Assessment of Alzheimer's Disease Imaging Biomarkers in World Trade Center Responders with Cognitive Impairment at Midlife

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Abstract

Purpose Incidence of early onset neurocognitive dysfunction has been reported in World Trade Center (WTC) responders. Ongoing studies are investigating the underlying etiology, as we are concerned that an underlying risk of neurodegenerative dementia may be occurring because of their stressful and neurotoxic exposures to particulate matter when they responded to the search and rescue efforts on September 11, 2001. The purpose of this study is to report preliminary results from two ongoing positron emission tomography (PET)/magnetic resonance imaging (MRI) imaging studies investigating the presence of Alzheimer's disease (AD) biomarkers, such as β-amyloid, tau, and neurodegeneration, and compare our findings to published norms.

Methods We present findings on 12 WTC responders diagnosed with either cognitive impairment (CI) or mild cognitive impairment (MCI), now at midlife, who underwent PET/MRI brain imaging as part of ongoing studies. Six responders with CI received [^{18}F] florbetaben (FBB) to detect β-amyloidosis and six separate responders with MCI

Keywords
- world trade center responders
- mild cognitive impairment
- PET/MRI
- β-amyloid
- tau
- neurodegeneration

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received [^{18}F] flortaucipir (FTP) to detect tauopathy. All 12 responders underwent concomitant MRI scans for gray matter volume analysis of neurodegeneration.

Results PET analysis revealed 50% FBB and 50% of FTP scans were clinically read as positive and that 50% of FTP scans identified as consistent with Braak's stage I or II. Furthermore, one responder identified as centiloid positive for AD. Gray matter volumes from MRI analyses were compared with age/sex-matched norms (Neuroquant), identifying abnormally low cortical volumes in the occipital and temporal lobes, as well as the inferior temporal gyri and the entorhinal cortex.

Conclusion These preliminary results suggest that WTC responders with neurocognitive dysfunction may be at increased risk for a neurodegenerative dementia process as a result of their exposures at September 11, 2001.

Introduction

The World Trade Center (WTC) responders endured extreme emotional and neurotoxic insults following the terrorist attacks on September 11, 2001. Ongoing work has identified increased incidence of multiple physical and psychiatric diseases such as posttraumatic stress disorder (PTSD) and increased incidence of mild cognitive impairment (MCI).[1] Prior studies investigating the chemical composition of the dust cloud at ground zero revealed that it contained known neurotoxins[2–4] which could potentially have contributed to the observed early-onset MCI through an underlying neurodegenerative dementia pathological process. Indeed, recent evidence has demonstrated that WTC responders display cortical thinning,[5] evidence of Alzheimer's disease (AD) peripheral biomarkers,[6] and that posttraumatic stress disorder (PTSD) among responders may contribute to neurocognitive dysfunction.[7] These observations have raised concerns that a disproportionate number of responders presenting with MCI may develop neurodegenerative cerebral pathology. The nature of this medical uncertainty has prompted investigations into identifying the underlying etiology for the observed risk and to which neurodegenerative dementia subgroup they might subscribe to.

The most common causes of neurodegenerative dementia is AD, whose neuropathological cascade is the common cause of MCI and as is clear in the new research ATN framework,[8,9] is characterized by brain infiltration of two amyloid-β (Aβ) isoforms; $A\beta_{1-42}$, and $A\beta_{1-40}$, leading to Aβ deposition and the formation of two different types of Aβ plaques (dense-core and diffuse plaques [A]), resulting in increased phosphorylation of tau protein and accumulation of neurofibrillary tangles (T), followed by irreversible neurodegeneration (N). Therefore, in our first investigation as to which neurodegenerative dementia subgroup WTC responders with early-onset MCI may subscribe to, we examined PET/MRI markers of ATN as a small case series of 12 responders. The uptake, distribution, and retention of two PET ligands, that is, [^{18}F] florbetaben (FBB) which is used to detect the presence of Aβ amyloid fibrils (A), along with [^{18}F] flortaucipir (FTP) which is used to detect the presence of tauopathy (T), and structural brain MRI which can be used to measure cortical volume and loss of which indicates the presence of cerebral atrophy due to neurodegeneration (N), were employed for the current study. This is the first study to report preliminary data for ATN neuroimaging biomarkers of AD in a small subset of WTC responders presenting with early-onset MCI.

