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Genetic Risk for Alzheimer Disease and Plasma Tau Are Associated With Accelerated Parietal Cortex Thickness Change in Middle-Aged Adults

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Abstract

Background and Objectives

Neuroimaging and biomarker studies in Alzheimer disease (AD) have shown well-characterized patterns of cortical thinning and altered biomarker concentrations of tau and β-amyloid (Aβ). However, earlier identification of AD has great potential to advance clinical care and determine candidates for drug trials. The extent to which AD risk markers relate to cortical thinning patterns in midlife is unknown. The first objective of this study was to examine cortical thickness change associated with genetic risk for AD among middle-aged military veterans. The second objective was to determine the relationship between plasma tau and Aβ and change in brain cortical thickness among veterans stratified by genetic risk for AD.

Methods

Participants consisted of post-9/11 veterans (N = 155) who were consecutively enrolled in the Translational Research Center for TBI and Stress Disorders prospective longitudinal cohort and were assessed for mild traumatic brain injury (TBI) and posttraumatic disorder (PTSD). Genome-wide polygenic risk scores (PRSs) for AD were calculated using summary results from the International Genomics of Alzheimer's Disease Project. T-tau and Aβ40 and Aβ42 plasma assays were run using Simoa technology. Whole-brain MRI cortical thickness change estimates were obtained using the longitudinal stream of FreeSurfer. Follow-up moderation analyses examined the AD PRS × plasma interaction on change in cortical thickness in AD-vulnerable regions.

Results

Higher AD PRS, signifying greater genetic risk for AD, was associated with accelerated cortical thickness change in a right hemisphere inferior parietal cortex cluster that included the supramarginal gyrus, angular gyrus, and intraparietal sulcus. Higher tau, but not Aβ42/40 ratio, was associated with greater cortical thickness change among those with higher AD PRS. Mild TBI and PTSD were not associated with cortical thickness change.

Discussion

Plasma tau, particularly when combined with genetic stratification for AD risk, can be a useful indicator of brain change in midlife. Accelerated inferior parietal cortex changes in midlife may be an important factor to consider as a marker of AD-related brain alterations.

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Glossary

AD = Alzheimer disease; **Aβ** = β-amyloid; **CV** = coefficient of variation; **DSM** = Diagnostic and Statistical Manual of Mental Disorders; **FWHM** = full width half maximum; **GWAS** = genome-wide association study; **LLOQ** = lower limit of quantification; **MP-RAGE** = magnetization-prepared rapid gradient echo; **mTBI** = mild traumatic brain injury; **PRS** = polygenic risk score; **p-tau** = phosphorylated tau; **PTSD** = posttraumatic disorder; **ROI** = region of interest; **TBI** = traumatic brain injury; **TRACTS** = Translational Research Center for TBI and Stress Disorders; **t-tau** = total tau.

Disease processes underlying late-onset Alzheimer disease (AD) begin decades before clinical symptoms appear,[1] and few treatment options are available by the time a formal diagnosis is made. As such, identifying preclinical biomarkers and endophenotypes of AD is critical for early detection and intervention. To date, biomarker research involving in vivo measures of β-amyloid (Aβ) and pathologic tau has predominantly been conducted in older adulthood, closer to the time of conversion to AD. However, numerous failed therapeutic trials suggest that treatment needs to be implemented in high-risk individuals earlier in the disease course.[2] As evidence has indicated that Aβ deposits occur as early as age 30 years and abnormal tau aggregates earlier in the lifespan than previously identified,[3] there is growing recognition that markers of preclinical AD in midlife are necessary for understanding pathology at the earliest stages of disease.[4] However, studying neuropathologic changes in the decades prior to dementia requires a sample at high risk for early pathology and endophenotypes that reflect AD pathology. Military service members may be a particularly vulnerable group given high comorbidity rates of disorders associated with dementia including traumatic brain injury (TBI), posttraumatic disorder (PTSD), depression, metabolic conditions, and sleep disorders.[5,6] Post-9/11 era veterans with blast exposures show diffuse tau accumulation on PET,[7] and the presence of multiple risk factors is associated with higher inflammation,[8] lower cortical thickness,[9] and functional disability,[10] suggesting heightened future risk of dementia.

Our previous work identified factors associated with preclinical vulnerability to AD. In a cohort of young to middle-aged veterans, we found that the interaction of genetic risk for AD and mild TBI was associated with lower cortical thickness in brain regions that atrophy in early AD.[11] Genetic risk for AD is an important vulnerability factor for conversion to AD. Because genetic variants do not change through the lifespan, analysis of risk variants offers a way to investigate AD-related variation in biomarker measurements in younger individuals. The *APOE* ε4 allele confers 7.5 times greater risk of developing AD in European ancestry cohorts.[12] Beyond *APOE*, polygenic risk scores (PRSs), which are based on the cumulative effects of genetic variants across the genome, have gained traction as important predictors of AD and cognitive decline[13] and explain more phenotypic variance than *APOE* alone.[14] A concern of the prior literature, however, is that few studies have examined risk factors and intermediate outcomes longitudinally, and therefore, a key piece of evidence linking early risk markers with progressive neurodegenerative decline is lacking. Furthermore, there is a critical need to identify early biomarkers that improve on genetic prediction models. In older adulthood, CSF Aβ, phosphorylated tau (p-tau), and total tau (t-tau) are well-established markers of preclinical AD. With the invention of highly sensitive blood-based fluid assays that are less invasive and more cost-effective than CSF collection, plasma and serum-based measurements of Aβ and tau are promising in vivo precursors of neurodegenerative processes.[15,16] Plasma measurements of the Aβ 42/40 ratio and tau have been associated with changes in brain regions implicated in AD pathology. However, the importance of these markers measured earlier in the neurodegenerative trajectory is unknown. Blood-based markers may be particularly useful if they can predict neuropathologic change in the brain measured by tools such as MRI, which is more accessible and less expensive and invasive than PET.

