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.

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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 health-care 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).
“MAny/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).
“MAny/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 Initiative (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...
sufficiently preserved activities of daily living precluding
diagnosis of AD were also required for the diagnosis of
MCI. ADNI enrolled mildly affected AD subjects who met
the National Institute of Neurologic and Communicative
Disorders and Stroke/Alzheimer’s Disease and Related Dis-
orders Association (NINDS/ADRDA) criteria for probable
AD (McKhann et al., 1984). AD subjects had MMSE scores
between 20 and 26 and CDR of 0.5 or 1.

The present study used ADNI baseline and 1-year
follow-up cognitive and imaging data of 243 amnestic
MCI, 96 AD, and 145 NC subjects. Subjects were strat-
ified based on their family history of dementia collected
through self-report. Out of 484 subjects, 68 (14%) re-
ported paternal (MHany/PHany) and 167 (35%) maternal
history (MH+/PH-) of dementia. One hundred forty-
ine subjects had maternal but not paternal history of
deficiency (MH+/PH-). Fifty subjects had paternal but
not maternal history of dementia (MH-/PH+). Eighteen
subjects had both maternal and paternal history of de-
mentia (MH+/PH+) and 267 had neither maternal nor
paternal history of dementia (MH-/PH-).

2.2. Image acquisition and preprocessing

All subjects were scanned at 1.5 T magnetic field
strength, on scanners from 1 of 3 manufacturers (General
Electric Healthcare, Siemens Medical Solutions, and Philips
Medical Systems) with a scanner-specific standardized MRI
protocol (http://www.loni.ucla.edu/ADNI/Research/Cores/
index.shtml) (Jack et al., 2008; Leow et al., 2006). The
TE/TR/TI (echo, repetition, and inversion time) parameters
were set to optimize contrast with noise in a feasible acquisi-
tion time. The raw data had an acquisition matrix of 192 ×
192 × 166 and voxel size 1.25 × 1.25 × 1.2 mm³ (Jack
et al., 2008). Following an in-plane, zero-filled reconstruc-
tion (i.e., sinc interpolation) yielded a matrix of 256 × 256
and a voxel size of 0.9375 × 0.9375 × 1.2 mm³. Two
T1-weighted MRI sessions were collected from each subject
at each visit. The image with greater apparent signal-to-
noise ratio was selected by the ADNI MRI quality control
center at the Mayo Clinic (Rochester, MN, USA) (Jack et
al., 2008). The ADNI MRI quality control center reviewed
each scan (including T2-weighted and proton density scans)
for structural abnormalities such as cortical or subcortical
strokes, significant white matter ischemic changes, focal
lesions, etc. Subjects in whom structural abnormalities were
found were excluded from participation. All scans were sub-
jected to additional image corrections including GradWarp
correction for geometric distortions due to gradient nonlinear-
arity (Jovicich et al., 2006), “B1-correction” for image
intensity nonuniformity (Jack et al., 2008) and “N3” bias
field correction, for reducing intensity inhomogeneity (Sled
et al., 1998). Both uncorrected and corrected imaging data
were transmitted to the central repository site at the Labo-

2.4. Statistical methods

We used analysis of variance (ANOVA) to compare age, education and MMSE score between the diagnostic groups. A chi-squared test was used to compare the gender distribution between the groups. We used a 2-tailed Student’s t-test to compare the baseline and follow-up volume of all subjects with positive maternal history of dementia (MH+/PHany) vs. all subjects with negative maternal history of dementia (MH−/PHany) and all subjects with positive paternal history of dementia (MHany/PH+) vs. all subjects with negative paternal history of dementia (MHany/PH−), as well as MH+/PH− vs. MH−/PH+ in the pooled sample and in each diagnostic group. Next we constructed multiple linear regression models with hippocampal volume or hippocampal radial distance at 12 months, respectively as the dependent variables and MH, PH, as well as ApoE4 genotype (coded as ApoE4 allele present or absent) as predictor variables. Age and hippocampal volume at baseline were included as covariates in the volumetric and radial distance linear regression models. The 3D radial distance regression results were further corrected for multiple comparisons using permutation testing at a predefined threshold of \( p < 0.01 \). Permutation analyses allow us to derive a single overall corrected \( p \)-value for each 3D statistical output based on the number of surface points surviving a particular a priori threshold (0.01 in our analyses). For more details on the permutation approach, please see Thompson and Apostolova (2007).

