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Relationship of cognitive reserve and cerebrospinal fluid biomarkers to the emergence of clinical symptoms in preclinical Alzheimer's disease

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ABSTRACT

The levels of β-amyloid (Aβ) and phosphorylated tau (p-tau), as measured in cerebrospinal fluid, have been associated with the risk of progressing from normal cognition to onset of clinical symptoms during preclinical Alzheimer's disease. We examined whether cognitive reserve (CR) modifies this association. Cerebrospinal fluid was obtained at baseline from 239 participants (mean age, 57.2 years) who had been followed for up to 17 years with clinical and cognitive assessments (mean follow-up, 8 years). A composite score based on the National Adult Reading Test, vocabulary, and years of education at baseline was used as an index of CR. Cox regression models showed that the increased risk of progressing from normal cognition to symptom onset was associated with lower CR, lower baseline Aβ, and higher baseline p-tau. There was no interaction between CR and Aβ, suggesting that the protective effects of higher CR are equivalent across the observed range of amyloid levels. In contrast, both tau and p-tau interacted with CR, indicating that CR was more protective at lower levels of tau and p-tau.

1. Introduction

Alzheimer's disease (AD) is the most common cause of cognitive decline and dementia among adults. It is characterized pathologically by the presence of β-amyloid (Aβ) plaques and tau tangles in the brain. There is substantial evidence that amyloid and tau begin to accumulate a decade or more before the onset of dementia when individuals are still cognitively normal (Jack et al., 2013; Sperling et al., 2011). In fact, about one-third of older adults who are cognitively normal at the time of death meet pathologic criteria for possible or probable AD (Bennett et al., 2006; Hulette et al., 1998; Knopman et al., 2003), and a similar proportion of adults have abnormal levels of Aβ protein, as measured by amyloid imaging or cerebrospinal fluid (CSF) assessment (De Meyer et al., 2010; Morris et al., 2010; Reiman et al., 2009; Rowe et al., 2010).

The concept of cognitive reserve (CR) has been proposed as an explanation for individuals with similar levels of AD pathology who can differ markedly in the clinical manifestation of that pathology, with some individuals being symptom free and others showing cognitive impairment. CR is a theoretical construct that postulates that certain lifetime experiences, including education, occupational breadth and complexity, and engagement in activities that are cognitively and socially stimulating, increase the efficiency, capacity, and flexibility of brain networks. As a result, individuals with higher levels of CR are thought to be able to sustain greater levels of brain pathology before showing clinically significant levels of impairment (see Stern, 2009 for a review). In support of the concept of CR, many epidemiologic studies have shown that the risk of dementia is reduced among individuals with more education (e.g., Fitzpatrick et al., 2004; Stern et al., 1994), higher literacy (e.g., Manly et al., 2005), greater occupational attainment (e.g., Andel et al., 2005; Stern et al., 1994), and higher levels of engagement in cognitively and socially stimulating activities (e.g., Scarmeas et al., 2001; Wilson et al., 2002). In addition, cross-sectional studies of non-demented and demented individuals have reported that CR, as measured by education or literacy, modifies the relationship between AD pathology and cognition, such that the effects of pathology on cognition are reduced in individuals with higher CR (Bennett et al., 2003, 2005; Rentz et al., 2010; Roe et al., 2008a, 2008b; Vemuri et al., 2011).

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Few studies, however, have examined the degree to which CR may modify the effect of specific AD biomarkers on the risk of developing cognitive impairment among individuals who are still cognitively normal. For example, one study suggests that among cognitively normal individuals with higher levels of CSF total tau (t-tau) and phosphorylated tau (p-tau), more education is associated with reduced time to incident cognitive impairment (e.g., a Clinical Dementia Rating score of 0.5 or above) over a mean interval of approximately 3 years (Roe et al., 2011a). Likewise, in a community sample of nondemented older adults, CR was found to modify the association between plasma $A\beta_{40/42}$ and cognitive decline, such that a low level of plasma $A\beta_{40/42}$ was a greater risk factor for cognitive decline over a 9-year period in individuals with lower CR, compared with those with higher CR (Yaffe et al., 2011).