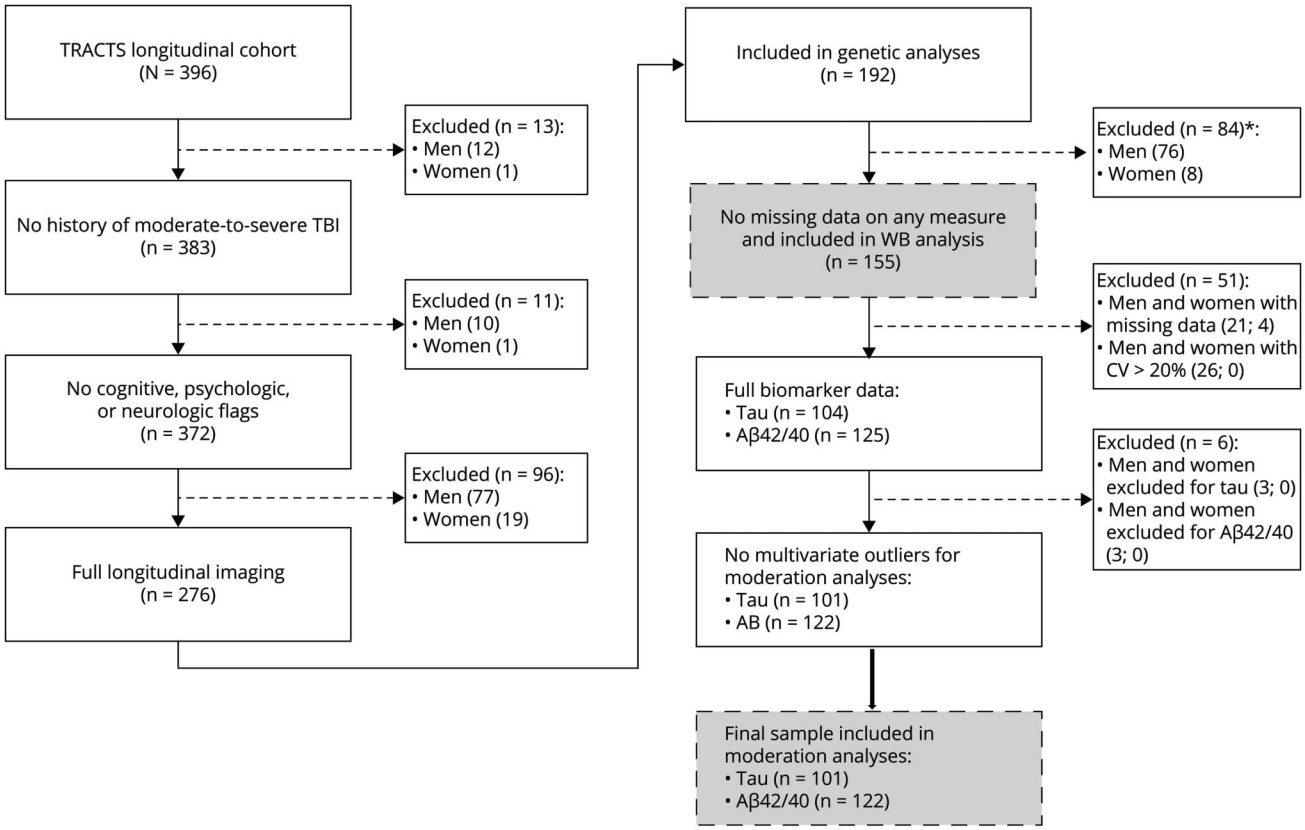
The goal of the current study was to characterize predictors of cortical thickness change over a 2-year period in a middle-aged sample who were at risk for negative brain outcomes. We first identified AD-vulnerable brain regions that declined over time as a function of genetic risk for AD, TBI, and their interaction. We next examined whether plasma markers of AD pathology (t-tau and Aβ42/40 ratio) were associated with change in cortical thickness in AD-vulnerable brain regions. Based on our previous cross-sectional work,[11] we hypothesized that the combination of higher AD PRS scores and TBI would be associated with cortical thickness change in areas of the brain that are the first to reflect AD pathology, including the medial temporal lobes and parietal cortex.

Methods

Participants

Participants consisted of men (n = 142) and women (n = 13) post-9/11 veterans who were consecutively enrolled in the Translational Research Center for TBI and Stress Disorders (TRACTS) prospective longitudinal cohort, an ongoing study taking place at VA Boston Healthcare System. Detailed information about recruitment, inclusion/exclusion criteria, and measures in the battery has been previously described.[19] Figure 1 provides a flow chart of inclusion and exclusion criteria and a description of missing data. Briefly, exclusion criteria included the following: (1) history of seizures or serious neurologic illnesses other than mild traumatic brain injury (mTBI);

Figure 1 Exclusion Process and Missing Data



Exclusion process for a priori exclusion criteria and missing data. Only participants with complete data for all variables were included in each analysis. Genetic analyses were restricted to genetically confirmed European ancestry participants. Aβ = β-amyloid; CV = coefficient of variation; TBI = traumatic brain injury; WB = whole brain.

(2) moderate to severe TBI; (3) active homicidal and/or suicidal ideation with intent; (4) current diagnosis of bipolar or other psychotic disorder (except psychosis not otherwise specified that was due to trauma-related hallucinations) based on the Diagnostic and Statistical Manual of Mental Disorders (DSM[20]); and (5) cognitive disorder due to general medical condition other than TBI. Genetic analyses were restricted to genetically confirmed European ancestry participants.

All participants completed two 10-hour research sessions that occurred approximately 18 months apart. Each session consisted of psychiatric interviews, clinical interviews, self-report psychological questionnaires, and comprehensive neuropsychological and biological assessments.

Standard Protocol Approvals, Registrations, and Patient Consents

The Institutional Review Board at the VA Boston Healthcare System approved all research procedures, and participants provided written informed consent prior to participating in the study.

Demographics and Psychiatric Assessment

A demographic questionnaire was used to collect information related to sex, education, and general health. History of TBI was assessed using the Boston Assessment of TBI–Lifetime,[21] which is a validated, semistructured interview. The Clinician-Administered PTSD Scale[22] for DSM-IV was used to assess for a lifetime history of PTSD. The Structured Clinical Interview for DSM-IV Axis I disorders[23] was used to determine mood, anxiety, substance use, psychotic, and other DSM-based mental health disorders. All clinical diagnoses were determined by consensus of at least 3 licensed clinical psychologists.

