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Longitudinal MRI identifies associations between cognitive decline, inflammatory markers, and hippocampal subregion volumes in individuals with knee osteoarthritis

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Abstract

Background Knee osteoarthritis (KOA) is common in older adults and may relate to cognitive decline. We explore whether changes in specific brain areas and body inflammation levels help explain this connection, focusing on the hippocampus-a memory-critical brain region.

Methods We studied 36 older adults with KOA over time. Using brain scans, we measured volumes of hippocampal subregions (especially the fimbria). Blood tests tracked six inflammation markers, including brain-derived neurotrophic factor (BDNF), interferon-gamma (IFN-γ), programmed death 1(PD-1), recombinant cannabinoid receptor 1 (CNR1), recombinant cannabinoid receptor 2 (CNR2), and T cell immunoglobulin domain and mucin domain 3 (TIM3). Memory was tested using the Wechsler Memory Scale - Chinese Revision (WMS-CR), while global cognition used the Montreal Cognitive Assessment (MoCA). Relationships between knee pain, brain structure, inflammation, and cognition were analyzed statistically.

Results Here, we show that shrinking fimbria volume predicts cognitive decline in those developing dementia. We identify a robust correlation between fimbria volume and cognitive performance. Higher IFN-γ levels are protective against cognitive decline. Critically, fimbria volume serves as a mediator in the relationship between pain, TIM3/IFN-γ levels, and cognitive scores.

Conclusions Fimbria serves as a key pathway through which KOA may drive cognitive impairment, while IFN-γ could help protect memory. Monitoring these hippocampal changes and inflammation levels might help identify at-risk patients early.

Plain language summary

Knee osteoarthritis (KOA) occurs when the protective cartilage at the end of the bones wears down, and can result in inflammation of the joint. In addition to pain and stiffness, arthritis can also affect memory in older adults. We studied 36 people with KOA over 5 years and found that a part of the brain known to be involved in memory shrank. The volume of this brain area impacted the amount of knee pain experienced, levels of blood-based markers of inflammation, and extent of memory loss. Our results suggest that monitoring blood-based markers and imaging the brain could enable dementia, a condition in which people have memory issues, to be identified earlier in people with KOA.

Knee osteoarthritis (KOA), a progressive degenerative joint disease affecting millions globally, drives substantial functional impairment and healthcare resource utilization through its disabling effects. Global KOA prevalence rose 48% from 1990 to 2019[1]. As the fourth leading cause of global disability, KOA represents 2.2% of the worldwide disease burden[2]. Chronic pain associates with increased dementia susceptibility, with systematic reviews showing elevated risk for all-cause dementia (OR = 1.26) and Alzheimer's disease (OR = 1.28)[3]. Persistent pain increases cognitive decline risk by 21% biannually in older adults[4]. This relationship operates through a biopsychosocial framework wherein pain, aging, and dementia dynamically interact, modulated by predisposing and concurrent biological, psychological (cognitive-affective), and social factors[5]. Critically, emerging evidence

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positions osteoarthritis as a systemic disorder mediated by the bone-brain axis—a bidirectional network where joint-derived signals propagate through neuronal pathways and molecular mediators to drive central neuroplasticity[6]. Neurophysiological advances have elucidated the KOA-cognition relationship, demonstrating declines in global cognition and auditory verbal learning function among elderly KOA patients[7]. Memory impairment is the predominant form of cognitive decline observed in older adults[8], yet quantitative evidence characterizing multidimensional cognitive deficits, particularly domain-specific memory decline—remains limited in KOA populations.

Neuroimaging research has demonstrated that the occurrence of brain imaging changes in KOA is closely associated with cognitive decline[9,10]. A recent multiscale study utilizing structural MRI data revealed accelerated brain aging specifically in KOA patients, characterized by increased predicted age difference (PAD) compared to healthy controls. This acceleration was predominantly driven by hippocampal degeneration and predicted longitudinal memory decline and dementia risk[11]. Prior evidence demonstrates that the baseline functional connectivity between hippocampus and thalamus, combined with brain-derived neurotrophic factor (BDNF) levels, predicts longitudinal cognitive decline in KOA patients[12]. Complementarily, spatial transcriptomics reveals region-specific associations of *SLC39A8* expression with KOA-related neuroimaging endophenotypes within hippocampus[11]. Chronic pain disorders such as KOA exhibit hippocampal structural and functional reorganization, potentially mediating pain-related disability and comorbid psychiatric manifestations, including depression and anxiety[13,14].

The hippocampus is composed of multiple subregions, each playing a specific role in memory formation and consolidation. Iglesias et al.'s cytostructural analysis delineates 12 distinct subregions: hippocampal tail, subiculum, CA1, hippocampal fissure, presubiculum, parasubiculum, molecular layer (HP), granule cell layer and molecular layer of the dentate gyrus (GC-ML-DG), CA3, CA4, fimbria, and the hippocampal amygdala transition area (HATA)[15]. The regulation of pain signals involves the activation of the hippocampus, which plays a critical role in processing and modulating painful stimuli[16]. Chronic pain may compromise synaptic plasticity at mossy fiber-CA3 synapses and inhibit neurogenesis within the dentate gyrus (DG)[16]. Vaculik et al. identified selective volume loss in specific hippocampal subfields among classic trigeminal neuralgia patients[17]. Investigations in chronic low back pain have revealed elevated cortisol levels compared to healthy controls, with this hypercortisolemia showing important associations with both diminished hippocampal volume and enhanced pain-related neuronal activation in the anterior parahippocampal gyrus[18]. Moreover, Ma et al. demonstrated that persistent spontaneous pain disrupts the connectivity between the ventral hippocampal CA1-infralimbic cortex and modulates infralimbic cortex neuronal activity in rats with peripheral inflammation[19]. These alterations in properties within the hippocampus may be associated with the volume loss observed in patients with chronic pain[20]. Although numerous studies have investigated hippocampal involvement in various pain conditions and neurodegenerative diseases, there remains a notable gap in research specifically addressing the role of hippocampal subregions in the context of KOA[21,22]. Current evidence indicates that only a limited number of studies have systematically examined the role of hippocampal subregions in KOA, and most have focused on broader hippocampal regions rather than distinct subregions[12,23]. Therefore, the distinctive contribution of our study is its emphasis on investigating the specific involvement of hippocampal subregions in KOA-related cognitive and neurobehavioral alterations.

