Received: 11 September 2023 | Revised: 12 January 2024 | Accepted: 18 January 2024

DOI: 10.1002/dad2.12550

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

APOE ε4 allele status modulates the spatial patterns of progressive atrophy in the temporal lobes after mild traumatic brain injury

Shuoqiu Gan[1,2,3,4] | **Yingxiang Sun**[4] | **Kejia Liu**[1] | **Xiaoyan Jia**[1] | **Xuan Li**[1] | **Ming Zhang**[4] | **Lijun Bai**[1]

[1]The Key Laboratory of Biomedical Information Engineering, Ministry of Education, Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an, China

[2]Institute of Artificial Intelligence, Hefei Comprehensive National Science Center, Hefei, China

[3]Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China

[4]Department of Medical Imaging, the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Correspondence
Ming Zhang, Department of Medical Imaging, The First Affiliated Hospital of Xi'an Jiaotong University, No.277, West Yanta Road, Xi'an 710061, Shaanxi, P.R. China.
Email: zhangming01@mail.xjtu.edu.cn

Lijun Bai, The Key Laboratory of Biomedical Information Engineering, Ministry of Education, Department of Biomedical Engineering, School of Life Science and Technology, Xi'an Jiaotong University, No.28, Xianning West Road, Xi'an 710049, Shaanxi, P.R. China.
Email: bailijun@xjtu.edu.cn

Funding information
National Natural Science Foundation of China, Grant/Award Numbers: 82071993, 81871331; Funds for Distinguished Youths in Shaanxi Province, Grant/Award Number: 2022JC-55; China Postdoctoral Science

Abstract

INTRODUCTION: We evaluated how the apolipoprotein E (*APOE*) ε4 allele modulated the spatial patterns of longitudinal atrophy in the Alzheimer's disease–vulnerable brain areas of patients with mild traumatic brain injury (mTBI) from the acute to chronic phase post injury.

METHODS: Fifty-nine adult patients with acute mTBI and 48 healthy controls with *APOE* ε4 allele testing underwent T1-weighted magnetic resonance imaging and neuropsychological assessments with 6 to 12 months of follow-up. Progressive brain volume loss was compared voxel-wise in the temporal lobes.

RESULTS: Patients with the *APOE* ε4 allele presented significant longitudinal atrophy in the left superior and middle temporal gyri, where the progressive gray matter volume loss predicted longitudinal impairment in language fluency, whereas mTBI *APOE* ε4 allele noncarriers showed mainly significant longitudinal atrophy in the medial temporal lobes, without significant neuropsychological relevance.

DISCUSSION: The atrophy progression observed in mTBI patients with the *APOE* ε4 allele may increase the possibility of developing a specific phenotype of Alzheimer's disease with language dysfunction.

KEYWORDS
Alzheimer's disease risk, *APOE* ε4 allele status, longitudinal atrophy, mild traumatic brain injury, temporal lobes

Highlights

- The apolipoprotein E (*APOE*) ε4 allele and mild traumatic brain injury (mTBI) are risk factors for Alzheimer's disease (AD) progression.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2024 The Authors. Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring published by Wiley Periodicals LLC on behalf of Alzheimer's Association.

Foundation, Grant/Award Number: 2023M733421; Funds for Scientific Research of Postdoctoral Researchers in Anhui Province, Grant/Award Number: 2023A659

- It is unclear how the interaction of mTBI with the *APOE* ε4 allele impacts the progressive atrophy topography in AD-vulnerable brain regions.
- In this study, patients with the *APOE* ε4 allele showed progressive atrophy patterns similar to the early stage of logopenic variant of primary progressive aphasia (lvPPA) phenotype of AD.
- *APOE* ε4 allele carriers with mTBI history may be at the risk of developing a given AD phenotype with language dysfunction.

1 | BACKGROUND

Traumatic brain injury (TBI), even mild TBI (mTBI), is an environmental risk factor for Alzheimer's disease (AD),[1,2] increasing the risk by more than two-fold.[3] The interaction of a history of TBI with AD genetic determinants, such as the apolipoprotein E (*APOE*)-ε4 allele, could lead to chronic neuropathological changes related to AD in the brain[4–6] and exacerbate the long-term risk of AD development. However, it is unclear whether and how the interaction between brain injury and the genetic risk of AD impacts the progressive neuroanatomic changes in the brain, particularly the early progression post injury.

The *APOE* ε4 allele is a recognized genetic determinant for several AD phenotypes, and relevant to poor outcomes and AD-like pathology after TBI.[4,6,7] It is linked to brain neuroanatomic changes in AD phenotypes, primarily located in the temporal lobes,[8–10] where severe amyloid beta (Aβ) protein plaques are deposited in *APOE* ε4 allele carriers post TBI.[11] Recent studies have proposed that TBI increases the risk of dementia in some specific subtypes.[12–14] Neuropsychological impairments post TBI contain multiple cognitive domains, which are found as in AD.[15,16] Underlying those dysfunctional phenotypes, there are distinct neuropathological hallmarks of neurodegeneration pathways in AD-vulnerable areas. The initial atrophy in either the medial or lateral temporal lobes is involved in the early stages of different AD phenotypes with typical or atypical symptoms, including the language dysfunction variant.[17] Previous studies focused primarily on typical AD-relevant neurodegeneration in the medial temporal lobe (MTL) after TBI[18,19]; for example, researchers found that TBI patients with the *APOE* ε4 allele had no significant difference in hippocampal volumes compared to those without the allele.[20] Further study is required to investigate how the interaction of the *APOE* ε4 allele and TBI modulates the neuroanatomic changes in AD-vulnerable areas.

The AD-like neurodegenerative changes in AD-vulnerable brain areas are commonly detected in the TBI chronic phase.[21–23] The first-year post injury is critical for long-term prognosis. Significant brain atrophy caused by a single TBI can be detected 6-months post injury and progress for years.[3,24] Neuronal loss and microglial activation could last for up to 1-year post injury, during which more than 50% of patients reported neurocognitive impairments.[25,26] This evidence has suggested that neurodegeneration in AD-vulnerable areas appeared rapidly and progressed over a long-term course after TBI,[27,28] highlighting the need for further examination of the progression of neuroanatomic changes from the acute to chronic phases post injury.

In this prospective study, we evaluated the longitudinal brain volume changes voxel-wise using magnetic resonance imaging (MRI) scans, on which a within-subject longitudinal registration approach was adopted to directly model the progressive brain atrophy with high sensitivity.[29,30] By using this method, we illustrated the progressive atrophy spatial patterns in the temporal lobes under the interaction of mTBI and the *APOE* ε4 allele within the first-year post injury, and examined its neuropsychological association. We hypothesized that patients with the *APOE* ε4 allele would present a distinct atrophy spatial pattern in the temporal lobes, and that the atrophy was related to AD-vulnerable neuropsychological impairments; however, patients without the *APOE* ε4 allele would show that the atrophy was irrelevant to AD-vulnerable neuropsychological performance.

