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A Novel Computational Proxy for Characterizing Cognitive Reserve in Alzheimer's Disease

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Abstract.
Background: Although the abnormal depositions of amyloid plaques and neurofibrillary tangles are the hallmark of Alzheimer's disease (AD), converging evidence shows that the individual's neurodegeneration trajectory is regulated by the brain's capability to maintain normal cognition.
Objective: The concept of cognitive reserve has been introduced into the field of neuroscience, acting as a moderating factor for explaining the paradoxical relationship between the burden of AD pathology and the clinical outcome. It is of high demand to quantify the degree of conceptual cognitive reserve on an individual basis.
Methods: We propose a novel statistical model to quantify an individual's cognitive reserve against neuropathological burdens, where the predictors include demographic data (such as age and gender), socioeconomic factors (such as education and occupation), cerebrospinal fluid biomarkers, and AD-related polygenetic risk score. We conceptualize cognitive reserve as a joint product of AD pathology and socioeconomic factors where their interaction manifests a significant role in counteracting the progression of AD in our statistical model.
Results: We apply our statistical models to re-investigate the moderated neurodegeneration trajectory by considering cognitive reserve, where we have discovered that 1) high education individuals have significantly higher reserve against the neuropathology than the low education group; however, 2) the cognitive decline in the high education group is significantly faster than low education individuals after the level of pathological burden increases beyond the tipping point.
Conclusion: We propose a computational proxy of cognitive reserve that can be used in clinical routine to assess the progression of AD.

Keywords: Alzheimer's disease, cognitive reserve, computational proxy

INTRODUCTION

Alzheimer's disease (AD) is a common neurodegenerative disorder with a long preclinical period and diverse progression across individuals [1–10]. A plethora of neuroimaging studies has found the presence of AD-related pathologies, such as amyloid-β (Aβ) deposition [11–16] and pathological tau [17–21], among cognitively normal individuals, which begins years before the emergence of

[1]These authors contributed equally to this work.

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the clinical symptom of mild cognitive impairment (MCI). In this regard, AD is defined by its underlying pathologic processes that can be documented by postmortem examination or *in vivo* by biomarkers [22, 23]. In general, the biomarkers are grouped into Aβ deposition [11–16], pathologic tau [12, 13, 15, 17–21], and neurodegeneration [22, 24–29].

A major challenge in the care and management of AD is the paradoxical relationship between the burden of AD pathology and its clinical outcome [30, 31]. Converging evidence shows that the individual's neurodegeneration trajectory is not only regulated by the abnormal deposition of pathology burden but also moderated by the brain's capability to maintain normal cognition [30, 32–34]. In this regard, the concept of resilience has been introduced into the field of neuroscience, acting as a moderate factor to preserve normal cognition despite underlying neuropathology [32, 33, 35]. These individual differences could be explained by higher capital (higher to start with), better maintenance (slower decline trend), or greater resilience and compensation capacities [32, 35]. For example, the most frequently used tests for AD diagnosis include verbal memory for the word list, story, and other verbal materials. There is a lifelong female advantage in verbal memory that sustains until reaching amnestic MCI [36–38]. The downside is that such a female advantage is eliminated at higher levels of pathology burden, resulting in delayed MCI diagnosis at the cost of a more severe burden of disease at the time of diagnosis and decline rapidly, and eventually missing the window for early intervention [39–41].

Most people with AD have the late-onset form of the disease, i.e., symptoms become apparent in their mid-60s and later. Although no specific gene has been identified as having a direct cause on late-onset AD, a number of generic risk factors have been found to be associated with AD. For example, 11 novel susceptibility single nucleotide polymorphisms (SNPs) were identified in a meta-analysis of genome-wide association studies (GWAS) that recruited over 74,046 individuals with and without late-onset AD [42]. Since each of the identified genetic variants has a small effect size, polygenetic risk scores (PRSs) have been widely used as a predictor in many AD studies [43–45], which combine the effects of many individual SNPs. For example, AD PRS showed promising results in detecting MCI in adults who were only in their 50s [46]. Although tremendous strides have been made in studying genetic associations in AD, limited attention has been given to investigate the role of genetic factors in cognitive reserve.

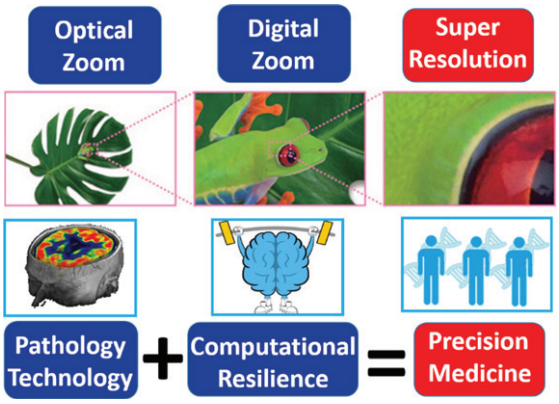

Fig. 1. As the digital zoom is a complementary technique to achieve super-resolution beyond optical zoom, our computational model allows us to quantify an individual's brain resilience using the current pathology technology and sets the stage for precision medicine.