Immune-inflammatory responses play pivotal roles in both KOA and cognitive processing. Inflammatory mediators substantially influence pain perception and hippocampal function: a positive correlation exists between serum BDNF levels and human hippocampal volume. Conversely, whereas Interferon-gamma (IFN-γ) lowers amyloid-β (Aβ) deposition[24], PD1/PD-L1 pathways potentially drive cognitive decline in the aging hippocampus[25]. Cannabinoid receptor (CNR1/CNR2) activation attenuates Aβ deposition and tau phosphorylation[26]. Osteoarthritis is a highly prevalent form of arthritis, in which T cell responses and cytokine profiles may play a crucial role in disease progression. T cell immunoglobulin domain and mucin domain 3 (TIM3) gene polymorphisms modulate cytokine expression in multiple cell types and directly associate with KOA susceptibility[27]. Collectively, these findings position inflammatory pathways as key biological mediators linking KOA to hippocampal dysfunction.

Individual variability in disease progression represents a critical consideration—not all KOA patients develop cognitive decline. Elucidating mechanisms differentiating susceptibility versus resilience to cognitive deterioration is essential for developing precision interventions. This heterogeneity underscores the importance of identifying predictive biomarkers, such as structural features of hippocampal subregions and inflammatory profiles.

This longitudinal study aims to compare cognitive function and hippocampal subregion volumes between dementia converters and non-converters with KOA, determine correlations between specific brain regions, inflammatory cytokine levels, and cognitive performance, validate whether hippocampal subregions mediate cognitive decline progression, and identify serum inflammatory biomarkers predictive of dementia conversion over a five-year follow-up period.

This study demonstrates that while baseline hippocampal volume shows no significant difference between groups, fimbria volume reduction specifically associates with dementia conversion in KOA patients. Dementia converters show accelerated decline in language and memory functions compared to non-converters. The fimbria mediates cognitive changes and moderates relationships between inflammatory markers (TIM3, IFN-γ) and memory performance, with distinct regulatory patterns observed between converters and non-converters. Serum IFN-γ exerts protective effects against dementia progression, while CNR1 and CNR2 levels show disease-stage-specific correlations with cognitive decline. These findings establish the fimbria as a critical neuroanatomical substrate and inflammatory pathways as central biological mediators linking KOA to cognitive deterioration.

Methods

This study employed data from a 5-year longitudinal investigation registered in the Clinical Trial Registry (Clinical trial registration number: ChiCTR-IOR-16009308, 03/10/2016). The study received approval from the Medical Ethics Committee of the Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine and the Second Affiliated People's Hospital of Fujian University of Chinese Medicine (ethical approval number: 2015KY-017-01). All participants provided written informed consent prior to participating.

Participants

Participants completed baseline assessments and were subsequently followed up for a period of five years. Potential participants were recruited from community centers in Fuzhou, Fujian Province, between June and October 2015 via posters, WeChat, and telephone invitations. Individuals diagnosed with KOA who did not meet the exclusion criteria consented to undergo MRI scans and complete relevant scale assessments. The total sample size consisted of 36 participants, including 21 dementia-non-converters and 15 dementia converters.

All enrolled participants were actively monitored throughout the study period. For individuals lost to follow-up, we documented last available assessment timepoints and reasons for discontinuation (where available) and restricted primary analyses to participants with complete longitudinal data. Sensitivity analyses using multiple imputation methods were planned if attrition exceeded 20%.

The study enrolled patients with KOA who met the following inclusion criteria: (1) aged between 40 and 75 years; (2) diagnosed with KOA in at least one knee by an orthopedic physician based on the diagnostic criteria established by the American College of Rheumatology[28]; (3) graded as Kellgren-Lawrence Scale 2 or 3; (4) scored below 14 on the Beck Depression Inventory (BDI), which is consistent with the criteria established in our

previous studies[29,30]; (5) participants had a body mass index (BMI) of ≤30 kg/m²; (6) scores on the Mini-Mental State Examination (MMSE) were ≥24[31], indicating cognitive normality during baseline session; and right-handed. These criteria are consistent with our previous study[12,30].

Patients were excluded if they met any of these criteria: history of knee surgery within six months or intra-articular corticosteroid injections within three months; knee pain associated with other diseases; muscle disease or severe knee deformity; inability to cooperate due to abnormal mental state; severe organ failure or cardiovascular and cerebrovascular disease; MRI contraindications such as porcelain teeth, dentures, pacemakers; bleeding disorders or use of opioids/benzodiazepines.

Outcome measures

Cognitive assessments. Cognitive assessments involved the utilization of the MMSE as a screening tool for subject eligibility. The MMSE is a widely employed 30-point questionnaire in clinical and research settings to evaluate cognitive impairment[31]. The sensitivity and specificity of the MMSE to differentiate between cognitively normal and dementia in older adults is greater than 0.80, which is of value in screening for dementia[32].

During the confirmation of staging, the Montreal Cognitive Assessment (MoCA) and the Wechsler Memory Scale-Chinese Revision (WMS-CR) were employed to evaluate specific domains of cognitive decline. The global cognitive functioning of the subjects was assessed using the MoCA scale, which covers domains of visuospatial/executive skills, naming ability, attention, language proficiency, abstraction capacity, memory, and orientation. The MoCA scale has a total score of 30 points, with higher scores indicating better overall cognitive function[33]. The MoCA detected mild AD with a sensitivity of 1.00 and specificity of 0.87[33]. The MoCA_Language subtest comprises two components: the Sentence Repetition subtest, which evaluates verbal functioning, attention, and immediate memory; and the Letter Fluency subtest, which assesses phonological and semantic fluency[34].

Memory was assessed using the Wechsler Memory Scale-Chinese Revision (WMS-CR)[35]. Its primary function is memory assessment, operationalized via Memory Quotient (MQ) and associated sub-scores. The subtests include counting from 1 to 100, counting from 100 to 1, accumulation, picture, recognition regeneration, association, touch, comprehension, and digit span. The WMS-CR_1-100 subtest evaluates the sub-components of memory related to mental control[36].

