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# Exposure duration and cerebral amyloidosis in the olfactory cortex of World Trade Center responders: A positron emission tomography and magnetic resonance imaging study

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## Abstract

**Background:** Amyloid-β proteins, a hallmark of Alzheimer's disease, are believed to play an adaptive role in the cerebral immune response.

**Objective:** Amyloid is believed to play a role in cerebral immune response and could play a similar role in response to air pollution exposures. In the present study, we examined whether WTC exposure duration was associated with cerebral amyloidosis in WTC responders.

**Methods:** WTC responders (aged 44–65 years) who varied in exposure duration but did not use personalized protective equipment were assessed using positron-emission tomography with [$^{18}$F]-Florbetaben. The outcome was the cortical [$^{18}$F]-Florbetaben burden, measured using regional standardized uptake value ratios (SUVRs) in 34 Desikan-Killiany regions of interest. Spearman's $\rho$ and generalized linear models were used to estimate correlations between WTC exposure duration and cortical [$^{18}$F]-Florbetaben SUVR. Cognitive and behavioral symptoms were measured. Magnetic resonance imaging was used to measure cortical thickness and diffusivity.

**Results:** The mean age of imaged responders was 56 years old. WTC exposure duration was associated with olfactory [$^{18}$F]-Florbetaben SUVR (Spearman's $\rho = 0.43$, $p = 0.011$), which was in turn associated with elevated [$^{18}$F]-Florbetaben SUVR in ventral regions ($\rho = 0.41$, $p = 0.016$). Cortical [$^{18}$F]-Florbetaben in ventral regions was associated with reduced response speed ($\rho = -0.72$, $p < 0.001$), was co-located with cortical diffusivity across regions in the parietal and frontal

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lobes and reduced cortical thickness in the isthmus cingulate ($\rho = -0.53$, $p = 0.001$).
**Conclusions:** Low-grade amyloidosis in the olfactory and frontal lobes was associated with WTC exposure duration. Future work should examine whether low-grade amyloidosis is correlated with the location or distribution of neurofibrillary tangles in WTC responders.

**Keywords**
Alzheimer's disease, amyloidosis, cognitive impairment, first responders, World Trade Center

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## Introduction

World Trade Center (WTC) responders were acutely and chronically exposed to neurotoxic chemicals and airborne particulate matter (PM) following the terrorist attacks on the WTC on September 11, 2001. These exposures have been associated with an increased risk of dementia.[1] This exposure has been found to contain multiple neurotoxic agents including metals, and polychlorinated biphenyls in the dust, and dioxins, solvents, polycyclic aromatic hydrocarbons, acrylonitrile, formaldehyde, and diesel fumes as products of the prolonged jet fuel combustion.[2] The initial dust plume from the uncontrolled collapse of the WTC towers engulfed much of lower Manhattan, but settled throughout the WTC sites in the following days while responders conducted search and rescue projects that lasted for months.[3] Since then, studies have reported that WTC exposures are associated with increased neuroimmune responses both in studies of animals[4,5] and humans,[6,7] alongside changes to serology indicating increased presence of neuropathology[8] concurrent with reduced cognitive functioning[9,10] and evidence of neurodegeneration in regions that partially match regions reported in Alzheimer's disease and related dementias (ADRD).[11–13]

ADRD is characterized by the presence of increasingly large and dense fibrillary plaques made up of β-amyloid (Aβ) protein in the brain.[15] However, ADRD is increasingly seen as a heterogeneous condition, with evidence supporting the presence of varying patterns in the burden of cerebral amyloidosis, co-pathologies, and symptom severity.[14] The influence of air pollution on the aging brain has long been a topic of serious inquiry, with several studies suggesting that fine (<2.5 μm) $PM_{2.5}$ can enter the brain.[16] Chronic and severe exposures to inhaled neurotoxic chemicals and airborne particulate matter can maladaptively mobilize the neuroimmune system[17] and activate neuroinflammatory responses resulting in ADRD.[18] Recent epidemiological studies have shown a greater incidence of dementia associated with higher residential levels of $PM_{2.5}$.[19]

Aβ is central to ADRD but also plays an important role in maintaining homeostasis within the body and brain and is still under investigation. Studies have demonstrated that Aβ can accumulate centrally as part of neuroimmune response, particularly to noxious insults such as short- and long-term viral and microbial infections.[20–23] However, a similar process may also be used to respond to air pollution exposure, meaning that Aβ might arise as part of a homeostatic neuroprotective response to cerebral infiltrate.[6,7] For example, prior work has suggested that a majority of children who are exposed to high levels of aerosolized metals and die in accidents in Mexico City also have evidence of cerebral amyloidosis.[24] Animal models support the view that these early responses might grow to become ADRD, suggesting that when subjected to chronic air pollution inhalation animals who displayed strong neuroinflammatory responses[25] might also develop cortical and hippocampal atrophy.[26]

If neurotoxic amyloid plaque formation is associated with inhaled particulate exposures,[27] then immune-related amyloidosis presenting in the olfactory regions may be a distal outcome of this response.[28] Since Aβ dispersion studies show that Aβ takes at decades to grow to the levels usually seen in mild cognitive impairment,[29] we sought to investigate in-vivo cortical levels of fibrillar amyloid burden in responders with varying levels of WTC exposure using simultaneous magnetic resonance imaging (MRI) and positron emission tomography (PET) scans. This study would enable us to determine whether longer WTC exposure durations could be associated with cerebral amyloid burdens at first in the most affected regions surrounding the point of entry, presumably the olfactory nerves (Figure 1). We hypothesized that the olfactory cortex and surrounding regions would be the locus for the WTC dust infiltration,[3] as protruding cilia from the roof of the nasal cavity that separates the frontal lobe could permit the passage of APM particles.[30] Furthermore, we theorized that Aβ burden would also be evident in olfactory-adjacent regions and might also grow in terms of the severity of associated symptoms.