Besides aging and biology factors, socioeconomic status (SES) such as education and occupation also have a significant role in regulating the progression of AD. In an early longitudinal study of 593 non-demented individuals aged 60 years or older, the follow-up examining results showed that increased education and occupational attainment might reduce the risk of AD [47]. Furthermore, lifestyle, physical illness, health care, and environmental factors associated with poverty are considered as other possible reasons for diminishing the brain's reserve of persons with AD [48].

Although the concept of cognitive reserve has been put forward to account for the individual difference of cognitive decline in the neuroscience field, many pathology studies are more likely to attribute the reason for such difference to the limitation of current pathology technology [49, 50]. However, there is one common agreement across the AD research community that the lack of direct measurement of cognitive reserve makes it difficult to quantify the degree of individual differences in susceptibility to age-related brain changes and pathologic changes in AD. To address this challenge, we propose a novel statistical approach to define an operational proxy of the cognitive reserve by quantifying longitudinal clinical phenotypic expression in relation to the underlying neurodegenerative processes on an individual basis. We demonstrate the rationale of our approach in Fig. 1, where we analogize the complementary role between pathology assay technology (hardware) and computational resilience proxy (software) to the technology of optical zoom and digital zoom function

in computer vision. In this regard, the major contribution of our work is a novel operational definition of cognitive reserve that can improve the precision of measuring pathological burden and disentangle the variable relationships between neuropathological substrates and clinical outcomes.

To do so, we first present a regression model to investigate the cognitive reserve proxy, where the response is the diagnosis label (indicating the severity of AD progression), and the predictors include age, sex, pathology burden, education, AD PRS, and their interactions. Our hypothesis is that the pathophysiology of AD is defined by AD-specific biological changes. However, the progression of AD is also moderated by socioeconomic factors such as education. In this context, we conceptualize the mechanism of the cognitive reserve as a joint product of AD pathology (measured by tau/Aβ_{42} ratio) and socioeconomic factors (measured by educational level), where their counteracting effect size of moderating the cognitive decline can be used as the computational proxy of cognitive reserve. Given the new proxy of cognitive reserve, we further investigate the following two hypotheses: 1) Does the high education group have a higher cognitive reserve to AD pathology? 2) Does a high level of education have the same downside as a female advantage in AD progression in the way of a more rapid cognitive decline after going beyond the moderate level of pathology? We perform significant testing in our regression model to test the first hypothesis. Regarding the second hypothesis, we employ a Cox model [51, 52] on the longitudinal data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database to examine the influence of cognitive reserve across educational differences.

MATERIALS AND METHODS

Data descriptions

The data used in our study were obtained from the ADNI database (https://ida.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see https://www.adni-info.org. There are four phases of the ADNI study (ADNI1, ADNI-GO, ADNI2, and ADNI3). Some participants were carried forward from previous phases for continued monitoring, while new participants were added with each phase to further investigate the evolution of AD.

Cerebrospinal fluid (CSF) biomarker data

Aβ_{42}, CSF t-tau, and phosphorylated-tau$_{181p}$, which are biomarkers of amyloid, neuronal injury, and neurofibrillary, respectively, were measured in the ADNI baseline. Full details of the collection are described in a previous study [53]. As shown in [54], CSF tau/Aβ_{42} ratio shows higher sensitivity and specificity in identifying the risk of AD than either just using tau or Aβ_{42}. To that end, we adopted the CSF tau/Aβ_{42} ratio as the AD pathology hallmark in the following analysis, where higher CSF tau/Aβ_{42} indicates the higher risk of developing AD.

Education and occupation

The years of education and occupations were recorded in the ADNI database in recruiting subjects. We classified education and occupation using the same criteria in Lo's study [55]. Years of education was divided into three categories: high (years of education >17 years), intermediate (years of education 15–17 years), and low (years of education <15 years). For the occupation that the ADNI subject performed during most of his/her adult life or with the longest time of service, it was classified into three levels according to the National Statistics Socio-economic classification [56]: 1) high level (professional or managerial), 2) intermediate level (skilled), and 3) low level (partly skilled or unskilled).

Genotyping data and quality control

The genetic data of four phases: ADNI-1, ADNI-GO/2, ADNI-GO/2nd, and ADNI-WGS have been used in our study. The ADNI-1, ADNI-GO/2, ADNI-GO/2nd, and ADNI-WGS contain 757, 432, 361, and 812 subjects with genotyping data, respectively. The ADNI-WGS phase consists of 261 subjects from ADNI-1, 427 subjects from ADNI-GO/2, and 124 new subjects.

For 757 subjects in ADNI-1, genotyping was performed by the Human610-Quad BeadChip (Illumina, Inc., San Diego, CA) included 620,901 SNP and CNV markers. For 432 subjects in ADNI GO/2, genotyping of 730,525 SNPs and CNVs were performed by Illumina HumanOmniExpress BeadChip.