Materials and Methods

Setting and Participants

The Stony Brook University (SBU), together with Centers for Disease Control and Prevention (CDC), has monitored WTC responders since July 2002. Using the Montreal Cognitive Assessment (MoCA) as a cognitive screening tool,[1,10] 12 WTC responders at midlife diagnosed with MCI (MoCA < 23) or CI (MoCA < 20) were recruited into two neuroimaging studies utilizing the same Siemens mMR 3T positron emission tomography (PET)/magnetic resonance imaging (MRI) scanner (Siemens Healthcare, Erlangen, Germany). The MoCA is a widely used measure of cognitive impairment developed to identify age-related CI objectively and reliably.[11] Six responders were recruited at the SBU site for PET FTP tau scans with MCI and six separate responders were recruited at Icahn School of Medicine at Mount Sinai (ISMMS) for PET FBB Aβ scans with CI. All 12 responders underwent the same MRI sequences for determining gray matter volumes. Inclusion criteria were as follows: (1) 45 to 65 years of age; (2) MoCA ≤ 23 within 3 months of scan; (3) body mass index (BMI) $\leq 40\,kg/m^2$. Exclusion criteria were as follows: (1) history of psychosis, (2) drinking/substance abuse, (3) stroke, (4) head trauma, (5) epilepsy, (6) brain tumor, (7) renal failure/dialysis, (8) liver disease/hepatitis, (9) diabetes, (10) major depressive disorder, (11) heart failure, (12) metal implants, (13) claustrophobia, (14) current pregnancy or breastfeeding, (15) current anticoagulant medications, and (16) neurotropic medications (antidepressants, antipsychotics, antiparkinsonian drugs, etc.).

Magnetic Resonance Imaging Acquisition and Cortical Volumes of Interest

The Siemens mMR scanner was used at both sites to acquire structural brain MRI sequences during the PET

scan, for anatomical delineation including dedicated T1-weighted 3D MPRAGE (TR/TE/TI = 1,900/2.5/900 ms, matrix size = 256 × 256, voxel size = 0.87 × 0.87 × 0.87 mm^3). Cortical volumes of interest (VOI's) investigation included frontal and temporal cortices, brain regions typically associated with cognitive domains such as learning, memory, executive functions, and information processing speed[12–16]; limbic system (including the hippocampus, amygdala, parahippocampal regions including the entorhinal cortex), brain regions typically associated with processing and consolidation of traumatic, and stressful memories[17,18]; and the occipital lobes, brain regions typically associated with reexperiencing of traumatic memories through mental imagery, states of depersonalization, and dissociation.[19–21]

Magnetic Resonance Imaging Neurodegeneration Analysis

Quantitative volumetric analysis of cortical gray matter volumes was performed utilizing the T1 MPRAGE scans and NeuroQuant (CorTechs Labs, Inc, San Diego, CA), a Food and Drug Administration (FDA) approved software package for automatic labeling, visualization, and volumetric quantification of structural brain VOI's (as percentage of total intracranial volume) which then compares them to an age- and sex-matched normative cohort, generating a brain atrophy report of the responders' volumetric percentiles as compared with norms.[22] We compiled bilateral volumetric percentile data from the 12 study participants and set the cut-off for identifying VOI neurodegeneration at the 5th percentile for age, as per NeuroQuant guidelines.[23]

Positron Emission Tomography Image Acquisition

Six responders with CI received FBB (5–8 millicurie) and six others with MCI received FTP (3–5 millicurie) followed by a list-mode acquisition during concomitant MRI scans. Sinograms were binned covering a period of 20 minutes starting 90 (FBB) or 80 minutes (FTP) of postinjection according to established protocols.[24,25] Images were reconstructed using ordered subset expectation maximization (OSEM) algorithm with point spread function modeling, six iterations and 21 subsets, and 3-mm full-width half-maximum (FWHM) Gaussian postfiltering. Quantitative corrections included attenuation, scatter, random, detector efficiency, decay, and deadtime. Acquired PET data were scaled to injected dose and body weight to produce standardized uptake value (SUV) images. Attenuation correction was estimated with a "pseudo-CT" approach customized for brain imaging[26] which is based on T1-MPRAGE sequence and accounts for skull attenuation.