## Methods

Responders were recruited from individuals attending a clinic-based WTC health monitoring program[31,32] who participated in an epidemiologic study of cognitive aging.[33]

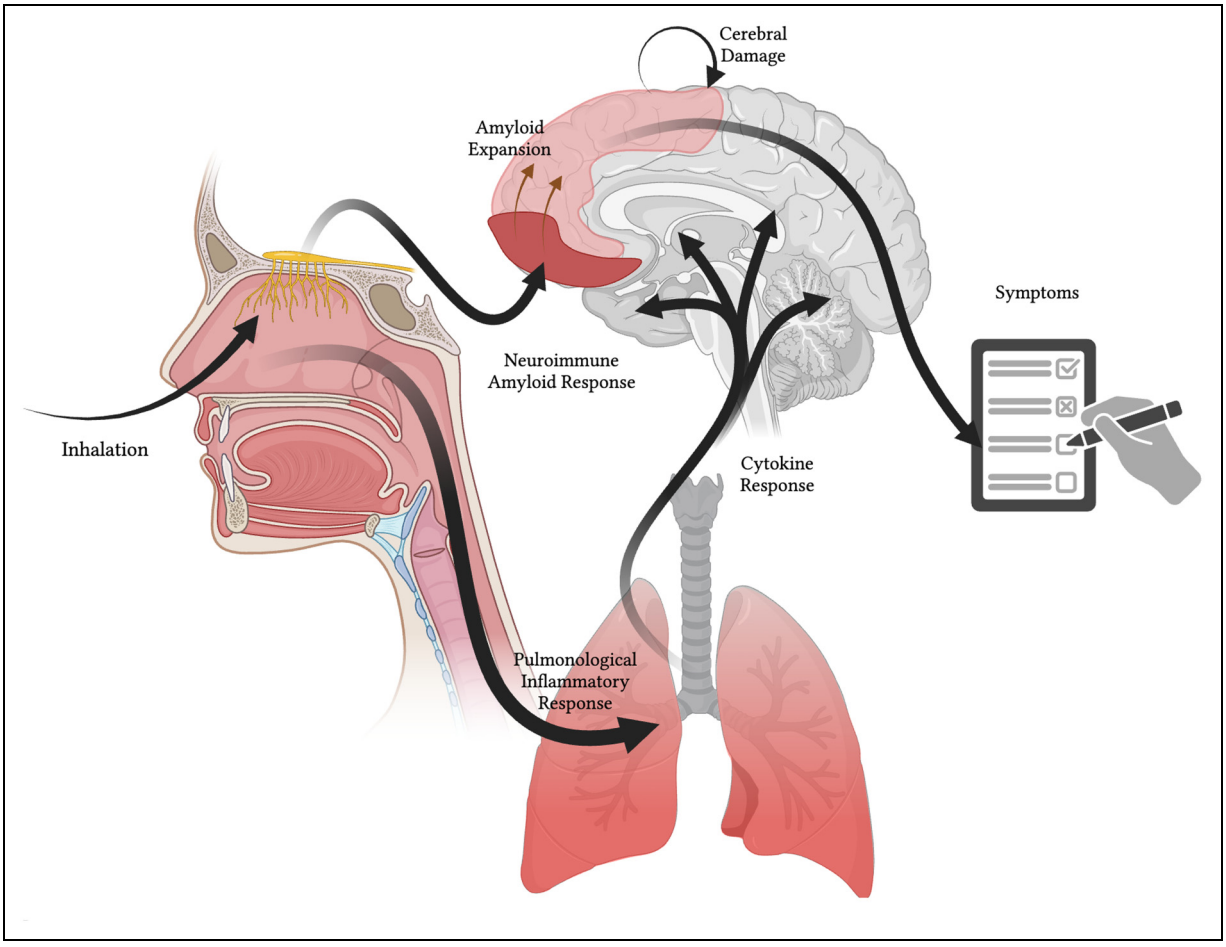


**Figure 1.** Hypothesized linkages between neurotoxic exposures at the World Trade Center (WTC). We theorize that due to the possible presence of chronic (>20 years) cerebral WTC dust infiltrates that have actively and passively flowed from the initial sites of insult, i.e., the olfactory nerve area, to anatomically connected neighboring neural networks such as, but not limited to, the inferior frontal lobe. Clouston S. 2023. BioRender.com/w86b800.

Responders were included if they had evidence of cognitive impairment at the time of screening, or if they were cognitively unimpaired at the time of enrollment. Participants whose case status was not confirmed during screening were excluded. Participants were also eligible if they either had no evidence of post-traumatic stress disorder (PTSD) or if they had chronic PTSD consistently since exposure. Responders were excluded if they had a history of psychosis, severe head trauma from military or WTC response efforts, or diagnosed neurological conditions including stroke, Parkinson's disease, or all-cause dementia where the date of diagnosis is unknown; brain cancer; current renal, liver, or autoimmune disease including multiple sclerosis; heart failure or myocardial infarction in the past year; current use of cognitively active medications; or uncontrolled diabetes. Participants also satisfied the eligibility criteria for MRI scanning (body mass index $\leq 40$, no known claustrophobia, no known metal implants not deemed safe for MRI, and no current pregnancy or breastfeeding). To account for differences between cognitive status groups, we matched groups on age, race/ethnicity, sex, occupation, educational attainment, and chronic PTSD status. While not an explicit exclusion criterion, no participants in this study consistently wore personalized protective equipment during their WTC response.

