Received: 29 August 2024 | Revised: 24 December 2024 | Accepted: 17 January 2025

DOI: 10.1002/alz.14606

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Moderation of midlife cognitive activity on tau-related cognitive impairment

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Funding information
Ministry of Science, ICT, and Future Planning, Republic of Korea, Grant/Award Numbers: NRF-2014M3C7A1046042, RS-2022-00165636, HI18C0630, HI19C0149, HU23C0140, U01AG072177

Abstract

INTRODUCTION: We investigated the moderating effects of midlife and late-life cognitive activity (CA) on the relationship between tau pathology and both cognition and cognitive decline.

METHODS: Eighty-nine non-demented older adults from a Korean cohort underwent comprehensive evaluations, including CA assessments and tau neuroimaging at baseline, and Mini-Mental State Examination (MMSE) at baseline and the 2-year follow-up.

RESULTS: Greater midlife CA was associated with higher MMSE scores in a given amount of tau pathology, whereas higher levels of midlife CA were associated with faster tau-related decline in MMSE scores, particularly in individuals with mild cognitive impairment. Late-life CA did not exhibit any interaction with tau on either MMSE scores or their 2-year change.

DISCUSSION: Greater midlife CA is generally associated with better cognitive performance despite the presence of tau pathology. However, paradoxically, increased midlife CA appears to be linked to a more rapid tau-related cognitive decline in already cognitively impaired individuals.

KEYWORDS
Alzheimer's disease, cognitive activity, cognitive impairment, cognitive reserve, late life, midlife, tau

Highlights

- Greater midlife cognitive activity (CA) was generally associated with better cognitive performance in a given amount of tau pathology.
- Paradoxically, higher levels of midlife CA were related to a more rapid tau-related cognitive decline in already cognitively impaired individuals.
- Late-life CA did not exhibit any moderation effect on the association between tau and cognitive performance or decline.

1 | BACKGROUND

Numerous studies suggest that engaging in cognitive activity (CA), as a modifiable lifestyle factor, is linked to better cognition in later life,[1–3] a decreased risk of incident mild cognitive impairment (MCI),[4,5] all-cause dementia,[6,7] and Alzheimer's disease (AD) dementia.[5,6] However, the exact mechanisms that underpin the protective role of CA in AD-related cognitive impairment remain unclear.

While a *post mortem* brain study reported no direct correlation between the level of CA and AD-specific neuropathologies, such as amyloid beta (Aβ) and pathologic tau deposition,[5] a recent neuropathologic study suggested an association between early life cognitive enrichment, including CA, and fewer AD neuropathological changes.[8] Several neuroimaging studies investigated the relationship between participation in CA and in vivo Aβ deposition, but the results were mixed.[1,9] Another multivariate neuroimaging study demonstrated an association between lifetime CA and tau pathology but did not find any association between CA and Aβ deposition in cognitively unimpaired individuals with a parental or multiple-sibling family history of sporadic AD.[10]

However, CA might mitigate the adverse impact of AD pathologies on cognition (i.e., cognitive resilience to AD pathology) by enhancing cognitive reserve (CR),[11–13] as well as directly affect the accumulation of AD-specific pathology itself (i.e., resistance to AD pathology).[14] Regarding the possibility, a couple of studies have investigated the moderating role of CA on the association between AD pathology and cognitive decline. One study reported that midlife CA did not affect the association of Aβ deposition with baseline cognition or the rate of cognitive decline in cognitively healthy individuals.[15] Furthermore, our research group previously reported no interactive association between lifetime CA and Aβ burden on cognition in older adults with a diverse cognitive spectrum.[16] However, there is limited information available regarding the moderating effect of CA on the relationship between tau pathology and cognitive impairment. Compared to Aβ pathology, tau deposition not only exhibits a stronger correlation with the degree of cognitive impairment but also has a more immediate temporal relationship with cognitive decline.[17]

Therefore, we aimed to investigate the moderating effect of midlife and late-life CA on the association of in vivo tau deposition with current cognition and cognitive decline over a 2-year period in non-demented older adults.

2 | METHODS

2.1 | Participants

The present study was conducted as part of the Korean Brain Aging Study for the Early Diagnosis and Prediction of Alzheimer's Disease (KBASE), an ongoing prospective cohort study.[18] Participants were recruited through two university hospitals and two public centers for dementia prevention around Seoul, South Korea. In addition, volunteers from the community were recruited through advertisements on an online homepage, posters, and brochures provided at the main recruitment sites and word of mouth (recommended by other participants, family members, friends, or acquaintances). At the study's baseline, a total of 89 non-demented older adults, comprising 61 cognitively normal (CN) individuals and 28 individuals with MCI aged between 55 and 90 years, who underwent brain tau positron emission tomography (PET) imaging, were recruited. The CN group included participants with a Clinical Dementia Rating (CDR)[19] score of 0 and no diagnosis of MCI or dementia. All individuals with MCI met the core clinical criteria for amnestic MCI according to the recommendations of the National Institute on Aging and Alzheimer's Association guidelines,[20] which are as follows: (1) memory complaint corroborated by self, an informant, or clinician; (2) objective memory impairment; (3) largely intact functional activities; and (4) not demented. Regarding criterion 2, the age-, education-, and sex-adjusted *z* scores for at least one of four episodic memory tests were less than −1.0. These four memory tests were Word List Memory, Word List Recall, Word List Recognition, and Constructional Recall, which are part of the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K) neuropsychological battery.[21] All individuals with MCI had a CDR score of 0.5. The exclusion criteria were as follows: (1) the presence

of a major psychiatric illness, including major depressive disorder; (2) significant neurological conditions (e.g., cerebrovascular disease) or medical conditions that could affect mental function; (3) contraindications for magnetic resonance imaging (MRI), such as a pacemaker or claustrophobia; (4) illiteracy; (5) significant visual/hearing difficulties and/or severe communication or behavioral problems that would hinder clinical examinations or brain scans; (6) taking an investigational drug; and (7) being pregnant or breastfeeding. More detailed information on the recruitment of the KBASE cohort is presented in a previous report from our research group.[18]

