FINAL PROGRESS REPORT

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Project Title: Structural and Functional Neuroimaging of Post-Traumatic Stress Disorder and Cognitive Impairment in World Trade Center Responders

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LIST OF TERMS AND ABBREVIATIONS

AD	Alzheimer's Disease
AUDIT	Alcohol Use Disorder Inventory Test
CI	Cognitive Impairment
CTX	Cortical Thickness
ISSM	Icahn School of Medicine at Mount Sinai
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
PAH	Polycyclic aromatic hydrocarbons
PET	Positron Emission Tomography
PCB	PolyChlorinated Biphenyl
PTSD	Post-Traumatic Stress Disorder
SBU	Stony Brook University
TMII	Translational and Molecular Imaging Institute
WTC	World Trade Center
WTCHP	World Trade Center Health Program

ABSTRACT

Project Title: Structural and Functional Neuroimaging of Post-Traumatic Stress Disorder and Cognitive Impairment in World Trade Center Responders
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Exposure to psychological trauma and fine particulate matter may increase the risk of dementia in traumatized populations including military veterans and World Trade Center responders. WTC responders were exposed to neurotoxicants including metals, PCBs, dioxins, and PAHs. Ultrafine particles can reach the brain through the olfactory pathway causing oxidative stress and chronic inflammation leading to neurodegeneration. In the Stony Brook WTCHP cohort, 20% of responders developed PTSD since 9/11. In 2,400 responders screened with the MoCA, the rate of CI (scores <20) was 2.6%, and the association with PTSD was highly statistically significant.

The purpose of this study was to assess brain atrophy and dysfunction among responders with CI and PTSD. Similar to the growing body of research on veterans with PTSD, there may be unique structural patterns in the brain associated with CI in WTC responders. *In vivo* functional MRI and, in a pilot study, PET/MRI imaging were used to examine these patterns.

Our analyses have indicated several unique brain characteristic patterns of CI among WTC responders compared to other signatures, such as AD. Diffuse brain atrophy, reduced cortical thickness and hippocampal sub-field volume analysis suggesting that reductions in specific subregions are associated with duration of WTC exposure. Taken together these findings support the hypothesis that WTC exposure to neurotoxicants is causing long term neurodegenerative impacts. The neuro-phenotype of this impairment is different from the AD, and inconsistent with signatures developed for known neurodegenerative diseases. Our work supports the view that WTC-CI may be a WTC-specific encephalopathy with an unknown etiology characterized by widespread cortical atrophy.

SECTION 1 OF THE FINAL PROGRESS REPORT

SIGNIFICANT OR KEY FINDINGS

Our first aim was to test whether structural and functional changes in the brain, measured with MRI, are associated with cognitive impairment assessed by the MoCA, among the WTC responders.
To test this association, we performed multi-modality MRI (structural MRI, diffusion tensor imaging, resting state fMRI, and functional MRI) and compared the resulting MRI features among subjects with CI (MoCA score ≤20) and subjects with no cognitive impairment (MoCA ≥26), with the same age and occupation.

Our second aim was to test whether structural and functional changes in the brain, measured with MRI, are associated with PTSD, among the WTC responders.
To test this association, we performed multi-modality MRI (structural MRI, diffusion tensor imaging, resting state fMRI, and functional MRI) and compared the resulting MRI features among subjects with PTSD and subjects without PTSD, matched on age and occupation.

This application targeted originally 120 SBU-WTC responders: 30 with cognitive functioning cutoffs described above and PTSD, 30 with cognitive impairment without PTSD, 30 with normal cognitive functioning and PTSD, and 30 with normal cognitive functioning without PTSD. All responders had to be matched on age and occupation as well as 30 non-WTC exposed, matched controls with MoCA scores ≥26.
The operationalized aim 1 and 2 were modified into smaller groups in each cell, for a final overall number of 112 subjects.

The original third exploratory aim was to test whether PET/MRI modalities are associated with PTSD and CI. To further understand the mechanisms of CI among a subsample of subjects with PTSD and CI, we originally aimed to pilot a PET/MRI protocol to examine the association between MoCA and 1) glucose uptake, 2) presence of β-amyloid 3) and tau protein accumulation.
The operationalized aim three included a larger number of PET scan that did not include the assessment of tau protein accumulation.

Our analyses have indicated several unique brain characteristic patterns of CI among WTC responders compared to other signatures, such as AD. Diffuse brain atrophy, reduce cortical thickness and hippocampal sub-field volume analysis suggesting that reductions in specific subregions are associated with duration of WTC exposure. Taken together these findings support the hypothesis that WTC exposure to neurotoxicants is causing long term neurodegenerative impacts. The neuro-phenotype of this impairment is different from the AD, and inconsistent with signatures developed for known neurodegenerative diseases. Our work supports the view that WTC-CI may be a WTC-specific encephalopathy with an unknown etiology characterized by widespread cortical atrophy.

TRANSLATION OF FINDINGS

A vital takeaway message from this research is that cognitive function is an important outcome to assess when conducting medical surveillance after future disasters where workers are exposed to potentially neurotoxic chemicals and/or experience post-disaster mental health problems. Cognitive function testing should begin at the first surveillance visit and use a normed, validated screening instrument that is sensitive to change over time. Additionally, it may be helpful to frontline workers – especially workers suffering from mental health problems – if clinicians initiate conversations about cognitive function, describe how mental health problems and medications used to treat mental health

problems may impact cognitive function, and provide suggestions to address any objective or perceived concerns about cognitive function. Individuals at highest risk for cognitive dysfunction should also be offered comprehensive neuropsychological evaluations.
Finally, any additional exposure to known neurotoxicants such as heavy metals, solvents, and other organic pollutants, should be adequately controlled both in the workplace and in the home environment.

