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Effects of ApoE4 and maternal history of dementia on hippocampal atrophy

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Abstract

We applied an automated hippocampal segmentation technique based on adaptive boosting (AdaBoost) to the 1.5 T magnetic resonance imaging (MRI) baseline and 1-year follow-up data of 243 subjects with mild cognitive impairment (MCI), 96 with Alzheimer's disease (AD), and 145 normal controls (NC) scanned as part of the Alzheimer's Disease Neuroimaging Initiative (ADNI). MCI subjects with positive maternal history of dementia had smaller hippocampal volumes at baseline and at follow-up, and greater 12-month atrophy rates than subjects with negative maternal history. Three-dimensional maps and volumetric multiple regression analyses demonstrated a significant effect of positive maternal history of dementia on hippocampal atrophy in MCI and AD after controlling for age, ApoE4 genotype, and paternal history of dementia, respectively. ApoE4 showed an independent effect on hippocampal atrophy in MCI and AD and in the pooled sample.

Keywords: Alzheimer's disease; AD; Magnetic resonance imaging; MRI; Imaging; Maternal history; Hippocampus; Atrophy; Biomarker; Hereditary; Genetic

1. Introduction

As the world population continues to age, Alzheimer's disease (AD) is rapidly becoming a major, and increasing, health care concern. If novel successful therapeutic approaches do not become available, the number of patients with AD is expected to rise from 4.5 million in 2000 to 13.2 million in 2050 in the United States alone (Cummings, 2004; Hebert et al., 2003). The annual cost of care for AD patients worldwide is estimated at $83.9 billion (in 1996 US dollars) and will continue to increase with the rising prevalence of AD (Cummings, 2004; Wimo and Winblad, 2001). The predictions of significant limitations in healthcare resources for elderly care in the near future underscore the pressing need for understanding the pathophysiology of AD and more effective therapies.

The rare variants of early-onset familial AD have been attributed to autosomal dominant mutations in the amyloid precursor protein genes, presenilin 1 and presenilin 2 (Bertram and Tanzi, 2008). The genetics of late onset, sporadic AD are much less clear. Family history is the second greatest risk factor for sporadic AD after age (Tanzi and Bertram, 2001). Having a first-degree relative with AD increases one's risk for AD 4–10 fold (Cupples et al., 2004; Green et al., 2002; Mosconi et al., 2009; Silverman et al., 2005)

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suggesting a significant genetic component to the sporadic form of the disease. The apolipoprotein E4 (APOE4) gene has repeatedly demonstrated a strong association with late onset AD, but its prevalence of 40%–70% in the AD population suggests that additional genetic risk factors will be discovered (Bertram and Tanzi, 2009; Seripa et al., 2009; Slooter et al., 1998). Several genome-wide association studies have reported other candidate AD-associated genes that warrant further exploration (Bertram and Tanzi, 2009; Li et al., 2006; Rogaeva et al., 2007; Sundar et al., 2007). At the same time, epidemiologic studies have suggested that subjects with maternal history of AD have increased risk of developing the disease (Edland et al., 1996; Ehrenkrantz et al., 1999; Green et al., 2002). The Framingham Offspring study reported that middle-aged individuals with AD-affected mothers show deficient neuropsychological test performance compared with those with AD-affected fathers and those lacking parental history of AD (Wolf et al., 2005). Recently Mosconi et al. reported that relative to subjects with no paternal history of AD those with maternal history of AD not only show decreased glucose uptake in AD-vulnerable regions on positron emission tomography (PET) examination cross-sectionally (Mosconi et al., 2007) but also exhibit progressive decline in glucose uptake in these regions over time (Mosconi et al., 2009). In addition, two recent structural MRI studies examined the effect of parental history of dementia on hippocampal and total brain volume (Debette et al., 2009) and gray matter volume (Honea et al., 2010). The larger study (Debette et al., 2009) reported no effect of history of parental dementia on hippocampal and total brain volume at baseline, or on total brain volume and hippocampal atrophy rates, in cognitively normal subjects. No significant associations were detected after stratification for ApoE4 status as well as for maternal/paternal history of dementia. The smaller study (Honea et al., 2010) likewise studied the effect of maternal and paternal history of AD on brain structure in cognitively normal elderly. They found significantly smaller inferior frontal, middle frontal, inferior temporal, and precuneal gray matter volumes, but no effect on hippocampal volume.

Here we wanted to further explore the effect of maternal history of dementia on the hippocampus, an area affected early by AD pathology. We hypothesized that maternal history of dementia would be associated with greater hippocampal atrophy relative to that seen in groups of subjects with paternal or no parental history of dementia.

1.1. List of important abbreviations

"MH" denotes maternal history.
"PH" denotes paternal history.
"MH+/PHany" denotes positive maternal history of dementia (including subjects with positive and negative paternal history of dementia).
"MHany/PH+" denotes positive paternal history of dementia (including subjects with positive and negative maternal history of dementia).
"MH−/PHany" denotes negative maternal history of dementia (including subjects with positive and negative paternal history of dementia).
"MHany/PH−" denotes negative paternal history of dementia (including subjects with positive and negative maternal history of dementia).
"MH+/PH+" denotes positive maternal and paternal history of dementia.
"MH+/PH−" denotes positive maternal and negative paternal history of dementia.
"MH−/PH−" denotes no maternal and no paternal history of dementia.

2. Methods

2.1. Subjects

The Alzheimer Disease Neuroimaging Intitiative (ADNI) is a large scale multi-site longitudinal study collecting detailed clinical, imaging, and laboratory data from 200 normal control (NC), 400 amnestic mild cognitive impairment (MCI), and 200 AD subjects at multiple time points over a 4-year period (Mueller et al., 2005) (also see http://www.loni.ucla.edu/ADNI and ADNI-info.org). ADNI's goal is to establish risk factors associated with cognitive decline from normal aging to MCI and from MCI to AD, as well as to assist the development of sensitive disease-specific biomarkers for early diagnosis and the development of effective therapeutic agents for AD. All ADNI participants were 55–90 years old at the time of enrollment. Subjects were excluded if they had any significant neurologic disease other than AD, abnormal baseline magnetic resonance imaging (MRI) scan or contraindications to MRI, psychiatric disorder, alcohol or substance abuse or dependency within the last 2 years, and medical illnesses that could affect cognition or protocol compliance. Other grounds for exclusion were residence in a skilled nursing facility, use of psychoactive medications other then certain antidepressants, warfarin, or investigational agents. The full list of inclusion/exclusion criteria can be accessed on pages 20–30 of the online ADNI protocol (www.adni-info.org/images/stories/Documentation/adni_protocol_9_19_08.pdf).

NC subjects scored within age- and education-adjusted norms on the Logical Memory II subscale from Wechsler Memory Scale-Revised (LM II) (Wechsler, 1987), between 24 and 30 on the Mini Mental State Examination (MMSE) (Folstein et al., 1975), and 0 on the global score of the Clinical Dementia Rating Scale (CDR) (Morris, 1993). Subjects with MCI had memory complaints and scored below age- and education-adjusted norms on Logical Memory II subscale from Wechsler Memory Scale-Revised. The MMSE scores of MCI subjects at baseline were between 24 and 30 and their global CDR was 0.5. General cognition and