Longitudinal MRI atrophy biomarkers: Relationship to conversion in the ADNI cohort

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Abstract

Atrophic changes in early Alzheimer’s disease (AD) and amnestic mild cognitive impairment (MCI) have been proposed as biomarkers for detection and monitoring. We analyzed magnetic resonance imaging (MRI) atrophy rate from baseline to 1 year in 4 groups of participants from the Alzheimer’s Disease Neuroimaging Initiative (ADNI): AD (\(n = 152\)), converters from MCI to probable AD (MCI-C, \(n = 60\)), stable MCI (MCI-S, \(n = 261\)), and healthy controls (HC, \(n = 200\)). Scans were analyzed using multiple methods, including voxel-based morphometry (VBM), regions of interest (ROIs), and automated parcellation, permitting comparison of annual percent change (APC) in neurodegeneration markers. Effect sizes and the sample required to detect 25\% reduction in atrophy rates were calculated. The influence of \textit{APOE} genotype on APC was also evaluated. AD patients and converters from MCI to probable AD demonstrated high atrophy APCs across regions compared with minimal change in healthy controls. Stable MCI subjects showed intermediate atrophy rates. \textit{APOE} genotype was associated with APC in key regions. In sum, APC rates are influenced by \textit{APOE} genotype, imminent MCI to AD conversion, and AD-related neurodegeneration.

Keywords: Alzheimer’s Disease Neuroimaging Initiative (ADNI); Magnetic resonance imaging (MRI); Voxel-based morphometry (VBM); Mild cognitive impairment (MCI); Hippocampus; Longitudinal change; Genetic factors; Apolipoprotein E (APOE) epsilon 4 allele

1. Introduction

Alzheimer’s disease (AD) is the most common age-related neurodegenerative disease affecting nearly 25 million people worldwide, a number expected to triple in the next 50 years (Ferri et al., 2005; Wimo et al., 2003). Patients with AD show significant impairment in multiple cognitive domains, including deficits in memory and executive functioning. Progress in the early clinical diagnosis of AD has led to the characterization of a prodromal syndrome featuring relatively isolated memory deficits termed “amnestic mild cognitive impairment” (mild cognitive impairment; MCI) (Petersen and Negash, 2008; Petersen et al., 2001). Amnestic MCI is conceptualized as a preliminary stage of AD-associated neurodegeneration with the majority of pa-
patients eventually progressing to AD at a rate of 10%–15% per year (Petersen et al., 1999; Petersen, 2000).

The increasing recognition that early diagnosis and therapeutic intervention will be necessary to prevent the development of AD underscores the need to develop sensitive and specific biomarkers for detecting and monitoring MCI and AD. Structural magnetic resonance imaging (MRI) has shown significant promise as a biomarker to detect early MCI and AD-associated changes, as well as to predict the rate of disease progression (de Leon et al., 2007; Jack et al., 1999; Risacher and Saykin, in press). Cross-sectional studies evaluating the utility of structural MRI in detecting neurodegeneration have identified significant brain atrophy in patients with MCI and AD, particularly in regions of the medial temporal lobe (MTL) using regional volumetric extraction tools such as manual tracing of regions of interest (ROIs) (de Leon et al., 2007; De Toledo-Morrell et al., 2000; Dickerson et al., 2001; Du et al., 2001; Jack et al., 1992; Killiany et al., 2002; Pennanen et al., 2004; Saykin et al., 2006; Xu et al., 2000), and more recently, automated segmentation and parcellation of target regions (Becker et al., 2006; Colliot et al., 2008; Du et al., 2007; Fischl and Dale, 2000a; Risacher et al., 2009). Other semiautomated tools which provide 3-dimensional mapping of brain morphology, including voxel-based morphometry (VBM), tensor-based morphometry (TBM) and related techniques have also identified significant global and local tissue changes in patients with MCI and AD, including decreased whole brain, hippocampal, and temporal lobar gray matter (GM) density (Busatto et al., 2003; Chetelat et al., 2002; Frisoni et al., 2002; Jack et al., 2008b; Karas et al., 2003; Pennanen et al., 2005; Saykin et al., 2006; Trivedi et al., 2006). Structural MRI techniques have also been shown to provide sensitive prediction of disease progression. Hippocampal volume and GM density, as well as measures of MTL volume and cortical thickness, have been identified as sensitive biomarkers for predicting conversion from MCI to probable AD (Apostolova et al., 2006; Bozzali et al., 2006; Chetelat et al., 2005; Devanand et al., 2001; Jack et al., 1999; Kinkingnehun et al., 2008; Risacher et al., 2009; Visser et al., 2002; Whitwell et al., 2008b).

Longitudinal monitoring of rate of decline on MRI measures has also proven sensitive to AD-related changes. Increased rates of whole brain and MTL atrophy in patients with MCI and AD relative to healthy elderly controls (HC) are routinely reported in studies of brain aging and dementia (for recent review, see Frisoni et al., 2010). Manual tracing or automated ROI techniques and analysis of deformation fields reflecting brain shrinkage are the most commonly employed methods for evaluating longitudinal changes in global and regional volume, particularly in the MTL. Previous studies have reported rates of hippocampal annual decline of 4.5% in patients with AD and 3% in patients with MCI in contrast to 1% decline in controls (for meta-analysis see Barnes et al., 2009). Furthermore, increased atrophy rates can also predict future decline, including MCI to probable AD conversion (Erten-Lyons et al., 2006; Jack et al., 2000, 2004, 2005; Sluimer et al., 2008; Stoumb et al., 2008), with patients who convert from MCI to probable AD showing higher rates of hippocampal atrophy compared with patients with a stable diagnosis of MCI, reported as 3.5% and 2.2%, respectively (Jack et al., 2000, 2004).

