Archival Report

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Association of Psychological Resilience With Decelerated Brain Aging in Cognitively Healthy World Trade Center Responders

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ABSTRACT

BACKGROUND: Despite their exposure to potentially traumatic stressors, the majority of World Trade Center (WTC) responders—those who worked on rescue, recovery, and cleanup efforts on or following September 11, 2001—have shown psychological resilience, never developing long-term psychopathology. Psychological resilience may be protective against the earlier age-related cognitive changes associated with posttraumatic stress disorder (PTSD) in this cohort. In the current study, we calculated the difference between estimated brain age from structural magnetic resonance imaging (MRI) data and chronological age in WTC responders who participated in a parent functional MRI study of resilience (N = 97). We hypothesized that highly resilient responders would show the least brain aging and explored associations between brain aging and psychological and cognitive measures.

METHOD: WTC responders screened for the absence of cognitive impairment were classified into 3 groups: a WTC-related PTSD group (n = 32), a Highly Resilient group without lifetime psychopathology despite high WTC-related exposure (n = 34), and a Lower WTC-Exposed control group also without lifetime psychopathology (n = 31). We used *BrainStructureAges*, a deep learning algorithm that estimates voxelwise age from T1-weighted MRI data to calculate decelerated (or accelerated) brain aging relative to chronological age.

RESULTS: Globally, brain aging was decelerated in the Highly Resilient group and accelerated in the PTSD group, with a significant group difference (p = .021, Cohen's d = 0.58); the Lower WTC-Exposed control group exhibited no significant brain age gap or group difference. Lesser brain aging was associated with resilience-linked factors including lower emotional suppression, greater optimism, and better verbal learning.

CONCLUSIONS: Cognitively healthy WTC responders show differences in brain aging related to resilience and PTSD.

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More than 2 decades after the 2001 World Trade Center (WTC) attacks, many individuals who responded to the call to assist in rescue, recovery, and cleanup efforts still feel the impacts of their involvement. Known collectively as WTC responders, tens of thousands of individuals participated in their capacity as police officers, firefighters, construction personnel, volunteers, and many others (1). Longitudinal data from the WTC Health Program (2), established to monitor and treat the physical and psychological impacts of 9/11 on WTC responders (3), has identified higher rates of psychiatric conditions and neurocognitive disorders and impairment in this cohort, likely owing to their exposures to adverse psychological and environmental conditions. However, most WTC responders have demonstrated substantial resilience (4–6) comparable to that seen in other trauma-exposed populations (7), and they have been able to return to baseline levels of well-being and avoid developing chronic psychopathology, despite some acute stress effects (8). Multiple genetic, psychological, and environmental factors have been shown to be associated with resilience in WTC responders (5,6,9) and in trauma survivors more broadly (8,10). Whether there are particular neurobiological characteristics of responders that might have allowed a subset of these individuals to remain psychologically healthy despite a traumatic experience (i.e., resilient responders) has been examined less often.

Significant deviations from the norm in brain morphology are associated with the development of disease, particularly in psychiatric disorders (11). Therefore, structural brain features may be important for understanding trauma resilience. For example, greater hippocampal and prefrontal brain volume are associated with lower rates of trauma-related psychopathology (12). Deep learning analysis of structural neuroimaging data has emerged in the last decade as a promising tool for early detection of neurodegenerative disease and perhaps to better understand common psychopathological conditions (13) based on knowledge of typical age-related changes in brain structure, which may manifest sooner or later in different individuals (14). The variation between an individual's brain age calculated from their structural data and their chronological age is termed the brain age gap (15).

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There is considerable interest in brain aging in WTC responders because dementia and cognitive impairment can emerge earlier in this cohort and have been linked both to PTSD and to environmental exposures such as neurotoxic particulates carried by the dust cloud (16–18). Accelerated global brain aging—indicated by a greater positive brain age gap—has been associated with multiple psychiatric disorders including schizophrenia, bipolar disorder, and depression (19). A study from the large ENIGMA (Enhancing Neuro Imaging Genetics through Meta Analysis) neuroimaging cohort did not find a consistent association between PTSD and brain age (20) using the deep learning algorithm *brainageR* (21,22) to predict brain age from voxelwise T1-weighted magnetic resonance imaging (MRI) data. However, brain aging exerts variable impacts in different anatomical regions, diseases, and individuals. For example, a longitudinal MRI study conducted with 653 cognitively healthy adults identified characteristic patterns of age-related changes (23), with local variation in cortical gray matter volume loss such that there was more and faster atrophy in the frontal and temporal than in the occipital and parietal lobes. Another characteristic of brain aging was a multiphasic process of volume loss with advancing age, in which the slope of atrophy was steeper before the age of 50 years and more gradual in the 60s, but resumed a steep decline around 70. However, it is notable that the individual expression of these patterns varied widely, even in a sample that showed no clinically significant changes in memory or cognition over the course of the study (23). To obtain more granular information about specific structural changes and their deviation from typical aging, Nguyen *et al.* (24) introduced the *BrainStructureAges* pipeline. This approach estimates brain age in discrete structures via deep learning, using multiple U-Nets trained to predict voxelwise age from 3-dimensional subvolumes of T1-weighted data. U-Nets' outputs are combined to map predicted age across the brain at the voxel level and then segmented based on anatomical parcellations (24). While much of this work so far has focused on the advantages of brain structure ages for multidisease classification and improved diagnostic accuracy at the individual level, it could also provide insight into different trajectories of brain aging in WTC responders.

Here, we conducted a secondary analysis of structural MRI data from a Centers for Disease Control and Prevention (CDC)/National Institute for Occupational Safety and Health (NIOSH)–funded parent neuroimaging study of resilience in WTC responders. We hypothesized that compared with responders with very chronic WTC-related PTSD, responders who remained psychologically healthy despite substantial exposure to potentially traumatic WTC-related stressors (i.e., those who were highly resilient) would show less brain aging, while individuals in a Lower WTC-Exposed control group would not show this difference from the group with PTSD. We also examined relationships between brain aging, cognitive measures, and resilience-linked psychological factors in the entire sample.

