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High-dimensional morphometry

Amygdalar atrophy in symptomatic Alzheimer's disease based on diffeomorphometry: the BIOCARD cohort☆

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ABSTRACT

This article examines the diffeomorphometry of magnetic resonance imaging-derived structural markers for the amygdala, in subjects with symptomatic Alzheimer's disease (AD). Using linear mixed-effects models we show differences between those with symptomatic AD and controls. Based on template centered population analysis, the distribution of statistically significant change is seen in both the volume and shape of the amygdala in subjects with symptomatic AD compared with controls. We find that high-dimensional vertex based markers are statistically more significantly discriminating ($p < 0.00001$) than lower-dimensional markers and volumes, consistent with comparable findings in presymptomatic AD. Using a high-field 7T atlas, significant atrophy was found to be centered in the basomedial and basolateral subregions, with no evidence of centromedial involvement.

1. Introduction

Magnetic resonance imaging (MRI) studies have substantially advanced our knowledge of brain atrophy in Alzheimer's disease (AD). MRI measures are an indirect reflection of the neuronal injury that occurs in the brain as the AD pathophysiological process evolves. Several MRI measures are known to be altered among individuals with AD dementia or mild cognitive impairment (MCI). In the initial stages of AD, atrophy appears to have a predilection for brain regions in the medial temporal lobe with heavy deposits of neurofibrillary tangles (Arnold et al., 1991; Braak and Braak, 1991; Price and Morris, 1999). Consistent with this pattern of neurofibrillary pathology, the volume of the entorhinal cortex and hippocampus have been shown to discriminate patients with AD dementia or MCI versus cognitively normal subjects and to be associated with likelihood of progression from MCI to AD dementia (Atiya et al., 2003; Kantarci and Jack, 2004).

To date, most MRI studies of subcortical gray matter nuclei have defined a single measure of structural volume (Bossa et al., 2011; McEvoy et al., 2011; Roh et al., 2011). Although this has the advantage of being quantitative, it does not give specific information about subregions of atrophied nuclei. This information would be useful to determine whether morphometric results correlate with neuropathologic studies, define better the subregional distribution of atrophy, and correlate pathologic changes with clinical features of AD.

Diffeomorphometry and geodesic positioning in computational anatomy (Miller et al., 2014) for the study of the distribution of functional and structural change in neurodegeneration has already proved to be very powerful. Statistical shape analysis has been useful for studying normal age-related changes in subcortical nuclei, and a number of other diseases (Ashburner et al., 2003; Csernansky et al., 1998, 2000; Qiu et al., 2010; Thompson et al., 2004; Wang et al., 2007). The study described here follows our previous work (Miller et al., 2013), in which we used diffeomorphometry to measure subregional atrophy in 3 temporal lobe

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structures, entorhinal cortex, hippocampus, and amygdala, in subjects with preclinical AD, that is, individuals who were clinically and cognitively normal at the time of their MRI scans. This approach allows for a fine-scale high-dimensional analysis of nonuniform change patterns in the structures and complements coarser measures, such as measures of total volume. Despite its proximity to the hippocampus, relatively little is known about the role of amygdala in MCI and AD. Following earlier histopathologic findings (Arriagada et al., 1992; Herzog and Kemper, 1980; Scott et al., 1991, 1992; Tsuchiya and Kosaka, 1990), neuroimaging studies of AD patients suggest that amygdala volume may correlate with that of the hippocampus (Poulin et al., 2011). Further, recent shape analysis (Cavedo et al., 2011; Qiu et al., 2009) suggests there is substantial atrophy within the amygdala in AD.

The study described here focuses on the examination of the amygdala via diffeomorphometry. By mapping features across coordinate systems, it was possible to identify morphometric changes obtained in 1.5 T scans within high-field 7T parcellations of the amygdala. We demonstrate that the location of statistically significant change is distributed across the core amygdala, including the basolateral and basomedial nuclei, in subjects with symptomatic AD compared with controls.

2. Methods

2.1. Study design

In the present study, known as the BIOCARD study, all subjects were cognitively normal when they were recruited. The mean age of the BIOCARD subjects at baseline was 57.1 years. MRI scans were acquired during the period 1995–2005. The participants have now been followed for up to 17 years. Table 1 provides summary of the demographic characteristics of the subjects.

2.2. Selection of participants

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 National Institute of Mental Health (NIMH). 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. Toward that end, subjects were administered a comprehensive neuropsychological battery annually. MRI scans, cerebrospinal fluid, and blood specimens were obtained approximately every 2 years. The study was initiated at the NIMH in 1995 and was stopped in 2005. In 2009, a research team at the Johns Hopkins School of Medicine was jointly funded by the National Institute on Aging (NIA) and NIMH to reestablish the cohort, continue the annual clinical and cognitive assessments, collect blood, and evaluate the previously acquired MRI scans, cerebrospinal fluid, and blood specimens. To the best of our knowledge, this is the only study in participants who were cognitively normal at entry, with this set of measures, and with such a long duration of follow-up.

At baseline, all participants completed a comprehensive evaluation at the Clinical Center of the National Institutes of Health (NIH). This evaluation consisted of a physical and neurologic examination, an electrocardiogram, standard laboratory studies (e.g., complete blood count, vitamin B12, thyroid function, and so forth), 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 349 participants who were followed over time.

2.3. MRI assessments

The MRI scans acquired at the NIH were obtained using a standard multimodal protocol using GE 1.5 T 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 fluid-attenuated inversion recovery 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), and sagittal SPGR sequence (TR = 24, TE = 3, FOV = 256 × 256, thickness/gap 1.5/0.0 mm, flip angle = 45°, 124 slices). The analyses described here used the coronal SPGR scans. A total of 805 scans were acquired from the participants with a mean of 2.4 scans per person.

2.4. Clinical and cognitive assessment

The clinical and cognitive assessments of the participants have been described elsewhere (Moghekar 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. This included the following: a physical and neurologic 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).

2.5. Consensus diagnoses

Each case included in these analyses has received a consensus diagnosis by the staff of the BIOCARD Clinical Core at Johns Hopkins. This research team included: neurologists, neuropsychologists, research nurses, and research assistants. During the study visit, each subject had received a comprehensive cognitive assessment and a CDR, as well as a comprehensive medical evaluation (including a medical, neurologic, and psychiatric assessment).

Table 1
Participant characteristics stratified by outcome status

Variable	Control group (N = 230)	MCI during scan (N = 9)	AD dementia during scan (N = 7)
Age at time of baseline MRI scan, mean number of years (SD)	55.4 (9.8)	64.3 (9.96)	63.8 (8.04)
Gender, females (%)	61	33	57

Key: AD, Alzheimer's disease; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; SD, standard deviation.