Genetic factors play a significant role in the development and progression of MCI and AD. Genetic variation in the apolipoprotein E gene (APOE) is the most commonly reported genetic risk factor associated with AD, with the presence of a single ε4 allele conferring a 2-fold or 3-fold increased risk of developing AD and 2 ε4 alleles associated with nearly an 11-fold increased risk (Bertram and Tanzi, 2008; Farrer et al., 1997; Gatz et al., 2006). In addition to an increased risk of AD, the presence of an ε4 allele has been associated with imaging markers. An increased rate of hippocampal and whole brain atrophy in ε4 carriers has been reported in nondemented individuals, as well as in MCI and AD patients, in some studies (Cohen et al., 2001; Fjell et al., 2010a; Fleisher et al., 2005; Hamalainen et al., 2008; Jack et al., 2008c, 2008d; Mori et al., 2002; Morra et al., 2009; Schuff et al., 2009; Wang et al., 2006) but not in others (Du et al., 2006; Wang et al., 2009).

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a 5-year consortium study designed to assess the utility of various biomarkers for detecting early changes associated with MCI and AD and predicting disease course over time, including cross-sectional and longitudinal neuroimaging biomarkers from structural MRI and positron emission tomography (PET), genetic factors, psychometric scores, cerebrospinal fluid (CSF) markers, and other variables. A number of studies utilizing MRI data from this cohort have been published within the last year. Using both ROI and 3-dimensional mapping techniques the expected differences in structural MRI markers have been found between diagnostic (AD, MCI, HC) groups at baseline assessment, including atrophy in hippocampal and other MTL regions and enlarged ventricles in patients with AD and MCI (Chou et al., 2009; Chupin et al., 2009; Fan et al., 2008; Fennema-Notestine et al., 2009; Nestor et al., 2008; Querbes et al., 2009; Risacher et al., 2009; Vemuri et al., 2009, 2008; Walthovd et al., 2008). Hippocampal volume has also been found to be sensitive and specific for predicting 1-year conversation from MCI to probable AD (Calvini et al., 2009; Chupin et al., 2009; McEvoy et al., 2009; Misra et al., 2009; Nestor et al., 2008; Querbes et al., 2009; Risacher et al., 2009). MRI studies of the ADNI cohort have also examined longitudinal change in brain volumes using ROI and whole-brain structural change techniques (e.g., Jacobian determinants, boundary shift integral [BSI]), and have detected differences in annual change in whole brain volume, hippocampal volume, and ventricular volume as a function of baseline diagnostic group (AD, MCI, HC) (Evans et al., 2009; Fjell et al., 2010b; Ho et al., 2009;
Holland et al., 2009; Hua et al., 2009; Jack et al., 2009; Leow et al., 2009; McDonald et al., 2009; McEvoy et al., 2009; Misra et al., 2009; Morra et al., 2009; Nestor et al., 2008; Schuff et al., 2009) and of APOE ε4 genotype (Fjell et al., 2010a; Morra et al., 2009; Nestor et al., 2008; Schuff et al., 2009). Several studies have reported larger declines in whole brain and regional volumes, as well as larger ventricular volume increases in MCI to AD converters than MCI nonconverters (Evans et al., 2009; Leow et al., 2009; Misra et al., 2009; Nestor et al., 2008).

In order to better evaluate the effectiveness of future disease modifying therapeutics, biomarkers of disease state and progression are likely to be more sensitive and reliable than clinical measures, which may be highly variable within and between participants. When designing clinical trials, an important consideration is the sample size needed to detect a therapeutic effect that is both statistically significant and clinically meaningful in a target biomarker with 80% or 90% power. Several previous studies in the ADNI cohort have calculated the relative sample size needed to detect a hypothetical treatment-induced 25% reduction in brain atrophy for various regional MRI markers and have suggested that to achieve 80% power approximately 35–100 AD and 100–200 MCI participants are required (Ho et al., 2009; Holland et al., 2009; Hua et al., 2009; Nestor et al., 2008).

Despite the extensive MRI analyses in AD and MCI, prior studies have not directly compared the relative sensitivity of longitudinal changes in GM density and volume, cortical thickness and ROI volumes in relation to changes in clinical status. In ADNI, longitudinal studies have primarily focused on baseline diagnostic groups rather than 1-year clinical conversion status. The present study was designed to compare the annual percent change (APC) of different types of structural MRI markers in groups defined by baseline diagnosis and 1-year MCI to AD conversion status using the final 1-year sample. We hypothesized that patients with more advanced clinical indicators of disease progression, particularly AD and converters from MCI to probable AD (MCI-C), would show significantly greater APC in major structural MRI markers. We also evaluated the relative sensitivity of these markers to progression of atrophy over time. Because of the important implications for design of future therapeutic trials of disease-modifying agents, we also calculated the sample size needed to detect a 25% reduction in atrophy rate for selected markers. We hypothesized that the MTL changes would constitute the most sensitive regional markers of progression and therefore require the smallest potential sample sizes. Prior ADNI reports have not evaluated the sample size needed for trials in rapidly progressing MCI participants (MCI converters; MCI-C) compared with stable MCI participants (MCI-S), an important distinction for trial design. Additionally, previous reports have focused primarily on sample sizes needed for MRI markers that were extracted using a single technique. In the present study, we compared GM density and volume, cortical thickness, and ROI volumetric markers. Finally, we assessed the impact of APOE genotype on APC in several key target regions, which to date has not been examined in patients who converted from MCI to probable AD in the ADNI cohort to our knowledge. We hypothesized that the presence of an ε4 allele would increase the annual rate of decline in selected MRI markers of MTL integrity.