Genotyping and Polygenic Risk Score Computation

Genotyping in the TRACTS cohort has been described elsewhere and will only be briefly summarized here.[24,25] The Illumina HumanOmni2.5–8 BeadChip was used for genotyping. Cleaning of genotype data, imputation based on the Thousand Genomes Phase 3 reference panel,[26] and genetically based ancestry determination were performed using a consortium-developed pipeline.[27,28]

PRSs for a target cohort are computed as a weighted sum of single nucleotide variations (SNVs [formerly SNPs]) across the genome, with the beta (or log odds ratio in the case of dichotomous traits) used as the weights. Here, we computed PRSs for AD in the TRACTS sample based on the summary

Table 1 Participant Demographics as a Function of Polygenic Risk for Alzheimer Disease

	Total (N = 155)	Low AD risk (n = 74)	High AD risk (n = 81)	Group comparison
Age at baseline, M (SD)	33.50 (9.13)	33.99 (8.28)	32.84 (9.91)	$p = 0.438$
Age at follow-up, M (SD)	35.25 (9.05)	35.80 (8.15)	34.75 (9.82)	$p = 0.475$
Years of education, M (SD)	14.15 (2.06)	13.84 (2.00)	14.44 (2.09)	$p = 0.067$
Years since baseline, M (SD)	1.87 (0.78)	1.83 (0.65)	1.91 (0.89)	$p = 0.501$
Males, n (%)	142 (91.6)	69 (93.24)	73 (90.12)	$p = 0.484$
History of mTBI, n (%)	100 (64.5)	49 (66.22)	51 (62.96)	$p = 0.672$
History of PTSD, n (%)	111 (71.6)	57 (77.03)	54 (66.67)	$p = 0.153$
Polygenic risk for AD	−0.033 (0.008)	−0.039 (0.004)	−0.027 (0.006)	$p < 0.001$
Log Aβ40 pg/mL (n = 122), M (SD)	5.37 (0.16)	5.35 (0.15)	5.39 (0.17)	$p = 0.169$
Log Aβ42 pg/mL (n = 122), M (SD)	2.10 (0.17)	2.08 (0.18)	2.11 (0.17)	$p = 0.546$
Log Aβ42/40 pg/mL (n = 122), M (SD)	0.39 (0.03)	0.39 (0.03)	0.39 (0.02)	$p = 0.863$
Log tau pg/mL (n = 101), M (SD)	0.37 (0.51)	0.42 (0.45)	0.31 (0.57)	$p = 0.272$

Abbreviations: Aβ = β-amyloid; AD = Alzheimer disease; mTBI = mild traumatic brain injury; PTSD = posttraumatic stress disorder.

results of a European ancestry genome-wide association study (GWAS)[29] in lieu of a more recent AD meta-analysis GWAS which included proxy (reported parental) cases[30] that can affect odds ratio estimates.[31] PRSs were computed using PRSice[32] from the best-guess genotypes with an 80% certainty threshold. SNVs with a minor allele frequency of less than 1% or a missing rate of greater than 5% were excluded from PRS calculation. Clumping was performed based on PRSice's default parameters. PRSs are often computed based on a set of SNVs that pass a significance threshold. Here, to limit our multiple testing burden, we calculated our PRS using SNVs that were genome-wide significant ($p < 5 \times 10^{-8}$) based on a recent publication, indicating that AD risk is oligogenic rather than polygenic.[33] There were 72 SNVs used in the PRS calculation and are listed in eTable 1, links.lww.com/WNL/C601. Additional characteristics of the SNVs that comprised the risk score can be obtained by qualified researchers who apply at niagads.org. PRSs were standardized (mean 0 SD 1 scaled) prior to analysis to improve the interpretability of PRS effect size estimates.

