53.9%	51.1%	.782
Yes	47.5%	46.2%	48.9%	
Posttraumatic stress symptomatology				
Re-experiencing	17.48 (6.73)	17.16 (7.02)	17.83 (6.45)	.620
Avoidance	24.07 (9.54)	24.18 (10.56)	23.96 (8.44)	.910
Hyperarousal	17.76 (6.73)	17.45 (7.25)	18.08 (6.21)	.643
Negative experiences	12.23 (4.59)	12.41 (4.83)	12.04 (4.36)	.691
Severe WTC exposure				
No	87.4%	90.2%	84.1%	.172
Yes	12.6%	9.8%	15.9%	
Sex				
Male	85.3%	80.8%	76.6%	.612
Female	14.7%	19.2%	23.4%	
Minority status				
White	77.8%	86.5%	68.1%	.087
Black	10.1%	5.8%	14.9%	
Hispanic	12.1%	7.7%	17.0%	
Occupation				
NYPD	56.6%	60.8%	52.1%	.383
Other	43.4%	39.2%	47.9%	
Education				
High school or less	23.2%	17.7%	29.2%	.359
Some college	47.5%	49.0%	45.8%	
University degree	29.3%	33.3%	25.0%	

Note: Means (standard deviations) or percentages (%) reported. *P*-values examine the extent to which noted characteristics differ across cognitive status and were derived using χ^2 tests for categorical variables, and Student's *t*-tests for continuous variables. All significant effects passed the false discovery rate. Abbreviations: NYPD, New York Police Department; WTC, World Trade Center.

justifying a focus on CI in this study; however, because PTSD-related differences were potentially important in this population, additional analyses of PTSD-related reductions in CTX were completed (Figure S1 in supporting information).

3.1 | CTX in WTC-CI

In region-based analyses of the 34 ROIs (Table 2), CTX was significantly reduced in WTC-CI in 23/34 regions throughout the frontal,

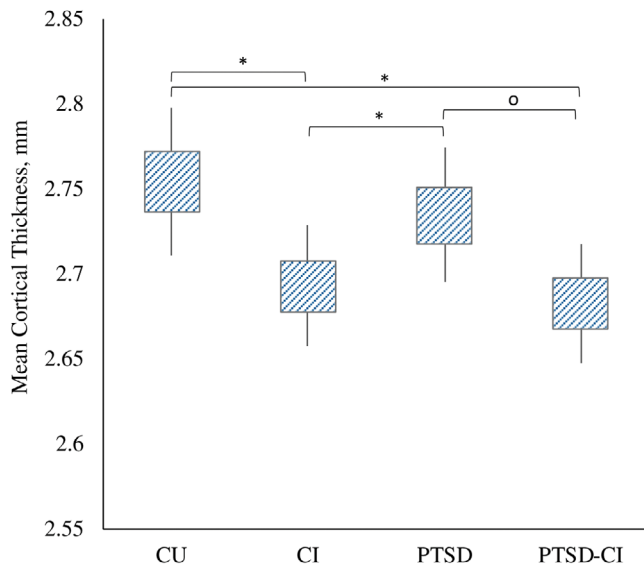


FIGURE 1 Absolute differences in mean whole-brain mean cortical thickness expressed in mm by patient diagnostic group. Note: Group differences were evident across groups when using one-way analysis of variance across all group profiles ($P = .002$) that was concentrated in cognitively impaired responders. 95% confidence intervals shown using capped error bars. *Statistically significant at $P < .05$; ° $P = .055$

temporal, and occipital lobes of which 21/23 (91.3%) of these ROIs remained significantly different after accounting for multiple comparisons. ROIs with the largest CTX reductions included the precentral, supramarginal, lateral occipital, superior temporal, and transverse temporal regions.