2. Methods

2.1. ADNI

ADNI is a consortium study initiated in 2004 by the National Institute on Aging (NIA), the National Institute of Biomedical Imaging and Bioengineering (NIBIB), the Food and Drug Administration (FDA), private pharmaceutical companies, and nonprofit organizations. More than 800 participants age 55–90 have been recruited from 59 sites across the USA and Canada to be followed for 2–3 years, with repeated structural MRI and positron emission tomography scans and functional, psychological, and psychometric test data collected every 6 or 12 months. For additional information about ADNI, see www.adni-info.org and Mueller et al. (2005a, 2005b).

2.2. MRI scans

Raw baseline 1.5 T MRI scans from 820 participants were downloaded from the ADNI public web site (www.loni.ucla.edu/ADNI/) onto local servers at Indiana University School of Medicine between January and April 2008 and processed using Freesurfer (version 4, http://surfer.nmr.mgh.harvard.edu/), Boston, MA) and VBM as implemented in SPM5 (www.fil.ion.ucl.ac.uk/spm/, London, UK) as previously described (Risacher et al., 2009). All available 1.5 T magnetization-prepared rapid gradient-echo (MP-RAGE) scans collected at the 1-year follow-up visit (“12-month scans”) were also downloaded for all participants (n = 693) as of June 2009. A minimum of 2 MP-RAGE images were acquired at each time point for each participant, using a standard MP-RAGE protocol that was selected and tested by ADNI (Jack et al., 2008a).

Participants were only included in the present analysis if their baseline and 12-month MRI scans were successfully preprocessed. Four participants failed Freesurfer processing and were not included in any analyses. Thirty additional participants were excluded from only the VBM analyses due to failed processing of scans from either the baseline or 12-month visit. Participants who did not have either baseline (n = 2) or 12-month (n = 124) scans were also excluded. Included participants (n = 673 for Freesurfer analyses, n = 643 for VBM analyses) were divided into groups by baseline and 1-year clinical diagnosis and 12-month MCI to probable AD conversion status, resulting in 4 groups: (1) participants with a stable AD diagnosis (AD; n = 152 for Freesurfer analyses, n = 143 for VBM analy-
ses); (2) participants with an MCI diagnosis at baseline who converted to a diagnosis of probable AD at either the 6- or 12-month time point (MCI-C; \( n = 60 \) for Freesurfer analyses, \( n = 57 \) for VBM analyses); (3) participants with a stable diagnosis of MCI (MCI-S; \( n = 261 \) for Freesurfer analyses, \( n = 253 \) for VBM analyses); and (4) participants with a stable designation of healthy elderly control (HC; \( n = 200 \) for Freesurfer analyses, \( n = 190 \) for VBM analyses). Participants who showed other forms of conversion, reversion, or otherwise unstable diagnostic designation were excluded (e.g., conversion from HC to MCI at the 6-month visit, followed by a reversion from MCI to HC at the 12-month visit, etc.; \( n = 16 \)). Details of the ADNI design, participant recruitment, clinical testing, and additional methods have been published previously (Jack et al., 2008; Mueller et al., 2005a, 2005b; Petersen et al., 2010) and at www.adni-info.org.

### 2.3. Demographic and clinical data

Demographic information, APOE genotype, neuropsychological test scores, and diagnosis information for all analyzed visits were downloaded from the ADNI clinical data repository (https://www.loni.ucla.edu/ADNI/Data/ADCS-Download.jsp). The “8/9/09” version of the ADNI clinical database was used for all analyses. By this time all 1-year clinical and scan data were complete. Participants were classified into groups based on baseline and 12-month diagnoses as reported in the conversion/reversion database.

To evaluate the impact of APOE genotype on annual rate of atrophy, we also classified participants by the presence or absence of an APOE ε4 allele. Given the unknown impact of having an εε4 genotype (i.e., possessing a potential protective allele [ε2] and a risk allele [ε4] for AD), we chose to run analyses both including and excluding the εε4 participants (\( n = 13; \) 3 AD, 7 MCI-S, 3 HC). We found similar results from the 2 comparisons (data not shown), and thus, chose to use the largest available sample in the results presented in this report. For the evaluation of hippocampal volume and entorhinal cortex (EC) thickness, 673 participants were included: 99 AD, 35 MCI-C, 143 MCI-S, and 56 HC who were APOE ε4 positive (εε4, εεε4, or εεεε genotypes) and 53 AD, 25 MCI-C, 118 MCI-S, and 144 HC who were APOE ε4 negative (εεε2, εεε3, or εεεε3 genotypes). Thirty participants were excluded due to failed VBM processing, as previously described. Thus, the analysis of the effect of APOE ε4 genotype on bilateral mean hippocampal GM density and volume included the following participants (\( n = 643 \)); 95 AD, 34 MCI-C, 142 MCI-S, and 53 HC who were APOE ε4 positive and 48 AD, 23 MCI-C, 111 MCI-S, and 137 HC who were APOE ε4 negative.

