Cognitive Reserve Proxies, Alzheimer Pathologies, and Cognition

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Abstract

Background

Limited information is available regarding which of the commonly used cognitive reserve (CR) proxies are more appropriate to precisely reflect moderation effect for the relationship between a specific Alzheimer's disease (AD) pathology and cognitive decline. We examined the moderating effects of the frequently used four CR proxies [*i.e.*, education, premorbid intelligence quotient (pIQ), occupational complexity (OC), and lifetime cognitive activity (LCA)] on the relationships between various *in vivo* AD pathologies and cognitive decline.

Methods

This study included 361 older adults (268 cognitively unimpaired, 52 mild cognitive impairment with beta-amyloid (A β) deposition, 41 AD dementia with A β deposition). All participants underwent multi-modal brain imaging including [^{11}C] Pittsburgh Compound B positron emission tomography (PET), [^{18}F] Fluorodeoxyglucose-PET, and magnetic resonance imaging to measure AD pathologies as well as comprehensive clinical and neuropsychological assessments. Information on education, pIQ estimated with an adult reading test, OC, and LCA was obtained. The Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery total score (CERAD-TS) was used as the cognitive measure. We used linear regression model predicting cognition to examine the interactions of each CR proxy and each AD pathology.

Results

Among the CR proxies, only education significantly moderated the relationship between A β deposition and CERAD-TS. Education, pIQ, and LCA, but not OC, showed moderating effect on the relationship between AD-signature cerebral hypometabolism and CERAD-TS. In contrast, only OC had a significant moderating effect on the relationship between cortical atrophy of the AD-signature regions and CERAD-TS.

Conclusions

The present findings suggest that the proposed CR proxies have different moderating effects on the relationships between specific AD pathologies and cognitive decline. To investigate CR or related issues, it is necessary to select a proper CR proxy considering the target brain pathology.

Introduction

The concept of cognitive reserve (CR) has been introduced to explain how some people can tolerate more brain pathologies or age-related brain changes than others.[1] It is defined as the capacity to preserve cognitive function better in the presence of brain pathology and it acts as a moderator between brain changes and the degree of cognitive impairment.[1–3] Various measures have been proposed as proxies

of CR, including education, the premorbid intelligence quotient (pIQ), occupational complexity (OC), and lifetime cognitive activity (LCA), and have been used to estimate the CR of an individual indirectly.[4,5]

Regarding moderating effects on the relationships between the *in vivo* pathologies of Alzheimer's disease (AD) and cognition, education was reported to moderate the relationships of senile plaques,[6,7] cerebrospinal fluid (CSF) beta-amyloid (A β),[8] cerebral A β -positive status on positron emission tomography (PET),[9] or medial temporal atrophy on Magnetic Resonance Imaging (MRI)[10] with cognitive function, but not that of neurofibrillary tangles.[6,7] Two studies showed that pIQ, estimated using an adult reading test, interacted with inferior temporal tau deposition[11] and precuneus A β deposition on PET[12] to predict cognitive function, while another study suggested that pIQ does not moderate the relationship of various AD biomarkers with cognition, including CSF A β , t-tau, and structural abnormalities on MRI.[13] However, no study has yet investigated the moderating effects of OC and LCA on the relationship between AD pathologies and cognition. Moreover, limited information is available on which of the commonly used CR proxies is appropriate to reflect moderation effect more precisely for the relationship between a specific AD pathology and cognitive decline.

