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Inferring changepoint times of medial temporal lobe morphometric change in preclinical Alzheimer's disease

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ABSTRACT

This paper uses diffeomorphometry methods to quantify the order in which statistically significant morphometric change occurs in three medial temporal lobe regions, the amygdala, entorhinal cortex (ERC), and hippocampus among subjects with symptomatic and preclinical Alzheimer's disease (AD). Magnetic resonance imaging scans were examined in subjects who were cognitively normal at baseline, some of whom subsequently developed clinical symptoms of AD. The images were mapped to a common template, using shape-based diffeomorphometry. The multidimensional shape markers indexed through the temporal lobe structures were modeled using a changepoint model with explicit parameters, specifying the number of years preceding clinical symptom onset. Our model assumes that the atrophy rate of a considered brain structure increases years before detectable symptoms.

The results demonstrate that the atrophy changepoint in the ERC occurs first, indicating significant change 8–10 years prior to onset, followed by the hippocampus, 2–4 years prior to onset, followed by the amygdala, 3 years prior to onset. The ERC is significant bilaterally, in both our local and global measures, with estimates of ERC surface area loss of 2.4% (left side) and 1.6% (right side) annually. The same changepoint model for ERC volume gives 3.0% and 2.7% on the left and right sides, respectively. Understanding the order in which changes in the brain occur during preclinical AD may assist in the design of intervention trials aimed at slowing the evolution of the disease.

1. Introduction

Brain imaging and MRI studies have substantially advanced our knowledge of regional brain atrophy in Alzheimer's disease (AD). Magnetic resonance imaging (MRI) measures are an indirect reflection of the neuronal injury that occurs in the brain as the AD pathophysiological process evolves. In the initial stages of AD, atrophy on MRI appears to have a predilection for the brain regions with heavy deposits of neurofibrillary tangles (Braak and Braak, 1991; Arnold et al., 1991; Price and Morris, 1999). Consistent with this pattern, the volume of the entorhinal cortex, the hippocampus and other medial temporal lobe structures has been shown to discriminate between patients with AD dementia and controls, and between subjects with mild cognitive impairment (MCI) and controls, and to be associated with time to progress from MCI to AD dementia (Kantarci and Jack, 2003; Atiya et al., 2003). Longitudinal MRI data in cognitively normal individuals who have progressed to mild impairment (i.e., preclinical AD) is limited but suggests that volumetric measures of medial temporal lobe regions may predict progression from normal cognition to mild impairment. Differences in atrophy rate of the entorhinal cortex (Jack et al., 2004; Miller et al., 2013a), the hippocampus or subvolumes of the hippocampus (Jack et al., 2004; Apostolova et al., 2010) and ventricular volume (Carlson et al., 2008) have been demonstrated during preclinical AD. It has also been demonstrated that baseline measures of the hippocampus and amygdala in controls predict subsequent development of MCI (den Heijer et al., 2006), with hippocampus shape differences being reported among controls who subsequently developed cognitive impairment (Rusinek et al., 2003; Chiang et al., 2009; Csernansky et al., 2005; den Heijer et al., 2006; Thambisetty et al., 2010).

Methods of statistical analysis based on diffeomorphometry for studying normal age-related changes in subcortical nuclei and in a

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment; ERC, entorhinal cortex; NIH, Clinical Center of the National Institutes of Health; NIA, National Institute on Aging; NIMH, National Institute for Mental Health; GPB, Geriatric Psychiatry Branch; SPGR, spoiled gradient echo; CDR, clinical dementia rating; FWER, family-wise error rate; ROI-LDDMM, region-of-interest large deformation diffeomorphic metric mapping; RSS, residual sum of squares; MMSE, mini-mental state exam; diffeomorphometry, study of shape using a metric on the diffeomorphic connections between structures.

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number of other diseases have already been enlightening (Qiu et al., 2010; Qiu et al., 2009a; Csernansky et al., 1998; Csernansky et al., 2000; Wang et al., 2007; Ashburner et al., 2003; Thompson et al., 2004; Younes et al., 2012; Tang et al., 2013). This study follows our previous study in the same subject population (Miller et al., 2013a) in which we used diffeomorphometry to measure subregional atrophy in three structures of the temporal lobe, entorhinal cortex (ERC), hippocampus and amygdala and demonstrated statistically significant changes in brain structures during preclinical AD. These prior results are consistent with histopathological findings that suggest that these regions are affected during the earliest phase of AD (Arriagada et al., 1992; Herzog and Kemper, 1980; Scott et al., 1991; Scott et al., 1992; Tsuchiya and Kosaka, 1990). This approach allows for a fine-scale, high-dimensional, analysis of non-uniform change patterns in the structures, and complements coarser low-dimensional measures, like structure volume.