METHODS AND MATERIALS

Participants

In the parent neuroimaging study (CDC/NIOSH U01OH011473), participants up to 65 years (N = 97 MRI completers) (Table 1) were recruited from 2018 to 2023 from the WTC Health Program General Responder Cohort (WTC-HP GRC) (1) in collaboration with the WTC-HP GRC Data Center and the WTC Mental Health Program at Mount Sinai. The Data Center supplied data on the severity of WTC-related exposure and the prevalence of specific exposures in the WTC-HP GRC cohort. At their first clinic visit, WTC-HP GRC members were asked about 10 different adverse experiences that they may have encountered in their work on the recovery effort (e.g., encountering human remains, being injured, or being caught in the dust cloud). Incorporating the WTC exposures data, participants were categorized into 3 groups. Participants with PTSD (n = 32) could have any number of WTC exposures. In participants without PTSD (n = 65), the distribution of WTC exposures was bimodal, with peaks at 3 (22%) and 5 exposures (26%). Highly resilient individuals (n = 34) were those with ≥4 WTC exposures, and lower WTC-exposed individuals (n = 31) were those with ≤3 WTC exposures.

Additionally, the Highly Resilient and Lower WTC-Exposed groups were required to have no lifetime psychopathology, while those in the PTSD group met DSM-5 criteria for lifetime WTC-related PTSD and either full (75%) or subthreshold (25%) past-month PTSD. All participants had normal estimated Full Scale IQ scores (>80) based on the Weschler Test of Adult Reading (WTAR) (25). Key exclusion criteria included lifetime psychotic or bipolar disorders, lifetime substance use disorder (SUD) (for the non-PTSD groups), or SUD within the last 3 months (for the PTSD group), antipsychotic medications, uncontrolled medical conditions, significant head/brain trauma, neurocognitive disorders, Montreal Cognitive Assessment (MoCA) (26) score of ≤23, pregnancy, and claustrophobia.

Procedures

Prospective participants were screened for provisional study eligibility, and eligible individuals completed an initial study visit for written informed consent, followed by completion of the MoCA and WTAR and self-report questionnaires. A doctoral or masters-level clinician then administered the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) (27) and the Structured Clinical Interview for DSM-5-Research Version (28) to determine participants' eligibility for one of the 3 study groups in combination with WTC exposure data. Enrolled participants completed an MRI session during a second visit and were invited to return for a third visit to complete the Cogstate battery. Due to the emergence of COVID-19 in 2020, some participants completed the clinical interview and/or Cogstate visit remotely via a Health Insurance Portability and Accountability Act–compliant videoconference platform. Participants were compensated for their time, and all aspects of the study were approved by the Icahn School of Medicine at Mount Sinai's Institutional Review Board Human Subjects Protection Program.

Measures

The WTAR measures premorbid intelligence and comprises a list of words that progressively become more difficult to pronounce. Raw scores (number of correct pronunciations) are converted to a normed estimated Full Scale IQ (29).

The MoCA is a widely used cognitive impairment screening tool that assesses multiple domains, including memory, verbal fluency, attention, and executive function (30). A cutoff score of

Table 1. Participant Characteristics by Group Classification

	Highly Resilient, *n* = 34	Lower WTC-Exposed, *n* = 31	PTSD, *n* = 32	*p*
Age, Years	54 (4.6)	53 (6.2)	54 (6.4)	.68
Gender				
Female	4 (12%)	7 (23%)	6 (19%)	.506
Male	30 (88%)	24 (77%)	26 (81%)	
Race				
Asian	2 (6%)	0 (0%)	2 (6%)	.505
Black	4 (12%)	1 (3%)	4 (12%)	
White	22 (65%)	26 (84%)	20 (62%)	
Not specified[a]	6 (18%)	4 (13%)	6 (19%)	
Ethnicity				
Hispanic or Latino	6 (19%)	7 (21%)	4 (13%)	.707
Not Hispanic or Latino	26 (81%)	27 (79%)	27 (87%)	
Employment				
Disabled, not WTC related	2 (6%)	1 (3%)	2 (6%)	.088
Disabled, WTC related	0 (0%)	0 (0%)	4 (12%)	
Full-time	20 (59%)	13 (42%)	16 (50%)	
Not reported	0 (0%)	0 (0%)	1 (3%)	
Part-time	5 (15%)	6 (19%)	3 (9%)	
Retired	7 (21%)	10 (32%)	4 (12%)	
Unemployed	0 (0%)	0 (0%)	2 (6%)	
Other	0 (0%)	1 (3%)	0 (0%)	
Education				
High school degree	4 (12%)	1 (3%)	6 (19%)	.199
Some college, no degree	9 (26%)	4 (13%)	5 (16%)	
Undergraduate degree, 2 years	2 (6%)	3 (10%)	5 (16%)	
Undergraduate degree, 4 years	11 (32%)	17 (55%)	7 (22%)	
Some graduate or professional school	1 (3%)	2 (6%)	1 (3%)	
Graduate or professional degree	7 (21%)	4 (13%)	8 (25%)	
Estimated IQ, WTAR	111 (9.2)	112 (8.5)	107 (11.3)	.096
MoCA	27 (2.2)	27 (1.8)	27 (2.0)	.849
Cogstate Composite Score, *n* = 85	−0.05 (0.56)	0.18 (0.57)	−0.07 (0.48)	.170
Right-Handed, Yes	29 (91%)	28 (82%)	28 (90%)	.519
Responder Type				
Traditional	31 (91%)	26 (84%)	13 (41%)	<.001
Nontraditional	3 (9%)	5 (16%)	19 (59%)	
Number of WTC Exposures, Range 0–10	5.5 (1.2)	2.4 (0.89)	5.4 (2.4)	<.001
Item B: Caught in Dust Cloud, Yes	11 (32%)	1 (3%)	11 (34%)	.005
Item C: Worked Directly on Pit/Pile, Yes	32 (94%)	17 (55%)	27 (84%)	<.001
CAPS-5 Past Month Total Score	0.9 (1.1)	0.9 (1.5)	28.4 (10)	<.001
CAPS-5 Worst Month Total Score	2.4 (2.4)	2.4 (2.6)	42.4 (14)	<.001
Number of Lifetime Diagnosed Health Conditions, Self-Reported	2.1 (1.8)	1.8 (1.8)	5.2 (2.5)	<.001
Health Conditions				
Asthma, respiratory, pulmonary	9 (26%)	6 (19%)	19 (59%)	.002
Diabetes	3 (9%)	1 (3%)	6 (19%)	.121
Hypertension	13 (38%)	7 (23%)	11 (34%)	.376
Sleep apnea	6 (18%)	5 (16%)	20 (62%)	<.001
Ever smoked	8 (24%)	4 (13%)	9 (28%)	.323
Lifetime Substance Use Disorder Diagnosis, SCID-5	0	0	14 (44%)	<.001

Values are presented as mean (SD) or *n* (%). *p* values are from χ^2 (categorical variables) or *F* (numeric variables) tests. WTC-related exposures represents a count (of a list of 10) of adverse WTC-related experiences as defined by the WTC Health Program Data Center.