Positron Emission Tomography Data Analysis

For each dataset, cortical reconstruction and segmentation of the associated T1-MPRAGE images was performed using FreeSurfer[27] (V.6.0.0) followed by regional parcellation according to the Desikan–Killiany brain atlas. Using the PETSurfer tools within FreeSurfer,[28,29] we extracted the VOI data from the PET images which also allowed for partial volume correction (PVC) of the VOIs using the Symmetric Geometric Transfer Matrix method.

For FBB data, we implemented previously described protocols and cut-offs.[30] We constructed SUV ratios (SUVRs) for four regions (frontal cortex [0.93], lateral temporal cortex [0.93], parietal cortex [0.98], and posterior cingulate cortex [1.10]), as well as 0.96 for a composite SUVR (cSUVR) which was the mean of frontal, occipital, parietal, lateral temporal, anterior, and posterior cingulate cortex SUVRs. PVC was not used for these SUVRs, whole cerebellum was the reference region, and their published cut-offs for AD were used.[30] Finally, we performed centiloid (CL) analysis of FBB data in which we used PMOD software (PMOD Technologies, Zurich, Switzerland) instead of FreeSurfer and followed the protocol for this tracer to calculate a CL value for each responder where CL values can fall on a 0 to 100 scale and where a CL value of over 25 can be used as a cut-off for AD.[31] Briefly, the CL method provides a universal scaling metric that can account for differences involving quantitative values obtained from using different tracers for Aβ, thus permitting for the integration and interpretation of various clinical and research studies with a standard measurement. The calculation to derive CL in this study was performed as previously described[31] with the following formula: $153.4 \times SUVR_{FBB} - 154.9$.

For FTP data, we implemented previously described protocols and cut-offs[25] in which the cSUVR was defined as the mean of entorhinal cortex, amygdala, lateral occipital cortex, and inferior temporal gyrus, and used the established cut-off of 1.22 to identify preclinical AD. Per that protocol, PVC data were used, and cerebellar cortex was the reference region. We also estimated Braak's staging of the FTP data (PVC used and cerebellar cortex as reference) as previously described.[32] Briefly, Braak's staging is classified as the buildup of neurofibrillary tangles with neurodegeneration in stages I and II (transentorhinal region), stages III and IV (limbic regions, including the hippocampus), and stages V and VI (neocortex). We classified each responder into Braak's staging by calculating the volume-weighted average *Z*-score of the composite regions corresponding to each image-based tau stage, with values greater than 2.5 considered as positive in each respective stage.

Visual Image Interpretation and Qualitative Assessment

Image interpretation was conducted by a fellowship-trained, board-certified neuroradiologist with dedicated PET/MRI training and 8 years clinical and research experience in the field. The neuroradiologist reader interpreted the brain MRI and FBB or FTP PET images independently, followed by adjudication of PET images with a board-certified nuclear medicine physician with 25 years of clinical and research experience in brain PET imaging. Qualitative assessment for scan positivity was visually assessed following post-processing with MIMneuro (V.6.9.5; MIM Software, Inc. Cleveland, Ohio, United States).

Statistical Methods

Means with standard deviations (SDs) across responders were calculated. Box and whisker plots depict median and

interquartile ranges (IQR) for VOI's as volumetric percentiles with a 5th percentile cut-off line representing neurodegeneration. Box and whisker plots depict median and interquartile ranges (IQR) for VOI FBB and FTP SUVR activity. Analyses were performed in GraphPad Prism [V.9] GraphPad Software, San Diego, California, United States).

Results

Participants

Twelve WTC responders' mean age was 54.9 (±5.4) years, mean education was 14.4 (±1.8) years, mean BMI was 30.3 (±4.0) kg/m^2, 75% were male, mean MoCA was 18.9 (±2.4), and they were tested between March 2018 and April 2019 as part of a larger parent study conducted jointly by SBU and ISMMS. Their occupations during WTC search and rescue efforts included New York Police Department (NYPD), mechanics, technicians, private business owners, and construction specialists.

