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ORIGINAL ARTICLE

Interaction effect of Alzheimer's disease pathology and education, occupation, and socioeconomic status as a proxy for cognitive reserve on cognitive performance: *in vivo* positron emission tomography study

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Key words: *Alzheimer's disease, amyloid, cognitive reserve, educational status, positron emission tomography, tau proteins.*

Abstract

Aim: Educational attainment, occupation, and socioeconomic status have been regarded as major factors influencing cognitive reserve (CR). This study aimed to investigate the interaction effect of amyloid-β/tau burden and education/occupation/socioeconomic status as a proxy for CR on cognitive performance.

Methods: We analyzed the datasets of the Alzheimer's Disease Neuroimaging Initiative. We included clinically normal subjects and patients with mild cognitive impairment or Alzheimer's disease who had undergone a florbetapir scan within 1 year of a flortaucipir (AV-1451) scan (n = 127). Partial correlation analysis between the standardized uptake value ratio of florbetapir/AV-1451 and the proxy for CR was performed with the 13-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score as a covariate. Stepwise multiple linear regression analysis was performed to determine the predictors of ADAS-cog performance based on the interaction between the imaging biomarkers and the proxy for CR.

Results: We found a significant positive partial correlation between educational level and tau pathology in Braak stage 1/2 areas, and we observed significantly higher tau accumulation among participants with higher education when ADAS-cog score was used as a covariate. The interaction between tau and education was a good predictor of cognitive function, with higher tau accumulation showing a greater association with higher ADAS-cog score among participants with less education than among those with more education.

Conclusion: Our findings indicate the protective effect of education against cognitive dysfunction in early-stage Alzheimer's disease pathology and suggest that education may exert a beneficial effect by reducing the adverse cognitive consequences of tau aggregation.

INTRODUCTION

Thanks to advances in positron emission tomography (PET) using radiotracers that bind to amyloid-β (Aβ), it has become clear that Alzheimer's disease (AD) has a long preclinical course whereby clinically normal (CN) subjects show biomarker abnormalities up to 15 years before the onset of dementia.[1-3] Consequently, medical researchers have turned their focus to the identification and treatment of preclinical AD,[4] particularly the factors that influence the relationship between cognition and pathological burden. Cognitive reserve (CR) is one such factor.

Previous studies have attempted to clarify how some individuals, despite the burden of AD pathology, maintain normal cognitive performance,[5,6] which

decreases the risk or delays the appearance of symptomatic AD.[7,8] With regard to CR, it has been postulated that individual differences in the cognitive processes or neural networks underlying task performance allow some people to cope better than others with brain damage.[8] It is believed that greater CR compensates for the damage due to neurodegeneration: individuals with high CR cope better with the onset of dementia and can maintain a normal cognitive level for a longer time than individuals with low CR.[9-11] Patients with AD who have high CR should have more advanced AD pathology than those with low CR but the same level of cognitive dysfunction.[6]

Previous PET studies using radiotracers that bind to Aβ demonstrated that amyloid accumulation has a weak but continual effect on brain function.[12-14] Recently, the availability of radiotracers that bind to tau (e.g.^{18}F-flortaucipir (AV-1451)[15]) has allowed *in vivo* imaging of tau pathology. Rentz *et al*. examined whether intelligence quotient as a proxy for CR modified the effect of tau and/or amyloid on cognitive function in clinical and preclinical AD.[13] They showed that intelligence quotient may protect against AD processes and can enable some patients to maintain stable cognitive function despite increased tau and Aβ burden.[13]

Educational attainment, occupation, and socioeconomic status (SES) have been regarded as major factors reflecting or influencing CR.[7,12,14,16-18] Education mainly reflects the intellectual and environmental factors during the early-life stage, while occupation and SES are related to those at the mid- to late-life stage. However, no study has assessed the interaction effect of AD pathology and education, occupation, and SES as a proxy for CR on cognitive performance. In this study, we investigated the interaction between Aβ/tau burden and education/occupation/SES in a sample of CN subjects and patients with mild cognitive impairment (MCI) or AD. Our aim was to examine whether intellectual and environmental factors affecting CR during the early-life stage and/or the middle- to late-life stage can protect against AD pathology.