CAPS-5, Clinician-Administered PTSD Scale for DSM-5; MoCA, Montreal Cognitive Assessment; PTSD, posttraumatic stress disorder; SCID-5, Structured Clinical Interview for DSM-5, Research Version; WTAR, Weschler Test of Adult Reading; WTC, World Trade Center.

[a]The survey design combined race and ethnicity into a single item. Participants whose race is listed as not specified are those who selected Hispanic alone.

23 has been shown to discriminate clinically significant changes in cognition from normal aging most accurately (31).

The Cogstate battery consists of computerized tasks that measure cognitive functioning in multiple domains from performance indicators such as reaction time and accuracy, which are designed to minimize cultural and educational impacts on performance. Cogstate performance has shown good 3-month test-retest reliability in healthy control individuals and in individuals with mild cognitive impairment and Alzheimer's disease (32). In the current study, participants (n = 85) completed tasks for verbal learning (International Shopping List [ISL]), verbal memory (ISL Recall), processing speed (Detection [DET]), working memory (One-Back [ONB]), visual attention (Identification [IDN]), visual learning and memory (OCL [One-Card Learning]), and visuospatial learning (Groton Maze Learning [GML]) and memory (Groton Maze Recall [GMR]) during the third study visit. Of these 85 participants, 51 were able to complete the reaction time–based tasks that required in-person testing.

The CAPS-5 is a structured diagnostic interview and the gold standard for assessing the DSM-5 symptoms of PTSD. The CAPS-5 uses a single 5-point ordinal rating scale to measure symptom severity, with severity ratings reflecting information about symptom frequency and intensity obtained by the interviewer (27).

The Structured Clinical Interview for DSM-5, Research Version (SCID-5) is the most widely used structured diagnostic interview for determining psychiatric diagnoses in clinical research settings based on DSM-5 criteria (28).

Self-report measures of lifetime medical conditions (33) and individual differences related to psychological resilience and cognitive reserve included dispositional positive affect [Positive and Negative Affect Schedule (PANAS) (34)], optimism [Revised Life Orientation Test (LOT-R) (35)], emotion regulation strategies [Emotion Regulation Questionnaire (ERQ) (36)], purpose in life [Ryff Scales of Psychological Wellbeing (37)], and perceived social support [Medical Outcomes Survey-Social Support Scale (MOS-SSS) (38)]. The PANAS positive affect subscale (PANAS-PA) contained 10 items (of 20 total PANAS items) on a scale of 1 to 5 (possible range 10–50), with higher scores indicating a greater tendency to experience positive emotions. The LOT-R contained 6 items on a scale of 0 to 4 (possible range 0–24), with higher scores indicating a greater tendency to take an optimistic perspective. The ERQ reappraisal subscale contained 7 items on a scale of 1 to 7 (possible range 7–49), and the suppression subscale contained 4 items (possible range 7–28), with higher scores indicating frequent use of cognitive reappraisal/emotional suppression. The Ryff Scales of Psychological Wellbeing purpose in life (PIL) subscale contained 8 items on a scale of 1 to 6 (possible range 6–48), with higher scores indicating a greater sense of life purpose. The MOS-SSS overall support scale contained 19 items on a scale of 1 to 5 [total scores transformed to a range of 1–100 as described in (38)], with higher scores indicating greater perceived social support across different domains.

MRI Acquisition and Processing

High-resolution T1-weighted structural brain images were acquired on a Siemens Skyra 3T scanner at the Icahn School of Medicine at Mount Sinai (ISMMS) Biomedical Engineering and Imaging Institute: isotropic voxel size = 0.8 × 0.8 × 0.8 mm^3, TR = 2400 ms, TE = 2.07 ms, inversion time = 1000 ms, flip angle = 8°, matrix size = 320 × 320. Parallel imaging was used with a reduction factor of 2 to improve acquisition speed. DICOM files were converted to a Brain Imaging Data Structure–compliant NIfTI dataset using dcm2niix (39) and HeuDiConv (40). Estimated brain age and volume per structure were computed via the *BrainStructureAges* pipeline (24) hosted on the volBrain platform (https://volbrain.net, RRID:SCR_021020). Briefly, *BrainStructureAges* (24) preprocessing involves denoising and inhomogeneity artifact correction, affine registration into Montreal Neurological Institute space, intensity standardization, and intracranial cavity extraction. The T1-weighted image is then divided into multiple 3D subvolumes for voxelwise prediction of age by multiple U-Nets, a convolutional neural network architecture developed for biomedical image segmentation, trained with the participant's chronological age as ground truth. Combining the outputs of multiple U-Nets produces a 3D map of estimated brain age per voxel. This map is then segmented into 133 brain structures using AssemblyNet parcellation (41). The average value of voxels within each structure is the structure's estimated brain age, or BSAGE. For each T1-weighted image/participant, the output of *BrainStructureAges* includes the estimated BSAGE overall and per structure.

Quality control of input T1-weighted images was performed manually and in *BrainStructureAges*, which assigns each input a letter grade from A to C for image quality. All were rated "A" but one had a minor motion artifact upon visual inspection. Including versus excluding this participant did not significantly impact the results.

Statistical Analysis

The discrepancy between BSAGE and chronological age (overall and for each structure), here termed the BSAGE gap, was calculated as the residual from a linear regression model predicting BSAGE from chronological age. While brainAGE studies traditionally use the raw difference between values, residuals provide a clearer measure of over- or underestimation by controlling for the baseline correlation between chronological age and BSAGE (here, r = 0.65, $p \leq .0001$). Using residuals also helps account for potential confounding factors such as regression to the mean or systematic differences in the range of possible values in older versus younger participants and ensures that the BSAGE gap is independent from chronological age (here, $r \leq 0.0001$, $p = >.99$).

Planned contrasts via the rempsych R package (42) tested the predicted effect of group (Highly Resilient > Lower WTC-Exposed > PTSD) across 3 models: 1) no covariates; 2) including covariates that represented the presence or absence of health conditions that have been shown to be strongly associated with brain aging or cognitive function [hypertension, diabetes, respiratory/pulmonary conditions, sleep apnea, and smoking (43–45)]; and 3) with the PTSD group divided by the presence of a SCID-5 lifetime substance use disorder diagnosis (SUD) (yes: n = 14, no: n = 18). Next, we explored correlations of the BSAGE gap with cognitive (MoCA, WTAR, Cogstate) and self-report (PIL, LOT-R-optimism, ERQ-

reappraisal, ERQ-suppression, PANAS-PA, MOS-SSS) measures. When variables showed different associations with BSAGE by group, we compared the groups using Fisher's *z* test in cocor (46). The R packages ggseg, ggsegHO, and ggsegExtra (47) were used for data visualization, with *BrainStructureAges* cortical structures plotted using the Harvard-Oxford atlas (Figure S1).