Heat maps examining associations between dimensional measures of cognitive performance and PTSD symptomatology (Figure 2) showed significant differences showing that worse performance in episodic memory, throughput, visual memory, and the continuance MoCA score were significantly associated with reduced CTX across similar regions to those noted above; however, more CTX subregions were significantly associated cognitive subdomains including episodic memory (17 ROIs), throughput (25 ROIs), intra-individual response variability (one ROI), working memory (16 ROIs), and MoCA score (25 ROIs). PTSD symptom subdomains were not associated with CTX.

Results from surface-based analysis identified broad reductions in CTX throughout the brain (Figure 3). This report reflects three dominant statistically significant clusters with 11 cluster-peaks that remained after adjustment for multiple comparisons ($FDR = 0.05$). Clusters-peaks were evident across the frontal, temporal, and occipital lobes with the most severe reductions, ordered by location, in the right medial orbitofrontal region (MNI coordinate: 8/67/-6 mm, $t_{TFCE} = 31,662.6$, $P = .003$). Other cluster-peaks were identified in the left insula, left posterior cingulate, left superior frontal, left and right precentral, left precuneus, left inferior parietal, left superior parietal, right pericalcarine, left medial orbitofrontal, and left rostral anterior cingulate (Table S2 in supporting information).

3.2 | Comparison to published norms

When compared to published norms, CTX was significantly reduced in 7/34 ROIs in CU responders, and in 14/34 ROIs in WTC responders with CI (Table 3). Differences in CU responders included regions within the temporal lobe including, in order of effect size, reduced CTX in the entorhinal cortex, fusiform gyrus, middle temporal, parahippocampal gyrus, temporal pole, inferior temporal, and superior temporal regions. Regions that were reduced in CU responders were further reduced in WTC-CI, while other regions such as the medial orbitofrontal, precentral, pars opercularis, supramarginal, transverse temporal, and insula, which were not reduced in CU WTC responders, were decreased in WTC responders with CI.

3.3 | Sensitivity analyses

Matching variables were not incorporated as covariables in these analyses due to concerns of over-matching. Sensitivity analyses using generalized linear modeling comparing the association between CI and CTX when adjusting for matching variables including age, sex, occupation, education, and intracranial volume did not explain the association between CI and CTX shown above. Additional efforts to consider cardiovascular and metabolic risk factors identified associations with white matter hypointensities but did not explain the results shown in this study. While the study was not sufficiently large to power analyses examining interactions, preliminary analyses examining interactions between domains of cognitive dysfunction and PTSD symptoms identified a small number of interaction effects (Figure S2 in supporting information). For example, slower processing speed among responders with more severe re-experiencing symptoms was associated with lower CTX in the lateral orbitofrontal and pars opercularis. Additional associations were found between increased avoidance and hyperarousal symptoms with poorer visuospatial learning and higher CTX in some parts of the temporal lobe.

4 | DISCUSSION

WTC responders were exposed to a range of inhaled neurotoxins and also to extreme psychosocial stressors,³⁷ exposures that have been linked to increased risk for CI.³³ The goal of the current study was to determine whether CI was associated with reduced CTX in WTC responders at midlife. Results suggested that CI was characterized by reduced CTX, a parameter that is often used in the adult brain as a surrogate marker for neurodegeneration. Affected regions of the brain for both WTC responders with CI and those with PTSD-CI involved a wide array of regions that have been previously implicated in conditions such as early onset AD/AD or a related dementia, sporadic AD/AD, inhaled particulate matter exposures, aging, and PTSD (Table S3 in supporting information).

The pattern of cortical thinning arising from the SBM reported results appear to be consistent, in part, with a relatively

TABLE 2 Regional estimates of mean cortical thickness and estimated standardized mean differences among cognitively impaired and cognitively unimpaired responders