3. Results

The mean group demographic characteristics are presented in Table 1. There were statistically significant differences in age and the prevalence of the ApoE4 allele between the groups. There were no differences in sex, race, education, or mean MMSE scores.

3.1. Volumetric results

Hippocampal volumetric data are provided in Table 2. In the pooled sample, MH+/PHany subjects had smaller right hippocampal volumes at both baseline (\( p = 0.056 \); mean absolute difference 3.7%) and follow-up (\( p = 0.009 \); mean absolute difference 5.5%), and significantly greater right hippocampal atrophy rate (3.9% vs. 2.1%, \( p = 0.035 \)) relative to MH−/PHany subjects. MH+/PH− showed trend-level smaller right hippocampal volume at follow-up relative to to MH−/PH− (\( p = 0.057 \)).

Relative to MH−/PHany MCI subjects, MH+/PHany MCI subjects had smaller right hippocampal volumes at both baseline (\( p = 0.032 \); mean absolute difference 6%) and follow-up (\( p = 0.04 \); mean absolute difference 9.5%) and significantly greater mean atrophy rate on the right (5.7% vs. 2.7%, \( p = 0.01 \)). MH+/PH− MCI subjects showed trend-level smaller hippocampal volumes relative to MH−/PH− MCI subjects at baseline (\( p = 0.072 \)), significantly smaller right hippocampal volume in follow-up (\( p = 0.011 \)), and significantly greater right atrophy rate (5.7% vs. 2.8%, \( p = 0.027 \)). In both the pooled sample and the MCI group, left-sided atrophy rates among MH+/PHany subjects were higher than in MH−/PHany subjects (pooled sample: 3.7% vs. 2.6%; MCI 3% vs. 2.2%) but the group difference failed to reach statistical significance.

In AD, MH+/PHany subjects had generally larger volumes than MH−/PHany subjects. This difference reached statistical significance on the left at both time points (baseline \( p = 0.01 \); mean absolute difference 9%; at follow-up, \( p = 0.013 \); mean absolute difference 14%); however the atrophy rates were not statistically different. When comparing MH+/PH− to MH−/PH− AD subjects the findings remained unchanged.

There were no significant volumetric or atrophy rate differences between MH+/PHany and MH−/PHany or between MH+/PH− and MH−/PH− in the NC group.

MHany/PH+ subjects had consistently larger hippocampal volumes than MHany/PH− subjects across all groups, but the difference reached significance only in the pooled sample on the left (left hippocampal baseline volume \( p = 0.033 \), mean absolute difference 6.7%; left follow-up volume \( p = 0.036 \), mean absolute difference 6%). When comparing MH−/PH− to MH−/PH+ subjects, the difference was no longer statistically significant.

### Table 1

Demographic characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>MH+/PH− (n = 149)</th>
<th>PH+/MH− (n = 50)</th>
<th>MH+/PH+ (n = 18)</th>
<th>MH−/PH− (n = 267)</th>
<th>ANOVA/chi-squared p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>74.1 (6.1)</td>
<td>75.2 (6.8)</td>
<td>76.3 (6.7)</td>
<td>74.8 (7.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>Education, yr</td>
<td>16.1 (2.7)</td>
<td>15.4 (7.2)</td>
<td>15.6 (3.1)</td>
<td>16.5 (2.5)</td>
<td>0.16</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>78:71</td>
<td>27:23</td>
<td>11:7</td>
<td>166:101</td>
<td>0.24</td>
</tr>
<tr>
<td>Race, % white</td>
<td>94.6%</td>
<td>98%</td>
<td>92.1%</td>
<td>94.4%</td>
<td>0.51</td>
</tr>
<tr>
<td>ApoE4+, %</td>
<td>61.1%</td>
<td>48%</td>
<td>76.5%</td>
<td>40.1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diagnostic breakdown</td>
<td>28% NC</td>
<td>32% NC</td>
<td>17% NC</td>
<td>32% NC</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>48% MCI</td>
<td>52% MCI</td>
<td>50% MCI</td>
<td>51% MCI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24% AD</td>
<td>16% AD</td>
<td>33% AD</td>
<td>17% AD</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>26.7 (2.6)</td>
<td>27.0 (2.3)</td>
<td>27.1 (2.5)</td>
<td>26.0 (3.3)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Chi-squared test for differences in diagnostic breakdown between MH+/PHany and PH+/MHany, \( p = 0.5 \)