### 2.4. Image processing

#### 2.4.1. VBM

Scans were processed with VBM in SPM5, using previously described methods (Ashburner and Friston, 2000; Good et al., 2001; Mechelli et al., 2005). Briefly, after conversion from DICOM to NIFTI, both baseline MP-RAGE scans were aligned to the T1 template and both 12-month scans were coregistered to the T1-aligned baseline scans. After alignment, all scans were bias corrected and segmented into GM, white matter (WM), and CSF compartments using standard SPM5 templates. GM maps were normalized to Montreal Neurological Institute (MNI) atlas space as 1 mm × 1 mm × 1 mm voxels and smoothed using a 10 mm full-width-at-half maximum (FWHM) Gaussian kernel. Both modulated and unmodulated GM maps were generated. To maximize signal and minimize variability in the imaging markers, we chose to create a mean GM image of the 2 independent MP-RAGE-derived GM maps using SPM5. These mean GM volumes were then employed in all subsequent VBM analyses. This process was completed for both unmodulated and modulated normalized GM maps from each individual, yielding a mean GM density image and a mean GM volume image, respectively.

#### 2.4.2. Regions of Interest (ROIs)

A hippocampal ROI template was created by manual tracing of the left and right hippocampi in an independent sample of 40 HC participants enrolled in a study of brain aging and MCI (McHugh et al., 2007; Saykin et al., 2006; Shen et al., 2010). Hippocampal GM density and GM volume values were extracted from baseline and 12-month mean GM maps from VBM as previously described (Risacher et al., 2009). Additionally, mean GM density and mean GM volume were extracted from 90 cortical and 26 cerebellar regions using MarsBaR ROI templates (http://marsbar.sourceforge.net/; Brett et al., 2002). Mean lobar measures from MarsBaR regions were calculated from target ROIs as follows: mean frontal lobe is the mean of GM values from inferior frontal operculum and triangularis, inferior, medial, middle, and superior orbital frontal, middle and superior frontal, and medial superior frontal regions; mean parietal lobe is the mean of inferior and superior parietal, angular gyrus, supramarginal gyrus, and precuneus GM values; and mean temporal lobe value is the mean of GM values from the amygdala and hippocampus, middle and superior temporal pole, inferior, middle, and superior temporal gyri, and fusiform, Heschl’s, lingual, olfactory, and parahippocampal gyri.

#### 2.4.3. Automated parcellation

Bilateral volumetric and cortical thickness estimates from the baseline and 12-month scans were extracted using Freesurfer V4 (Dale et al., 1999; Fischl and Dale, 2000b; Fischl et al., 1999, 2002; Shen et al., 2010) as previously described (Risacher et al., 2009). Each scan from each time point was processed independently. The final extracted values were then used to calculate a mean volume or cortical thickness for each region for both the baseline and 12-month time points. Mean lobar cortical thickness measures were calculated from selected ROI mean cortical thick-
nesses from Freesurfer as follows: mean frontal lobe was the mean of caudal midfrontal, rostral midfrontal, lateral orbitofrontal, medial orbitofrontal, and superior frontal gyri, pars opercularis, orbitofrontal, and triangularis, and frontal pole thicknesses; mean parietal lobe was the mean of inferior parietal, superior parietal, supramarginal gyri, and precuneus thicknesses; and mean temporal lobe was the mean of the fusiform, lingual, parahippocampal, inferior temporal, middle temporal, and lateral temporal gyri, as well as temporal and transverse temporal pole thicknesses.

2.5. VBM statistical analysis

A two-way analysis of variance (ANOVA) assessing time and group membership (AD, MCI-C, MCI-S, HC) was performed to compare the change over 1 year between groups using the smoothed, unmodulated, normalized mean GM maps. Statistical analyses were performed on a voxel-by-voxel basis using a general linear model (GLM) approach implemented in SPM5. A threshold of \( p < 0.0001 \) (uncorrected for multiple comparisons) and minimum cluster size \((k)\) of 27 voxels was considered significant. We chose to show the VBM comparison images at this threshold \((p < 0.0001\) uncorrected) for display purposes although all comparisons, except for AD versus MCI-C, survive \(p < 0.05\) with a false discovery rate (FDR) correction for multiple comparisons and all 6 comparisons have at least 1 cluster with \(p < 0.05\) with FDR correction for multiplicity. Baseline age, gender, years of education, handedness, and baseline mean intracranial volume (ICV) were included as covariates, and an explicit GM mask was used to restrict analyses to GM regions.

2.6. Other statistical analyses

Annual percent change (APC) estimates were calculated using mean values from left and right ROIs from baseline and 12-month scans for each participant using the following equation:

\[
\text{APC} = \frac{(12\text{-mo ROI value} - \text{BL ROI value})}{(\text{BL ROI value})} \times \frac{\text{time [years] between BL and 12-mo visits}}{2}
\]

A one-way multivariate ANOVA was used to assess differences in mean MRI change measures between groups. Baseline age, gender, education, handedness, and baseline mean ICV were included as covariates. Pairwise comparisons with a Bonferroni adjustment for multiple comparisons were also used to assess differences between individual group pairs. One-way ANOVA and \(\chi^2\) tests were used to determine group differences in demographic variables, as well as baseline values and annual change of psychometric test scores. SPSS (version 17.0.2, Chicago, IL) was used for statistical analysis.