Cortical Region	Abbrev.	Cognitively Impaired		Cognitively Unimpaired		Cohen's D
		Mean	SD	Mean	SD	
Banks Superior Temporal Sulcus	BSTS	2.39	0.18	2.45	0.14	
Caudal Anterior Cortex	CAC	2.53	0.20	2.56	0.18	
Caudal Middle Frontal Cortex	CMF	2.43	0.12	2.49	0.13	
Cuneus Cortex	CUN	1.77	0.11	1.84	0.10	
Entorhinal Cortex	ENT	3.14	0.26	3.11	0.24	
Fusiform Cortex	FUS	2.52	0.14	2.60	0.10	
Inferior Parietal Cortex	INFP	2.36	0.14	2.44	0.13	
Inferior Temporal Cortex	INFT	2.63	0.12	2.69	0.13	
Isthmus Cingulate	ISTH	2.36	0.16	2.41	0.17	
Lateral Occipital Cortex	LOCC	2.16	0.09	2.23	0.12	
Lateral Orbitofrontal Cortex	LORB	2.50	0.11	2.55	0.13	
Lingual Cortex	LING	1.91	0.11	1.97	0.10	
Medial Orbitofrontal Cortex	MORB	2.25	0.11	2.32	0.16	
Middle Temporal Cortex	MTEM	2.68	0.14	2.76	0.13	
Parahippocampal Cortex	PHIP	2.49	0.23	2.54	0.27	
Para-central Cortex	PARC	2.29	0.16	2.35	0.14	
Pars Opercularis	POPE	2.43	0.11	2.50	0.12	
Pars Orbitalis	PORB	2.60	0.13	2.59	0.15	
Pars Triangularis	PTRI	2.32	0.11	2.35	0.12	
Pericalcarine Cortex	PCAL	1.51	0.09	1.56	0.10	
Postcentral Cortex	PCEN	2.02	0.11	2.08	0.10	
Posterior Cingulate	PCIN	2.40	0.11	2.45	0.13	
Precentral Cortex	PCEN	2.37	0.13	2.47	0.12	
Precuneus Cortex	PREC	2.26	0.15	2.35	0.14	
Rostral Anterior Cingulate	RAC	2.67	0.16	2.72	0.20	
Rostral Middle Frontal Cortex	RMF	2.24	0.08	2.30	0.10	
Superior Frontal Cortex	SUPF	2.57	0.12	2.64	0.12	
Superior Parietal Cortex	SUPP	2.12	0.13	2.19	0.12	
Superior Temporal Cortex	SUPT	2.58	0.14	2.68	0.14	
Supramarginal Cortex	SUPM	2.43	0.11	2.52	0.12	
Frontal Pole	FPOL	2.63	0.20	2.77	0.25	
Temporal Pole	TPOL	3.45	0.30	3.52	0.28	
Transverse Temporal Cortex	TVTM	2.19	0.20	2.31	0.15	
Insula	INS	2.88	0.16	2.97	0.14	

Note: Because there were no significant positive results, only negative associations are reported. Standardized mean differences (Cohen's D) shown using blue bars with 95% confidence intervals. *Statistically significant in bivariate analyses after adjusting for the false discovery rate.

uncommon parietal-dominant subtype of ADRD.³⁸ Interestingly, parietal-dominant ADRD is more common in early onset ADRD patients and is characterized by cognitive deficits in episodic memory alongside changes in a wide range of cognitive domains such as executive function, visuospatial functioning, visuospatial and self-processing, as is also common in amnesic hippocampal-sparing early-onset ADRD.³⁹ The spread of neuropathology in parietal-dominant ADRD does not match the topography of amyloid beta ($A\beta$) deposition or neurofibrillary tauopathy of late-onset ADRD.³⁸ Prognosis for both parietal-dominant and hippocampal-sparing subtypes of ADRD is also often poor, irrespective of age of onset, potentially because $A\beta$ deposits more broadly throughout the brain⁴⁰ thereby causing cognitive declines across a broader range of cognitive domains than seen in other AD subtypes.⁴¹

