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Received: 25 March 2026 | Revised: 3 September 2026 | Accepted: 6 September 2026

DOI: 10.1002/alz.71878

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

World Trade Center neurotoxicant exposure severity is associated with cortical thinning and regional brain atrophy: a neuroimaging study of general responders at midlife

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[#]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

Abstract

INTRODUCTION: Exposure to aerosolized pollutants is a risk factor for cognitive impairment and dementia, but the specific features of exposure-related neurodegeneration remain unclear.

METHODS: We measured the World Trade Center Neurotoxicant Exposure Severity Index (WTC-NESI) in 218 responders and unexposed controls aged 44-65 years. The main outcome was cortical thickness. Correlation analyses reported unadjusted associations and multiple linear regression to adjust for correlates. Vertex-wise analyses were used with threshold-free cluster enhancement to examine associations after adjusting for cross-vertex clustering in atrophy.

RESULTS: Cortical thickness was associated with WTC-NESI ($R = -0.38$, $p < 0.001$) that survived multivariable adjustment. Vertex-wise analyses revealed reduced cortical thickness across much of the cortical surface that was associated with WTC expo-

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Funding information
NIOSH, Grant/Award Numbers: U01OH011314, R01AG049953, R01AG067590, P30 AG066514; Cure Alzheimer's Fund, Grant/Award Numbers: R01AG084699, R01AG093879, R01AG093281; I.B. Ertegun Project for Cognitive Health Extension at ISMMS; (ADNI) (National Institutes of Health, Grant/Award Number: U01 AG024904; DOD ADNI, Grant/Award Number: W81XWH-12-2-0012; AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics; Canadian Institutes of Health Research; Foundation for the National Institutes of Health

sure severity. Results were right-hemisphere asymmetric and focused in the precentral regions (partial $\eta^2 \geq 0.07$).

CONCLUSION: Our results provide an important reference for neurotoxicological investigators mapping the implications of airborne pollutant exposures. This study suggests that efforts to mitigate exposures in first responders might have long-term implications for cerebral health.

KEYWORDS
Alzheimer's disease and related dementias, cortical atrophy, pollutant exposures, World Trade Center responders

Highlights

- This imaging identified loci of cortical atrophy after severe exposures to World Trade Center dust.
- Evidence of atrophy was generalized and included most of the cortical surface.
- Evidence of atrophy was also present in the cerebellum and hippocampus.
- Analyses did not suggest that psychiatric comorbidities fully mediated results.

1 | INTRODUCTION

Severe exposure to aerosolized pollutants is a potentially modifiable risk factor for neurodegenerative diseases in the general population.[1] Airborne pollutant exposures have been linked to mixed neuropathology, neurodegeneration, and cognitive dysfunction.[2] Following the September 11, 2001 attacks, World Trade Center (WTC) responders were exposed to aerosolized pollutants.[3,4,5] Researchers have linked WTC exposure duration with cognitive decline[6] and imaging evidence of neuroinflammation in WTC responders.[7,8] Recent work has developed novel metrics to find that WTC exposure severity is associated with changes to amyloid beta levels (Aβ42, Aβ40) in plasma[9,10] and to heightened incidence of early-onset dementia[11] and lung cancer.[12] Studies aimed at explaining the presence of dementia have revealed neurodegeneration[13] and cortical atrophy.[14] Thus, diagnostic validation studies have noted that dementia before age 65 years is accompanied by reduced cortical thickness in WTC responders.[13,15]

To date, the cerebral features of exposure-related neurodegeneration are unclear, so we examined WTC responders with varying levels of exposure and a control group of minimally exposed and unexposed participants. To date, no researchers have examined the association between WTC exposure severity and neurodegeneration. This study fills that gap by examining the association between a validated measure of WTC exposure severity and established measures of cerebral atrophy.

2 | METHODS

2.1 | Participants

Data for this analysis come from the WTC responder neuroimaging archive, and recruitment for these studies has been described elsewhere.[8,13,16] To be eligible for these studies, certified WTC responders were aged 44 to 65 years at the time of assessment and willing to complete cognitive assessments and undergo neuroimaging. Participants were also required to be eligible to complete magnetic resonance imaging (MRI) and have no history of recent heart or brain diseases (e.g., frontotemporal dementia, stroke, recent myocardial infarctions, or other cerebrovascular diseases), no chronic psychiatric conditions predating WTC exposures, no traumatic brain injury, and eligible to safely undergo MRI, including being able to fit into the standard MRI tube (body mass index < 40 kg/m^2).