### *Image acquisition*

PET and MRI images were acquired simultaneously on a 3T Siemens Biograph mMR (software version VE11P, Siemens Healthcare, Erlangen, Germany). PET data were acquired from participants 90–110 min after intravenous injection of 230–333 MBq of [$^{18}$F]florbetaben radiotracer. [$^{18}$F]-florbetaben was synthesized by Life Molecular, Inc., and delivered to the PET imaging facility at Stony Brook University for all research participants. Three-dimensional volumetric T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) images were collected to facilitate PET signal localization and to measure neurodegenerative burden using a

vendor-provided 20-channel PET-compatible head/neck coil with TR/TE/TI = 1900/2.49/900 ms; Flip Angle = 9∘; acquisition matrix: 256 × 256; voxel resolution: 0.89 × 0.89 × 0.89 mm.

Diffusion tensor imaging was also performed with the following parameters: TE/TR = 87.6/4680 ms, b value = 1200, 64 diffusion directions, in-plane resolution = 2 mm, slice thickness = 2 mm, matrix size = 128 × 128, multiband factor = 2. After data collection, post-processing incorporated standard techniques for acquisition-based artifact elimination. Subject motion and eddy corrections were accounted for using the FMRIB Software Library (FSL).[34]

T2-weighted anatomical scans used a turbo spin-echo pulse sequence (34 axial slices, TR = 6170 s, 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.

### PET image reconstruction

PET images were reconstructed offline using vendor-provided reconstruction software (e7tools, Siemens Healthcare, Erlangen, Germany). To improve the accuracy of attenuation correction with bone compartment, the "Boston method" was used to generate attenuation maps using the MPRAGE images.[35] PET reconstruction was performed using OSEM with point-spread function modeling and 100 iterations (21 subsets) to ensure convergence for optimal quantitative accuracy,[36] followed by 4 mm Full-width half maximum Gaussian post-filtering to control noise (effective spatial resolution = 5.1 mm) determined using the Joshi method.[37]

### Image processing

Sinograms were binned covering 20 minutes starting 90 minutes post-injection of [$^{18}$F]-florbetaben according to established protocols.[38] PET images were scaled to injected dose and body weight to produce standardized uptake value (SUV) images.

Cortical segmentation of the associated T1-MPRAGE images was performed using *FreeSurfer*[39] [V.6.0.0] followed by regional parcellation according to the Desikan-Killiany brain atlas.[40] Using the *PETSurfer* tools within *FreeSurfer* we extracted the VOI data from the PET images which also allowed for partial volume correction of the VOIs using the Symmetric Geometric Transfer Matrix method[41] using the 5.1 mm FWHM resolution determined above.

Diffusion images were visually inspected to check for major image artifacts or significant motion during the acquisition. All images passed inspection. No radiological abnormalities were identified in the images. The diffusion data were reconstructed in the Montreal Neurological Institute space using q-space diffeomorphic reconstruction[42] to obtain the spin distribution function (diffusion sampling length ratio = 1.25) using DSI Studio (5/4/2019 build).[43] Cortical mean diffusivity (b = 0 & 1000) is a highly sensitive measure of cortical inflammation[44] and microstructural cortical changes[45] that often reflects early changes in cerebral structure resulting from amyloidosis. We extracted for a region of interest (ROI) based analysis using Desikan-Killiany atlas[40] and DSI studios' FreeSurferSeg atlas. All 34 unilateral ROI pairs from the Desikan-Killiany atlas[40] were studied along with left and right ROI pairs of the hippocampus and amygdala, and five subsections of the corpus callosum from the FreeSurferSeg atlas provided by DSI Studio.

### Global fibrillar [$^{18}$F]-florbetaben burden

To determine whether potential WTC amyloidosis was similar in cortical topology to that found in AD, we performed a centiloid score analysis of [$^{18}$F]-florbetaben data,[46] in which we used PMOD software (PMOD Technologies, Zurich, Switzerland). We strictly followed the protocol for this tracer to calculate a centiloid value for each responder, where centiloid values nominally fall on a 0–100 scale such that a centiloid score exceeding 25 can be used as a cutoff for AD positivity.[47] The centiloid method provides a universal scaling metric targeted at identifying AD amyloidosis.

### Regional amyloidosis

Since [$^{18}$F]-florbetaben distribution in the left and right hemispheres was strongly correlated (r = 0.99), and directions were similar across subregions, regional analyses focused on bilateral abnormalities. We defined three subregions of interest in this study. First, we defined a meta-region consisting of regions near the olfactory bulb and tract including the pars orbitalis, medial orbitofrontal, and lateral orbitofrontal regions. Next, we examined a meta-ROI made up of smaller ROIs that were adjacent to the olfactory bulb and cortex including the accumbens, rostral anterior cingulate, superior frontal, caudal middle frontal, and precentral regions. Finally, a meta-ROI made up of WTC-affected regions identified during a neuroimaging study of WTC responders with early-onset dementia[11,48,49] consisted of the following regions: hippocampus, entorhinal cortex, parahippocampal gyrus, inferior parietal cortex, inferior/middle/superior temporal gyri (including banks of the superior temporal sulcus), supramarginal gyrus, inferior frontal gyrus, posterior cingulate, isthmus of the cingulate gyrus, precuneus, amygdala, putamen, and ventral diencephalon. All regional SUVs were normalized by the uptake of the whole cerebellum for SUV ratios (SUVR).