RESULTS

Participant Characteristics

There were no group differences in age; gender; race; ethnicity; employment; education; handedness; smoking history; or MoCA, WTAR, and Cogstate composite scores. The Highly Resilient and PTSD groups did not differ in WTC exposure severity (Table 1). Consistent with the full WTC-HP GRC, the Highly Resilient group had a higher proportion of responders in traditional first-responder occupations (e.g., law enforcement, paramedics) versus nontraditional occupations (e.g., construction workers, journalists) ($p < .001$). The PTSD group had a greater number of total self-reported health conditions ($p < .001$). Of the specific health conditions that we examined for known impact on brain perfusion, the PTSD group had a significantly higher proportion of participants with sleep apnea and asthma or other respiratory or pulmonary conditions. From the WTC-HP Data Center WTC exposures data, we also had information on whether or not responders were caught in the dust cloud and whether or not they worked directly on the pit or pile. Both environmental exposures were similarly represented in the Highly Resilient and PTSD groups but were rarer in the Lower WTC-Exposed group ($p \leq .005$) (Table 1).

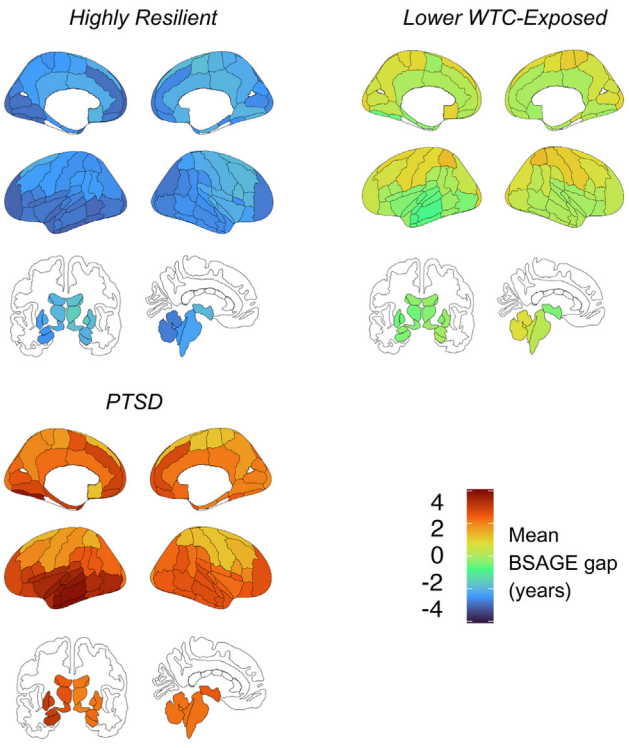

Figure 1. Brain structure age (BSAGE) gap by group. Mean BSAGE gap (years) in cortical (top) and subcortical (bottom) brain regions within each group. PTSD, posttraumatic stress disorder; WTC, World Trade Center.

Table 2. Unadjusted Planned Contrasts for the Global BSAGE Gap

Contrast	*t*	*p*	*d*	95% CI
PTSD > Highly Resilient	$t_{94} = 2.34$	.021*	0.58	0.08 to 1.07
PTSD > Lower WTC-Exposed	$t_{94} = 0.99$	.323	0.25	−0.27 to 0.76
Highly Resilient > Lower WTC-Exposed	$t_{94} = -1.31$	.192	−0.33	−0.78 to 0.15

BSAGE gap indicates the residual of linear regression model predicting overall estimated brain age from chronological age; a residual of 0 would mean there is no difference between estimated age and chronological age.

*$p < .05$.

BSAGE, brain structure age; PTSD, posttraumatic stress disorder; WTC, World Trade Center.

Group Differences in Global BSAGE Gap

In both cortical and subcortical structures, the PTSD group showed accelerated brain aging (i.e., a positive BSAGE gap), whereas the Highly Resilient group showed decelerated brain aging (i.e., a negative BSAGE gap) (Figure 1). Aging was significantly more decelerated in the Highly Resilient group than in the PTSD group, with a medium effect size ($t_{94} = 2.34$; $p = .021$; Cohen's $d = 0.58$; bootstrapped 95% CI, 0.08 to 1.07). Other group contrasts were not statistically significant (Table 2), with the BSAGE gap for individuals in the Lower WTC-Exposed group approximating their chronological age (i.e., aging as expected).

We saw similar results (e.g., PTSD > Highly Resilient group, Cohen's $d = 0.56$, $p = .05$) after controlling for health variables that have been robustly linked to structural brain aging (hypertension, diabetes, asthma/respiratory/pulmonary conditions, sleep apnea, and lifetime smoking) (Table 3 and Figure 2).

To explore whether differential prevalence of lifetime SUD might explain the PTSD versus Highly Resilient group difference in brain aging, we divided the PTSD group into subgroups based on the absence ($n = 18$) or presence (alcohol only $n = 10$, alcohol+stimulants $n = 2$, alcohol+opioids $n = 1$,

Table 3. Planned Contrasts for the Global BSAGE Gap, Adjusted for Health Covariates

Contrast	*t*	*p*	*d*	95% CI
PTSD > Highly Resilient	$t_{89} = 1.99$	.050	0.56	0.01 to 1.05
PTSD > Lower WTC-Exposed	$t_{89} = 0.74$	.459	0.22	−0.26 to 0.77
Highly Resilient > Lower WTC-Exposed	$t_{89} = -1.35$	.180	−0.34	−0.78 to 0.14

BSAGE gap indicates the residual of linear regression model predicting overall estimated brain age from chronological age. Health covariates were dichotomous variables representing presence/absence of lifetime smoking, diabetes, hypertension, sleep apnea, and asthma or other pulmonary or respiratory conditions.

BSAGE, brain structure age; PTSD, posttraumatic stress disorder; WTC, World Trade Center.

