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Behavioral Impairments and Increased Risk of Cortical Atrophy Risk Scores Among World Trade Center Responders

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Abstract

Objective: World Trade Center (WTC) responders are susceptible to both cognitive and neuropsychiatric impairments, particularly chronic posttraumatic stress disorder. The present study examined self-reported behavioral impairments in a sample of 732 WTC responders, 199 of whom were determined to have high risk of WTC-related cortical atrophy by an artificial neural network. **Results:** We found that responders at increased risk of cortical atrophy showed behavioral impairment across five domains: motivation, mood, disinhibition, empathy, and psychosis (14.6% vs 3.9% in the low-risk group; $P = 3.90 \times 10^{-7}$). Factor analysis models revealed that responders at high risk of cortical atrophy tended to have deficits generalized across all aspects of behavioral impairment with focal dysfunction in sensory psychosis. We additionally describe how relationships are modulated by exposure severity and pharmacological treatments. **Discussion:** Our findings suggest a potential link between sensory deficits and the development of cortical atrophy in WTC responders and may indicate symptoms consistent with a clinical portrait of parietal dominant Alzheimer's disease or a related dementia (ADRD). Results underscore the importance of investigating neuropsychiatric symptomatology in clinical evaluations of possible ADRD.

Keywords

mild behavioral impairment, neuropsychiatric symptoms, cortical atrophy, world trade center, Alzheimer's disease and related dementias

Alzheimer's disease and related dementias (AD/ADRD) are important public health issues. Consequently, researchers have focused on identifying appropriate measures for prevention, early identification, and treatment. One impediment to developing treatments for ADRD is accurately defining and characterizing disease onset.[1,2] A promising approach involves examining the risk of mild cognitive impairment (MCI) and dementia in the context of general brain and psychiatric health.[1,3] A large body of evidence suggests that neuropsychiatric symptoms and behavioral impairments are correlated with MCI, precede the development of dementia,[4-12] and increase the risk of progressing along the dementia continuum.[7,11] Further, recent evidence suggests that the severity of neuropsychiatric symptomatology is correlated with an earlier onset diagnosis of ADRD.[13] Thus because the promotion of both brain and behavioral health are likely to be important for potential monitoring, prevention, and amelioration of cognitive

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decline,[14,15] comprehensively assessing behavioral impairments indicative of neuropsychiatric symptomatology in patient populations is a promising approach to refine the assessment and treatment of MCI.

Previous studies have found that World Trade Center (WTC) responders are notably susceptible to both psychiatric disorders[16] and to MCI of unknown etiology.[17] Given the complex, disastrous, and traumatic circumstances that WTC responders faced, many have since developed chronic post-traumatic stress disorder (PTSD).[18,19] Moreover, with the damage and debris produced by the collapse of the WTC towers, this population was exposed to fine particulate matter that infiltrated the respiratory and central nervous systems to negatively impact neuronal function.[20,21] The severity of these exposures may be implicated in the development of a unique condition or a rare form of ADRD called parietal dominant AD.[20,22,23] For example, a recent imaging study that utilized parietal cortical coordinates from the Montreal Neurological Institute[22] found that WTC responders with early onset dementia exhibit profuse cortical atrophy compared to cognitively unimpaired responders, with focal atrophy evident within the parietal cortex. Although this finding revealed potential anatomical markers of dementia in WTC responders, this atypical dementia subtype has rarely been characterized in clinical populations.[24] Thus, the significance of ADRD in WTC responders remains unclear. Moreover, research on the association between PTSD and parietal dominant ADRD is relatively scarce, and the role of behavioral impairments in this population remains unknown.

Neurodegeneration in WTC responders does not fit a pattern consistent with known ADRD.[25,26] Noting that, we previously improved our cognitive profiling efforts by applying a deep learning approach to data from neuroimaging[27] and cognitive impairment diagnoses to estimate the risk of cortical atrophy for WTC responders.[28] This classification algorithm allows researchers to study and monitoring the potential progression of WTC-related neurodegenerative disease in this population using the results of cognitive testing when lacking intrusive and expensive methods such as structural neuroimaging and molecular diagnosis. Based on these classifications, we tested whether cortical atrophy risk is associated with behavioral impairments indicative of psychiatric disorders in a cohort of WTC responders. Specifically, we created a self-report version of the Mild Behavioral Impairment (MBI) checklist, an assessment that past studies have found to be associated with clinical and molecular features of ADRD.[29-35] We hypothesized that high cortical atrophy risk, as classified by our previously developed ANN,[28] would be associated with self-reported behavioral impairment in various domains.