METHODS

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). The ADNI was launched in 2003 as a public–private partnership; it is led by Michael W. Weiner, MD, the principal investigator. The primary goal of ADNI has been to test whether serial magnetic resonance imaging, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. For up-to-date information, see http://www.adni-info.org. Approval has been obtained from the appropriate institutional review boards. Written informed consent was obtained from all ADNI participants before the study.

Participants

This study consisted of patients diagnosed with MCI or AD and CN subjects. The inclusion criteria for CN were a Mini-Mental State Examination (MMSE) score of 24–30 and the absence of depression, MCI, and dementia. For patients with MCI, the criteria were an MMSE score of 24–30, objective memory loss measured by education-adjusted scores on the Wechsler Memory Scale Logical Memory II, a Clinical Dementia Rating of 0.5, the absence of significant levels of impairment in other cognitive domains, essentially preserved activities of daily living, and an absence of dementia. For participants with AD, the criteria were an MMSE score of 20–26 and probable AD according the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association criteria.[19]

We included ADNI-2 and ADNI-3 data, with no duplicate entries, from subjects aged 60–80 years (inclusive) who had undergone a florbetapir (AV-45) scan within 1 year of an AV-1451 scan (total, n = 189; CN, n = 134; MCI, n = 44; AD, n = 11). Information on education, occupation, and SES index classification was complete for all subjects. The subjects had also undergone neuropsychological assessment within 1 year of both AV-45 and AV-1451 PET imaging. We excluded subjects who were taking antidementia, antidepressant, and/or other behavioural medication (CN, n = 33; MCI, n = 20; AD, n = 9). Finally, we used the data from 127 subjects for the analysis.

The sample for analysis consisted of 101 CN individuals and 26 individuals diagnosed with either MCI (n = 24) or mild AD dementia (n = 2). Those with MCI and AD were placed in a single group (MCI/AD group). For all participants, general data (i.e. age, sex, years of education, primary occupation during most of adult life, MMSE score, and 13-item Alzheimer's Disease Assessment Scale-cognitive

subscale (ADAS-cog) score) were extracted from the ADNI databases.

Education and occupation were examined as proxy candidates for CR. Occupation was coded as 1–9 based on the Hollingshead Index of Social Status (HI)[20]; educational level was graded on a 1–7 scale. Occupation was coded based on a full-time job or, if it was the only source of income for the subject, a part-time job. Education was coded based on the highest year of schooling completed by the subject. Further, SES was calculated as another proxy for CR based on the education and occupation scores by using the following equation: HI = education level $\times$ 3 + occupation $\times$ 5.[20] HI was categorized into four groups: group 1, score <29; group 2, score 29–41; group 3, score 42–53; and group 4, score >53.

Analysis of Aβ and tau PET

The neuroimaging data were also obtained from the ADNI databases (https://ida.loni.usc.edu) for our study. Data for ^{18}F-AV-1451 imaging from ADNI-2 and ADNI-3 were analyzed in this study, and AV-45 scans were collected within 1 year of the AV-1451 scans. The acquisition protocol and image preprocessing of these data are publicly available on the ADNI website (http://adni.loni.usc.edu/). Details of ADNI methods for image acquisition and processing can be found at www.adni-info.org/methods.

The dataset indicates the mean AV-45 uptake in cortical grey matter-weighted florbetapir in the regions of interest (ROIs) for all participants. The ROIs included the bilateral frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal cortices, as defined by the ADNI group. ROI-based AV-45 standardized uptake value ratios (SUVRs) were calculated with reference to the AV-45 uptake mean of the whole cerebellum. The details of the data processing method are described in 'UC Berkeley- AV45 Analysis Methods' which is available online (https://ida.loni.usc.edu/).

For the dataset of AV-1451, tracer retention was quantified in ROIs that anatomically approximate the pathological stages of tangle deposition delineated by Braak and Braak.[21] Weighted mean SUVR was calculated from three composite ROIs that correspond to the anatomical definitions of Braak stages 1/2 (entorhinal cortex and hippocampus), 3/4 (limbic), and 5/6 (neocortical) with reference to the AV-1451 uptake mean of the inferior cerebellum. The details of the data processing method are described in 'UC Berkeley-Flortaucipir (AV-1451) Processing Methods' which is available online (https://ida.loni.usc.edu/).