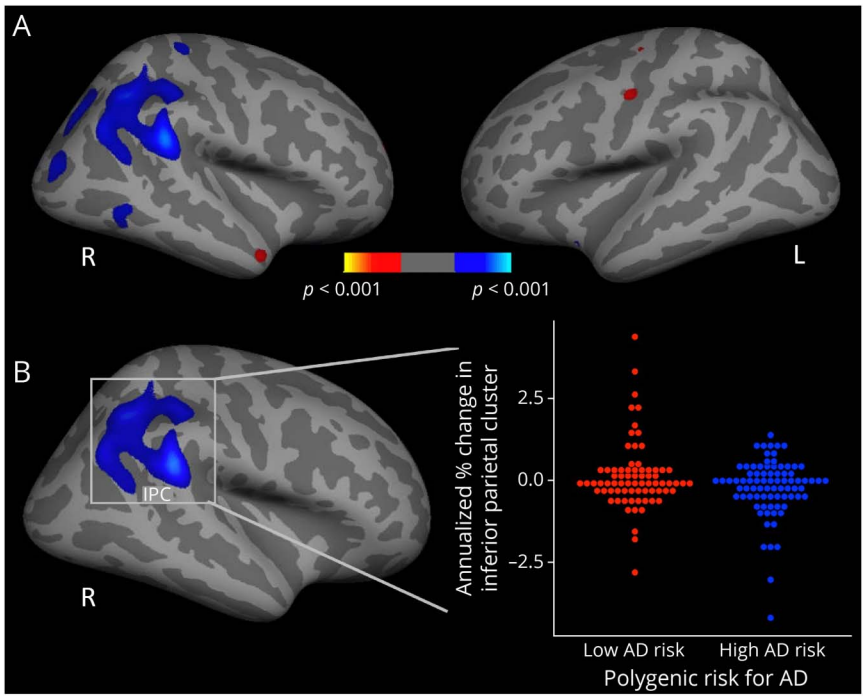
Plasma-Based Biomarkers

Fasting blood draws were conducted between 7:00 AM and 7:30 AM. Plasma was collected in EDTA tubes, centrifuged, and then immediately frozen and stored at −70°C. To avoid multiple freeze-thaw cycles, tau (t-tau), Aβ 40, and Aβ 42 assays were conducted in batches. Plasma assays were run in duplicate using the ultra-sensitive Simoa technology on the automated high-definition 1 analyzer (Quanterix, Billerica, MA). T-tau was run as part of the neurology 4-plex assay, and Aβ 40 and Aβ 42 were run as part of the neurology 3-plex assay. Plasma samples were aliquoted into 96-well plates using the same template for each plate and diluted according to the manufactures' specifications. Data from plasma samples were excluded if the coefficient of variation (CV) between duplicate runs was over 20% and/or the measured analyte concentrations were below the lower limit of quantification (LLOQ). The average CV for t-tau was 7.96% (SD = 5.08), and the LLOQ was 0.024. Plasma concentrations of t-tau were not normally distributed and were log transformed for statistical analysis. The average CV for Aβ 40 was 3.33% (SD = 3.76) and the LLOQ was 1.90, and the average CV for Aβ 42 was 5.50% (SD = 4.57) and the LLOQ was 0.225. The Aβ42/40 ratio was calculated and used for all subsequent analyses.

MRI Acquisition and Processing

Neuroimaging data were acquired on a 3-T Siemens (Erlangen, Germany) TIM Trio scanner and after scanner upgrade with a MAGNETOM Prisma^{fit} scanner (Trio-upgrade). Data for 78 participants were acquired with the TIM Trio for both baseline and follow-up time points, 39 were acquired with a MAGNETOM Prisma^{fit} scanner for both time points, and 38 were acquired across scanner upgrade. TIM Trio data were collected with a 12-channel phased-array head coil, and the Prisma^{fit} data were collected with a 20-channel head coil. The acquisition on both scanners included 2 high-resolution whole-brain T1-weighted images using magnetization-prepared rapid gradient echo (MP-RAGE) volumes with approximately matched parameters across upgrade (Trio: TR/TE = 2.53 s/3.32 ms, Prisma^{fit}: TR/TE = 2.53 s/3.35 ms, flip angle = 7 deg, and 1 mm isotropic). Scans were 3D sagittal acquisitions with 176 contiguous slices (imaging matrix = 256 × 176, in-plane resolution = 1 mm, and slice thickness = 1 mm). To create a single high contrast-to-noise image, the 2 MP-RAGE volumes were averaged.

Figure 2 Polygenic Risk for AD Is Associated With Reduced Cortical Thickness in the Inferior Parietal Cortex



(A) Results from uncorrected significance map for whole-brain analysis examining the relationship between AD polygenic risk and annualized percent change in cortical thickness. (B) Significance map after clusterwise correction shows cortical thickness change in right IPC with higher polygenic risk for AD. AD = Alzheimer disease; IPC = inferior parietal cortex.

The FreeSurfer image analysis suite (version 7.1; downloadable at; surfer.nmr.mgh.harvard.edu) was used to perform automated cortical reconstruction and volumetric segmentation. Participant data are run through a standard processing stream that includes motion correction, averaging volumetric T1-weighted images, removal of nonbrain tissue using a hybrid watershed/surface deformation procedure, automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures, intensity normalization, tessellation of the gray and white matter boundary, automated topology correction, and surface deformation to optimally place the gray/white and gray/CSF borders at the location where the greatest shift in intensity defines the transition to the other tissue class. Every image was manually inspected and edited for accuracy of the gray/white and gray/pial surfaces and run through a second reconstruction that began at the point where edits were applied.

Longitudinal cortical thickness change metrics were estimated using the longitudinal stream of FreeSurfer version 7.1 as described in our previous work.[34] Briefly, an unbiased within-subject template space and image was created based on cross-sectional images from the 2 time points for each participant using robust, inverse consistent registration. The within-subject template is used to impose consistent segmentation across time points, reducing confounds associated with longitudinal analysis. Surface maps were resampled, transformed via spherical registration to a common surface space, and smoothed using a circulatory symmetric Gaussian kernel with a full width half maximum (FWHM) of 20 mm.[35]

Statistical Analyses

Whole-Brain Analysis

Vertex-wise general linear models were performed using FreeSurfer 7.1, and statistical analyses and plots were produced using R (version 4.0.4). To limit the interindividual variability in scan intervals, longitudinal change in cortical thickness for each hemisphere was calculated as an annualized measure of the symmetrized percent change (i.e., the annual rate of change with respect to the average thickness measure across the 2 time points). Statistical correction for multiple comparisons was performed using a Monte Carlo simulation-based clusterwise procedure to determine the distribution of the maximum cluster size under the null hypothesis. Five thousand iterations of simulations were performed, using a threshold of $p < 0.050$ and an FWHM of 20 for each analysis. Whole-brain analyses examined the relationship between annual percent change of cortical thickness and main and interaction effects of AD PRS, mild TBI, and PTSD, adjusting for age. Regions of interest (ROIs) that survived multiple comparisons correction were extracted from FreeSurfer output and used for plasma biomarker analyses.

Plasma Biomarker Analysis

A subset of participants had blood biomarker data available (t-tau N = 101; Aβ42/40 ratio N = 122; Figure 1). Hierarchical linear regression and simple slopes analyses were conducted using the pequod package in R. Residualized mean annual percent change of the thickness within the significant ROI from the whole-brain analysis was calculated for all

Table 2 Regression Model for AD Polygenic Risk Score by Tau Interaction on Change in Cortical Thickness in the Inferior Parietal Cluster

Residualized % change in inferior parietal ROI		
	Step 1	**Step 2**
Constant	−0.031	−0.076
PRS	−0.237[a]	−0.223[a]
Log tau	−0.131	−0.094
PRS × tau	—	−0.266[b]
R^2	0.063	0.132
Adjusted R^2	0.044	0.106
R^2 change	0.063[a]	0.070[b]
F change	3.29[a]	7.77[b]
***F*(2,98)**	3.28 (*p* = 0.042)	4.93 (*p* = 0.003)

Abbreviations: ROI = region of interest; PRS = polygenic risk score; R^2 = coefficient of determination; F = ratio of 2 variances.
[a] <0.05.
[b] <0.01.