2.2 | Clinical assessment

All participants underwent comprehensive clinical assessments conducted by trained psychiatrists and neuropsychologists, following the KBASE assessment protocol,[18] which includes the CERAD-K.[22] These assessments were conducted at the time of tau imaging (i.e., study baseline, T0) and 2 years later (T2). We assessed global cognition using the Mini-Mental State Examination (MMSE) score[21] at both T0 and T2. Additionally, we estimated premorbid intelligence quotient (IQ) using the Korean Adult Reading Test (KART).[23]

2.3 | Assessment of cognitive activities

The frequency of CA participation was assessed using a 39-item structured questionnaire[3,5] at 2 years before the baseline visit of the current study (i.e., the initial enrollment time of the KBASE). The questionnaire included items that fulfilled three criteria: (1) seeking or processing information was central to the activity, (2) relatively few physical or social barriers to participating in the activity, and (3) participation in the activity was likely to be relatively common (e.g., reading newspapers, magazines, or books; visiting a museum or library; attending a concert, play, or musical). Participation frequency was rated on a scale from 1 (once a year or less) to 5 (approximately daily). The questionnaire comprised 9 items for the current (i.e., late-life) period, 9 items for midlife (at age 40), 10 items for young adulthood (at age 18), and 11 items for childhood (ages 6–12). The item scores for midlife and the current period were averaged to calculate separate values for midlife and late-life CA, respectively. Using age 40 as a midlife CA measurement point has the advantage of minimizing the negative effect of AD pathology on CA participation, as cerebral Aβ deposition usually begins after the fourth decade of life.[24] Using the current age (age range of participants, 57 to 83 years) as a late-life CA measurement point could reflect the most recent activity.

2.4 | Laboratory tests of blood samples

Genomic DNA was extracted from whole blood, and apolipoprotein E (*APOE*) genotyping was performed as previously described.[25] *APOE* ε4 positivity was defined as the presence of at least one ε4 allele.

RESEARCH IN CONTEXT

1. **Systematic review**: Many studies suggest that cognitive activity (CA) is associated with better late-life cognition and a reduced risk of Alzheimer's disease (AD). However, it remains unclear whether midlife or late-life CA moderates the relationship between AD pathology and cognitive impairment.
2. **Interpretation**: Our study showed that greater midlife CA was associated with better cognitive performance despite the presence of tau pathology, whereas late-life CA did not have the same effect. This finding generally emphasizes the protective effect of midlife CA against AD pathology-related cognitive impairment by enhancing cognitive reserve or resilience. However, our study also demonstrated that higher midlife CA was related to a more rapid tau-related cognitive decline in already cognitively impaired individuals, highlighting a paradoxical faster cognitive decline after the onset of cognitive impairment in individuals with greater midlife CA.
3. **Future directions**: Future studies with larger sample sizes and longer follow-up periods are needed to confirm these findings.

2.5 | Measurement of cerebral tau deposition

All participants underwent [^{18}F] AV-1451 PET scans using a Biograph True Point 40 PET/CT scanner (Siemens) following the manufacturer's guidelines. The details of the AV-1451 PET imaging acquisition and preprocessing have been previously described.[26] AV-1451 PET standardized uptake value ratio (SUVR) images based on the mean uptake over minutes post-injection were normalized by the mean uptake in the inferior cerebellar gray matter, following the published code. We used tau deposition in the inferior temporal (IFT) region of interest (ROI) as a proxy for AD-related neocortical tau deposition, as previously reported.[27] The IFT gyrus is an early site of tau spread into the neocortex during Braak stage III,[28] and an association of this spread from the medial temporal lobe to the neocortex with early cognitive impairment has been reported.[27] We used a size-weighted average of partial volume-corrected SUVR in the IFT ROI for our analyses.

2.6 | Measurement of cerebral Aβ deposition

Participants also underwent [^{11}C] Pittsburgh compound B (PiB) PET scans using a 3.0T Biograph mMR (PET-MR) scanner (Siemens) following the manufacturer's guidelines. The details of PiB PET imaging acquisition and preprocessing have been previously described.[26] To determine ROIs for characterizing PiB retention levels in the frontal, lateral parietal, posterior cingulate-precuneus, and lateral temporal

regions, we applied an automatic anatomical labeling algorithm and a region-combining method.[29] SUVR values for each ROI were calculated by dividing the mean value for all voxels within each ROI by the mean cerebellar uptake value in the same image. Additionally, a global cortical ROI was defined, comprising the four individual ROIs, and a global Aβ retention value was generated by dividing the mean value for all voxels within the global cortical ROI by the mean cerebellar uptake value in the same image.[29,30] Participants were classified as Aβ positive if the SUVR was > 1.4 in at least one of the four ROIs, or as Aβ negative if the SUVR in each of the four ROIs was ≤ 1.4.[31]