For 361 subjects in ADNI GO/2nd, genotyping of 716,503 SNPs and CNVs were performed by Illumina HumanOmniExpress BeadChip. For 812 subjects in ADNI WGS, genotyping of 3.7 million SNPs were performed by Illumina Omni 2.5M (WGS Platform).

We performed quality control on the genotype data of each phase of ADNI by plink 1.90, similar to the procedure described in [57]. We only consider autosomal SNPs and SNPs are excluded from further analysis if they do not meet any criteria listed: 1) call rate per SNPs >95%; 2) minor allele frequency $\geq$1%; 3) Hardy-Weinberg equilibrium test of $p \geq 10^{-6}$. Subjects are excluded from further analysis if they do not meet any criteria listed: 1) call rate per participant $\geq$95%; 2) genotypic sex check with reported sex; 3) genotypic check for cryptic relatedness (3 related pairs were identified with PI_HAT >0.2, one of them was randomly excluded). The same quality control procedures were repeated for ADNI GO/2 and ADNI WGS.

After the quality control procedure, 541,007 SNPs in 751 participants in ADNI-1 were left for imputation. For ADNI-GO2 643,511 SNPs and 429 participants were left for imputation. For ADNI-GO2nd 637,069 variants and 359 subjects were left for imputation. ADNI-WGS left 1527166 SNPs, 808 subjects for imputation. Then we used the Michigan Imputation Server to impute each phase of the ADNI genotype data. ADNI-1 data was lifted from hg18 to hg19, as it was recorded on the human reference genome, GRCh37. While the other ADNI data are originally in GRCh38. Here, we follow the workflow in [58] to perform the imputation: 1) 1000 Genome Phase 3 v5 (hg19) as the reference panel; 2) Phased by Eagle; 3) used mixed population as reference panel; 4) Rsq filter was 0.3. After the imputation, we merged all four ADNI phases data together and filtered the SNPs by MAF >0.05 and performed an identity check for cryptic related pairs (7 related pairs were identified with PI_HAT >0.2, one of each pair was randomly excluded). For the subjects genotyped in multiple phases, we keep the most recent genotyping record for further analysis. After all the former quality control procedures, 9,432,719 SNPs in 1,661 subjects were kept.

Calculation of PRS

We are interested in testing the association between PRS of AD and the AD pathophysiology. First, we filtered the SNP in the GWAS results in CTG lab (https://ctg.cncr.nl/software/summary_statistics) by MAF greater than 0.01. Then, the SNPs were LD pruned with $r^2 = 0.1$ in a 1000 kb window, 324,982 SNPs were left after the pruning. And we utilized Plink 1.9 to calculate the weighted PRS of AD using SNPs with AD association of $p < 10^{-4}$.

Statistical methods

In the following, we first seek for the operational definition of the cognitive reserve by applying a logistic regression model on the baseline data. Second, we examine the prognostic value of the cognitive reserve proxy by applying the Cox proportional hazards model on the longitudinal data.

Logistic regression model for the computational proxy of cognitive reserve

We assume that the pathophysiology of AD is defined by the AD-specific biological changes (i.e., the increasing CSF tau/Aβ_{42} ratio), which underlines the clinic manifestations. However, the progression of AD is also moderated by socioeconomic statuses, such as education and occupation. In this regard, we conceptualize the mechanism of cognitive resilience as a joint product of pathology risk indicators and socioeconomic factors, where the resistant level can be captured by modeling the relationship between pathological burden and the clinical manifestation of cognitive decline.

Each subject has the diagnostic label where $y = 1$ indicates being diagnosed as AD and otherwise $y = 0$. The response of our model is the probability of being diagnosed as AD with logit link function, i.e., $\log it(P(y = 1) = \log\left(\frac{p(y=1)}{1-p(y=1)}\right)$, which is modeled as a linear function of age, gender, education, occupation, tau/Aβ_{42} ratio, and AD PRS. In order to measure the counteract of cognitive reserve, we also included the interactions between AD pathology and educational levels in the model. The logistic model was represented as:

$$\begin{aligned} logit(P(y_i = 1)) &= \beta_0 + \beta_1 x_{Age,i} + \beta_2 x_{Gender,i} \\ &+ \beta_3 x_{Mid\_Edu,i} + \beta_4 x_{High\_Edu,i} + \beta_5 x_{Mid\_Occ,i} \\ &+ \beta_6 x_{High\_Occ,i} + \beta_7 x_{PA,i} + \beta_8 x_{PRS,i} \\ &+ \beta_9 (x_{PA,i} \cdot x_{Mid\_Occ,i}) \\ &+ \beta_{10} (x_{PA,i} \cdot x_{High\_Occ,i}) \end{aligned} \quad (1)$$

where $x_{Age,i}$ is age (in years), $x_{Gender,i}$ is gender (male: 1; female: 0), $x_{PA,i}$ is pathological burden measured by CSF tau/Aβ_{42} ratio, and $x_{PRS,i}$ is AD