Statistics

Differences in demographic characteristics between the CN and MCI /AD groups were examined with *t*-tests for continuous variables and χ^2 tests for dichotomous variables.

Partial correlation analysis between the mean SUVR of AV-45/AV-1451 from composite ROIs and the CR proxy (level of education, occupation, and SES (HI)) for all subjects was evaluated with age, sex, clinical status (CN and MCI /AD), and ADAS-cog score as covariates. Mean SUVR values of AV-45/AV-1451 from composite ROIs were compared between groups of lower and higher CR proxy (level of education, occupation, and SES (HI)) with ANCOVA using age, sex, clinical status, and ADAS-cog score as covariates.

In addition, a stepwise backward deletion multiple linear regression analysis was performed to determine the predictors of ADAS-cog performance; the analysis was based on the interaction between the PET biomarker (AV-45 and/or AV-1451 SUVR) and the CR proxy for which the analysis showed a relationship. The dependent variable was the ADAS-cog score, and the independent variables were age, sex, clinical status, PET biomarker, the proxy for CR, and the interaction between the PET biomarker and the proxy for CR.

Statistical analysis was performed with SPSS for Windows 23.0 (IBM Japan, Tokyo, Japan). Statistical tests were two-tailed, and significance was defined as $P < 0.05/n$ using Bonferroni's correction (where n refers to the number of multiple comparisons).

RESULTS

Demographic characteristics

The demographic characteristics of the CN and MCI/AD groups are displayed in Table 1. There were no differences between groups in terms of sex, age, level of education, occupation, and SES (HI). We found no significant difference in MMSE scores between the groups, but the MCI/AD group had significantly higher ADAS-cog scores. Cortical Aβ accumulation was similar between the groups, but the MCI/AD group had higher levels of tau in the measured brain areas.

Table 1 Descriptive characteristics of clinically normal (CN) subjects and patients with mild cognitive impairment (MCI) or Alzheimer's disease (AD)

Characteristic/test†	All	CN	MCI/AD	*t* or χ^2	*P*-value
n	127	101	26 (24 MCI, 2 AD)		
Men/women (*n*)	62/65	46/55	16/10	2.12	0.15
Age (years)	72.4 ± 4.6 (61–80)	72.1 ± 4.5 (61–80)	73.3 ± 5.1 (61–80)	1.13	0.26
Education (years)	16.9 ± 2.4 (12–20)	17.0 ± 2.2 (12–20)	16.3 ± 2.8 (12–20)	1.23	0.23
Education (HI score 1–7)	6.2 ± 1.0 (4–7)	6.3 ± 0.9 (4–7)	6.0 ± 1.1 (4–7)	1.34	0.18
Occupation (HI score 1–9)	7.5 ± 1.5 (2–9)	7.7 ± 1.3 (3–9)	7.0 ± 1.9 (2–9)	1.61	0.12
SES (HI)	56.4 ± 9.5 (22–66)	57.2 ± 8.5 (30–66)	53.2 ± 12.3 (22–66)	1.57	0.13
MMSE	29.1 ± 1.3 (23–30)	29.2 ± 1.0 (26–30)	28.6 ± 2.1 (23–30)	1.49	0.15
ADAS-cog	12.2 ± 4.9 (2.00–29.67)	11.3 ± 3.8 (2.00–20.33)	15.6 ± 6.9 (3.00–29.67)	3.01	0.005 *
Cortical AV-45 SUVR	1.11 ± 0.16 (0.90–1.71)	1.10 ± 0.15 (0.90–1.71)	1.14 ± 0.21 (0.92–1.66)	0.91	0.37
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	1.27 ± 0.21 (0.93–1.94)	1.24 ± 0.18 (0.93–1.89)	1.41 ± 0.28 (1.08–1.94)	2.97	0.006 *
Braak 3/4 AV-1451 SUVR (limbic)	1.39 ± 0.17 (1.07–2.03)	1.36 ± 0.15 (1.07–2.03)	1.50 ± 0.18 (1.29–1.97)	3.74	0.0003 *
Braak 5/6 AV-1451 SUVR (neocortical)	1.44 ± 0.16 (1.13–2.09)	1.42 ± 0.15 (1.13–2.09)	1.53 ± 0.15 (1.25–1.96)	3.23	0.002*

