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Cognitive reserve and cortical thickness in preclinical Alzheimer's disease

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Abstract

This study examined whether cognitive reserve (CR) alters the relationship between magnetic resonance imaging (MRI) measures of cortical thickness and risk of progression from normal cognition to the onset of clinical symptoms associated with mild cognitive impairment (MCI). The analyses included 232 participants from the BIOCARD study. Participants were cognitively normal and largely middle aged ($M_{age} = 56.5$) at their baseline MRI scan. After an average of 11.8 years of longitudinal follow-up, 48 have developed clinical symptoms of MCI or dementia (M_{time} from baseline to clinical symptom onset = 7.0 years). Mean thickness was measured over eight 'AD vulnerable' cortical regions, and cognitive reserve was indexed by a composite score consisting of years of education, reading, and vocabulary measures. Using Cox regression models, CR and cortical thickness were each independently associated with risk of clinical symptom onset within 7 years of baseline, suggesting that the neuronal injury occurring proximal to symptom onset has a direct association with clinical outcomes, regardless of CR. In contrast, there was a significant interaction between CR and mean cortical thickness for risk of progression more than 7 years from baseline, suggesting that individuals with high CR are better able to compensate for cortical thinning that is beginning to occur at the very earliest phase of AD.

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Compliance with ethical standards

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Keywords

Cognitive reserve; Cortical thickness; Preclinical AD; Magnetic resonance imaging; Alzheimer's disease

Dementia due to Alzheimer's disease (AD) includes widespread neuronal injury to both medial temporal and cortical regions, with accumulating evidence suggesting that subtle AD-related atrophy begins years before the emergence of clinical symptoms of mild cognitive impairment (MCI). This period, known as the preclinical phase of AD, is hypothesized to be characterized by the accumulation of AD pathology in the absence of clinical impairment (Sperling et al. 2011). Some of the most convincing evidence for brain atrophy during preclinical AD comes from studies using magnetic resonance imaging (MRI) biomarkers of neuronal injury among cognitively normal individuals who have been followed for longitudinal clinical outcomes. These studies have demonstrated that both medial temporal lobe (MTL) (e.g., hippocampus, entorhinal cortex) and a subset of AD vulnerable cortical regions (1) have a greater rate of atrophy among cognitively normal individuals who subsequently progress to MCI relative to individuals who remain cognitively normal (Jack et al. 2004; Miller et al. 2013; Pacheco et al. 2015) and that (2) measures of volume and thickness in these regions are associated with time to progression from normal cognition to the onset of clinical symptoms of MCI (Pettigrew et al. 2016; Soldan et al. 2015), time to diagnosis of MCI (Csernansky et al. 2005), and time to diagnosis of dementia (Dickerson et al. 2011). Much less, however, is known about whether risk factors reflective of lifetime cognitive activity, typically referred to as 'cognitive reserve', modify the association between MRI biomarkers of neuronal injury and longitudinal clinical outcomes during the preclinical phase of AD.

As described by Stern (2006, 2012), cognitive reserve (CR) is a theoretical concept proposing that individual differences in lifetime experiences, such as educational and occupational attainment, leisure activities, and literacy, increase the flexibility, efficiency and capacity of brain networks, thereby allowing individuals with higher CR to sustain greater levels of brain pathology before demonstrating clinical symptoms. Within the context of AD and MRI biomarkers of neuronal injury, cross-sectional studies have reported smaller brain volumes or reduced cortical thickness among high CR individuals with MCI and dementia, compared to those with low CR, even with differences in cognition controlled (e.g., Liu et al. 2012; Seo et al. 2011; Solé-Padullés et al. 2009; Querbes et al. 2009). These results suggest that despite the presence of more brain pathology, individuals with higher levels of CR are performing at a similar cognitive level as those with lower CR. This supports the view that individuals with high reserve are better able to sustain neuronal injury than individuals with low reserve. Relatedly, other cross-sectional studies have shown that, given a certain level of brain pathology, as measured by structural abnormality on MRI, cognitively impaired individuals with high CR perform better on cognitive tests than those with low CR (Vemuri et al. 2011).