The Ascertain Dementia 8 (AD8) is a concise questionnaire characterized by high sensitivity and specificity, developed to detect dementia[37]. The AD8 has a cut-off score of 2, wherein higher scores are indicative of poorer cognitive performance[38]. In the present study, participants were grouped based on their final AD8 scores into two categories: those who showed no signs of dementia (AD8 < 2, dementia-non-converters) and those who exhibited possible dementia (AD8 ≥ 2, dementia-converters). Additionally, AD8 with an internal consistency of 0.78, a sensitivity of 93.9%, and a specificity of 76.0% in detecting dementia[39]. It is robustly associated with biomarkers of AD and has greater sensitivity than MMSE in detecting AD, particularly in the initial symptomatic stages[40].

KOA symptoms assessment. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was employed to evaluate knee structure and function in terms of pain, stiffness, and joint function, encompassing fundamental signs and symptoms of knee arthritis. Of the 24 items assessed, five pertained to pain, two related to stiffness, and 17 were associated with joint function. A higher score indicated greater severity[41]. Prior research demonstrates that the WOMAC scale exhibits high reliability for assessing pain, stiffness, and physical function, with reliability coefficients of 0.91, 0.81, and 0.84, respectively[42].

Serum BDNF, IFN-γ, PD-1, CNR1, CNR2 and TIM3 levels analyses

Based on our prior research findings, which demonstrated altered hippocampal-thalamus and superior frontal gyrus connectivities in KOA patients relative to healthy controls, as well as the correlation between hippocampal connectivities and serum BDNF levels, we aimed to further explore the association between these biomarkers and cognitive decline in KOA patients[12]. Given the hippocampus's critical role in mood regulation, pain perception, and its neuroplastic changes in response to chronic pain and depression, we focused specifically on these biomarkers. Common neuromodulators, which are implicated in both conditions, may contribute to the comorbidity observed in arthritis patients[21].

To accurately quantify the levels of serum BDNF, IFN-γ, PD-1, CNR1, CNR2, and TIM3, we adhered strictly to the manufacturer's recommended testing protocols and incorporated methodologies established in our previous research[43,44], we utilized the enzyme-linked immunosorbent assay (ELISA, ELISA kits: Huamei Biological Engineering Co. LTD, Wuhan, China) to accurately quantify the levels of serum biomarkers. Venous blood samples were collected in the morning using sterile serum separator tubes from the upper arm vein of patients at baseline. Following 15 min room temperature clotting, and 3000 × *g* centrifugation (10 minutes), serum was harvested and promptly transferred to −80 °C storage. The absorbance of both standard and test samples for BDNF, IFN-γ, PD-1, CNR1, CNR2, and TIM3 was measured at a wavelength of 450 nm using an ELISA reader (model ELX800; BioTek, Winooski, Vermont).

MRI data acquisition

Each participant underwent MRI scans at the beginning of the study and during a five-year follow-up period. The MRI data were acquired at the Second Affiliated People's Hospital of Fujian University of Chinese Medicine (Fuzhou, Fujian, China) using a 3.0 T GE scanner (General Electric, Milwaukee, WI, USA) equipped with an eight-channel head coil. T1-weighted images were obtained with the following parameters: a flip angle of 15°, a slice thickness of 1 mm, a field-of-view (FOV) of 240 mm, and an acquisition of 160 slices. Simultaneously, T2-weighted images were acquired to evaluate cerebral hemorrhage or other space-occupying lesions in subjects.

Brain imaging processing

MRI data were preprocessed in SPM12. All T1/T2 images underwent visual inspection in MRIcron, excluding scans with structural dislocations, artifacts, or incomplete coverage. Concurrently, T2-weighted imaging underwent clinical review by senior radiologists to exclude neuropathological cases. T1-weighted datasets received additional verification for structural completeness via MRIcron prior to analysis.

The hippocampus and its subregions were calculated and segmented using Freesurfer 7.1.0 software[45]. Utilizing the built-in Freesurfer algorithm, the recon-all command was employed for automated preprocessing steps, including head motion correction, standardized signal intensity processing, nonlinear registration, removal of nonessential components such as head and neck regions, cortical segmentation, etc., followed by registration to a standard brain space. Brain regions were segmented based on the Desikan-Killiany atlas template.

Statistics and reproducibility

Sample size and experimental design. This study analyzed data from 36 biologically independent human participants (21 dementia-non-converters, 15 dementia converters) enrolled in a longitudinal cohort. No data replicates were performed, as all measurements represent unique biological samples and individual participants. The sample size was determined through a priori power analysis for hippocampal volume differences (Cohen's $d = 0.98$, $\alpha = 0.05$, power = 0.8), indicating $n \geq 34$ participants are required for group comparisons[46], while accounting for projected 20–30% attrition rates from prior longitudinal neuroimaging studies to ensure statistical power retention at follow-up.

Statistical Analysis Framework

Comparison of baseline data. The statistical analysis was performed using IBM SPSS statistical software (IBM Corp., Armonk, NY, USA). All statistical analyses were performed using two-tailed *t*-tests with $P < 0.05$ as the level of significance. Continuous variables were presented as

mean ± standard deviation (SD) or median (25–75 percentile) according to whether they followed a normal distribution, and independent samples t-tests or Mann-Whitney U-tests were used to compare characteristics between groups. Classification variables were presented as frequencies, and comparisons between groups were made using chi-square tests. In all statistical analyses performed using SPSS, missing data were automatically excluded via pairwise deletion during computation.

Comparison of cognitive function and hippocampal subregion volumes

We employed a general linear model (GLM) or generalized linear model (GLM) with analysis of covariance (ANCOVA) to evaluate group differences in [dependent variable, e.g., cognitive score] between AD8-defined cohorts, adjusting for gender and age. The model was specified as:

$$Y_{ij} = \beta_0 + \beta_1 \cdot AD8Group_i + \beta_2 \cdot Gender_j + \beta_3 \cdot \left(Age - \overline{Age}\right) + \epsilon_{ij}$$

Where Y_{ij} represents the dependent variable (e.g., cognitive score) for the j-th participant in the i-th AD8 group (dementia-non-converters vs. dementia-converters), β_0 is the intercept, β_1 denotes the group effect, β_2 and β_3 are regression coefficient for gender (coded as 0 = female, 1 = male) and age (mean-centered), and ϵ_{ij} is residual error.

A GLM with whole hippocampus volume/the estimated total intracranial volume, age, and gender as covariates was employed to compare differences in the volume of whole hippocampus and hippocampal subregions between groups. All exploratory analyses apply Benjamini-Hochberg False Discovery Rate (FDR) Correction ($\alpha = 0.05$).