RESEARCH OUTCOMES/IMPACT

The main outcome from this project is confirming that cognitive function is an emerging condition of high concern among WTC rescue/recovery workers, but that the current medical monitoring data are insufficient to fully understand the complex relationship among WTC exposure, physical health conditions, mental health conditions, and cognitive function. The results from this study suggest that further work must be completed to better understand the unique characteristics of WTC responders compared to individuals in the general population. Previous WTC exposure to neurotoxicants and psychological trauma may be an important factor in the development and severity of CI among WTC responders. Artificial intelligence can be utilized to help predict which WTC responders may be at higher risk for cognitive impairment, which could lead to earlier interventions and better care.

The recommendation most relevant to occupational safety and health is that cognitive function should be an included condition when implementing medical monitoring and surveillance after future disasters. Exposure to neurotoxic agents such as metals, solvents, pesticides, and fine particulate matter is common in many workplaces. The effects to cognitive health are not immediate and, therefore, are often overlooked. To prevent long term effects potentially leading into clinical impairment of cognition, it is imperative to minimize exposure to neurotoxic agents in the workplace and in any other non-occupational occurrence. Regulatory agencies should also utilize the research findings to update the protective standards to prevent long term impacts.

SECTION 2 OF THE FINAL PROGRESS REPORT

SCIENTIFIC REPORT

More detail should be provided in this section than in the Section 1 "Significant or Key Findings." This section can be as technical as the author would like, although PIs are encouraged to limit the Scientific Report to less than 50 pages. Each of the specific aims originally planned or added during the project must be addressed in terms of what was accomplished or what barriers and obstacles impeded progress. In this way there will be a complete documentation of the efforts for the grant.

Background:

Moderate-severe cognitive impairment, meaning dysfunctions in fluid cognition, including memory, executive functioning, and verbal and category fluency (1), can make it difficult to interact or navigate daily activities. Such burden and loss of functioning is a major public health problem because at present, the course of cognitive impairment (CI) is unpredictable, seemingly irreversible, and incurable (2). Cognitive impairment often represents significant losses in capabilities that are individually meaningful and are indicative of later clinical levels of pathology (3-6). Indeed, a large body of evidence suggests that in its earliest stages, CI is commonly indicated by rapid losses in cognitive capability in the years preceding clinical pathology (7) and diagnosis with dementia (8).

Our study emerged from reports suggesting that posttraumatic stress disorder is associated with both cognitive impairment and brain changes, particularly among veterans. In the Stony Brook WTCHP cohort, 20% of responders developed PTSD since 9/11. In 2,400 responders screened with the Montreal Cognitive Assessment (MoCA), the rate of cognitive impairment (CI) (scores <20) was 2.6%, and the association with PTSD was highly significant.

Given the complex exposures leading to PTSD, the etiology needs to be fully understood. Since the NIOSH CDC is mandated to pay for care for WTC-related diseases, there is a pressing need for a better understanding of the nature of this impairment, including its presentation in brain tissue, in highly exposed and traumatized WTC responders. The proposed effort used neuropsychological assessments and both along with structural and functional MRI measures to describe the neurological nature of cognitive impairment in this cohort. We also proposed to pilot the use of three PET ligands, [^{18}F] Fluorodeoxyglucose, [^{18}F] Amyvid, and [^{18}F] T807, to test the acceptability and obtain preliminary data on abnormalities seen in cognitively impaired responders which could serve as the basis for future grant applications if deemed acceptable to WTC responders and of evident scientific value. Given the unobserved nature of some of the exposures experienced by this cohort, a non-exposed control group was also assessed.

The first question that posed by the observation of cognitive decline among the 9/11 responders is whether this is potentially a consequence of mental health disorders. PTSD has been broadly associated with reduced cognitive functioning and increased risk of dementia (9, 10). PTSD involves complex memory, emotional, and behavioral processes (11), and encompasses distinct domains including re-experiencing, effortful avoidance, emotional numbing, and hyperarousal resulting from a traumatic event (12). Exact mechanisms for this association remain unclear (13). Theories alternatively suggest that: posttraumatic stress may be a unique part of the causal pathway leading to cognitive aging (14); the association may be confounded by co-morbid features that are independently associated with PTSD and dementia, such as traumatic brain injury (15); or finally that symptoms indicative of PTSD, which is commonly comorbid with major depressive disorder (MDD) (16), are also manifestations of dementia or related pathology (17). Moreover, consistent with these findings, structural, functional, and positron emission tomography (PET) MRIs have been successful in detecting

associations between PTSD and neurological functioning. For example, structural MRI studies have highlighted hippocampus and amygdala volume (18). Functional MRI studies have further noted the consistent associations found between PTSD and white matter lesions (19) and PTSD, white matter integrity, diffusivity, and anisotropy (20) (21). Finally, studies of neuronal functioning highlight the role of PTSD in modulating glucose uptake in the amygdala (22, 23) as well as generally elevated neuroinflammation (24) and even reduced microglial activation (25).

Mounting evidence is also accumulating that exposure to air pollutants, especially fine particulate matter (FPM), contributes to an increased risk of CI. For example, epidemiologic work by Lucchini, Guazzetti (26) found memory decline and CI in children, adults and elderly exposed to various airborne contaminants. Furthermore, prior imaging studies using structural MRI found reductions in total brain volume and white matter structures after lifetime exposure (27, 28), while (27, 28), while work by Gandy (Co-I) has found that amyloid increases in animal models exposed to air pollution (29). These studies have theorized that airborne FPM may interrupt brain functioning in two ways: 1) via circulation through the increased distribution of proinflammatory cytokines (30) resulting in neuroinflammation, blood-brain barrier dysfunction, and neural degeneration (31); or 2) intranasally by direct translocation through the olfactory bulb (32). Several animal studies have shown increased brain inflammation in response to air particulate exposures (33), signs of blood-brain barrier dysfunction, neural degeneration, cerebrovascular pathologic signs, and apoptosis in glial cells (31). Decrement in the ability to identify odors was observed in a group of 99 WTC exposed subjects compared to 99 controls (34). Carbon nanotubes (CNT) were found in the lung biopsies of WTC responders and in samples of WTC dust (35). Furthermore, research on the role of exposures at the WTC has found elevated levels of systemic inflammation (serological c-reactive protein), indicative of more rapid systemic aging (36). We have hypothesized different exposure-related potential mechanisms of neuroinflammation leading to neurodegeneration that needs further investigations (37).