Analyses of differences in samples between sources of controls indicate that, after adjusting for sample differences in sex/gender and age, participants from the National Institute of Mental Health Research Volunteer (NIMH-RV) Study had higher cerebellar volumes than Alzheimer's Disease Neuroimaging Initiative (ADNI) participants ($p = 0.036$), but no other differences were found between control groups. Minimally exposed WTC responders were considered controls since there were no signs suggesting that they had lower brain volumes or cortical thickness than other controls (all $p > 0.10$; mean values within the range of the controls).

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RESEARCH IN CONTEXT

1. **Systematic review**: We tested theory developed in a published review of the association between air pollution exposures and neurodegeneration in the general population and in WTC responders and systematically reviewed updates.
2. **Interpretation**: Results showed that WTC exposure severity was associated with reduced cortical thickness across most of the cortical surface and identified volumetric reductions in the cerebral gray matter, hippocampus, and cerebellum.
3. **Future directions**: Future research should consider identifying molecular targets that help to explain symptomatology and identify pathological cascades.

2.2 | WTC Neurotoxicant Exposure Severity Index (WTC-NESI)

WTC exposures included chemicals, fumes, and particulate matter, all occurring under conditions of substantial psychological stress. Consistent with research on air pollution exposures and dementia, the central concern here was exposure to fine particulate matter. Fine particulate matter and other pollutants were abundant in WTC dust[4] but could not be directly assessed by responders on site because aerosolized fine particulate matter is invisible to humans. Therefore, to rank possible dust exposure, we used self-reported questionnaires that asked responders proxy questions like how long they spent doing several different exposure activities, when they did this work, and where they were located while doing this work. Exposure activities are modestly correlated because responders who worked in search-and-rescue missions often continued working during the months following the attack. However, these activities are not collinear since participation in one activity reduces the time spent in other activities (Table S1). The WTC-NESI (range: minimal = 0 to severe = 4) classifies exposure activities according to their likely dust exposure severity and duration (September 11, 2001 to June 30, 2002).[17] Activities considered high risk included working in enclosed spaces, on search and rescue, on "the pile" in September, or sifting versus working in clean rooms or outside of WTC sites where there was no visible dust for ≥10 h. Activities associated with lower exposure included working in clean rooms or at locations away from the WTC sites. Responders who reported no dust exposure and those who always worked using full-body personalized protective equipment (PPE) were characterized as having minimal exposure, irrespective of response duration. WTC-NESI code is publicly available online (osf.io/hxye6/overview).

Control recruitment: Since WTC-NESI is a proxy measure and few responders were minimally exposed, we also recruited a group of unexposed residents of Long Island, New York, who lived in the same counties as WTC responders but were not WTC exposed. To be eligible as controls, participants were required to be medically healthy adults with the ability to read, speak, and understand English. To match WTC neuroimaging program requirements, participants were recruited through mailings, bulletin boards, outreach exhibits, print advertisements, and electronic media. Participants with a reported history of chronic mental illness prior to WTC exposures, current illicit drug use, suicidal or self-injury thoughts or behavior, abnormal medical exams, and no higher than 8th grade education were excluded. Participants were required to be eligible for MRI and lack MRI-unsafe metal implants or claustrophobia, for example.

Since "normal controls" from a local cohort might differ in meaningful ways based on where or how they are recruited and screened, we compared data from the intake imaging appointments for participants enrolled in several national neuroimaging studies including the NIMH-RV[18] Study and the ADNI.[19] Data obtained from the ADNI database (adni.loni.usc.edu) were collected starting in 2003 as a public-private partnership with a primary goal of testing whether serial MRI or other biological markers and clinical and neuropsychological assessment might be combined to measure the progression of mild cognitive impairment (MCI). Inclusion criteria required unexposed participants to be cognitively unimpaired, aged 44 to 65 years old, and have completed a T1-weighted magnetization-prepared rapid gradient-echo protocol (T1-MPRAGE) on a Siemen's MRI scanner.

2.3 | MRI protocol

WTC responders who completed MRI alongside any functional, structural, or molecular imaging study have structural images stored and archived for secondary analyses in a secure sharing site. Structural imaging follows a standard three-dimensional T1-MPRAGE. Imaging was completed on a 3T Siemens multimodal MRI machine using standard settings.