participants and used as the dependent variable. All predictor variables were mean centered before entering the model. Hierarchical regression models were conducted to examine the interaction between AD PRS and plasma-based biomarker (t-tau or Aβ42/40 ratio) on annual percent change of the significant ROI. For each hierarchical regression biomarker analysis, AD PRS and plasma-based biomarker were entered in step 1 to examine main effects, and the AD PRS by biomarker interaction was added in step 2 to determine whether a significant amount of additional variance was accounted for by the interaction. Mahalanobis distance scores were generated from the moderation model. Distance scores that exceeded the critical χ^2 value for 3 degrees of freedom (χ^2 = 16.27, a = 0.001) were considered outliers. Three participants met this criterion and were excluded from moderation analyses for t-tau, and 6 individuals met this criterion for the Aβ42/40 ratio. Simple slope analysis was conducted to decompose interaction effects.

Data Availability

GWAS summary statistics for AD can be downloaded with permission from NIAGADS: niagads.org. Deidentified data may be shared via DUA by contacting the TRACTS program.

Results

Participants

Demographic characteristics of the entire sample are reported in Table 1. Participants were divided into high (>−0.06) and low (<−0.06) AD PRS risk groups by median split to assess differences in demographic and covariate variables according to AD risk. Independent sample *t* tests revealed no group differences in age, $t(153) = 0.72$, $p = 0.475$, interval since baseline visit, $t(153) = -0.68$, $p = 0.501$, or years of education, $t(153) = -1.84$, $p = 0.067$. Chi-squared tests revealed no significant differences between risk groups in regard to sex, $\chi^2\ (1) = 0.49$, $p = 0.484$, history of mTBI, $\chi^2\ (1) = 0.18$, $p = 0.672$, lifetime PTSD diagnosis, $\chi^2\ (1) = 2.04$, $p = 0.153$, or group by scanner pairings (Trio-Trio, Prism-Prisma, and Trio-Prisma), $\chi^2\ (2) = 0.95$, $p = 0.620$.

Whole-Brain Analysis

General linear model analysis revealed that there was no mild TBI × AD PRS or PTSD × AD PRS interaction on cortical thickness change. However, there was a main effect of AD PRS after adjusting for age, mild TBI, and PTSD in a right hemisphere inferior parietal cortex cluster that included the supramarginal gyrus (peak voxel Montreal Neurological Institute coordinates = 59.73, −37.81, 22.74), angular gyrus, and intraparietal sulcus. Figure 2 provides significance map and scatterplot of cluster scores plotted by PRS for the AD risk group. Although additional regions near the temporal pole, superior frontal gyrus, and occipital parietal boundary showed nominal associations with higher AD PRS (Figure 2A and eTable 2, links.lww.com/WNL/C602), the inferior parietal cluster was the only region to survive multiple comparisons correction (Figure 2B).

Plasma Biomarker Analysis

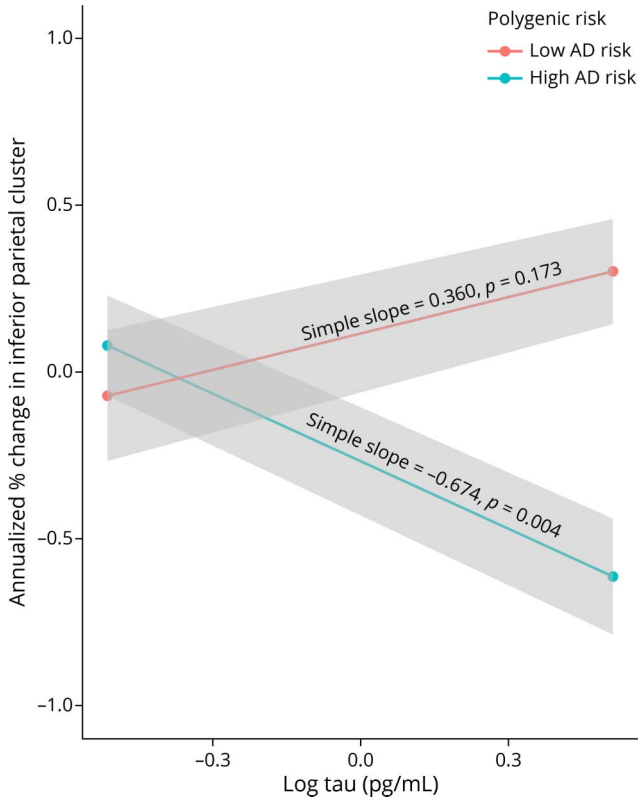
We next determined the influence of plasma biomarkers (t-tau and Aβ42/40 ratio) on the relationship between AD PRS and cortical thickness change in the region identified in the whole-brain analysis (i.e., the inferior parietal cortex cluster). Table 2 provides model statistics, and eTable 3, links.lww.com/WNL/C603, provides demographic information for participants in the biomarker analysis. There was a significant AD PRS by t-tau interaction on cortical thickness change in the inferior parietal cortex (β = −0.266, $p = 0.006$). To decompose the interaction, a simple slope analysis was conducted, in which the relationship between t-tau and inferior parietal thickness change was assessed at 1 SD above and below the mean of AD PRS (Figure 3). The relationship between t-tau and inferior parietal thickness was significant at high AD PRS (β = −0.674, $p = 0.004$) but not low AD PRS (β = 0.360, $p = 0.173$). These results indicate that among those with higher genetic risk for AD, greater concentrations of t-tau were associated with decreased cortical thickness over time in the inferior parietal cortex.

By contrast, there was no main effect of Aβ42/40 (β = 0.009, $p = 0.919$) on inferior parietal cortex thinning change, nor was there an Aβ42/40 × AD PRS interaction (β = 0.006, $p = 0.951$). eTable 4, links.lww.com/WNL/C604, provides full regression results for the Aβ42/40 ratio model and the results for Aβ42 and Aβ40 separately.