To test these hypotheses we examined the factor structure of the self-report version of the MBI. We then investigated whether cortical atrodphy risk was associated with behavioral impairments, including psychotic symptoms related to sensory dysfunctions, which are key characteristics of parietal-dominant cortical atrophy.[36-39] Lastly, we examined the contributions of potential explanatory factors (WTC exposure severity; medication and psychiatric status; demographic factors) to the association between high cortical atrophy risk and behavioral impairments.

Methods

Setting

The present investigation was conducted at Stony Brook University's WTC monitoring program, which has monitored the health and well-being of responders since 2002. Enrollment is voluntary, and annual monitoring is offered. WTC responders are mostly male, and currently or formerly in law enforcement. Their average age was 39 years in 2001 when the disaster happened. The Stony Brook University site primarily monitors WTC responders from Long Island, New York. Stony Brook University's IRB provides annual approval for local research. Participants provide written informed consent before participation.

Design

The sample included WTC responders who completed cognitive testing in 2018-2019 and later completed the Mild Behavioral Impairment checklist (SB-MBI-SR). Previously,[25] we analyzed results from the same cognitive tests along with neuroimaging data in a different sample of 99 WTC responders. Briefly, we used a four-layer artificial neural network (ANN) to estimate high vs low cortical atrophy risk (HCAR vs LCAR) from the cognitive test results,[25] as described below. The ANN underwent two rounds of classification validation, trained using neuropsychological testing, neuroimaging, and mild cognitive impairment diagnoses as inputs to predict cortical atrophy based on neuropsychological testing. The ANN was then applied to the neuropsychological testing results from the present sample of 732 responders who also had self-reported information on behavioral impairments, in the absence of clinical cognitive impairment diagnosis or neuroimaging results. This generated a binary classification of WTC responders with those having high or low atrophy risk.

Measures

Behavioral Impairments. Responders completed the Mild Behavioral Impairment checklist tailored as a self-report measure for use in the Stony Brook University WTC

Monitoring Program (SB-MBI-SR).[40] The MBI was developed as a case ascertainment instrument to capture mild behavioral impairment, an at-risk state for incident cognitive decline and dementia. The scale was designed for administration in dementia-free, functionally independent, community-dwelling older adults.[41] An emerging body of literature has linked the MBI with incident cognitive decline and dementia,[42-44] as well as AD genes and biomarkers of amyloid, tau, and neurodegeneration.[29-35] For the present study, a single administration of the SBU-MBI-SR was given to responders. Appendix A contains the 30 items that comprise the SB-MBI-SR, which were rated on a Likert scale from 1 (strongly disagree) to 5 (strongly agree). Based on the established coding scheme, mean cluster scores (i.e., subscales) were calculated from items measuring impairments related to motivation, mood, disinhibition, empathy, and psychosis. The modal response for all items was "strongly disagree". Therefore, we also recoded ordinal scores to binary responses, where individuals either disagreed (≤4) or agreed (>3) with the item.

Cortical Atrophy Risk. Cognitive functioning was measured with the CogState Brief battery as previously described.[28] Briefly, responders were given a computer-based battery of cognitive tests that measure fluid cognition in a game-like format. The measured domains included reaction speed (detection task; "Has this card flipped?"), processing speed (identification task, "Is this card orange?"), intra-item variability (within-person variability), attention (measured as a function transformation of correct responses per task completed), visual memory (1 card learning task; "Have you seen this card previously?"), and throughput (1 card learning task, measured as accuracy and speed). While informative on their own, these measured domains are non-diagnostic. To improve our prediction of neuroimaging results we, therefore, trained a deep-learning algorithm to classify individuals based on their cognitive scores. After training, the algorithm provided a method to use a generated cutoff to determine high or low atrophy risk classifications based on neuropsychological testing results.[28] The accuracy of binary classification (high cortical atrophy risk vs low cortical atrophy risk) was determined by using area under the receiver operating curve (AUC). The ANN was trained with a subsample of WTC responders who completed a neuroimaging protocol, using neuropsychological testing to predict the presence of cortical atrophy consistent with a WTC neuroimaging signature. Subsequently, the ANN underwent another round of training with a subsample of WTC responders using neuropsychological testing to predict cortical atrophy, as well as mild cognitive impairment. The resultant ANN had strong predictive power (AUC, .87; 95% CI, .70-1.00). Because the WTC-HAR responders followed a bimodal distribution, we used Youden's method to determine cutoffs post-validation. The final analysis was applied to the present sample of 732 responders; n = 199 (27.2%) were grouped as high risk for atrophy and n = 533 (72.8%) as low risk. We then compared these two sample groups on domains of behavioral measures as described below.