Relatively little is known about causes of CI at midlife, partially because dementing diseases at midlife are fairly rare with estimates at < 1/1000 individuals.⁴² CI at midlife carries an increased risk of mortality when compared to non-demented individuals or patients with late-onset dementia.⁴³ Affected ROIs, identified as those with

reduced CTX, were not limited to cortical regions commonly associated with ADRD including, for example, the inferior temporal gyrus and precuneus.¹³ Analyses also identified additional ROIs such as the post-central gyri that are associated with neuroinflammatory disease,⁴⁴ and the peri-calcarine cortex, which has been associated with sensory dysfunction in aging.¹³

Studies have recently suggested that severe and/or chronic exposure to inhaled fine particulate matter (PM < 2.5 μ m) may also lead to neurodegeneration.⁶ Exposure to fine particulate matter has been linked to similar processes as those discussed in PTSD including systemic inflammation,⁴⁵ changes to glutamatergic functioning,⁴⁶ increased amyloid accumulation⁴⁷ and deposition,⁴⁸ with the end result being cognitive decline⁴⁹ and increased risk of dementia.⁵⁰ In our analyses, we found that compared to normative data even unimpaired responders had reduced CTX in the entorhinal and temporal cortices, previously shown to be vulnerable to exposure to inhaled neurotoxins,⁶ when adjusting for age, sex, scanner type, and scanner resolution. Further work that integrates information about vulnerability to ADRD and related dementias derived from genotypes shown