Key: ANOVA, analysis of variance; F, female; M, male; MH, maternal history; MMSE, Mini Mental State Examination; PH, paternal history.
Table 2
Hippocampal volumetric data

<table>
<thead>
<tr>
<th>Side</th>
<th>MH+/PH−</th>
<th>PH+/MH−</th>
<th>MH+/PH+</th>
<th>MH−/PH−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled sample (n)</td>
<td>n = 149</td>
<td>n = 50</td>
<td>n = 18</td>
<td>n = 267</td>
</tr>
<tr>
<td>Left</td>
<td>3787 (725)</td>
<td>4039 (639)</td>
<td>3928 (693)</td>
<td>3796 (831)</td>
</tr>
<tr>
<td>Right</td>
<td>3572 (776)</td>
<td>3888 (656)</td>
<td>3502 (799)</td>
<td>3669 (760)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3654 (775)</td>
<td>3949 (675)</td>
<td>3804 (752)</td>
<td>3708 (852)</td>
</tr>
<tr>
<td>Right</td>
<td>3441 (801)</td>
<td>3796 (682)</td>
<td>3348 (902)</td>
<td>3598 (800)</td>
</tr>
<tr>
<td>NC (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>4019 (696)</td>
<td>4309 (675)</td>
<td>4557 (487)</td>
<td>4088 (628)</td>
</tr>
<tr>
<td>Right</td>
<td>3933 (552)</td>
<td>4222 (670)</td>
<td>3746 (494)</td>
<td>3946 (709)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3909 (799)</td>
<td>4237 (725)</td>
<td>4363 (640)</td>
<td>4054 (591)</td>
</tr>
<tr>
<td>Right</td>
<td>3922 (536)</td>
<td>4128 (717)</td>
<td>3661 (431)</td>
<td>3971 (697)</td>
</tr>
<tr>
<td>MCI (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3700 (747)</td>
<td>4013 (617)</td>
<td>3765 (765)</td>
<td>3806 (802)</td>
</tr>
<tr>
<td>Right</td>
<td>3422 (774)</td>
<td>3797 (642)</td>
<td>3479 (106)</td>
<td>3620 (743)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3586 (790)</td>
<td>3929 (633)</td>
<td>3737 (657)</td>
<td>3721 (789)</td>
</tr>
<tr>
<td>Right</td>
<td>3233 (801)</td>
<td>3714 (664)</td>
<td>3350 (117)</td>
<td>3525 (766)</td>
</tr>
<tr>
<td>AD (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3700 (669)</td>
<td>3586 (345)</td>
<td>3858 (737)</td>
<td>3231 (962)</td>
</tr>
<tr>
<td>Right</td>
<td>3465 (878)</td>
<td>3516 (365)</td>
<td>3416 (470)</td>
<td>3303 (725)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>3500 (656)</td>
<td>3435 (368)</td>
<td>3626 (913)</td>
<td>3027 (103)</td>
</tr>
<tr>
<td>Right</td>
<td>3311 (838)</td>
<td>3402 (364)</td>
<td>3191 (656)</td>
<td>3123 (783)</td>
</tr>
</tbody>
</table>

Key: AD, Alzheimer’s disease; MCI, mild cognitive impairment; MH, maternal history; NC, normal control; PH, paternal history.