Additional Risk Factors. Four sets of risk factors were included: (1) WTC exposure duration, previously found to be a risk factor for neurodegenerative disease and cognitive symptoms,[18] was operationalized as the number of weeks working on-site at the WTC. (2) Medical status indicators derived from medical records included medications (antihistamines, anti-vertigo medications, atypical antidepressants, benzodiazepines, BRA, β-blockers, H2 receptor antagonist, opioids, proton pump inhibitors, serotonin and norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, antipsychotics, spinal muscle, relaxant, statins, and tricyclic antidepressants), psychiatric diagnoses (depression, PTSD, anxiety disorder, substance use disorder, and adjustment disorder), and PTSD symptom severity measured using the PTSD checklist from the DSM-IV (PCL-17) modified for the WTC events.[45] Symptoms were rated on a scale of 1 to 5, and sum scores were calculated for individuals who answered at least 60% of the 17 items (score range 17-85). (3) Occupational, service-related, and chemical exposures were self-reported by responders (eg, working on the pile of debris, torch cutting, working with concrete, encountering human remains, blood, mold, fumes, sewage, etc.; See Appendix Tables S5 and S6). Finally, (4) age in years, sex, and race/ethnicity (White, black, Hispanic, or other) were self-reported by responders.

Data Availability

Medical diagnoses and dates of diagnosis are private health information. Therefore, partial access to deidentified data is available from the corresponding author upon reasonable written request.

Statistical Analyses

Analyses were conducted in several steps. First, we examined the psychometric properties of the SB-MBI-SR by calculating measures of internal consistency and general factor saturation for total and subscale scores, including Cronbach's alpha (α), omega hierarchical (ω_H), omega asymptotic (ω_A), omega total (ω_T), and explained common variance (ECV). Second, we determined whether the subscales reported for the community

sample corresponded to those observed in WTC responders. Specifically, a confirmatory factor analysis (CFA) model was estimated using maximum likelihood with robust standard errors and again using diagonally weighted least squares in the Lavaan package in R.[43] In the CFA model, simple structure was assumed; factor variances were fixed to 1, each item loaded onto only 1 factor, residual variances were freely estimated and assumed to be independent, and latent factors were allowed to correlate. Model fit was evaluated using model χ^2, root mean squared error of approximation (RMSEA), and comparative fit index (CFI).

Third, we examine differences in SB-MBI-SR item, total, and subdomain scores between the high and low atrophy risk groups, with tests of proportions for dichotomous items scores and Welch's t-tests for continuous total and subdomain scores. A two-tailed $\alpha = .05$ was used to determine statistical significance. Bivariate odds ratios (OR) and multivariable-adjusted odds ratios were then estimated with log-binomial models, and again with ordinal logistic models as a sensitivity analysis.[46] In all cases, the proportional odds assumption was upheld. Because results that were statistically significant in log-binomial models were upheld in ordinal logistic models, we report results from log-binomial models. In factor analyses, the derived factor scores were gamma distributed. Consequently, we used Mann-Whitney rank-sum tests for bivariate analyses of empirically derived subdomains across high and low cortical atrophy risk. Multivariable-adjusted analyses of factor scores were based on generalized linear models with a gamma distributional family and a logarithmic link function. Inferential analyses were performed in Stata 17/MP (StataCorp).

Finally, to investigate whether associations between cortical atrophy risk and mild behavioral impairments varied for responders across exposure severity, psychiatric treatments and diagnoses, and demographic characteristics, we calculated stratified Welch's t-tests comparing differences in behavioral domains across high and low cortical atrophy risk.