2.4 | Volumetric measures

Preprocessing of structural T1-MPRAGE images was completed using the computational anatomy toolbox (CAT)[20] because of strong reported reliability and comparability.[21,22] Images were segmented using standard CAT12 procedures to estimate cortical thickness, total intracranial volume (TIV), and tissue-specific brain volumes. Cortical regions of interest (ROIs) were defined using the Desikan-Killiany atlas.[23] Hippocampal and cerebellar volumes were automatically segmented using Cobra tissue probability maps.[24]

2.5 | Clinical measures

Age in years since birth, sex/gender (female or male), educational attainment (categories included high school diploma or less, some college, or university degree or higher), and occupation during the response period (categorized as police, military, firefighter/emergency

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medical services, construction worker, or other) were collected. Models that included external controls were used also adjusted for neuroimaging site. Post-traumatic stress disorder (PTSD) is a common psychiatric condition after traumatic exposures and was diagnosed in this study using a structured clinical interview.[25] Although PTSD has not been strongly linked to cortical atrophy,[13] we conducted sensitivity analyses to examine whether results changed when adjusting for PTSD diagnosis. We also recorded a diagnosis of cognitive impairment (e.g., Montreal Cognitive Assessment score < 24; clinical diagnosis of dementia was exclusionary), all-cause cancer (excluding brain cancer), hypertension, diabetes, obstructive airway disease, interstitial lung disease, or obstructive sleep apnea.

2.6 | Statistical analysis

We began by describing the demographics and cerebral markers for the whole sample and then stratified by exposure category. Next, we examined scatter plots showing unadjusted associations between WTC-NESI and global cerebral volume stratified by parenchymal type into cerebral gray and white matter, cerebrospinal fluid, and cerebellar volume expressed as a percentage of TIV (%TIV). Pearson's *r* was reported for unadjusted analyses.

To visualize the location and severity of results across ROIs within the cortical gray matter, the locus of the largest potential atrophy, we used generalized linear models to compare data within ROIs using four comparable statistical models. Standardized regression coefficients (β) were estimated to maintain comparability when reporting results across models and ROIs.

We examined correlations between WTC-Exposed and Unexposed groups before examining associations between WTC-NESI and cortical atrophy and replicated results when off-site controls retrieved from the ADNI and NIMH-RV databases were excluded. We mapped the extent of atrophy across the cerebral surface using vertex-wise measures of cortical thickness. To facilitate vertex-wise analyses, we first combined, resampled, and then smoothed hemispherical data using a full-width half-maximum protocol (12 mm). All images passed both automated and visual assessments to determine quality, so we completed statistical analyses using CAT12 via multivariable-adjusted generalized linear modeling.[20] Models examined the association between WTC-NESI and cortical thickness after adjusting for participant age, sex, education, and PTSD. Because cortical changes often occur in spatially contiguous clusters rather than as isolated vertices, vertex-wise analyses used threshold-free cluster enhancement (n = 10,000 permutations), followed by false discovery rate (FDR) adjustment across vertices.[26] We used surface-based mapping to map the effect sizes using η^2 after thresholding images at FDR = 0.05 to provide both evidence of statistical significance; partial $\eta^2 \geq 0.06$ is often interpreted as a moderate to strong effect size. We reported coordinates for cluster peaks and FDR-adjusted *p* value maps were provided in supplemental materials.

To facilitate interpretation and comparison with prior studies, we also conducted ROI-based analyses. To assess robustness, we repeated analyses using alternative covariate adjustments. Associations that were nominally significant (two-tailed $\alpha = 0.05$) were identified using a dotted cell border, while associations that were significant after adjusting for the FDR were identified using an asterisk (*). Statistical analyses for global and regional studies were completed using Stata V17/MP (StataCorp).

As shown in Table S2, some potential confounders were unavailable across studies. *Sensitivity* analyses examined the extent to which inclusion of smoking (pack-years), body mass (kg/m^2), or apolipoprotein ε4 (APOE4) allele possession changed expectations despite limiting sample size. Since psychomedical factors may be confounders but could also be intermediary variables, we considered the implications of models including a history of all-cause cancer (excluding brain cancer), hypertension, diabetes, obstructive airway disease, interstitial lung disease, or obstructive sleep apnea. We reported associations with both exposure and global cerebral outcomes in supplemental materials.

3 | RESULTS

After application of inclusion/exclusion criteria (Figure S1), we used neuroimaging data from 218 participants, including 137 WTC responders of varying exposure levels (two were minimally exposed) alongside 81 unexposed controls. Sample characteristics (Table 1) show that participants were aged 54.6 years, on average, 42.2% were female, 26.1% had PTSD, and 37.2% had cognitive impairment. WTC responders with at least mild exposure spent ≥3.9 months at the WTC sites. Table S3 shows that measures of cortical thickness did not differ across control populations.