* $P < 0.05$. † Data are presented as mean ± SD (range) unless otherwise indicated. SES, socioeconomic status; HI, Hollingshead Index of Social Status; MMSE, Mini-Mental State Examination; ADAS-cog, 13-item Alzheimer's Disease Assessment Scale-cognitive subscale; SUVR, standardized uptake value ratio; AV-45, florbetapir; AV-1451, flotaucipir.

Partial correlation between education/occupation/SES and AV-45/AV-1451 SUVR

We found a significant partial correlation between level of education and tau accumulation in Braak stage 1/2 areas, including the entorhinal cortex and hippocampus, with age, sex, clinical status, and ADAS-cog score as covariates (Table 2; Fig. 1). We did not observe a relationship between level of education and cortical amyloid or tau accumulation in Braak stage 3/4 and 5/6 areas. We did not find a significant partial correlation between occupation/SES and accumulation of amyloid/tau (Table 2).

Comparison of SUVRs between the groups with lower and higher levels of education/occupation/SES

We found a significantly larger tau accumulation in Braak stage 1/2 areas in the group with a higher level of education, with age, sex, clinical status, and ADAS-cog score as covariates. We did not observe a difference in cortical amyloid or tau accumulation in Braak stage 3/4 and 5/6 areas (Table 3). We found no significant difference in covariates between the groups according to level of education (lower vs higher): age: 71.8 ± 4.6 and 72.7 ± 4.6 years ($t = 1.09$, $P = 0.28$); sex (men/women): 26/32 and 37/32 ($\chi^2 = 0.98$, $P = 0.32$); clinical status (MCI + AD/CN): 13/45 and 13/56 ($\chi^2 = 0.25$, $P = 0.62$); ADAS-cog score: 13.0 ± 5.5 and 11.4 ± 4.3 ($t = 1.81$, $P = 0.07$).

We did not find a significant difference in amyloid or tau accumulation between groups according to occupation or SES (lower vs higher) (Table 3).

Table 2 Partial correlation between education/occupation and AV-45/AV-1451 standardized uptake value ratios (SUVRs)†

Variable	*r*	*P*-value
Education level (HI score)		
Cortical AV-45 SUVR	0.08	0.37
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	0.26	0.003*
Braak 3/4 AV-1451 SUVR (limbic)	0.15	0.10
Braak 5/6 AV-1451 SUVR (neocortical)	0.06	0.51
Occupation (HI score)		
Cortical AV-45 SUVR	0.09	0.30
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	0.10	0.27
Braak 3/4 AV-1451 SUVR (limbic)	−0.003	0.97
Braak 5/6 AV-1451 SUVR (neocortical)	−0.07	0.47
SES (HI)		
Cortical AV-45 SUVR	0.10	0.27
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	0.16	0.07
Braak 3/4 AV-1451 SUVR (limbic)	0.05	0.62
Braak 5/6 AV-1451 SUVR (neocortical)	−0.03	0.73

* $P < 0.0125$ (0.05/4). † Partial correlation with age, sex, clinical status, and Alzheimer's Disease Assessment Scale-cognitive subscale score as covariates. SES, socioeconomic status; HI, Hollingshead Index of Social Status; AV-45, florbetapir; AV-1451, flotaucipir.