Results

Internal Consistency and Factor Analysis

Measures of internal consistency and general factor saturation are reported in Table 1. Cronbach's α for the SB-MBI-SR subscales and total scores met conventional standards for high internal consistency (range of α = .80-.98) but greater variation was observed for omega coefficients (range = .68-.98). Moreover, ECV, ω hierarchical, and ω total provided evidence for moderate-to-high general factor saturation. For example, approximately 84% of the variance in SB-MBI-SR total scores was accounted for by a general factor, whereas 14% was accounted for by multidimensionality, and only 2% was due to unsystematic measurement error. These results suggest higher general factor saturation for SB-MBI-SR items in the WTC responder population than might be expected based on the established coding scheme.

Baseline Characteristics and Behavioral Associations

In Table 2, the clinical and demographic characteristics of both HCAR and LCAR groups are reported (for the greater WTC population, see Appendix Table S8). The participants were mostly men (92.3%). Consistent with our initial analysis, the HCAR group was older than the LCAR group and exhibited lower cognitive performance and greater PTSD symptom severity. Based on the 4 clusters derived from the factor analysis of SB-MBI-SR, Mann-Whitney tests revealed higher overall behavioral dysregulation ($P = .005$) in the HCAR group (Mean = 1.49 ± .57) compared to the LCAR group (mean = 1.36 ± .43), and more sensory impairments ($P < .001$) in the HCAR group (mean = 1.16 ± .445) compared to LCAR group (mean = 1.00 ± .35). However, we did not identify statistically significant differences in the factors indicated by disinhibitory and erratic behavioral impairments ($P > .05$). Moreover, we found that the sensory domain was the only factor significantly impacted by HCAR after controlling for age, sex, race/

Table 1. Indices of Internal Consistency and General Factor Saturation for the Mild Behavioral Impairment Self-Report Checklist Tailored for Use in the Stony Brook University World Trade Center Health Monitoring Program.

Index	Total score	Motivation	Mood	Disinhibition	Empathy	Psychosis
Cronbach's α	.98	.95	.93	.95	.92	.80
Hierarchical (ω_H)	.84	.93	.87	.82	.85	.68
Asymptotic (ω_A)	.85	.95	.91	.85	.89	.77
Total (ω_T)	.98	.97	.96	.96	.96	.88
ECV	.75	.88	.80	.75	.75	.66

Note: α = alpha. Ω = omega. ECV = explained common variance (the eigen value for the general factor divided by the sum of all eigen values).

ethnicity, WTC exposure severity, and PTSD status (see Table 3), such that the sensory domain score was greater in the HCAR group when compared to the LCAR group.

Differences for SB-MBI-SR items across high and low atrophy risk groups are reported in Appendix Table S3. Based on the established coding scheme for the MBI-C, multivariable-adjusted odds ratios for reporting impairments (score ≥ 3) in each behavioral cluster for responders at high risk of cortical atrophy are reported in Figure 1 (and Appendix Table S4). Notably, the scoring schemes based on the original MBI-C subscales and the factor analysis produced reasonably similar results, both providing evidence for higher behavioral impairments in the high-risk group generalized across behavioral clusters but with particularly pronounced differences found for sensory-related deficits related to psychosis. For example, at the item-level, odds ratios were especially large for "hear voices" and "see things that are not there". See supplemental material for more details.

Additional Risk Factors

We next tested whether associations between high cortical atrophy risk and behavioral impairments varied across

Table 2. Sample Characteristics of WTC Responders, Stratified by High and How Atrophy Risk.