Several other potential risk factors for CI need to be considered in addition to PTSD and massive exposure to air pollutants. They include family history, Apolipoprotein ε4 allele, other early life and adult-onset extreme stress, head injury, educational attainment and childhood cognition, mid-life obesity and hypertension, smoking, lack of exercise, and excessive use of alcohol and drugs. Responders and controls participating in the proposed study where fully characterized with respect to established individual risk factors for both CI and for dementia.

At the start of this research program, very little was known about the cognitive profile of the WTC Health Program cohort apart from epidemiological analyses conducted at Stony Brook. As WTC responders age, they are increasingly faced with aging-related disease burden, especially CI. It is, therefore, critical to understand the role of WTC-PTSD and extreme exposure to toxic pollutants in accelerating the onset of CI. As noted, the SBU-WTC Health Program began routine screening with the MoCA. In addition to data available through the monitoring program, other established risk factors not included in the basic monitoring program were also routinely collected. We therefore are positioned to take the next step, to evaluate potential systematic patterns in the brains of responders with CI compared to similarly exposed responders scoring in the normal range and non-WTC exposed controls. Therefore, the present study aimed to identify structural and functional neural markers of CI and PTSD in WTC responders.

Specific Aims

The purpose of this study was to assess brain dysfunction among responders with CI and PTSD. Similarly to the growing body of research on veterans with PTSD, there may be unique structural

patterns in the brain associated with CI in WTC responders. *In vivo* functional MRI (fMRI) and positron emission tomography (PET/MRI) imaging were used to examine these patterns.

Specific Aims of the studies were the following:

AIM 1: MRI phenotypes (structural and functional changes in the brain) are associated with cognitive impairment (CI) assessed by the MoCA.
To test this association, we performed multi-modality MRI (structural MRI, diffusion tensor imaging, resting state fMRI, and functional MRI) and compared MRI phenotypes among subjects with CI (MoCA ≤20) and subjects with no cognitive impairment (MoCA ≥26) matched on age and occupation.

AIM 2: MRI phenotypes (structural and functional changes in the brain) are associated with PTSD.
To test this association, we performed multi-modality MRI (structural MRI, diffusion tensor imaging, resting state fMRI, and functional MRI) and compared MRI phenotypes among subjects with PTSD and subjects without PTSD matched on age and occupation.

AIM 3: [Exploratory]: PET/MRI modalities are associated with PTSD and CI. To further understand the mechanisms of CI among a subsample of subjects with PTSD and CI, we originally aimed to pilot (n = 18) a PET/MRI protocol to examine the association between MoCA and 1) glucose uptake, 2) presence of β-amyloid 3) and tau protein accumulation.

Methodology

Target population

This study capitalized on strengths of two WTC Health Program centers including 1) large institutional and medical imaging program at ISMMS and 2) data collection and multidisciplinary expertise of the SBU-WTC Health Program located on Long Island, NY.

This study targeted individuals from the existing SBU-WTC clinic that has enrolled ~8,000 WTC responders primarily from Nassau or Suffolk counties on Long Island, NY (population 3 million). Each year, the clinic conducts ~4,500 monitoring examinations. Since 2015, 3,674 responders were screened for CI as baseline.

Table 1. SBU baseline CI data (n=3,674)

Age (mean)	52.8
Female, %	7.6
African American, %	4.3
Hispanic, %	7.1
Some College, %	47.2
University degree, %	27.6
Persistent PTSD, %	10.3
Remitted PTSD, %	7.3
Cognitive Impairment, %	2.6

As noted in pilot data (Tab.1), the average age of the sample at the time of testing was ~53. Close to 20% developed WTC-PTSD; some have remitted, and others were still symptomatic. Based on the MoCA, administered as part of the ongoing National Institute of Aging funded study of cognitive aging (R01 AG049953; Clouston, PI), 2.6% (n=96/3,679) have CI (defined as MoCA <20). This cut-point is more stringent than cutoffs used in the literature to indicate “mild cognitive impairment” (38, 39). The WTC responders were enrolled from this existing set of individuals (n=3764) already screened by SBU for CI using the MoCA. Two subgroups of 60 subjects each were targeted randomly from the CI (MoCA ≤20) and from the normal range (MoCA ≥26) groups. Each subgroup was further divided in two groups of subjects according to the presence or not of PTSD. The four subgroups of SBU-WTC responders (with and without CI and with and without PTSD) were frequency matched on age (within 5 years) gender, race/ethnicity, education level, and occupation (law enforcement vs other manual labor occupation).

Controls were recruited with a variety of methods including clinical trials lists, Craigslist, flyering, phone list. The Project Coordinator conducted telephone-screening interview to identify individuals who were

near the WTC in September 2001 but did not work at a WTC site in 2001-2002. Those willing to participate in the study were asked for age, sex, occupation, height and weight, presence of metal implants, and history of dementia, stroke, psychosis diagnosis, and claustrophobia. Individuals who are demographically and occupationally comparable to the SBU-WTC subgroups were invited to attend a further interview to determine final eligibility and collect risk factor data.