Such cross-sectional studies do not, however, address the question of whether CR alters the relationship between MRI biomarkers of neuronal injury and the risk of developing clinical

symptoms over time among asymptomatic individuals. In light of the fact that hypothetical models of AD biomarker changes (Jack et al. 2013) incorporate cognitive reserve as an important modifying factor of clinical outcomes, longitudinal studies are critically needed to test if measures of CR influence the expression of AD pathology on functional outcomes. Only one prior study, to our knowledge, has examined whether CR modifies the association between structural MRI biomarkers of AD pathology in relation to longitudinal *clinical* outcomes. In this prior study by our group, Soldan et al. (2015) focused on medial temporal lobe regions and found that CR and MRI biomarkers of atrophy, measured while individuals were cognitively normal, conferred largely independent effects on risk of progression from normal cognition to the onset of clinical symptoms of MCI. Specifically, smaller hippocampal volumes and entorhinal cortex thickness measures at baseline, as well as rates of change in the entorhinal cortex and amygdala volumes, were associated with an increased risk of clinical symptom onset, while higher CR was associated with a reduced risk. Because atrophy in medial temporal lobe is thought to represent an earlier phase in the course of AD than atrophy in cortical regions, it is unclear whether measures of CR modify the association between atrophy in AD vulnerable *cortical* regions (measured on MRI) and subsequent clinical symptom onset among cognitively normal individuals. The present study was designed to address this gap.

We used data from the BIOCARD study, a large cohort ($N = 349$) of participants who have undergone longitudinal follow-up for up to 20 years. Participants were cognitively normal when first enrolled, and a subset have since progressed to MCI or dementia due to AD over time. Using data from this cohort, we previously reported that mean cortical thickness of 'AD vulnerable' cortical regions was significantly associated with time to onset of clinical symptoms of MCI for progression proximal to baseline (i.e., within 7 years of baseline), but not more distally from baseline (i.e., after 7 years from baseline) (Pettigrew et al. 2016). In the present study, we use the same 'AD vulnerable' cortical regions to test whether CR modifies the association between mean thickness of AD vulnerable regions and risk of clinical symptom onset within, and after, 7 years from the baseline MRI scan. In addition to informing biomarker models of AD, the results from the current study may be relevant to theoretical models of CR. While many studies have observed lower rates of progression to MCI and dementia due to AD among cognitively normal (e.g., Lindsay et al. 2002; Pettigrew et al. 2013; Sattler et al. 2012) or non-demented (e.g., Ngandu et al. 2007; Stern et al. 1994) individuals with higher CR, it is not known if the beneficial effects of higher CR on clinical outcomes are dependent on levels of cortical thickness.

Method

Study design and participant selection

The data used in this study were drawn from the BIOCARD study, which was designed to recruit and follow a cohort of cognitively normal individuals who were primarily in middle age at baseline. By design, approximately 75 % of the participants had a first degree relative with 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 dementia due to AD. Recruitment procedures, baseline evaluations,

and annual clinical and cognitive assessments have been described in detail elsewhere (Albert et al. 2014). Briefly, the study was initiated at the National Institutes of Health (NIH), with recruitment conducted by the staff of the Geriatric Psychiatry Branch of the intramural program of the National Institute of Mental Health, beginning in 1995 and ending in 2005. Individuals were excluded from participation if they were cognitively impaired, as determined by cognitive testing, or had significant medical problems such as severe cerebrovascular disease, epilepsy or alcohol or drug abuse. After providing written informed consent, a total of 349 primarily middle-aged individuals ($M_{age} = 57.3$, $SD = 10.4$) were enrolled in the study. While the study was at the NIH, participants were administered a comprehensive neuropsychological battery and clinical examination annually, and MRI scans, cerebrospinal fluid (CSF), and blood specimens were obtained approximately every two years. In 2005, the study was stopped for administrative reasons, and 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 and evaluate the previously acquired MRI scans, CSF, and blood specimens. In 2015, the collection of both MRI and CSF was reinitiated, and amyloid imaging was begun.

Clinical assessments and consensus diagnoses

Since the study was re-established at Johns Hopkins, annual visits have included comprehensive neuropsychological testing and a clinical evaluation consisting of a physical and neurological examination, record of medication use, behavioral and mood assessments, family history of dementia, history of symptom onset, and a Clinical Dementia Rating (CDR), based on a semi-structured interview (Hughes et al. 1982; Morris 1993) (for further detail, see Albert et al. 2014). Clinical assessments given at the NIH covered similar domains. The consensus diagnosis procedures implemented by the Johns Hopkins team are comparable with those used in the National Institute on Aging Alzheimer's Disease Centers program. Each case is handled in a similar manner: (1) clinical data pertaining to the medical, neurologic, and psychiatric status of the participant are examined; (2) reports of changes in cognition by the participant and collateral sources are reviewed; and (3) decline in cognitive performance, based on review of longitudinal testing from multiple domains, is established. These sources of data are used to determine whether a participant is cognitively impaired, as indicated by evidence of both clinical change (i.e., a CDR rating = 0.5) and cognitive decline (i.e., evidence of significant decline on cognitive testing, relative to the individual's prior performance). Once an individual receives a diagnosis of MCI, we use information in the CDR interview, conducted with both the subject and the informant, to estimate the age at which the clinical symptoms began. In most cases, the age of clinical symptom onset precedes the date of MCI diagnosis. In contrast, individuals with evidence of cognitive change on testing or reports of change in function (based on the CDR), but not both, are given a diagnosis of 'Impaired not MCI' because they do not meet the research criteria for a diagnosis of MCI. The decision by the consensus panel concerning the likely etiology of the cognitive decline incorporates information concerning the course and duration of cognitive change, based on the CDR, as well as the medical, neurologic and psychiatric information available on the participant. Consensus diagnosis procedures are carried out by the staff of the BIOCARD Clinical Core, which includes neurologists, neuropsychologists, research nurses, and research assistants. This same diagnostic process is