3.1 | Mapping differences in cortical thickness and cerebral volume

We began by examining the association between WTC-NESI and global cortical thickness and cerebral or cerebellar gray matter volume (Figure S2). Scatter plots revealed wide variation and statistically significant negative correlations with cortical thickness ($r = -0.38$, $p < 0.001$), gray matter volume ($r = -0.39$, $p < 0.001$), and in the cerebellum ($r = -0.27$, $p < 0.001$). Proportionally, we saw increases in cerebrospinal fluid volume ($r = 0.24$, $P < 0.001$). Only results for the cortical thickness remained statistically significant after adjusting for age, sex, education, and PTSD ($\beta = -0.27$, $p = 0.005$).

Because gray matter showed the strongest association, subsequent analyses focused on cortical thickness (Figure 1; *p* value maps in Figure S3). Vertex-wise analyses identified large bilateral clusters with peaks in the precentral region that survived FDR correction. These clusters broadly mapped surface vertices, containing 29,007 vertices in the right hemisphere and 21,118 in the left hemisphere, together accounting for 82.3% of mapped surface vertices.

Noting that the cerebral cortex was the most strongly affected parenchymal area, we examined variation in the strength of association between WTC-NESI in pre-defined ROIs (Figure 2). Comparisons

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TABLE 1 Sample characteristics of the three unexposed samples alongside minimally and variably exposed WTC responder samples.

Sample characteristics	Neuroimaging sample (*N* = 218)	Unexposed or minimally exposed, *n* = 83	Mild exposure, *n* = 71	Moderate exposure, *n* = 35	High exposure, *n* = 13	Severe exposure, *n* = 16
Age, years	54.6 (7.5)	52.1 (9.8)	56.2 (5.2)	55.8 (5.1)	58.4 (5.1)	55.0 (5.0)
Female sex/gender	92 (42.2%)	66 (79.5%)	17 (23.9%)	5 (14.3%)	0 (0%)	4 (25%)
Post-traumatic stress disorder	57 (26.1%)	1 (1.2%)	25 (35.2%)	17 (48.6%)	6 (46.2%)	8 (50.0%)
Cognitive impairment	81 (37.2%)	18 (21.7%)	32 (45.1%)	16 (45.7%)	9 (69.2%)	6 (37.5%)
WTC exposure duration, months	2.8 (3.3)	0.0 (0.2)	4.1 (3.2)	3.9 (2.8)	6.3 (3.4)	5.6 (3.4)
Educational attainment						
High school	46 (21.1%)	6 (7.2%)	20 (28.2%)	9 (25.7%)	5 (38.5%)	6 (37.5%)
Some college	66 (30.3%)	8 (9.6%)	29 (40.8%)	16 (45.7%)	6 (46.2%)	7 (43.8%)
University degree	106 (48.6%)	69 (83.1%)	22 (31.0%)	10 (28.6%)	2 (15.4%)	3 (18.8%)
Intracranial volume, cm^3	1486.9 (161.2)	1403.4 (143)	1523.6 (155.4)	1581.2 (149.8)	1567.2 (134.3)	1486.3 (121.6)

Note: Mean (SD) or *N* (%).
Abbreviations: CSF, cerebrospinal fluid; WTC, World Trade Center.