Eligibility criteria.

All eligibility criteria were confirmed at an in-person assessment. They included: MoCA score ≤20 or ≥26; willingness to travel to ISSM and undergo imaging; body mass index less than or equal to 40 (due to size of MRI internal coil); no history of stroke; not in renal failure or receiving dialysis; not being treated for severe liver disease or hepatitis; no indication of unmanaged diabetes; not actively taking cognitively active medications (e.g., methylphenidate); absence of claustrophobia and fear of needles/blood; history of psychosis and no indication on the ISMMS imaging screening questionnaire of exclusion factors (e.g., shrapnel, pacemakers, wires, including non-MRI safe surgically implanted devices).

Written consent for the proposed study was obtained at the eligibility visit at SBU and the Project Coordinator scheduled both the eligibility and imaging visits. All imaging protocols took place at ISMMS

Imaging Schedule

Full details about the imaging study were given at the eligibility visit at the SBU-WTC clinic. Written consent for imaging was obtained also at ISMMS. Each subject was provided with specific appointment details. The SBU Project Coordinator organized a car service to ISMMS for the imaging visit. The study participants arrived on average 30 minutes prior of the imaging appointment. An ISMMS Research Assistant greeted the participants at the car service and escorted them to the imaging suite at the ISSMS-TMII. Ocular Xray or CT screening were scheduled before the MRI exam if the subject indicated working around lathes or similar machines and may have metal shrapnel in the eyes. Participants were provided lunch following their appointment. Additionally, an ISMMS Research Assistant debriefed them about the absence of presence of any medical abnormality upon conclusion of the MRI (or PET) scan and after the scans are examined by a radiologist. Responders were be provided with their scan image, if desired, and were accompanied to the car service by ISMMS research staff. A debriefing and feedback about the study experience was conducted by phone by the SBU Project Coordinator

MRI Assessments

All imaging were performed on a Siemens 3T PET/MR at the TMII of ISMMS. This instrument simultaneously acquires PET and MRI. Prior to administering the research PET/MRI protocol, a dual echo sequence was also obtained to screen for incidental abnormalities. The protocol included the following modalities:

i) anatomical T1-weighted MPRage (TR/TE=1900/2.5ms, FOV=23cm, Matrix 256x256, slice thickness 1.0mm);
ii) ii) DTI using a Pulsed-Gradient Spin Echo sequence with 33 gradient directions (TR/TE=7800ms/101ms, FOV=23cm, Matrix = 128x128, slice thickness 3mm, b-value=1200s/mm^2, 33 directions);
iii) resting state fMRI scan (10 min);
iv) Task driven fMRI performed using a working memory task (N-back letter sequences).

Images were acquired using a Gradient-Echo-EPI sequence (TR/TE=2000ms/27ms, FOV=23cm, Matrix 64x64, slice thickness 2.5mm). All visual stimuli were presented using a high definition goggle system by Resonance Technology Inc., Northridge, CA. Stimulus presentation and subject responses

were acquired using Eprime and a fiber optic response glove by Psychology Software Tools (PST Inc. Pittsburgh PA).

PET Image Acquisition (PET/MR)

PET/MR (3T) Siemens mMR. The 3T MR/PET is a fully integrated and capable of simultaneous whole body PET and MRI scanning. This allows more precisely co-registered functional and structural acquisition while reducing the radiation dose in PET imaging by replacing the CT scans with an MRI scan. True simultaneous acquisition of MR and PET data by the hybrid system merges the highly sensitive PET metabolic information with the highly specific MR anatomical and functional information. Attenuation data in PET/MRI are derived from the MRI scan. For each bed position, the MRI sequence for attenuation correction (AC) purposes is acquired first. The sequence used in the integrated PET/MRI system is a 2-point Dixon volume-interpolated breath-hold examination (VIBE). This sequence is preceded by scanning preparations that include shimming to optimize the homogeneity of the magnetic field (~40 s). The MRI data are then segmented to identify air, brain tissue, fatty tissue, and watery tissue as required for AC. We view the mMR as an optimal imaging resource for our project.

We originally proposed to perform [^{18}F]fluorodeoxyglucose)[^{18}F]FDG) brain imaging on the 18 most cognitively impaired subjects in the SBU WTC cohort. We also proposed to investigate these most impaired subjects with brain imaging for amyloidosis or tauopathy, both of which are associated with neurodegenerative pathology. ISMMS was one of the first centers to employ clinical brain PET scanning with [^{18}F]florbetapir (also known as [^{18}F]Amyvid®) ((40)) and with [^{18}F]T807.

[^{18}F] Fluorodeoxyglucose PET Imaging: To administer the [^{18}F]2-deoxyglucose, one catheter is placed in an intravenous line in an antecubital vein. Ten mCi (370 MBq) of [^{18}F]2-deoxyglucose are injected. ^{18}FDG is used according to its FDA approved indication and labeling. Thirty minutes after radiotracer injection, the subject is then positioned supine in the mMR PET scanner, image acquisition period lasts 15 minutes.

[^{18}F] Amyvid PET Imaging: To administer the [^{18}F]florbetapir (Amyvid™), one catheter is placed in an intravenous line in an antecubital vein. Ten mCi (370 MBq) of [^{18}F]florbetapir are injected. Florbetapir is used according to its FDA approved indication and labeling. Sixty minutes after radiotracer injection, the subject is then positioned supine in the mMR-PET scanner. The imaging data acquisition lasts 15 minutes.

[^{18}F]T807 PET Imaging: It is acquired on the PET/MR scanner, with a T1 FLASH sequence from the same location as the PET images. Region of interest are defined on the T1 MRI and transferred to the PET images. Mean SUV values are extracted for all ROIs of interest. This approach allows to define correct anatomical locations without relying on standard co-registration algorithms that fail with T807 in cases with low T807 uptake. The simultaneous PET/MR scanner allows this approach.