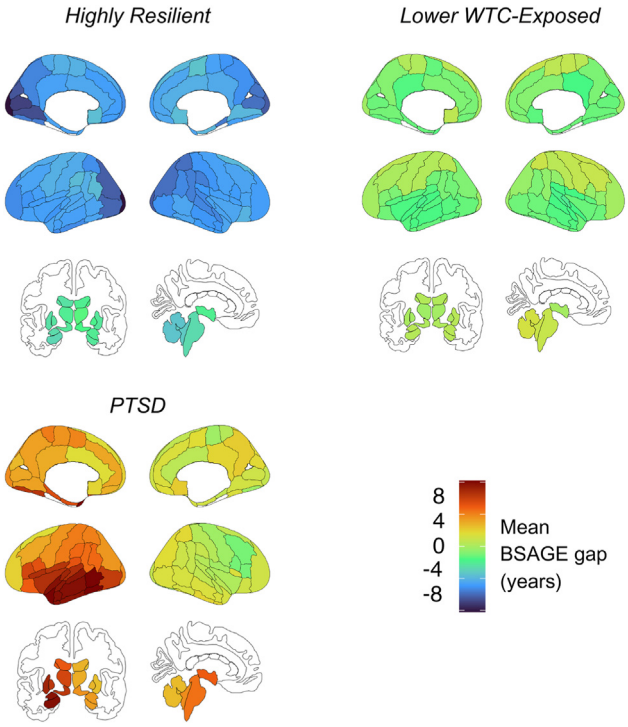

Figure 2. Brain structure age (BSAGE) gap by group, adjusted for health covariates. Mean BSAGE gap (years) in cortical (top) and subcortical (bottom) brain regions within each group adjusted for presence/absence of self-reported diagnoses of sleep apnea, respiratory/pulmonary conditions, diabetes, hypertension, and lifetime smoking. PTSD, posttraumatic stress disorder; WTC, World Trade Center.

phencyclidine n = 1) of DSM-5 lifetime SUDs. The contrast between PTSD and PTSD+SUD was not statistically significant. However, contrary to expectation, the difference from the Highly Resilient group was larger in the PTSD group without SUD (p = .021, d = 0.68) than in the PTSD+SUD group (p = .172, d = 0.44) (Table 4).

Exploration of Group Differences in BSAGE Gap by Structure

The large number of brain structures relative to our sample size precluded statistical testing of a group × structure interaction including all possible brain structures to identify whether certain structures were differentially affected by aging in different groups. Given this limitation, we visualized the data, and we note our observations here for descriptive purposes (Figure 2 and Figure S2). No group differences in specific structures were statistically significant after correcting for multiple comparisons.

In the Highly Resilient group, after adjusting for health covariates, 1-sample t tests indicated that BSAGE gap was significantly <0 for the bilateral lingual gyrus, cuneus, and calcarine (uncorrected $p < .05$), as well as the right cerebellum, cerebellum white matter, fusiform gyrus, inferior and middle temporal gyri, angular gyrus, inferior occipital gyrus, and left gyrus rectus (Figure S3). None of these differences remained statistically significant after multiple comparison corrections (false discovery rate–corrected p [p_{FDR}] > .140, Bonferroni-corrected $p > .99$).

Accelerated brain aging in the PTSD group was most prominent in multiple regions (Figure S4). However, 1-sample t tests indicated that only the left fusiform gyrus and left inferior temporal gyrus BSAGE gaps were significantly >0 (uncorrected $p < .045$) but not after correction for multiple comparisons ($p_{FDR} > .230$, Bonferroni-corrected $p > .99$). After adjusting for health covariates, we observed even greater accelerated aging, especially affecting left frontotemporal and subcortical structures.

In the Lower WTC-Exposed group, no brain areas had a BSAGE gap significantly different from 0 (uncorrected $p > .26$) (Figure S5). After adjusting for health covariates, BSAGE appeared to track even more closely with chronological age.

Global BSAGE Gap and Psychological Self-Report Measures

In the total sample, decelerated brain aging (a negative BSAGE gap) was associated with less use of emotional suppression (ERQ-suppression), higher trait positive emotion and optimism (PANAS-PA, LOT-R), and higher perceived social support (Table 5 and Figure S6). In correlations within each group (Table S1 and Figure 3), associations with BSAGE gap were strongest in the Highly Resilient group, particularly for LOT-R and ERQ-suppression, although only the association with ERQ-suppression was statistically significant (r = 0.35, p = .043). A Fisher's z test indicated that the ERQ-suppression correlation in the Highly Resilient group was higher than in the Lower WTC-Exposed group although at a nonstatistically significant level (z = 1.90; p = .057; 95% CI, −0.91 to 0.017), while the PTSD group showed a similar pattern to that of the

Table 4. Planned Contrasts for Global BSAGE Gap, With PTSD Grouped by Lifetime SUD

Contrast	t	p	d	95% CI
Highly Resilient > Lower WTC-Exposed	t_{93} = −1.31	.194	−0.33	−0.76 to 0.17
PTSD > Highly Resilient	t_{93} = 2.34	.021*	0.68	0.08 to 1.24
PTSD+SUD > Highly Resilient	t_{93} = 1.38	.172	0.44	−0.28 to 1.07
PTSD > Lower WTC-Exposed	t_{93} = 1.20	.232	0.36	−0.21 to 0.97
PTSD+SUD > Lower WTC-Exposed	t_{93} = 0.35	.729	0.11	−0.67 to 0.78
PTSD > PTSD+SUD	t_{93} = 0.69	.494	0.24	−0.55 to 1.02

BSAGE gap indicates the residual of linear regression model predicting overall estimated brain age from chronological age. PTSD indicates PTSD without lifetime SUD and PTSD+SUD indicates PTSD with lifetime SUD diagnosis.

*$p < .05$.

BSAGE, brain structure age; PTSD, posttraumatic stress disorder; SUD, substance use disorder; WTC, World Trade Center.

Table 5. BSAGE Gap Correlations With Self-Report and Cognitive Measures in the Full Sample

Measure	Pearson's *r*	*p*
ERQ-Reappraisal	−0.04	.707
ERQ-Suppression	0.24	.020*
LOT-R-Optimism	−0.26	.009**
MOS-SSS Overall Support	−0.18	.074
PANAS-Positive Affect	−0.21	.043*
PANAS-Negative Affect	0.17	.096
RWS-Purpose in Life	−0.08	.411
MoCA	0.01	.922
WTAR, Standardized	−0.19	.059
Cogstate		
Composite score	−0.15	.173
GML	−0.03	.815
GMR	−0.10	.360
ONB	−0.25	.081
ISL	−0.08	.470
ISLR	−0.04	.699
OCL[a]	−0.20	.069
IDN[a]	−0.33	.019*
DET[a]	−0.21	.143

Cogstate composite score is an average of scaled scores on all valid tests.
*$p < .05$, **$p < .01$.

