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Cortical thickness in relation to clinical symptom onset in preclinical AD

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ABSTRACT

Mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia are preceded by a phase of disease, referred to as 'preclinical AD', during which cognitively normal individuals have evidence of AD pathology in the absence of clinical impairment. This study examined whether a magnetic resonance imaging (MRI) measure of cortical thickness in brain regions, collectively known as 'AD vulnerable' regions, predicted the time to onset of clinical symptoms associated with MCI and whether cortical thickness was similarly predictive of clinical symptom onset within 7 years post baseline versus progression at a later point in time. These analyses included 240 participants from the BIOCARD study, a cohort of longitudinally followed individuals who were cognitively normal at the time of their MRI (mean age = 56 years). Participants have been followed for up to 18 years (*M* follow-up = 11.8 years) and 50 participants with MRIs at baseline have developed MCI or dementia over time (mean time to clinical symptom onset = 7 years). Cortical thickness in AD vulnerable regions was based on the mean thickness of eight cortical regions. Using Cox regression models, we found that lower mean cortical thickness was associated with an increased risk of progression from normal cognition to clinical symptom onset within 7 years of baseline ($p = 0.03$), but not with progression >7 years from baseline ($p = 0.30$). Lower cortical thickness was also associated with higher levels of phosphorylated tau, measured in cerebrospinal fluid at baseline. These results suggest that cortical thinning in AD vulnerable regions is detectable in cognitively normal individuals several years prior to the onset of clinical symptoms that are a harbinger of a diagnosis of MCI, and that the changes are more likely to be evident in the years proximal to clinical symptom onset, consistent with hypothetical AD biomarker models.

1. Introduction

Evidence indicates that the neuropathological changes underlying Alzheimer's disease (AD) begin many years before the manifestation of clinical symptoms (Sperling et al., 2011). A number of magnetic resonance imaging (MRI) studies demonstrate alterations in selected regions within the medial temporal lobe (MTL) that are thought to be an indirect reflection of neuronal injury during this preclinical phase of AD. For example, there is evidence that measures of the volume and thickness of MTL regions, such as the entorhinal cortex and hippocampus, are associated with the time to diagnosis of mild cognitive impairment (MCI) or time to onset of clinical symptoms associated with MCI (e.g., Csernansky et al., 2005; Soldan et al., 2015). A greater rate of atrophy in MTL regions has also been demonstrated among cognitively normal individuals who subsequently progress to MCI (e.g., Jack et al., 2004; Miller et al., 2013; Pacheco et al., 2015) compared to individuals who remain cognitively normal.

It is currently hypothesized that structural brain changes are also evident outside of the MTL during the preclinical phase of AD, though most of this work is based on cross-sectional or short-term longitudinal studies. Several groups have identified 'AD vulnerable' or 'AD signature' regions comprised of cortical areas thought to be particularly sensitive to the effects of early AD pathology (e.g., Dickerson et al., 2009; Sabuncu et al., 2011; Wang et al., 2015). Although the regions identified as 'AD vulnerable' or 'AD signature' have differed across studies, they predominantly include parts of inferior and anterior temporal lobe, inferior and superior parietal lobe, and posterior cingulate cortex. For example, a larger percentage of cognitively normal individuals with

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reduced cortical thickness in AD vulnerable regions showed cognitive decline over a three-year follow-up (Dickerson and Wolk, 2012), and reduced thickness in these regions was associated with time to diagnosis of dementia (Dickerson et al., 2011). Additionally, studies that have compared cognitively normal individuals who subsequently progress to MCI or AD dementia to those who remain cognitively normal have demonstrated between-group differences in baseline MRI volumes (Smith et al., 2007) or atrophy measures (Pacheco et al., 2015) in a subset of cortical regions, including parietal and temporal areas.

A number of cross-sectional studies have also examined cortical thickness differences between cognitively normal individuals with versus without biomarker profiles consistent with AD pathology, as determined by amyloid imaging or cerebrospinal fluid (CSF). These studies have demonstrated associations between biomarker positivity and reduced mean cortical thickness of AD vulnerable regions (Dickerson et al., 2009; Sabuncu et al., 2011) or similar cortical regions (e.g., Becker et al., 2011; Doré et al., 2013).