Neuropsychological assessments

Cognitive impairment was measured using the MoCA, which assesses a broad number of domains believed to be foundational parts of fluid cognition, such as executive function, memory, or visuospatial capability, that are known to be sensitive to cognitive aging and are implicated in dementia. It is the most sensitive assessment of diagnosed amnestic mild CI, and dementia (39, 41). Notably, the MoCA has been used to indicate CI with specificity and sensitivity exceeding 90% in a number of samples of community-dwelling older adults (38, 39), though reported specificity and sensitivity statistics in those studies to end-stage Alzheimer's disease using more conservative cutoffs tend to exceed 95% (AUC~0.98).

Fluid cognition was objectively measured as part of the CBB battery (www.cogstate.com), a detailed neuropsychological battery that measures processing speed, reaction time, learning, throughput, and memory through the computer-administered Cogstate platform (42). The CBB utilizes a computer-

administered approach (42) that uniformly measures processing speed during a game-like task. It was developed for multiple administrations to precisely detect small changes in cognitive functioning (43-45). Specifically, CBB tasks involving a deck of cards on a green background as well as the Groton Maze Task and Continuous Paired Associate Learning Task are administered under staff supervision. Participants interact with the battery only after first receiving full instructions. The Cogstate platform was administered in the cohort (R01 AG049953), and e readministered to eligible responders prior to imaging appointments to provide an accurate characterization of their current cognition level.

Rationale for MoCA cut-off scores used: These two cutoffs were chosen for two reasons: first, there is some disagreement about the appropriate cutoff in the general population. The original validation study suggested that scores under 26 are poor scores in a highly homogeneous sample of well educated individuals in a neurological clinic in Montreal (46); however, in more diverse samples and in the general population this has resulted in large proportion of the population being called cognitively impaired. More recent studies suggest that more constrained cutoffs of 23 (38) and 22 (39) may perform better in a diverse population sample to capture CI, while even lower cutoffs were also found to robustly indicate dementia and Alzheimer's disease. To ensure specificity to dementia-related pathology without compromising feasibility in this sample, MoCA ≤20 was used as a cutoff. This cutoff worked best using cutoffs validated against more comprehensive battery measures in the CBB Battery in our data (LR+=10.1, 94% of cases were deemed correctly classified, 94.0% specificity, and AUC=0.82).

Statistical Approach

Before applying statistical regression methods to test our hypotheses, we conducted standard explorations of the data. Distributions of relevant variables were examined, and appropriate transformations (e.g., natural log) was performed to satisfy model assumptions. Outliers were identified using the generalized extreme studentized deviation procedure (47, 48) and extreme observations were checked with original data. Results with and without extreme values were compared in sensitivity analyses.

To test our hypothesis that changes in brain structure and function are associated with CI (Aim 1), we used correlation analyses to compare imaging metrics between WTC responders with CI and responders without CI. We also carried out similar comparisons between WTC responders with CI and non-exposed controls without CI. To test the hypothesis that changes in brain structure and function are associated with PTSD (Aim 2), we used correlation analyses to compare imaging metrics of WTC responders with PTSD to those of WTC responders with no PTSD. All the aforementioned analyses were carried out on the following imaging metrics: volumetric and cortical thickness measures, rsfMRI connectivity z-scores, fMRI BOLD% for working memory tasks, and FA & MD values from DTI. Comparisons of metrics from each modality allowed us to assess different aspects of brain structure or function: (1) To compare brain matter degeneration/loss between subjects with CI and without CI (and also with and without PTSD), volumetric and cortical thickness measures and hippocampal measures were generated, and group differences were tested. (2) To compare white matter microstructure health between the CI and non-CI groups (and also PTSD vs. no PTSD groups), DTI was used to generate FA and MD values and group differences in these measures were tested using voxel-wise general linear modeling, carried out with RANDOMISE, an FSL (www.fmrib.ox.ac.uk/fsl) routine used for permutation-based inference testing. (3) To test the association of resting state connectivity with CI (and also with PTSD), general linear modeling and permutation-based inference testing were used for group comparisons on various resting state networks.

Approach to multiple comparisons Because our outcomes reflect correlated phenotypes, we accounted for multiple comparisons qualitatively by looking for concordance among phenotypes and using multiple-outcomes models (i.e., latent variables, linear mixed models that treat correlated phenotypes as a repeated measure) to reduce number of comparisons. To avoid overadjustment or adjusting for

downstream correlates and introducing bias, we selected *potential* confounding variables with directed acyclic graphs.

Results and discussion

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. Despite our best efforts to recruit non-WTC controls, only 10 individuals were recruited, and they did not match the WTC responder groups across various factors, such as age, gender ratio, education, and occupation. Due to the smaller size of this group and their poor matching to the WTC responders, these individuals were excluded from many analyses. On average, 26.2 (standard deviation [SD] = 17.2) days (inter-quartile range = 14 to 35 days) elapsed between screening and neuroimaging.

All subjects completed the neuropsychological assessment and were examined with MRI and PET scans. The subgroups distribution is reported in table 1. We were able to examine more subjects with PET imaging compared to the original proposal.

Table 1: MRI and PET scans in the enrolled population

	Year 1	Year 2	Year 3	Overall
MRI - WTC CI only	19	3	2	24
MRI - WTC PTSD only	14	7	4	25
MRI – WTC PTSD and CI	11	12	2	25
MRI – WTC Unaffected	19	8	1	28
MRI - Non-WTC controls	0	7	3	10
PET scans	10	10	7	27
Total patients scanned	63	37	12	112

Responders who completed T1-weighted imaging in this study (table 2) 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.