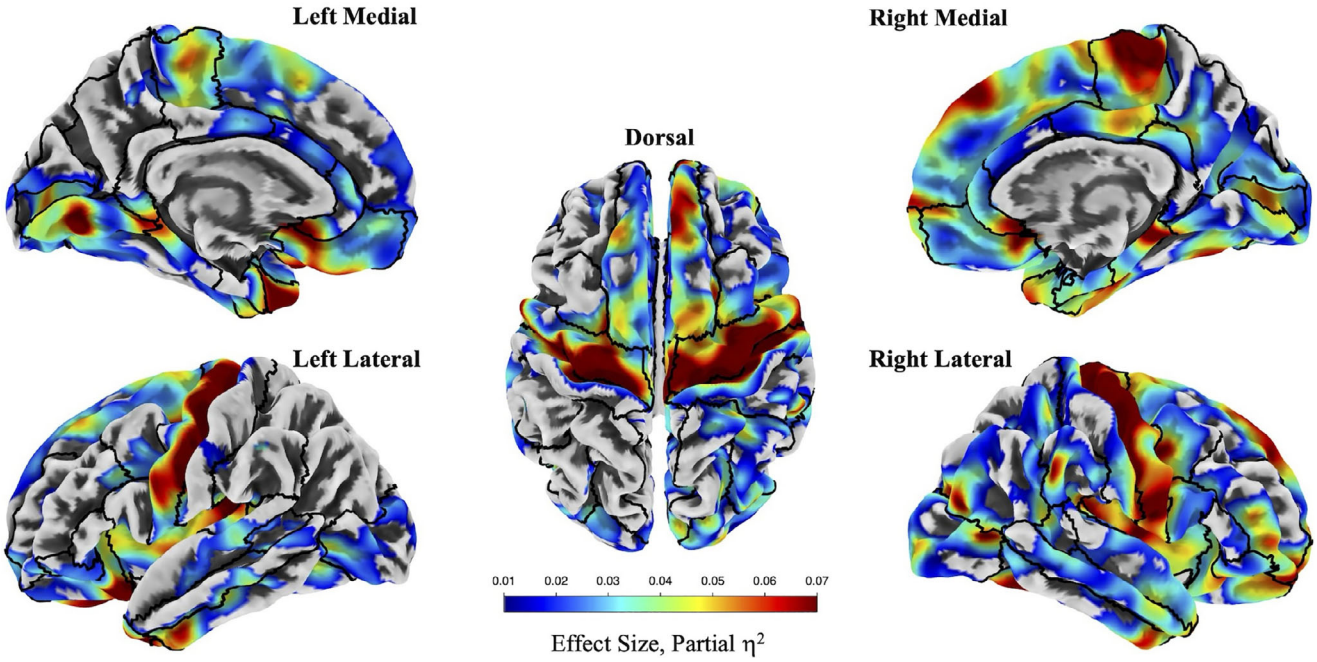


FIGURE 1 Partial η^2 estimates derived from vertex-wise analyses of cortical thickness associated with WTC-NESI. Models adjusted for age, sex, education, and PTSD (*N* = 218). Partial η^2 estimates exceeding 0.07 are consistent with moderate to high effect sizes. Models identified clusters within vertex-wise analyses using threshold-free cluster enhancement. Results shown are statistically significant after FDR adjustment. Results revealed two large clusters with cluster peaks in the left and right precentral cortices (coordinates at [36, −17, 50] and [−30, −23, 64]) with areas that cover 82.3% of vertices used to map the cortical surface.

of cortical thickness (Figure 2A) in WTC exposed versus unexposed (first column) revealed moderate statistically significant associations between WTC exposure and reduced cortical thickness bilaterally across ROIs in the frontal, occipital, and temporal lobes and the cingulate. Volumetric analyses (Figure 2B) in subcortical and cerebellar regions showed similar statistically significant associations between WTC-exposure and WTC-NESI and regional atrophy near bilateral central superior regions of the cerebellum including focal changes across all models located in the cerebellar crus II and lobes VIIb, VIIIa, and VIIIb. We also found associations with hippocampus atrophy with focal changes in the cornu ammonis (CA1) and alveus subfields.

3.2 | Sensitivity analyses

We began by examining the importance of the APOE4 genotype. Of 155 participants with genotype data, only five were homozygous APOE4 (vs 37 heterozygous carriers) and there was no association

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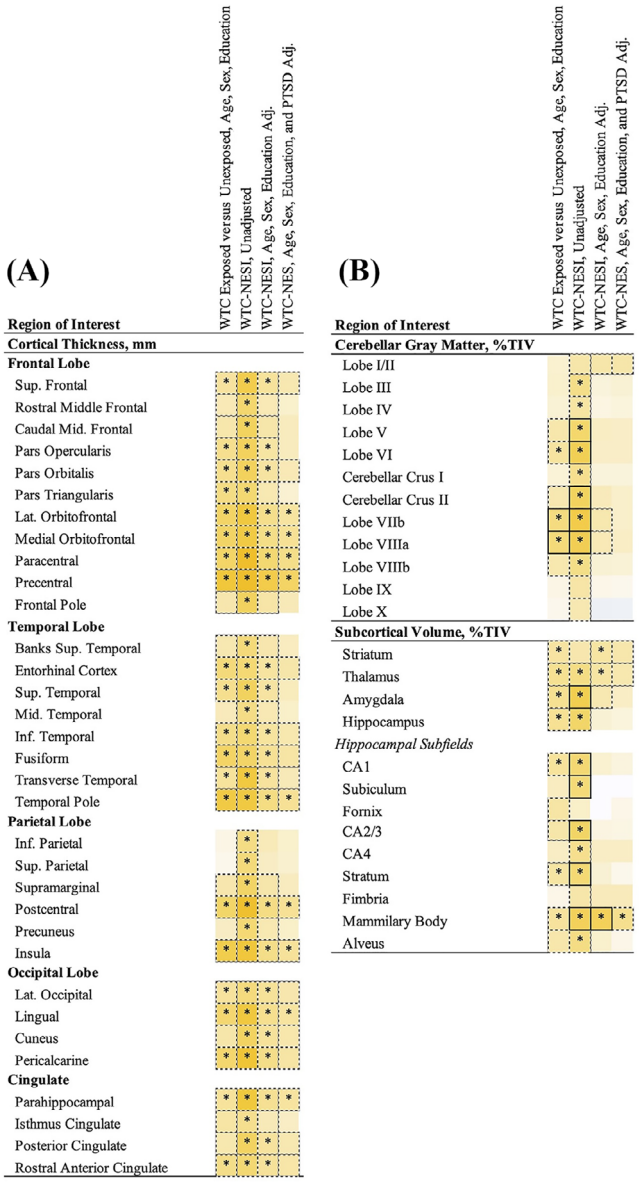