The sample size needed to detect a 25% reduction in mean APC (2-sided \(t\) test; \(\alpha = 0.05\)) with 80% or 90% power was also calculated using Microsoft Excel (2007) for the absolute change over 1 year of all target variables for all 4 diagnostic groups to determine the relative sensitivity of MRI change measures for monitoring atrophy progression. Only participants with values for all analyzed regions were included in these calculations (\(n = 643\); 143 AD, 57 MCI-C, 253 MCI-S, 190 HC). Sample size was calculated using the following equation:

\[
n = \frac{2\sigma^2(Z_{1-\alpha} + Z_{\beta})^2}{(0.25\beta)^2}
\]

where \(n\) is the target sample size, \(\alpha = 0.05\), \(\beta\) is the adjusted mean absolute change, \(\sigma\) is the standard deviation of the measure, and \(z_\alpha\) is the value from the standard distribution for 80% or 90% power (Ho et al., 2009; Hua et al., 2009; Rosner, 1990).

Effect sizes for the comparisons between pairs of diagnostic groups were also calculated for bilateral mean APC and baseline values of selected imaging markers. Left and right adjusted means, covaried for baseline age, gender, education, handedness, and baseline mean ICV, were averaged to yield a bilateral estimate. These bilateral mean values were then used to calculate the effect size (Cohen’s \(d\)) between group pairs for all imaging measures in Microsoft Excel (2007) as follows:

\[
d = \frac{(M_1 - M_2)}{\sqrt{(\sigma_1^2 + \sigma_2^2)/2}}
\]

where, for a target marker, \(M_1 = \text{mean value for group 1}, M_2 = \text{mean value for group 2}, \sigma_1 = \text{standard deviation for group 1}, \text{and} \sigma_2 = \text{standard deviation for group 2} (Cohen, 1988). In order to accurately compare the resulting effect sizes, only participants with values for all analyzed regions were included in this comparison (\(n = 643\); 143 AD, 57 MCI-C, 253 MCI-S, 190 HC).

Finally, a two-way ANOVA was used to assess the impact of diagnostic group and APOE e4 genotype on sensitive imaging phenotypes as determined by large effect sizes in the comparison of MCI-C and MCI-S participants, namely the APC in bilateral mean hippocampal GM density and volume, hippocampal volume, and EC thickness. Additionally, two-sample \(t\) tests were used to evaluate the influence of APOE e4 genotype within each of the 4 diagnostic groups on MTL change measures. Age, gender, education, handedness, and baseline ICV were included as covariates in all analyses. All graphs were created using SigmaPlot (version 10.0, San Jose, CA).

3. Results

3.1. Group characteristics and change in psychometric scores

Demographic information and the baseline values and change in selected psychometric scores over the first year are found in Table 1. Significant differences were demon-
Table 1
Demographic information and neuropsychological test scores

<table>
<thead>
<tr>
<th></th>
<th>AD (n = 152)</th>
<th>MCI-C (n = 60)</th>
<th>MCI-S (n = 261)</th>
<th>HC (n = 200)</th>
<th>p-value</th>
<th>Significant pair comparisons (p &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline age</td>
<td>75.33 (0.5)</td>
<td>74.04 (0.9)</td>
<td>75.07 (0.4)</td>
<td>75.95 (0.5)</td>
<td>NS</td>
<td>None</td>
</tr>
<tr>
<td>Education</td>
<td>14.8 (2.0)</td>
<td>15.15 (0.4)</td>
<td>15.89 (0.2)</td>
<td>16.08 (0.2)</td>
<td>p &lt; 0.001</td>
<td>HC, MCI-S &gt; AD</td>
</tr>
<tr>
<td>Gender (M, F)</td>
<td>80, 72</td>
<td>35, 25</td>
<td>166, 95</td>
<td>105, 95</td>
<td>p = 0.06</td>
<td>MCI-S versus AD, HC</td>
</tr>
<tr>
<td>Handedness (R, L)</td>
<td>144, 8</td>
<td>55, 5</td>
<td>239, 22</td>
<td>185, 15</td>
<td>NS</td>
<td>None</td>
</tr>
</tbody>
</table>

Data are given as mean (standard error of the mean) or n.

- Seven participants missing data (2 AD, 1 MCI-S, 4 HC).
- Two participants missing data (1 MCI-S, 1 HC).
- Three participants missing data (1 AD, 2 HC).
- Fourteen participants missing data (8 AD, 3 MCI-C, 3 HC).

strated in education level (F = 6.53, p < 0.001) and APOE genotype (percentage positive for at least 1 e4 allele; $\chi^2 = 56.64, p < 0.001$), specifically between HCs and patient groups. Expected differences between groups in psychometric test scores were found to be significant for both baseline scores and annual change in scores on the Clinical Dementia Rating-Sum of Boxes (CDR-SB; baseline, $F = 352.91, p < 0.001$; annual change, $F = 21.42, p < 0.001$), Mini Mental State Examination (MMSE; baseline, $F = 342.97, p < 0.001$; annual change, $F = 23.14, p < 0.001$), and Rey Auditory Verbal Learning Test (RAVLT; baseline, $F = 193.85, p < 0.001$; annual change, $F = 8.02, p < 0.001$).