2.7 | Statistical analyses

We performed *t* tests and chi-square tests to compare the characteristics between CN and MCI groups and between participants who were followed up and those who were not followed up. To investigate the direct effect of tau pathology on baseline cognition and cognitive decline, we initially conducted multivariate linear regression models. In these models, IFT tau deposition served as the independent variable, and MMSE score (at T0) or MMSE change (calculated as [MMSE at T2 – MMSE at T0]/MMSE at T0) was the dependent variable. To account for the potential influence of baseline cognitive function,[32,33] MMSE change was calculated as the difference between MMSE scores at T2 and T0, divided by the baseline MMSE score at T0. We controlled for age, sex, education, *APOE* ε4 positivity, baseline cognitive status (i.e., CN vs. MCI), and Aβ positivity as covariates in Model 1. In Model 2, we included premorbid IQ as another covariate, in addition to the covariates from Model 1. Next, to examine the moderating effect of CA on the relationship between IFT tau deposition and cognition (which is the primary objective of this study), we tested multiple regression models. In these models, the midlife CA (or late-life CA) × IFT tau interaction term was included as an additional independent variable, along with the main effect of midlife CA (or late-life CA), IFT tau, and the covariates mentioned above. For the analyses on the primary objective of this study (main analyses), we applied the Bonferroni corrected *P* value (i.e., *P* value/number of tests [= 2 for midlife CA and late-life CA]) < 0.05 as a threshold for statistical significance. Furthermore, if the moderating effect of CA was significant in the overall participant group, we performed additional analyses to investigate whether the moderating effect of CA varies by cognitive status (i.e., CN and MCI). To this end, we tested a three-way interaction model that included cognitive status and related interaction terms (midlife CA [or late-life CA] × cognitive status, IFT tau × cognitive status, and midlife CA [or late-life CA] × IFT tau × cognitive status). If a significant three-way interaction was observed, we carried out subsequent subgroup analyses to examine the moderating effect of CA in each cognitive status group (i.e., CN and MCI). Finally, we tested a three-way interaction model that included the midlife CA × late-life CA × IFT tau interaction term, as well as midlife CA × IFT tau and late-life CA × IFT tau, as independent variables, to explore the synergistic effect of CA across life stages. *P* value < 0.05 was applied as a threshold for statistical significance if not otherwise specified. All statistical analyses were performed using SPSS 23.0 (IBM Corporation).

TABLE 1 Participant characteristics.

Characteristic	Overall (*n* = 89)	CN (*n* = 61)	MCI (*n* = 28)	*P**
Age, mean (SD), y	70.1 (7.3)	69.2 (6.9)	72.0 (7.9)	0.086
Sex, no. (%)				0.097
Male	30 (34)	24 (39)	6 (21)	
Female	59 (66)	37 (61)	22 (79)	
APOE ε4 carriers (%)	22 (25)	11 (18)	11 (39)	0.031
Education level, mean (SD), y	11.1 (4.3)	11.5 (4.0)	10.2 (4.8)	0.19
Premorbid intelligence, mean (SD), score	114.9 (9.1)	116.2 (8.6)	112.0 (9.8)	0.046
CA score, mean (SD), score				
Midlife CA	2.2 (0.8)	2.3 (0.8)	2.1 (0.9)	0.37
Late-life CA	2.4 (0.7)	2.5 (0.6)	2.1 (0.7)	0.011
AD pathology, mean (SD), SUVR				
Global Aβ	1.3 (0.4)	1.3 (0.4)	1.4 (0.5)	0.67
IFT tau	1.5 (0.4)	1.4 (0.3)	1.7 (0.6)	0.031
Cognitive score, mean (SD), score				
MMSE	26.4 (3.2)	27.6 (2.0)	23.6 (2.1)	< 0.001
MMSE change over 2 years	−0.9 (2.8)	−0.3 (2.1)	−2.1 (3.7)	0.012

Note: *Comparison between CN and MCI groups by *t* tests or chi-square tests.
Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; *APOE*, apolipoprotein E; CA, cognitive activity; CN, cognitively normal; IFT, inferior temporal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SD, standard deviation; SUVR, standardized uptake value ratio.

2.8 | Standard protocol approvals, registrations, and patient consents

The research protocol was approved by the institutional review boards of Seoul National University Hospital (SNUH; C-1401–027-547) and Seoul National University-Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center (26-2015-60) and was conducted in accordance with the current version of the Declaration of Helsinki. Written informed consent was obtained from all participants.

3 | RESULTS

Baseline characteristics of the participants are presented in Table 1, and a brief scheme of the analyses is provided in Figure S1 in supporting information. Out of the total 89 non-demented participants, 67 received a scheduled 2-year (mean [standard deviation (SD)], 2.36 [0.46]) follow-up cognitive assessment. Among them, four participants progressed to AD dementia. There was no significant difference in the demographic and clinical characteristics between the participants who were followed up and those who were not (Table S1 in supporting information).

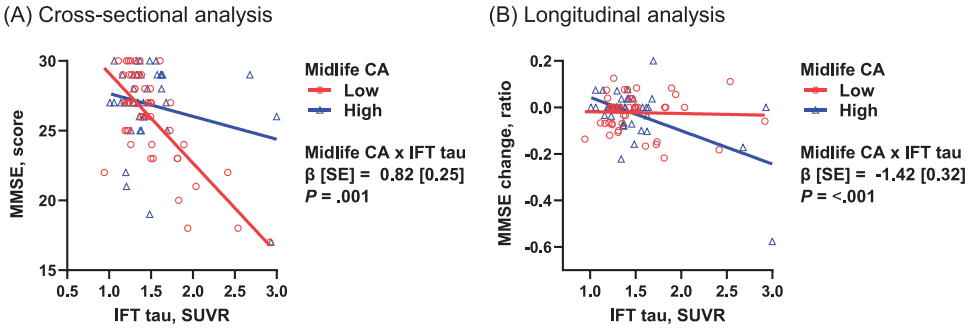

FIGURE 1 Interactive associations of midlife CA and tau on MMSE score and MMSE change. CA was stratified into high (≥ 2.22) and low (< 2.22) levels based on the median value. For cross-sectional analyses (A), the baseline MMSE score was used as a dependent variable, and for longitudinal analyses (B), the MMSE change over 2 years was used as a dependent variable. Adjusted for age, sex, education, *APOE ε4* carrier status, cognitive status, and Aβ positivity. Aβ, amyloid beta; *APOE*, apolipoprotein E; CA, cognitive activity; IFT, inferior temporal; MMSE, Mini-Mental State Examination; SE, standard error; SUVR, standardized uptake value ratio.