Correlation between brain regions, biomarkers, and cognitive function

Partial correlations (covariates: whole hippocampus volume, age, gender) evaluated cognition-hippocampal subregional volume relationships.

Moderating role of hippocampal subregions

All moderation analyses were carried out using the PROCESS macro for SPSS. Model 1 was utilized to assess moderating effects.

Identification of predictive biomarkers

Binary logistic regression predicted dementia development in KOA patients using baseline predictors: (1) Cognitive performance (MoCA_Language subtest and WMS-CR_1-100 subtest), which exhibited significant group differences in cognition (see results); (2) Serum levels of BDNF, IFN-γ, PD-1, CNR1, CNR2, and TIM3-these factors represent variations that demonstrated significant group differences in hippocampal subregion volumes according to our findings.

Results

Baseline description

The baseline characteristics such as age, gender, years of education, metabolic profiles (Type 2 diabetes, hypertension, hyperlipidemia, and cardiovascular disease), BMI, and total BDI scores exhibited no significant differences between the two study cohorts (Supplementary Table 1). No discernible distinctions were found in terms of KOA symptoms assessed using the WOMAC scale between both study cohorts (Supplementary Data 1). Notable disparities were not detected regarding serum biomarker levels among both study groups (Supplementary Table 2). In relation to whole hippocampal volume and its subregions' measurements at baseline (Supplementary Table 3), there were no noteworthy discrepancies identified between both study cohorts.

Comparisons of clinical outcome changes in groups (follow-up minus baseline)

Despite comparable baseline characteristics in demographics, clinical profiles, and hippocampal measures (Supplementary Tables 1–3), dementia-converters showed accelerated cognitive decline. Specifically, converters exhibited significantly greater reductions in MoCA_Language and WMS-CR scores on the 1–100 subtest compared to non-converters over 5 years (Table 1). However, there were no significant differences observed between groups regarding KOA symptoms (Table 1).

Although whole hippocampus volume showed no group difference, dementia-converters exhibited significantly smaller fimbria volumes (Table 2).

Correlation analyses

Further exploratory analysis using partial correlation analysis revealed significant associations between baseline fimbria volume, clinical outcomes, and serum biomarkers. Fimbria volume correlated positively with WMS-CR_1-100 in dementia-non-converters ($r = 0.497$, $P = 0.036$) but negatively correlated with MoCA_Language and CNR2 in the dementia-converters ($r = -0.626$, $P = 0.030$; $r = -0.746$, $P = 0.013$). No other statistically significant associations were found between baseline hippocampal subregion volumes and baseline clinical outcomes (Supplementary Data 2 and Fig. 1).

No significant correlation was observed between baseline fimbria volume and changes in cognitive scores (MoCA_Language and WMS-CR_1-100 subtests) in dementia-non-converters. However, a significant positive correlation was found between baseline fimbria volume and score change of MoCA_Language and WMS-CR_1-100 in dementia-converters ($r = 0.771$, $P = 0.003$; $r = 0.751$, $P = 0.005$, respectively). Additionally, there was a significant negative correlation between baseline BDNF levels and score change of MoCA_Language in dementia-non-converters ($r = -0.601$, $P = 0.011$), while a significant negative correlation existed between baseline CNR2 levels and score change of WMS-CR_1-100 in dementia-converters ($r = -0.693$, $P = 0.018$). No association was found between other serum biomarkers and changes in cognitive scores (Supplementary Data 3 and Fig. 1).

Moreover, using partial correlation analysis, we found significant associations between fimbria volume and serum biomarkers. Specifically, in the dementia-non-converters group, a notable inverse correlation was observed between baseline CNR2 levels and changes in fimbria volume ($r = -0.573$, $P = 0.020$). Conversely, in the dementia-converters group, a significant positive correlation was found between baseline CNR1 levels and changes in fimbria volume ($r = 0.649$, $P = 0.042$), as shown in Supplementary Data 4 and Fig. 1.

Moderating effect analyses

We observed a significant moderation effect of baseline fimbria volume on the relationship between WOMAC_Pain scores and WMS-CR_1-100 in dementia-non-converters (Supplementary Data 5 and 6 and Fig. 2). However, this moderation effect was not evident in dementia-converters.

Interestingly, the data indicated that the baseline volume of the fimbria substantially moderated the association between TIM3 levels and WMS-CR_1-100 scores in dementia-non-converters (Supplementary Data 7 and Fig. 2). Additionally, fimbria volume moderated the relationship between IFN-γ levels and WMS-CR_1-100 scores in dementia-converters (Supplementary Data 8 and Fig. 2).

Binary logistic regression analysis of factors affecting cognitive progress

The binary logistic regression model demonstrated that only the levels of BDNF, IFN-γ, CNR2, CNR1, PD1, and TIM3 as independent variables were predictors of dementia risk during the follow-up session. Our findings revealed that baseline IFN-γ levels acted as a protective factor against dementia progression in KOA patients (OR = 0.843, 95% CI: 0.713–0.995, $P = 0.044$). Additionally, the Hosmer-Lemeshow test indicated a good fit for the equation ($P = 0.387$) (Supplementary Data 9 and Fig. 3).

Discussion

In this study, we investigated the cognitive performance of patients diagnosed with KOA in different cognitive states at baseline and after a five-year follow-up, while exploring the underlying mechanisms involving brain

Table 1 | Comparisons of cognitive function performance changes (follow-up minus baseline)