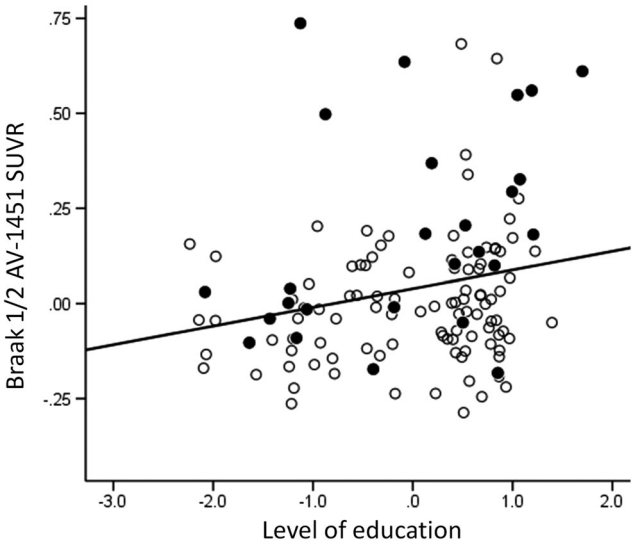

Figure 1 Scatter plot of individual AV-1451 standardized uptake value ratios (SUVRs) in Braak stage 1/2 areas and the level of education after adjustment for age, sex, clinical status, and 13-item Alzheimer's Disease Assessment Scale-cognitive subscale-13 score. Open circles represent clinically normal subjects. Filled circles represent patients with mild cognitive impairment. The line shows the linear fit of AV-1451 SUVR in Braak stage 1/2 stage areas and level of education data.

Results of multiple linear regression analyses for predicting ADAS-cog score

Stepwise backward deletion multiple linear regression analysis was performed to determine which factors were the best predictors of cognitive ability (Table 4). The dependent variable was the ADAS-cog score. The independent variables were age, sex, clinical status, education (HI score), tau (AV-1451 SUVR in Braak stage 1/2 areas), and the interaction of tau and education (tau × education). Sex and education were removed, and age, clinical status, tau, and interaction between tau and education remained in the final model as predictors of ADAS-cog score (Table 4). The interaction between tau and education indicated that higher tau accumulation led to a stronger relationship with higher ADAS-cog score among participants with a lower level of education than among those with a higher level. Figure 2 shows a visual representation of the association between slope in ADAS-cog score and tau accumulation in the groups with lower and higher levels of education after adjustment for age and clinical status.

Table 3 Comparison of standardized uptake value ratios (SUVRs) between lower and higher educational level, occupation, or socioeconomic status

	SUVR (mean ± SE)[†,‡,§]		ANCOVA	
Factors and regions	Lower	Higher	$F_{1,121}$	*P*-value
Education				
n	58	69		
Years of education	12–16	17–20		
HI score (range)	4–6	7		
Cortical AV-45 SUVR	1.09 ± 0.15	1.12 ± 0.15	1.12	0.29
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	1.22 ± 0.18	1.31 ± 0.18	7.45	0.007*
Braak 3/4 AV-1451 SUVR (limbic)	1.37 ± 0.15	1.41 ± 0.15	2.57	0.11
Braak 5/6 AV-1451 SUVR (neocortical)	1.43 ± 0.14	1.45 ± 0.14	0.49	0.49
Occupation				
n	55	72		
HI score (range)	2–7	8		
Cortical AV-45 SUVR	1.11 ± 0.16	1.10 ± 0.15	0.04	0.85
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	1.27 ± 0.19	1.27 ± 0.19	0.01	0.93
Braak 3/4 AV-1451 SUVR (limbic)	1.41 ± 0.16	1.38 ± 0.15	0.91	0.34
Braak 5/6 AV-1451 SUVR (neocortical)	1.47 ± 0.15	1.43 ± 0.14	2.28	0.13
SES (HI)				
n	48	69		
HI score (range)	1–3	4		
Cortical AV-45 SUVR	1.09 ± 0.15	1.12 ± 0.15	1.28	0.26
Braak 1/2 AV-1451 SUVR (entorhinal cortex and hippocampus)	1.25 ± 0.19	1.29 ± 0.19	1.14	0.29
Braak 3/4 AV-1451 SUVR (limbic)	1.39 ± 0.15	1.39 ± 0.15	0.04	0.84
Braak 5/6 AV-1451 SUVR (neocortical)	1.45 ± 0.15	1.44 ± 0.14	0.41	0.52

*$P < 0.0125$ (0.05/4). †Data are presented as mean ± SE unless otherwise indicated. ‡ANCOVA with age, sex, clinical status, and 13-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) score as covariates. §SUVR values were adjusted for age, sex, clinical status, and ADAS-cog score. SES, socioeconomic status; HI, Hollingshead Index of Social Status; AV-45, florbetapir; AV-1451, flortaucipir.