The present study addresses several issues that remain unresolved by these studies. First, only 1 study (Roe et al., 2011a) has examined the relationship among CR, CSF AD biomarkers (i.e., CSF $A\beta_{1-42}$, tau and p-tau), and the risk of progressing from normal cognition to incident cognitive impairment, but the follow-up time in that study was relatively short (an average of 3 years). Second, little is known about how CR and CSF AD biomarkers in middle age are related to subsequent cognitive decline because most studies have tended to enroll individuals older than the age of 70 years. The present study reports on individuals who were primarily middle-aged at baseline (mean age, 56.9 years) and have been followed for up to 17 years (mean, 8 years). Third, previous longitudinal studies (Roe et al., 2011a; Yaffe et al., 2011) have used education as a proxy for CR, although education is static and unlikely to change after early adulthood. The present study used a composite measure of CR based on not only education but also literacy and vocabulary, which may change over the lifetime and be a better reflection of CR (Manly et al., 2003, 2005). Fourth, it remains unclear whether the degree to which CR modifies the onset of clinical symptoms varies with the level of CSF biomarkers. Current theoretical models suggest that CR may be more effective in mediating the association between pathology and its clinical progression when pathology levels are low rather than high (Stern, 2009). Additionally, some cross-sectional studies suggest that the protective effect of CR may be more closely associated with Aβ pathology than tau pathology (e.g., Bennett et al., 2005; Roe et al., 2008b; Sole-Padulles et al., 2011), but this hypothesis has not been prospectively examined in cognitively normal adults. Finally, no study, to our knowledge, has examined whether CR modifies the relationship between the rates of change of CSF biomarkers over time and the risk of developing clinical symptoms. The present study examines if the rate of change in these CSF biomarkers differs as a function of CR.

2. Methods

2.1. Study design

The overall study was designed to recruit and follow a cohort of cognitively normal individuals who were primarily in middle age at baseline. By design, approximately three-quarters of the participants had a first degree relative with a history of dementia of the Alzheimer type. The overarching goal was to identify variables among cognitively normal individuals that could predict the subsequent development of mild to moderate symptoms of AD. The participants were administered a comprehensive neuropsychological battery annually. Magnetic resonance imaging (MRI) scans, CSF, and blood specimens were obtained approximately every 2 years. The study was initiated at the National Institutes of Health (NIH) in 1995, and was stopped in 2005 for administrative reasons. In 2009, a research team at the Johns Hopkins School of Medicine was funded to re-establish the cohort, continue the annual clinical and cognitive assessments, collect blood, and evaluate the previously acquired MRI scans, CSF, and blood specimens. CSF and MRI scans have not been collected since the study has been at Johns Hopkins, because of limitations in funding, but future collection is planned.

2.2. Selection of participants

A total of 349 individuals were initially enrolled in the study, after providing written informed consent. CSF was obtained from 307 participants via lumbar puncture at the baseline visit. Of these 307 participants, 199 had additional lumbar punctures in subsequent years. The analyses presented here are based on 239 of the 307 participants who provided baseline CSF (see Supplementary data for reasons for excluding specific groups of participants). Recruitment was conducted by the staff of the Geriatric Psychiatry branch of the intramural program of the National Institute of Mental Health. Participants were enrolled over time, beginning in 1995 and ending in 2005. The participants were recruited via printed advertisements, articles in local or national media, informational lectures, or word-of-mouth. At baseline, all participants completed a comprehensive evaluation at the Clinical Center of the NIH. This evaluation consisted of a physical and neurologic examination, an electrocardiogram, standard laboratory studies, and neuropsychological testing. Individuals were excluded from participation if they were cognitively impaired, as determined using cognitive testing, or had significant medical problems such as severe cerebrovascular disease, epilepsy, or alcohol or drug abuse (see Supplementary data for details regarding the evaluation of participants at enrollment.).

2.3. CSF assessments

The CSF specimens were analyzed by the current group of investigators using the same protocol used in the Alzheimer's Disease Neuroimaging Initiative. This protocol used the xMAP-based AlzBio3 kit (Innogenetics, Ghent, Belgium) run on the Bioplex 200 system. The kit contains monoclonal antibodies specific for $A\beta_{1-42}$ (4D7A3), t-tau (AT120), and p-tau_{181p} (AT270), each chemically bonded to unique sets of color-coded beads, and analyte-specific detector antibodies (HT7 and 3D6). Calibration curves were produced for each biomarker using aqueous buffered solutions that contained the combination of 3 biomarkers at concentrations ranging from 25 to 1555 pg/mL for recombinant tau, 54–1,799 pg/mL for synthetic $A\beta_{1-42}$ peptide, and 15–258 pg/mL for a tau synthetic peptide phosphorylated at the threonine 181 position (i.e., the p-tau181p standard). Each participant had all samples (run in triplicate) analyzed on the same plate (see Supplementary data for details regarding the performance characteristics of the assay; additional details have been published in Moghekar et al., 2012.).

2.4. Clinical and cognitive assessment

The annual cognitive assessment consisted of a neuropsychological battery covering all major cognitive domains (see Albert et al., unpublished data, for the contents of the neuropsychological battery). A clinical assessment was also completed annually. Since the study has been conducted at Johns Hopkins, the clinical evaluation has included the following: a physical and neurologic examination, record of medication use, behavioral and mood assessments (Cummings et al., 1994; Yesavage et al., 1982), family history of dementia, history of symptom onset, and a Clinical Dementia Rating, based on a semistructured interview (Hughes et al., 1982; Morris, 1993). The clinical assessments given at the NIH covered similar domains.