Therefore, we examined the moderating effects of education, pIQ, OC, and LCA on the relationships between various *in vivo* AD pathologies and global cognition to compare their appropriateness as CR proxies for specific pathologies. We used three AD neuroimaging biomarkers to measure different *in vivo* AD pathologies: cerebral A β deposition on ^{11}C -Pittsburg compound B (PiB)-PET, AD-signature region cerebral glucose metabolism (AD-CM) on ^{18}F -fluoro-2-deoxyglucose (FDG)-PET, and AD-signature region cortical thickness (AD-CT) on structural brain MRI.[14,15]

Methods

Subjects

This study is part of the Korean Brain Aging Study for the Early Diagnosis and Prediction of AD (KBASE), an ongoing prospective cohort study designed to identify novel AD biomarkers and to explore various lifetime experiences contributing to AD-related brain changes. Details on the KBASE study have been described previously.[16] The current study included 361 middle-aged and elderly individuals with age between 55 and 90 years. The subjects consisted of 221 cognitively unimpaired (CU) with no A β deposition on PiB-PET (CU-), 47 CU with A β deposition (CU+), 52 mild cognitive impairment (MCI) with A β deposition (MCI+), 41 AD dementia with A β deposition (ADD+). CU individuals had no diagnosis of mild cognitive impairment or dementia, and a global Clinical Dementia Rating (CDR) score of 0.[17,18] All individuals with MCI met the current consensus criteria for amnesic MCI, which are as follows: (1) memory complaints confirmed by an informant, (2) objective memory impairments, (3) preserved global cognitive function, (4) independence in functional activities, and (5) no dementia. Regarding criterion 2, the age-, education-, and sex adjusted z-scores for at least 1 of 4 episodic memory tests was <-1.5 . The four memory tests were the Word List Memory (WLM), Word List Recall (WLR), Word List Recognition (WLRc), and Constructional Recall (CR) tests, which are included in the Korean version of the Consortium

to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological assessment battery.[18,19] All individuals with MCI had a CDR score of 0.5. All individuals with AD dementia meet both the Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) criteria[20] for dementia and National Institute on Aging and Alzheimer's Association (NIA-AA) criteria[21] for probable AD dementia, and had a global CDR score of 0.5 or 1. Individuals with medical, psychiatric, or neurological conditions or a history of conditions that may affect brain structures or functions, such as stroke, head trauma, depression, hydrocephalus, or focal brain lesions on MRI were excluded. Each subject was diagnosed at a consensus conference of board-certified psychiatrists and neuropsychologists before inclusion in the study. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital and Seoul National University-Seoul Metropolitan Government Boramae Center (Seoul, South Korea) and conducted in accordance with the recommendations of the current version of the Declaration of Helsinki. All participants or their caregivers gave informed consent to participate in this study.

Clinical and neuropsychological assessments

All participant underwent comprehensive clinical and neuropsychological assessments following the KBASE assessment protocol,[16] which incorporated the Korean version of the CERAD assessment packet.[18,19] CERAD-total score (CERAD-TS),[22,23] which is calculated by summing the scores of six tests included in the CERAD neuropsychological battery (i.e., Semantic Verbal Fluency Tasks, 15-item Boston Naming Test, WLM, WLR, WLRc, and Constructional Praxis), was used as an established composite measure of global cognition. CERAD-TS has a maximum of 100 points.

CR proxies

The years of formal education, pIQ, OC, and LCA participation frequency were included as candidate CR proxies. Years of formal education was self-reported by the subjects and confirmed by reliable informants. pIQ was estimated by the performance on the Korean Adult Reading Test (KART),[24] a word-reading test for Korean-speaking adults using 50 irregularly pronounced words that is useful for estimating premorbid intelligence. The KART-predicted Full-Scale IQ, derived from the KART error score, was used as the pIQ of an individual. Information about occupation was self-reported by the participant and confirmed by reliable informants. Only the longest-held occupation was considered. We then classified OC into four levels based on the skill levels described in the International Standard Classification of Occupations (ISCO-08).[25,26] Occupations at skill level 1 typically involve the simple and routine physical or manual tasks (*i.e.*, office cleaners, freight handlers or garden laborers). Occupations at skill level 2 typically involve the performance of tasks, such as operating machinery and electronic equipment; driving vehicles; maintenance and repair of electrical and mechanical equipment; and manipulation, ordering and storage of information (*i.e.*, butchers, bus drivers or secretaries). Occupations classified at skill level 3 typically involve the performance of complex technical and practical tasks that require complex problem solving, reasoning, and decision making in a specialized field (*i.e.*, shop managers, medical laboratory technicians or diagnostic medical radiographers). Occupations classified at skill level 4 typically involve the performance of tasks that require complex