Although prior studies, taken together, suggest that reductions in cortical thickness are predictive of time to progression from normal cognition to symptom onset of MCI, this question has not been directly examined previously, to our knowledge. The present study was designed to address this gap. Utilizing MRI data from the BIOCARD study, whose participants were cognitively normal when first enrolled, we examined whether mean cortical thickness of AD vulnerable regions is associated with time to onset of clinical symptoms of MCI.

The long follow-up of the cohort (mean = 11.8 years, max = 18.2 years), the substantial size ($N = 240$), and the availability of CSF measures in the same individuals allowed us to extend prior work in a number of ways. First, we examined the timing of cortical thinning in AD vulnerable regions relative to the onset of symptoms of MCI. To do so, we tested whether cortical thickness is similarly predictive of the risk of clinical symptom onset for progression within a relatively short time frame (less than 7 years from baseline) versus progression at a later point in time, i.e., more than 7 years from baseline. This analysis was motivated by current AD biomarker models that hypothesize structural MRI measures of brain atrophy become abnormal more proximal to clinical symptom onset than measures of amyloid accumulation, which are thought to become abnormal earlier during the preclinical phase of AD (Jack et al., 2013). Second, we examined whether cortical thickness of AD vulnerable regions was associated with CSF biomarkers of neuronal injury (i.e., tau, phosphorylated tau) or a CSF biomarker of β-amyloid. Lastly, previous studies on this general topic have tended to include individuals in their 70′s, so it remains unclear whether AD-related cortical thickness changes during preclinical AD can be identified at younger ages. The present study was able to address this issue since it included a large cohort of individuals who were primarily middle-aged at their baseline MRI scan (mean (M) age = 56 years).

2. Method

2.1. Study design and participant selection

The study from which these data were drawn is known as 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 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) in 1995, 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. After providing written informed consent, a total of 349 individuals were enrolled in the study. Participants were administered a comprehensive neuropsychological battery and clinical examination annually, and MRI scans, 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 biomarkers was reinitiated, and amyloid imaging was begun.

2.2. Clinical assessments and consensus diagnoses

Since the study has been conducted at Johns Hopkins, annual clinical assessments have 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 (CDR) based on a semi-structured interview (Hughes et al., 1982; Morris, 1993). Clinical assessments given at the NIH covered similar domains. Annual cognitive assessments consist of a neuropsychological battery covering all major cognitive domains (for comprehensive details, see Albert et al., 2014).

The consensus diagnosis procedures implemented by the Johns Hopkins team have been comparable with those used in the National Institute on Aging Alzheimer's Disease Centers program: (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. These three sources of data were used to determine whether a participant was impaired. If a participant was impaired, the likely etiology of the impairment was identified. Then, the age at which the clinical symptoms began was estimated, based primarily on the reports of the participant and collateral source derived from the CDR. This same diagnostic process was retrospectively applied to participants who had become cognitively impaired while the study was being conducted at the NIH.

2.3. MRI assessments, image processing and regions of interest

The baseline MRI scans included in the present study were acquired at the NIH. Scans were obtained using a standard multimodal protocol using a GE 1.5T scanner. The scanning protocol included localizer scans, axial Fast Spin Echo sequence (repetition time (TR) = 4250, echo time (TE) = 108, field of view (FOV) = 512 × 512, thickness/gap = 5.0/0.0 mm, flip angle = 90, 28 slices), axial Flair sequence (TR = 9002, TE = 157.5, FOV = 256 × 256, thickness/gap = 5.0/0.0 mm, flip angle = 90, 28 slices), 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), sagittal SPGR sequence (TR = 24, TE = 3, FOV = 256 × 256, thickness/gap 1.5/0.0 mm, flip angle = 45, 124 slices).

Cortical reconstruction and estimation of cortical thickness was performed on the coronal SPGR scans 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, 1999b, 2004b). Briefly, processing includes removal of non-brain tissue (Segonne et al., 2004), segmentation of the subcortical white matter and deep gray matter structures (Fischl et al., 2002, 2004a), tessellation of the gray matter-white matter boundary, and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders (Dale et al., 1999; Dale and Sereno, 1993; Fischl and Dale, 2000). Parcellation of the cerebral cortex into