## PET image clinical read

Each [$^{18}$F]-florbetaben image was qualitatively read by a trained analyst (SC) and a board-certified fellowship-trained neuroradiologist with ten years of clinical and research experience in PET/MRI (AF) without knowledge of prior study results or clinical status. The global level of amyloid positivity (positive/negative) and any regional findings were reported.

*WTC exposure duration was* assessed using an interview-administered exposure assessment questionnaire that was completed by all responders upon enrollment in the parent monitoring program used to document exposures at the WTC response sites.[31] All responders were dust-exposed during the WTC response efforts, so we defined exposure duration as the total duration (in months) of response efforts. None of the imaged responders reported regularly using personalized protective equipment, including masks, while working at the WTC sites.

*Clinical variables.* Cognitive Throughput is a corrected response rate measure giving the number of successes per unit of discretionary time and was measured using the CogState™ computerized battery. The battery consisted of five validated game-like tasks (detection, identification, one-card learning, continuous paired associate learning, and Groton maze learning and recall) and was administered to evaluate domains of cognitive dysfunction following a standard operating protocol.[50] Across these five tasks, we assessed episodic memory (accuracy measured by the paired associates learning test), visuospatial functioning learning and recall (total errors), visual working memory (accuracy), visuospatial memory, throughput (accurate responses per second), intra-individual item-response variability (measured in standard deviations), processing and response speed (responses per millisecond), and attention (accuracy).

*Cognitive status* was determined using the Montreal Cognitive Assessment[51]; a cutoff of <22 was used to identify individuals with cognitive impairment, whereas cognitively unimpaired individuals had a score ≥26. Prior work in this population has found that apolipoprotein ϵ4 (*APOE4*) status is not a central predictor of cognitive performance, but because this study examined amyloidosis,[52] we were able to examine *APOE4* allele possession among 28/35 participants who consented to genotype analysis. To accomplish this, deoxyribonucleic acid was extracted from blood samples of WTC responders and genotyped using the Infinium Global Screening Array (Illumina, San Diego, CA, USA), and *APOE4* status was recorded. In this small study, none of the participants in this small study were homozygous carriers so we dichotomized the genotype into possessing one allele (actually, only the ϵ3/ϵ4 allele combination was identified) versus non-possession.

*Demographics* included age in years, sex (male versus female), race/ethnicity (White, Black, Hispanic, and other), educational attainment (high school or less, some college/technical school, and college or more), and occupation on September 11, 2001 (law enforcement versus other) were included as covariates. *Post-traumatic stress disorder* was diagnosed using the Structured Clinical Interview for the DSM-IV,[53] a semi-structured interview administered by trained clinical interviewers.

## Statistical analysis

The sample was described using means and standard deviations, or frequencies and percentages comparing diagnostic categories using non-parametric trend tests and describing qualitative findings. Next, Welch's t-test was used to compare mean tracer uptake in regions previously identified as vulnerable in WTC responders using the WTC regional SUVR and, secondarily, to consider regions commonly examined in AD comparing the Centiloid.

The regional distribution of amyloid-β used Statistical Parametric Mapping (SPM12) to complete voxel-wise analyses of Gray Matter SUVR completed. All models were adjusted for age, education, and race/ethnicity. Models adjusted for the centiloid score to account for differences in [$^{18}$F]-florbetaben burden predominantly indicative of aging-related sporadic AD. To reduce the potential identification of false positives, p-values were estimated for clusters exceeding 50 voxels in size. FDR-adjusted p-values were estimated for cluster peaks. Results were then mapped onto the cerebral surface using SPM12's Computational Anatomy Toolbox.

We compared correlations between WTC exposure duration and tracer uptake in the olfactory and surrounding regions using scatter plots and linear regression. Spearman's $\rho$ was reported for these analyses to account for the potential for nonlinear associations between amyloidosis and potentially correlated features including markers of neurodegeneration and cognitive function. We observed correlations between localized and regional [$^{18}$F]-florbetaben burden, and between [$^{18}$F]-florbetaben burden and cortical atrophy. All models were adjusted for age, education, and race/ethnicity. We also adjusted for the centiloid score to account for differences in [$^{18}$F]-florbetaben burden predominantly indicative of aging-related sporadic AD.

A two-tailed $\alpha = 0.05$ was used to determine statistical significance; results from repeated testing analyses were adjusted for the false discovery rate (FDR = 0.05).[54] Statistical analyses were completed using Stata 17/MP [StataCorp].

## Ethics

The study was reviewed by the institutional review board (CORIHS #1315306). All participants provided informed written consent.

## Results

### Study participants

In total, 36 participants were deemed ineligible at screening and the 50 remaining individuals were scheduled for neuroimaging but five withdrew and nine were unable to complete the neuroimaging visit due to delays or imaging protocol failures (i.e., insufficient radioactive dose, delayed injection past the anticipated injection window, scanner failure). At one appointment, ligand production failed, and the participant refused to try again resulting in a final sample of 35 responders who underwent neuroimaging.

### Sample characteristics

We begin by showing the demographic and clinical characteristics of the WTC responder group (Table 1). On average, neuroimaging participants were 56 years old, had at least some college, and were trained as first responders. When stratifying the sample into high versus low exposure, we found no statistically significant differences in demographics or other covariates between the two groups.