FIGURE 2 Results showing effect sizes from multivariable-adjusted generalized linear models examining morphological differences associated with World Trade Center (WTC) exposure presence versus absence, and when examining the WTC Neurotoxicant Exposure Severity Index (WTC-NESI) with varying statistical controls. (A) Cortical thickness. (B) Cerebellar and subcortical volumes. Some cells include a darker gold hue to indicate evidence of more severe atrophy or a darker turquoise hue to indicate expansion. Cells with a dashed cell border are significant ($p < 0.05$). *Significant after adjusting for multiple comparisons with the Benjamini-Hochberg correction (FDR = 0.05).

between APOE4 possession and either WTC-NESI ($\chi^2 = 5.5, p = 0.239$) or cortical thickness ($t = -1.29, P = 0.197$). Figure S4 shows that models adjusting for APOE, PTSD, body mass, smoking, imaging site, or using various subsets of data provided similar results with expected variability depending in part on sample size involved in each study (Table S3). Brain tumors, recent heart attacks, history of any stroke, or the presence of a pacemaker were exclusions for this study, so sensitivity analyses examining their relevance are shown in Table S4. While most medical diagnoses were not associated with either exposure or measures of neurodegeneration, we found that WTC-NESI was associated with the presence of diabetes and that the presence of obstructive airway disease was associated with cerebellar cortical volume ($p = 0.010$).

3.3 | Exploratory analyses of specific WTC exposures and regional measures

Since responders recalled specific experiences, we examined associations between specific exposures reported on site and measures of cerebral atrophy (Figure 3). These analyses suggested that exposures to search-and-rescue efforts were closely associated with cortical thinning across much of the frontal lobe. In contrast, time spent sifting through debris appeared to be associated with atrophy both in the cortex and throughout the upper cerebellum. Interestingly, responders spending a greater share of their time working in perimeter security showed less cortical atrophy across the temporal lobe and in the cingulate.

4 | DISCUSSION

This study examined associations between WTC-NESI and indicators of cerebral atrophy in WTC responders and unexposed controls. We found that a validated measure of exposure severity – WTC-NESI – was associated with brain atrophy in WTC responders at midlife. Specifically, higher WTC-NESI scores were correlated with reduced global cortical thickness ($r = -0.38$, $p < 0.001$) with regional analyses identifying reduced cortical thickness focused on the precentral ($\beta = -0.54$, $p < 0.001$) and temporal pole ($\beta = -0.52$, $p < 0.001$). Vertex-wise analyses showed that affected regions integrated 82.3% of cortical vertices, supporting the conclusion that there is an association between WTC exposure and cortical atrophy. Regional clusters identified in the vertex-wise analyses included a majority of vertices mapped on the cortical surface.

The most striking finding was a dose-dependent relationship between exposure severity and cortical thickness. Unlike binary measures of exposure (e.g., dust cloud exposure or arrival on September 11, 2001), WTC-NESI captures the intensity and variety of activities performed by the responders where damaging exposure to fine particulate matter was likely present. This approach suggests that brain differences vary along a continuum of exposure severity and may be tied to probable exposure to fine particulate matter during response and recovery efforts. Sensitivity analyses also revealed that WTC responders characterized as minimally exposed because they either consistently wore full PPE or never reported working in areas with WTC dust showed a cortical thickness similar to that of unexposed individuals. Such measures could be used to help identify participants in other studies who might be similarly vulnerable.