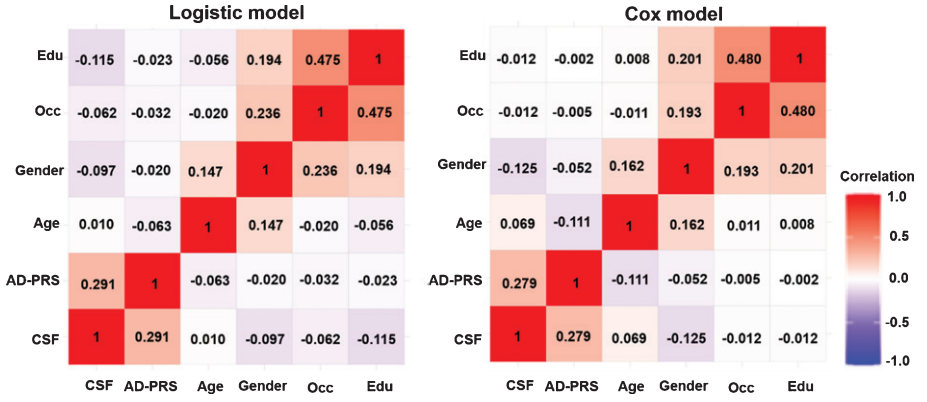

Fig. 2. The correlation heap map of demographic data for the logistic model (left) and Cox model (right).

polygenetic risk score for the i^{th} subject. Educational levels and occupational levels were categorized into three levels, and we used dummy coding for all the categorical variables. Female, low educational level, and low occupational level were set as the reference group, respectively. $x_{High\_Edu,i}$ equals 1 if the i^{th} subject has a high educational level and equals 0 otherwise. $x_{Mid\_Edu,i}$ equals 1 if the subject i has the medium educational level, and equals 0 otherwise. So are $x_{Mid\_Occ,i}$ and $x_{High\_Occ,i}$. The odds ratio (OR) quantifies the expected change in the odds of being diagnosed as AD, for a one-unit increase in the predictor. The area under the curve (AUC) for receiver operating characteristic (ROC) was calculated to access the logistic model's performance. Nagelkerke pseudo R-Squared was used to evaluate the goodness-of-fit of logistic models. Since educational levels are correlated with occupational levels (please see the correlation analysis in Fig. 2), we additionally conducted a sensitivity analysis by excluding occupational levels from the logistic model.

Cox model for investigating the influence of cognitive reserve

The Cox proportional hazards model is used to investigate possible factors that affect the progression from MCI to AD longitudinally for subjects with a baseline diagnosis of MCI. Specifically, the time (in months) is defined as the time between baseline visit and the first visit date of being diagnosed as AD for participants as known as MCI-converter. For participants whose progression remains at MCI stage (as known as non-converter), the time is defined from the baseline visit date to the last visit date. We use the same predictors as those in the logistic model. The Cox model is represented as:

$$h(t) = \lim_{\Delta t \to 0+} \frac{P(t \le T < t + \Delta t | T \ge t)}{\Delta t}$$

$$\begin{aligned} h_i(t|x_i) = h_0(t) \exp(&\beta_0 + \beta_1 x_{Age,i} + \beta_2 x_{Gender,i} \\ &+ \beta_3 x_{Mid\_Edu,i} + \beta_4 x_{High\_Edu,i} + \beta_5 x_{Mid\_Occ,i} \\ &+ \beta_6 x_{High\_Occ,i} + \beta_7 x_{PA,i} + \beta_8 x_{PRS,i} \\ &+ \beta_9 (x_{PA,i} \cdot x_{Mid\_Occ,i}) \\ &+ \beta_{10} (x_{PA,i} \cdot x_{High\_Occ,i})) \end{aligned} \quad (2)$$

where T denotes for time, $h(t)$ is the hazard function (instantaneous rate for progression to AD to occur for subjects that have survived up to time t), $h_i(t|x_i)$ was the hazard function at time t for the i^{th} participant, $h_0(t)$ was the unspecified baseline hazard function when all predictors are 0, and others are the same as the logistic model. The hazard ratio (HR) quantifies the relative hazard of progression from MCI to AD with a one-unit increase in the predictor. $HR > 1$ indicates that the progression hazard increased with a larger value of the predictor. Similarly, we additionally conducted a sensitivity analysis by excluding occupational levels from the Cox model.

RESULTS

Demographic data

We show the demographic characteristics of participants in the logistics model and the Cox model in Table 1, where data are presented in mean (std) for continuous variables and in (%) for categorical variables. For participants in the logistic model, the average age at baseline is 73.82 years old, 55.79% are male, 8.77% have a professional or managerial

Table 1
Demographic characteristics of participants in the logistics analysis and survival analysis