Table 4 Results of a stepwise backward deletion multiple linear regression analysis predicting the 13-item Alzheimer's Disease Assessment Scale-cognitive subscale score

Step	*t*	β	*P*-value	*F*	d.f.	*P*-value	Adjusted R^2
Model 1				9.16	6, 120	<0.001	0.28
Age	1.80	0.15	0.07				
Sex	−0.79	−0.07	0.43				
Education (HI score)	1.51	0.65	0.13				
Clinical status	3.07	0.25	0.003				
Braak 1/2 AV-1451 SUVR	2.68	1.22	0.008				
Braak 1/2 AV-1451 SUVR × education (HI score)	−2.21	−1.44	0.03				
Model 2				10.90	5, 121	<0.001	0.28
Age	2.12	0.17	0.04				
Education (HI score)	1.49	0.64	0.14				
Clinical status	3.31	0.27	0.001				
Braak 1/2 AV-1451 SUVR	2.60	1.17	0.01				
Braak 1/2 AV-1451 SUVR × education (HI score)	−2.17	−1.41	0.03				
Model 3				12.94	4, 122	<0.001	0.28
Age	1.92	0.15	0.06				
Clinical status	3.25	0.26	0.001				
Braak 1/2 AV-1451 SUVR	4.26	0.53	<0.001				
Braak 1/2 AV-1451 SUVR × education (HI score)	−3.89	−0.46	<0.001				

HI, Hollingshead Index of Social Status; d.f., degrees of freedom; SUVR, standardized uptake value ratio.

DISCUSSION

To our knowledge, this is the first *in vivo* PET imaging study to assess the interaction effect of AD pathology and education, occupation, and SES as a proxy for CR on cognitive performance. We found a significant positive correlation between educational level and tau pathology in Braak stage 1/2 areas and, when age, sex, clinical status, and ADAS-cog score were considered as covariates, a significantly larger tau accumulation in the same areas in the higher level of education group. The interaction between tau and education was a good predictor of cognitive function: higher tau accumulation led to a stronger relationship with higher ADAS-cog score among participants with a lower level of education than among those with a higher level. These findings are in line with the CR theory and with a number of previous neuroimaging studies, indicating a compensatory effect of education against the accumulation of pathological damage.[22] In other words, our findings suggest that, at least in the early stage of AD pathology, education compensates for neurodegeneration and allows the maintenance of patients' cognitive performance as previously argued by others.[22-25]

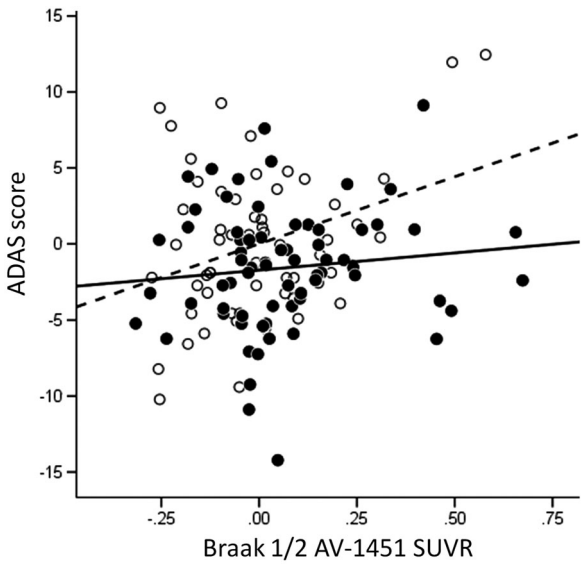

Figure 2 Scatter plot of individual 13-item Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) scores and AV-1451 standardized uptake value ratios (SUVRs) in Braak stage 1/2 areas in subjects according to educational level after adjustment for age and clinical state. Open circles represent subjects with a lower education level. Filled circles represent subjects with a higher education level. The line shows the linear fit of ADAS-cog score and AV-1451 SUVR in Braak stage 1/2 areas data in the groups with higher (solid line) and lower (dashed line) levels of education.