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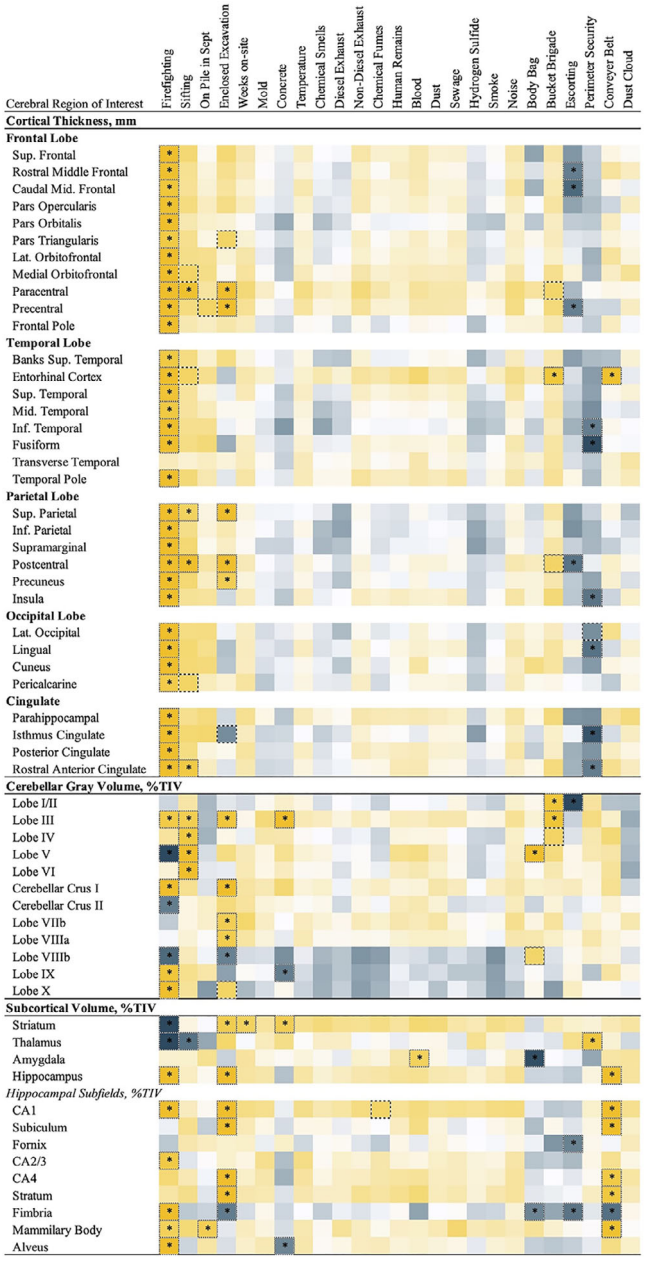


FIGURE 3 Exploratory analyses presented as a heat map showing standardized regression coefficients from multivariable-adjusted generalized linear models linking specific World Trade Center reported exposure activities and cerebral volumetric information. Cells include a darker gold hue to indicate evidence of more severe atrophy and a darker teal hue to indicate protective associations. Cells with a dashed cell border are nominally statistically significant ($p < 0.05$). *Significant after adjusting for multiple comparisons with FDR correction (FDR = 0.05).

Our findings provide support for accumulating evidence suggesting that environmental exposures might increase the risk of neurodegenerative changes. For example, mouse models identified peripheral inflammation and cognitive impairment,[27] neuroinflammation,[28] and metabolic dysregulation[29] in mice who ingested WTC dust. Brooks et al.[30] reported inhaled mixtures of burn-pit toxins are associated with blood-brain barrier damage in veterans. Calderón-Garcidueñas et al.[2] reported the presence of Alzheimer's and Parkinson's disease neuropathology in young urbanites who were chronically exposed to industrial exhaust. Put together, this work reveals the potential for insidious pathways leading from exposure to neuropathology. Our results provide new considerations on ROIs that could be useful in identifying other exposure-related conditions.

Until recently, work in WTC responders has focused on understanding the importance of PTSD in relation to the onset of mild cognitive impairment (MCI) and dementia.[31] Recent work suggested that only 10-15% of MCI cases in this cohort can be attributed to PTSD.[32] Despite not finding evidence of neurodegeneration here, previous studies have also reported that cognitive changes include difficulties with coordination and movement in individuals with PTSD[33] that may be linked to stress-induced cortical dysregulation.[31]

Neurodegeneration may result from multiple biological processes. In this study, we focused on examining whether a putative pathway potentially involving exposure to fine particles. One study of amyloidosis in WTC responders[16] identified fibrillar amyloid deposits near the olfactory bulb, consistent with the present study's results. Simultaneously, studies have reported that silica-induced pulmonary fibrosis (a composition that may be analagous to WTC dust[34]) is also associated with atrophy in the cerebellum and hippocampus[35] and throughout the cerebrum.[36] While the olfactory pathway might allow cerebral transduction, other areas especially since WTC responders ingested the dust and had it cover their skin and eyes. Future research should clarify whether other entry pathways are possible and could influence the type, location, or severity of neuropathology.