Discussion

The objective of this study was to examine midlife biomarkers of longitudinal cortical thickness change in regions of the

Figure 3 Polygenic Risk for AD Moderates the Relationship Between Plasma Tau and Change in Inferior Parietal Cortex Thickness



Annualized % change values represent residualized scores adjusting for mTBI, PTSD, and age. AD = Alzheimer disease; PTSD = posttraumatic disorder.

brain vulnerable to AD, toward the long-term goal of identifying early risk factors for AD. There were 2 main findings. First, in middle-aged veterans, higher genetic risk for AD was associated with accelerated cortical thickness change in the inferior parietal cortex, a region that has previously shown cortical thinning in early AD.[36] Second, genetic risk for AD moderated the relationship between plasma tau and accelerated change in the inferior parietal cortex. Contrary to our expectation, mild TBI did not predict cortical thickness change.

Identifying risk factors for AD decades prior to its onset requires a longitudinal approach to follow progression of neurodegeneration. However, most longitudinal studies of dementia risk do not adequately capture disease processes in midlife.[4] Here, we examined longitudinal change in cortical thickness in a midlife sample of US military veterans. After implementing a conservative whole-brain voxel-wise approach, we observed that PRS for AD predicted accelerated cortical thickness change in the inferior parietal cortex, providing evidence for this region as an early vulnerability site for AD. The inferior parietal cortex cluster found here includes the supramarginal gyrus, angular gyrus, and intraparietal sulcus. The inferior parietal cortex is a key polymodal association integration area that is involved in attention processing and semantic and episodic memory retrieval.[37,38] Although it shows large effects sizes in cortical thinning in early and mild AD[39] and declines with disease progression,[40] the inferior parietal cortex has not often been regarded as a site for early AD pathology. Braak staging protocols emphasize tau pathology in the medial temporal lobe regions, beginning in the entorhinal cortex and progressing to the visual cortex, with more recent work suggesting that tau may originate in regions such as the locus coeruleus prior to the entorhinal cortex.[3] However, the inferior parietal cortex is among the neocortical regions that are first to show Aβ deposits in studies of Aβ staging.[41] Aβ deposits are hypothesized to propagate forward to regions receiving neuronal inputs from the neocortex, eventually spreading to the medial temporal lobes.[41] Neuroimaging studies have provided converging evidence that the inferior parietal cortex serves as a network hub that propagates Aβ progression,[42] implicating its involvement in early AD-related changes. Although we cannot ascertain the mechanism of accelerated cortical thickness change in the inferior parietal cortex observed here, it will be important for future work to determine a link between genetic risk and AD neuropathology in this region.

With the growing emphasis on minimally invasive and inexpensive biomarkers to improve early diagnosis of AD, we examined the extent to which peripheral markers of AD pathology (i.e., tau and Aβ) could inform changes in cortical thickness. Plasma tau, but not Aβ, interacted with AD PRS to predict greater cortical thickness change. Tau protein in CNS neurons can travel across the blood-brain barrier, and tau in blood appears to originate in the CNS, making it a suitable peripheral biomarker of CNS pathology.[43] Although results are not consistently found,[44] plasma t-tau has shown promise as a preclinical marker of AD.[15,45] A recent meta-analysis showed that plasma tau was elevated among those with AD, making it a suitable biomarker for AD.[46] The relationship between plasma tau and cortical thickness in midlife has not been widely studied; however, the results found here are consistent with prior work showing that higher CSF tau levels were associated with lower inferior parietal cortex thickness among those with AD.[47] Of interest, the GWAS used to compute the AD PRS in this study implicated pathways associated with tau protein binding,[48] suggesting a synergistic genetic pathway to accelerated cortical change. Although further work in this area is necessary, the results provide support for the value of measuring genetic risk for AD and plasma tau as predictors of preclinical AD endophenotypes.

Although we expected to observe a relationship between plasma Aβ42/40 ratio and cortical thickness change, the nonsignificant results may suggest a more complex relationship between plasma Aβ and cortical thickness in midlife. In older adults, plasma Aβ42/40 ratio has been associated with Aβ and tau deposition in the inferior parietal cortex and medial and lateral temporal lobes.[18] However, growing evidence suggests that concentrations of Aβ follow a nonlinear

relationship with age in preclinical AD,[49] with initial higher concentrations of Aβ followed by a rapid decrease in Aβ concentrations following its deposition in the neocortex. This nonlinear relationship suggests that measuring longitudinal changes in the Aβ ratio may better predict cortical thinning. Alternatively, it is possible that plasma Aβ is an unreliable marker of Aβ in the CNS. Aβ in blood originates from both the CNS and the periphery including the liver, kidney, intestine, and platelets and is inconsistently associated with CSF Aβ.[50] It is possible that the plasma Aβ ratio may primarily reflect non-CNS processes and thus less likely to be associated with cortical thinning in midlife.

Although our previous work demonstrated lower cortical thickness among those with mild TBI and AD PRS in a cross-sectional study,[11] we did not observe a change in cortical thickness as a function of the mild TBI × genetic interaction. One possibility is that the 2-year timeframe was too brief to observe changes associated with mild TBI in midlife. Our ongoing work with these veterans at additional time points will be necessary to clarify the null findings.

Limitations of the study should be noted. With recent work suggesting that plasma p-tau may be a more specific marker of AD than t-tau, future work will be important to determine the optimal set of plasma markers for prediction of disease. Another limitation of examining participants in midlife is that we are unable to determine the extent to which accelerated cortical thickness will predict AD conversion, as disease symptoms will not become apparent for participants until later in their lifespan. Additional work that includes greater time since the baseline assessment will also be necessary to determine whether the change in cortical thickness continues to decline and is associated with neurodegeneration. Finally, the veteran sample examined here was primarily male and White, non-Hispanic, limiting generalizability to a broader population.

In conclusion, the current study provides support for PRS for AD and plasma tau as risk factors for accelerated cortical thinning in the inferior parietal cortex, an area that has been recognized as a neocortical hub of incipient AD pathology. The results underscore the importance of the parietal cortex in identification of higher risk for neurodegeneration, decades prior to the onset of AD. Future work considering blood biomarkers and MRI may reduce the need for highly invasive, painful, and expensive biomarker methods such as CSF collection and PET imaging.