Models	Logistic Model, $N = 889$			Cox Model, $N = 531$		
	Total ($n = 889$)	AD ($n = 217$)	Non-AD ($n = 672$)	Total ($n = 531$)	MCI convert ($n = 211$)	Non-convert ($n = 320$)
Age	73.82 (7.18)	74.75 (8.17)	73.52 (6.81)	72.8 (7.50)	73.52 (7.35)	72.32 (7.57)
Gender						
Male	496 (55.79)	125 (57.60)	371 (55.21)	320 (60.26)	130 (61.61)	190 (59.38)
Female	393 (44.21)	92 (42.40)	301 (44.79)	211 (39.74)	81 (38.39)	130 (40.63)
Occupation						
Low	78 (8.77)	29 (13.36)	49 (7.29)	45 (8.47)	16 (7.58)	29 (9.06)
Medium	292 (32.85)	70 (32.26)	222 (33.04)	183 (34.46)	75 (35.55)	108 (33.75)
High	519 (58.38)	118 (54.38)	401 (59.67)	303 (57.06)	120 (56.87)	183 (57.19)
Education						
Low	247 (27.78)	81 (37.33)	166 (24.70)	165 (31.07)	63 (29.86)	102 (31.88)
Medium	307 (34.54)	76 (35.02)	231 (34.38)	168 (31.64)	72 (34.12)	96 (30.00)
High	335 (37.68)	60 (27.65)	275 (40.92)	198 (37.29)	76 (36.02)	122 (38.12)
tau/Aβ_{42}	0.6536 (0.5090)	0.9786 (0.5460)	0.5486 (0.4490)	0.6557 (0.5242)	0.8605 (0.5412)	0.5207 (0.4666)
AD PRS	0.0346 (0.9838)	0.3046 (0.9565)	–0.0526 (0.9773)	0.0509 (1.0036)	0.2074 (1.0589)	–0.0524 (0.9532)

Table 2
The statistical summary of the logistic regression model

Predictors	Coefficient	Std.	Odds ratio (95% CI)	p
Age	$\beta_1 = 0.022$	0.012	1.022 (0.999, 1.047)	0.065
Gender	$\beta_2 =$ **0.395**	**0.187**	**1.484 (1.029, 2.143)**	**0.035**
Medium education	$\beta_3 = 0.568$	0.433	1.765 (0.754, 4.125)	0.190
High education	$\beta_4 = 0.259$	0.450	1.296 (0.536, 3.133)	0.565
Medium occupation	$\beta_5 = -0.554$	0.314	0.575 (0.310, 1.063)	0.077
High occupation	$\beta_6 = -0.375$	0.320	0.687 (0.367, 1.287)	0.241
tau/Aβ_{42}	$\beta_7 =$ **2.482**	**0.384**	**11.965 (5.641, 25.381)**	**<0.001**
AD PRS	$\beta_8 = 0.160$	0.092	1.174 (0.981, 1.405)	0.081
tau/Aβ_{42} × Med. education	$\beta_9 =$ **−1.199**	**0.465**	**0.301 (0.121, 0.750)**	**0.010**
tau/Aβ_{42} × High education	$\beta_{10} =$ **−1.240**	**0.480**	**0.289 (0.113, 0.742)**	**0.010**

occupation, and 27.78% have years of education longer than 17 years. Among 889 participants, 217 (24.41%) patients are diagnosed as AD at baseline visit. Regarding the statistical difference between AD and non-AD group, participants of AD group had larger tau/Aβ_{42} ratio ($t = 10.51$, $p < 0.001$) and AD PRS ($t = 4.76$, $p < 0.001$) than non-AD group.

For participants in the Cox model, the average age at baseline is 72.80 years old, 60.26% are male, 8.47% have the professional or managerial occupation, and 31.07% have years of education longer than 17 years. Among 531 participants, 211 (39.74%) are MCI convertors, which have greater tau/Aβ_{42} ratio ($t = 7.47$, $p < 0.001$) and AD PRS ($t = 2.88$, $p = 0.004$) than non-convertors. For the logistic model, AD and Non-AD are defined by baseline diagnosis. For the Cox model (right columns in Table 1), the label MCI convert means participants developing AD from MCI during the study, and non-convert means participants remaining at MCI stage.

The correlation heatmaps of the demographic data used in the logistical model and Cox model are displayed in the left and right of Fig. 2, respectively. It is clear that education and occupation exhibit the highest correlation, followed by the correlation between AD-PRS and the CSF biomarker. It is worth noting that neither education nor occupation shows a positive correlation with the biological indicators (AD-PRS) and pathological burden. Although the magnitude of the correlation is small, the anti-correlation relationship partially supports the biological intuition of characterizing cognitive reserve through modeling the interaction between socioeconomic factors and AD risk factors.