Researchers using the UK Biobank similarly reported that exposure to ambient air pollution containing fine but not coarse particulate matter was associated with reduced gray matter volume.[37] We used WTC-NESI as a proxy measure of exposure to fine particulate matter, chemicals including persistent organic pollutants or polycyclic aromatic hydrocarbons, and heavy metals in aerosolized dust. Future work will be required to evaluate whether regional differences in cortical thickness evident in this study are consistent with those of other studies of cerebral atrophy following air pollution exposure. Similarly, future research should seek to determine the cognitive and noncognitive symptoms that are evident among individuals with similar forms of neurodegeneration.

4.1 | Limitations

The strengths of the study include the activity-based exposure index (WTC-NESI) and a cohort with varying degrees of exposure severity. Several limitations should also be acknowledged. First, the small sample size and small number of women in the study limits power and generalizability. Second, the use of a cross-sectional cohort is a limitation because it does not allow us to establish causality. Specifically, there is a risk of reverse causality if response activities are more severely ranked by those who already have established neurodegeneration. Several earlier studies using longitudinal data reported that

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the onset of cognitive decline occurred at unusually young ages in the decades after exposure and that cognitive decline was most severe in responders who were most severely exposed. Further research is needed to establish a timeline for neurodegenerative changes in responders. Third, the population of interest was exposed to a relatively unique exposure for lengthy periods of time. While exposures at the WTC may be consistent with exposures at other response sites (including when fighting urban and forest fires, bombings, or accidental building collapses) and near military burn pits, the extent to which our results are generalizable to ambient exposures in the general population is unclear. Fourth, there is a risk of recall bias in measures of WTC exposure activities, though we are studying a memorable exposure, and we collected information on exposures soon after response efforts ended. Fifth, controls were brought from several studies to improve power, but this can introduce confounding by including subjects studied at multiple sites. We assessed this by integrating our own controls and by comparing control databases and by statistical adjustment. We found that controls from the WTC responder databases were not measurably different from controls retrieved from ADNI and NIMH-RV databases and that adjustment for site did not change results. Sixth, our sample might have excluded individuals who were most significantly impacted by the WTC exposures since they might have already developed moderate to severe dementia or may have died. If such survival bias is present, results from this study are likely to be conservative. However, it is worth noting that the mortality rates in WTC responders are lower than in many studies of dementia, due to the population's relative youth, and that mortality rates in the WTC cohort as a whole tend to be lower than usually present in the general population due to a healthy worker effect coupled with the strong preventive and diagnostic programs that are available to responders.[38] Seventh, while we found evidence of cortical atrophy, our study cannot explain the biochemical mechanisms that might lead to neurodegeneration. Hence, mechanistic research is warranted to identify factors underpinning similar neurodegenerative conditions.

4.2 | Implications

The severity of exposure to fine particulate matter at the WTC sites is associated with cortical atrophy, highlighting the need to understand mechanisms and prevention. Some research has pointed to a great utility of PPE when undergoing severe exposures to inhaled heavy metals.[39] Our results highlight the importance of improving protective measures to better safeguard future responders from similar exposure-related cortical atrophy. This study also identifies a pressing need for intervention studies to identify ways to slow or stop progression in exposed individuals. Finally, this study highlights the need for ongoing monitoring and research focused on the neurological implications of WTC exposures.

ACKNOWLEDGMENT

The authors have nothing to report. The authors acknowledge the support of NIOSH U01OH011314, NIA R01AG049953, NIA R01AG067590, NIA P30 AG066514, the Cure Alzheimer's Fund, R01AG084699 and R01AG093879, R01AG093281, and the I.B. Ertegun Project for Cognitive Health Extension at ISMMS. Data collection and sharing for this project was funded by the **Alzheimer's Disease Neuroimaging Initiative** (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012), and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

CONFLICT OF INTEREST STATEMENT

Dr. Gandy is a co-founder of Recuerdo Pharmaceuticals. He has served as a consultant for Johnson & Johnson, Diagenic, and Pfizer, and he currently consults for Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Third Bridge, MEDACORP, Altpep, Vigil Neurosciences, Memory Garden, and Eisai. He has received research support from Warner-Lambert, Pfizer, Baxter, and Avid. The authors declare no other competing interests. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

This study was reviewed and approved by the Institutional Review Board at the Renaissance School of Medicine at Stony Brook University. All participants provided informed written consent.

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How to cite this article: Clouston SAP, Huang C, Askarov T. et al., World Trade Center neurotoxicant exposure severity is associated with cortical thinning and regional brain atrophy: a neuroimaging study of general responders at midlife. *Alzheimer's Dement*. 2026;22:e71878. https://doi.org/10.1002/alz.71878

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