2.5. CR composite score

We created a CR composite score based on 3 measures that were thought to reflect CR: (1) baseline scores on the National Adult Reading Test (Nelson, 1982); (2) baseline scores on the Wechsler Adult Intelligence Scale-Revised vocabulary subtest (Wechsler, 1981); and (3) years of education. These 3 measures were highly correlated with each other and loaded on a single factor (see Supplementary data for details of the factor analysis). To calculate the CR composite score, these individual measures were transformed to *z* scores and then averaged. The use of CR composite scores such as these has been shown to have construct validity and be preferable to using a single measure (Siedlecki et al., 2009).

2.6. Consensus diagnoses

Each study participant received a consensus diagnosis that was handled in a similar manner: (1) clinical data pertaining to the medical, neurologic, and psychiatric status of the participant were examined; (2) reports of changes in cognition by the participant and collateral sources were reviewed; and (3) decline in cognitive performance, based on review of longitudinal testing from multiple domains, was established (test scores were compared with standardized norms; however, cut points were not used.). First, a determination was made concerning whether the participant was impaired. Second, if the participant was impaired, the likely etiology of the impairment was identified. These 2 decisions were based on the 3 sources of information mentioned previously. Then, the age at which the clinical symptoms began was estimated, based primarily on the reports of the participant and collateral source. In many instances, the estimated age of onset of clinical symptoms preceded the date of diagnosis. This diagnostic method is comparable with the procedures used in the National Institute on Aging Alzheimer's Disease Centers program. The clinical diagnoses were made blinded to the results of CSF analyses (see Supplementary data for further details regarding the evaluation of the participants and the diagnostic procedures.).

2.7. Statistical methods

2.7.1. Baseline CR in relation to baseline CSF biomarkers and rate of change in CSF biomarkers

First, we tested whether there was an association between baseline CR and CSF biomarker values (obtained from the participants when they were first enrolled and cognitively normal). To do so, linear regressions were conducted separately for each of the 5 biomarker measures (i.e., $A\beta_{1-42}$, t-tau, p-tau, p-tau/$A\beta_{1-42}$, and p-tau/$A\beta_{1-42}$), with the CSF biomarker as the dependent variable and the CR composite score, age at baseline, and gender as independent variables. Second, we examined if baseline CR was predictive of the rate of change in CSF biomarkers over time to determine if CR influences the rate of biomarker accumulation. The rate of change was calculated as the difference in CSF measurements between the last follow-up and the baseline visits, divided by the corresponding difference in time. Linear regression analyses were performed separately for each of the 5 biomarkers, with the rate of change in the CSF value as the dependent variable and the CR composite score, baseline CSF value, age at baseline, and sex as independent variables.

2.7.2. Baseline CR and baseline CSF biomarkers in relation to time to onset of clinical symptoms

These analyses were designed to determine whether the CR composite score, in combination with the baseline CSF measures, was associated with the time to onset of clinical symptoms. Data from 2 groups were included, based on the diagnosis at their last visit: (1) participants who remained cognitively normal ($n = 186$) and (2) participants who received a diagnosis of mild cognitive impairment (MCI) or dementia ($n = 53$). A set of Cox regression analyses were performed for each CSF biomarker, using baseline CSF value, CR, and the interaction between the baseline CSF value and the CR composite score as predictors and age at onset of clinical symptoms as the outcome variable. The censoring time was defined as the last date of diagnosis. Because participants were required to be symptom-free at baseline, we adjusted for left truncation in the data (Wang et al., 1993). For models in which the interaction was significant, separate Cox regression analyses were performed for participants with CSF biomarker values at or greater than the median versus less than the median. The goal of these post hoc comparisons was to determine the difference in the association between the CR and the risk of progression for participants with high levels compared with those with low levels of the CSF biomarker. All models included terms adjusting for age at baseline and gender.

2.7.3. Baseline CR and longitudinal CSF biomarkers in relation to time to onset of clinical symptoms

Previous analyses demonstrated a differential rate of change in the ratios of CSF t-tau/$A\beta_{1-42}$ and CSF p-tau/$A\beta_{1-42}$ in cognitively normal participants who later develop clinical symptoms and subsequent MCI (data not shown). Therefore, a second set of Cox regression analyses was conducted to determine whether the time-dependent rate of change in these ratios, in combination with CR, was associated with the time to onset of clinical symptoms. The outcome variable in these analyses was age of onset of clinical symptoms, and the predictors were the baseline CSF values (t-tau/$A\beta_{1-42}$ or p-tau/$A\beta_{1-42}$), time-dependent rate of change in CSF values, CR composite score, as well as the interaction between the CR composite score and the time-dependent rate of change in CSF values, adjusting for baseline age and gender (the relationship of CR to time-dependent rate of change in $A\beta_{1-42}$, t-tau, and p-tau was not examined because the rate of change of these biomarkers was not associated with the progression from normal cognition to onset of clinical symptoms in previous analyses; data not shown.). Details about how the rate of change was calculated are provided in the Supplementary data.