2 | METHODS

2.1 | Participants

The recruitment flowchart of this cohort study is outlined in Figure 1. We first recruited 100 acute mTBI patients from the emergency department of a local hospital (the Second Affiliated Hospital of Wenzhou Medical University) (Table S1), and all of them had no non-hemorrhagic and microhemorrhagic lesions. Of the 100 patients, 21 were initially excluded because of lack of blood sample for *APOE* genotyping, and another 20 patients were excluded because of loss in communication. We finally recruited 59 adult patients with acute mTBI (31 male; median age 36.0 years, interquartile range [IQR] 29.0–43.5; Table S2); and all the patients had MRI scans in the acute (median 3.0 days post injury, IQR 2.0–4.0) and chronic phases (6–12 months post injury). The longitudinal MRI scans were also acquired from matched 48 healthy controls (HCs; 22 male; median age 33.0 years, IQR 28.8–48.5 years). Screening for mTBI was based on the World Health Organization's Collaborating Centre for Neurotrauma Task Force.[31] The inclusion criteria included: (1) Glasgow Coma Scale score of 13–15; (2) one or more of the following: loss of consciousness (if present) <30 min, post-traumatic amnesia (if present) <24 h, and/or other tran-

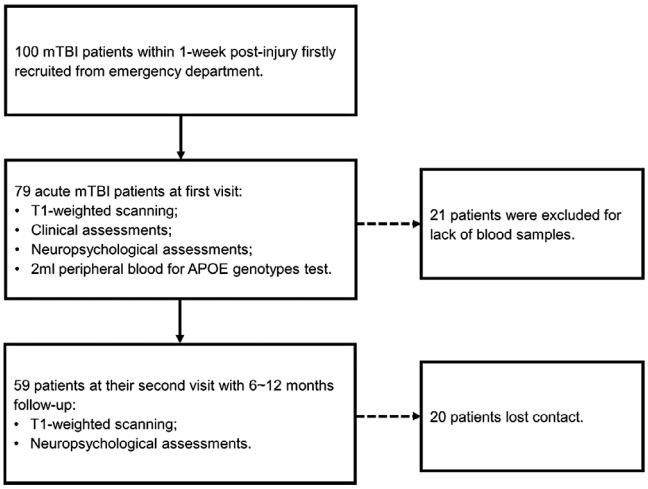

FIGURE 1 The flowchart of mTBI patient recruitment. mTBI, mild traumatic brain injury.

sient neurological abnormalities such as focal signs and seizure; and (3) no contraindications to MRI. The exclusion criteria were: history of neurological disease or psychiatric disorder, head injury, history of substance or alcohol abuse, intubation, and/or presence of a skull fracture and administration of sedatives on arrival in the emergency department, spinal cord injury, manifestation of mTBI due to medications by other injuries (e.g., systemic injuries, facial injuries, or intubation) or caused by other problems (e.g., psychological trauma, language barrier, or coexisting medical conditions), or caused by penetrating craniocerebral injury. HCs were enrolled through an advertisement calling for healthy participants and carefully screened for any neurological or psychiatric disorders. All participants signed written informed consent after the experimental procedures had been fully explained. The research procedures were approved by the local ethics committee board and conducted in accordance with the Declaration of Helsinki.

2.2 | Clinical symptom and neuropsychological assessments

Clinical assessments for patients were performed on their first visit, including postconcussive symptoms (PCS), duration of anterograde amnesia, and coma. The PCS status was evaluated using the International Classification of Diseases, Tenth Edition, Clinical Criteria, according to whether they reported three or more symptoms.

Neuropsychological assessments were conducted at two timepoints for patients and HCs. We focused on information processing speed (IPS) and language fluency because they were the prominently affected cognitive domains in AD.[32,33] IPS was evaluated using the digit symbol coding test (DSCT)[34] and the trail-making test part A (TMT-A).[35] Language fluency was evaluated using the forward digit span test (FDST) and the verbal fluency test (VFT),[17] which assessed phonemic and semantic fluency respectively, with high discrimination for language impairment.[36] The performance of IPS and language

RESEARCH IN CONTEXT

1. **Systematic review**: Mild traumatic brain injury (mTBI) is a risk factor for Alzheimer's disease (AD), but it remains unclear how mTBI interacts with AD genetic risk factors that affect the neurodegeneration progression from the acute to chronic phase post injury.
2. **Interpretation**: We designed a perspective study in patients with acute mTBI, with apolipoprotein E (*APOE*) ε4allele status testing, longitudinal T1-weighted magnetic resonance imaging (MRI) scanning, and neuropsychological assessments. Patients with the *APOE* ε4 allele showed progressive atrophy in the left superior and middle temporal gyri. This atrophy spatial pattern and its neuropsychological relevance were similar to the logopenic variant of primary progressive aphasia phenotype of AD at early stages, whereas patients without the *APOE* ε4 allele showed the atrophy mainly in the medial temporal lobes, without neuropsychological relevance.
3. **Future directions**: The *APOE* ε4 allele interacting with mTBI may increase the risk of developing a given AD phenotype with language dysfunction.

fluency was summarized by averaging the Z-score of tests in each domain with the whole sample, respectively; the lower score denoted the worse performance. The Z-score of each domain was expressed as: $\text{Z-score}_{IPS} = [Z_{DSCT}+Z_{(1/TMT\_A)}]/2$, $\text{Z-score}_{language\ fluency} = [Z_{FDST}+Z_{VFT}]/2$.

2.3 | *APOE* genotyping

A 2 mL peripheral blood sample per participant was collected for *APOE* genotyping. DNA was extracted from the blood sample using the Omega D3494-01 Blood DNA Midi Kit (Omega Biotek, Inc., USA). Two single nucleotide polymorphisms (SNPs; rs429358 and rs7412) were genotyped to identify *APOE* genotypes including the *APOE* ε2, ε3, and ε4 allele, using the Assay Design Suite v2.0 (Agena Bioscience, Inc., San Diego, CA). All genotypes containing the ε4 allele (ε4/ε4; ε4/ε3; ε4/ε2) were combined as the composite *APOE* ε4+, and others (ε2/ε2; ε2/ε3; ε3/ε3) were combined as the composite *APOE* ε4-.

2.4 | Neuroimaging data acquisition and processing

MRI data acquisition and processing procedures are showed in Figure 2. High-resolution structural T1-weighted images for two timepoints were acquired using a 3T GE 750 MRI scanner with a 32-channel head coil (Figure 2A). High-resolution sagittal three-dimensional (3D) T1 images were collected using the BRAVO sequence: repetition time