	dementia-non-converters ($n = 21$)	dementia-converters ($n = 15$)	t/Wald χ^2	95%CI	P	FDR p value
WOMAC						
Pain[a]	−3.43 ± 3.36	−2.67 ± 1.80	−0.509	(1.463, −2.437)	0.614	1.842
Stiffness[a]	−2.24 ± 1.89	−2.47 ± 2.10	0.224	(1.532, −1.228)	0.824	0.824
Function[a]	−9.29 ± 9.65	−8.73 ± 7.77	0.043	(6.399, −6.132)	0.966	0.966
MoCA						
Visuospatial/Executive [b]	0.00(−1.00 to 0.00)	0.00(−1.00 to 1.00)	0.372	(1.031, −0.541)	0.542	0.759
Naming [b]	0.00(0.00–0.00)	0.00(0.00–1.00)	0.156	(0.613, −0.407)	0.693	0.809
Attention [b]	0.00(−1.00 to 0.00)	0.00(−1.00 to 0.00)	0.510	(1.450, −0.675)	0.475	0.831
Language [b]	−1.00(−1.00 to 0.00)	−1.00(−2.00 to −1.00)	6.069	(1.503, 0.171)	0.014	0.098
Abstraction [b]	1.00(0.00–2.00)	1.00(0.00–1.00)	0.036	(0.723, −0.596)	0.850	0.850
Memory [a]	-0.16 ± 1.74	-0.60 ± 1.77	1.011	(1.838, -0.623)	0.324	0.756
Orientation [b]	0.00(0.00–0.00)	0.00(0.00–0.00)	1.231	(1.461, -0.405)	0.267	0.935
Total score[a]	0.11 ± 3.11	−0.47 ± 3.56	1.240	(7.156, −1.739)	0.224	
WMS-CR						
1-100[b]	−1.00(−2.00 to 1.50)	−2.00(−6.00 to 1.00)	4.117	(4.882, 0.084)	0.042	0.210
100-1[b]	0.00(1.50 to 1.50)	0.00(−2.00 to 2.00)	0.097	(2.250, −1.632)	0.755	1.080
Accumulation[b]	0.00(−3.00 to 1.00)	0.00(−3.00 to 1.00)	2.990	(6.114, −0.383)	0.084	0.280
Picture[a]	−1.95 ± 2.75	−1.20 ± 2.91	−0.736	(1.261, −2.686)	0.467	0.778
Recognition[a]	−1.24 ± 2.43	-0.80 ± 4.26	−0.306	(1.984, −2.684)	0.762	0.953
Regeneration[b]	0.00(−2.00 to 2.00)	2.00(−1.00 to 4.00)	5.236	(−0.261, −3.381)	0.022	0.220
Association[a]	−2.10 ± 3.67	−0.27 ± 4.25	−1.425	(0.837, −4.742)	0.164	0.410
Touch[a]	−3.00 ± 3.52	−4.80 ± 5.65	1.161	(5.095, −1.395)	0.254	0.508
Comprehension[a]	−1.57 ± 1.60	−1.80 ± 2.18	0.218	(1.461, −1.179)	0.829	0.829
Digit span[a]	2.05 ± 3.15	2.07 ± 3.41	−0.274	(1.967, −2.578)	0.786	0.873
Memory quotient[a]	−7.05 ± 7.08	−6.40 ± 11.51	−0.240	(5.680, −7.199)	0.812	

[a]A general linear model was carried out with age, and gender as the covariate, and mean ± SD was used for statistical description.
[b]A generalized linear model was carried out with age, and gender as the covariate, and median (25–75th percentile) was used for statistical description.
BDI Beck Depression Inventory, *BPI* Brief Pain Inventory; *WOMAC* Western Ontario, *McMaster* Universities Osteoarthritis Index, *MoCA* Montreal Cognitive Assessment, *WMS-CR* Wechsler Memory Scale-Chinese Revised.

Table 2 | Comparisons of hippocampal subregions volume changes (follow-up minus baseline)

	dementia-non-converters ($n = 21$)	dementia-converters ($n = 15$)	t/Wald χ^2	95% CI	P	FDR p Value
Whole hippocampus[a]	−133.46 ± 204.28	−152.89 ± 180.90	0.679	(185.775, −93.108)	0.503	
Hippocampal tail[b]	−54.21 ± 86.17	−54.12 ± 81.31	0.029	(50.929, −49.508)	0.977	1.066
Subiculum[b]	−13.83 ± 33.83	−11.32 ± 36.03	−0.615	(10.913, −20.334)	0.543	1.629
CA1[b]	−2.63 ± 34.51	−9.99 ± 44.39	0.254	(33.539, −26.112)	0.801	1.202
Hippocampal fissure[c]	25.84(10.07–39.69)	5.07(−16.72 to 39.19)	0.671	(32.633, −13.391)	0.413	1.652
Presubiculum[c]	4.03(−23.57 to 27.29)	−0.49(−14.00 to 14.41)	0.026	(14.233, −16.780)	0.872	1.046
Parasubiculum[b]	-2.36 ± 13.45	2.39 ± 14.21	−1.618	(1.722, −14.954)	0.116	0.696
Molecular layer HP[b]	-20.17 ± 28.72	−22.22 ± 28.94	−0.363	(9.779, −14.008)	0.719	1.233
GC-ML-DG[b]	−19.13 ± 23.56	−21.54 ± 19.71	−0.014	(9.901, −10.039)	0.989	0.989
CA3[b]	−14.44 ± 23.47	−15.27 ± 18.58	−0.386	(8.912, −13.078)	0.702	1.404
CA4[b]	−17.81 ± 22.95	−19.00 ± 18.21	−0.220	(9.246, −11.477)	0.828	1.104
Fimbria[b]	11.80 ± 12.52	−0.66 ± 24.31	2.343	(25.903, 1.792)	0.026	0.312
HATA[d]	−0.48 ± 11.08	−0.29 ± 7.27	0.499	(8.397, −5.100)	0.621	1.490

[a]A general linear model was carried out with the estimated total intracranial volume, age, and gender as the covariate, mean ± SD was used for statistical description.
[b]A general linear model was carried out with whole hippocampus volume, age, and gender as the covariate, mean ± SD was used for statistical description.
[c]A generalized linear model was carried out with whole hippocampus volume, age, and gender as the covariate, median (25–75th percentile) was used for statistical description.
[d]A general linear model was carried out with whole hippocampus volume, baseline HATA volume, age, and gender as the covariate, mean ± SD was used for statistical description. *HATA* hippocampal amygdala transition area, *GC-ML-DG* granule cell layer, and molecular layer of the dentate gyrus. The unit of volume is cubic millimeters.