We also calculated hazard ratios (HRs) (i.e., the relative hazard) for each of the significant variables in the baseline models and the models examining rate of change over time. Before this analysis, the CSF values were converted to *z*-scores (i.e., scores with a mean of 0 and a standard deviation (SD) of 1, averaged over the scores for the normal participants), so that it would be possible to compare the HRs for each predictor with each other. The HR indicates the change in risk of progression per unit change in the predictor. For example, if the HR for CSF $A\beta_{1-42}$ is 0.69, the hazard of clinical symptom onset is reduced by a factor of 0.69 (i.e., 31%) for each SD increase in this CSF value. Likewise, if the HR for CSF p-tau is 1.51, the hazard of clinical symptom onset is increased by a factor of 1.51 (i.e., 51%) for each SD increase in this CSF value.

Group differences in demographic and baseline characteristics were assessed using 2-tailed *t* tests, with a significance level of $p < 0.05$, uncorrected for multiple comparisons (see Tables 1 and 2). All data analyses presented here used R, version 2.14.1.

3. Results

Of the 307 participants who provided CSF at baseline, 239 were included in the analyses involving baseline CSF measures, described in the following sections 3.1 and 3.3 (mean duration of follow-up, 8.03 years; SD, 3.42). Of these 239 participants, 152 provided

Table 1
Participant characteristics at baseline

Variable	Cohort as a whole ($N = 349$)	Subjects in analyses	
		At least 1 cerebrospinal fluid measure ($N = 239$)	More than 1 cerebrospinal fluid measure ($N = 152$)
Age, y	57.2 (10.3)	56.9 (10.1)	57.0 (10.6)
Gender, female (%)	58	62	59
Ethnicity, Caucasian (%)	97	97	97
ApoE-4 carrier (%)	34	39	38
MMSE, score	29.5 (0.9)	29.6 (0.9)	29.6 (0.8)
Education, y	17.0 (2.4)	17.1 (2.3)	17.1 (2.4)
NART-IQ	119.6 (7.9)	120.5 (7.6)	120.6 (7.1)
WAIS-R vocabulary subtest	14.2 (2.3)	14.4 (2.2)	14.6 (2.2)
Cognitive reserve composite score	0.0 (0.8)	0.1 (0.8)	0.1 (0.8)

The values are expressed as mean (SD) unless otherwise mentioned. There is no significant difference in baseline characteristics between groups (all $p > 0.05$).
Key: MMSE, Mini-Mental State Examination; NART-IQ, National Adult Reading Test; WAIS-R, Wechsler Adult Intelligence Scale-Revised.

multiple CSF measures over time and were included in the analyses involving time-dependent rate of change in CSF measures, described in the following sections 3.2 and 3.4. The mean interval between the baseline and the last follow-up CSF collection for those with multiple samples was 4.2 years, with an SD of 2.6 (mean number of samples per participant, 3.3; SD, 1.3; range, 2–7). The baseline characteristics for the cohort as a whole ($N = 349$), participants included in the baseline CSF analyses ($N = 239$), and those included in the rate of change CSF analyses ($N = 152$) did not differ (see Table 1).The reasons for exclusion of specific groups of participants are summarized in the Supplementary data.

Table 2 lists the characteristics of participants who remained normal at their last visit ($N = 186$) at baseline in the analyses versus those who subsequently received a diagnosis of MCI ($N = 42$) or dementia ($N = 11$, total $N = 53$). The mean time from baseline to onset of clinical symptoms for participants who developed symptoms was 5.41 (±3.21) years. Of the 152 participants with multiple CSF measures, 33 subsequently developed MCI or AD dementia (MCI, 23; AD dementia, 10). Analyses comparing subjects with a family history of dementia with those without will require longer follow-up because only one quarter of the cohort has no family history (see Supplementary data for details of the family history of dementia among the participants.).

Table 2
Baseline characteristics of participants in analyses stratified by outcomes

Variable	Remained normal ($N = 186$)	Progressed to MCI or AD ($N = 53$)
Age, y	55.4 (9.5)	62.0 (10.4)**
Gender, female (%)	63	58
Ethnicity, Caucasians (%)	99	91*
MMSE, score	29.5 (0.8)	29.4 (1.0)*
Education, y	17.2 (2.3)	16.7 (2.3)
NART-IQ	121.5 (6.4)	116.9 (10.1)
WAIS-R vocabulary subtest	14.7 (2.0)	13.3 (2.6)
Cognitive reserve composite score	0.20 (0.70)	−0.27 (0.90)**
$A\beta_{1-42}$, pg/mL	416.28 (92.8)	339.40 (114.8)
T-tau, pg/mL	64.29 (24.18)	94.63 (48.0)
P-tau_{181}, pg/mL	36.54 (12.89)	49.54 (23.79)
T-tau/$A\beta_{1-42}$	0.17 (0.14)	0.34 (0.27)
P-tau/$A\beta_{1-42}$	0.09 (0.09)	0.19 (0.16)

The values are expressed as mean (SD) unless otherwise mentioned.
Key: Aβ, β-amyloid; AD, Alzheimer's disease; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; NART, National Adult Reading Test; P-tau, phosphorylated tau; T-tau, total tau; WAIS-R, Wechsler Adult Intelligence Scale—Revised.
* $p < 0.05$; ** $p < 0.001$.