When directly comparing MH+/PH− vs. MH−/PH+ subjects, we found significantly smaller hippocampal volumes at baseline (left \( p = 0.03 \), mean absolute difference 6.7%; right \( p = 0.011 \), mean absolute difference 8.8%) and in follow-up (left \( p = 0.017 \), mean absolute difference 8.1%; right \( p = 0.005 \), mean absolute difference 10.3%) in the pooled sample. Next we examined these differences in each diagnostic group. The MCI comparison included 72 MH+/PH− and 26 MH−/PH+ MCI subjects. We found significantly smaller right hippocampal volume at baseline (left \( p = 0.06 \), mean absolute difference 8.5%; right \( p = 0.029 \), mean absolute difference 11%) and in follow-up (left \( p = 0.049 \), mean absolute difference 9.6%; right \( p = 0.007 \), mean absolute difference 14.9%) in MH+/PH− MCI vs. MH−/PH+ MCI subjects. For the NC comparison we had 41 MH+/PH− and 16 MH−/PH+ subjects. While we found smaller hippocampal volumes in MH+/PH− NC vs. MH−/PH+ NC subjects both at baseline and follow-up (baseline mean absolute difference 7.2% on the left and 7.4% on the right; follow-up mean absolute difference 8.4% on the left and 5.3% on the right), these differences failed to reach statistical significance. For the AD comparison we had 36 MH+/PH− and 8 MH−/PH+ AD subjects. MH+/PH− AD subjects had 3.2% larger left and 1.5% smaller right hippocampal volumes at baseline and 1.4% larger left and 2.8% smaller right hippocampal volumes at follow-up relative to MH−/PH+ AD subjects. These differences failed to reach statistical significance, again most likely because the available sample sizes in the subdivided categories were small. MH+/PH− subjects had nonsignificantly greater atrophy rates relative to MH−/PH+ both in the NC (left 3.2% vs. 2%; right 5.6% vs. 2.2%) and in the AD stage (left 5.2% vs. 4.2%; right 4% vs. 3.2%).

In the pooled sample ApoE4+ subjects had significantly smaller hippocampal volume at follow-up relative to ApoE4− subjects (left \( p = 0.01 \), mean absolute difference 5.2%; right \( p = 0.008 \), absolute difference 5.5%). ApoE4+ subjects also showed nonsignificantly smaller hippocampal volumes at baseline (left mean absolute difference 2.2%; right mean absolute difference 3.3%). There were no significant differences between baseline and follow-up hippocampal volumes between ApoE4+ and ApoE4− subjects in any diagnostic subgroup. The ApoE4 effects on hippocampal atrophy rates were reported in a previous publication (Morra et al., 2009).

All regression models were adjusted for age, education, and baseline hippocampal volume. After controlling for paternal history of dementia and ApoE4 genotype, positive MH was significantly associated with smaller right hippocampal volume at follow-up in the pooled sample (\( p = 0.04 \)) and in MCI (\( p = 0.007 \)). Positive MH showed no significant association with hippocampal volume at follow-up in NC and AD. Positive PH showed no statistically significant associations with hippocampal volume in the pooled sample or in any of the diagnostic groups.

After controlling for maternal and paternal diagnosis of dementia, ApoE4+ showed significant association with smaller hippocampal volume at follow-up in the pooled sample bilaterally (left \( p < 0.0001 \); right \( p = 0.005 \)) and on the left in MCI (\( p = 0.04 \)). A trend-level effect was present in AD on the left (\( p = 0.07 \)).

3.2. 3D imaging results

All 3D regression models (Fig. 1) were adjusted for age, education, and baseline hippocampal volume. After controlling for PH, ApoE4 genotype, age, and baseline hippocampal volume in our linear regression model and applying
Fig. 1. Three-dimensional maps showing the regionally significant effects of ApoE4 genotype and parental history of Alzheimer’s disease (AD) on hippocampal radial distance (areas in red and white show significant associations at $p < 0.05$; areas in blue are nonsignificant, $p > 0.1$).
stringent permutation-based correction for multiple comparisons MH showed a significant negative association with hippocampal radial distance on the left in subjects with MCI while showing a trend-level effect on the right (left $p_{\text{corrected}} = 0.033$; right $p_{\text{corrected}} = 0.08$). In some areas these effects were positive and in others negative. In AD, a significant negative effect of MH was seen on the right only ($p_{\text{corrected}} = 0.023$). There was no effect of MH on hippocampal radial distance in NC. PH did not show a significant effect on hippocampal radial distance in any of the statistical models after controlling for ApoE4 genotype and MH. ApoE4+ had a statistically significant negative effect on hippocampal radial distance independent of dementia history in any parent on the left in MCI (left $p_{\text{corrected}} = 0.02$) and bilaterally in AD (left $p_{\text{corrected}} = 0.05$; right $p_{\text{corrected}} = 0.043$) as well as in the pooled sample (left $p_{\text{corrected}} = 0.0003$; right $p_{\text{corrected}} = 0.0015$). ApoE4 showed no effect on hippocampal radial distance in NC after controlling for age and parental history of dementia ($p_{\text{corrected}} > 0.4$).