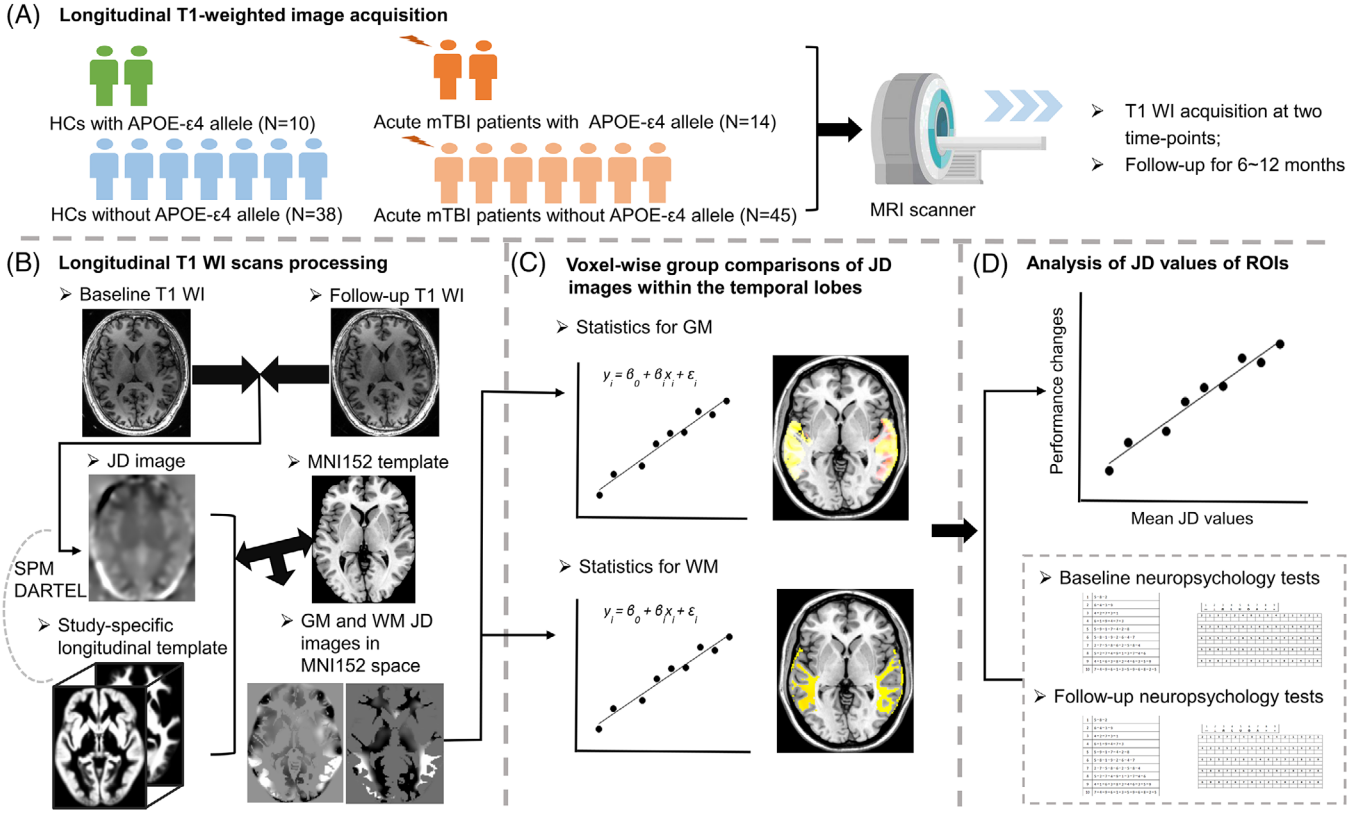

FIGURE 2 MRI data acquisition and processing procedure. (A) Longitudinal T1-weighted image acquisition. The longitudinal T1-weighted images were acquired from 59 patients with acute mTBI (14 *APOE* ε4 allele carriers) and 48 HCs (10 *APOE* ε4 allele carriers) with 6–12 months of follow-up. (B) Processing of longitudinal analysis on T1-weighted images. Here, an initial symmetric within-subject registration for each participant's baseline and follow-up scans was employed. The within-subject temporal average image and JD image were generated and segmented into GM and WM; the JD value represented the voxel-wise spatial expansion or contraction between the baseline and follow-up scans. A random selection of 20 patients with mTBI and 20 HCs was used to define a study-specific longitudinal template with DARTEL for the following registration use. Subsequently, the GM and WM JD images were normalized to MNI152 space with resampling to 1.5 mm×1.5 mm×1.5 mm voxels via the longitudinal template using DARTEL. (C) Voxel-wise group comparisons on normalized GM and the WM JD images. In the present study, we used FSL 6.0 Randomise software to conduct the voxel-wise between-group comparisons for the bilateral temporal lobes according to the MNI structural atlas. (D) Within each *APOE* subgroup of patients with mTBI, the linear regression was conducted between the regional JD value and the longitudinal changes in neuropsychological performance. *APOE*, apolipoprotein E; DARTEL, diffeomorphic anatomical registration using exponentiated Lie algebra; FSL, FMRIB software library; GM, gray matter; HCs, healthy controls; JD, Jacobian determinant; MNI, Montreal Neurological Institute; mTBI, mild traumatic brain injury; ROIs, regions of interest; T1 WI, T1-weighted image; WM, white matter.

(TR) = 8.15 ms, echo time (TE) = 3.17 ms, slice thickness = 1 mm, field of view (FOV) = 256 × 256 mm^2, matrix size = 256 × 256, flip angle = 9°.

Here, we followed the standard pipeline of within-subject longitudinal registration in Statistical Parametric Mapping 12 (SPM12)[37] to obtain the Jacobian determinant (JD) images (Figure 2B; details in Supplementary eMethods). The JD image characterized the longitudinal brain volume changes, and the JD value represented the geometric warping amount between baseline and follow-up T1-weighted scans. We got the JD images of gray matter (GM) and white matter (WM) segmentation after the pre-processing of longitudinal registration, and then registered to Montreal Neurological Institute (MNI)−152 space with resampling to 1.5 mm^3 voxels. We kept the default settings in SPM for bias correction (bias regularization: 0.001, bias FWHM: 60 mm cutoff); the GM and WM JD images were then smoothed with an 8-mm full-width half-maximum kernel to improve signal-to-noise ratio and reduce the impact of potential misregistration, representing the longitudinal volume change for the subsequent voxel-wise statistical analysis. The positive or negative JD value denoted the increase or decrease in GM and WM volume within the follow-up period, respectively.

TBI damages the neuroanatomic integrity of the temporal lobes,[24,38] in which the AD-like pathology can be detected after TBI and tends to worsen over the long term.[27,39] Given the vulnerability of the temporal lobes to mTBI, voxel-wise group comparisons of JD images were performed within the bilateral temporal lobes defined by the MNI structural atlas (Figure 2C). Subsequently, for mTBI patients with different *APOE* ε4 allele status, linear regressions were conducted between the mean JD value extracted from regions with significant group-comparison differences and the longitudinal changes in neuropsychological assessments (Figure 2D).

2.5 | Statistics

Voxel-wise statistical analysis on JD images was conducted using FSL 6.0 Randomise software[40] for a two-way between-subject (groups: HCs vs mTBI; *APOE* ε4 allele status: APOE ε4+ vs APOE ε4-) analysis of variance in a generalized linear model, with age, sex, education, and intracranial volume as covariates. Multiple testing correction used 5000 permutations to generate statistically corrected voxel-wise *p*-values for each contrast, with threshold-free cluster enhancement (TFCE) correction ($p < 0.05$). Significant regions were defined as regions of interest (ROIs) for the next analysis in mTBI *APOE* ε4 allele status subgroups (i.e., mTBI-*APOE* ε4+ and mTBI-*APOE* ε4-).