3.1 | Moderation of CA on the association between tau and MMSE

Higher IFT tau showed a significant direct cross-sectional association with lower MMSE scores (for Model 1, β [standard error (SE)] = −0.32 [0.09], $P < 0.001$; for Model 2, β [SE] = −0.30 [0.09], $P = 0.002$), while neither midlife nor late-life CA directly related to MMSE scores (Table 2). The main analyses examining the moderating effect of CA on the relationship between IFT tau and MMSE scores revealed significant midlife CA × IFT tau interaction effects on MMSE scores irrespective of the models. However, there was no significant interaction between late-life CA and IFT tau in relation to MMSE scores (Table 2). For visualization purposes, multiple regression analyses using a dichotomized variable of midlife CA by the median were also conducted. As illustrated in Figure 1A, the negative association between IFT tau and MMSE scores was weaker in the group with higher midlife CA compared to the group with lower midlife CA. The three-way interaction effect of midlife CA, IFT tau, and cognitive status (CN vs. MCI) was not significant (for Model 1, β [SE] = −0.23 [0.13], $P = 0.10$; for Model 2, β [SE] = −0.17 [0.14], $P = 0.22$). The three-way interaction effect of midlife CA, late-life CA, and IFT tau on MMSE scores was also not significant (Table S2 in supporting information).

3.2 | Moderation of CA on the association between tau and 2-year change in MMSE

IFT tau deposition was significantly associated with a decrease in MMSE scores over the 2-year follow-up period (for Model 1, β [SE] = −0.33 [0.14], $P = 0.019$; for Model 2, β [SE] = −0.33 [0.14], $P = 0.020$). However, neither midlife nor late-life CA showed any significant relationship with the 2-year change in MMSE score (Table 2). Regarding the moderating of CA, a significant interaction between midlife CA and IFT tau was observed in the 2-year change of MMSE scores, irrespective of the models used (Table 2). In contrast to midlife CA, however, late-life CA did not exhibit an interaction with IFT tau regarding the longitudinal change in MMSE. As illustrated in Figure 1B, MMSE scores declined more rapidly over 2 years in the group with higher midlife CA compared to the group with lower midlife CA. The three-way interaction effect of midlife CA, IFT tau, and cognitive status (CN vs. MCI) was significant (Table 3). This suggests that the interaction effect of midlife CA and IFT tau on longitudinal MMSE change could be moderated by cognitive status. Because the three-way interaction effect was significant, we conducted additional analyses to investigate the moderating effect of midlife CA for the relationship between IFT tau and the longitudinal change of MMSE scores within each cognitive status subgroup: Midlife CA exhibited a significant moderating effect in the MCI subgroup (Table 4 and Figure 2A), but not in the CN subgroup (Table 4 and Figure 2B). The three-way interaction effect of midlife CA, late-life CA, and IFT tau on the change in MMSE scores was not significant (Table S2).

4 | DISCUSSION

Our study, which uses both cross-sectional and longitudinal approaches, has revealed that midlife CA, not late-life CA, moderates the association of in vivo tau pathology with current cognition and cognitive decline over a 2-year period in non-demented older participants. Increased participation in CA during midlife is associated with a better cognitive score in a given amount of tau pathology and a more rapid cognitive decline related to tau pathology. Subgroup analyses further demonstrated that greater midlife CA is related to faster tau-related cognitive decline exclusively within MCI, but not in CN.

Our finding regarding the moderating effect of CA on the relationship between tau and current cognition could be explained by CR theory.[11,12] CR is a widely used theoretical concept that explains why some individuals exhibit better cognition than others despite having a similar amount of AD or other brain pathology. Individuals with higher CR can better withstand the negative influence of brain pathology on cognitive impairment and maintain higher cognitive function than those with lower CR. Our present cross-sectional analysis suggests that CA during midlife may play a protective role against tau-induced

TABLE 2 Effect of brain tau and CA on baseline MMSE scores and longitudinal change of MMSE scores.