Reduced cortical thickness in WTC CI subgroup

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.

Table 2: Subgroup descriptive characteristics

Characteristic	WTC Unaffected (N=27)	CI (N=25)	PTSD (N=24)	PTSD with CI (N=23)	P
Age	57.55 (4.31)	56.14 (6.23)	55.04 (4.61)	56.6 (5.46)	0.819
Age at 9/11/2001	41.04 (4.76)	39.15 (6.43)	38.4 (4.48)	39.55 (5.47)	0.342
Intracranial volume, cm^3	1521.81 (143.47)	1512.24 (188.34)	1535.08 (120.79)	1488.1 (156.82)	0.762
MoCA Score	27.63 (1.04)	18.76 (1.88)	28.08 (1.18)	18.17 (2.1)	<0.001
Cognitive Domains					
Response Speed	0.08 (0.01)	0.07 (0.01)	0.08 (0.01)	0.07 (0.01)	0.001
Processing Speed	0.07 (0.00)	0.06 (0.00)	0.06 (0.00)	0.06 (0.01)	0.003
Episodic Memory	0.7 (0.20)	0.57 (0.09)	0.74 (0.19)	0.56 (0.11)	<0.001
Response variability	0.09 (0.03)	0.1 (0.03)	0.08 (0.02)	0.13 (0.04)	<0.001
Visuospatial Function	58.19 (16.63)	78.46 (20.86)	55.83 (14.19)	113.14 (83.03)	<0.001
Visuospatial Memory	9.93 (4.46)	16.25 (8.47)	8.96 (4.21)	18.86 (13.29)	<0.001
Working Memory	0.97 (0.12)	0.89 (0.11)	1.02 (0.10)	0.93 (0.10)	<0.001
Throughput	0.32 (0.04)	0.29 (0.03)	0.34 (0.03)	0.31 (0.03)	<0.001
Posttraumatic Stress Symptoms					
Re-experiencing	11.3 (1.94)	13.12 (3.85)	23.75 (4.16)	22.96 (4.48)	<0.001
Avoidance	15.37 (2.36)	17.24 (3.78)	34.08 (6.53)	31.26 (5.45)	<0.001
Hyperarousal	11.3 (2.15)	13.04 (3.4)	24.38 (3.8)	23.57 (3.06)	<0.001
Negative Experiences	8.81 (1.36)	9.28 (1.93)	16.46 (4.04)	15.04 (4.3)	<0.001
Severe WTC Exposure					
No	92.6%	64.0%	100.0%	65.2%	0.055
Yes	7.4%	36.0%	0.0%	34.8%	
Sex					
Male	77.8%	76.0%	83.3%	78.3%	0.936
Female	22.2%	24.0%	16.7%	21.7%	
Minority status					
White	77.8%	64.0%	91.7%	60.9%	0.161
Black	11.1%	12.0%	4.2%	17.4%	
Hispanic	11.1%	24.0%	4.2%	21.7%	
Occupation					
NYPD	66.7%	64.0%	54.2%	39.1%	0.174
Other	33.3%	36.0%	45.8%	60.9%	
Education					
High school or less	18.5%	20.0%	16.7%	39.1%	
Some College	44.4%	40.0%	54.2%	52.2%	
University Degree	37.0%	40.0%	29.2%	8.7%	

CTX measurement from MR) provides a powerful non-invasive method for quantifying neurodegenerative disease risk including for AD (49). 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 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, and are included in the supporting material of our first publication produced by this grant (50).

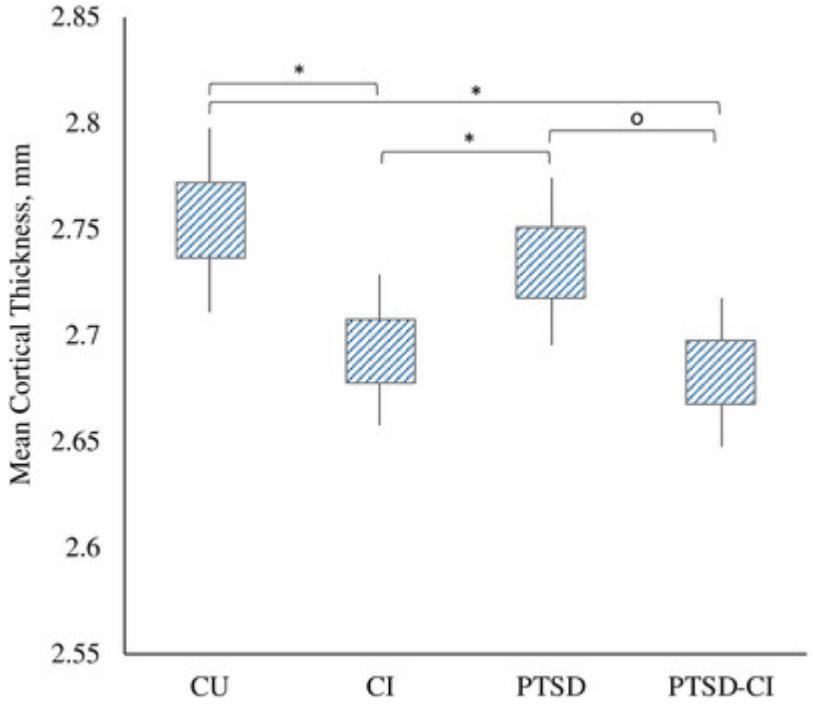


Figure 1: Absolute differences in mean whole-brain mean cortical thickness expressed in mm by patient diagnostic group. Note: Group differences were evident across groups when using one-way analysis of variance across all group profiles (P = .002) that was concentrated in cognitively impaired responders.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