Paired comparisons between groups also indicated significant differences in both baseline values and annual change as shown in Table 1. No significant difference between groups was detected in baseline or 12-month age, gender distribution, handedness distribution, or baseline mean intracranial volume (ICV).

### 3.2. VBM comparisons

AD participants showed greater decline in global GM density than HCs (Fig. 1a, p < 0.0001 [uncorrected], k = 27) and MCI-S participants (Fig. 1d, p < 0.0001 [uncorrected], k = 27) in widespread regions including bilateral medial and lateral temporal lobe, frontal lobe, and parietal lobe, with maximal differences found in the left MTL. MCI-C participants also showed greater decline in global GM density relative to HCs (Fig. 1b, p < 0.0001 [uncorrected], k = 27) in bilateral medial and lateral temporal lobes, which was maximal in the left MTL (global peak).

Differences in decline in GM density were also detected in bilateral hippocampal regions between HC and MCI-S participants and between MCI-C and MCI-S participants (Fig. 1c and 1e, p < 0.0001 [uncorrected], k = 27). Finally, greater decline in global GM density was detected for AD participants relative to MCI-C in a small cluster of voxels in the anterior parietal/posterior frontal lobe region (Fig. 1f, p < 0.0001 [uncorrected], k = 27).

### 3.3. Target region comparisons

Results from regional assessments of GM density and volume, as well as cortical thickness and volumetric measures, show a similar magnitude and anatomical pattern of decline over 12 months by group as seen in the results from the VBM comparisons. The APC values for all selected ROIs, including hippocampal GM density and GM volume extracted using 2 ROI methods (Brett et al., 2002; McHugh et al., 2007; Saykin et al., 2006; Shen et al., 2010), hippocampal volume, EC thickness, and mean lobar thickness values extracted using Freesurfer (Dale et al., 1999; Fischl and Dale, 2000a; Fischl et al., 1999; Fischl et al., 2002), and mean lobar GM density and GM volume extracted using MarsBaR ROIs (Brett et al., 2002) are found in Figs. 2–4 and Table 2.

3.4. Sample sizes

The sample size needed to detect a 25% reduction in APC of MRI biomarkers was calculated for 80% or 90% power and a type I error (α) of p < 0.05 (Table 3). Mean bilateral hippocampal GM density and GM volume estimates measured using either the independent or MarsBaR ROIs would require the smallest sample size to detect the
desired reduction for all the target groups. Other relatively sensitive ROIs for detecting a reduction in regional brain atrophy include hippocampal volume extracted using Free-surfacer, mean temporal lobar GM density and GM volume, mean temporal lobe cortical thickness (MCI-C only), and mean frontal lobar GM density and GM volume. A full list of sample sizes needed to detect a 25% decline in brain atrophy at either 80% or 90% power for selected ROIs is found in Table 3.

3.5. Effect sizes

In order to effectively compare the relative sensitivity of MRI markers to distinguish between groups, we calculated the effect size for all available baseline and APC ROIs from VBM and Freesurfer for each group pair. Effect sizes for the comparison of AD and HC participants and MCI-C and MCI-S participants are found in Fig. 5, while those for other pairs (MCI-C vs. HC; MCI-S vs. HC; AD vs. MCI-S; AD vs. MCI-C) are found in Supplementary Fig. 1. Baseline temporal lobe biomarkers, including EC thickness, hippocampal volume, and middle temporal gyri cortical thickness, had the highest effect sizes for the comparison of AD versus HC (Fig. 5a), with Cohen’s $d$ values of 1.846, 1.628, and 1.579, respectively. The APC in hippocampal GM density extracted using the MarsBaR ROIs had the highest effect size of the APC measures for AD versus HC with a Cohen’s $d$ of 1.308. Measures with maximal effect sizes for the comparison of MCI-C and MCI-S participants included APC in hippocampal GM volume (independent sample ROI, Cohen’s $d = 0.853$; MarsBaR ROI, Cohen’s $d = 0.852$), APC in inferior temporal gyri GM volume (Cohen’s $d = 0.842$), and APC in mean temporal lobe GM volume (Cohen’s $d = 0.830$). Temporal lobe ROIs also had high effect sizes for some of the other comparisons with baseline hippocampal volume showing the highest effect sizes for MCI-C versus HC (Suppl. Fig. 1a, Cohen’s $d = 1.652$) and MCI-S versus HC (Suppl. Fig. 1b, Cohen’s $d = 0.958$), and baseline middle temporal gyri thickness having the highest effect size for AD versus MCI-S (Suppl. Fig. 1c, Cohen’s $d = 0.890$). APC in superior parietal gyri GM volume demonstrated the highest effect size for AD versus MCI-C with a Cohen’s $d$ of 0.456 (Suppl. Fig. 1d).

3.6. Influence of APOE ε4 genotype

The presence of one or more APOE ε4 alleles increased APC atrophy markers for hippocampal GM density ($p = 0.001$, Fig. 6a), hippocampal GM volume ($p < 0.001$; Fig. 6b), hippocampal volume ($p = 0.001$; Fig. 6c), and EC...
thickness \( (p = 0.003; \text{ Fig. 6d}) \). Additionally, a significant interaction between diagnosis group and \textit{APOE} e4 genotype was observed for the APC in EC thickness \( (p = 0.029) \). Subsequent analyses within diagnostic group demonstrated that for AD patients \textit{APOE} e4 carriers showed greater decline in hippocampal GM density \( (p = 0.031) \) and EC thickness \( (p = 0.002) \). For MCI-C, \textit{APOE} e4 positive participants also showed greater rate of atrophy in hippocampal GM density \( (p = 0.031) \) and GM volume \( (p = 0.001) \). For the MCI-S group, the atrophy rate in all evaluated regions was greater in \textit{APOE} e4 positive than negative participants, including APCs for hippocampal GM density \( (p = 0.004) \), hippocampal GM volume \( (p < 0.001) \), hippocampal volume \( (p = 0.006) \), and EC thickness \( (p = 0.004) \). Finally, \textit{APOE} e4 positive HC participants showed a significantly greater APC in hippocampal volume than those who were \textit{APOE} e4 negative \( (p = 0.004) \).