	Main effects				With interaction term			
Models	**B (SE)**	***β***	***P***	***Pc****	**B (SE)**	***β***	***P***	***Pc****
Dependent variable: MMSE ($n = 89$)								
Model 1: Midlife CA								
Age	−0.05 (0.28)	−0.02	0.85	> 0.99	0.09 (0.27)	0.03	0.73	> 0.99
Sex	−0.09 (0.31)	−0.03	0.77	> 0.99	−0.13 (0.30)	−0.04	0.67	> 0.99
Education	0.42 (0.38)	0.13	0.28	0.56	0.34 (0.36)	0.11	0.35	0.71
*APOE ε*4	−0.26 (0.31)	−0.08	0.39	0.78	−0.24 (0.29)	−0.07	0.42	0.84
Cognitive status	−1.42 (0.28)	−0.45	< 0.001	< 0.001	−1.41 (0.26)	−0.44	< 0.001	< 0.001
A*β* positivity	−0.05 (0.31)	−0.01	0.89	> 0.99	−0.14 (0.30)	−0.05	0.63	> 0.99
IFT tau	−1.02 (0.29)	−0.32	0.002	0.003	−0.92 (0.27)	−0.29	0.001	0.004
Midlife CA	0.25 (0.34)	0.08	0.47	0.93	0.33 (0.32)	0.10	0.31	0.62
Midlife CA × IFT tau					0.79 (0.25)	0.24	0.003	0.005
Model 1: Late-life CA								
Age	−0.06 (0.26)	−0.02	0.81	> 0.99	0.00 (0.26)	0.00	> 0.99	> 0.99
Sex	−0.09 (0.30)	−0.03	0.75	> 0.99	−0.15 (0.29)	−0.05	0.61	> 0.99
Education	0.20 (0.34)	0.06	0.55	> 0.99	0.14 (0.33)	0.04	0.68	> 0.99
*APOE ε*4	−0.21 (0.30)	−0.07	0.49	0.98	−0.14 (0.29)	−0.05	0.62	> 0.99
Cognitive status	−1.31 (0.27)	−0.41	< 0.001	< 0.001	−1.27 (0.27)	−0.40	< 0.001	< 0.001
A*β* positivity	−0.17 (0.31)	−0.05	0.60	> 0.99	−0.30 (0.31)	−0.10	0.33	0.66
IFT tau	−0.96 (0.30)	−0.30	0.002	0.004	−0.57 (0.34)	−0.18	0.099	0.20
Late-life CA	0.69 (0.31)	0.22	0.031	0.061	0.82 (0.31)	0.26	0.010	0.020
Late-life CA × IFT tau					0.86 (0.38)	0.21	0.028	0.056
Model 2: Midlife CA								
Age	0.12 (0.28)	0.04	0.67	> 0.99	0.26 (0.27)	0.08	0.33	0.65
Sex	−0.07 (0.31)	−0.02	0.83	> 0.99	−0.10 (0.29)	−0.03	0.73	> 0.99
Education	−0.30 (0.48)	−0.09	0.54	> 0.99	−0.37 (0.45)	−0.12	0.41	0.83
*APOE ε*4	−0.33 (0.30)	−0.10	0.27	0.54	−0.30 (0.28)	−0.10	0.29	0.57
Cognitive status	−1.35 (0.27)	−0.42	< 0.001	< 0.001	−1.33 (0.26)	−0.42	< 0.001	< 0.001
A*β* positivity	−0.17 (0.31)	−0.05	0.59	> 0.99	−0.27 (0.30)	−0.08	0.37	0.74
Premorbid intelligence	1.00 (0.42)	0.31	0.020	0.040	0.99 (0.40)	0.31	0.015	0.029
IFT tau	−0.93 (0.30)	−0.29	0.003	0.005	−0.80 (0.29)	−0.25	0.007	0.013
Midlife CA	0.13 (0.33)	0.04	0.69	> 0.99	0.21 (0.31)	0.07	0.50	> 0.99
Midlife CA × IFT tau					0.79 (0.25)	0.24	0.002	0.004
Model 2: Late-life CA								
Age	0.10 (0.27)	0.03	0.72	> 0.99	0.15 (0.26)	0.05	0.57	> 0.99
Sex	−0.06 (0.29)	−0.02	0.85	> 0.99	−0.11 (0.29)	−0.03	0.71	> 0.99
Education	−0.44 (0.45)	−0.14	0.33	0.66	−0.46 (0.44)	−0.15	0.29	0.59
*APOE ε*4	−0.28 (0.29)	−0.09	0.35	0.70	−0.21 (0.29)	−0.07	0.46	0.93
Cognitive status	−1.26 (0.27)	−0.40	< 0.001	< 0.001	−1.23 (0.26)	−0.39	< 0.001	< 0.001
A*β* positivity	−0.26 (0.31)	−0.08	0.40	0.80	−0.39 (0.31)	−0.12	0.21	0.42
Premorbid intelligence	0.89 (0.41)	0.28	0.035	0.071	0.83 (0.41)	0.26	0.043	0.086
IFT tau	−0.89 (0.29)	−0.28	0.003	0.006	−0.52 (0.33)	−0.16	0.12	0.24
Late-life CA	0.57 (0.31)	0.18	0.070	0.14	0.70 (0.31)	0.22	0.026	0.052
Late-life CA × IFT tau					0.81 (0.38)	0.20	0.034	0.068

(Continues)

TABLE 2 (Continued)