retrospectively applied to participants who had become cognitively impaired while the study was being conducted at the NIH.

APOE genotyping

APOE genotype was established in all but one of the study participants ($n = 348$). Genotypes were determined by restriction endonuclease digestion of polymerase chain reaction amplified genomic DNA (performed by Athena Diagnostics, Worcester, MA). In these analyses, APOE-4 carrier status was coded as a dichotomous variable, such that individuals with at least one $\epsilon 4$ allele were coded 1, otherwise 0. Eight individuals with one APOE-4 and one APOE-2 allele were excluded from all analyses, since the APOE-4 allele increases dementia risk whereas the APOE-2 allele reduces dementia risk (Corder et al. 1994; Farrer et al. 1997).

Cognitive reserve composite score

CR was operationalized by a composite score based on three measures thought to reflect lifetime cognitive experiences: 1) baseline scores from the National Adult Reading Test (NART; Nelson 1982); 2) baseline scores on the vocabulary subtest of the Wechsler Adult Intelligence Scale – Revised (WAIS-R; Wechsler 1981); and 3) years of education. To create the CR composite score, the three individual measures were z-scored and then averaged. Due to missing values, composite scores for 16 individuals were calculated on only two of these measures, one of which was always education. As reported by Soldan et al. (2015), these individual CR measures were strongly correlated and loaded on a single factor in factor analysis. Composite scores such as these have construct validity (e.g., Siedlecki et al. 2009) and evidence suggests they may be more sensitive CR proxies than years of education alone (Manly et al. 2005; Pettigrew et al. 2013).

MRI assessments, image processing, and regions of interest

The present study utilized baseline MRI scans acquired at the NIH. Scans were obtained using a standard multimodal protocol using a GE 1.5 T scanner. The present analyses used scans obtained from the coronal Spoiled Gradient Echo (SPGR) sequence (TR = 24, TE = 2, FOV = 256×256 , thickness/gap = 2.0/0.0 mm, flip angle = 20, 124 slices). Cortical reconstruction and estimation of cortical thickness was performed using FreeSurfer (version 5.1), an automated image processing pipeline that is documented and freely available online (<http://surfer.nmr.mgh.harvard.edu/>). The technical details of these methods have been described in prior publications (e.g., Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999a; Fischl et al. 1999b; Fischl et al. 2004). Following completion of the automated FreeSurfer pipeline, all scans were reviewed to assess the quality of skull stripping and ensure that cortical surfaces followed the gray and white matter boundaries. Where needed, manual edits were performed to improve segmentation and parcellation accuracy, which primarily included the correction of pial surface misplacement (e.g., the inclusion of non-brain tissue) and errors in white matter segmentation. This editing procedure was conducted by operators blinded to the diagnostic status of the subjects on follow-up. See Online Resource 1 for details on the additional scan sequences obtained at the NIH and a summary of the FreeSurfer processing stream.

The present study examined cortical thickness measures in eight FreeSurfer-labeled regions of interest (ROI) selected to reflect regions classified as ‘AD vulnerable’ cortical regions by at least two previous studies’ (i.e., cross-study overlap includes Dickerson et al. 2009; Sabuncu et al. 2011; Wang et al. 2015), suggesting these regions are sensitive to AD-related atrophy across multiple cohorts. The ROIs included: the entorhinal cortex, temporal pole, inferior temporal gyrus, middle temporal gyrus, inferior parietal cortex, superior parietal cortex, precuneus, and posterior cingulate cortex (averaged over the left and right hemispheres) (see Fig. 1). For each participant, the eight cortical thickness measures were averaged to create a measure of mean thickness of AD vulnerable regions, which served as the primary cortical thickness measure in the analyses below. These ROIs have been shown to demonstrate sensitivity to risk of progression from normal cognition to the onset of clinical symptoms of MCI (Pettigrew et al. 2016).