DET, Detection; ERQ, Emotion Regulation Questionnaire; GML, Groton Maze Learning; GMR, Groton Maze Recall; IDN, Identification; ISL, International Shopping List; ISLR, International Shopping List Recall; LOT-R, Life Orientation Test-Revised; MoCA, Montreal Cognitive Assessment; MOS-SSS, Medical Outcomes Study Social Support Survey; OCL, One-Card Learning; ONB, One-Back; PANAS, Positive and Negative Affect Schedule; RWS, Ryff Wellbeing Scale; WTAR, Weschler Test of Adult Reading.

[a]*n* = 51 completed the reaction time–based Cogstate tasks, which required an in-person study visit.

Highly Resilient group ($z = -0.04$; $p = .966$; 95% CI, −0.45 to 0.43).

Global BSAGE Gap and Cognitive Measures

In the total sample (Table 5 and Figure S7), better estimated Full Scale IQ (WTAR) and Cogstate OCL (visual learning and memory) and ONB (working memory) performance showed small-to-moderate, nonstatistically significant (*p*s = .059–.081) negative associations with BSAGE gap. In the subset of participants who completed reaction time–based tasks in person at visit 3 ($n = 51$), BSAGE gap was inversely associated with performance on the Cogstate IDN, a measure of attention and vigilance. BSAGE gap was not significantly associated with MoCA or Cogstate composite scores. However, when we examined these relationships separately within each group (Table S2 and Figure 4), we observed a moderate negative correlation between WTAR scores and BSAGE gap in the PTSD group ($r = -0.35$; $p = .051$; 95% CI, −0.63 to 0.00) but little to no relationship between these variables in the Highly Resilient group ($r = 0.03$; $p = .876$; 95% CI, −0.31 to 0.36) or the Lower WTC-Exposed group ($r = -0.05$; $p = .776$; 95% CI, −0.40 to 0.31). However, a Fisher's *z* test indicated that the correlation in the PTSD group was not significantly different than that in the Highly Resilient group ($z = -1.52$; $p = .129$; 95% CI, −0.81 to 0.11) or the Lower WTC-Exposed group ($z = -1.18$; $p = .238$; 95% CI, −0.75 to 0.20).

There was a moderate negative correlation between Cogstate ISL (verbal learning) and BSAGE gap in the PTSD group ($r = -0.46$; $p = .014$; 95% CI, −0.71 to −0.11) but not in the Highly Resilient ($r = 0.14$; $p = .447$; 95% CI, −0.23 to 0.48) or Lower WTC-Exposed ($r = -0.07$; $p = .729$; 95% CI, −0.44 to 0.32) groups. Using Fisher's *z* test, the negative correlation in the PTSD group was significantly stronger than the weak positive correlation in the Highly Resilient group ($z = -2.30$; $p = .0215$; 95% CI, −1.02 to −0.09) but not significantly different from that in the Lower WTC-Exposed group ($z = -1.49$; $p = .135$; 95% CI, −0.85 to 0.12). Additionally, higher BSAGE gaps were associated with lower Cogstate OCL performance in the Lower WTC-Exposed group only, although not at a statistically significant level ($r = -0.36$; $p = .067$; 95% CI, −0.65 to 0.03), and Cogstate IDN ($r = -0.89$; $p < .001$; 95% CI, −0.97 to −0.60), although we note that there were only 10 lower WTC-exposed participants in the latter group.

DISCUSSION

We examined the relationship between psychological resilience, cognition, and brain aging in WTC responders, using a new deep learning–based pipeline for structural MRI (24) to study a unique sample of highly resilient responders and 2 comparison groups: responders without lifetime psychopathology but lower potentially traumatic exposures and responders with very chronic WTC-related PTSD. The results revealed group differences in brain aging, with highly resilient WTC responders showing decelerated brain aging relative to WTC responders with PTSD. This is particularly notable given the Highly Resilient group's exposure to a high level of traumatic stressors and environmental hazards (e.g., via working in search and rescue) in the aftermath of 9/11, similar to that of the PTSD responder group (and higher than that of the Lower WTC-Exposed group). Furthermore, decelerated brain aging was related to resilience-linked psychological factors, including higher positive emotionality and optimism and lower use of maladaptive emotion regulation strategies. The study also identified prominent accelerated brain aging in the PTSD group in areas involved in language, memory, and emotional processing, consistent with previous volumetric studies in PTSD. Accelerated brain aging in this group was associated with poorer verbal encoding (Cogstate ISL), even with cognitive impairment being exclusionary for this study. Previous studies have suggested that trauma exposure, in and of itself, can be associated with accelerated aging and worse cognition (48) together with PTSD (20,49,50). Recent studies have found that WTC responders may have an elevated risk of developing early dementia (16) and linked cognitive impairment and a PTSD diagnosis (51).

The results of the current study may also be relevant to aging more generally. In previous studies, optimism and positive emotionality have been linked to increased life satisfaction (52,53), and a recent study of 35,749 individuals found that decelerated brain age was associated with life and relationship satisfaction (54). In older adults without cognitive impairment, increased life satisfaction and social health has been shown to be associated with decelerated brain aging and an apparently