	Main effects				With interaction term			
Models	**B (SE)**	***β***	***P***	***Pc****	**B (SE)**	***β***	***P***	***Pc****
Dependent variable: MMSE change ($n = 67$)								
Model 1: Midlife CA								
Age	−0.01 (0.01)	−0.08	0.55	> 0.99	−0.02 (0.01)	−0.16	0.15	0.30
Sex	0.00 (0.02)	0.02	0.93	> 0.99	0.01 (0.02)	0.06	0.69	> 0.99
Education	−0.00 (0.02)	−0.01	> 0.99	> 0.99	0.00 (0.02)	0.03	0.85	> 0.99
*APOE ε*4	0.01 (0.02)	0.12	0.46	0.91	0.02 (0.02)	0.13	0.35	0.69
Cognitive status	−0.03 (0.01)	−0.27	0.049	0.098	−0.03 (0.01)	−0.27	0.025	0.051
Aβ positivity	−0.01 (0.02)	−0.04	0.77	> 0.99	0.00 (0.01)	0.03	0.82	> 0.99
IFT tau	−0.04 (0.02)	−0.33	0.022	0.043	−0.05 (0.01)	−0.50	< 0.001	< 0.001
Midlife CA	−0.00 (0.02)	−0.02	0.92	> 0.99	−0.01 (0.02)	−0.06	0.69	> 0.99
Midlife CA × IFT tau					−0.05 (0.01)	−0.49	< 0.001	< 0.001
Model 1: Late-life CA								
Age	−0.01 (0.01)	−0.07	0.58	> 0.99	−0.01 (0.01)	−0.08	0.52	> 0.99
Sex	0.00 (0.02)	0.03	0.85	> 0.99	0.01 (0.02)	0.05	0.77	> 0.99
Education	−0.01 (0.02)	−0.04	0.81	> 0.99	−0.00 (0.02)	−0.03	0.88	> 0.99
*APOE ε*4	0.01 (0.02)	0.12	0.46	0.91	0.01 (0.02)	0.10	0.52	> 0.99
Cognitive status	−0.03 (0.02)	−0.26	0.060	0.12	−0.03 (0.01)	−0.25	0.062	0.12
Aβ positivity	−0.01 (0.02)	−0.06	0.70	> 0.99	−0.00 (0.02)	−0.04	0.81	> 0.99
IFT tau	−0.04 (0.02)	−0.32	0.025	0.050	−0.04 (0.02)	−0.41	0.012	0.024
Late-life CA	0.01 (0.02)	0.05	0.76	> 0.99	0.00 (0.02)	0.03	0.86	> 0.99
Late-life CA × IFT tau					−0.02 (0.02)	−0.17	0.24	0.49
Model 2: Midlife CA								
Age	−0.01 (0.02)	−0.09	0.51	> 0.99	−0.02 (0.01)	−0.17	0.14	0.29
Sex	0.00 (0.02)	0.01	0.93	> 0.99	0.01 (0.02)	0.06	0.70	> 0.99
Education	0.01 (0.03)	0.04	0.87	> 0.99	0.01 (0.02)	0.08	0.73	> 0.99
*APOE ε*4	0.01 (0.02)	0.12	0.46	0.92	0.02 (0.02)	0.13	0.35	0.70
Cognitive status	−0.03 (0.02)	−0.27	0.049	0.099	−0.03 (0.01)	−0.27	0.026	0.051
Aβ positivity	−0.00 (0.02)	−0.03	0.83	> 0.99	0.00 (0.02)	0.04	0.77	> 0.99
Premorbid intelligence	−0.01 (0.02)	−0.06	0.77	> 0.99	−0.01 (0.02)	−0.06	0.74	> 0.99
IFT tau	−0.04 (0.02)	−0.33	0.023	0.045	−0.05 (0.01)	−0.50	< 0.001	< 0.001
Midlife CA	−0.00 (0.02)	−0.01	0.97	> 0.99	−0.01 (0.02)	−0.05	0.75	> 0.99
Midlife CA × IFT tau					−0.05 (0.01)	−0.49	< 0.001	< 0.001
Model 2: Late-life CA								
Age	−0.01 (0.02)	−0.09	0.52	> 0.99	−0.01 (0.02)	−0.10	0.45	0.89
Sex	0.00 (0.02)	0.03	0.87	> 0.99	0.00 (0.02)	0.04	0.80	> 0.99
Education	0.00 (0.03)	0.02	0.93	> 0.99	0.01 (0.03)	0.04	0.86	> 0.99
*APOE ε*4	0.01 (0.02)	0.12	0.45	0.90	0.01 (0.02)	0.10	0.51	> 0.99
Cognitive status	−0.03 (0.02)	−0.26	0.060	0.12	−0.03 (0.02)	−0.26	0.062	0.12
Aβ positivity	−0.01 (0.02)	−0.05	0.76	> 0.99	−0.00 (0.02)	−0.03	0.88	> 0.99
Premorbid intelligence	−0.01 (0.02)	−0.08	0.70	> 0.99	−0.01 (0.02)	−0.10	0.66	> 0.99
IFT tau	−0.04 (0.02)	−0.32	0.026	0.051	−0.04 (0.02)	−0.40	0.012	0.025
Late-life CA	0.01 (0.02)	0.06	0.70	> 0.99	0.01 (0.02)	0.06	0.78	> 0.99
Late-life CA × IFT tau					−0.02 (0.02)	−0.16	0.24	0.48

Note: **P* value corrected by the Bonferroni method (= *P* value × number of comparisons [2]).

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; B, unstandardized coefficient; CA, cognitive activity; IFT, inferior temporal; MMSE, Mini-Mental State Examination; SE, standard error; *β*, standardized coefficient.

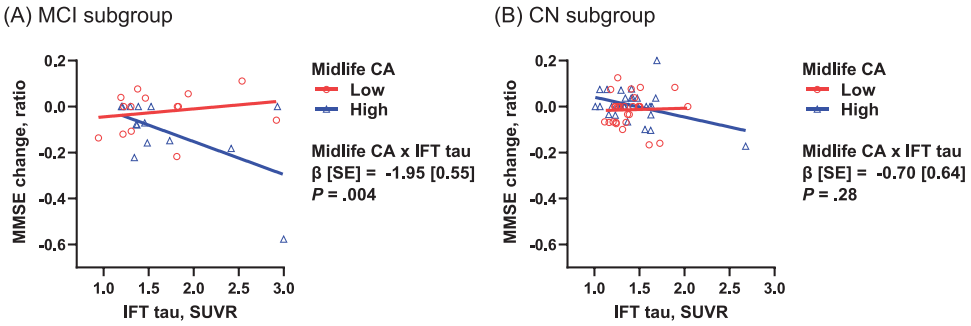

FIGURE 2 Interactive associations of midlife CA and tau on MMSE change (CN vs. MCI). CA was stratified into high (≥ 2.22) and low (< 2.22) levels based on the median value. MMSE change over 2 years was used as a dependent variable. Adjusted for age, sex, education, *APOE* ε4 carrier status, and Aβ positivity. Aβ, amyloid beta; *APOE*, apolipoprotein E; CA, cognitive activity; CN, cognitively normal; IFT, inferior temporal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SE, standard error; SUVR, standardized uptake value ratio.