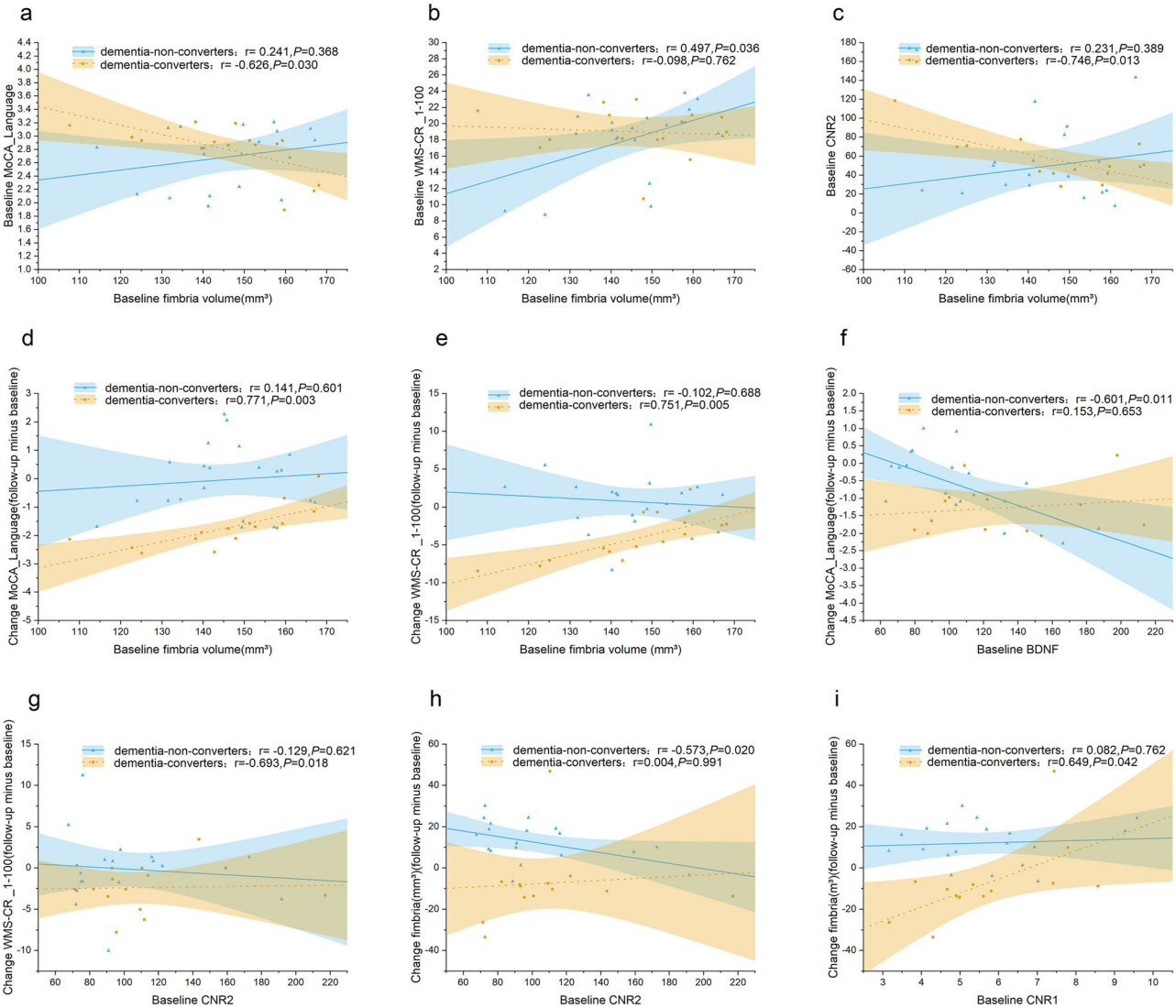

Fig. 1 | Correlations of baseline hippocampal fimbria volume and serum biomarkers with cognitive outcomes in knee osteoarthritis patients stratified by dementia conversion status ($n = 15$ dementia-converters; $n = 21$ dementia-non-converters biologically independent human participants). **a**–**c** Baseline fimbria volume associations. **a** Negative correlation with MoCA_Language (dementia-converters). **b** Positive correlation with WMS-CR_1-100 (dementia-non-converters). c Negative correlation with serum CNR2 (dementia-converters). **d**–**g** Longitudinal cognitive change associations. Baseline fimbria volume positively correlates with MoCA_Language (**d**) and WMS-CR_1-100 (**e**) changes (dementia-converters). **f** Baseline BDNF negatively correlates with MoCA_Language change (dementia-non-converters). **g** Baseline CNR2 negatively correlates with WMS-CR_1-100 change (dementia-non-converters). **h**, **i** Fimbria volume change associations. **h** Baseline CNR2 negatively correlates with fimbria volume change (dementia-converters). **i** Baseline CNR1 positively correlates with fimbria volume change (dementia-converters). MoCA Montreal Cognitive Assessment, WMS-CR Wechsler Memory Scale-Chinese Revision, CNR2 recombinant cannabinoid receptor 2, BDNF brain-derived neurotrophic factor, CNR1 recombinant cannabinoid receptor 1. Shaded areas represent 95% confidence bands.

structure and peripheral inflammatory factors. Our findings reveal important associations between various peripheral inflammatory factors and hippocampal subregion fimbria volume as well as cognitive function in KOA patients. These observations align with the bone-brain axis paradigm wherein peripheral joint pathology triggers CNS alterations through neuroimmune cascades[6]. Furthermore, the data showed that fimbria volume mediates the impact of WOMAC_Pain score, serum IFN-γ levels, and TIM3 levels on memory function (WMS-CR_1-100 subscore). Additionally, our results suggest that serum IFN-γ levels may exert a protective effect against cognitive decline in individuals with KOA.

In present study, we observed a pronounced decline in the MoCA_Language subscore and the WMS-CR_1-100 subscore among dementia-converters compared to dementia-non-converters, indicating more pronounced cognitive impairment over time in these two cognitive dimensions. In our previous study—which also employed age-adjusted MQ scores and included age as a covariate—changes in MoCA and MQ scores showed no significant association with patient age[12]. This aligns partially with prior studies reporting cognitive impairment in KOA patients[7,47]. Moreover, our present study further showed that the decline in cognitive function may be related to language and memory dimensions. The primary manifestation of KOA is pain, which is a multifaceted experience encompassing sensory, emotional, and cognitive processes. Consistent with a biopsychosocial model of pain and dementia[5], changes in the cognitive domain— including impairments in semantic/episodic pain memory, executive function, and pain anticipation—are proposed as key dementia-related alterations potentially relevant to KOA patients experiencing cognitive decline. For instance, Zhao et al. discovered that individuals with chronic pain exhibit accelerated aging in the hippocampal region, which in turn mediates cognitive impairment in these patients[48]. Other researchers have also reported memory and language deficits among this population. Our findings are similar to those of Cardoso et al. [49], who found a decline in verbal function in chronic pain patients, and Lysne et al. [50] also found that older adults