We also calculated mean cortical thickness for four ‘control’ regions that included the lateral occipital lobe, cuneus, precentral gyrus, and postcentral gyrus. These were selected as control regions because previous studies have indicated that these regions demonstrate minimal differences between controls and patients with dementia due to AD (e.g., Dickerson et al. 2009; Sabuncu et al. 2011; Wang et al. 2015). Thickness measures were not adjusted for intracranial cavity size, as is standard in the field (e.g., Westman et al. 2013).

MRI scans used in the analyses

MRI scans were obtained from 331 BIOCARD participants at baseline; of these, 62 scans were excluded, either because coronal SPGRs were not available ($n = 22$) or FreeSurfer surface reconstructions were deemed unreliable (e.g., motion artifact or low contrast resulted in poor scan quality or regions were missing from surfaces, $n = 40$). Of the 269 subjects with useable FreeSurfer data, an additional 37 were not considered for analysis for reasons unrelated to scan quality ($n = 22$ participants have not yet re-enrolled or withdrawn from the study; $n = 7$ had clinical symptom onset at or prior to baseline, based on the estimated age of onset established during the consensus diagnosis procedure; $n = 8$ had one APOE-4 and one APOE-2 allele). The analyses reported below therefore include 232 participants who were cognitively normal at baseline (M duration of follow-up = 11.8 years, $SD = 3.6$).

Statistical analyses

Group differences in demographic variables at baseline for subjects who progressed to cognitive impairment versus those who remained normal over time were assessed by t-test or Wilcoxon rank sum test for continuous variables, as appropriate, or chi-square tests for dichotomous variables. Using linear regression, we first tested whether there was a cross-sectional association between the CR composite score and mean cortical thickness of AD vulnerable regions at baseline. This model included mean cortical thickness of ‘AD vulnerable’ regions (referred to below as ‘mean cortical thickness’) as the dependent variable, and the CR composite score, age at scan, and gender as the independent variables.

We used Cox regression models (i.e., proportional hazard models) to examine the association between the mean cortical thickness measure, CR, and time (in years) to progress from normal cognition to the onset of clinical symptoms of MCI (based on the

estimated age of clinical symptom onset, as described in the consensus diagnosis procedures). As in our prior study (Pettigrew et al. 2016), these models included an indicator term for time (within 7 years) as part of the coefficient for cortical thickness. Because the thickness coefficient for each individual was allowed to be time-dependent and different within versus after 7 years from baseline (i.e., the mean time to clinical symptom onset), this coefficient allowed us to examine the association between cortical thickness and risk of clinical symptom onset for progression within 7 years of baseline compared to for risk of progression after 7 years from baseline. Statistically, this is equivalent to treating thickness as a composition of two time-dependent variables, one only having an effect on risk of progression within 7 years, the other after 7 years (Fisher and Lin 1999), with coefficients estimated using these corresponding methods. The analyses included data from two groups of subjects: (1) participants who were cognitively normal at their baseline visit and have remained cognitively normal over time ($n = 184$) and (2) participants who were cognitively normal at baseline but who received a diagnosis of MCI or dementia at their last consensus diagnosis ($n = 48$). All quantitative variables were standardized before model fitting. Participants with a diagnosis of 'Impaired not MCI' at their last consensus review were included in the group of cognitively normal subjects; results were comparable when these subjects were excluded from the analyses.

Given the present study builds on our prior work examining the association between cortical thickness and risk of clinical symptom onset, we ran two Cox regression models: a simple and a full model. The simple model examined whether the association between mean cortical thickness and clinical symptom onset for progression within versus after 7 years from baseline remained significant when the CR composite score was included as a main effect in the model. This model included the following predictors: age at scan, gender (dichotomous), APOE-4 (dichotomous), CR composite score, and mean cortical thickness of AD vulnerable regions, with the coefficient of the latter modeled with an indicator for progression within versus after 7 years from baseline. In the full model, we examined whether CR *modified* the association between cortical thickness and time to clinical symptom onset for progression within, versus after, 7 years from baseline; to do so, we included two additional terms reflecting the interaction (i.e., cross-products) of (1) CR and cortical thickness for risk of progression within 7 years, and (2) CR and cortical thickness for risk of progression after 7 years. Non-significant interaction terms were removed from the model and the model was re-run without these terms.