cognitive impairment by enhancing CR or cognitive resilience to tau.[14] In line with our findings, a cross-sectional study reported an interactive association between premorbid IQ as a proxy measure of CR and IFT tau on cognition.[34] Other studies have also indicated that highly educated AD patients (i.e., individuals with higher CR) may tolerate a greater burden of brain tau[35] or mitigate the impact of tau on neuronal function.[36] The exact biological mechanisms by which midlife CA enhances CR and mitigates tau-related cognitive impairment are not yet fully understood. Neuroplasticity, synaptogenesis, or increased functional connectivity may be involved.[37]

In contrast to the results from cross-sectional analyses, longitudinal analyses demonstrated that higher midlife CA was associated with faster tau-related cognitive decline. While existing evidence generally supports the idea that higher levels of CR, as measured by proxy variables reflecting lifetime experiences, including midlife CA, are associated with better cognitive performance,[11] the impact of CR on longitudinal cognitive trajectories remains unclear and is a topic of controversy.[11,15,38] As suggested by Stern's model of CR,[12] higher CR is associated with the delayed onset of cognitive impairment but a faster cognitive decline after cognitive impairment has started. Our findings from cognitive subgroup analyses for longitudinal change of MMSE scores also support such a paradoxical relationship between CR and cognitive decline, depending on clinical status. Higher midlife CA had an association with more rapid tau-related cognitive decline in MCI but not in CN individuals. Similarly, a study reported that while higher CR scores were associated with better cognitive performance, they did not modify the rate of change in cognition among those who remained CN, and higher CR scores were associated with faster cognitive decline after the onset of MCI symptoms.[38] Other studies also reported that higher CR scores were associated with faster cognitive decline, especially in the AD dementia individuals[39] or the individuals with greater atrophy.[40]

The moderating effect of late-life CA did not reach statistical significance in both cross-sectional and longitudinal analyses. The differing results between midlife and late-life CA can possibly be explained by age-related brain changes. Changes in long-term potentiation, gene expression, and neuronal ensembles may result in decreased neural plasticity in old age, and potentially correlate with the diminished protective effects of CA in later life.[41] Furthermore, late life is more closely associated with ongoing AD pathologies or neurodegenerative changes in the brain compared to midlife.[42] Such pathological changes could also negatively affect neuronal plasticity.[43] A recent randomized clinical trial suggested that cognitive and social enrichment cannot improve cognitive function in non-demented older adults with chronic stroke.[44] While several studies have reported associations between late-life CA and better cognition[2] or slower cognitive decline,[5] these studies did not account for in vivo AD pathology. It is also possible that older individuals with a lower burden of AD pathology were more likely to participate in CA, leading to better cognition or slower cognitive decline in late life. Additionally, we analyzed a three-way interaction between midlife CA, late-life CA, and IFT tau on MMSE scores or their changes but could not find any positive evidence supporting the synergistic effect of CA across life stages for greater cognitive resilience against tau pathology.

The present study is novel in that it is the first to investigate the moderating effect of both midlife and late-life CA on the relationship between brain tau and cognitive function using both cross-sectional and longitudinal approaches. Additionally, we rigorously controlled for well-known CR proxies, such as education and premorbid IQ, which could influence the association between AD pathology and cognition[16,34] or cognitive decline.[11,38] This allowed us to specifically evaluate the moderating effect of CA. Nevertheless, our study also has some limitations. First, the follow-up duration was relatively short, and longitudinal analyses were conducted on only a subset of participants who completed the 2-year follow-up. Given that there was no significant difference in the characteristics between the participants who were followed up ($n = 67$) and those who were not ($n = 22$; Table S1), the potential biases introduced by attrition are unlikely to affect the generalizability of the findings. Nevertheless, future studies with a larger sample size and longer follow-up periods are needed to confirm these findings. Second, our retrospective measurement of CA may be susceptible to recall bias. To minimize recall bias due to memory impairment, we excluded dementia patients and individuals with major psychiatric illnesses and significant neurological conditions that could affect mental function. In addition, we assessed midlife and late-life CA with a widely used instrument that has demonstrated

TABLE 3 Three-way interaction effect of midlife CA, tau, and cognitive status on longitudinal change of MMSE scores.

Models	B	SE	β	P
Dependent variable: MMSE change ($n = 67$)				
Model 1				
Age	−0.03	0.01	−0.23	0.028
Sex	0.00	0.01	0.01	0.94
Education	0.01	0.02	0.07	0.64
APOE ε4	0.03	0.01	0.24	0.062
Cognitive status	−0.04	0.01	−0.32	0.003
Aβ positivity	−0.00	0.01	−0.01	0.95
IFT tau	−0.05	0.02	−0.45	0.003
Midlife CA	0.00	0.02	0.01	0.96
Midlife CA × IFT tau	−0.02	0.02	−0.15	0.45
Midlife CA × cognitive status	−0.03	0.01	−0.28	0.007
IFT tau × cognitive status	−0.03	0.01	−0.30	0.024
Midlife CA × IFT tau × cognitive status	−0.04	0.02	−0.47	0.020
Model 2				
Age	−0.03	0.01	−0.24	0.028
Sex	0.00	0.01	0.01	0.96
Education	0.01	0.02	0.12	0.53
APOE ε4	0.03	0.01	0.24	0.064
Cognitive status	−0.04	0.01	−0.32	0.003
Aβ positivity	0.00	0.01	0.00	0.98
Premorbid intelligence	−0.01	0.02	−0.07	0.66
IFT tau	−0.05	0.02	−0.45	0.003
Midlife CA	0.00	0.02	0.02	0.87
Midlife CA × IFT tau	−0.02	0.02	−0.14	0.48
Midlife CA × cognitive status	−0.03	0.01	−0.28	0.008
IFT tau × cognitive status	−0.03	0.01	−0.30	0.027
Midlife CA × IFT tau × cognitive status	−0.04	0.02	−0.48	0.020