Analysis of demographic, neuropsychological, and clinical measurements, and the relationships of ROI-based mean JD values with longitudinal changes in neuropsychological assessments were performed using SPSS (version 21.0; IBM, Armonk, NY). The group comparisons for categorical data were analyzed using chi-square[2] tests. All the analysis for continuous data were based on the normality distribution test. The group differences for demographics, clinical, neuropsychological assessments, and mean JD value were compared using Mann–Whitney or independent *t*-tests, as appropriate. To evaluate whether the longitudinal atrophy was symptomatic related in mTBI *APOE* subgroups, stepwise linear regressions were estimated to determine the associations between ROI-based mean JD value and longitudinal changes in neuropsychological assessments. The threshold for significance was set at two-tailed $p < 0.05$.

3 | RESULTS

3.1 | Demographic, clinical, and neuropsychological assessments

Demographic, clinical, and neuropsychological information for all participants is listed in Table 1. There was no evidence of a statistically significant difference between mTBI and HC for these variables: age (median [IQR], 36.0 [29.0–43.5] years vs 33.0 [28.8–18.5] years; $Z = 0.39$, $p = 0.70$), education (median [IQR], 8.0 [6.0–12.0] years vs 11.0 [5.8–15] years; $Z = 1.66$, $p = 0.10$), sex (31 mTBI male [52.5%] vs 22 HC male [45.8%]; $\chi^2 = 0.48$, $p = 0.49$), the *APOE* ε4 allele carrier status (14 mTBI *APOE* ε4 allele carriers [23.7%] vs 10 HC *APOE* ε4 allele carriers [20.8%]; $\chi^2 = 0.13$, $p = 0.72$), and the scan interval (median [IQR], 10.0 [6.0–11.7] months vs 12.0 [9.0–12.0] months; $Z = 1.81$, $p = 0.07$). Compared to HCs, patients with mTBI showed worse performance in IPS (mean [SD], −0.2 [0.8] vs 0.2 [1.0]; $t = -2.23$, $p = 0.01$) and language fluency (mean [SD], −0.2 [0.8] vs 0.2 [0.8]; $t = -2.12$, $p = 0.02$) in their acute phase. However, patients performed slightly worse than HC follow-up in language fluency in their chronic phase (mean [SD], −0.14 [0.76] vs 0.17 [0.96]; $t = -1.85$, $p = 0.07$), but not the IPS (mean [SD], −0.04 [0.85] vs 0.16 [0.96]; $t = -1.18$, $p = 0.24$). Within the mTBI group, there was no evidence of a change between the acute and chronic phases in IPS (mean [SD], −0.2 [0.8] vs −0.1 [0.9]; $t = -0.60$, $p = 0.55$) and language fluency (mean [SD], −0.2 [0.8] vs −0.0 [0.8]; $t = -1.73$, $p = 0.09$).

3.2 | Longitudinal atrophy of the temporal lobes after mTBI

During the nearly 10-months post-injury follow-up, patients with mTBI showed significant brain volume loss in their temporal lobes (GM: 0.27% per year [0.43], $t = 4.82$, $p < 0.001$; WM: 0.27% per year [0.50], $t = 4.63$, $p < 0.001$). In contrast, HCs showed slight volume changes for GM and WM of the temporal lobes during the follow-up (GM: 0.07% per year [SD = 0.40] loss; WM: 0.04% per year [SD = 0.46] increase); and the volume changes showed no significant difference with zero, neither in GM nor WM (GM: $t = 1.17$, $p = 0.21$; WM: $t = 0.62$, $p = 0.54$).

Voxel-wise between-group comparisons (mTBI patients vs HCs) on the JD image of GM and WM revealed the spatial patterns of progressive volume loss in the temporal lobes after mTBI (Figure 3). By comparison, patients with mTBI exhibited significant longitudinal atrophy of the GM in the bilateral temporal lobe areas, primarily involving extensive areas of the left medial and lateral temporal lobes, and a part of the right lateral temporal lobe (Figure 3A; $p < 0.05$, TFCE corrected). Similarly, the patients showed progressive atrophy of the WM primarily in the left temporal lobe and the right middle temporal gyrus regions (Figure 3B; $p < 0.05$, TFCE corrected), corresponding to the topography of GM atrophy.

3.3 | *APOE* ε4 allele status modulating longitudinal atrophy topography in the temporal lobes after mTBI

Compared to healthy *APOE* ε4 allele carriers, mTBI *APOE* ε4 allele carriers exhibited a significant longitudinal volume loss in the left superior and middle temporal gyri for GM and WM (Figure 4A and 4B; $p < 0.05$, TFCE corrected), which was replicated when we removed the protective effect of *APOE* ε2 allele (see eResults in Supplement). These regions were defined as the *ROIs of mTBI-APOE ε4+*. In contrast, mTBI patients without the *APOE* ε4 allele exhibited a significant longitudinal atrophy of the GM in the right lateral temporal lobe and bilateral MTL areas (Figure 4C; $p < 0.05$, TFCE corrected), and a significant longitudinal atrophy of the WM under the right lateral and medial temporal cortices (Figure 4D; $p < 0.05$, TFCE corrected), compared to HCs without the *APOE* ε4 allele. These regions were defined as the *ROIs of mTBI-APOE ε4-*.

3.4 | Neuropsychological association with longitudinal atrophy in mTBI patients with the *APOE* ε4 allele

For mTBI *APOE* ε4 allele carriers, the mean JD value of GM and WM in *ROIs of mTBI-APOE ε4+* was significantly related to the performance

TABLE 1 Demographic, clinical, and neuropsychological characteristics of patients and healthy controls.

Variable	mTBI (*N* = 59)	HCs (*N* = 48)	Statistics[‡]	*p* value[§]
Age, median (IQR), y	36.0 (29.0–43.5)	33.0 (28.8–48.5)	–0.39	0.70
Sex, No. (%)*				
Female	28 (47.5)	26 (54.2)	0.4n	0.49
Male	31 (52.5)	22 (45.8)		
Education, median (IQR), y	8.8 (6–12)	11 (5.8–15)	-1.66	0.10
APOE, no. (%)*				
ε4+	14 (23.7)	10 (20.8)	0.13	0.72
ε2/ε4	2	2		
ε3/ε4	9	7		
ε4/ε4	3	1		
ε4–	45 (76.3)	38 (79.2)		
ε2/ε3	8	8		
ε3/ε3	37	30		
ε2/ε2	0	0		
Scan interval, median (IQR), mo	10.0 (6.0–11.7)	12.0 (9.0–12.0)	–1.81	0.07
Injury causes, no. (%)*				NA
Traffic accident	34 (57.6)	NA		
Fall	5 (8.5)	NA		
Assault	16 (27.1)	NA		
Other	4 (6.8)	NA		
PCS, no. (%)*				NA
PCS+	48 (81.4)	NA		
PCS–	11 (18.6)	NA		
Coma duration, median (IQR), min	10.0 (4.0–20.0)	NA		NA
AA duration, median (IQR), min[†]	0.0 (0.0–0.0)	NA		NA
Zscore_IPS, mean (SD)	–0.2 (0.8)	0.2 (1.0)	2.23	0.03[§]
DSCT, median (IQR)	34.0 (26.5–48.0)	55 (28.0–60.0)	–1.49	0.02[§]
TMT_A, median (IQR), s	50.0 (29.0–72.5)	38.0 (25.8–70.2)	–2.41	0.14
Zscore_Language fluency, mean (SD)	-0.2 (0.8)	0.2 (0.8)	2.12	0.04[§]
VFT, median (IQR)	15.0 (13.0–20.0)	16.5 (14.8–23.0)	–1.90	0.06
FDST, median (IQR)	8.0 (7.0–9.0)	8.0 (8.0–9.0)	–1.42	0.16