The study described here focuses on the temporal order of atrophy of the same three structures. The diffeomorphometry pipeline follows our general pattern (Younes et al., 2012; Tang et al., 2013; Miller et al., 2013a), first involving an initial coarse rigid alignment phase followed by a high-dimensional template-matching phase. This registers all shape morphometry to a single template coordinate system, which is centered to the population, producing a high-dimensional representation of the data in a coordinate system in which each coordinate is directly comparable across the population. The statistical analysis uses multivariate models including a nonlinear component defining a changepoint in atrophy over time, with significance assessed while taking multiple comparisons into account. The introduction of the changepoint model offers the opportunity to quantify the temporal ordering of morphometric changes among these temporal lobe structures in preclinical AD (i.e., the ERC, hippocampus and amygdala), which we have already found to be discriminating in these groups of temporal lobe structures in preclinical AD (Miller et al., 2013a). No modeling of the order in years preceding clinical onset has yet been explicitly modeled or demonstrated to our knowledge.

2. Subjects and data acquisition

2.1. Study design

The overall study (known as the BIOCARD study), is a longitudinal characterization of individuals funded jointly by the National Institutes on Aging (NIA) and Mental Health (NIMH). All BIOCARD subjects were cognitively normal when recruited with mean age at baseline of 57.1 years. Scans were acquired during the period 1995–2005. A total of 805 scans have been collected during the 10-year period. The participants have now been followed for up to 18 years.

A total of 354 individuals were initially enrolled in the study. Recruitment was conducted by the staff of the Geriatric Psychiatry branch of the Intramural Program of the NIMH, beginning in 1995 and ending in 2005. Subjects were recruited via printed advertisements, articles in local or national media, informational lectures, or word-of-mouth. The study was designed to recruit and follow a cohort of cognitively normal individuals who were primarily in middle age. By design, approximately three-quarters 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. Subjects were administered a comprehensive neuropsychological battery annually. MRI scans, cerebrospinal fluid (CSF), and blood specimens were obtained every 2 years. The study was initiated at the Clinical Center of the National Institutes of Health (NIH) in 1995, and was stopped in 2005. In 2009, our research team 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.

At baseline, all participants completed a comprehensive evaluation at the NIH. This evaluation consisted of a physical and neurological examination, an electrocardiogram, standard laboratory studies (e.g., complete blood count, vitamin B12, thyroid function), and neuropsychological testing. 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. Five subjects did not meet the entry criteria and were excluded at baseline, leaving a total of 349 participants followed over time.

2.2. MRI assessments

MRI scans were obtained on 335 participants at baseline. An additional 470 scans were obtained in subsequent years for a total of 805 scans. The mean interval between scan acquisitions on follow-up was 2.02 years. The MRI scans acquired at the NIH were obtained using a standard multi-modal protocol using GE 1.5 T scanner. The scanning protocol included localizer scans, axial FSE sequence (TR = 4250 ms, TE = 108 ms, FOV = 512 × 512, thickness/gap = 5.0/0.0 mm, flip angle = 90°, 28 slices), axial FLAIR sequence (TR = 9002 ms, TE = 157.5 ms, FOV = 256 × 256, thickness/gap = 5.0/0.0 mm, flip angle = 90°, 28 slices), coronal SPGR (spoiled gradient echo) sequence (TR = 24 ms, TE = 2 ms, FOV = 256 × 256, thickness/gap = 2.0/0.0 mm, flip angle = 20°, 124 slices), sagittal SPGR sequence (TR = 24 ms, TE = 3 ms, FOV = 256 × 256, thickness/gap 1.5/0.0 mm, flip angle = 45°, 124 slices).

2.3. Clinical and cognitive assessments

The clinical and cognitive assessments of the participants have been described elsewhere (Soldan et al., 2013). The cognitive assessment consisted of a neuropsychological battery covering all major cognitive domains (i.e., memory, executive function, language, spatial ability, attention and processing speed). A clinical assessment was also conducted annually. Since the study has been conducted by the current research team, this has included the following: a physical and neurological 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). The clinical assessments given at the NIH covered similar domains. The diagnostic procedures in this study are comparable to those used in the Alzheimer's disease research centers program, funded by the National Institute on Aging. This involves a two-step process by which a decision is first made about whether the subject is normal, mildly impaired or demented (based on the clinical history, medical, neurologic and psychiatric evaluations and the cognitive testing), and then (if the subject is judged not to be normal) the likely cause(s) of the cognitive impairment is determined. This same diagnostic process was applied retrospectively to participants who had become cognitively impaired while the study was being conducted at the NIH, but who (by the time the study had been re-established) were either moderate-to-severely impaired or were no longer living. It should be noted that the estimated age-of-onset of clinical symptoms, which is the primary outcome in these analyses, was established on the basis of clinical information elicited during the CDR interview by the clinician who evaluated the subject (or on the basis of clinical notes in the record), and re-confirmed during the consensus conference.

2.4. MRI scans available for analysis

Some subjects were removed from the analysis for uncertain diagnostic (impairment not categorized as MCI) and several scans had to