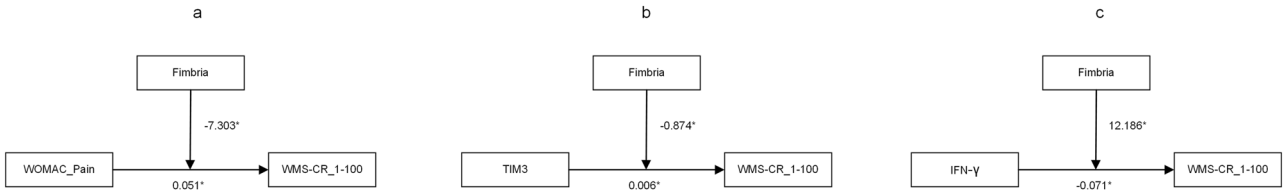

Fig. 2 | Moderating effects of baseline hippocampal fimbria volume on pain-inflammation-cognition relationships in knee osteoarthritis patients ($n = 21$ dementia-non-converters; $n = 15$ dementia-converters biologically independent human participants). a Significant moderation by fimbria volume on WOMAC_Pain-WMS-CR_1-100 association (dementia-non-converters). **b** Significant moderation by fimbria volume on TIM3-WMS-CR_1-100 association (dementia-non-converters). **c** Moderation by fimbria volume on IFN-γ-WMS-CR_1-100 association (dementia-converters). WOMAC Western Ontario and McMaster Universities Osteoarthritis Index, WMS-CR Wechsler Memory Scale-Chinese Revision, TIM3.T cell immunoglobulin domain and mucin domain 3, IFN-γ Interferon-gamma.

reporting chronic musculoskeletal pain performed worse than normal older adults and younger adults on a test of nonverbal fluency. Additionally, nonverbal fluency performance was linked to cortical thickness in the temporal lobes, such as the hippocampus.

In addition, we found that the memory subcomponent, mental control, was markedly lower in dementia-converters than in dementia-non-converters. Memory is the earliest and most obvious symptom of cognitive decline, and in the early stages of AD[51]. Chronic pain drives accelerated cognitive decline and elevates dementia risk[52]. partly through tau-mediated hippocampal pathology that induces memory deficits—a region essential for memory consolidation[22]. It is likely that memory loss in chronic pain patients is closely linked to the hippocampus. Further studies exploring the mechanisms of cognitive decline in older adults with chronic pain are imperative to examining its potential clinical implications in dementia progression. While dementia-related changes in pain processing often involve the cognitive domain (e.g., memory for pain), the specific interplay between KOA-related chronic pain, hippocampal subregion integrity (like the fimbria), and these cognitive aspects of pain requires further elucidation.

The fimbria plays a crucial role in maintaining cognitive function and the hippocampal memory circuit[53]. It serves as an important connection between thalamus and hippocampus. Abnormalities in structural and functional connectivity between these two regions are important pathological features of cognitive dysfunction, such as AD[54]. Our findings suggest that fimbria volume increases in dementia-non-converters but decreases in dementia-converters. These results align with previous research demonstrating smaller grey matter volumes within the fimbria associated with poorer cognitive performance among cognitively normal individuals[55]. Previous studies[56,57] have also shown compensatory increases in volume for certain hippocampal subregions during cognitive decline, which may explain our study's negative correlation between fimbria volume and cognitive function among people at risk of dementia. Based on our findings regarding decreased fimbria subregion volume among dementia-converters compared to dementia-non-converters, we speculate this decrease may be a key factor contributing to develop dementia. This aligns with evidence that hippocampal subregions (including fimbria) are primary contributors to accelerated brain aging in KOA, as demonstrated by a brain age model showing PAD increases mediated by hippocampal atrophy[11]. The fimbria serves as an important connection between the thalamus and hippocampus —key relay stations in pain processing circuits."

Interestingly, a positive correlation was observed between fimbria volume and the baseline WMS-CR_1-100 subscore in dementia-non-converters, while a negative correlation was found between fimbria volume and the baseline MoCA_Language subscore in dementia-converters. These findings suggest that there may be differential implications of fimbria involvement in cognitive function changes among patients with KOA. Specifically, increased fimbria volume could potentially serve as compensatory protection for long-term memory (as measured by the WMS-CR_1-100 subscore) in individuals who do not develop dementia, whereas decreased fimbria volume might contribute to language-related cognitive decline in those at risk of developing dementia. The fimbria, a critical component of the hippocampus involved in memory formation and retention, may exhibit enhanced structural integrity and functionality with increased volume. Consequently, this could enable the hippocampus to more effectively resist the adverse effects of aging or neurodegenerative processes on memory. Further studies are warranted to validate our results.

Moreover, our study demonstrated that fimbria volume mediated the relationship between WOMAC_pain and TIM3 scores on one hand, and long-term memory performance on the other, particularly among individuals who did not convert to dementia. These findings indicate that the association between pain levels, TIM3 concentrations, and their effects on long-term memory may be partially or fully accounted for by fimbria volume. In essence, fimbria size appears to play a critical role in modulating the impact of pain and TIM3 on memory performance.

Chronic pain, as assessed using the WOMAC pain scale, has been demonstrated to have a negative impact on cognitive function, including memory performance[58,59]. TIM3, an immune checkpoint protein that plays a critical role in regulating immune cells such as macrophages, has been associated with chronic pain conditions[60]. Lower levels of TIM3 expression have been correlated with reduced IL-10 secretion, which may potentially exacerbate inflammatory responses and thereby further compromise cognitive function[61]. In the context of our study, individuals with an AD8 score below 2 (indicating a lower likelihood of dementia) and increased fimbria volume showed a reduced impact of pain and TIM3 levels on their long-term memory performance. This underscores the fimbria's protective role in this subset of individuals, potentially shielding their memory from the detrimental effects of pain and altered immune function.

In summary, our findings underscore a complex interaction wherein fimbria volume serves as a critical factor in sustaining long-term memory function among individuals at risk of dementia. It functions not only as a compensatory mechanism but also as a mediator of the relationship between pain and a biological marker (TIM3) with respect to long-term memory performance, particularly in individuals with lower dementia risk scores. These observations enhance our understanding of the potential mechanisms underlying cognitive resilience and decline during aging and neurodegenerative processes, offering insights into how structural brain changes, pain perception, and immune function interact to influence cognitive outcomes.