Magnetic Resonance Imaging

MRI volumetric analyses with NeuroQuant age- and sex-matched normative parcellation displayed composite mean gray matter volumetric percentiles for the occipital, temporal, inferior temporal, and entorhinal cortices and temporal pole that were below the 5th percentile, as shown in ►**Fig. 1**. Specifically, the percentage of 12 responders displaying regional volumes below the 5th percentile was as follows: 50% frontal lobe, 92% temporal lobe, 67% temporal pole, 75% entorhinal cortex, and 92% inferior temporal cortex. The hippocampus displayed the least volumetric reduction across these 12 cases.

Florbetaben Positron Emission Tomography

Out of the six WTC responders with CI who received the FBB tracer during their PET/MRI scan, three responders displayed visually excess FBB activity on qualitative assessment. Quantification of FBB SUVRs revealed that among the three responders visually assessed as positive, one had a positive CL value, with cSUVR and individual SUVR positivity (i.e., above published threshold[30]) in all four VOIs (frontal cortex, lateral temporal cortex, parietal cortex, and posterior cingulate cortex). The remaining two responders who were visually assessed as positive had below cut-off CL values and cSUVRs, except for one responder who displayed above cut-off SUVR in the frontal cortex. The three responders qualitatively read as negative were quantitatively below cut-offs, except for one responder who quantified above SUVR cut-off in the posterior cingulate cortex and another responder who quantified above SUVR cut-off for the lateral temporal cortex. Combined FBB SUVR activity for each VOI is shown in ►**Fig. 2**.

Flortaucipir Positron Emission Tomography

Six separate WTC responders with MCI received the FTP tracer during their PET/MRI scan and three responders displayed visually excess FTP retention on qualitative assessment. Quantification of FTP SUVRs revealed two out of the three responders visually assessed as positive with above cutoff cSUVRs with the third slightly subthreshold at 1.21. Of the three responders qualitatively read as negative, one responder displayed a positive cSUVR. Combined FTP SUVR activity for each VOI is shown in ►**Fig. 3**. In addition, an example of a qualitatively assessed positive and negative PET/MRI FTP scan is shown in ►**Fig. 4**.

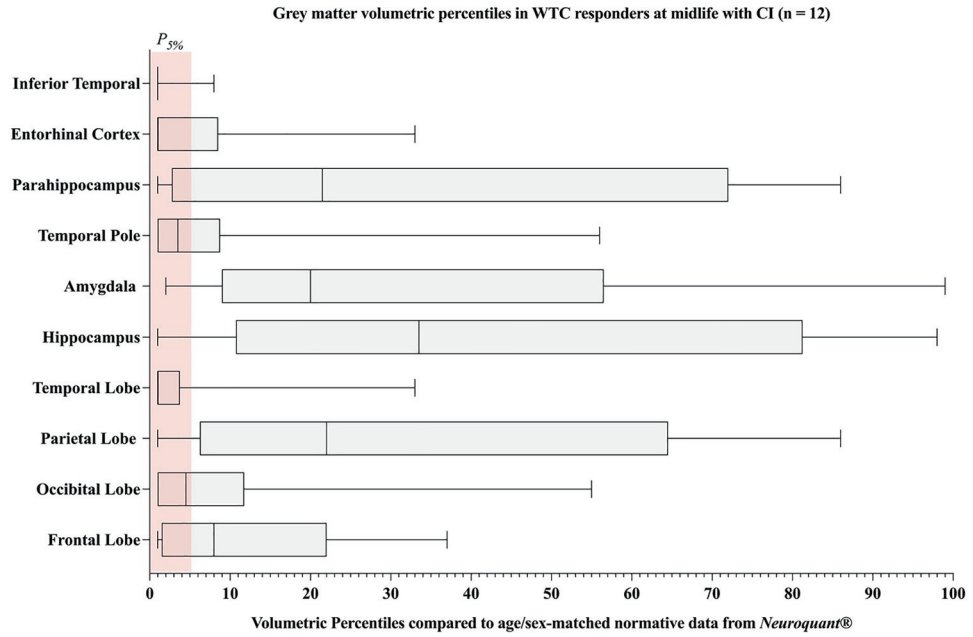

Fig. 1 Box and whisker plot showing age/sex/cranial volume-matched percentiles against a normative cohort (NeuroQuant) in each cortical volume regions of interest (VOI) for 12 World Trade Center (WTC) responders with cognitive impairment (CI). Cut-offs for neurodegeneration at the 5th percentile are indicated by a red shaded area.