For each variable included in the Cox models, we calculated the hazard ratio (HR; i.e., relative hazard). Because all quantitative variables were standardized before model fitting, the hazard ratios for variables in each model can be directly compared. The HR indicates the change in relative risk of progression for each one unit change in the predictor. A HR of 0.51, for example, means the hazard of clinical symptom onset is reduced by a factor of .51 (i.e., by 49 %) for each standard deviation increase in a particular measure. In contrast, a HR of 1.70 means the hazard of clinical symptom onset is increased by a factor of 1.70 (i.e., by 70 %) for each standard deviation increase in a measure. All analyses were run in R, version 3.2.2.

Results

Table 1 displays baseline characteristics for the entire BIOCARD cohort ($N = 349$) and the subset of participants included in the present analyses ($n = 232$). For participants in the analyses, Table 2 compares baseline characteristics for those who have remained cognitively normal over time ($n = 184$) versus those who were cognitively normal at baseline but have since developed clinical symptoms of MCI or dementia ($n = 48$). Of the 48 subjects who progressed to MCI, 96 % (46/48) received a consensus etiological diagnosis of probable or possible AD, and 4 % (2/48) received an etiological diagnosis of vascular disease. We chose to include the latter subjects in the analysis, since the majority of older patients with progressive cognitive decline have mixed pathology and vascular dementia is uncommon. At baseline, individuals who have since progressed to MCI or dementia were older, had marginally lower MMSE scores (though still well within normal limits), and had a lower CR composite score. The mean time from baseline to clinical symptom onset was 7.0 years ($SD = 3.6$). See Online Resource 2 for additional information about the characteristics of the subjects who progress.

In the linear regression model co-varying age at scan and gender, we found no cross-sectional association between mean cortical thickness of AD vulnerable regions and the CR composite score at baseline, $\beta = 0.03$, $p = .66$.

The results of the simple Cox model, evaluating the association between mean cortical thickness of 'AD vulnerable' regions and clinical symptom onset with the CR composite score included as a main effect, are shown in Table 3 (top). The mean time from baseline to clinical symptom onset for the 22 individuals who progressed within 7 years of their baseline scan was 3.9 years ($SD = 2.2$), versus 9.7 years ($SD = 2.1$) for the 26 individuals who progressed more than 7 years from their baseline scan. In the simple model, greater mean cortical thickness was associated with reduced risk of clinical symptom onset for progression within 7 years of baseline ($p = .03$), but not for progression after 7 years from baseline ($p = .41$). CR was also significantly associated with risk of progression ($p < .001$), such that higher CR was associated with a reduced relative risk of clinical symptom onset. Additionally, the presence of at least one APOE-4 allele was associated with an increased risk of clinical symptom onset ($p = .04$), even after adjusting for differences in CR and cortical thickness.

The full model evaluated whether CR *modified* the association between mean cortical thickness and risk of clinical symptom onset for progression within, versus after, 7 years. The interaction between CR and cortical thickness for risk of progression within 7 years was non-significant ($HR = 1.15$, $p = .64$), suggesting that CR and cortical thickness are independently associated with risk of progression within 7 years. The final model shown in Table 3 (bottom) therefore excludes this interaction term. In contrast, there was a significant interaction between CR and cortical thickness for risk of progression after 7 years ($p < .001$). The 0.68 hazard ratio of this interaction term suggests that there is a stronger association between thickness and time to onset of clinical symptoms for progression after 7 years in individuals with low CR relative to individuals with high CR (see Online Resource 3 for additional information).

To examine the specificity of these findings, the simple and full model analyses were repeated for mean cortical thickness of the control regions (described above). In the simple model, there was no significant association between mean cortical thickness and risk of clinical symptom onset for progression within or after 7 years of baseline ($p = .07$ and $p = .23$, respectively). In the full model, there was a significant interaction between CR and cortical thickness for risk of progression after 7 years ($p < .001$; as for mean thickness of the AD vulnerable regions), but the main effects of mean cortical thickness for progression within and after 7 years of baseline were again not significant (both $ps > .13$) (see Online Resource 4).

We also ran two sets of follow-up analyses to provide a more extended exploration of CR. First, we examined whether the pattern of results obtained for the CR composite score would be the same using each of the individual CR measures. For both the simple and full models, the individual CR measures produced the same pattern of results, as reported above for the CR composite score (see Online Resource 5). However, the protective effects of the individual reading and vocabulary measures on risk of clinical symptom onset were stronger than the effects associated with years of education. That is, for reading and vocabulary, each standard deviation increase in scores was associated with ~50 % reduction in risk, compared to a ~24 % reduction in risk for years of education. Second, we ran an additional Cox regression model in which the indicator term for time (within 7 years) was included as part of the coefficient for both mean cortical thickness (as in the above analyses) and the CR composite score. This allowed us to examine whether the association between the baseline CR composite score and risk of progression differed before and after 7 years from baseline. Covarying age, gender, APOE-4, and mean cortical thickness, higher CR was associated with reduced risk of clinical symptom onset, both for progression within 7 years of baseline ($HR = 0.66$, $p = .046$), and for progression after 7 years from baseline ($HR = 0.33$, $p < .001$).