problem-solving, decision-making and creativity based on an extensive body of theoretical and factual knowledge in a specialized field (*i.e.*, sales and marketing managers, civil engineers or secondary school teachers). The LCA participation frequency was measured with a 39-item structured questionnaire.[27] The included items were relatively common activities with few barriers to participation, such as reading newspapers, magazines, or books; visiting a museum or library; attending a concert, play, or musical; writing letters; and playing games. The frequency of participation was rated from 1 (once a year or less) to 5 (approximately daily). There were nine items for current, 11 items for childhood (6–12 years of age), 10 items for young adulthood (18 years of age), and nine items for midlife (40 years of age) cognitive activities. Item scores for childhood, young adulthood, and midlife periods were averaged to yield a separate value for the corresponding age period. We then calculated the composite LCA score to use in the subsequent analysis, which was an average of the three epoch values. The items for current activities were not included to calculate LCA score to avoid the influence of current cognitive impairment state on LCA score.

Measurement of cerebral A β deposition

All participants underwent simultaneous three-dimensional [^{11}C]-PiB-PET and T1-weighted MRI using a 3.0 T Biograph mMR scanner (Siemens; Washington DC, WC, USA), according to the manufacturer's guidelines. The details of PiB-PET acquisition and preprocessing were described previously.[28] An automatic anatomic labeling algorithm and a region-combining method[29] were applied to determine the regions of interest (ROIs) for characterizing the PiB retention levels in the frontal, lateral parietal, posterior cingulate–precuneus, and lateral temporal regions. The standardized uptake value ratio (SUVR) value for each ROI was calculated by dividing the mean value for all voxels within each ROI by the mean cerebellar uptake value for the same image. A global cortical ROI consisting of the four ROIs was also defined and a global A β retention value was generated by dividing the mean value for all voxels of the global cortical ROI by the mean cerebellar uptake value in the same image.[29,30] A β deposition positivity was determined with global A β retention > 1.21[31].

Measurement of AD-CM

All subjects underwent [^{18}F]-FDG-PET imaging using the machine described above. The details of FDG-PET acquisition and preprocessing were described previously.[28] AD-signature FDG ROIs, such as the angular gyri, posterior cingulate cortex, and inferior temporal gyri, which are sensitive to the changes associated with AD,[32] were determined. AD-CM was defined as the voxel-weighted mean SUVR extracted from the AD-signature FDG ROIs.

Measurement of AD-CT

All T1-weighted images were acquired in the sagittal orientation using the same PET-MR machine. MRI acquisition and preprocessing were described previously.[28] AD-CT was defined as the mean cortical thickness obtained from AD-signature regions, including the inferior frontal sulcus, superior frontal gyrus,

temporal pole, inferior temporal gyrus, medial temporal cortex, precuneus, superior parietal lobule, angular gyrus, and supramarginal gyrus, based on Desikan-Killany atlas.[33,34]

Statistical analysis

To investigate the moderating effects of the CR proxies on the relationships between *in vivo* AD pathologies and cognition, we tested multiple linear regression models with CERAD-TS as the dependent variable, each CR proxy, each AD neuroimaging biomarker, and CR proxy × AD neuroimaging biomarker interaction term as independent variables controlling for age, sex, and apolipoprotein ε4 (APOE4) carrier status. All analyses were done with SPSS 23.0 (IBM Corporation, New York) and results were examined at $p < 0.05$.

Results

Subject characteristics

The characteristics of the subjects are presented in Table 1.

Moderating effects of CR proxies on the relationship between Aβ deposition and cognition

Of the four CR proxies, only education had a significant moderating effect on the relationship between global Aβ deposition and CERAD-TS (Table 2). Individuals with higher education showed shallower slope of decline in CERAD-TS when Aβ deposition increased compared to those with lower education. The result remained unchanged when we re-examined the model using the education as groups stratified into tertiles [≥ 13 years, 10~12 years, and < 10 years] instead of a continuous value, for illustrative purpose (Figure 1A).