Study Funding

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Appendix *(continued)*

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References

1. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging.* 1997;18(4):351-357. doi: 10.1016/s0197-4580(97)00056-0.
2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement.* 2011;7(3):280-292. doi: 10.1016/j.jalz.2011.03.003.
3. Braak H, Thal DR, Ghebremedhin E, Del Tredici K. Stages of the pathologic process in Alzheimer disease: age categories from 1 to 100 years. *J Neuropathol Exp Neurol.* 2011;70(11):960-969. doi: 10.1097/NEN.0b013e318232a379
4. Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol.* 2013;12(2):207-216. doi: 10.1016/S1474-4422(12)70291-0.
5. Rafferty LA, Wessely S, Stevelink SAM, Greenberg N. The journey to professional mental health support: a qualitative exploration of the barriers and facilitators impacting military veterans' engagement with mental health treatment. *Eur J Psychotraumatol.* 2020;10(1):1700613. doi: 10.1080/20008198.2019.1700613.
6. Raza Z, Hussain SF, Ftouni S, et al. Dementia in military and veteran populations: a review of risk factors—traumatic brain injury, post-traumatic stress disorder, deployment, and sleep. *Mil Med Res.* 2021;8(1):55. doi: 10.1186/s40779-021-00346-z.
7. Robinson ME, McKee AC, Salat DH, et al. Positron emission tomography of tau in Iraq and Afghanistan Veterans with blast neurotrauma. *Neuroimage Clin.* 2019;21:101651. doi: 10.1016/j.nicl.2019.101651.
8. Hayes JP, Pierce ME, Valerio KE, et al. The association between blast exposure and transdiagnostic health symptoms on systemic inflammation. *Neuropsychopharmacol.* 2022;47(9):1702-1709. doi: 10.1038/s41386-021-01138-8.
9. Santhanam P, Wilson SH, Oakes TR, Weaver LK. Accelerated age-related cortical thinning in mild traumatic brain injury. *Brain Behav.* 2019;9(1):e01161. doi: 10.1002/brb3.1161.
10. Fortenbaugh FC, Fonda JR, Fortier CB, Amick MM, Milberg WP, McGlinchey RE. The impact of common psychiatric and behavioral comorbidities on functional disability across time and individuals in post-9/11 veterans. *J Trauma Stress.* 2020;33(5):750-761. doi: 10.1002/jts.22501.
11. Hayes JP, Hayes S, Miller DR, Lafleche G, Logue MW, Verfaellie M. Automated measurement of hippocampal subfields in PTSD: evidence for smaller dentate gyrus volume. *J Psychiatr Res.* 2017;95:247-252. doi: 10.1016/j.jpsychires.2017.09.007.
12. Raber J, Huang Y, Ashford JW. ApoE genotype accounts for the vast majority of AD risk and AD pathology. *Neurobiol Aging.* 2004;25(5):641-650. doi: 10.1016/j.neurobiolaging.2003.12.023.
13. Kauppi K, Rönnlund M, Nordin Adolfsson A, Pudas S, Adolfsson R. Effects of polygenic risk for Alzheimer's disease on rate of cognitive decline in normal aging. *Transl Psychiatry.* 2020;10(1):250-258. doi: 10.1038/s41398-020-00934-y.
14. Stocker H, Möllers T, Perna L, Brenner H. The genetic risk of Alzheimer's disease beyond APOE ε4: systematic review of Alzheimer's genetic risk scores. *Transl Psychiatry.* 2018;8(1):166-169. doi: 10.1038/s41398-018-0221-8.
15. Pase MP, Beiser AS, Himali JJ, et al. Assessment of plasma total tau level as a predictive biomarker for dementia and related endophenotypes. *JAMA Neurol.* 2019;76(5):598-606. doi: 10.1001/jamaneurol.2018.4666.
16. Schindler SE, Bollinger JG, Ovod V, et al. High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis. *Neurology.* 2019;93(17):e1647–e1659. doi: 10.1212/WNL.0000000000008081.
17. Dage JL, Wennberg AMV, Airey DC, et al. Levels of tau protein in plasma are associated with neurodegeneration and cognitive function in a population-based elderly cohort. *Alzheimers Dement.* 2016;12(12):1226-1234. doi: 10.1016/j.jalz.2016.06.001.
18. Risacher SL, Fandos N, Romero J, et al. Plasma amyloid beta levels are associated with cerebral amyloid and tau deposition. *Alzheimers Dement (Amst).* 2019;11(1):510-519. doi: 10.1016/j.dadm.2019.05.007.
19. McGlinchey RE, Milberg WP, Fonda JR, Fortier CB. A methodology for assessing deployment trauma and its consequences in OEF/OIF/OND veterans: the TRACTS longitudinal prospective cohort study. *Int J Methods Psychiatr Res.* 2017;26(3):e1556. doi: 10.1002/mpr.1556.
20. APA. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. American Psychiatric Association; 2013.
21. Fortier CB, Amick MM, Grande L, et al. The Boston Assessment of Traumatic Brain Injury-Lifetime (BAT-L) semistructured interview: evidence of research utility and validity. *J Head Trauma Rehabil.* 2014;29(1):89-98. doi: 10.1097/HTR.0b013e3182865859.
22. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD Scale. *J Trauma Stress.* 1995;8(1):75-90. doi: 10.1002/jts.2490080106.
23. First MB, Spitzer RL, Gibbon M, Williams JB. Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. SCID-I/P; 2002.
24. Logue MW, Baldwin C, Guffanti G, et al. A genome-wide association study of post-traumatic stress disorder identifies the retinoid-related orphan receptor alpha (RORA) gene as a significant risk locus. *Mol Psychiatry.* 2013;18(8):937-942. doi: 10.1038/mp.2012.113.
25. Miller MW, Wolf EJ, Sadeh N, et al. A novel locus in the oxidative stress-related gene ALOX12 moderates the association between PTSD and thickness of the prefrontal cortex. *Psychoneuroendocrinology.* 2015;62:359-365. doi: 10.1016/j.psyneuen.2015.09.003.
26. Abecasis GR, Auton A, Altshuler DM, et al. A global reference for human genetic variation. *Nature.* 2015;526(7571):68-74. doi: 10.1038/nature15393.
27. Logue MW, Amstadter AB, Baker DG, et al. The psychiatric Genomics consortium posttraumatic stress disorder workgroup: posttraumatic stress disorder enters the age