	Sample (n = 732)		Low atrophy risk (n = 533)		High atrophy risk (n = 199)		
Sample characteristics	Mean	SD	Mean	SD	Mean	SD	P
Age, years	54.16	8.10	52.88	7.69	57.61	8.18	<.001
Female sex	6.15		6.57		5.03		.440
Race/Ethnicity							
White	87.02		86.87		87.44		.965
Black	3.69		3.75		3.52		
Hispanic	5.60		5.82		5.03		
Other	3.69		3.56		4.02		
Computerized cognition	.00	.68	.26	.50	-.68	.63	<.001
Memory	.99	.09	1.01	.08	.93	.09	<.001
Throughput	.33	.03	.34	.03	.30	.03	<.001
Attention	1.41	.15	1.42	.14	1.38	.18	.011
Response speed	.08	.01	.08	.01	.07	.01	<.001
Processing speed	.07	.01	.07	.00	.06	.01	<.001
Intraindividual variability	.13	.02	.13	.02	.12	.03	<.001
Pencil-paper cognition							
Episodic memory	13.06	1.69	13.24	13.24	12.58	1.84	4.00.001
Verbal fluency	13.30	4.59	13.54	13.54	12.65	4.73	.026
Orientation	5.93	.31	5.95	5.95	5.87	.44	.018
Executive function	2.90	.32	2.91	2.91	2.88	.34	.420
Numeracy	4.21	1.14	4.29	4.29	3.98	1.29	.003
Visuospatial functioning	3.58	1.22	3.68	3.68	3.33	1.22	.001
Attention	2.78	.45	2.81	2.81	2.70	.55	.010
Language	1.42	.70	1.44	1.44	1.38	.73	.306
Abstraction	1.73	.50	1.73	1.73	1.71	.51	.580
WTC-related factors							
Weeks on-site	3.19	5.63	3.23	5.63	3.09	5.66	.293
Ln-duration risk score	2.10	.81	2.12	.78	2.02	.88	.132
Activity risk score	.14	.33	.12	.31	.18	.36	.038
PTSD symptoms	28.29	12.95	27.63	12.56	30.08	13.82	<.001
Re-experiencing symptoms	8.14	3.97	7.81	3.68	9.02	4.55	<.001
Avoidance symptoms	3.66	2.25	3.47	2.09	4.17	2.56	.015
Numbing symptoms	7.92	4.17	7.53	3.79	8.97	4.90	<.001
Hyperarousal symptoms	9.52	5.00	9.01	4.61	10.91	5.68	<.001

Note: *P*-values were derived from Welch's t-tests for continuous variables and tests of proportions for categorical variables. WTC: World Trade Center; Ln-Duration: natural logarithm transformation of weeks working at the WTC. Percentages are reported for biological sex and race/ethnicity.

Table 3. Means, Standard Deviations, and Multivariable Associations Between Atrophy Risk and Empirically Derived Factors of Behavioral Impairments Based on the Preferred Four-Factor Model.

	Sample with complete data (n = 703)		Low atrophy risk (N = 516)		High atrophy risk (N = 187)		Multivariable-adjusted gamma regression		
Behavioral factor	Mean	SD	Mean	SD	Mean	SD	β	SE	P
Generalized impairment	1.40	.48	1.36	.43	1.49	.57	.000	.022	.998
Disinhibition	1.57	.41	1.55	.39	1.61	.45	.010	.023	.669
Erratic behavior	2.02	.47	2.01	.45	2.05	.53	-.001	.019	.945
Sensory	1.04	.39	1.00	.35	1.16	.45	.138	.031	<.001

Note: SD = standard deviation; SE = standard error; β = prediction of behavioral factor by high atrophy risk derived from a multivariable-adjusted generalized linear model with a gamma distribution. In addition to atrophy risk, the gamma model adjusted for age, gender, race/ethnicity, WTC exposure severity, and PTSD status.

additional risk factors, which included psychiatric diagnoses, use of psychotropic medications, and specific types of WTC-related exposures, including chemical exposures and a wide range of occupational and service-related factors.[47] Results of stratified analyses are reported in the appendix (Appendix Table S5-S6). Notably, those that were exposed to mold, chemicals, and smoke during their participation in rescue and recovery operations exhibited statistically significant differences in erratic behaviors across HCAR and LCAR risk groups (Welch'sT test; Mold: Low vs High atrophy risk % with erratic behaviors = 1.99 vs 2.07, $P = .033$; Chemicals: Low vs High atrophy risk % = 1.98 vs 2.05, $P = .036$; Smoke: Low vs High atrophy risk % = 1.92 vs 2.04, $P = .006$). Moreover, HCAR vs LCAR group differences in sensory-related deficits were apparent for responders with canteen (Welch'sT test, $P < .05$), cable repair ($P < .001$), counseling ($P < .01$), and towing exposures ($P < .05$). Crucially, multivariable analyses revealed that adjustment for these factors did not change the previously reported findings that high atrophy risk was significantly associated with sensory-related deficits.

Regarding concurrent use of psychotropic medications (Appendix Table S7), we found associations between HCAR and sensory-related impairments for responders taking serotonin reuptake inhibitors, second-generation antipsychotics, and H2 antihistamines (Welch's*t* test, $P < .01$). Finally, regarding concurrent psychiatric diagnoses, adjusting estimated effects for any general non-PTSD psychiatric diagnosis (e.g., depression, anxiety, substance abuse, and externalizing disorder), we found no significant impact on associations between HCAR and behavioral impairments (likelihood ratio test, $P = .555$). Furthermore, applying the same analysis for any single specific diagnosis, we found there is no significant impact on estimated associations ($P = .513$-$.800$).