Moderating effects of CR proxies on the relationship between AD-CM and cognition

For the association between AD-CM and CERAD-TS, education, pIQ, and the LCA score showed significant moderating effects, except for the OC (Table 3). For the three significant proxies, the higher CR group showed shallower slope of decline of CERAD-TS associated with AD-CM compared with the lower CR group (Figure 1B-1D).

Moderating effects of CR proxies on the relationship between AD-CT and cognition

Of the four proxies, only OC showed significant moderating effect on the relationship between AD-CT and CERAD-TS (Table 4). The higher OC subgroup showed shallower slope of decline in CERAD TS when AD-CT decreased compared to the lower OC subgroup (Figure 1E).

Discussion

We found that various CR proxies showed different moderating effects on the relationships between *in vivo* AD pathologies and cognition. First, for the relationship of cerebral A β deposition with cognition, only education had a significant moderating effect. Secondly, education, pIQ, and LCA had significant moderating effects on the association between AD-CM and cognition. Thirdly, only OC had significant moderating effect on the relationship between AD-CT and cognition.

Our finding on the significant moderating effect of education on the association between A β deposition and cognitive decline is in line with the findings from two postmortem neuropathological studies[6,7] and an amyloid PET study.[9] However, for the other CR proxies, we did not find presence of moderating effect influencing the effect of A β on cognition. Similar to our result, a previous study with smaller sample (133 CN, 17 MCI, and 6 ADD) showed that pIQ did not moderate the relationship between global A β deposition on PET and cognition, whereas it moderated the association of tau deposition with cognition.[11] There are no prior reports on the moderating effects of OC and LCA on the relationship between A β pathology and cognitive decline.

Although it is not easy to explain why only education moderated the negative effect of A β pathology on cognition, a possible explanation is that education level is not only associated with the level of cognitive activity[27,35] but also with establishing healthy lifestyle (*e.g.*, regular exercise, restricted caloric intake, avoiding harmful substance use, etc.) for maintaining brain health,[36] whereas pIQ, OC, and LCA may largely reflect intellectual ability, demand, or activity. Such difference between education and other CR proxies may be the reason for the differential moderation of A β -related cognitive decline. In addition, although not directly examined in the currently study, education may moderate the relationship between A β and cognitive decline by delaying or lowering tau pathology, given that brain tau deposition is a key mediator of A β -driven cognitive decline[15,37]. A previous study reported that education was related to lower CSF t-tau concentrations at similar CSF A β 42 levels.[38] Another study also showed that education could mitigate age-related changes in CSF tau biomarkers.[39]

We observed significant moderating effect of education, pIQ, and LCA on the relationship between AD-CM and CERAD-TS. The findings for education and pIQ were consistent with previous reports that indicated individuals with higher education or pIQ can better tolerate the influence of hypometabolism on cognitive decline.[40–42]

In contrast to other CR proxies, OC moderated the relationship between AD-CT and cognition, whereas it did not change the effect of AD-CM. The finding for the significant moderation of OC for the negative influence of cortical atrophy is in line with a prior report that showed greater OC is associated with increased brain atrophy in a cohort at risk for AD while holding cognition constant.[43] However, the mechanisms by which OC moderate the effect of AD-CT on cognitive decline differentially from other proxies are not clear. Some explanation might be possible. OC may encapsulate interpersonal or social component as well as intellectual one,[43,44] whereas other CR proxies are mainly related to intellectual abilities or activities. A previous study showed that when OC was broken down into components (*i.e.*, complexity of work with people, complexity of work with data, and complexity of work with things), only

the complexity of work with people had a significant impact on brain volume.[43] Social interaction, which could be related to complexity of work with people is known to delay progression of AD.[45,46] In addition, previous studies demonstrated that occupation and participating in social activities exerted similar protective effects on cognition.[47,48]

