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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.