Abbreviations: AA, anterograde amnesia; *APOE* ε4-, without *APOE* ε4 allele; *APOE* ε4+, with *APOE* ε4 allele; DSCT, Digit Symbol Coding Test; FDST, Forward Digit Span Test; HCs, healthy controls; IPS, information processing speed; IQR, interquartile range; mTBI, mild traumatic brain injury; NA, not applicable; PCS-, without post-concussion symptom complaint; PCS+, with post-concussion symptom complaint; SD, standard deviation; TMT_A, Trail-making Test Part A; VFT, Verbal Fluency Test.

*Percentages for sex, *APOE* ε4 allele status, injury causes, and PCS status were calculated according to the total participants with available data in HCs or mTBI patient group, respectively.

[†]Seven mTBI patients exhibited anterograde amnesia post injury, lasting for 60–120 min.

[‡]Unless otherwise indicated, statistics for number (%), median (IQR), or mean (SD) types were χ^2 for chi-square test, *Z* value for Mann–Whitney *U* test, or *t* value for independent *t*-test, respectively.

[§]*p* value indicating a statistically significant difference was set at two-tailed $p < 0.05$. *p* values are derived from with the χ^2 test, independent *t*-test, or Mann–Whitney *U* test, as appropriate.

changes in language fluency (GM: $r = 0.58$, $p = 0.03$; WM: $r = 0.55$, $p = 0.04$), instead of IPS (GM: $r = 0.42$, $p = 0.13$; WM: $r = 0.38$, $p = 0.19$). The stepwise linear regression showed that the performance changes in language fluency could be predicted by the mean JD value of GM in *ROIs of mTBI-APOE ε4+* (standardized coefficient, $\beta = 0.58$, $p = 0.03$), whereas the mean JD value of WM in *ROIs of mTBI-APOE ε4+* was excluded from the regression. Moreover, the atrophy of GM in *ROIs of mTBI-APOE ε4+* still could predict the performance changes in language fluency ($\beta = 0.58$, $p = 0.03$) after controlling for sex, age, and education level (Table 2).

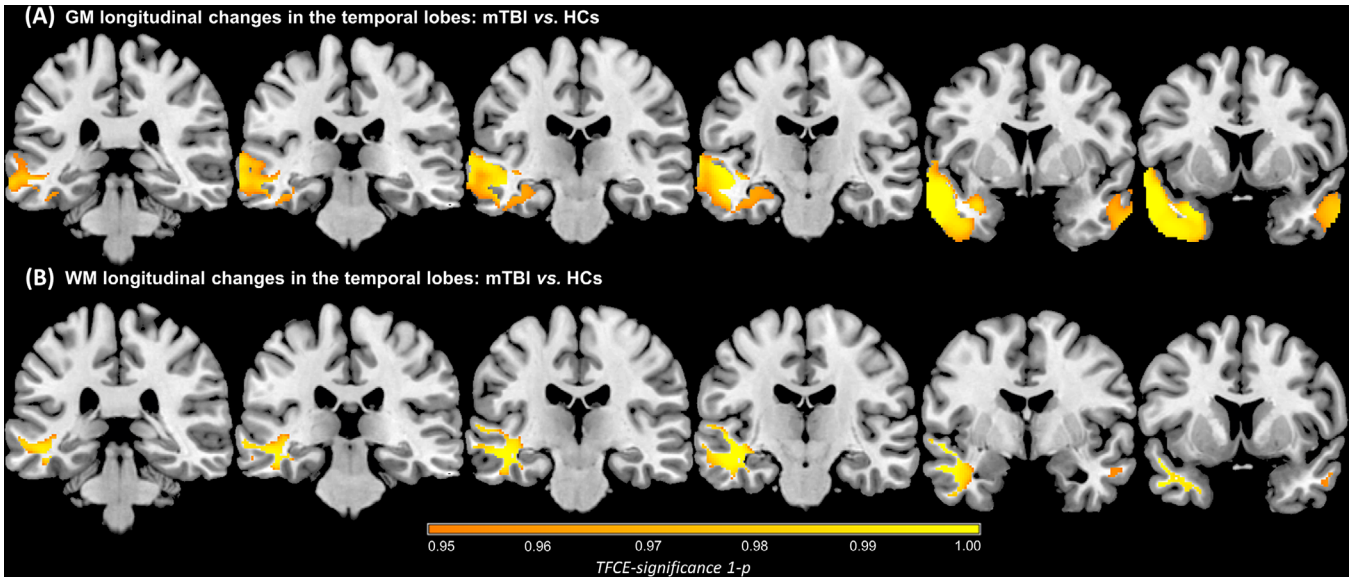

FIGURE 3 Voxel-wise comparisons on JD images of the temporal lobes in contrast of mTBI patients vs HCs. (A) Patients with mTBI exhibited longitudinal GM volume loss located in the bilateral temporal lobes, primarily including extensive areas in the left medial and lateral temporal lobes. (B) Patients with mTBI exhibited the longitudinal WM volume loss primarily located in the left temporal lobe, which corresponded to the GM atrophy spatial pattern. Results are thresholded at voxel-wise $p < 0.05$, with TFCE correction. GM, gray matter; HCs, healthy controls; JD, Jacobian determinant; mTBI, mild traumatic brain injury; TFCE, threshold-free cluster enhancement; WM, white matter.