In this sample, the relationship between education and amyloid aggregation showed no statistical significance ($P = 0.37$), whereas the relationship between education and tau aggregation in Braak stage 1/2 areas was significant ($P = 0.003$). The increased strength of the relationship between tau and education compared to Aβ may be associated with the more proximal association of tau to cognitive

dysfunction.[26,27] Overall, our findings support the idea that education as a proxy for CR may protect against AD pathology. The relationship between education and tau only in the Braak stage 1/2 areas further indicates the possibility that education provides a protective effect, especially in early-stage AD, when pathology has started to spread within Braak stage 1/2 areas.

The mechanism by which education provides these effects is unknown. Higher educational attainment may be suggestive of early cognitive enrichment, which may increase neuronal signalling, neurogenesis, and synaptic plasticity.[28,29] Alternatively, educational achievement may be a marker for those with high pre-existing neural or cognitive capacity. These factors may be related to CR. In contrast, we found no significant relationship between tau pathology and occupation/SES, which is directly associated with lifelong mental and cognitive stimulation. Higher occupation/SES is often associated with higher intelligence and a healthier lifestyle, less disease, and lower exposure to toxic factors because of a better environment. Although we expected that individuals with higher occupation/SES had better intellectual and environmental factors at the mid- to late-life stage, protection against AD pathology was not observed in them. One explanation for the relationship between protection against AD pathology and education, but not occupation/SES, might be that these are mainly determined by intellectual and environmental factors during the early-life stage, and their effect in the midlife stage may be smaller. Further study is necessary to verify this speculation.

In our previous study, we found significantly larger cortical Aβ accumulation in CN subjects with a low level of education than in subjects with a high level of education.[30] Our previous findings suggested that education in the early-life stage has a negative relationship with Aβ deposition. This suggestion is not inconsistent with the CR hypothesis. More educated people might be prone to a greater inhibitory effect against Aβ deposition in the early stage of AD pathology. At the same time, they have a greater CR capacity, and for dementia to manifest, greater pathological changes are required. However, in this study, no relationship was found between level of education and Aβ deposition. The discrepancies in the findings between these two studies may be due to the differences in the number of participants and population background. The ADNI may include individuals with relatively high social status, which would cause potential population bias. Indeed, the percentage of individuals who completed tertiary education was 73.2% in this study versus 46.7% in our previous study.

There are several limitations to our study. First, because we excluded subjects who were taking antidementia, antidepressant, and/or other behavioural medication, a relatively small number of patients with MCI or AD dementia was included in our study, which limits the applicability of our results to late-stage AD pathology. As to the possibility that the inclusion of small number of AD patients ($n = 2$) drove the observed results, it is unlikely: we found no change in the results with a subanalysis excluding the AD patients (data not shown). Second, we analyzed only the cross-sectional datasets of the ADNI, which did not allow us to examine the direct causality between educational attainment and AD-related biomarkers based on brain imaging. Third, unlike a recent report that indicated a modifying effect of CR on Aβ deposition in apolipoprotein E4 carriers,[31] we could not examine this association as genotyping of apolipoprotein E4 was not performed in the entire sample. Lastly, our findings might be, at least in part, attributable to the sampling bias of the ADNI study per se, because ADNI participants were those who had access to research institutes or major psychiatric hospitals in the USA and had some interest in participating in this study. This kind of bias would especially affect SES. However, we emphasize that we were still able to identify the significant effect of interaction between tau and education on cognitive function despite the possibly skewed distribution of the data used in this study.

In summary, we found that the interaction between tau and education was a good predictor of cognitive function and that larger tau accumulation had a stronger relationship with higher ADAS-cog score among participants with a lower level of education than among those with a higher level. Our findings provide further evidence of the protective effect of education on cognitive dysfunction in the early stage of AD pathology and indicate that education may decrease the adverse cognitive consequences of tau aggregation. However, we found no significant relationship between the tau pathology and occupation/SES, which is directly associated with lifelong mental

and cognitive stimulation. Although we expected that the people with higher occupation/SES had a better environment at the mid- to late-life stage, they have no protective effect on cognitive dysfunction due to AD pathology. One explanation of CR's relationship with education, rather than with occupation/SES, was that CR was mainly determined by intellectual and environmental factors during early-life stage; the effect of factors on CR after the midlife stage is smaller than those of early stage. Further study is necessary to verify this speculation.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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