Computational proxy of cognitive reserve

Significance testing

The statistical testing results of our logistic model (in Eq. 1) are summarized in Table 2. First, we observed significant effects ($p < 0.05$) of gender, tau/Aβ_{42} ratio, and interaction between tau/Aβ_{42} ratio and educational levels on being diagnosed as AD. Second, the likelihood ratio test showed that the

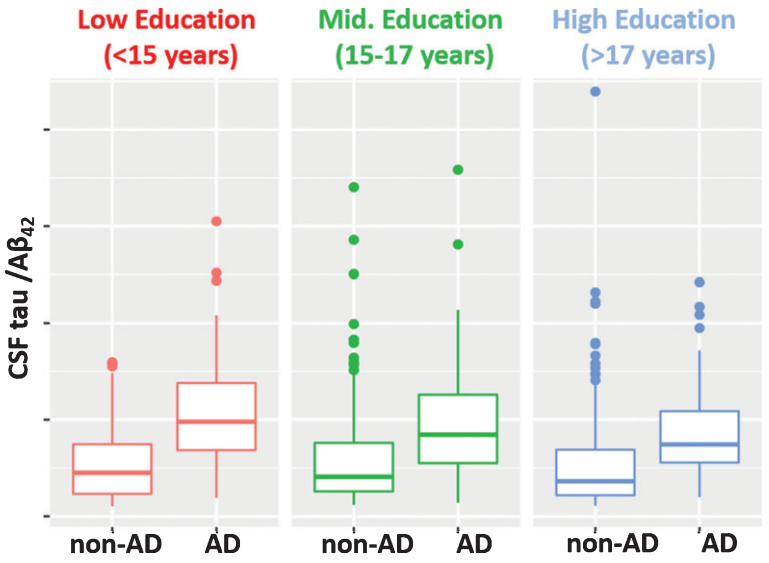

Fig. 3. The boxplot of tau/Aβ_{42} ratio stratified by baseline diagnostic and educational levels.

prediction of being diagnosed as AD based on our model with interaction terms is stronger than prediction without interaction (Chi-Square = 8.8533, $p = 0.012$). Third, males are more likely to be diagnosed as AD compared to females ($p = 0.035$), where the odds of being diagnosed as AD for males is 1.484 (95% CI 1.029–2.143) times of the odds for females. Fourth, tau/Aβ_{42} ratio is a significant risk factor of being diagnosed as AD ($p < 10^{-3}$). However, the effect of CSF tau/Aβ_{42} ratio decreases as the educational level increases, which is strongly suggested by the significant negative interaction coefficients (β_9 and β_{10}). Specifically, the odds of being diagnosed as AD increase by 11.965 (95% CI 5.641–25.381) times with an increase of one unit of tau/Aβ_{42} ratio for the low educational level group (<15 years), 3.607 times for the medium educational level group (15–17 years), and 3.463 times for the high educational level group (>17 years).

Computational definition of cognitive reserve

Our model shows that participants with higher educational level are less likely to be diagnosed as AD and have high resilience to pathology burden compared to lower educational level after controlling for tau/Aβ_{42} ratio. As shown in Fig. 3, the difference of tau/Aβ_{42} ratio between participants with AD and non-AD diagnosis at baseline visit has been attenuated with higher educational levels. Since the interaction between AD pathology and education not only pass significant testing but also exhibit negative estimations, cognitive reserve can be defined as the multiplication of CSF tau/Aβ_{42} and categorical education label. As a result, our new cognitive reserve can be calculated for each subject as follows: 1) If the underlying subject received less than 15 years of education, the cognitive reserve is zero since our model takes the low education group as the reference; 2) If the subject's education attendance is between 15 and 17 years, the cognitive reserve is $-1.199 \times$ CSF (tau/ Aβ_{42} ratio); 3) if the subject received more than 17 years of education, the cognitive reserve is $-1.24\times$ CSF (tau/Aβ_{42} ratio). Note, the negative value reflects the fact that cognitive reserve acts as a moderating role in counteracting the progression of AD pathology (positive value).

DISCUSSION

Age, occupational levels, and AD-PRS show moderate significance ($0.05 < p < 0.1$) in our statistical model. The AUC for logistic model with the interaction term (parameterized by β_9 or β_{10}) is 0.78 (0.62% higher than that of the model without interaction terms), which indicates the interaction between tau/Aβ_{42} ratio and educational levels has a better capability of distinguishing between AD and non-AD. Specifically, the Nagelkerke pseudo R-Squared for logistic model with interaction is 22.53%, and the Nagelkerke pseudo R-Squared for logistic model without interaction is 21.26%. In conclusion, the interaction is significant; however,

Table 3
The statistical summary of the logistic regression model without occupational levels

Predictors	Coefficient	Std	Odds ratio (95% CI)	p
Age	$\beta_1 = 0.023$	0.012	1.023 (0.999, 1.048)	0.060
Gender	$\boldsymbol{\beta_2 = 0.404}$	**0.184**	**1.498 (1.044, 2.148)**	**0.028**
Medium education	$\beta_3 = 0.526$	0.427	1.692 (0.733, 3.908)	0.219
High education	$\beta_4 = 0.257$	0.431	1.293 (0.556, 3.009)	0.551
tau/Aβ_{42}	$\boldsymbol{\beta_7 = 2.483}$	**0.382**	**11.977 (5.665, 25.323)**	**<0.001**
AD PRS	$\beta_8 = 0.156$	0.091	1.169 (0.978, 1.397)	0.086
tau/Aβ_{42} × Med-Edu	$\boldsymbol{\beta_9 = -1.195}$	**0.463**	**0.303 (0.122, 0.750)**	**0.010**
tau/Aβ_{42} × High-Edu	$\boldsymbol{\beta_{10} = -1.260}$	**0.478**	**0.284 (0.111, 0.724)**	**0.008**