of large-scale genomic collaboration. *Neuropsychopharmacology.* 2015;40(10): 2287-2297. doi: 10.1038/npp.2015.118.
28. Nievergelt CM, Maihofer AX, Klengel T, et al. International meta-analysis of PTSD genome-wide association studies identifies sex- and ancestry-specific genetic risk loci. *Nat Commun.* 2019;10(1):4558. doi: 10.1038/s41467-019-12576-w.
29. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet.* 2019;51(3):414-430. doi: 10.1038/s41588-019-0358-2.
30. Jansen IE, Savage JE, Watanabe K, et al. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet.* 2019; 51(3):404-413. doi: 10.1038/s41588-018-0311-9.
31. Liu JZ, Erlich Y, Pickrell JK. Case-control association mapping by proxy using family history of disease. *Nat Genet.* 2017;49(3):325-331. doi: 10.1038/ng.3766.
32. *PRSice: Polygenic Risk Score Software|Bioinformatics*. Oxford Academic. Accessed July 25, 2022. academic-oup-com.proxy.lib.ohio-state.edu/bioinformatics/article/31/9/1466/200539.
33. Zhang Q, Sidorenko J, Couvy-Duchesne B, et al. Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture. *Nat Commun.* 2020;11(1):4799. doi: 10.1038/s41467-020-18534-1.
34. Brown EM, Salat DH, Milberg WP, Fortier CB, McGlinchey RE. Accelerated longitudinal cortical atrophy in OEF/OIF/OND veterans with severe PTSD and the impact of comorbid TBI. *Hum Brain Mapp.* 2022;43(12):3694-3705. doi: 10.1002/hbm.25877.
35. Fischl B, Sereno MI, Dale AM. Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage.* 1999;9(2):195-207. doi: 10.1006/nimg.1998.0396.
36. Sabuncu MR, Desikan RS, Sepulcre J, et al. The dynamics of cortical and hippocampal atrophy in Alzheimer disease. *Arch Neurol.* 2011;68(8):1040-1048. doi: 10.1001/archneurol.2011.167.
37. Cabeza R. Role of parietal regions in episodic memory retrieval: the dual attentional processes hypothesis. *Neuropsychologia.* 2008;46(7):1813-1827. doi: 10.1016/j.neuropsychologia.2008.03.019.
38. Jacobs HIL, Van Boxtel MP, Jolles J, Verhey FRJ, Uylings HBM. Parietal cortex matters in Alzheimer's disease: an overview of structural, functional and metabolic findings. *Neurosci Biobehavioral Rev.* 2012;36(1):297-309. doi: 10.1016/j.neubiorev.2011.06.009.
39. Dickerson BC, Bakkour A, Salat DH, et al. The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. *Cereb Cortex.* 2009;19(3):497-510. doi: 10.1093/cercor/bhn113.
40. Greene SJ, Killiany RJ. Subregions of the inferior parietal lobule are affected in the progression to Alzheimer's disease. *Neurobiol Aging.* 2010;31(8):1304-1311. doi: 10.1016/j.neurobiolaging.2010.04.026.
41. Thal DR, Rüb U, Orantes M, Braak H. Phases of Aβ-deposition in the human brain and its relevance for the development of AD. *Neurology.* 2002;58(12):1791-1800. doi: 10.1212/WNL.58.12.1791.
42. Sepulcre J, Grothe MJ, d'Oleire Uquillas F, et al. Neurogenetic contributions to amyloid beta and tau spreading in the human cortex. *Nat Med.* 2018;24(12): 1910-1918. doi: 10.1038/s41591-018-0206-4.
43. Banks WA, Kovac A, Majerova P, Bullock KM, Shi M, Zhang J. Tau proteins cross the blood-brain barrier. *J Alzheimers Dis.* 2016;55(1):411-419. doi: 10.3233/JAD-160542.
44. de Wolf F, Ghanbari M, Licher S, et al. Plasma tau, neurofilament light chain and amyloid-β levels and risk of dementia; a population-based cohort study. *Brain.* 2020; 143(4):1220-1232. doi: 10.1093/brain/awaa054.
45. Fossati S, Ramos Cejudo J, Debure L, et al. Plasma tau complements CSF tau and P-tau in the diagnosis of Alzheimer's disease. *Alzheimers Dement (Amst).* 2019;11(1): 483-492. doi: 10.1016/j.dadm.2019.05.001.
46. Ding X, Zhang S, Jiang L, Wang L, Li T, Lei P. Ultrasensitive assays for detection of plasma tau and phosphorylated tau 181 in Alzheimer's disease: a systematic review and meta-analysis. *Translational Neurodegeneration.* 2021;10(1):10. doi: 10.1186/s40035-021-00234-5.
47. Fjell AM, Walhovd KB, Fennema-Notestine C, et al. CSF biomarkers in prediction of cerebral and clinical change in mild cognitive impairment and Alzheimer's disease. *J Neurosci.* 2010;30(6):2088-2101. doi: 10.1523/JNEUROSCI.3785-09.2010.
48. Kunkle BW, Grenier-Boley B, Sims R, et al. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. *Nat Genet.* 2019;51(3):414-430. doi: 10.1038/s41588-019-0358-2.
49. de Leon MJ, Pirraglia E, Osorio RS, et al. The nonlinear relationship between cerebrospinal fluid Aβ42 and tau in preclinical Alzheimer's disease. *PLoS One.* 2018;13(2): e0191240. doi: 10.1371/journal.pone.0191240.
50. Toledo JB, Xie SX, Trojanowski JQ, Shaw LM. Longitudinal change in CSF Tau and Aβ biomarkers for up to 48 months in ADNI. *Acta Neuropathol.* 2013;126(5): 659-670. doi: 10.1007/s00401-013-1151-4.

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