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; B, unstandardized coefficient; CA, cognitive activity; IFT, inferior temporal; MMSE, Mini-Mental State Examination; SE, standard error; β, standardized coefficient.

adequate internal consistency and temporal stability for individuals without dementia.[3,5,45] Nevertheless, we could not completely rule out the possibility that recent memory problems in participants with MCI might have affected assessment for CA, particularly late-life CA. Third, we used the MMSE as a global cognitive measure. Although the MMSE is well validated and widely used in both clinical and research settings, it is known to be less sensitive in assessing visuospatial function and detecting subtle cognitive impairment.[46] Therefore, using a composite measure derived from multiple neuropsychological tests may reflect overall cognitive function or its change more accurately and reduce the chance of random errors more than using the MMSE alone. Fur-

TABLE 4 Results from subgroup analyses: interaction effect of midlife CA and tau on longitudinal change of MMSE scores in each cognitive subgroup.

Models	B	SE	β	P
Dependent variable: MMSE change				
For CN ($n = 45$)				
Model 1				
Age	−0.03	0.01	−0.33	0.059
Sex	−0.00	0.02	−0.03	0.89
Education	0.01	0.02	0.17	0.49
APOE ε4	0.01	0.02	0.14	0.42
Aβ positivity	0.00	0.01	0.02	0.91
IFT tau	−0.03	0.02	−0.23	0.19
Midlife CA	0.01	0.03	0.04	0.40
Midlife CA × IFT tau	0.01	0.03	0.05	0.81
Model 2				
Age	−0.04	0.02	−0.44	0.028
Sex	−0.01	0.02	−0.11	0.62
Education	0.04	0.03	0.53	0.18
APOE ε4	0.01	0.02	0.13	0.46
Aβ positivity	0.01	0.01	0.07	0.71
Premorbid intelligence	−0.03	0.03	−0.37	0.25
IFT tau	−0.03	0.02	−0.25	0.16
Midlife CA	0.01	0.03	0.08	0.38
Midlife CA × IFT tau	0.01	0.03	0.08	0.66
For MCI ($n = 22$)				
Model 1				
Age	−0.01	0.03	−0.08	0.69
Sex	−0.02	0.05	−0.11	0.65
Education	0.03	0.05	0.25	0.51
APOE ε4	0.06	0.04	0.50	0.13
Aβ positivity	−0.01	0.03	−0.07	0.76
IFT tau	−0.10	0.02	−0.94	0.001
Midlife CA	−0.07	0.05	−0.45	0.15
Midlife CA × IFT tau	−0.06	0.02	−0.73	0.003
Model 2				
Age	−0.01	0.03	−0.06	0.79
Sex	−0.03	0.05	−0.14	0.60
Education	0.03	0.05	0.24	0.53
APOE ε4	0.07	0.04	0.54	0.14
Aβ positivity	−0.01	0.03	−0.09	0.71
Premorbid intelligence	0.01	0.04	0.10	0.72
IFT tau	−0.10	0.02	−0.95	0.001
Midlife CA	−0.08	0.05	−0.50	0.16
Midlife CA × IFT tau	−0.06	0.02	−0.73	0.004

Abbreviations: Aβ, amyloid beta; *APOE*, apolipoprotein E; B, unstandardized coefficient; CA, cognitive activity; CN, cognitively normal; IFT, inferior temporal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SE, standard error; β, standardized coefficient.

ther studies are needed to replicate our findings using other composite cognitive measures.

Our findings suggest that increased midlife CA moderates the effect of tau pathology on cognitive impairment, but late-life CA does not: greater midlife CA is generally associated with better cognitive performance in a given amount of tau pathology. However, paradoxically, higher levels of midlife CA appear to be linked to a more rapid tau-related cognitive decline in already cognitively impaired individuals.

AUTHOR CONTRIBUTIONS

Kang Ko and Dong Young Lee: conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript or figures; Dahyun Yi, Min Soo Byun, Joon Hyung Jung, Nayeong Kong, Gijung Jung, Hyejin Ahn, Yoon Young Chang, Musung Keum, Jun-Young Lee, Yun-Sang Lee, Yu Kyeong Kim: acquisition and analysis of data, and drafting a significant portion of the manuscript or figures. Kang Ko, Dahyun Yi, Min Soo Byun, and Dong Young Lee were major contributors in writing the manuscript and critically revising the manuscript for intellectual content. Dong Young Lee served as principal investigator and supervised the study. All authors read and approved the final manuscript.

ACKNOWLEDGMENTS

The authors thank all the members of the KBASE Research Group for their contribution. A complete list of KBASE research group members can be found at http://kbase.kr/. They sincerely appreciate the time and effort of all the participants in the research. This study was supported by the following agencies: NRF-2014M3C7A1046042 & RS-2022-00165636 (Ministry of Science, ICT, and Future Planning, Republic of Korea), HI18C0630, HI19C0149 & HU23C0140 (KHIDI), and NIA (U01AG072177). The funding source had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript, or decision to submit it for publication.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

CONSENT STATEMENT

The research protocol was approved by the institutional review boards of Seoul National University Hospital (SNUH) and Seoul National University-Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center and was conducted in accordance with the current version of the Declaration of Helsinki. Written informed consent was obtained from all participants or their legal representatives.

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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: Ko K, Yi D, Byun MS, et al. Moderation of midlife cognitive activity on tau-related cognitive impairment. *Alzheimer's Dement*. 2025;21:e14606. https://doi.org/10.1002/alz.14606