Discussion

Using longitudinal data from the BIOCARD study, the present study examined the association between MRI biomarkers of neuronal injury, measured by mean cortical thickness in 'AD vulnerable' regions, and cognitive reserve, in relation to risk of developing clinical symptoms of MCI over time among individuals who were cognitively normal at baseline. Specifically, we were interested in (1) the association between the MRI biomarkers and risk of clinical symptom onset for progression within 7 years of baseline, versus after 7 years from baseline, controlling for individual differences in cognitive reserve, and (2) whether levels of cognitive reserve modified the relationship between these MRI biomarkers and risk of clinical symptom onset. We found that mean cortical thickness of AD vulnerable regions was significantly associated with time to onset of clinical symptoms for progression within 7 years of baseline, but not for progression more than 7 years from baseline. Higher levels of CR were associated with a reduced risk of symptom onset both within and after 7 years from baseline. There was no interaction between CR and mean cortical thickness for risk of progression within 7 years (i.e., for thickness measured proximal to clinical symptom onset). In contrast, there was a significant interaction between CR and mean cortical thickness for risk of progression more than 7 years from baseline, i.e., for thickness measured more distally from clinical symptom onset; this indicates a stronger association

between mean cortical thickness and risk of progression after 7 years in individuals with low CR, relative to individuals with high CR.

These findings suggest that changes in cortical thickness in AD vulnerable regions may be most evident in the years closer to the onset of clinical symptoms of MCI. The time frame of these changes is in line with studies in sporadic and familial AD which have estimated that greater cortical atrophy begins to occur ~2–6 years prior to the emergence of clinical symptoms (e.g., Carlson et al. 2008; Fox et al. 2001; Quiroz et al. 2013; Ridha et al. 2006; Smith et al. 2007). These findings also support a hypothetical model of biomarkers in AD, which proposes that structural MRI biomarker abnormality becomes evident in the years most proximal to cognitive impairment (Jack et al. 2013). Additionally, we did not observe a significant association between mean cortical thickness in the control regions and risk of clinical symptom onset. These findings strengthen the hypothesis that the AD vulnerable regions are more predictive of progression during the preclinical phase than other cortical regions, though it remains possible that atrophy occurs in regions not included in our analyses.

Increased levels of CR – thought to be a proxy for lifetime cognitive activity (Stern 2009) – were associated with an approximately 50 % reduction in relative risk of clinical symptom onset after accounting for baseline cortical thickness, APOE-4 genotype, age, and gender. The lack of an interaction between CR and mean cortical thickness for progression within 7 years of baseline suggests that the protective effects of CR are independent of the degree of thinning in these cortical regions occurring proximal to clinical symptom onset. These results are consistent with prior findings among cognitively normal individuals that suggested CR and MRI measures have largely independent effects on cross-sectional cognitive (Vemuri et al. 2011) or longitudinal clinical outcomes (Soldan et al. 2015).

Our follow-up analyses revealed that higher CR was associated with a 34 % reduction in risk of progression within 7 years of baseline, but a 67 % reduction in risk of progression after 7 years of baseline. If we assume that AD pathology increases closer to symptom onset, these results are consistent with the hypothesis that the protective effect of CR decreases as AD pathology levels increase. The present study cannot speak to the mechanism(s) by which CR allows individuals with high reserve to cope with accumulating pathology, resulting in a reduced relative risk of progression from normal cognition to clinical symptoms of MCI or dementia due to AD, or the mechanisms by which these effects may differ proximally or distally to progression. However, a number of closely related theoretical models have been proposed. As reviewed by Barulli and Stern (2013), the protective effects of CR could be related to a number of factors, including increased brain size (e.g., number of neurons and synapses); increased functional efficiency or flexibility of neural networks; and increased compensatory mechanisms through the use of additional, alternative, or new neural networks and/or cognitive strategies.