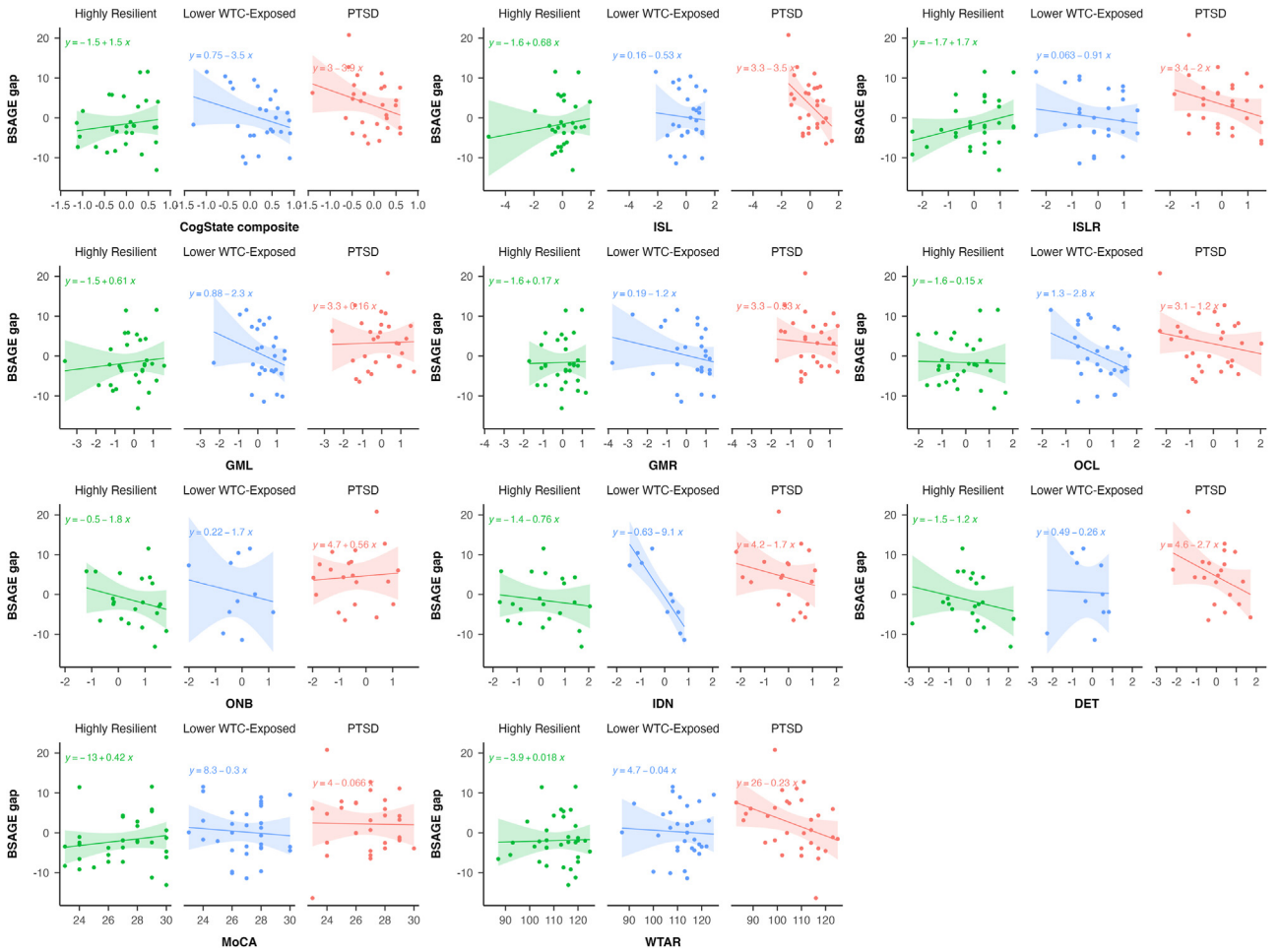

Figure 3. Cognitive measures and brain structure age (BSAGE) gap by group. The Cogstate composite score is an average of scaled scores on all valid tests. DET, Detection; GML, Groton Maze Learning; GMR, Groton Maze Recall; IDN, Identification; ISL, International Shopping List; ISLR, International Shopping List Recall; MoCA, Montreal Cognitive Assessment; OCL, One-Card Learning; ONB, One-Back; PTSD, posttraumatic stress disorder; WTC, World Trade Center; WTAR, Wechsler Test of Adult Reading.

younger brain (55,56). Broader studies have provided evidence that resilience is associated with successful aging (57), and resilience may serve as a protective factor against stress-induced physical and psychiatric comorbidities (57). Structures with the least aging in the current study are highly consistent with recent work that has linked psychological resilience to greater cortical thickness in lateral occipital, fusiform, and inferior temporal and parietal structures (58) and a multimodal resting state network that connects a similar set of regions with the prefrontal cortex (59,60). Because the current study is cross-sectional, we cannot establish whether psychological resilience buffers brain aging or structural resilience to aging buffers risk for PTSD. It is possible that coordinated processing among distributed brain regions in structural and functional networks is protective against neurodegenerative effects of aging, because more distributed networks are more robust to insult even if they are less efficient (61,62).

There are several candidate pathways that may link accelerated brain aging and PTSD. Particularly relevant to the chronic WTC-related participants with PTSD in this study, it has been suggested that PTSD is a protracted stress state (e.g., chronic hypervigilance, physiological arousal, disrupted sleep) that increases vulnerability to oxidative stress and cellular aging (63) via dysregulation in immunological, neuroendocrine, metabolic, and epigenetic pathways (64). For example, PTSD severity has been linked to greater DNA methylation, a marker of cellular aging, in WTC responders (65), and DNA methylation has been indirectly related to poorer working memory in PTSD through reduced corpus collosum integrity (50). In addition, a postmortem brain tissue study identified accelerated RNA transcriptomic aging in PTSD in the ventromedial prefrontal cortex (66), a region with differential functioning seen in resilient trauma-exposed individuals versus individuals with PTSD in functional MRI studies (60). Behavioral pathways, including PTSD's impact on health behaviors (e.g., smoking, physical activity, substance use) and social connection, also likely play a role in vulnerability to cellular aging and may serve as modifiable factors for clinical intervention (67).