Table 4
The results of Cox proportional hazards model

Variable	Coefficient	Std	Hazard ratio (95% CI)	p
Age	$\boldsymbol{\beta_1 = 0.023}$	**0.010**	**1.023 (1.003, 1.044)**	**0.027**
Gender	$\beta_2 = 0.125$	0.151	1.133 (0.844, 1.523)	0.406
Medium education	$\beta_3 = 0.111$	0.273	1.117 (0.654, 1.906)	0.685
High education	$\beta_4 = -0.390$	0.295	0.677 (0.380, 1.206)	0.185
Medium occupation	$\beta_5 = -0.138$	0.283	0.871 (0.501, 1.516)	0.626
High occupation	$\beta_6 = -0.173$	0.289	0.841 (0.478, 1.480)	0.548
tau/Aβ_{42}	$\boldsymbol{\beta_7 = 0.524}$	**0.191**	**1.689 (1.161, 2.455)**	**0.006**
AD-PRS	$\beta_8 = 0.100$	0.072	1.105 (0.960, 1.273)	0.166
tau/Aβ_{42} × Medium education	$\beta_9 = 0.143$	0.238	1.154 (0.724, 1.839)	0.548
tau/Aβ_{42} × High education	$\boldsymbol{\beta_{10} = 0.673}$	**0.268**	**1.960 (1.160, 3.310)**	**0.012**

the gain of modeling additional variability over the logistic model without interaction term is marginal. Comparing the regression result in Table 2 (with modeling occupation) and Table 3 (without modeling occupation), the interaction term between tau/Aβ_{42} and educational levels still shows significance ($p < 0.01$).

Understand the role of cognitive reserve by longitudinal analysis

Significance testing in Cox model

The statistical results of the Cox model are summarized in Table 4. Without doubt, age is the significant factor of cognitive decline ($p = 0.027$). Specifically, our Cox model shows that an increase of one year of aging results in 1.023 (95% CI 1.003–1.044) times increasement of the hazard (progression from MCI to AD). Since CSF biomarker is the hallmark of neurodegenerative process, the tau/Aβ_{42} ratio also exhibits a strong significance in determining the neurodegeneration ($p = 0.006$). Besides these two determinant factors, our cognitive reserve proxy defined in our statistical model also shows significant effects ($p = 0.012$) in moderating the trajectory of cognitive decline, which suggests the association between the hazard of progression to AD and tau/Aβ_{42} ratio depended on educational levels.

The role of cognitive reserve in AD

After fitting the parameters in our Cox model, we can quantitatively investigate the influence of cognitive reserve (i.e., interaction of tau/Aβ_{42} and education) in moderating neurodegeneration. As the log-slope shows in Fig. 4, an increase of one unit of tau/Aβ_{42} results in 1.689 (95% CI 1.161–2.455) times of the hazard of converting to AD for the low educational level group (red line), 1.948 (95% CI 1.450–2.616) times for the medium educational level group (green line), and 3.310 (95% CI 2.243–4.879) times for the high educational level group (blue line), respectively. Furthermore, the plot of log-hazard function in Fig. 4 suggests that participants with higher educational level have smaller hazard of progression from MCI to AD before the pathology burden reaches the tipping point. However, the education advantage shows downside after the tipping point, where the risk of converting to AD in the high education group grows much faster than low education group.

Discussion

The likelihood ratio test showed that prediction of progression from MCI to AD based on model with interaction was stronger than prediction without interaction (Chi-Square = 6.8023, $p = 0.0333$). The concordance index for the model with interaction is

0.675, while the concordance index for the model without interaction is 0.669. The model with interaction has a better predictive ability than the model without interaction. Furthermore, we apply the Cox model without including the occupation level on the same longitudinal dataset. Compared to the Cox model with occupation level, the statistical results in Table 5 suggests that our cognitive reserve proxy (the interaction between tau/Aβ_{42} and educational levels) shows consistent effect with and without considering occupation.

DISCUSSION

In this paper, we present an operational definition for measuring cognitive reserve by investigating the relationship between clinical data, CSF biomarker, and SES in the aging population. In general, our statistical model suggests that 1) the high education group has the advantage in preserving cognition compared to the low education group; 2) the education advantage has the downside of more rapid neurodegeneration after the pathological burden is beyond the tipping point.

Converging evidence shows that the individual's neurodegeneration trajectory is not only regulated by the abnormal deposition of pathology burden but also moderated by the brain's capability to maintain normal cognition [30, 32–34, 59]. In current cognitive studies [30, 34, 47, 59], SES in factors of education, wealth, and occupation are widely used as the proxy to measure cognitive reserve. One possible explanation regarding the role of SES factors in cognitive reserve is neural compensation [34], where task-related activation occurs in the presence of structural brain changes, and this may results in improved performance for those who compensate.