Our study has several strengths: First, we used three different neuroimaging modalities including amyloid PET, FDG-PET, and 3D MRI to examine the abilities of CR proxies to moderate the influence by various *in vivo* AD pathologies. In addition, we included relatively large number of subjects with diverse cognitive spectrum from CU, MCI to dementia. Moreover, we included only A β -positive MCI and AD dementia individuals selected by using amyloid PET to investigate specifically the effect of AD pathologies on cognition moderated by candidate CR proxies considering that 29~63% of MCI and 7~21% of AD dementia patients do not actually have A β deposition in brain.[49,50]

Nevertheless, several limitations need to be mentioned. First, due to its cross-sectional design, moderation for the causal relationships of brain pathologies with cognitive decline could not be assessed precisely. Longitudinal follow-up studies are required to confirm the findings. Second, the cognitive activity questionnaire used to assess LCA was based on retrospective recall and might be influenced by recall bias related to cognitive impairment or depression. To minimize the recall bias, we excluded the individuals with major depressive disorder or advanced dementia (CDR > 1). Remote memory for early or midlife experience is usually maintained in mild AD dementia patients with CDR 0.5 or 1.[17] Third, we did not assess brain tau pathology, although it is one of the key AD pathologies. Further studies including tau PET or CSF tau measurement could provide additional insight into the differential moderation of CR proxies.

In conclusion, the present findings suggest that the proposed CR proxies have different moderating effects on the relationships between specific AD pathologies and cognition. To investigate CR or related issues, it may be necessary to select proper CR proxies considering the target brain pathology. For A β pathology, education seem the best CR proxy. Education, pIQ, and LCA are suitable for evaluating the moderating effect on the relationship of AD-related hypometabolism with cognition, while OC may be the best proxy for the influence of AD-related brain atrophy with cognitive decline.

Abbreviations

CR, Cognitive Reserve; pIQ, Premorbid intelligence quotient; OC, Occupational complexity; LCA, Lifetime cognitive activity; AD, Alzheimer's disease; CSF, Cerebrospinal fluid; A β , Beta-amyloid; MRI, Magnetic resonance imaging; PET, Positron emission tomography; PiB, ¹¹C-Pittsburg compound B; AD-CM, AD-signature region cerebral glucose metabolism; FDG, ¹⁸F-fluoro-2-deoxyglucose; AD-CT, AD-signature region cortical thickness; KBASE, Korean Brain Aging Study for the Early Diagnosis and Prediction of AD; CU, Cognitively unimpaired; CU-, CU without A β deposition; CU+, CU with A β deposition; MCI, Mild cognitive impairment; MCI+, MCI with A β deposition; ADD, AD dementia; ADD+, AD dementia with A β deposition; CDR, Clinical Dementia Rating; WLM, Word List Memory; WLR, Word List Recall; WLRc, Word

List Recognition; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders; NIA-AA, National Institute on Aging and Alzheimer's Association; CERAD-TS, CERAD-total score; KART, Korean Adult Reading Test; ISCO, International Standard Classification of Occupations; ROI, regions of interest.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital and written informed consent was obtained from all participants.

Consent for publication

Not applicable

Availability of data and material

The datasets that were generated and analyzed during the present study are not publicly available due to ethical considerations and privacy restrictions. Data may be obtained from the independent data sharing committee of the KBASE research group on reasonable request. Requests for data access can be submitted to the administrative coordinator of the KBASE group by e-mail (kbasecohort@gmail.com), who is independent of the authors.

Competing interests

The authors declare that they have no competing interests

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Author contributions

KK and DYL contributed to the conception, design of this study, drafting the manuscript and preparing the figures. All authors (KK, DY, MSB, JHL, SYJ, WJK, GB, KS, DH, YHL, HJ, GJ, JYL, HK, YKK, KMK, CHS, and DYL) contributed to the acquisition, analysis and interpretation of the data, and critically revised the manuscript.