Having found a strong association between HCAR and sensory-related impairments (Table 3), we investigated whether incorporating psychiatric diagnoses impacted the magnitude of this association and found that the association between HCAR and sensory-related impairments was not significantly impacted by psychiatric diagnosis (Chow's test, $P = .703$). However, stratifying across PTSD diagnosis, we found that the association between HCAR and sensory-related symptoms was more pronounced for responders diagnosed with PTSD (interaction β = .530, SE = .219, $P = .016$).

Discussion

The present study found evidence of diffuse or generalized associations between high cortical atrophy risk and individual behavioral impairments and behavioral clusters, as measured by the SB-MBI-SR, regardless of whether the clusters were defined theoretically based on the established coding scheme or empirically based on observed patterns of variance and covariance. In analysis of theoretically derived MBI clusters, no unique associations were observed, in that associations of similar magnitude were observed across all clusters. However, in analysis of empirically derived SB-MBI-SR clusters and individual items, notable and statistically significant associations between sensory dysfunctions and high cortical atrophy risk were evident. We emphasize here that when considering the complex patterns in the data, both bivariate and multivariate analyses contribute to the understanding of the results.

Recent research has focused on the relationship between neuropsychiatric symptoms and the progression of ADRD.[4,5,11] The WTC responder population is a unique cohort because individuals were exposed to factors that increased risk for both psychiatric conditions and the development of cognitive dysfunction. However, it was

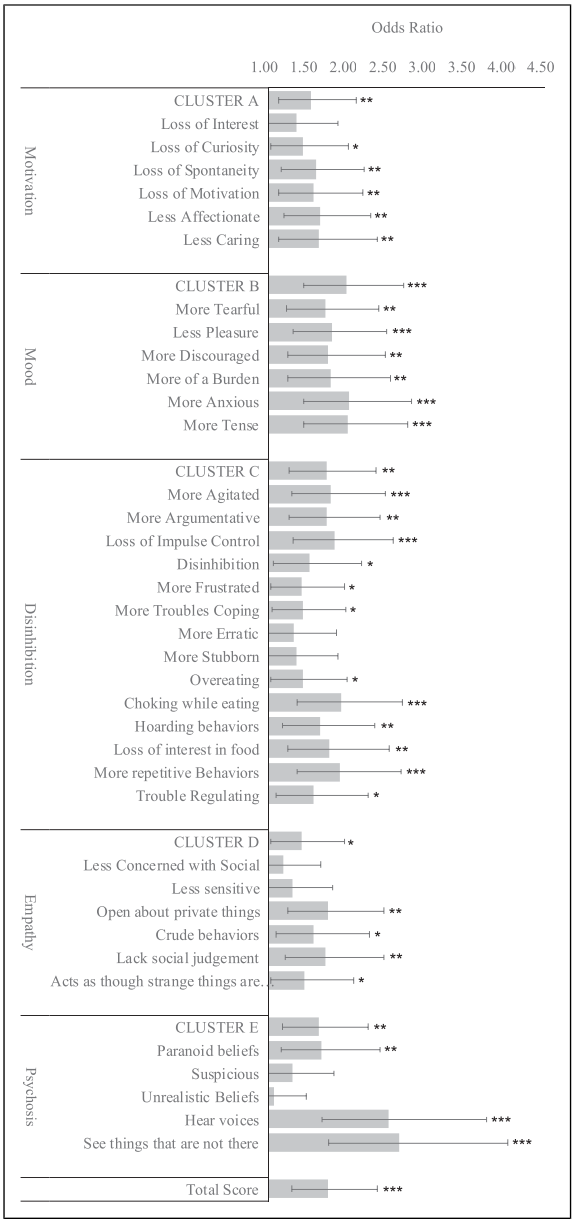

Figure 1. Associations between behavioral impairments and high cortical atrophy risk. Notes: Multivariable-adjusted odds ratios with 95% confidence intervals are reported, adjusting for age, sex, post-traumatic re-experiencing stress, and number of weeks on-site. Clusters A-E are based on the original MBI-C coding scheme. One, 2, and 3 asterisks denote $P < .05$, $P < .01$, $P < .001$, respectively.

unknown how closely linked psychiatric symptomatology was to cognitive dysfunction in this population. In this study, we found that WTC responders at high risk of cortical atrophy (as determined by an artificial neural network applied to cognitive testing) exhibited a constellation of impairments across behavioral domains related to motivation, mood, disinhibition, empathy, and particularly sensory-related psychosis.