In contrast, the association between mean cortical thickness and risk of progression distally from baseline depends on levels of CR. We hypothesize that this interaction may be due to individual differences in the ability to cope with underlying pathology. Biomarkers of neuronal injury and atrophy are hypothesized to become increasingly abnormal as

individuals get closer in time to clinical symptom onset (Jack et al. 2013) and they tend to correlate with cognitive performance and clinical impairment (e.g., Dickerson et al. 2009; Fox et al. 1999; Wang et al. 2015; Wirth et al. 2013). In line with this, there was no direct association between mean cortical thickness and risk of clinical symptom onset more than 7 years from baseline. However, the significant interaction reported here indicates that the association between mean cortical thickness and risk of symptom onset distally from baseline was stronger in individuals with lower levels of CR (see Soldan et al. 2015, for similar results for left entorhinal cortex volume and Vuoksima et al. 2013 for similar results with cross-sectional cognitive outcomes). This may reflect the fact that individuals with low CR have difficulty compensating for minor cortical thinning which may be beginning to occur a decade prior to symptom onset, whereas individuals with high CR can compensate for the neuronal injury that is beginning to occur in this early phase of disease. This interpretation suggests that CR provides a compensatory mechanism that enables high CR individuals to accommodate early cortical changes (e.g., Arenaza-Urquijo et al. 2015; Stern 2009). In contrast, the lack of interaction between CR and mean cortical thickness and risk of progression proximally to baseline suggests that as biomarkers of neuronal injury become increasingly abnormal closer to clinical symptom onset (i.e., for progression proximal to baseline), the neuronal injury that is occurring during this period has a direct association with clinical expression in all individuals, regardless of CR (for a similar discussion, see Soldan et al. 2015).

An alternative interpretation for the interaction between CR and mean cortical thickness for risk of progression distally from baseline is that CR has a direct, neuroprotective effect that slows the initial stages of cortical thinning (e.g., Arenaza-Urquijo et al. 2015). It should be noted, however, that we found no direct association between level of CR and mean cortical thickness cross-sectionally in the linear regression model (for similar MRI findings, see Lo and Jagust 2013; Soldan et al. 2015; Vemuri et al. 2011, 2012). In line with theoretical models of CR (e.g., Stern 2009), this suggests that CR does not have a direct impact on the amount of AD pathology, as indicated by MRI measures of neuronal injury, but that CR instead modifies the impact of this pathology on clinical outcomes. However, it is important to acknowledge that some cross-sectional and short-term longitudinal studies have provided preliminary evidence suggesting that lifestyle factors may have direct effects on the accumulation of amyloid during preclinical AD (e.g., Landau et al. 2012; Vemuri et al. 2016; Wirth et al. 2014; for a review, see Arenaza-Urquijo et al. 2015). It will be important for future studies to evaluate possible mechanisms along the continuum of AD – that is, both during preclinical AD when AD pathology is accumulating and neuronal injury is relatively minor, and during symptomatic disease phases when the mechanisms of reserve may be altered by more severe AD pathology.

These results extend prior studies in a number of ways. Building on our previous work examining the timing of cortical thickness changes during preclinical AD (Pettigrew et al. 2016), this study provides the first test, to our knowledge, of whether CR modifies the association between atrophy in ‘AD vulnerable’ cortical regions and subsequent onset of clinical symptoms among individuals who were asymptomatic when their MRI scans were acquired. This study also expands our prior work examining whether CR modifies the association between MTL atrophy and subsequent clinical outcomes (Soldan et al. 2015). In

line with the findings for most of the MTL regions examined by Soldan and colleagues, CR and mean cortical thickness conferred independent effects for progression proximally to baseline, the time frame during which mean thickness was most directly associated with risk of progression. Additionally, these findings have relevance to hypothetical models of biomarkers for AD (Jack et al. 2013), as they support the notion that factors above and beyond measures of brain pathology itself have an impact on the emergence of clinical symptoms during the preclinical phase of AD. For a given level of pathology, lifestyle and genetic factors may impact the timing of symptom onset, such that the onset of clinical symptoms are delayed in individuals with multiple protective factors (see also Vemuri et al. 2011).

Across the AD spectrum, studies examining cross-sectional differences in MRI measures as a function of CR have reported that symptomatic individuals with high CR have greater atrophy than individuals with low CR, even after adjustment for differences in cognition (Liu et al. 2012; Seo et al. 2011; Solé-Padullés et al. 2009; Querbes et al. 2009). Although these findings support the notion that CR has protective effects, Christensen et al. (2007; see also Vuoksimaa et al., 2013) have argued that the most direct tests of models of reserve – i.e., whether reserve enables individuals with more AD pathology to better maintain their cognitive or clinical status – require that analyses include an interaction term to examine whether reserve moderates the association between biomarkers of pathology and cognitive or clinical outcomes. To date, however, only a few studies have taken this approach to evaluate models of CR using MRI measures reflective of underlying pathology among cognitively normal individuals (e.g., Soldan et al. 2015; Vemuri et al. 2011; Vuoksimaa et al. 2013).