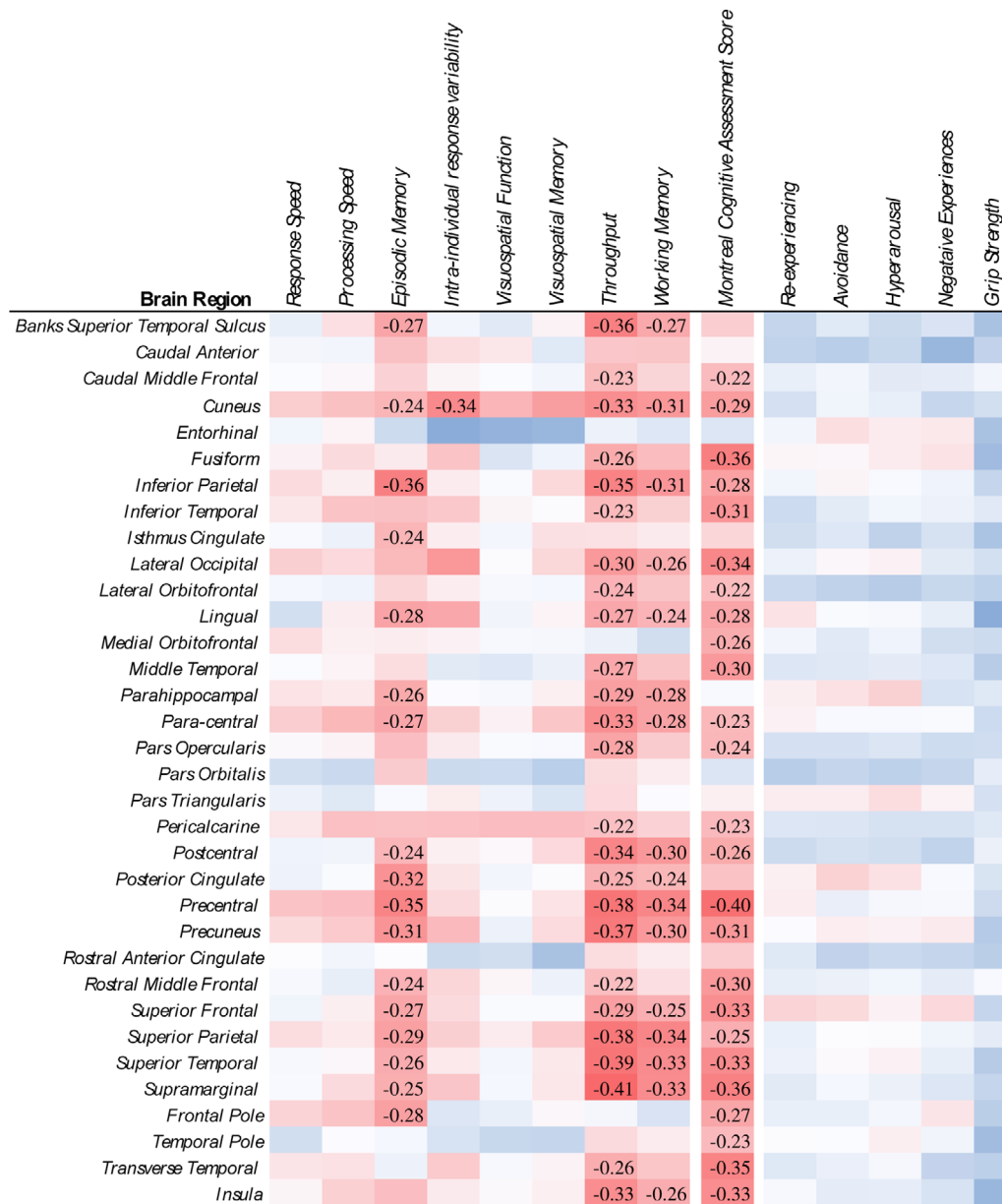


FIGURE 2 Heat map showing levels of association between dimensional measures of cognition and posttraumatic stress disorder and regional measures of cortical thickness (CTX). Note: Coefficients were transformed so that increases in dimensional scores are consistent with worse outcomes. Standardized Mean Differences (Cohen's D) were estimated from generalized linear modeling; all coefficients deemed statistically significant upon adjusting for the false discovery rate (FDR = 0.05) were reported. Red indicates reduced CTX; blue indicates increased CTX.

to be sensitive to air pollution may, therefore, be critical in future analyses.

Prior studies have reported associations between chronic PTSD and increased risk of CI in this population.^{18,33} CI in responders with PTSD was indistinguishable from CI without PTSD in this study, though analyses were suggestive of greater severity in PTSD-CI. While PTSD is not an accepted risk factor for neurodegenerative diseases, it has been linked to many of the features of neurodegenerative diseases, including widespread cortical thinning,³ neural network dysfunction,⁵¹ and accumulation of A β and the microtubule-associated protein tau.⁵²⁻⁵⁴ Evidence in combat veterans has linked chronic PTSD with widespread

cortical thinning across regions including the frontal, temporal, occipital, and insular regions³ as well as the prefrontal cortex, and anterior and posterior cingulate.⁵¹ It is unclear why PTSD might increase risk of neurodegenerative disease, but current theories suggest that it may engage a chronic stress response⁵⁵ by activating the hypothalamic-pituitary-adrenal axis⁵⁶ and engaging an immune response^{57,58} when processing emotionally stressful memories.⁵⁹ An additional possibility is that PTSD may cause the proliferation of norepinephrine engaging concomitant microglial⁶⁰ and tau⁶¹ response.

In this study, trends toward reduced CTX were evident in 21 regions after adjusting for multiple comparisons. The entorhinal cortex and