Direct comparisons of MH+/PH− vs. MH−/PH+ at baseline and at follow-up are shown in Fig. 2. Regionally significant areas showed 10%–35% smaller radial distance in MH+/PH− vs. MH−/PH+ in the pooled sample. After permutation-based correction for multiple comparisons, we found significant differences between the groups in the pooled sample on the right at baseline ($p_{\text{corrected}} = 0.028$) and on the left at follow-up ($p_{\text{corrected}} = 0.048$). The only diagnostic subgroup where the direct MH+/PH− vs. MH−/PH+ comparison resulted in significant permutation-corrected findings was MCI at follow-up (left $p_{\text{corrected}} = 0.03$; right $p_{\text{corrected}} = 0.09$). Despite observing regionally significant differences between MH+/PH− and MH−/PH+ in the NC and AD groups these statistical maps did not survive stringent permutation-based correction for multiple comparisons.

4. Discussion

A recently published positron emission tomography (PET) study demonstrated significant baseline hypometabolism in the posterior association cortices—known to be affected early in AD—in cognitively normal subjects with maternal history of dementia, while such an effect was absent in those with a paternal history of AD (Mosconi et al., 2007). In a follow-up study, the authors demonstrated progressive decline in posterior cortical glucose uptake in those with a maternal history of AD (Mosconi et al., 2009). The authors hypothesized that the observed differences may potentially reflect increased AD vulnerability in the offspring of female AD subjects. This theory can be tested only after prospective follow-up of large cohorts of subjects with and without parental history of AD and after assessing progression to AD. Other approaches using pre-existing longitudinal datasets such as the ADNI data as we have done here can examine evidence to support or refute this hypothesis.

Hippocampal atrophy is a well-established early imaging marker of AD (Apostolova et al., 2006a, 2006b; De Leon et al., 1997; Henneman et al., 2009; Jack et al., 1998, 2000). The factors that determine the rate of hippocampal atrophy are not yet completely understood. Recently several computational anatomy techniques have been successfully employed in predicting and tracking AD progression in vivo (Apostolova and Thompson, 2008; Apostolova et al., 2006b, 2009; Csernansky et al., 2000; Morra et al., 2009; Thompson et al., 2004; Wang et al., 2003). Here we used the radial distance mapping technique and conventional volumetric analyses to investigate the effects of MH and PH on hippocampal atrophy in a large ADNI cohort spanning the spectrum from normal aging to mild AD. As hypothesized, MH was associated with greater hippocampal atrophy in both the volumetric and 3D radial distance analyses independently of ApoE4 genotype and PH. As others have reported, we found no effect of maternal history of dementia on hippocampal volume in NC (Debette et al., 2009; Honea et al., 2010). PH showed no effect on hippocampal volume or radial distance. In agreement with previous reports we also found significant independent effects of ApoE4 genotype on hippocampal volume in MCI and AD (Fleisher et al., 2005; Mueller and Weiner, 2009; Mueller et al., 2008; van de Pol et al., 2007). We observed a negative MH effect in the pooled sample, and in MCI, but not in AD and NC. Others have also found no effect of maternal history of dementia on hippocampal volume in NC (Debette et al., 2009; Honea et al., 2010), yet metabolic differences have been seen in the NC stage (Mosconi et al., 2007, 2009). It is now well accepted that metabolic changes generally precede structural ones (Jack et al., 2010). The fact that we observe no effect in the AD group may be a true observation but it may also result from the smaller sample size of AD subjects (AD $n = 96$ as opposed to MCI $n = 243$). The latter possibility is also supported by the fact that absolute differences of approximately the same magnitude are present in AD subjects both at baseline and at follow-up, as demonstrated by the percentage maps in Fig. 2.

Our findings suggest that MH indirectly influences brain structure and that this effect is independent of PH and ApoE4 genotype. This unique predisposition may be mediated by X chromosome (Kehoe et al., 1999; Zubenko et al., 1998) or mitochondrial DNA susceptibility genes (Mancuso et al., 2008; Onyango et al., 2006; Schapira, 2006). The theory of causative mitochondrial DNA alterations is especially compelling as a decline in mitochondrial respiratory function invariably leads to metabolic disruption, increased generation of reactive oxygen species, enhanced apoptosis (Lin and Beal, 2006), cell loss, and brain atrophy, all of which occur in AD (Markesbery, 1997).