Table 3
Hazard ratios for baseline cerebrospinal fluid value and CR in relation to onset of clinical symptoms

Variable	Hazard ratio (95% confidence interval)	*p*-value
$A\beta_{1-42}$	0.69 (0.53–0.90)	0.0045
CR composite score	0.54 (0.40–0.72)	<0.0001
Interaction	0.96 (0.82–1.32)	n.s.
P-tau	1.50 (1.18–1.90)	0.00061
CR composite score	0.51 (0.37–0.68)	<0.0001
Interaction	1.41 (1.12–1.79)	0.0031
T-tau	1.17 (0.90–1.52)	n.s.
CR composite score	0.47 (0.34–0.64)	<0.0001
Interaction	1.52 (1.18–1.97)	0.001
P-tau/$A\beta_{1-42}$	1.10 (0.85–1.31)	n.s.
CR composite score	0.55 (0.40–0.71)	<0.0001
Interaction	1.02 (0.87–1.44)	n.s.
T-tau/$A\beta_{1-42}$	1.05 (0.92–1.30)	n.s.
CR composite score	0.54 (0.41–0.73)	<0.0001
Interaction	1.12 (0.84–1.23)	n.s.

Note: all models adjusted for baseline age and gender.
Key: Aβ, β-amyloid; CR, cognitive reserve; n.s., not significant at $p = 0.1$; P-tau, phosphorylated tau; T-tau, total tau.

3.1. Association of baseline CR and baseline CSF biomarker values

The linear regression analyses showed that after controlling for age at baseline and gender, there were no associations between the baseline CR composite score and CSF values for any of the 5 biomarkers (all $p > 0.3$).

3.2. Association of baseline CR and longitudinal rate of change of CSF biomarker values

Linear regression analyses revealed no associations between the baseline CR composite score and the rate of change in CSF values (all $p > 0.22$). The same pattern of results was obtained when the analyses were performed separately for participants who remained normal (all $p > 0.23$) and those who received a diagnosis of MCI or AD dementia (all $p > 0.12$).

3.3. Baseline CR and CSF in relation to time to onset of clinical symptoms

The results from the Cox regression models evaluating baseline CSF values, CR, and their interaction in relation to onset of clinical symptoms are listed in Table 3. CR was a significant predictor of the time to onset of clinical symptoms in all models. After accounting for baseline biomarker levels, each SD increase in CR was associated with approximately a 50% decrease in the risk of progressing from normal cognition to onset of clinical symptoms for each of the 5 biomarkers (all HR ≤ 0.55; all $p < 0.0001$).

For baseline $A\beta_{1-42}$, there was no interaction with CR. $A\beta_{1-42}$ and CR independently predicted the time to onset of clinical symptoms (both $p < 0.005$). This finding suggests that the effect of CR on the time to onset of clinical symptoms is equivalent across the observed range of CSF $A\beta_{1-42}$ levels. Each SD decrease in $A\beta_{1-42}$ was associated with a 31% increase in the risk of progressing from normal cognition to onset of clinical symptoms, and each SD increase in CR was associated with a 46% reduction in risk (Fig. 1B).

There were, however, significant interactions between baseline t-tau and CR ($z = 3.29$, $p = 0.001$) and baseline p-tau and CR ($z = 2.96$, $p = 0.003$) in relation to time to onset of clinical symptoms, indicating that the association between baseline t-tau and p-tau and

