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Progressive medial temporal lobe atrophy during preclinical Alzheimer's disease

Corinne Pettigrew[a], Anja Soldan[a,*], Kelly Sloane[a], Qing Cai[b], Jiangxia Wang[b], Mei-Cheng Wang[b], Abhay Moghekar[a], Michael I. Miller[c], Marilyn Albert[a], the BIOCARD Research Team

[a] Department of Neurology, Johns Hopkins School of Medicine, Baltimore, MD 21205, United States
[b] Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, United States
[c] Department of Biomedical Engineering, Johns Hopkins University, Baltimore, MD 21218, United States

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ABSTRACT

This study examined whether longitudinal MRI trajectories in medial temporal lobe (MTL) brain regions differed among groups of cognitively normal individuals defined by their cerebrospinal fluid (CSF) levels when they were first enrolled (N = 207; mean clinical follow-up = 13.3 years (max = 20 years), mean MRI follow-up = 2.4 - years (max = 8 years)). We first compared atrophy rates among groups defined by CSF amyloid and phosphorylated-tau (p-tau) vs. CSF amyloid and total tau (t-tau). We also examined whether, in the presence of amyloid or tau/p-tau, the atrophy rates differed based on whether the subjects ultimately progressed to a diagnosis of mild cognitive impairment (MCI), as well as whether apolipoprotein ε4 (Apoε4) status had an impact on the longitudinal MRI trajectories. The primary finding was that when the groups were defined using CSF amyloid and p-tau, individuals with low levels of CSF amyloid and high levels of CSF p-tau (referred to as Stage 2) showed a significantly greater rate of atrophy in a composite measure of MTL volumes compared to groups defined by evidence of abnormal CSF levels in only one of the brain proteins (but not both), or no evidence of CSF abnormality. In contrast, there were no differences in rate of MTL atrophy when the groups were defined by levels of CSF amyloid and t-tau (instead of p-tau). Additionally, the rate of MTL atrophy did not differ between subjects who progressed to MCI at follow-up vs. those who remained cognitively normal when CSF levels of amyloid, t-tau, or p-tau were covaried. Lastly, the presence of an APOE ε4 genotype did not modulate the degree of MTL atrophy once baseline levels of CSF amyloid, p-tau or t-tau were accounted for. These results suggest that abnormal levels of CSF amyloid and CSF p-tau (but not t-tau) maximize the likelihood of observing significant MTL atrophy over time among individuals with normal cognition at baseline, and emphasize the importance of differentiating biomarkers that primarily reflect neurofibrillary tangle pathology (CSF p-tau) compared with biomarkers of neuronal injury (CSF t-tau).

1. Introduction

The pathological processes underlying Alzheimer's disease (AD) begin years to decades prior to the emergence of clinical symptoms, during the preclinical phase of AD (Sperling et al., 2011). The early development of AD pathology has particular importance for the timing of intervention strategies, as it is hypothesized that interventions will be most successful if initiated prior to the occurrence of substantial neuronal loss, and progression to the symptomatic phase of AD, commonly referred to as Mild Cognitive Impairment (MCI). As a result, considerable effort is being devoted to planning clinical trials for those with preclinical AD. Magnetic resonance imaging (MRI) measures are of particular interest in this regard, since studies among individuals with MCI suggest that MRI may be well suited for tracking the evolution of disease and thus informative with respect to response to treatment. There are, however, few studies that can provide information about MRI measures that might be most useful for tracking disease during the preclinical phase of AD.

A small number of studies have examined regional brain volumes, demonstrating that a set of MRI measures obtained when individuals are cognitively normal are associated with the time to onset of the clinical symptoms of MCI (Csernansky et al., 2005; Soldan et al., 2015; Pettigrew et al., 2016). Several studies have examined the relationship of atrophy rates in various brain regions to the presence of abnormal levels of the primary brain proteins associated with AD, as measured in cerebrospinal fluid (CSF) (Desikan et al., 2011; Pegueroles et al., 2017),

* Corresponding author at: Division of Cognitive Neuroscience, 1620 McElderry Street, Reed Hall 1-West, Baltimore, MD 21205, United States.
E-mail address: asoldan1@jhmi.edu (A. Soldan).

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or in relation to cut-points derived from brain imaging, such as Flourodeoxyglucose (FDG) (Knopman et al., 2013; Jack et al., 2014; Gordon et al., 2016; Knopman et al., 2016). Taken together, these studies have reported greater atrophy in the medial temporal and temporo-parietal cortical regions among cognitively normal individuals who have evidence of abnormalities based either on CSF protein levels or imaging cut-points.

The primary limitation of these studies is, however, that the follow-up period for the participants has been quite limited, approximately 2–4 years for most studies. Moreover, none of the analyses published to date, to our knowledge, have examined atrophy rates in cognitively normal individuals in relation to their subsequent development of MCI. In the current analyses, we stratified cognitively normal participants based on their CSF levels of AD-related proteins and examined MRI atrophy rates in relation to these subgroups. We also compared these findings between those cognitively normal individuals who remained normal vs. those who progressed to MCI. Additionally we examined the impact of apolipoprotein E (ApoE) genetic status on MRI atrophy rates.