Although the main effect of MH on hippocampal volume was in the negative direction, the 3D maps showed some areas with positive association. 3D hippocampal
mapping is an advanced method that allows us to examine disease effects in far greater detail than hippocampal volumetry and has the capability of demonstrating subtle regional effects. Diseases, genetic predisposition, environmental factors, etc., can affect the hippocampal sub-regions differentially and can show an anterior/posterior effect gradient (reflecting the very complex hippocampal structure and connectivity). Such complex interactions cannot be visualized with simple volumetric measures but are easily discernible with more complex imaging protocols.

To our knowledge, this is the first report of parental history affecting hippocampal atrophy in MCI and AD subjects. Several strengths and limitations of our study need to be recognized. The strengths include the selection of a well-established, large, prospectively collected and exceptionally well-characterized longitudinal subject sample for our analyses and the use of an advanced hippocampal ana-

Fig. 2. Three-dimensional comparison of hippocampal radial distance at baseline and at follow-up between maternal history positive (MH+/PH−) and paternal history positive (MH−/PH+) subjects in the pooled sample and in each diagnostic group (areas in red and white show significant associations at $p < 0.05$; areas in blue are nonsignificant, $p > 0.1$; % difference $= \frac{\text{radial distance at follow-up}}{\text{radial distance at baseline}} \times 100$).
lytic technique. Several limitations of the study should be considered. First, in ADNI, parental history of dementia is provided by subject self-report. This ascertainment method is inferior to definite neuropathologic diagnosis, although more practical to perform. Prevalence rates recorded via self-report are frequently lower than the true prevalence due to poor recollection, uncertainty about parental medical history, denial, or data censoring due to early parental death. We chose to use the parental history of dementia variable as opposed to the parental history of AD variable, as in many instances the etiology of parental dementia was never recorded. This likely led to the inclusion of some subjects with parental non-AD dementia, such as vascular dementia, dementia with Lewy bodies, or Parkinson’s disease dementia. Both limitations may have influenced our analyses by reducing our power to detect the presence or true extent of the parental history effect in AD. It could be argued that focusing on history of AD might give clearer and more interpretable results than combining people at risk for different dementia subtypes, including forms of dementia not so strongly associated with hippocampal atrophy. For example, there might be a grouping bias, as men tend to develop strokes, vascular damage, and atherosclerosis more frequently than women, which may lead to PH more frequently reflecting vascular dementia than MH. If this were the case, then the lack of PH effects on hippocampal atrophy may be considered a false negative attributable to groupings based on nonspecific risk factors. Even so, the rationale for using “family history of dementia” instead of “family history of AD” was based on the number of subjects with available positive parental history in each diagnostic group. For example, in the MCI category there were 35 subjects with paternal history of dementia but only 16 with paternal history of AD. Similarly there were 81 MCI subjects with maternal history of dementia but only 46 with maternal history of AD. In our center, and perhaps in general, the variable parental diagnosis of AD is marked as positive only when the diagnosis has been pathologically ascertained. As AD is the most common dementia etiology—found in about 3/4 of dementia subjects post mortem—we would estimate that around 26 out of 35 subjects’ fathers with dementia, and 61 out of 81 subjects’ mothers with dementia would have AD pathology. As such, the “family history of dementia” variable allows us to develop a sample large enough to have sufficient statistical power, based on potentially more reliable information. This is because the level of ascertainment (pathological validation vs. diagnosis rendered by neurologist/geriatric psychiatrist/geriatrician vs. diagnosis rendered by internal medicine/family practice clinician) is likely highly variable for multicenter data.

As only a portion of MCI patients have underlying AD as the cause of their cognitive impairment it remains to be determined if those MCI patients with a maternal history of dementia are more likely to progress to AD. The documented parentally determined difference in AD predisposition in offspring of parents with AD is interesting and warrants further exploration.

Disclosure statement
The authors have no potential financial or personal conflicts of interest including relationships with other people or organizations within 3 years of beginning the work submitted that could inappropriately influence their work.

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