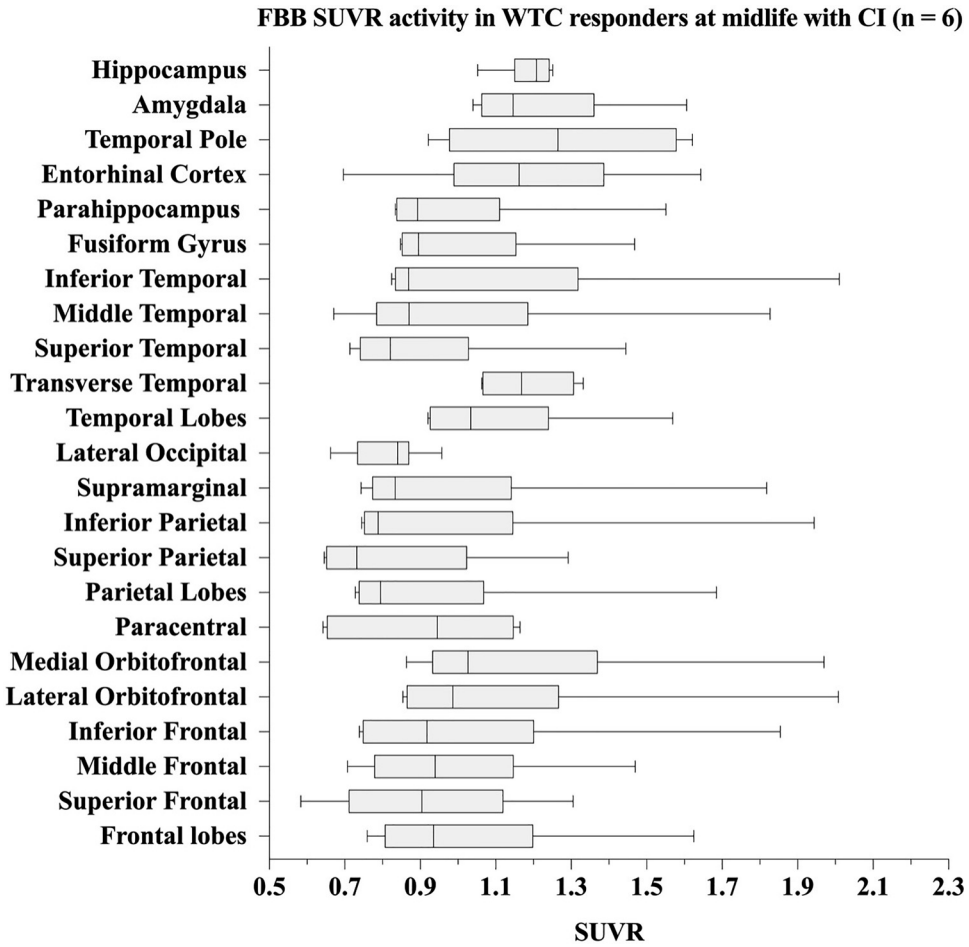

Fig. 2 Box and whiskers plot showing standard uptake volume ratio (SUVR) retention for (^{18}F)-florbetaben (FBB) for each cortical volume of interest (VOI) in six WTC responders with mild cognitive impairment at midlife. WTC, World Trade Center.

Results from the above analyses in all 12 responders are summarized in ►**Table 1**.

Discussion

WTC responders are presenting with early-onset neurocognitive dysfunction with an undetermined etiology. To address this, our first investigations utilized a simultaneous PET/MRI brain scan, employing PET tracers for either Aβ-type cerebral amyloidosis (FBB) or tauopathy (FTP) and MRI for gray matter volume analysis of neurodegeneration to examine evidence for ATN biomarkers of AD in a small sample of WTC responders presenting with CI, since AD is the most common neurodegenerative dementia.