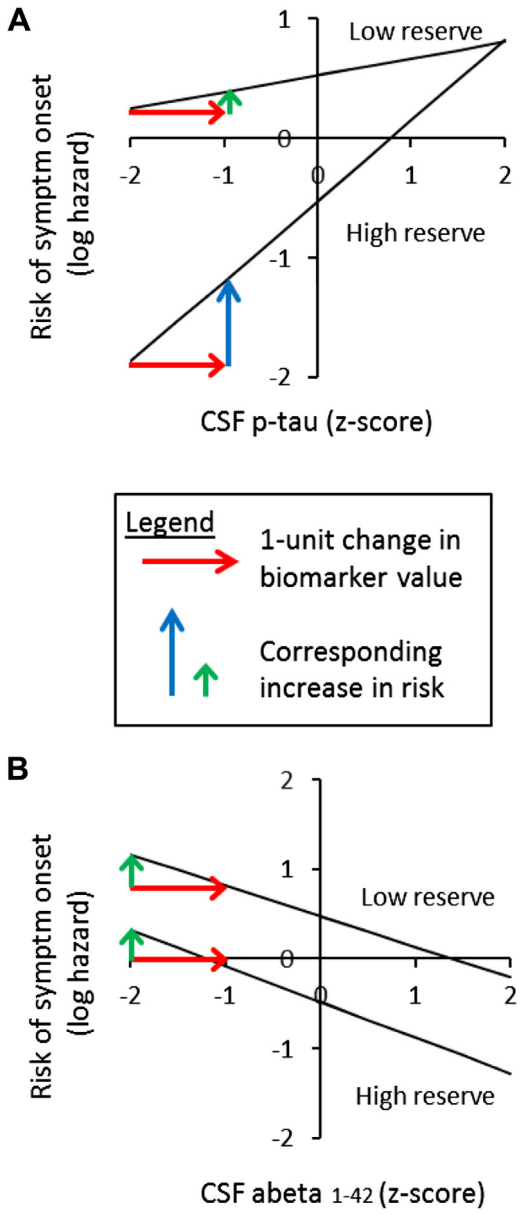

Fig. 1. Illustration of relationship between (A) CSF p-tau$_{181p}$ levels or (B) CSF Aβ_{1-42} levels and risk of onset of clinical symptoms preceding a diagnosis of mild cognitive impairment for individuals with higher CR (CR composite score at or above the median) and lower CR (CR composite score below the median), based on data from the present study. The x-axis represents the level of CSF p-tau (A) or CSF Aβ_{1-42} (B) in standard units (*z*-scores). The y-axis represents the log hazard from the Cox regression model that included baseline CSF values, CR, their interaction, age, and gender as predictors and age of onset of clinical symptoms as the outcome variable, as described in section 2.7.2. (A) For CSF p-tau, individuals with lower CR have a greater risk of symptom onset than those with higher CR, but the difference in risk between individuals with higher and lower CR decreases as CSF p-tau levels increase. For each unit increase in p-tau (red arrow), the risk of symptom onset increases more in individuals with higher CR (blue arrow) than that in individuals with lower CR (green arrow). (B) For CSF Aβ_{1-42}, the risk of symptom onset is equivalent for individuals with higher and lower CR, at each level of Aβ_{1-42}. Abbreviations: Aβ, β-amyloid; CR, cognitive reserve; CSF, cerebrospinal fluid; p-tau, phosphorylated tau.

onset of clinical symptoms is influenced by the level of CR. To clarify the meaning of this interaction effect, participants were split into 2 groups, 1 group with baseline t-tau and p-tau levels less than the median and the other group with baseline t-tau and p-tau levels at or greater than the median. Separate Cox regression models for the 2 groups indicated that in the low t-tau group, each SD increase in CR was associated with approximately a 67% reduction in the risk of progression, compared with 44% for the high t-tau group. Similarly, for the low p-tau group, the reduction in the risk of progression was 62% compared with 38% for the high p-tau group (see Table 4). This suggests that among individuals with low t-tau or p-tau at baseline, the reduction in risk of symptom onset associated with each SD increase in CR was approximately 20% greater than that among individuals with high levels of these biomarkers. Of note, there was no difference in CR at baseline between the high and the low p-tau groups ($p = 0.66$) and the high and the low t-tau groups ($p = 0.46$).

Table 4
Hazard ratio for CR composite score in relation to onset of clinical symptoms as a function of baseline t-tau and p-tau levels

Variable	Hazard ratio (95% confidence interval)	*p*-value
CR composite score in high p-tau group	0.62 (0.40–0.97)	0.035
CR composite score in low p-tau group	0.38 (0.19–0.74)	0.0035
CR composite score in high t-tau group	0.56 (0.34–0.91)	0.02
CR composite score in low t-tau group	0.33 (0.18–0.61)	0.0003

Note: all models were adjusted by baseline cerebrospinal fluid value, age at baseline, and gender.
Key: CR, cognitive reserve; p-tau, phosphorylated tau; t-tau, total tau.

The ratios of t-tau/Aβ_{1-42} and p-tau/Aβ_{1-42} at baseline were not associated with time to onset of clinical symptoms, and there were no significant interactions with CR and these ratios (see Table 3).

3.4. Baseline CR and longitudinal change in CSF in relation to time to onset of clinical symptoms

Cox regression models were performed to test whether baseline CR modifies the relationship between the rate of change in the ratios of t-tau/Aβ_{1-42} and p-tau/Aβ_{1-42} over time and clinical symptom onset (see Table 5). The time-dependent rate of change in p-tau/Aβ_{1-42} and baseline CR independently predicted the time to onset of clinical symptoms, with greater increases in p-tau/Aβ_{1-42} being associated with a greater risk (i.e., HR) of developing clinical symptoms (HR, 1.91, $p = 0.005$) and higher CR with a smaller risk of symptom onset (HR, 0.67, $p = 0.037$). However, there was no interaction between CR and the time-dependent rate of change of p-tau/Aβ_{1-42} ($p = 0.79$). This indicates that the beneficial effect of higher CR on the risk of progressing from normal cognition to onset of clinical symptoms is equivalent across the observed range of values for the time-dependent rate of change of p-tau/Aβ_{1-42}.