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

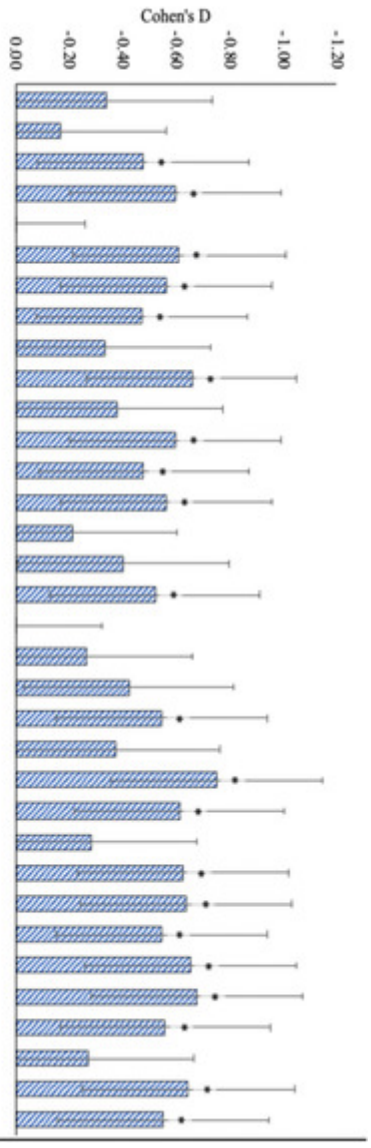
Heat maps examining associations between dimensional measures of cognitive performance and PTSD symptomatology (Figure 2) showed significant differences showing that worse performance in episodic memory, throughput, visual memory, and the continuance MoCA score were significantly associated with reduced 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 3: Regional estimates of mean cortical thickness and estimated standardized mean differences among cognitively impaired and cognitively unimpaired responders

		Cognitively Impaired		Cognitively Unimpaired	
Cortical Region	Abbrev.	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



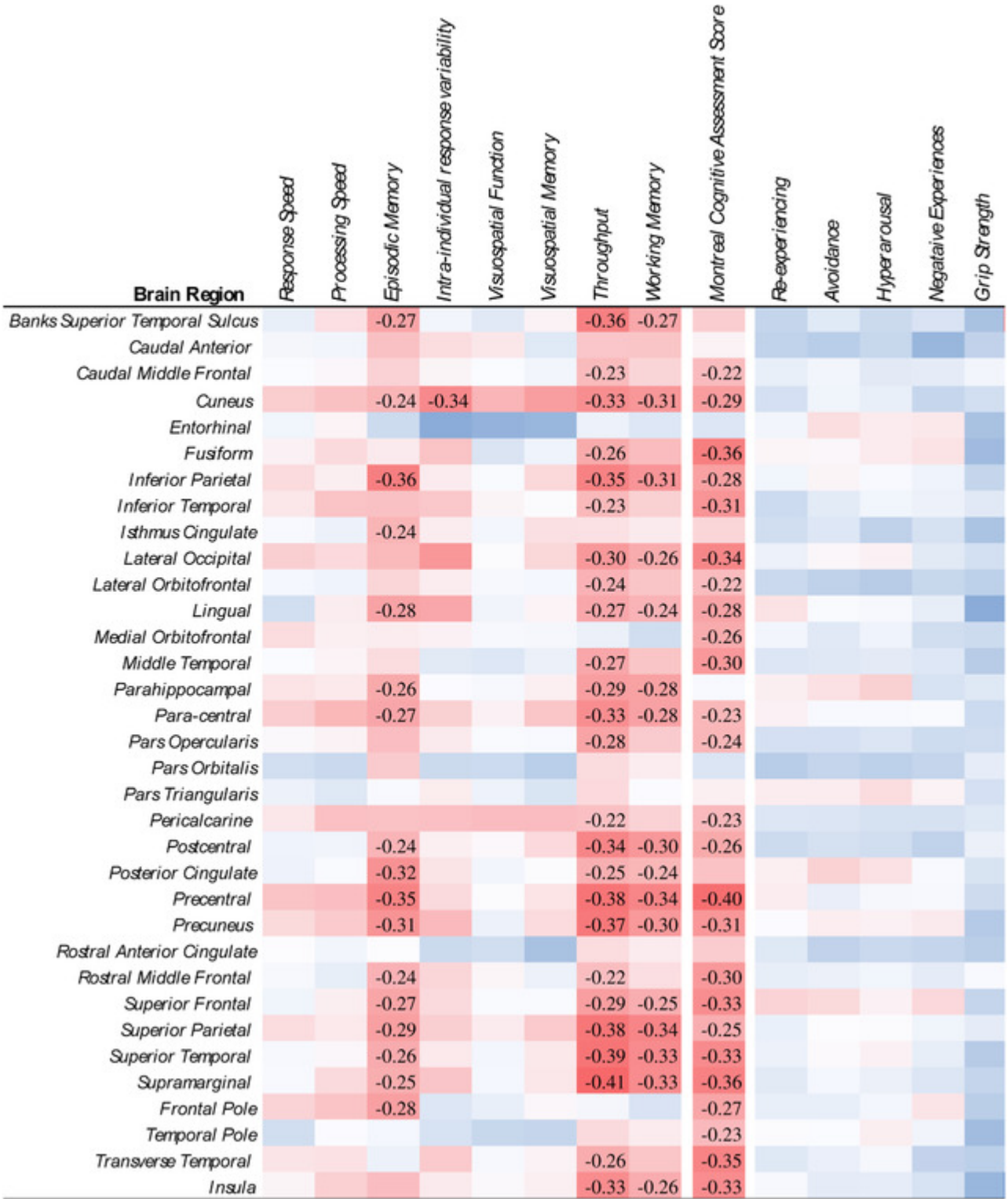


Figure 2: Heat map showing levels of association between dimensional measures of cognition and posttraumatic stress disorder and regional measures of cortical thickness (CTX). Note: Coefficients were transformed so that increases in dimensional scores are consistent with worse outcomes. Standardized 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.