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Tables

Table 1. Participant characteristics

	All subjects (n = 361)	CU- (n = 221)	CU+ (n = 47)	MCI+ (n = 52)	ADD+ (n = 41)	<i>p</i>
Age, y	69.8 (7.9)	67.9 (8.0)	73.7 (6.3)	72.8 (7.2)	71.7 (7.3)	<.001
Female (%)	201 (55.7%)	114 (51.6%)	26 (55.3%)	35 (67.3%)	26 (63.4%)	.15
APOE ε4 carriers ^a (%)	105 (29.2%)	33 (14.9%)	15 (31.9%)	29 (55.8%)	28 (68.3%)	<.001
GDS, score	5.8 (5.5)	4.7 (5.1)	5.7 (4.9)	9.5 (6.5)	7.6 (4.5)	<.001
CR proxies						
Education, years	11.4 (4.8)	11.6 (4.8)	11.9 (4.5)	10.7 (4.7)	10.2 (4.9)	.21
plQ, score	114.6 (11.0)	116.1 (9.7)	115.9 (10.0)	112.4 (11.5)	108.1 (15.1)	<.001
OC, score	2.3 (1.4)	2.5 (1.3)	2.5 (1.5)	1.8 (1.5)	2.2 (1.4)	.021
LCA, score	2.3 (0.7)	2.3 (0.7)	2.3 (0.6)	2.1 (0.7)	2.1 (0.7)	.077
Cognitive measures						
CERAD TS, score	66.2 (15.6)	73.3 (9.9)	71.9 (9.6)	50.6 (10.3)	41.1 (11.1)	<.001
<i>in vivo</i> AD biomarkers						
Global Aβ, SUVR	1.4 (0.4)	1.1 (0.1)	1.6 (0.4)	1.9 (0.4)	2.0 (0.4)	<.001
AD-CM, SUVR	1.4 (0.1)	1.4 (0.1)	1.4 (0.1)	1.3 (0.2)	1.2 (0.1)	<.001
AD-CT, mm	2.5 (0.2)	2.6 (0.1)	2.5 (0.1)	2.4 (0.2)	2.2 (0.2)	<.001

Note: Data are presented as mean (SD) unless otherwise indicated.

^aAPOE ε4 carriers are the percentage of individuals with at least one APOE4 allele.

Key: Aβ, beta-amyloid; CU-, Aβ-negative cognitively unimpaired; CU+, Aβ-positive cognitively unimpaired; MCI+, Aβ-positive mild cognitive impairment; ADD+, Aβ-positive Alzheimer's disease dementia; APOE ε4, apolipoprotein E ε4; GDS, Geriatric Depression Scale; CR, cognitive reserve; plQ, premorbid intelligence quotient; OC, occupational complexity; LCA, lifetime cognitive activity; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CERAD TS, Total Score of CERAD neuropsychological assessment battery; SUVR, standardized uptake value ratio; AD-CM, AD-signature region cerebral glucose metabolism; AD-CT, AD-signature region cortical thickness.

Table 2. Moderating effect of each CR proxy on the relationship between global A β and cognition

Model term	B	SE	Beta	<i>p</i>
Model 1				
Education	1.11	0.13	0.34	<.001***
Global A β	-17.75	1.49	-0.50	<.001***
Education x global A β	0.82	0.29	0.11	.005**
Model 2				
plQ	0.53	0.06	0.38	<.001***
Global A β	-16.00	1.46	-0.45	<.001***
plQ x global A β	0.08	0.10	0.03	.40
Model 3				
OC	2.37	0.49	0.21	<.001***
Global A β	-17.48	1.57	-0.49	<.001***
OC x global A β	1.60	0.99	0.06	.11
Model 4				
LCA	5.93	0.89	0.26	<.001***
Global A β	-16.86	1.55	-0.48	<.001***
LCA x global A β	2.21	2.05	0.04	.28

p* < 0.01; *p* < 0.001.

Note: Age, sex, and APOE4 carrier status were treated as covariates.