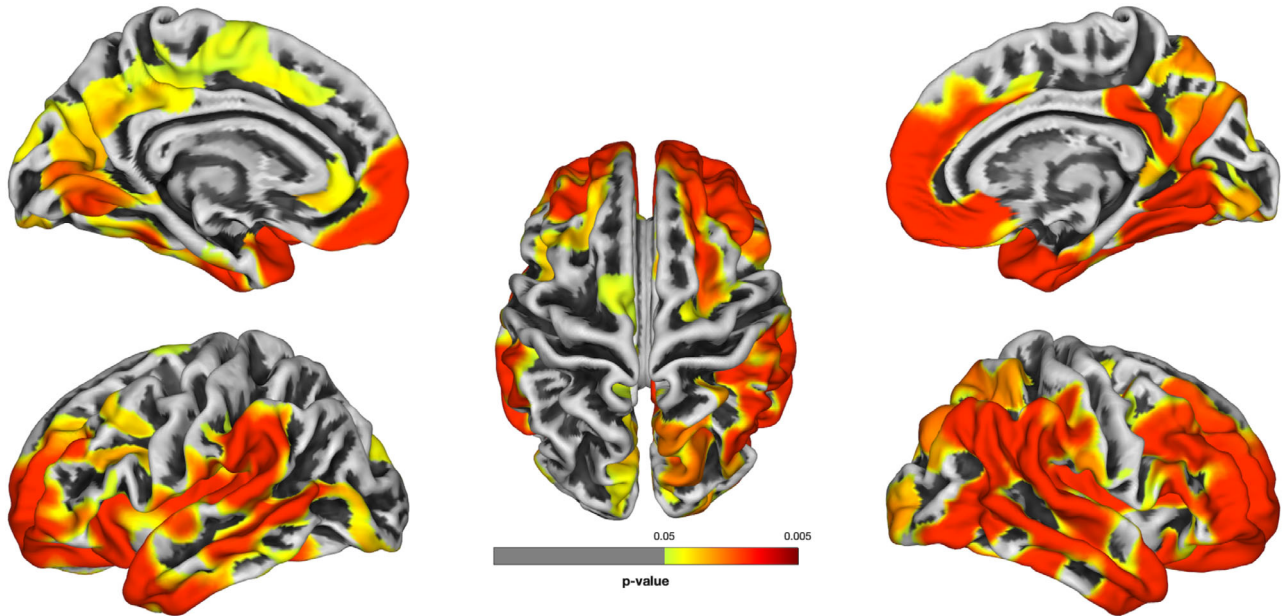


FIGURE 3 Group-wise analyses using surface-based morphometry comparing cognitively impaired to cognitively unimpaired responders
 Note: Group-wise analyses using surface-based morphometry identified areas of reduced cortical thickness (CTX) are shown since no regions with increased cortical thickness were identified. Regions lacking significant differences in CTX between groups are shown in gray; cluster locations provided in Table S2 in supporting information. Figure generated using Computational Anatomy Toolbox (CAT12)

pars orbitalis were the only regions where trends were not indicative of reduced CTX in WTC responders. The entorhinal cortex is concerning because it is commonly influenced by most dementing conditions, and thus the lack of results in the entorhinal cortex in particular is unusual. One interpretation of this finding may be that these regions are commonly reduced across the WTC responder population, but may not be sufficient to cause cognitive symptoms on their own.⁶² Results comparing CTX in cognitively unimpaired WTC responders with published normative data from 2,799 cognitively normal adults²⁷ identified substantial reductions in the entorhinal cortex and across the temporal lobe despite revealing thicker cortices on average across many other regions; results may suggest that cognitively unimpaired WTC responders also have some abnormalities in this region of the brain. Reduced CTX and volume of the entorhinal cortex is commonly interpreted as an early marker of the spread of tauopathy in ADRD,⁶³ which is often associated with greater neurodegeneration.⁶⁴ Because the temporal lobe has been implicated recently in exposure-based neurodegenerative diseases,⁶ the potential for proliferation of tauopathy in CU WTC responders is concerning. Future research should examine the extent to which these results are supported by neuropathology using molecular neuroimaging techniques.

4.1 | Limitations

Limitations include small sample size, the unique nature of the exposure, and a lack of non-WTC external control group. This study also examined severe CI and focused on PTSD status irrespective of exposure to inhaled neurotoxins during response efforts. Genotype has

been shown to be relevant to pathogenesis of exposure-related CI, thus the lack of genotype measures in this manuscript is a limitation. Though we did make efforts to increase recruitment of minorities and women to the point of doubling the numbers of both in this sample compared to the responder population, the sample would benefit from improved integration of persons from different backgrounds. This cross-sectional study could not provide information about rates of CTX reduction, and therefore does not allow us to estimate the age of onset of cortical thinning. Consequently, we could not determine whether atrophy occurred pursuant to WTC exposures. Further research is warranted to examine more mildly impaired responders to determine the prevalence of neurodegenerative disease in responders. The identification of reduced CTX does not clarify the extent to which neurodegeneration is ongoing or resulted instead from a one-time massive systemic shock or, instead, if chronic stressors involved in PTSD caused changes to the brain's structure. While relying on a well-established published normative database (N = 2799), results from comparisons with normative data may be subject to a range of selection biases. Though providing good specificity for multiple diagnostic categories, CTX cannot be used to definitively determine etiology of neurodegeneration.