### Group differences

Voxel-wise analyses mapped to the cerebral surface identified elevated amyloid that was generally bilaterally symmetric, presenting with cluster centroids in the medial orbitofrontal, superior frontal, and precentral regions (Figure 2). In this figure, you can see evidence of cortical uptake both in the frontal lobe and in the cingulate, as well as in the left temporal pole and across regions in the parietal lobe. These differences were supplemented by regional analyses showing evidence of [$^{18}$F]-florbetaben retention in WTC-related ROIs ($p = 0.025$), such as the superior temporal and parahippocampal cortices, isthmus cingulate, and hippocampus (Supplemental Figure 1).

### Clinical results

Qualitative clinical reads assessed one responder as [$^{18}$F]-florbetaben-positive consistent with ADRD (heterozygous apolipoprotein-$\epsilon$3/$\epsilon$4). Three other responders had at least one visual reader indicating the possibility of [$^{18}$F]-florbetaben positivity in one region of interest. Centiloid analysis (mean = −9.31, SD = 10.25) identified one responder who met centiloid criteria for the presence of cerebral amyloidosis. Apolipoprotein $\epsilon$4 allele possession was not associated with amyloidosis in any analysis, though individuals carrying one apolipoprotein $\epsilon$4 allele had evidence of higher SUVRs in WTC-related regions that might suggest that larger studies would find a difference (APOE- = 1.11, APOE + = 1.70, difference = 0.60, $p = 0.16$).

### [$^{18}$F]-florbetaben burden in more severely exposed responders

Since WTC responders do not match the topographical [$^{18}$F]-florbetaben burden pattern seen in AD, but rather in ROIs outside centiloid regions, we next focused on WTC susceptible ROIs, such as the olfactory bulb/tract and inferior frontal lobe. Next, we examined associations between WTC exposure duration and [$^{18}$F]-florbetaben retention (Figure 3) to find a positive association between [$^{18}$F]-florbetaben SUVR and longer WTC exposure duration in the olfactory regions (Spearman's $\rho = 0.43$, $p = 0.011$, Figure 3A). We also

**Table 1.** Clinical characteristics of the World Trade Center responder sample who completed the simultaneous positron emission tomography and magnetic resonance imaging protocol.

| Characteristic | Sample (N = 35) | WTC exposure duration < 6 months (n = 18) | WTC exposure duration ≥ 6 months (n = 17) | p |
|---|---|---|---|---|
| Age, y | 55.8 (5.24) | 55.61 (6.01) | 56 (4.46) | 0.79 |
| Body mass index, kg/m$^2$ | 29.22 (4.23) | 28.9 (4.24) | 29.57 (4.32) | 0.57 |
| Female versus Male | 9 (25.7%) | 4 (22.2%) | 5 (29.4%) | 0.63 |
| Non-White Race/Ethnicity versus White | 9 (25.7%) | 5 (27.8%) | 4 (23.5%) | 0.78 |
| Education | | | | |
| High School or less | 10 (28.6%) | 8 (44.4%) | 2 (11.8%) | – |
| Some College | 13 (37.1%) | 18 (1800%) | 17 (1700%) | 0.32 |
| College Diploma | 12 (34.3%) | 36 (1800%) | 34 (1700%) | 0.10 |
| Untrained Responder versus Trained | 8 (22.9%) | 4 (22.2%) | 4 (23.5%) | 0.37 |
| Early Arrival 9/11–9/12 | 28 (80%) | 14 (77.8%) | 14 (82.4%) | 0.74 |
| Post-Traumatic Stress Disorder versus None | 18 (51.4%) | 8 (44.4%) | 10 (58.8%) | 0.86 |
| Apolipoprotein $\epsilon$4$^{\dagger}$ allele versus none | 9 (32.1%) | 4 (25%) | 5 (41.7%) | 0.36 |

Means (standard deviation) or Percentages (%) reported. In dichotomous variables, frequencies and percentages for only one group was shown and the reference category was listed using the versus label. p-values were estimated using Welch's T-Test or Chi-Squared tests. SD: standard deviation; cs: centiseconds; kg/m$^2$: kilograms per meter squared. $^{\dagger}$Apolipoprotein-$\epsilon$4 status was only available for 28/35 participants.