Exploratory factor analysis and empirically derived behavioral clusters revealed a unique association between sensory deficits measured by the SB-MBI-SR and cortical atrophy risk. Thus, our study supports the existence of sensory deficits potentially associated with the mid-life aging WTC responder population as evinced here by self-reported behavioral data. Furthermore, links between sensory deficits and high cortical atrophy risk persisted across several occupational exposures and psychiatric treatments, despite the loss of statistical power that results from conducting stratified analyses. Remarkably, these findings are apparent even though the WTC responder population is, on average, currently at mid-life when neurodegeneration is relatively uncommon.[47,48] Additionally, the study of psychiatric co-morbidities indicate that many psychiatric conditions do not impact associations between cortical atrophy risk and behavioral impairments, but that a PTSD diagnosis strengthens the association between atrophy risk and sensory-related deficits. These sensory impairments are consistent with evidence suggesting the development of possible parietal-dominant AD in this population.[22,24,28,49] Although this study further validates the artificial neural network used to identify individuals at high risk for cortical atrophy and advances an understanding of associated behavioral impairments in the WTC responder population, patient treatment and future research will still benefit from neuroimaging and molecular follow-ups. For example, by exploring longitudinal associations of behavioral impairments with markers of neurodegeneration, future work can provide insights into the direction of associations between behavioral change and neurodegenerative disease in this unique population.

Deep learning methods allowed us to non-invasively use cognitive testing results to tease apart risk for developing cortical atrophy in this population.[28] Previous work has demonstrated that CI is highly prevalent in the WTC responder population, and research has recently begun to characterize this emergent clinical phenomenon. As such, our previous neuroimaging work has demonstrated that WTC responders develop a subtype of ADRD, perhaps akin to parietal dominant ADRD.[22] Parietal dominant ADRD is a rare form of neurodegeneration that is associated with sensory deficits and parietal cortical lesions that occur relatively earlier in life.[36-39] Although certain sensory impairments can occur in multiple ADRD subtypes,[50,51] early sensory dysfunction is characteristic of posterior cortical atrophy.[52] Furthermore, and consistent with our findings in the present study, both visual and auditory deficits have been found in populations with posterior cortical atrophy.[53,54] While sensory impairments are concerning, they are even worse in the elderly as psychosis is often

associated with poorer prognoses.[55,56] Building on this notion, researchers are currently beginning to understand the relationships between the auditory system and the neurodegenerative state.[57] For instance, based on neuropathological findings, the neurodegenerative subtype may correspond with specific psychotic or hallucinatory features.[58] Our empirical analysis allowed us to uncover a bias toward the development of sensory deficits, based on MBI data, for those at heightened risk for cortical atrophy. Although this result is consistent with our previous findings, the MBI data only indicated whether responders subjectively experienced and reported visual and auditory hallucinations. Thus, we were unable to study the fine-grained sensory deficits that may be present in this population, especially at this prodromal stage. Future studies may benefit from thoroughly dissecting the progression of sensory deficiencies in these responders.

In our inferential analyses, we observed pan-behavioral deficits. These broad bandwidth behavioral impairments are consistent with both overt PTSD symptomatology found in people exposed to traumatic events and potential development and progression of ADRD in this population.[59] Although studies documenting behavioral correlates are generally lacking, parietal cortical functionality and lesions have been associated with a variety of neuropsychiatric disorders such as autism spectrum disorder, schizophrenia, and bipolar disorder.[49] Regarding underlying biological mechanisms, the 9/11 events led to predisposing factors, particularly exposure to airborne hazardous neurotoxins.[47,60,61] We previously found that plasma tau and neurofilament levels correlated with cognitive impairment.[20] While this does not confirm a particular AD subtype, other research groups have shown a preponderance of tau in the lateral parietal cortex in patients with AD.[62] Consistent with this, recent mouse models have found that specific regions of the cortex may have differential levels of neurodegeneration due to differences in regional activity.[63] We speculate that generalized parietal cortical network dysfunction may underlie the behavioral impairments that we are beginning to observe in responders at heighted risk for cortical atrophy.