Analyzing MRI data in these 12 WTC responders and matching it to age- and sex-matched normative data revealed lower gray matter volumes across many cortical regions. Specifically, neurodegeneration was evident in the temporal lobe, entorhinal cortex, and inferior temporal gyrus regions that are essential to memory formation and recall.[12] In addition, half of these 12 WTC responders had frontal lobe volumes below the 5th percentile which is a cortical area affected in advanced AD and functionally involved in cognitive executive functions and information processing speed.[9] However, we observed the least neurodegeneration in the hippocampus, a feature that may have implications for clinical prognosis. A relatively unusual hippocampal-sparing form of AD has been reported to occur at a younger age which may apply to WTC responders now at midlife presenting with early-onset MCI or CI, as this early-onset form of AD is marked by a more pronounced longitudinal cognitive decline and a shorter disease duration as well as earlier mortality.[33–35] Moreover, half of these 12 WTC responders displayed neurodegeneration and high FTP retention in the occipital lobe which has been associated with visual hallucinations in AD as a result of atrophy[36] and is a region typically affected in advanced AD.[37] The occipital lobes and/or occipitoparietal border zones are involved in posterior cortical atrophy,[38] as well as in PTSD patients,[39] the latter possibly related to recurring visual "flashbacks" of mental imagery from chronically reexperiencing traumatic events[19–21,40] which may pertain to those experienced by WTC responders at September 11, 2001. Recent evidence has linked such PTSD states with underlying neuroinflammation,[41,42] leading to subsequent neurodegeneration,[36,37,39,43,44] thereby warranting a closer investigation and monitoring of WTC responder PTSD symptomatology as a possible contributor to the observed neurocognitive dysfunction which was recently suggested in one of our studies.[7]

Our preliminary PET results using quantitative and qualitative approaches identified three WTC responders with

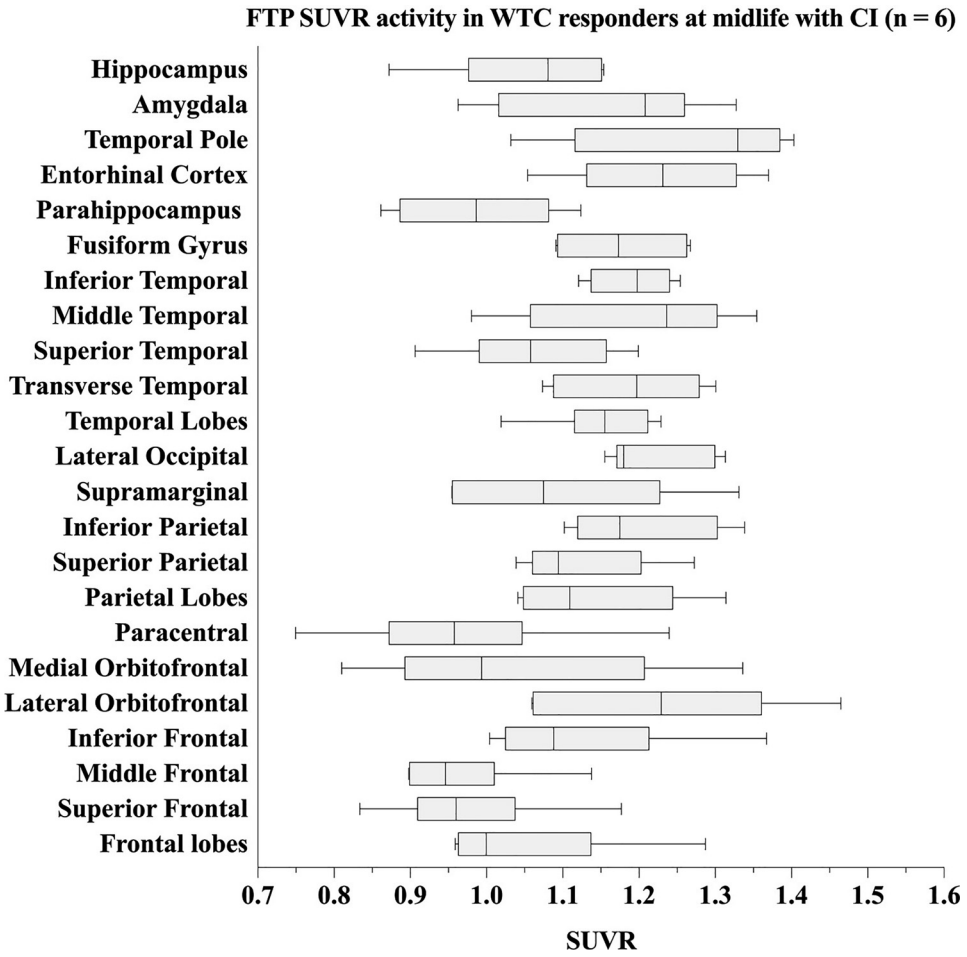

Fig. 3 Box and whiskers plot showing standard uptake volume ratio (SUVR) retention for (^{18}F)-flortaucipir (FTP) for each cortical volume of interest (VOI) in six WTC responders with mild cognitive impairment at midlife. WTC, World Trade Center.