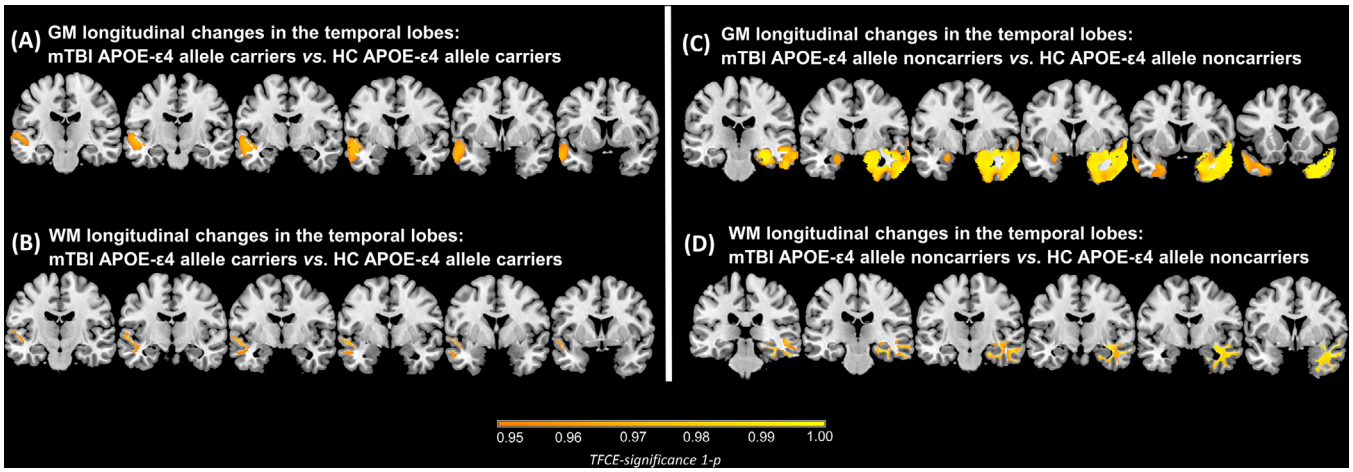

FIGURE 4 Voxel-wise comparisons on JD images of the temporal lobes in contrast of mTBI patients vs. HCs with different *APOE* ε4 allele status. (A) mTBI *APOE* ε4 allele carriers showed severe atrophy of GM in the left superior and middle temporal gyri. (B) mTBI *APOE* ε4 allele carriers showed severe WM atrophy corresponding to their GM atrophy topography. (C) mTBI *APOE* ε4 allele noncarriers showed severe atrophy in the bilateral medial temporal areas of the GM, and extensive areas in the right lateral temporal cortex. (D) mTBI *APOE* ε4 allele noncarriers showed severe WM atrophy under the right temporal cortex, which corresponded to their GM atrophy topography. Results are thresholded at voxel-wise $p < 0.05$, with TFCE correction. GM, gray matter; HCs, healthy controls; JD, Jacobian determinant; mTBI, mild traumatic brain injury; TFCE,threshold-free cluster enhancement; WM, white matter.

For mTBI *APOE* ε4 allele noncarriers, the mean JD value of GM or WM in *ROIs of mTBI-APOE ε4-* had no significant correlation with the longitudinal changes in language fluency (GM: $r = 0.00$, $p = 0.98$; WM: $r = -0.02$, $p = 0.88$) or IPS (GM: $r = -0.08$, $p = 0.63$; WM: $r = -0.06$, $p = 0.73$).

4 | DISCUSSION

In this study, we found that *APOE* ε4 allele status modulated the spatial patterns of longitudinal atrophy in the temporal lobes post mTBI. Patients with mTBI showed longitudinal atrophy primarily in the left

TABLE 2 Association between the longitudinal atrophy and language fluency changes in mTBI patients with the *APOE* ε4 allele.

	Standardized coefficient (β)	*p* value
Linear regression model 1		
JD value of GM in ROIs	0.58	0.03†
JD value of WM in ROIs *	−1.42	0.47
Linear regression model 2		
JD value of GM in ROIs	0.58	0.03†
Sex*	0.00	0.99
Age*	0.07	0.79
Education*	−0.16	0.54

Abbreviations: GM, gray matter; JD, Jacobian determinant; ROIs, regions of interest; WM, white matter.
*Variables were excluded from stepwise linear regressions.
†*p* value indicates significance was set at two-tailed $p < 0.05$.

temporal lobe during the 6–12 month follow-up period. mTBI *APOE* ε4 allele carriers exhibited longitudinal atrophy in the left superior and middle temporal gyri, where the atrophy of GM could predict the performance changes in language fluency. In contrast, patients without the *APOE* ε4 allele presented longitudinal atrophy primarily distributed in the bilateral medial and the right lateral temporal lobes, and there was no evidence of a relationship between atrophy in these regions and assessments of information processing speed and language fluency.

The temporal lobes are vulnerable to TBI, and AD-like plaque deposits (e.g., Aβ protein plaques) can be detected in the temporal cortex even a few hours after injury.[27] With the progression of neurodegeneration, chronic atrophy can be generally detected several years after the injury.[24,41] Regarding the longitudinal changes, previous findings have suggested that volume loss in the temporal lobes could be observed as early as 7 days after mTBI, and lasting for at least 1 year.[42] In the current study we adopted a deformation-based morphometry method to directly model the rate of brain atrophy voxel-wise, which allowed us to detect the subtle longitudinal atrophy in the temporal lobes within 1-year post injury. Our results were consistent with previous findings and supported the notion that the temporal lobes are vulnerable to TBI. Moreover, old traumatic contusional deficits in the temporal lobes could be found in AD patients with a TBI history as well.[39] In addition, by the analysis in the whole-brain (see eResults in Supplement), we found that mTBI *APOE* ε4 allele carriers showed longitudinal brain volume loss in the left frontal regions and the left superior and middle temporal gyri. However, once we controlled for the high genetic determinant of AD (i.e., the *APOE* ε4 allele), the patients showed longitudinal volume loss in the bilateral frontal regions, with limited areas in the bilateral temporal poles. We inferred that the temporal lobes might be involved in the risk of long-term AD incidents when we focused on the interaction of TBI with the *APOE* ε4 allele in the present study.

In the present study, patients with the *APOE* ε4 allele exhibited salient atrophy located primarily in the left superior and middle temporal gyri. These regions were reportedly the initial atrophy areas in the logopenic variant of the primary progressive aphasia (lvPPA)-AD phenotype and serve as a neuroimaging signature to identify the earlier risk of lvPPA-AD.[17] The *APOE* ε4 allele is an important genetic determinant for incidence of lvPPA-AD.[43] Moreover, the interaction of mTBI with the *APOE* ε4 allele might further increase the risk of lvPPA-AD and trigger the progressive volume reduction in vulnerable regions of the pathway of its atrophy. Our results supported the idea that the interaction of AD genetic factors with mTBI leads to brain atrophy in AD-vulnerable regions.[5] Regarding the neuropsychological signature, early lvPPA-AD is characterized by a decline in language fluency,[36,43] which is one of the neuropsychological complaints of patients with mTBI as well.[15,16] In addition, we found that the atrophy in GM, rather than the WM, within the left superior and middle temporal gyri could predict the decline in language fluency for mTBI *APOE* ε4 allele carriers. The longitudinal registration of pairs of T1 images was based on alignment between the first and second scans of each participant, in which a linear transform may be mostly influenced by the GM rather than the WM. Therefore, the measures of WM volume changes might be similar to the GM because of the regularization during the registration process. This potential collinearity could possibly explain why the variable of WM volume changes was excluded from the regression for predicting the language fluency decline. The regression analysis suggests that the atrophy topography resulting from the interaction of mTBI with high genetic risk for AD shares a similar neurodegeneration spatial pattern with a specific AD phenotype with language function decline.

Furthermore, in the present study, extensive atrophy in the MTL areas was observed in *APOE* ε4 allele noncarriers following mTBI. The MTL areas are selectively vulnerable to damage in response to biomechanical force impacts of TBI.[44,45] Therefore, the relevant neuroanatomic and neuropathological changes are often detected in these areas.[38,46,47] In the present study we observed longitudinal atrophy in the extensive MTL areas in mTBI patients with low genetic risk for AD, being consistent with the previous finding that the atrophy progression in MTL regions following TBI is independent of *APOE* ε4 allele and may have little reference to typical AD progression after injury.[20] Instead, such progressive atrophy observed in mTBI *APOE* ε4 allele noncarriers might indicate the injury-related deterioration in the temporal lobes.