The rate of increase in the t-tau/Aβ_{1-42} ratio was also associated with a greater risk of progressing to clinical symptom onset (HR, 1.94, $p = 0.004$). However, the main effect of CR only approached significance in this model (HR, 0.70, $p = 0.08$), and the interaction between CR and the rate of change in the t-tau/Aβ_{1-42} ratio was not significant ($p = 0.64$). When the nonsignificant interaction term

Table 5
Hazard ratio for rate of change in cerebrospinal fluid values and baseline CR in relation to onset of clinical symptoms

Variable	Hazard ratio (95% confidence interval)	*p*-value
P-tau/Aβ_{1-42}–rate	1.91 (1.20–3.04)	0.0054
CR composite score	0.67 (0.45–0.98)	0.037
Interaction CR composite score by rate	1.05 (0.72–1.53)	n.s.
T-tau/Aβ_{1-42}–rate	1.94 (1.23–3.06)	0.0038
CR composite score	0.70 (0.47–1.06)	0.082
Interaction CR composite score by rate	0.87 (0.48–1.57)	n.s.

Note: all models adjusted for baseline cerebrospinal fluid value, baseline age, and gender.
Key: Aβ, β-amyloid; CR, cognitive reserve; n.s., not significant at $p = 0.1$; P-tau, phosphorylated tau; T-tau, total tau.

was removed from the model, the effect of CR still only approached significance (HR, 0.69, $p = 0.065$).

4. Discussion

The present study produced several notable findings. First, our data show that, considering the same level of AD pathology measured using each of the 5 CSF biomarkers examined, participants with higher levels of CR had a significantly lower risk of progressing from normal cognition to onset of clinical symptoms. Because the onset of clinical symptoms may precede the diagnosis of MCI by several years, this extends previous findings that used the date of clinical diagnosis of MCI as the outcome of interest and shows that CR modifies the clinical expression of very early AD pathology during the preclinical phase of AD. Second, the average age of the cohort was 56.9 years at baseline. Because previous studies have been conducted among individuals who were over the age of 70 years, this extends the age at which CR may be observed to mediate the relationship between the CSF biomarker changes in normal individuals and the risk of developing clinical symptoms associated with MCI (Roe et al., 2011a, 2011b). These findings are consistent with cross-sectional studies suggesting that cognitively normal individuals with higher CR are able to tolerate higher levels of AD pathology measured according to the levels of CSF $A\beta_{1-42}$ (Arenaza-Urquijo et al., 2013; Vemuri et al., 2011), CSF tau (Vemuri et al., 2011), amyloid imaging (Rentz et al., 2010), or fluorodeoxyglucose PET (FDG-PET) metabolism (Ewers et al., 2013). They are also consistent with the studies of individuals with MCI or AD dementia, which have reported that, after controlling for neuropsychological test performance or disease severity, individuals with high CR have lower levels of CSF $A\beta_{1-42}$ compared with those with low CR (Dumurgier et al., 2010; Rolstad et al., 2009a, 2009b). Moreover, these results converge with recent neuropathologic findings showing that asymptomatic individuals with AD pathology (i.e., tau tangles and amyloid plaques) tend to have higher levels of education than symptomatic individuals (Monsell et al., 2013).

A third major finding is that the degree to which CR modified the risk of progressing to clinical symptom onset was independent of the level of $A\beta_{1-42}$ at baseline but dependent on the level of tau pathology at baseline. Specifically, among participants with higher baseline levels of t-tau and p-tau, the degree to which CR modified the risk of clinical symptom onset was less than that in participants with lower levels of t-tau and p-tau. This suggests that as levels of tau increase, the moderating effect of CR on clinical outcome decreases. This finding provides support for theoretical models of CR, which postulate that CR becomes less effective in mediating the clinical manifestation of pathology as pathology levels increase (e.g., Stern, 2009). Presumably, this occurs because the neural processes underlying the effects of CR themselves begin to break down, rendering an individual less able to compensate for the advancing pathology. This model of CR also hypothesizes that as AD pathology begins to develop, individuals with lower CR will exhibit clinical symptoms before individuals with higher CR as observed in this study. Additionally, the model proposes that, as pathology levels increase, the differential clinical expression of disease among individuals with higher and lower CR will diminish. To our knowledge, the present study provides the first direct evidence in support of this aspect of the model for individuals in the preclinical phase of AD.