We previously found that the high atrophy risk group tends to be predisposed to cardiovascular disease and diabetes; there is also a higher prevalence among Latino and African Americans.[28] It is important to note, however that stroke or cerebrovascular disease was not accounted for as these responders were excluded from the study. The current study extends these findings and characterizes the high atrophy risk group as exhibiting behavioral impairments indicative of psychiatric disorders. In agreement with this finding, a large body of evidence suggests that racial/ethnic disparities play a role in the presentation and etiology of ADRD and in the development of mental health dysfunction.[64-66] More specifically, the severity of self-reported neuropsychiatric symptoms in people diagnosed with AD appears to be influenced by Hispanic ancestry.[67] Future work will be required to determine the effects of race/ethnicity and ancestry on both the behavioral correlates and the risk of dementia in the high atrophy risk group.

Limitations

Our study enabled us to discover another clinical feature that can be monitored in the WTC responder population to assess the risk of development of cortical atrophy. However, we are unable to determine the temporal direction of associations documented in the present study. That is, some people in the high atrophy risk group might have recently developed symptoms and, therefore, the behavioral impairments may or may not precede development of the disease. Since patients with AD and parietal lobe dysfunction exhibit anosognosia deficits as identified by a lack of self-awareness,[68,69] this may limit our study due to reliance on self-reports. Notably, given that the WTC population may be predisposed to parietal-dominant AD, it is possible that these responders underreport or even deny psychiatric or behavioral impairments, resulting in a potential reduction of between-group differences. Furthermore, this study does not have direct measurements of visuospatial abilities and, thus, cannot make direct conclusions about parietal dysregulation in the high atrophy risk group. Nevertheless, our study reveals the potential importance of monitoring behavioral and sensory deficits related to ADRD. Future studies with more detailed psychiatric evaluations may be fruitful for identifying such cases in the WTC population.

Previous studies have shown that the WTC responders exhibit a greater incidence of cognitive impairment than the general population.[48] However, the present study did not make a direct comparison to a general population or external control group; it did, however, note significant differences between the high and low atrophy risk groups in terms of PTSD symptomatology and cognitive dysfunction, suggesting that there is a proportion of responders that are predisposed through multiple comorbid factors.[28] Furthermore, prior studies have validated the MBI-C as a measure to determine behavioral impairments associated with cognitively impairing disorders. Using SB-MBI-SR, our study revealed that within a large sample of WTC responders, those at high risk of cortical atrophy exhibit larger behavioral impairments than the converse population. Lastly, our SB-MBI-SR results do not

directly interface with clinical or biomolecular diagnostic categories. To fully understand behavioral impairments and its relationship with the development of neurodegenerative conditions, future studies will require multiple SB-MBI-SR administrations correlated with biomarker and neuroimaging progression. However, we point out that these behavioral surveys are non-invasive and advantageous in being able to capture population-level and statistically sound conclusions. Overall, we still found significant differences between behavioral impairments and atrophy risk within our WTC responder sample.

Conclusions

Neuropsychiatric symptoms are known to be common in diseases characterized by cortical atrophy. WTC responders are a unique cohort that is experiencing severe levels of cognitive dysfunction and impairment after their on-site experiences at the WTC. To date, little is known about the symptoms associated with cognitive dysfunction, aside from PTSD, and studies have not established the prognosis of cortical atrophy risk at midlife in this population of WTC responders. Here, we found that responders at high risk of WTC-related cortical atrophy, as determined by a previously published ANN algorithm, also reported elevated levels of generalized behavioral impairments indicative of psychiatric disorders and notably of symptoms consistent with psychosis. We emphasize here that monitoring and treating cortical atrophy has been problematic due to difficulties with parsing heterogenous manifestations.[15] Results of the present study indicate that a multi-dimensional WTC signature cognitive testing paradigm provides a nuanced platform to monitor and investigate behavioral impairments and the risk of progression to clinical diseases including dementia. In late-life, psychosis is often associated with greater risk for more severe cognitive decline[55] and often portends more rapid onset of functional limitations.[56] Future studies will require longitudinal monitoring and treatment of behavioral impairments to determine the progression of these impairments in relation to the development of dementia.

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Declaration of Conflicting Interests

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Supplemental Material

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