4. Discussion

Our main goal was to assess a detailed panel of longitudinal MRI atrophy markers in the ADNI cohort, including patients with probable AD, MCI to AD converters (within 12 months), stable MCI (over 12 months), and control...
participants. Our main findings were that AD and MCI-C groups had a significantly higher rate of annual decline in global and hippocampal GM density and GM volume, hippocampal total volume, EC thickness, and cortical thickness measures than MCI-S and HC participants. Sample size calculations indicated that hippocampal GM density and GM volume required the smallest samples to detect a 25% reduction in rate of regional brain atrophy. Finally, effect size estimates indicated that dynamic measures, including APC in MTL volumes and cortical thickness, showed the most discrimination between MCI-C and HC participants. However, baseline hippocampal volume and GM density, as well as baseline temporal lobe cortical thickness measures, demonstrated the greatest effect size when comparing MCI-S and MCI-C participants. Our estimates of APC in hippocampal volume, including −3.95% for AD patients, −4.10% for MCI-C participants, −2.65% for MCI-S participants, and −1.12% for HCs, were similar to estimates from previous reports in the ADNI cohort, as well as other samples (Table 2; Barnes et al., 2009). These results demonstrate a significantly accelerated rate of brain atrophy in participants diagnosed with AD, as well as those who show rapid clinical decline from MCI to AD. Participants who show stable clinical diagnoses (both MCI and HC) also show relatively stable brain volume and cortical thickness measures, as well as minimal change in psychometric variables (Table 1).

We examined the influence of APOE ε4 genotype on annual atrophy rate in selected MTL MRI markers given the mixed prior findings, including significant effects of APOE on brain atrophy in some reports (Jack et al., 2008c, 2008d), whereas others found no effect (Du et al., 2006; Wang et al., 2009). In the present study, we observed a modest but significant effect of APOE ε4 genotype on annualized hippocampal and EC atrophy rates. This effect was maximal in MCI-S participants, with ε4 positive participants demonstrating significantly greater APC in all measures evaluated. However, the effect of APOE genotype in AD and MCI-C groups was only observed on some measures, suggesting a more moderate yet still detectable effect of genotype. Fi-
Finally, APOE ε4 positive HC participants showed an enhanced rate of atrophy relative to ε4 negative participants only on hippocampal volume. Our results support the complicated nature of the relationship between APOE genotype and MRI markers of neurodegeneration and suggest that the magnitude of the effect may differ by diagnostic stage, as has been previously reported in the ADNI cohort (Nestor et al., 2008; Schuff et al., 2009). Future studies will further characterize the impact of APOE, as well as that of variation in other candidate genes, on MRI and other ADNI biomarkers which may assist in elucidating the role of genetic factors in the neuropathology of AD (Saykin et al., 2010).

This report adds to the body of research demonstrating the utility of MRI metrics in detecting and monitoring atrophy associated with AD and MCI, and extends prior research by focusing on identifying differences between rapidly declining MCI to AD converters and individuals with relatively stable MCI. Reports in other smaller samples have led to similar conclusions regarding the utility of MRI extracted measures of global and local brain volume, cortical thickness, and morphometry in detecting and monitoring brain atrophy associated with AD and MCI (Barnes et al., 2007; Cardenas et al., 2003; Erten-Lyons et al., 2006; Fox and Freeborough, 1997; Jack et al., 2000, 2004, 2005; Mungas et al., 2005; Sluimer et al., 2008; Stoub et al., 2008; Thompson et al., 2004; Whitwell et al., 2008a). As previously reported in the ADNI sample, baseline values of hippocampal GM density and volume, amygdalar volume,
Furthermore, two of these studies divided the MCI group by baseline Clinical Dementia Rating-Sum of Boxes (CDR-SB) (McDonald et al., 2009) and by atrophy pattern (AD-like vs. HC-like; McEvoy et al., 2009) and showed variability of APC values within the MCI group, similar to that seen in the present report between MCI-C and MCI-S participants. Two studies used various hippocampal ROIs and reported significantly greater APC in hippocampal volume in AD participants relative to MCI and HC participants (Morra et al., 2009; Schuff et al., 2009). Two studies examined changes in ventricular volume, demonstrating greater rates of ventricular enlargement in AD and MCI participants relative to HCs, as well as greater ventricular enlargement in participants who converted from MCI to AD within the first 6 months of the study relative to MCI-S participants (Jack et al., 2009; Nestor et al., 2008). Three additional studies employed TBM and Jacobian maps to investigate whole brain and temporal lobe atrophy rates and found a similar pattern of differences between participants as seen in the present study (Ho et al., 2009; Hua et al., 2009; Leow et al., 2009). One of these studies also reported a higher rate of atrophy in MCI-C relative to MCI-S participants, albeit in a