Lastly, in our analyses, men had an increased relative risk of clinical symptom onset. This may be due in part to increased prevalence of cardiovascular risk factors among the men (e.g., Artero et al. 2008; Scuteri et al. 2009). In line with this, 60 % of the men who progressed from normal cognition to MCI or dementia had vascular factors as part of their clinical etiology, while the same was true for only 39 % of the women who progressed. It is worth noting that our cohort was largely middle-age when they were enrolled and this differential may not be present among cohorts that are older.

The present study must be interpreted within the context of its limitations. The BIOCARD cohort is a sample consisting of well-educated, primarily Caucasian individuals, the majority of whom have a family history of dementia due to AD. These cohort characteristics may limit the generalizability of these results to the population at large. Additionally, although we included an indicator variable for progression within versus after 7 years from baseline in the coefficient for mean cortical thickness, it should be noted the 7 year cut-point was selected because it reflects the mean time from baseline to clinical symptom onset, rather than a quantitatively determined cut-point during which it is known that changes in cortical thickness begin to impact risk of progression during preclinical AD. In future studies, it will therefore be important to assess the rate of atrophy in cortical regions over time in order to better understand the time frame of cortical atrophy during preclinical AD, whether CR directly influences the rate of cortical atrophy, and whether the protective effects of CR

modify the association between rate of change in mean cortical thickness and risk of clinical symptom onset.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.
The eight regions included in the mean cortical thickness of AD vulnerable regions variable, depicted on the pial surface of the left hemisphere for lateral (left) and medial (right) views; although only the left hemisphere is shown, the mean cortical thickness variable reflects the average thickness in both hemispheres

Table 1

Baseline participant characteristics for the entire BIOCARD cohort and participants included in the analyses. Values reflect means (standard deviations) unless otherwise indicated

	Entire BIOCARD Cohort	Participants in Analyses
<i>N</i>	349	232
Age	57.3 (10.4)	56.5 (9.8)
Gender, male (%)	42 %	39 %
Ethnicity, Caucasian (%)	97 %	98 %
APOE-4 (%)	34 %	31 %
Education, years	17.0 (2.4)	17.1 (2.4)
MMSE score	29.5 (0.9)	29.6 (0.8)
Follow-up time, years	10.9 (4.6)	11.8 (3.6)
CR composite	0.0 (0.8)	0.04 (0.8)

Table 2

Baseline characteristics for participants included in the analyses stratified by outcome (remained normal, progressed to MCI or dementia due to AD). Values reflect means (standard deviations) unless otherwise indicated

	Remained normal	Progressed to MCI or AD	<i>p</i> -value
<i>N</i>	184	48	-
Age	54.8 (8.7)	62.9 (11.3)	< .01 *
Gender, male (%)	35 %	52 %	.03 *
Ethnicity, Caucasian (%)	99.5 %	91.7 %	< .01 *
APOE-4 (%)	29.9 %	33.3 %	.64
Education, years	17.1 (2.3)	16.8 (2.5)	.34
MMSE score	29.7 (0.7)	29.4 (1.0)	.01 *
Follow-up time, years	11.6 (3.7)	12.6 (3.1) *	.05 *
Thickness of AD vulnerable regions, mm	2.78 (0.12)	2.74 (0.15)	.09
CR	0.14 (0.78)	-0.34 (0.91)	< .01

* Significant difference between outcome groups, $p < .05$ uncorrected for multiple comparisons

Table 3

Hazard ratios [95 % confidence intervals] and p -values for the simple (top) and full (bottom) Cox regression models examining mean cortical thickness of AD vulnerable regions and cognitive reserve in relation to time to clinical symptom onset

	Hazard ratio [95 % CI]	p -value
Simple model		
Age at scan	1.10 [1.06, 1.14]	< .001
Gender (male)	1.98 [1.18, 3.30]	.009
APOE-4	1.79 [1.04, 3.06]	.04
CR composite	0.45 [0.33, 0.61]	< .001
Mean thickness for progression 7 years from baseline	0.52 [0.29, 0.94]	.03
Mean thickness for progression >7 years from baseline	1.15 [0.83, 1.59]	.41
Full model		
Age at scan	1.09 [1.06, 1.13]	< .001
Gender (male)	1.82 [1.10, 3.01]	.02
APOE-4	1.64 [0.95, 2.81]	.08
CR composite	0.47 [0.36, 0.61]	< .001
Mean thickness for progression 7 years from baseline	0.51 [0.28, 0.93]	.03
Mean thickness for progression >7 years from baseline	0.80 [0.59, 1.08]	.14
Interaction: CR $\times$ mean thickness for progression >7 years from baseline	0.68 [0.57, 0.80]	< .001