excess FBB retention, supportive of the possible presence of Aβ-type cerebral amyloidosis of which one responder had an abnormal CL in addition to an abnormal qualitative read suggestive of AD neuropathology. However, we also discovered multiple occurrences of excess FBB SUVR activity in regions outside of that used in the AD CL calculation, suggesting that the neuropathological etiology of the observed cognitive decline in WTC population may not necessarily subscribe to AD. In addition, the observed volumetric hippocampal sparing among these 12 WTC responders with neurocognitive dysfunction suggests the possibility that they may subscribe to a non-AD neurodegenerative dementia subgroup. Moreover, qualitative and quantitative analyses of the six FTP scans with responders presenting with MCI revealed three scans visually read as positive of which two had above cut-off cSUVR and met criteria for early Braak's stages I and II. Another responder who was visually read as negative displayed above cut-off cSUVR and met criteria for Braak's stages I and II tauopathy. While there was more evidence of A instead of T in all 12 responders, we surmise that this may simply reflect the early stages of the ATN cascade, as A can precede T before leading to N, thereby urging the need for follow-ups with responders with CI who demonstrated higher FBB activity.

These results are preliminary and while suggestive of an underlying neuropathological etiology for the observed early-onset neurocognitive dysfunction observed in WTC responders, they nevertheless highlight the importance for continuing investigations of this phenomenon. WTC responders are presenting with an alarming incidence of neurocognitive and neurobehavioral dysfunction and our group is actively working on identifying which neurodegenerative dementia subgroup, they subscribe to or if we are faced with a unique and emerging WTC-specific neurodegenerative dementia because of their unique exposures. This study represents our first PET modality investigation for the most common neurodegenerative dementia subgroup that is AD. Though there is evidence that one WTC responder with CI may subscribe to AD with an above threshold CL value, along with half of the other responders in this study at varying levels of risk for AD, the MRI data from this study, along with a cortical thickness study previously reporting cortical thinning in WTC responders,[5] strongly support ongoing and future investigations of the neurobiological etiology underlying WTC-related neurocognitive dysfunction.

Limitations

While being a pivotal study indicating the need for larger replication efforts, this study has limitations. First and foremost, this study was limited by the small sample size

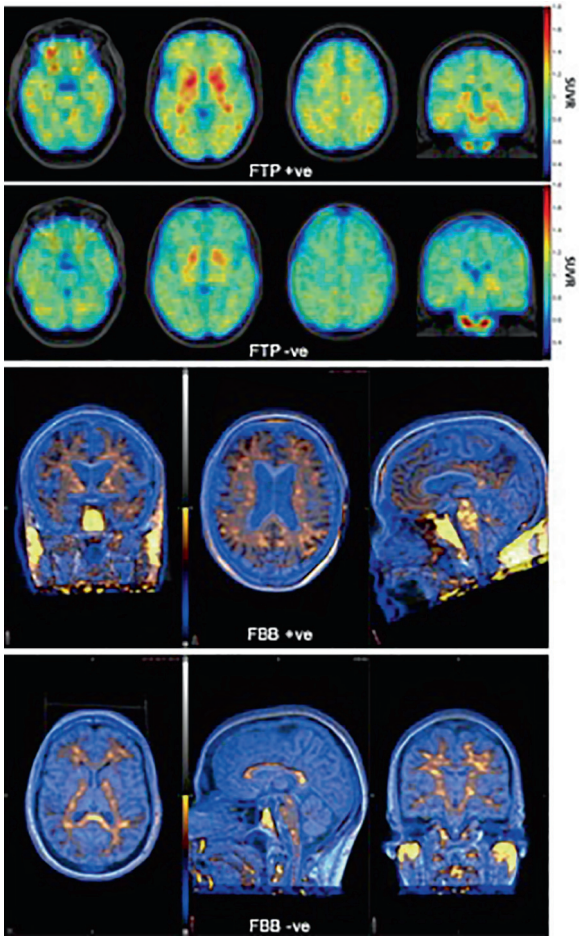

Fig. 4 Standard PET/MRI images showing axial and coronal cortical distribution of: (^{18}F) flortaucipir (FTP) in two World Trade Center (WTC) responder with MCI (first panel shows FTP positive responder and second panel shows FTP negative responder; (^{18}F) florbetaben (FBB) in two WTC responders with MCI (third panel shows FBB positive responder and fourth panel shows FBB negative responder). MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