There were some limitations to the present study. First, the *APOE* ε4 allele is termed a genetic determinant for AD, exerting a dosage-dependent effect.[48] Our study was limited to the sample size of mTBI *APOE* ε4 allele carriers ($N = 14$) without separating the *APOE* ε4/ε4 homozygotes from the heterozygote carriers. Further studies should include a larger sample to investigate the dosage effects of the *APOE* ε4 allele on the longitudinal atrophy after mTBI. Another limitation was the observation time-points for longitudinal atrophy spatial patterns. mTBI *APOE* ε4 allele carriers exhibited longitudinal atrophy in the left superior and middle temporal gyri during the first-year post injury. This atrophy pattern is characteristic of the initial areas in the neurodegeneration pathway of lvPPA-AD, wherein the deterioration of the MTL structure and several regions in the neocortex are involved in the disease progression.[17] The extra time-points for follow-up in the future might permit a complete observation of the lvPPA-AD-like atrophy trajectory post injury.

To conclude, *APOE ε4* allele status could modulate the spatial patterns of progressive atrophy in the temporal lobes after mTBI; the *APOE ε4* allele, combined with the injury, causes the longitudinal atrophy relevant to the AD phenotype with language dysfunction. These findings suggest that the interaction of TBI with AD genetic determinants may induce long-term neurodegenerative consequences related to a given AD phenotype.

AUTHOR CONTRIBUTIONS

Drs Zhang and Bai served as joint senior authors, and Dr Bai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Gan, Zhang, and Bai. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: Gan and Bai. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Gan and Sun. Obtained funding: Bai, Zhang, and Gan. Administrative, technical, or material support: Liu, Li, and Jia. Supervision: Zhang and Bai.

ACKNOWLEDGMENTS

The authors thank all the mild traumatic brain injury (mTBI) patients and the healthy participants for taking part in this study; the authors also thank Dr Qing He and Dr Shan Wang for their contribution in polishing the manuscript. This work was supported by the National Natural Science Foundation of China under Grant (Nos. 82071993, 81871331), the Funds for Distinguished Youths in Shaanxi Province (No. 2022JC-55), the China Postdoctoral Science Foundation (No. 2023M733421), and the Funds for Scientific Research of Postdoctoral Researchers in Anhui Province (No. 2023A659).

CONFLICT OF INTEREST STATEMENT

The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

Data presented in the article are available on request by contacting Dr Lijun Bai.

CONSENT STATEMENT

All human participants signed the written informed consent.

ORCID

Lijun Bai https://orcid.org/0000-0001-8790-5424

REFERENCES

1. Jellinger KA. Head injury and dementia. *Curr Opin Neurol*. 2004;17:719-723. doi:10.1097/00019052-200412000-00012
2. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J Neurol Neurosurg Psychiatry*. 2003;74:857-862. doi:10.1136/jnnp.74.7.857
3. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of mild traumatic brain injury with and without loss of consciousness with dementia in US military veterans. *JAMA Neurol*. 2018;75:1055-1061. doi:10.1001/jamaneurol.2018.0815
4. Nicoll JA, Roberts GW, Graham DI. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta-protein following head injury. *Nat Med*. 1995;1:135-137. doi:10.1038/nm0295-135
5. Hayes JP, Logue MW, Sadeh N, et al. Mild traumatic brain injury is associated with reduced cortical thickness in those at risk for Alzheimer's disease. *Brain*. 2017;140:813-825. doi:10.1093/brain/aww344
6. Atherton K, Han X, Chung J, et al. Association of APOE genotypes and chronic traumatic encephalopathy. *JAMA Neurol*. 2022;79:787-796. doi:10.1001/jamaneurol.2022.1634
7. Zhou W, Xu D, Peng X, Zhang Q, Jia J, Crutcher KA. Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *J Neurotrauma*. 2008;25:279-290. doi:10.1089/neu.2007.0489
8. Geroldi C, Pihlajamäki M, Laakso MP, et al. APOE-epsilon4 is associated with less frontal and more medial temporal lobe atrophy in AD. *Neurology*. 1999;53:1825-1832. doi:10.1212/wnl.53.8.1825
9. Ossenkoppele R, Schonhaut DR, Schöll M, et al. Tau PET patterns mirror clinical and neuroanatomical variability in Alzheimer's disease. *Brain*. 2016;139:1551-1567. doi:10.1093/brain/aww027
10. Filippini N, Rao A, Wetten S, et al. Anatomically-distinct genetic associations of APOE epsilon4 allele load with regional cortical atrophy in Alzheimer's disease. *Neuroimage*. 2009;44:724-728. doi:10.1016/j.neuroimage.2008.10.003
11. DeKosky ST, Abrahamson EE, Ciallella JR, et al. Association of increased cortical soluble abeta42 levels with diffuse plaques after severe brain injury in humans. *Arch Neurol*. 2007;64:541-544. doi:10.1001/archneur.64.4.541
12. Brett BL, Gardner RC, Godbout J, Dams-O'Connor K, Keene CD. Traumatic brain injury and risk of neurodegenerative disorder. *Biol Psychiatry*. 2022;91:498-507. doi:10.1016/j.biopsych.2021.05.025
13. Raj R, Kaprio J, Korja M, Mikkonen ED, Jousilahti P, Siironen J. Risk of hospitalization with neurodegenerative disease after moderate-to-severe traumatic brain injury in the working-age population: a retrospective cohort study using the Finnish national health registries. *PLoS Med*. 2017;14:e1002316. doi:10.1371/journal.pmed.1002316
14. 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;8:55. doi:10.1186/s40779-021-00346-z
15. Barton DJ, Kumar RG, Schuster AA, Juengst SB, Oh BM, Wagner AK. Acute cortisol profile associations with cognitive impairment after severe traumatic brain injury. *Neurorehabil Neural Repair*. 2021;35:1088-1099. doi:10.1177/15459683211048771
16. Calvillo M, Irimia A. Neuroimaging and psychometric assessment of mild cognitive impairment after traumatic brain injury. *Front Psychol*. 2020;11:1423. doi:10.3389/fpsyg.2020.01423
17. Phillips JS, Da Re F, Irwin DJ, et al. Longitudinal progression of grey matter atrophy in non-amnestic Alzheimer's disease. *Brain*. 2019;142:1701-1722. doi:10.1093/brain/awz091
18. Han P, Winkler N, Hummel C, Hähner A, Gerber J, Hummel T. Alterations of brain gray matter density and olfactory bulb volume in patients with olfactory loss after traumatic brain injury. *J Neurotrauma*. 2018;35:2632-2640. doi:10.1089/neu.2017.5393
19. Sandry J, Dobryakova E. Global hippocampal and selective thalamic nuclei atrophy differentiate chronic TBI from Non-TBI. *Cortex*. 2021;145:37-56. doi:10.1016/j.cortex.2021.08.011
20. Isoniemi H, Kurki T, Tenovuo O, Kairisto V, Portin R. Hippocampal volume, brain atrophy, and APOE genotype after traumatic brain injury. *Neurology*. 2006;67:756-760. doi:10.1212/01.wnl.0000234140.64954.12
21. Clark AL, Weigand AJ, Bangen KJ, Merritt VC, Bondi MW, Delano-Wood L. Repetitive mTBI is associated with age-related reductions in cerebral blood flow but not cortical thickness. *J Cereb Blood Flow Metab*. 2021;41:431-444. doi:10.1177/0271678X19897443
22. Asken BM, Tanner JA, Gaynor LS, et al. Alzheimer's pathology is associated with altered cognition, brain volume, and plasma biomarker