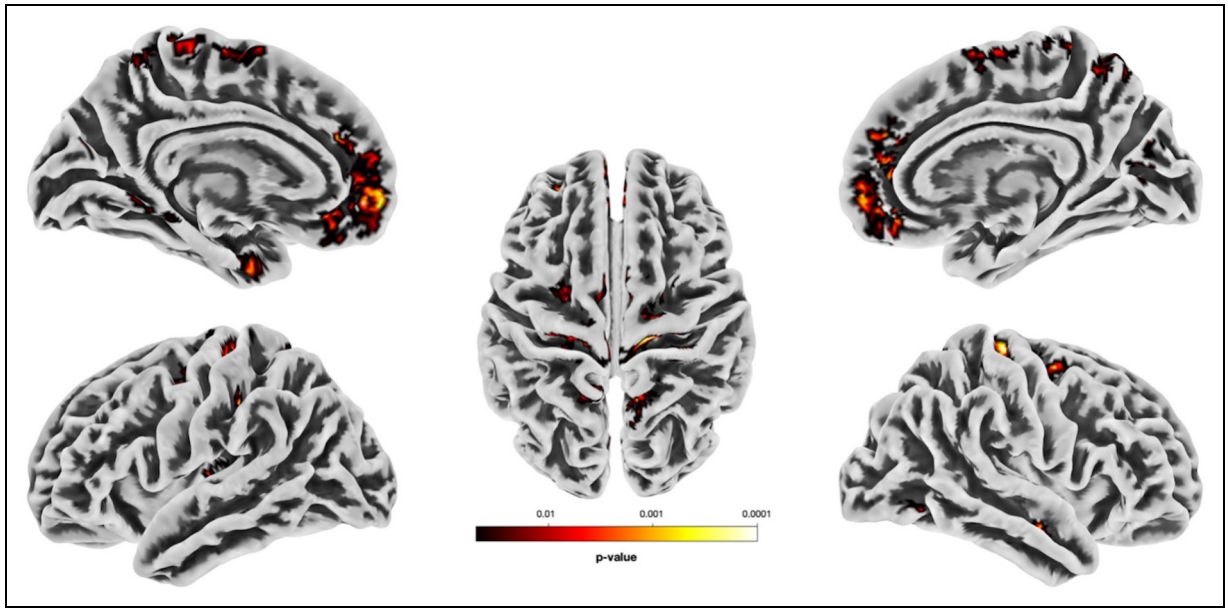


**Figure 2.** Surface projection of cortical amyloid burden in cognitively impaired World Trade Center responders as compared to cognitively unimpaired responders. Images only report increased [$^{18}$F]-Florbetaben Standardized Uptake Value Ratios (SUVR) where statistically significant results are evident ($p < 0.05$). Results are statistically significant at the cluster level after adjusting for the false discovery rate (FDR = 0.05) in three clusters (cluster-centroids ($p < 0.001$) located at: 15, −27, 70 [right precentral, P]; 16, 48, 1 [right superior frontal], and −8, 55, −7 [left medial orbitofrontal]).

identified a significant positive association between olfactory [$^{18}$F]-florbetaben uptake and [$^{18}$F]-florbetaben uptake in neighboring ROIs ($\rho = 0.93$, $p < 0.001$, Figure 3B), and a significant positive association between [$^{18}$F]-florbetaben uptake in olfactory neighboring ROIs and previously identified WTC ROIs ($\rho = 0.41$, $p = 0.016$, Figure 3C).

### *[$^{18}$F]-florbetaben burden and neurodegeneration*

Examinations of ROI-specific associations between tracer uptake and increased cortical mean diffusivity or decreased cortical thickness (Table 2) revealed statistically significant increases in cortical mean diffusivity linked to co-located cerebral amyloid burden across the parietal lobe, and throughout the occipital, temporal, and frontal lobes.

### *Meta-regional [$^{18}$F]-florbetaben burden and cognitive functioning*

Next, we evaluated associations between cognitive throughput and region-specific [$^{18}$F]-florbetaben burden (Table 3). These analyses revealed that Amyloidosis in olfactory-adjacent regions, and the centiloid scores were not associated with measures of cognitive functioning. However, we did find that the amyloid burden measured across the WTC meta-ROI showed statistically significant correlations with cognitive throughput ($\rho = -0.59$), response speed ($\rho = -0.72$), and visuospatial functioning ($\rho = -0.49$) that remained after accounting for multiple comparisons.

## Discussion

The present study of WTC responders primarily identified cerebral [$^{18}$F]-florbetaben burden, a surrogate *in vivo* measure of cerebral amyloidosis, that is only partially consistent with what is typically observed in sporadic AD.[15] Most studies of amyloidosis are completed when examining older adults who are experiencing sporadic Alzheimer's disease (AD). These studies report very high levels of amyloid are needed to elicit changes that ultimately result in cognitive decline. For example, the mean centiloid for patients with AD dementia was approximately 84.1 versus 47.5 among those with mild cognitive impairment due to AD.[55] The values shown in this study therefore represent a much lower amyloid burden overall (mean = −9.31, SD = 10.25). Our results imply a pattern of fibrillary amyloidosis that appears topologically distinct from AD. For example, while most studies of cerebral amyloidosis in AD report regional elevations throughout the frontal, temporal, and parietal lobes as well as in the precuneus and hippocampus,[56] our analyses identified a high Aβ burden that was bilaterally symmetric, presenting with cluster centroids in the medial orbitofrontal, superior frontal, and precentral regions. Thus, though a growing literature is clear about the critical importance of amyloidosis in AD, this is