and lack of cognitively intact case controls. Instead, we relied on MRI age- and sex-matched normative data and published PET cut-offs for FBB and FTP and CL scores, as these are well-validated quantitative methodologies to inform our conclusions. Furthermore, the small sample size meant that we were unable to examine potential explanations and/or correlates from the PET/MRI data with neurocognitive, neurobehavioral, and neuromotor variables which we collected at the WTC Health and Wellness Program and at research participant screening sessions. Moreover, since data on both FBB and FTP PET radiotracers were not available across the same 12 responders presented in this study, it was not possible to compare FBB and FTP retention and MRI gray matter volumes within patients to further probe the ATN model of AD. Finally, we have no postmortem neuropathology on any WTC responders with MCI, and clinicopathological correlations will be key to defining the molecular and cellular underpinnings and to identify membership to a potential neurodegenerative dementia subgroup.

Conclusion

Taken together, PET/MRI assessment of 12 WTC responders with neurocognitive dysfunction suggests that there is evidence for neurodegeneration across cortical regions. All 12 WTC responders in this study exhibited neurodegeneration in cortical regions related to AD, and half of the responders exhibited evidence for abnormal cortical aggregation of AD biomarkers. Future cross-sectional and longitudinal imaging studies performing concurrent PET/MRI assessments of both Aβ and tau in the same responder are needed to further the feasibility of the ATN model in WTC responders experiencing neurocognitive dysfunction. Future studies investigating cerebrospinal and plasma biomarkers of AD or ADRD are warranted, as are detailed quantitative postmortem examinations from potential brain donors. Identifying which neurodegenerative dementia subgroup WTC responders

Table 1 Summary table of findings from six WTC responders receiving FBB and six separate WTC responders with receiving FTP

Characteristic	FBB_1	FBB_2	FBB_3	FBB_4	FBB_5	FBB_6	FTP_1	FTP_2	FTP_3	FTP_4	FTP_5	FTP_6
Age (y)	50	52	53	64	62	46	53	57	50	55	56	61
MoCA (out of 30)	18	17	15	15	20	18	21	21	21	21	22	18
PTSD status	−	−	−	−	+	−	−	−	−	+	−	−
WTC exposure duration (d)	11	> 30	288	148	289	94	28	1	19	92	168	155
Family history of dementia/CI	−	−	−	+	−	−	−	−	+	−	+	−
Qualitative/clinical read	+	−	+	+	−	−	+	+	−	+	−	−
Whole brain $SUVR_{FBB}/SUVR_{FTP}$	0.97	1.04	0.95	1.29	1.02	0.96	1.24	1.1	1.22	1.2	1.26	1.21
$cSUVR_{FBB}$ (0.96)/ $cSUVR_{FTP}$ (1.22)	0.87	0.92	0.93	1.1	0.93	0.87	1.23	1.08	1.22	1.23	1.26	1.18
CL/Braak's stage	−6.5	4.1	−8.6	42.7	2	−7.8	I and II	−	I and II	−	I and II	−
Neuroquant ROIs < 5th percentile	6	6	22	31	43	14	34	10	15	31	26	23

Abbreviations: CI, cognitive impairment; CL, centiloid; cSUVR, composite standardized uptake value ratio; FBB, florbetaben; FTP, flortaucipir; MoCA, Montreal Cognitive Assessment; ROI, region of interest; PTSD, posttraumatic stress disorder; WTC, World Trade Center.

subscribe to or are at risk of as a result of their exposures at September 11, 2001, will be key in informing policy makers and their future efforts to develop appropriate clinical and patient care interventions.

Ethics

The Institutional Review Board (IRB) of each institution (no.: 983492; no.: 1257148) approved the study protocol which included informed consent.

Data Availability

Data can be made available upon reasonable request to the corresponding author.

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Conflict of Interest

The authors have no disclosures to report.

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