To address these issues, we examined data from a cohort of cognitively normal individuals who have been followed clinically for a mean of 13.3 years (SD = 3.8). The mean MRI follow-up time was 2.4 years, but 81 subjects had an MRI follow-up time of 4–8 years, allowing us to estimate longer MRI trajectories than previous studies. We classified the subjects into subgroups, based on their CSF levels of amyloid and either total tau (t-tau) or phosphorylated tau (p-tau), when they were first enrolled. We based our classification scheme on the hypothetical staging model proposed by the Preclinical AD Workgroup sponsored by the National Institute on Aging and the Alzheimer's Association (NIA-AA) (Sperling et al., 2011). This model proposed that the preclinical phase of AD can be divided into several successive stages: (1) Stage 0 includes individuals with no evidence of either amyloid or tau-related neuronal injury; (2) Stage 1 includes individuals with biomarker evidence of amyloid pathology, but no evidence of neuronal injury; (3) Stage 2 includes individuals with biomarker evidence of both amyloid accumulation and neuronal injury; and (4) Stage 3 includes individuals with evidence of subtle cognitive decline in combination with biomarker evidence of both amyloid pathology and neuronal injury. Subsequently, an additional group of individuals were described, those with no evidence of amyloid pathology but with evidence of tau-related neuronal injury, referred to as suspected non-AD pathology (SNAP) (Jack et al., 2012).

In the present study we compared MRI atrophy rates in several medial temporal lobe (MTL) brain regions in four groups of individuals who were cognitively normal when first enrolled: Stage 0, 1, 2 and SNAP, as defined above. Stage 3 was omitted, since criteria for this stage are not well developed. The substantial sample size in the current study (N = 207) allowed us to address several issues that remain unresolved by prior investigations. First, we compared atrophy rates among groups defined by CSF amyloid and p-tau vs. CSF amyloid and t-tau in order to determine if there were differential rates of atrophy depending on which brain proteins are abnormal. Based on prior analyses of cognitive and imaging data in this cohort (Pettigrew et al., 2016; Soldan et al., 2016b), we hypothesized that the individuals with accumulations of both amyloid and p-tau would show the highest atrophy rates. This issue is also of theoretical importance since a recent A/T/N classification system (Jack et al., 2016) proposes that biomarkers of neurofibrillary tangle pathology (as reflected by CSF p-tau and tau PET imaging) should be classified separately from biomarkers of neuronal injury (e.g., CSF t-tau, FDG PET). Second, we examined whether the atrophy rates differed based on whether the subjects ultimately progressed to a diagnosis of MCI. Previous studies have not been able to address this issue due to the limited duration of follow-up. Third, we examined whether genetic status, specifically ApoE-4 status, had an impact on the longitudinal MRI trajectories (the major genetic risk factor for AD; Corder et al., 1993); we hypothesized that atrophy rates would not differ between those who were ApoE ε4 positive vs. negative, based on prior analyses of cognitive change within this cohort (Albert et al., 2014).

2. Material and methods

2.1. Study design

The data reported here were derived from the BIOCARD study, which was designed to recruit and follow a cohort of cognitively normal individuals who were primarily middle-aged at baseline. The overarching goal was to identify variables among cognitively normal individuals that could predict subsequent development of mild to moderate symptoms of AD. The study was initiated at the National Institutes of Health (NIH) in 1995 and stopped in 2005 for administrative reasons. During the initial study at the NIH, participants were administered a comprehensive neuropsychological battery annually, and magnetic resonance imaging, CSF samples, and blood specimens were obtained approximately every 2 years. In 2009, a research team at the Johns Hopkins School of Medicine was funded to re-establish the cohort, continue annual cognitive and clinical assessments, and evaluate the previously collected MRI scans, and CSF and blood specimens. In 2015, the collection of MRI and CSF biomarkers was re-initiated, and amyloid imaging begun.

2.2. Selection of participants

Recruitment procedures, baseline evaluations, annual clinical and cognitive assessments, and consensus diagnosis procedures have been described in detail previously (Albert et al., 2014). Briefly, recruitment was conducted by the staff of the geriatric psychiatry branch of the intramural program of the National Institute of Mental Health between 1995 and 2005. At baseline, all individuals completed a comprehensive evaluation at the NIH consisting of a physical and neurological examination, an electrocardiogram, standard laboratory studies, and neuropsychological testing. Individuals were excluded from participation if they were cognitively impaired or had significant medical problems, such as severe cerebrovascular disease, epilepsy, or alcohol or drug abuse. A total of 349 cognitively normal individuals were initially enrolled in the study after providing written informed consent. By design, approximately 75% of the participants had a first-degree relative with dementia of the Alzheimer type. The analyses presented herein are based on 207 participants who provided baseline CSF biomarkers within 12 months of their baseline MRI scan (M gap time = 8.4 days between MRI and CSF measures, SD = 37.8). The study was approved by the Johns Hopkins University (JHU) Institutional Review Board.

2.3. Clinical and cognitive assessments

Cognitive and clinical assessments and consensus diagnosis procedures were completed annually at both the NIH and JHU (see Albert et al., 2014, for details). Each participant included in our analyses received a consensus diagnosis by the staff of the JHU BIOCARD Clinical Core. All cases were handled in a manner, comparable with those used in the National Institute on Aging Alzheimer's Disease Centers program: (1) clinical data pertaining to the medical, neurological, and psychiatric status of the individual were examined; (2) reports of changes in cognition by the individual and by collateral sources were reviewed; and (3) decline in cognitive performance, based on review of longitudinal testing from multiple domains, was established. We followed the diagnostic recommendations incorporated in the NIA-AA working group reports for the diagnosis of MCI (Albert et al., 2011) and dementia due to AD (McKhann et al., 2011). The clinical diagnoses were masked to biomarker assessments. Each individual's most recent (i.e., last) diagnosis was coded by a dichotomous indicator variable: 0 if participants have remained cognitively normal over time, or 1 if they have since progressed from normal cognition to clinical symptoms of MCI or