patterns in traumatic encephalopathy syndrome. *Alzheimers Res Ther*. 2023;15:126. doi:10.1186/s13195-023-01275-w
23. Kelley CM, Perez SE, Mufson EJ. Tau pathology in the medial temporal lobe of athletes with chronic traumatic encephalopathy: a chronic effects of neurotrauma consortium study. *Acta Neuropathol Commun*. 2019;7:207. doi:10.1186/s40478-019-0861-9
24. Bigler ED, Anderson CV, Blatter DD. Temporal lobe morphology in normal aging and traumatic brain injury. *AJNR Am J Neuroradiol*. 2002;23:255-266.
25. Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. *J Neuropathol Exp Neurol*. 2014;73:14-29. doi:10.1097/nen.0000000000000021
26. Nelson LD, Temkin NR, Dikmen S, et al. Recovery after mild traumatic brain injury in patients presenting to US level I trauma centers: a transforming research and clinical knowledge in traumatic brain injury (TRACK-TBI) study. *JAMA Neurol*. 2019;76:1049-1059. doi:10.1001/jamaneurol.2019.1313
27. Ikonomovic MD, Uryu K, Abrahamson EE, et al. Alzheimer's pathology in human temporal cortex surgically excised after severe brain injury. *Exp Neurol*. 2004;190:192-203. doi:10.1016/j.expneurol.2004.06.011
28. Newcombe VFJ, Ashton NJ, Posti JP, et al. Post-acute blood biomarkers and disease progression in traumatic brain injury. *Brain*. 2022;145:2064-2076. doi:10.1093/brain/awac126
29. Cole JH, Jolly A, de Simoni S, et al. Spatial patterns of progressive brain volume loss after moderate-severe traumatic brain injury. *Brain*. 2018;141:822-836. doi:10.1093/brain/awx354
30. Graham NSN, Jolly A, Zimmerman K, et al. Diffuse axonal injury predicts neurodegeneration after moderate–severe traumatic brain injury. *Brain*. 2020;143:3685-3698. doi:10.1093/brain/awaa316
31. Holm L, Cassidy JD, Carroll LJ, Borg J. Summary of the WHO collaborating centre for neurotrauma task force on mild traumatic brain injury. *J Rehabil Med*. 2005;37:137-141. doi:10.1080/16501970510027321
32. Appell J, Kertesz A, Fisman M. A study of language functioning in Alzheimer patients. *Brain Lang*. 1982;17:73-91. doi:10.1016/0093-934x(82)90006-2
33. Wiseman SJ, Booth T, Ritchie SJ, et al. Cognitive abilities, brain white matter hyperintensity volume, and structural network connectivity in older age. *Hum Brain Mapp*. 2018;39:622-632. doi:10.1002/hbm.23857
34. Ryan JJ, Ward LC. Validity, reliability, and standard errors of measurement for two seven-subtest short forms of the Wechsler Adult Intelligence Scale—III. *Psychol Assess*. 1999;11:207-211. doi:10.1037/1040-3590.11.2.207
35. Bowie CR, Harvey PD. Administration and interpretation of the Trail Making Test. *Nat Protoc*. 2006;1:2277-2281. doi:10.1038/nprot.2006.390
36. Staffaroni AM, Weintraub S, Rascovsky K, et al. Uniform data set language measures for bvFTD and PPA diagnosis and monitoring. *Alzheimers Dement (Amst)*. 2021;13:e12148. doi:10.1002/dad2.12148
37. Ashburner J, Ridgway GR. Symmetric diffeomorphic modeling of longitudinal structural MRI. *Front Neurosci*. 2012;6:197. doi:10.3389/fnins.2012.00197
38. Umile EM, Sandel ME, Alavi A, Terry CM, Plotkin RC. Dynamic imaging in mild traumatic brain injury: support for the theory of medial temporal vulnerability. *Arch Phys Med Rehabil*. 2002;83:1506-1513. doi:10.1053/apmr.2002.35092
39. Jellinger KA, Paulus W, Wrocklage C, Litvan I. Traumatic brain injury as a risk factor for Alzheimer disease. Comparison of two retrospective autopsy cohorts with evaluation of ApoE genotype. *BMC Neurol*. 2001;1:3. doi:10.1186/1471-2377-1-3
40. Winkler AM, Ridgway GR, Webster MA, Smith SM, Nichols TE. Permutation inference for the general linear model. *Neuroimage*. 2014;92:381-397. doi:10.1016/j.neuroimage.2014.01.060
41. Xu Y, McArthur DL, Alger JR, et al. Early nonischemic oxidative metabolic dysfunction leads to chronic brain atrophy in traumatic brain injury. *J Cereb Blood Flow Metab*. 2010;30:883-894. doi:10.1038/jcbfm.2009.263
42. MacKenzie JD, Siddiqi F, Babb JS, et al. Brain atrophy in mild or moderate traumatic brain injury: a longitudinal quantitative analysis. *AJNR Am J Neuroradiol*. 2002;23:1509-1515.
43. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 2004;55:335-346. doi:10.1002/ana.10825
44. Viano DC, Casson IR, Pellman EJ, Zhang L, King AI, Yang KH. Concussion in professional football: brain responses by finite element analysis: part 9. *Neurosurgery*. 2005;57:891-916. doi:10.1227/01.neu.0000186950.54075.3b
45. Bigler ED. Neuropsychology and clinical neuroscience of persistent post-concussive syndrome. *J Int Neuropsychol Soc*. 2008;14:1-22. doi:10.1017/s135561770808017x
46. Palacios EM, Sala-Llonch R, Junque C, et al. Long-term declarative memory deficits in diffuse TBI: correlations with cortical thickness, white matter integrity and hippocampal volume. *Cortex*. 2013;49:646-657. doi:10.1016/j.cortex.2012.02.011
47. Holli-Helenius K, Luoto TM, Brander A, Wäljas M, Iverson GL, Öhman J. Structural integrity of medial temporal lobes of patients with acute mild traumatic brain injury. *J Neurotrauma*. 2014;31:1153-1160. doi:10.1089/neu.2013.2978
48. Yan S, Zheng C, Paranjpe MD, et al. Sex modifies APOE ε4 dose effect on brain tau deposition in cognitively impaired individuals. *Brain*. 2021;144:3201-3211. doi:10.1093/brain/awab160

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Gan S, Sun Y, Liu K, et al. *APOE* ε4 allele status modulates the spatial patterns of progressive atrophy in the temporal lobes after mild traumatic brain injury. *Alzheimer's Dement*. 2024;16:e12550. https://doi.org/10.1002/dad2.12550