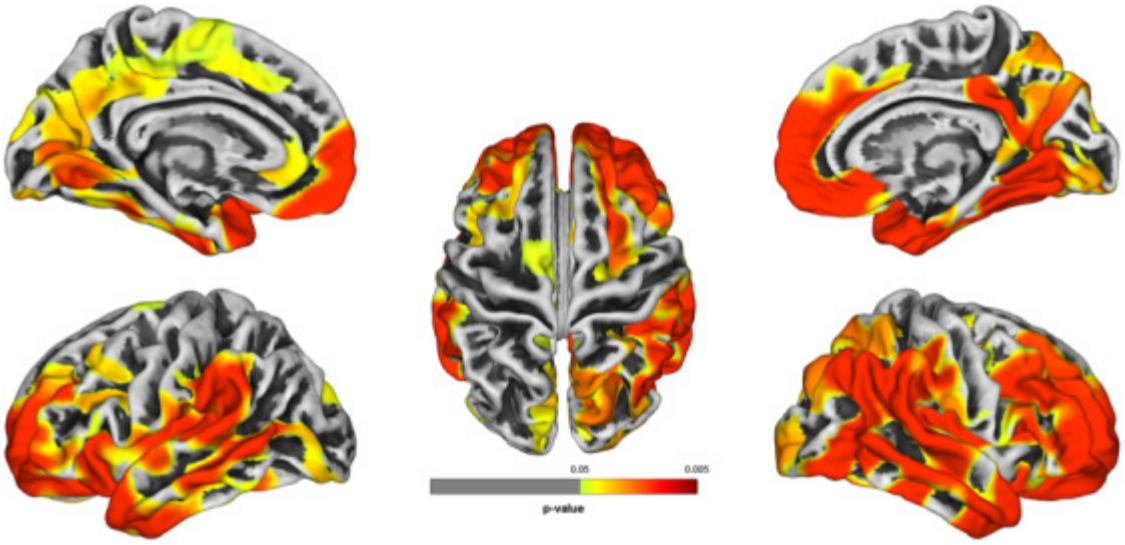


Figure 3: Group-wise analyses using surface-based morphometry comparing cognitively impaired to cognitively unimpaired responders

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)

Sensitivity analysis

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. 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.

Studies by Stein et al. (51) and by FDNY (52, 53) have shown that mental health is a predominant mediator on ‘cognitive concern’. This would mean that cognitive decline would not be observable in individuals without mental health conditions. This finding is based on the assessment of ‘concerns’ measured by Stein et al. through six questions on concentration, attention, asked to the WTC responders at their periodical monitoring visits. The study on firefighters used the Cognitive Function Instrument (CFI) to assess cognitive concern. These methods are different from the MOCA scale utilized in our study for the assessment of cognitive function, and this indicates the need for a uniform assessment to allow comparability across studies.

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 estimates suggest that at midlife, a growing number of WTC responders are experiencing early CI and dementia(54).

Our research 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. Our work supports the view that WTC-CI may be a WTC-specific encephalopathy with an unknown etiology characterized by widespread cortical atrophy.

We were also able to observe specific characteristics of CI among the WTC responders:

- Compared cortical thinning to normative data from almost 2,800 cognitively normal adults, finding differences among all responders in the study, not just those with CI (55)
- Hippocampal sub-field volume analysis suggests reductions in specific subregions are associated with duration of WTC exposure (56)
- Data collected as part of this study was used to train artificial neural network to accurately identify WTC responders who may be at higher risk for cognitive issues on MRI (57).
- PET information was used in a case study of WTC responders with CI (58).

PUBLICATIONS

1. Clouston S et al. Cognitive impairment and World Trade Centre-related exposures: Considerations when monitoring World Trade Center affected individuals. Nature Reviews [Manuscript submitted for publication].
2. Kritikos M, Clouston SAP, Huang C, Kuan PF, Pellecchia A, Santiago-Michels S, Carr MA, Kotov R, Lucchini RG, Gandy S, Bromet EJ, Luft BJ. Cortical Complexity in World Trade Center Responders with Chronic Posttraumatic Stress Disorder. Being Revised for publication in Translational Psychiatry.
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CUMULATIVE INCLUSION ENROLLMENT TABLE

Racial Categories	Year 1 *Not Hispanic or Latino*			Year 2 *Not Hispanic or Latino*			Year 3 *Not Hispanic or Latino*			Total
	Female	***Male***	***Unknown / Not reported***	***Female***	***Male***	***Unknown / Not reported***	***Female***	***Male***	***Unknown / Not reported***	
American Indian/ Alaska Native	0	0	0	0	**0**	0	0	0	0	0
Asian	0	0	0	0	**0**	0	0	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	1	0	0	0	0	1
Black or African American	2	3	0	2	4	0	0	1	0	12
White	8	46	0	10	16	0	1	7	0	88
More than One Race	2	2	0	0	4	0	1	1	0	10
Unknown or Not Reported	0	0	0	0	**0**	0	0	0	0	0
Total	12	51	0	12	25	0	2	10	0	112

MATERIALS AVAILABLE FOR OTHER INVESTIGATORS

Data sharing is facilitated by our open science framework website, which is directed towards data sharing for psychological and Neuroscientific studies (https://osf.io/g849b/). The website hosts the publications, study protocol, and a codebook of data that were collected alongside the data request form. The protocol directs researchers to the appropriate application, and data sharing oversight will be managed by the study team. Data sharing will be undertaken after a review process and data will be shared after completing a data use agreement.

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