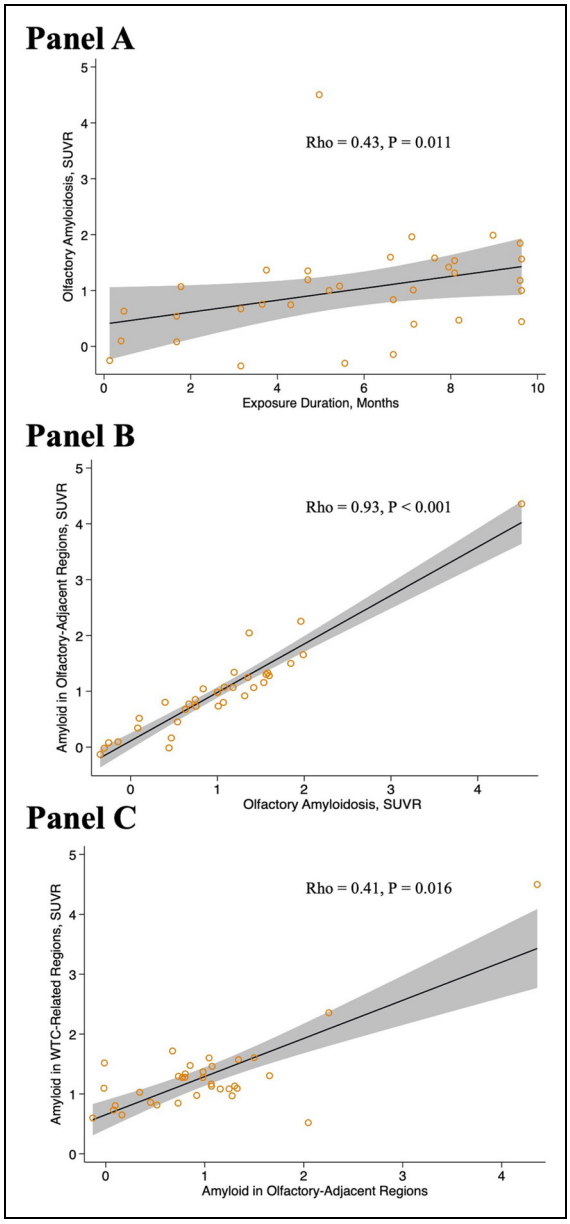


**Figure 3.** Scatter plots with best-fitting lines and 95% confidence intervals showing bivariate associations between (A) World Trade Center (WTC) site exposure duration (months) and regional [$^{18}$F]-Florbetaben uptake in the olfactory cortex, (B) [$^{18}$F]-Florbetaben uptake in the olfactory cortex and in olfactory-adjacent cortices, and (C) [$^{18}$F]-Florbetaben uptake in the olfactory olfactory-adjacent cortices and in previously identified WTC-affected regions of interest (C).

the first study to begin to determine the implications of low-grade exposure-related olfactory amyloidosis.

When we focused on studying the olfactory regions, we found that amyloidosis was higher in those who were exposed for longer periods. Nevertheless, while this WTC sample seems to be experiencing fibrillary amyloidosis, the hallmark of AD, it seems that those amyloid fibrils are forming topologically differently than in AD. Noting that cognitive symptoms are associated with lengthy exposures to WTC dust and that amyloidosis might be due to inhaled neurotoxic dust exposures, we hypothesized that amyloidosis might emerge in the olfactory cortex and neighboring inferior frontal regions.[1,3,5,57] Indeed, WTC dust contained a mixture of chemicals and particles of ultrafine dimension that responders ingested for months have the potential to cross the blood-brain barrier via through blood and cerebrospinal fluid exchange. These results support the view that olfactory and neighboring cortices might serve as one locus of entry for these WTC exposures, with an expectation that symptoms have emerged in the two decades since the event.

In this study, the most severely exposed responders, defined using duration (months) spent at the WTC site in our models, were significantly associated with olfactory Aβ burden and increasing [$^{18}$F]-florbetaben uptake in the neighboring frontal regions. Our models further identified that this Aβ burden was in turn associated with changes in gray-white matter contrast and cortical thinning of the gray matter ribbon. Furthermore, Aβ burden was associated with lower neurocognitive scores, such as cognitive response speed and throughput, episodic memory, and visual memory. Aβ burden in the olfactory region was associated with increased Aβ burden in proximal ROIs which were in turn associated with lower learning, memory, executive function, and information processing scores.[58–62]

One interpretation of the presence of a fibrillary Aβ accumulation in WTC responders could be a possible overactivation of the neuroimmune response[6,7] to noxious insults such as acute or chronic inhalation of neurotoxic air pollutants that could recruit Aβ as a central part of this process.[28] Considering the potential for an immunogenic amyloidosis we hypothesized that the amyloid burden would be greatest in the olfactory regions of the brain because the olfactory bulb would be the most vulnerable to externally inhaled cerebral infiltrate. Our findings support the view that Aβ burden, as measured by [$^{18}$F]-florbetaben uptake, is present in the olfactory bulb and cortex and that it is associated with amyloidosis in neighboring frontal regions, suggesting that the process of amyloidosis may continue to spread with time. Previous work has suggested that the influence of fibrillary amyloid is predominantly mediated by the presence of tauopathy in older age[27] indicating the need for further work studying the intensity of tauopathy in exposed WTC responders.

## *Strengths and limitations*

This study has several limitations including, for example, its small sample size and the relatively unique exposures this population endured. The small sample size can cause

**Table 2.** Associations between unilateral region-specific tracer uptake and two markers of neurodegeneration.

| | | Cortical mean diffusivity | | Cortical thickness, mm | |
|---|---|---|---|---|---|
| Lobe | Region | Left | Right | Left | Right |
| Frontal | Superior Frontal | 0.44 | 0.26 | −0.28 | −0.30 |
| | Rostral Middle Frontal | 0.09 | ***0.53*** | −0.32 | −0.36 |
| | Caudal Middle Frontal | 0.47 | 0.32 | −0.13 | −0.36 |
| | Pars Opercularis | ***0.55*** | 0.26 | −0.28 | −0.44 |
| | Pars Orbitalis | −0.05 | ***0.55*** | −0.04 | −0.19 |
| | Pars Triangularis | 0.44 | 0.51 | −0.44 | −0.44 |
| | Lateral Orbitofrontal | 0.08 | ***0.70*** | −0.20 | −0.09 |
| | Medial Orbitofrontal | 0.02 | ***0.56*** | −0.22 | −0.34 |
| | Paracentral | 0.39 | 0.50 | −0.10 | −0.14 |
| | Precentral | ***0.58*** | ***0.61*** | −0.17 | −0.14 |
| Parietal | Superior Parietal | ***0.64*** | ***0.59*** | −0.21 | −0.25 |
| | Inferior Parietal | ***0.57*** | ***0.65*** | −0.23 | −0.32 |
| | Supramarginal | ***0.63*** | ***0.67*** | −0.37 | −0.40 |
| | Postcentral | 0.35 | ***0.54*** | −0.09 | −0.16 |
| | Precuneus | 0.52 | ***0.62*** | −0.34 | −0.35 |
| | Insula | ***0.67*** | ***0.70*** | −0.37 | −0.04 |
| Temporal | Superior Temporal | 0.12 | 0.46 | −0.29 | −0.15 |
| | Middle Temporal | 0.24 | 0.22 | −0.38 | −0.28 |
| | Inferior Temporal | 0.17 | ***0.58*** | −0.10 | −0.26 |
| | Fusiform | ***0.58*** | 0.10 | −0.30 | −0.23 |
| | Transverse Temporal | ***0.71*** | 0.46 | −0.19 | −0.09 |
| Occipital | Lateral Occipital | ***0.55*** | ***0.63*** | −0.17 | −0.26 |
| | Lingual | ***0.57*** | 0.06 | −0.32 | −0.14 |
| | Cuneus | ***0.60*** | ***0.53*** | −0.36 | −0.34 |
| | Pericalcarine | 0.50 | 0.28 | −0.21 | −0.17 |
| Limbic | Para hippocampal Gyrus | 0.40 | 0.50 | 0.07 | −0.10 |
| | Rostral Anterior Cingulate | 0.19 | ***0.53*** | −0.17 | −0.33 |
| | Anterior Cingulate | 0.36 | 0.46 | −0.16 | 0.02 |
| | Isthmus Cingulate | ***0.61*** | 0.26 | −0.39 | ***−0.53*** |
| | Posterior Cingulate | 0.21 | 0.43 | −0.29 | −0.28 |