Key: CR, cognitive reserve; A β , beta-amyloid; plQ, premorbid Intelligence Quotient; OC, occupational complexity; LCA, lifetime cognitive activity; SE, standard error; APOE4, apolipoprotein E ϵ 4.

Table 3. Moderating effect of each CR proxy on the relationship between AD-CM and cognition

Model term	B	SE	Beta	<i>p</i>
Model 1				
Education	1.01	0.14	0.31	<.001***
AD-CM	39.25	4.42	0.36	<.001***
Education x AD-CM	-2.09	1.00	-0.08	.038*
Model 2				
plQ	0.51	0.06	0.36	<.001***
AD-CM	34.87	4.27	0.32	<.001***
plQ x AD-CM	-0.87	0.38	-0.09	.024*
Model 3				
OC	2.09	0.52	0.19	<.001***
AD-CM	39.15	4.65	0.36	<.001***
OC x AD-CM	-2.34	3.26	-0.03	.47
Model 4				
LCA	5.66	0.93	0.25	<.001***
AD-CM	37.53	4.50	0.35	<.001***
LCA x AD-CM	-13.60	6.30	-0.09	.032*

p* < 0.05; *p* < 0.01; ****p* < 0.001.

Note: Age, sex, and APOE4 carrier status were treated as covariates.

Key: CR, cognitive reserve; AD-CM, AD-signature region cerebral glucose metabolism; plQ, premorbid Intelligence Quotient; OC, occupational complexity; LCA, lifetime cognitive activity; SE, standard error; APOE4, apolipoprotein E ε4.

Table 4. Moderating effect of each CR proxy on the relationship between AD-CT and cognition

Model term	B	SE	Beta	<i>p</i>
Model 1				
Education	0.98	0.14	0.30	<.001***
AD-CT	38.79	3.50	0.49	<.001***
Education x AD-CT	-0.49	0.64	-0.03	.44
Model 2				
pIQ	0.54	0.06	0.38	<.001***
AD-CT	36.21	3.36	0.46	<.001***
pIQ x AD-CT	-0.20	0.24	-0.03	.42
Model 3				
OC	2.24	0.49	0.20	<.001***
AD-CT	38.30	3.63	0.49	<.001***
OC x AD-CT	-5.26	2.22	-0.10	.018*
Model 4				
LCA	5.98	0.89	0.27	<.001***
AD-CT	39.15	3.57	0.50	<.001***
LCA x AD-CT	1.82	4.28	0.02	.67

p* < 0.05; **p* < 0.001.

Note: Age, sex, and APOE4 carrier status were treated as covariates.

Key: CR, cognitive reserve; AD-CT, AD-signature region cortical thickness; pIQ, premorbid Intelligence Quotient; OC, occupational complexity; LCA, lifetime cognitive activity; SE, standard error; APOE4, apolipoprotein E ε4.

Figures

Figure 1

Visual representations showing the relationships between CR proxies, AD pathologies, and cognition. (A) Moderation of education for the relationship between A β deposition and CERAD TS. Moderation of (B) education, (C) pIQ, and (D) LCA for the relationship between AD-CM and CERAD-TS. (E) Moderation of OC for the relationship between AD-CT and CERAD-TS. Educational level was stratified into high (> 13 years), middle (10~12 years), and low (≤ 9) levels; pIQ was divided into high (> 120), middle (115~120), and low (≤ 114) levels; LCA was stratified into high (> 2.6), middle (2.0~2.6), and low (≤ 1.9) levels; and OC was stratified into high (3~4), middle (2), low (1) levels. Age, sex, and APOE $\epsilon 4$ carrier status are controlled as covariates. * $p < 0.05$; ** $p < 0.05$; *** $p < 0.001$. Key: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CERAD TS, Total Score of CERAD neuropsychological assessment battery; A β , beta-amyloid; AD-CM, AD-signature region glucose metabolism; AD-CT, AD-signature region cortical thickness; pIQ, premorbid Intelligence Quotient; LCA, lifetime cognitive activity; OC, occupational complexity; APOE $\epsilon 4$, apolipoprotein E $\epsilon 4$.

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