A notable implication of our results with respect to t-tau and p-tau is that the extent to which the levels of these biomarkers are predictive of subsequent clinical impairment varies as a function of CR. This conclusion is illustrated in Fig. 1, which is based on data from the present study. As shown in Fig. 1A, for each SD increase in baseline p-tau, the increase in risk is greater for individuals with high CR than that for individuals with low CR. Stated differently, these data suggest that the levels of CSF t-tau and p-tau in cognitively normal adults are more strongly associated with the development of clinical symptoms in individuals with high CR than those with lower CR. Consistent with this interpretation, when we examined the relationship between baseline t-tau and p-tau levels and time to onset of clinical symptoms separately in participants with high CR (at or above the median) and low CR (below the median), a significant association was only present in the high CR group (HR, 1.98, $p = 0.0014$ for p-tau and HR, 1.66, $p = 0.016$ for t-tau) but not in the low CR group (HR, 1.21, $p = 0.22$ for p-tau and HR, 0.96, $p = 0.84$ for t-tau). This finding is compatible with the theoretical model of CR suggesting that individuals with lower CR are already at a higher risk of developing clinical symptoms (by virtue of having lower CR) and the risk associated with increased tau pathology does not significantly add to this risk (Stern, 2009). In comparison, for individuals with high CR, whose overall risk is much lower, an increase in tau pathology represents a significant risk factor and is, therefore, an informative biomarker for the development of clinical symptoms.

The finding that the association between CR and clinical outcome was independent of baseline $A\beta_{1-42}$ levels suggests that the protective effect of higher CR is equivalent across the observed range of CSF $A\beta_{1-42}$ levels (as shown in Fig. 1B, which is based on data from the present study). Such a finding is consistent with the view that Aβ deposition represents an earlier phase of the disease that, by itself, is insufficient to cause clinical symptoms (e.g., Jack et al., 2013; Sperling et al., 2011), although it may negatively impact performance on some neuropsychological tasks in cognitively normal individuals (e.g., see Bennett et al., 2012; Hedden et al., 2012; Mormino et al., 2009; Rentz et al., 2011; Resnick et al., 2010; Villemagne et al., 2011). In comparison, CSF t-tau and p-tau accumulation are thought to represent a more advanced stage of AD that is more closely linked to neurodegeneration and clinical symptom onset (Monsell et al., 2013; Sperling et al., 2011).

Our findings differ somewhat from those by Roe et al. (2011a) the only prior longitudinal study of CR and CSF-AD biomarkers in preclinical AD. Specifically, Roe et al. (2011a) did not detect an effect of CR (measured according to years of education) on the risk of progression from normal cognition to incident cognitive impairment in individuals with low t-tau and p-tau levels. This difference in findings likely reflects the smaller sample size (and resulting reduction in power), shorter follow-up duration (3 years on an average), and the use of education as a single CR proxy in the study by Roe et al. (2011a).

Prior cross-sectional amyloid imaging (Rentz et al., 2010; Roe et al., 2008a) and neuropathologic studies (Bennett et al., 2003, 2005) have shown that CR mediates the relationship between amyloid pathology and cognition but not between tau pathology and cognition in cognitively normal and demented individuals. In particular, these studies suggest that the association between cognitive test performance and amyloid pathology is weaker in individuals with high CR than that in individuals with lower CR, whereas the association between cognitive test performance and amount of tau pathology does not differ as a function of CR (Bennett et al., 2003, 2005; Roe et al., 2008b). The results from the present study, however, cannot be directly compared with these findings because we examined the relationship between AD biomarkers and CR in relation to a future clinical outcome, not in relation to the current performance on cognitive tests. Nevertheless, our findings demonstrate that although there may be a weaker relationship between high amyloid load and cognitive test performance among individuals with high CR, those with high CR and amyloid are vulnerable, in that they are at increased risk for progressing from normal cognition to mild impairment.

The present study also demonstrated that when baseline and longitudinal rate of change in CSF biomarker levels are considered together, CR seems to have a smaller effect on the risk of progression. Although higher CR was associated with a reduced risk of progression to clinical symptoms, independent of the baseline and rate of change levels of p-tau/Aβ_{1-42} ratio, the HR for CR in the rate-of-change models (30%–34% reduction in risk per SD increase) was smaller than for any of the models that included baseline measures only (45%–55% reduction in risk per SD increase). Conclusions from these findings must be tempered by the fact that the mean time between baseline and the last follow-up CSF collection was 4.19 years. Future CSF collection in this cohort would help to address this issue.

Finally, our data showed that baseline levels of CR were not associated with those of CSF biomarkers or the rate of change in these biomarkers over time. This suggests that CR does not directly influence the aggregation of tau and amyloid pathology but rather serves to modify the effect of that pathology on the expression of clinical symptoms; higher CR reduces the risk of symptom onset, regardless of baseline amyloid levels, but it reduces the risk of symptom onset less if baseline levels of tau are high.

Our findings, however, must be interpreted in the context of its limitations. The participants are well educated and primarily Caucasian, so the results may not generalize to the US population at large. In particular, an interaction between CR and CSF Aβ levels might be observed in a sample with a greater range of education (and therefore a greater range of CR, see Fig. 1B). Additionally, most of the participants had a family history of dementia, which may also limit the generalizability of the findings. Finally, the average interval between the baseline and the last follow-up CSF collections was 4 years. Therefore, we cannot preclude the possibility that a direct association between CR and CSF biomarker accumulation would be observed with additional longitudinal CSF measures as suggested by others (Jagust & Mormino, 2011; Landau et al., 2012).

Disclosure statement

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2013.06.017.

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