Heat map (blue = positive; red = negative) displaying Spearman's associations between cortical region-specific FBB uptake with two measures of neurodegeneration – mean diffusivity and cortical thickness (mm). All nominally significant correlations are shown in black typeface and all correlations that survived multiple comparisons correction (FDR < 0.05) are shown in italicized black typeface.

several problems including a reduced ability to thoroughly map the full clusters of cerebral amyloidosis, and a reduced ability to identify correlations between amyloid and cognitive performance levels. Exposures at the WTC are like air pollution exposures, but the chemical mix is potentially unique and may therefore be generalizable to other occupational studies on disaster responses, where buildings are destroyed or burned unexpectedly or because of war conflicts, or also to the impact of climate-induced wildfires.

**Table 3.** Spearman correlations linking measures of whole-brain and regional [$^{18}$F]-Florbetaben uptake with measures of cognition.

| | | Episodic memory | Visual memory | Throughput | Intraindividual variability | Response speed | Processing speed | Visuospatial functioning | Visuospatial memory |
|---|---|---|---|---|---|---|---|---|---|
| Global | Olfactory Amyloid | −0.12 | −0.12 | −0.19 | 0.09 | −0.14 | −0.07 | 0.07 | 0.14 |
| | Olfactory-Adjacent | −0.20 | −0.19 | −0.29 | −0.06 | −0.12 | 0.00 | 0.05 | 0.09 |
| | WTC Regional Amyloid | −0.43 | −0.45 | ***−0.59*** | −0.12 | ***−0.72*** | −0.37 | ***−0.49*** | −0.27 |
| | Centiloid | 0.02 | −0.12 | −0.12 | 0.06 | 0.03 | −0.02 | 0.00 | 0.13 |

WTC Regional Amyloid levels indicate the average standardized uptake value ratio across regions of interest in WTC responder studies. All nominally significant correlations are shown in black typeface, and all correlations that survived multiple comparisons correction (FDR < 0.05) are shown in *bold italics*.

Prior results from this population are consistent with mouse models and other in vivo studies of brain structure in people exposed to high levels of air pollution globally.[3–5,57] We cannot determine whether these results align, since WTC dust contained a potentially unique mixture of neurotoxins, or whether the presence of any PM2.5 at the WTC was amenable to cerebral infiltration was sufficient. While our study included predominantly male subjects, this distribution matches our population as a whole and the makeup of WTC first responders in general. Finally, while the AD pathological cascade is believed to cause cerebral amyloidosis before the distribution of cerebral tauopathy and neurodegeneration, we reported that cerebral amyloidosis was associated with both cognitive dysfunction and indicators of cortical atrophy. Future research is needed to assess the extent to which cerebral tauopathy is evident in this potentially novel condition.

## Conclusions

WTC exposures included severe inhaled exposure to fine particulate matter as well as air pollutants like polycyclic aromatic hydrocarbons and dioxins. In this study, we found that responders who were exposed to the WTC worksites for months and who did not wear personalized protective equipment had a heightened burden of amyloidosis in the olfactory cortex as compared to those individuals with reduced lengths of exposure. Cerebral amyloidosis is concerning because it implies the presence of aging-related amyloidosis at younger ages. Findings imply that exposure to air pollution may be a cause of a novel form of neuropathology in severely and chronically exposed individuals. If true, then efforts to remediate workplace exposures and protect workers might reduce the long-term burden of dementia in the population.

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## Statements and declarations

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The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Gandy is a co-founder of Recuerdo Pharmaceuticals. He has served as a consultant in the past for J&J, Diagenic, and Pfizer, and he currently consults for Cognito Therapeutics, GLG Group, SVB Securities, Guidepoint, Third Bridge, MEDACORP, Altpep, Vigil Neurosciences, and Eisai. He has received research support in the past from Warner-Lambert, Pfizer, Baxter, and Avid. He currently receives research support from the NIH and the Cure Alzheimer's Fund. Dr Franceschi has served as consultant for Biogen, Life Molecular Imaging, Roche/Genentech, and Eisai. Sean Clouston is an Editorial Board Member of this journal but was not involved in the peer-review process of this article nor had access to any information regarding its peer review. The remaining authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### Data availability

The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

## Supplemental material

Supplemental material for this article is available online.

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