5 | CONCLUSIONS

The WTC disaster exposed tens of thousands of individuals including employees at, and near, the WTC site; residents of the area; and responders to a host of traumatic experiences and, at the same time, exposed many to the toxic detritus of the towers after they collapsed. Current

TABLE 3 Region-based standardized mean differences comparing cognitively unimpaired and cognitively impaired responders to norms from 2799 cognitively normal individuals in the general population

Region	CU versus norms		CI versus norms	
	D	P	D	P
Banks superior temporal sulcus	-0.26	.362	-0.80	.007
Caudal anterior	0.71	.015	0.32	.262
Caudal middle frontal	0.77	.009	-0.17	.543
Cuneus	1.29	<.001	-0.05	.874
Entorhinal	-3.33	<.001	-2.64	<.001
Fusiform	-1.75	<.001	-2.25	<.001
Inferior parietal	0.92	.002	-0.28	.332
Inferior temporal	-0.98	.001	-1.92	<.001
Isthmus cingulate	0.77	.009	0.07	.796
Lateral occipital	1.26	<.001	0.00	.998
Lateral orbitofrontal	0.39	.173	-0.45	.122
Lingual	0.71	.015	-0.53	.066
Medial orbitofrontal	0.20	.489	-0.92	.002
Middle temporal	-1.22	<.001	-2.12	<.001
Parahippocampal	-1.16	<.001	-1.71	<.001
Para-central	0.72	.014	-0.11	.706
Pars opercularis	0.23	.418	-0.85	.004
Pars orbitalis	-0.01	.981	0.11	.687
Pars triangularis	0.44	.130	-0.09	.747
Pericalcarine	0.41	.148	-0.44	.125
Postcentral	1.28	<.001	0.08	.772
Posterior cingulate	0.82	.006	0.15	.596
Precentral	0.40	.160	-1.11	<.001
Precuneus	0.77	.009	-0.49	.088
Rostral anterior cingulate	0.03	.905	-0.58	.047
Rostral middle frontal	1.05	.001	-0.23	.412
Superior frontal	0.99	.001	-0.31	.276
Superior parietal	1.04	.001	-0.15	.603
Superior temporal	-0.95	.002	-2.23	<.001
Supramarginal	0.72	.014	-0.74	.012
Frontal pole	1.06	<.001	-0.14	.625
Temporal pole	-1.15	<.001	-1.50	<.001
Transverse temporal	0.60	.039	-0.73	.013
Insula	0.32	.260	-0.81	.006

Note: *P*-values provided in the rightmost column were derived from one-sample *t*-tests. Regions where cortical thickness was significantly reduced upon accounting for the false discovery rate were highlighted in Bold. Codes to abbreviations are provided in Table 2.

Abbreviations: CU, cognitively unimpaired; CI, Cognitively impaired; D, Standardized Mean Differences (Cohen's *D*).

estimates suggest that at midlife, a growing number of WTC responders are experiencing early CI and dementia.³³ The current study showed for the first time in a sample of WTC responders that WTC-CI was accompanied by reduced CTX encompassing regions commonly influenced by neurodegenerative diseases. However, results also suggested that WTC-CI had an architecture that, while reminiscent of ADRD, was also inconsistent with signatures developed for known neurodegenerative diseases. This work supports the view that WTC-CI may be a WTC-specific encephalopathy with an unknown etiology characterized by widespread cortical atrophy.

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CONFLICTS OF INTEREST

The authors have no disclosures to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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