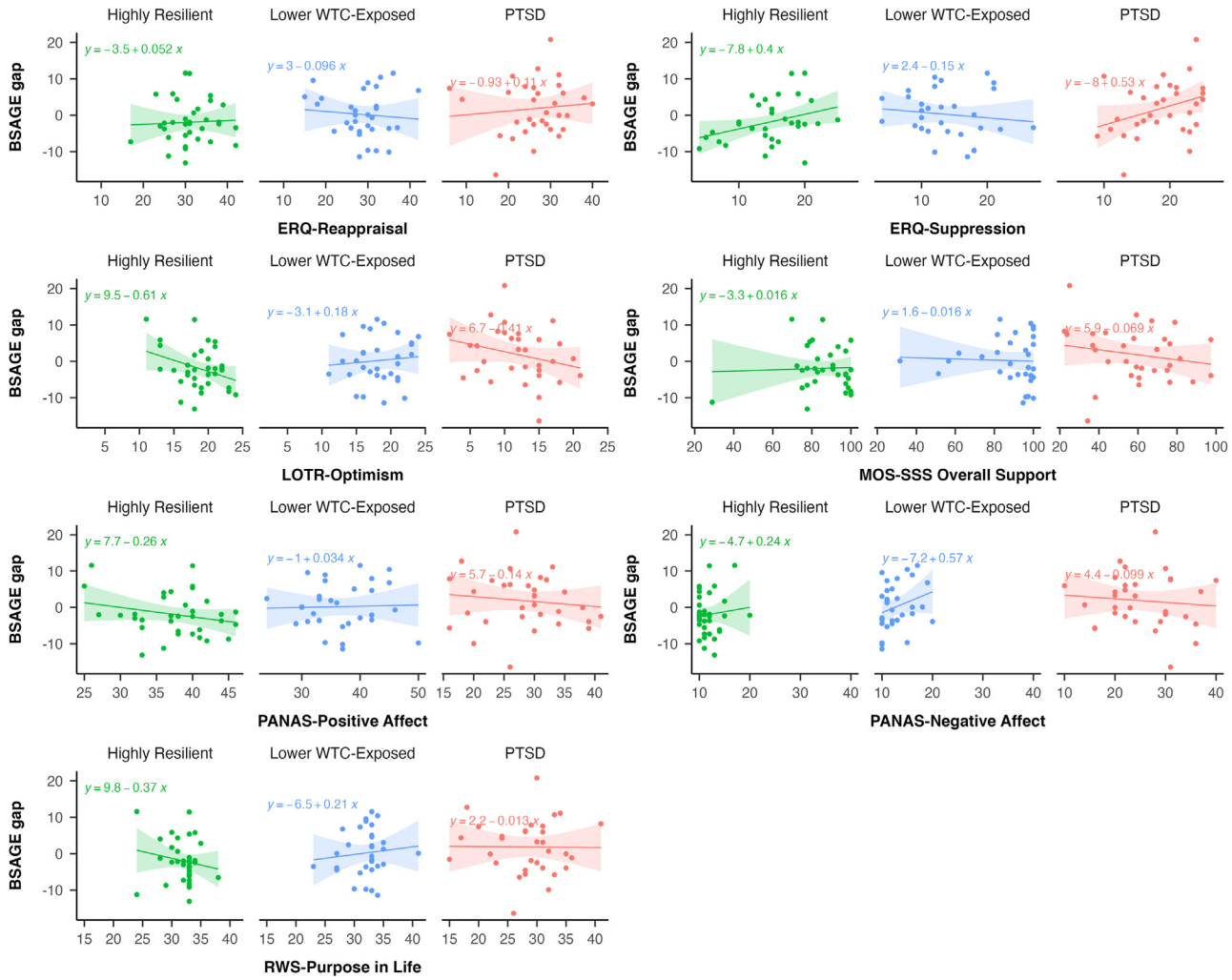

Figure 4. Self-report psychological resilience measures and brain structure age (BSAGE) gap by group. ERQ, Emotion Regulation Questionnaire; LOT-R, Life Orientation Test-Revised; MOS-SSS, Medical Outcomes Study Social Support Survey; PANAS, Positive and Negative Affect Schedule; PTSD, post-traumatic stress disorder; RWS, Ryff Wellbeing Scale; WTC, World Trade Center.

Although our findings point to novel directions for future studies that may help elucidate the relationship between psychological resilience and brain aging, there are also some important limitations. First, there were group differences on certain demographic variables, including responder occupation and self-reported health conditions, that might have contributed to some of the brain age differences that we observed (43). The PTSD group had more total self-reported health conditions ($p < .001$), as is typical for PTSD samples (68), including a higher incidence of sleep apnea and respiratory/pulmonary conditions (Table 1), which is consistent with previous studies that have identified a bidirectional relationship between pulmonary disease and PTSD in WTC responders (69) and with a recent study that showed moderation of the relationship between PTSD and cognitive impairment by pulmonary functioning in WTC responders (43). Biopsychosocial factors including age, sex, diabetes, hypertension, vascular diagnoses, coffee consumption, and smoking, among other factors, play a role in brain age (54). While we attempted to correct for some of these factors including the presence of pulmonary disease and hypertension, diabetes, and smoking history, the PTSD group had more comorbid health conditions overall and might also have had other lifestyle differences from the resilient group, including a history of SUD. Lifetime SUD was exclusionary for both non-PTSD groups, while 43% of the PTSD group met criteria for lifetime SUD (none met criteria within the past 6 months), which might have driven accelerated brain aging. Splitting the PTSD group by lifetime SUD showed no significant difference in BSAGE gap, and unexpectedly, there was a larger difference between the Highly Resilient group and the PTSD subgroup with lifetime SUD than the PTSD subgroup without SUD. However, it would be helpful for future studies to capture patterns of alcohol intake and other substances at a more granular level together with exercise and other health behaviors. We also lacked detailed data on environmental exposures. However, the pattern of accelerated

aging in PTSD versus decelerated aging in highly resilient responders is unlikely to be fully explained by differential occupational exposure to particulate matter that has been linked to neuroinflammation and cognitive aging (70,71). A similar proportion of individuals in the PTSD and the Highly Resilient group reported having been caught in the dust cloud and working directly on the pit or pile at the WTC site. Finally, taking full statistical advantage of the multivariate data from *BrainStructureAges* (24) would require a much larger sample to obtain reliable statistical estimates. Additional confirmatory work is needed in this area because we primarily explored and described the data here.

Conclusions

Notwithstanding these limitations, this study adds to the field's understanding of relationships between psychological resilience and brain aging in WTC responders. We hope that this work will 1) demonstrate the feasibility and potential utility of BSAGE in understanding factors that may have enabled some individuals to remain highly resilient despite significant exposure to WTC-related stressors and 2) suggest some possible directions for subsequent investigation of interindividual structural differences that may emerge without or before overt cognitive impairment in older trauma-exposed populations.

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AF is named co-inventor on a patent application in the United States and several issued patents outside the United States filed by the Icahn School of Medicine at Mount Sinai related to the use of ketamine for the treatment of PTSD. This intellectual property has not been licensed. AF and DSC are named co-inventors on issued patents in the United States and outside the United States filed by ISMMS related to the use of ketamine for the treatment of PTSD. DSC is named co-inventor on patents filed by the ISMMS related to treatment for treatment-resistant depression, suicidal ideation, and other disorders. DSC is a named co-inventor on a patent application filed by ISMMS for systems and methods for providing a resilience building application to support mental health of participants. This intellectual property has not been licensed. DSC and JWM are named co-inventors on a patent application filed by the ISMMS for the use of intranasally administered neuropeptide Y for the treatment of mood and anxiety disorders. This intellectual property has not been licensed. JWM has provided paid consultation services in the past 24 months for Autobahn Therapeutics, Inc.; Biohaven Pharmaceuticals, Inc.; Cliniclabs, Inc.; Clexio Biosciences, Ltd.; Compass Pathfinder, Plc.; Janssen Pharmaceuticals; KetaMed, Inc.; LivaNova, Plc.; Merck & Co., Inc.; WCG Clinical, Inc.; and Xenon Pharmaceuticals, Inc. MMP-R has received research grant funding from Neurocrine Biosciences, Inc.; Millennium Pharmaceuticals; Takeda; and Al Cure. She is a consultant for Neurocrine Biosciences, Inc., and Alkermes. She has served on an advisory board for Neurocrine Biosciences Inc. All other authors report no biomedical financial interests or potential conflicts of interest.

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