Our longitudinal study further revealed that fimbria volume mediated the association between INF-γ levels and WMS-CR_1-100 subscore in dementia-converters. Interestingly, IFN-γ was found to be a protective factor against dementia progression in KOA patients by rescuing cognitive deficits[24] while also improving quality of life for older adults[62]. These results highlight the potential role of fimbria as a co-mediating variable linking peripheral IFN-γ levels to cognitive function in KOA[63].

Immune-neurodysregulation crosstalk involves dementia-related cytokine dysregulation[64]. The endocannabinoid system (ECS) regulates pain, immunity, and cognitive plasticity[65,66], with CNR1/CNR2 receptors implicated in osteoarthritis degeneration and memory impairments[67]. Specifically, CNR1 activation on hippocampal GABAergic neurons protects against age-related cognitive deficits by attenuating neuroinflammation and

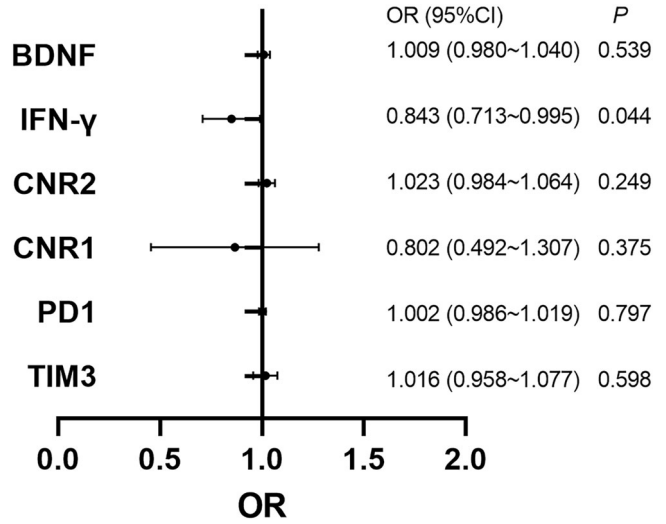

Fig. 3 | Binary logistic regression analysis of inflammatory biomarkers associated with dementia conversion in knee osteoarthritis patients ($n = 36$ biologically independent human participants). Forest plot displays odds ratios (OR) and 95% confidence intervals (95% CI) for dementia conversion risk per standard deviation increase in serum biomarker levels. Biomarkers analyzed: Brain-derived neurotrophic factor (BDNF), interferon gamma (IFN-γ), recombinant cannabinoid receptor 2 (CNR2), recombinant cannabinoid receptor 1 (CNR1), programmed death 1 (PD-1), and T-cell immunoglobulin domain and mucin domain 3 (TIM3). The vertical line at OR = 1.0 indicates no effect. A significant protective association was observed for IFN-γ (OR = 0.843, 95% CI: 0.713–0.995, $P = 0.044$). All other biomarkers showed non-significant associations with dementia conversion ($P > 0.05$). Statistical significance was assessed at $\alpha = 0.05$.

neuronal degeneration[68]. We observed divergent CNR-fimbria relationships across disease stages: in resilient non-converters, higher baseline CNR2 predicted fimbria preservation ($r = -0.573$, $P = 0.020$), suggesting compensatory signaling; conversely, in converters, elevated CNR1 associated with progressive fimbria atrophy ($r = 0.649$, $P = 0.042$), indicating receptor dysregulation during dementia progression. This aligns with evidence that CNR1 activation protects against neuroinflammation in early cognitive decline[68], whereas prolonged CNR2 signaling may drive pathological glial activation in advanced stages[69].

Our study highlights the impact of fimbria volume and inflammatory factors on cognitive decline in KOA patients. Fimbria volume is a key intermediary, while IFN-γ may protect against cognitive decline. CNR1/CNR2 levels correlate with cognitive function and KOA-related impairments. However, there are limitations to this study. First, the single-center design with modest sample size ($n = 36$) and gender imbalance may limit generalizability; future multi-center studies with balanced cohorts are needed. Second, exploratory analyses showed marginal significance after FDR correction, suggesting these preliminary findings require validation in larger cohorts. Third, we focused on selected inflammatory markers; omics approaches could provide broader insights. Fourth, lacking healthy controls prevents direct KOA-neuroinflammation comparisons. Finally, limited temporal data (e.g., symptom duration) and only two assessment time points constrain trajectory analyses. Extended follow-ups with serial measurements would strengthen causal inferences.

Conclusion

In summary, our study highlights the considerable influence of fimbria volume and peripheral inflammatory factors on cognitive decline in individuals diagnosed with KOA. Fimbria volume plays a pivotal role as an intermediary for alterations in cognitive function, whereas IFN-γ potentially exerts a protective effect against progressive cognition deterioration. Additionally, we observed close associations between levels of peripheral CNR1 and CNR2 and cognitive decline during dementia progression among KOA patients. These findings offer valuable insights into the intricate connection between cognition, peripheral inflammation markers, fimbria volume, and various degrees of impairment seen in KOA patients.

Data availability

The source data associated with the paper are available in Supplementary Data files as follows: Source data for Fig. 1a–c (baseline fimbria volume correlation analyses) are in Supplementary Data 2 and Fig. 1d–g (cognitive changes correlation analyses) in Supplementary Data 3 and Fig. 1h-i (fimbria volume changes correlation analyses) in Supplementary Data 4 and Fig. 2 (moderating effects of baseline fimbria volume) in Supplementary Data 5, 7 and 8 respectively; and Fig. 3 (binary logistic regression analysis of factors affecting cognitive progress) in Supplementary Data 9. All other datasets generated and analyzed during this study are available from the corresponding author on reasonable request. No new datasets were deposited in public repositories during this work.

Code availability

No custom code was generated; analyses used SPSS, FreeSurfer (7.1.0), and SPM 12 with default parameters.

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Author contributions

J.L. and J.T.: conceptualization, study design, funding acquisition. Y.J.W.: data curation, formal analysis, writing—original draft. G.Y.C.: investigation, methodology, visualization. M.L.: validation, resources, project administration. R.L.C.: software, investigation, data collection. P.L.Z.: investigation, experimental procedures. B.R.Z.: Investigation, data collection. J.L., J.T., Y.J.W., and G.Y.C.: writing—review and editing. All authors: final manuscript review and approval.

Competing interests

The authors declare no competing interests.

Additional information

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