In our previous work, we found education exhibits a strong association with cognitive reserve [60]. Figure 5 shows the scatter plot of the dementia stage (quantified by ADAS-Cog 11 [61]) versus whole-brain neurodegeneration burden (measured in tau/Aβ_{42} biomarker). We used a linear regression model to fit the latent relationship for relatively higher education (in red) and relatively lower education (in

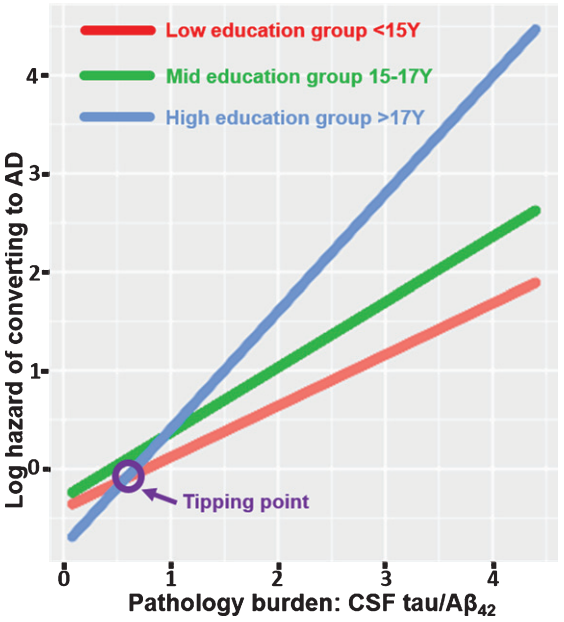

Fig. 4. AD risk curves of neuropathology burden in three education groups.

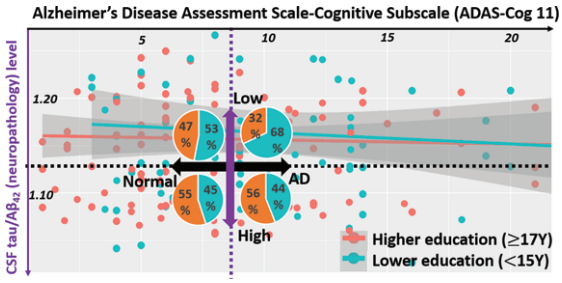

Fig. 5. Individual differences in the relationship between neuropathology level and clinic score with respect to education level.

Table 5
The results of Cox proportional hazards model excluding occupational levels

Variable	Coefficient	Std.	Hazard ratio (95% CI)	p
Age	$\boldsymbol{\beta_1 = 0.023}$	**0.010**	**1.023 (1.003, 1.044)**	**0.027**
Gender	$\beta_2 = 0.118$	0.150	1.125 (0.839, 1.510)	0.431
Medium education	$\beta_3 = 0.086$	0.269	1.090 (0.643, 1.846)	0.748
High education	$\beta_4 = -0.428$	0.284	0.652 (0.374, 1.137)	0.132
tau/Aβ_{42}	$\boldsymbol{\beta_7 = 0.525}$	**0.190**	**1.690 (1.165, 2.453)**	**0.006**
AD-PRS	$\beta_8 = 0.100$	0.072	1.105 (0.960, 1.273)	0.164
tau/Aβ_{42} × Med education	$\beta_9 = 0.139$	0.237	1.149 (0.722, 1.829)	0.557
tau/Aβ_{42} × High education	$\boldsymbol{\beta_{10} = 0.668}$	**0.267**	**1.950 (1.156, 3.291)**	**0.012**

blue) cohorts separately. The fitting for the higher education group shows a lower negative slope than the lower education group, suggesting that individuals with more educational attainment have the potential to reserve more neurodegeneration burdens at the same cognition level.

Regarding the neuroscience insight of our cognitive reserve proxy, our model assumes the AD-specific neuropathological changes (such as tau/Aβ_{42} biomarker) are the determinant factors in dementia progression, where SES factors (such as education and occupation) might moderate the trajectory of cognitive decline. To that end, our regression model in Eq. 1 is designed to characterize the interaction between the neurodegeneration process and environmental factors, which allows us to quantify the degree of cognitive reserve.

Although the definition of cognitive reserve works well for CSF biomarkers, there are several limitations. 1) Simple logistic model might not be less powerful to capture the non-linear relationship between clinical manifestations and neuropathological data. 2) The response is currently binarized to AD and non-AD. Since AD is a multi-factorial disease with heterogenous progression pathway, a fine-grained stratification (such as including early-MCI and late-MCI) is necessary to address the heterogeneity issue in AD. 3) AD-PRS does not show the strong effect in our model. The gloss simplification of the whole genome-wise polygenetic risk score might be the reason for the less sensitivity of AD-PRS. One possible solution is the pathway-specific PRS [62], which is the weighted effect from the preselected AD risk genes.

Mounting evidence shows that AD pathologies preferentially affect the aging brain [63–66]. We will further extend this computational framework of the cognitive reserve from CSF biomarkers to amyloid and tau PET imaging, which will allow us to measure cognitive reserve for each anatomical region and understand the spatial association with the development of neuropathology burden.

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