Our results are generally consistent with previous reports using subsets of the ADNI cohort and alternative methods. Four studies employed Freesurfer-based ROI techniques to estimate APC in selected cortical and subcortical regions and reported similar APC values and differences between diagnostic groups as those observed in the present analysis (Fjell et al., 2010b; Holland et al., 2009; McDonald et al., 2009; McEvoy et al., 2009). Furthermore, two of these

<table>
<thead>
<tr>
<th>APC of selected imaging biomarkers</th>
<th>AD ($n = 152$)</th>
<th>MCI-C ($n = 60$)</th>
<th>MCI-S ($n = 261$)</th>
<th>HC ($n = 200$)</th>
<th>p-value</th>
<th>Significant pair comparisons ($p &lt; 0.05$)</th>
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</thead>
<tbody>
<tr>
<td>Hippocampal GM density (independent ROI)$^{a,b}$</td>
<td>L: $-4.51$ (0.2)</td>
<td>$-3.94$ (0.4)</td>
<td>$-2.05$ (0.2)</td>
<td>$-0.88$ (0.2)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
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<td>Hippocampal GM density (Freesurfer)$^{b}$</td>
<td>R: $-4.62$ (0.2)</td>
<td>$-4.05$ (0.4)</td>
<td>$-2.33$ (0.2)</td>
<td>$-0.85$ (0.2)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
</tr>
<tr>
<td>Hippocampal GM volume (independent ROI)$^{a,b}$</td>
<td>L: $-4.69$ (0.2)</td>
<td>$-4.55$ (0.4)</td>
<td>$-2.07$ (0.2)</td>
<td>$-1.18$ (0.2)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
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<tr>
<td>Hippocampal GM volume (Freesurfer)$^{b}$</td>
<td>R: $-4.71$ (0.2)</td>
<td>$-4.30$ (0.4)</td>
<td>$-2.25$ (0.2)</td>
<td>$-1.07$ (0.2)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
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<tr>
<td>Hippocampal volume (Freesurfer)$^{b}$</td>
<td>L: $-4.67$ (0.2)</td>
<td>$-4.55$ (0.4)</td>
<td>$-2.14$ (0.2)</td>
<td>$-2.24$ (0.2)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
</tr>
<tr>
<td>Hippocampal volume (independent ROI)$^{a,b}$</td>
<td>R: $-4.85$ (0.3)</td>
<td>$-4.55$ (0.4)</td>
<td>$-2.39$ (0.2)</td>
<td>$-1.07$ (0.2)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
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<tr>
<td>Hippocampal volume (Freesurfer)$^{b}$</td>
<td>L: $-4.12$ (0.3)</td>
<td>$-4.20$ (0.5)</td>
<td>$-2.55$ (0.2)</td>
<td>$-0.94$ (0.3)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S &gt; MCI-C, AD</td>
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<tr>
<td>EC thickness (Freesurfer)$^{b}$</td>
<td>R: $-3.76$ (0.3)</td>
<td>$-3.99$ (0.5)</td>
<td>$-2.71$ (0.2)</td>
<td>$-1.38$ (0.3)</td>
<td>$p &lt; 0.001$</td>
<td>HC &gt; MCI-S, MCI-C, AD</td>
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</table>

Data are given as mean (standard error of the mean).

Key: AD, Alzheimer’s disease; APC, annual percent change; EC, entorhinal cortex; GM, gray matter; HC, healthy control; MCI-C, converters from mild cognitive impairment to probable AD; MCI-S, mild cognitive impairment-stable; ROI, region of interest.

$^a$ 30 participants excluded because of failed processing (9 AD, 3 MCI-C, 9 MCI-S, 9 HC).

$^b$ Covaried for baseline age, gender, education, handedness, and baseline intracranial volume (ICV).

EC thickness, and temporal and parietal lobe cortical thickness measures are significantly different between MCI-C and MCI-S participants (Risacher et al., 2009). In fact, MCI-C and AD participants show nearly equivalent atrophy at baseline, up to 12 months prior to equivalent clinical diagnoses, indicating that MRI can serve as an antecedent biomarker. Measures of annual decline provide further evidence that MCI to AD converters have characteristic cross-sectional and longitudinal brain atrophy more similar to AD patients than to those with stable MCI. The different longitudinal phenotypes warrant investigation and may be useful in examining genetic variation associated with rate of decline (Jack et al., 2008c; Saykin et al., 2009).
There are several limitations of the present study. First, we were unable to account for some other variables which may have impacted the results. Because the ADNI is an observational study, many participants were taking a number of medications prescribed for AD, MCI, or other conditions that could have affected the results. Additionally, differences in disease severity beyond clinical diagnostic classification (i.e., AD, MCI, HC) was not considered in the present analyses. Although diagnostic classification and conversion status incorporates information from psychometric performance, the present report does not explicitly examine the relationship between changes in MRI variables and changes in psychometric performance. Secondly, the inclusion of only 2 time points separated by approximately 1 year in the present study limited the specificity and accuracy of the APC estimations. One of the major advantages of the ADNI project is the extensive longitudinal data collection. Therefore, as full datasets from the 2- and 3-year time points become available, we plan to expand our analysis of annual atrophy rates in patients with AD, MCI converters, MCI stables, and healthy elderly. Furthermore, we will employ more advanced statistical modeling to compare the atrophy rates between MCI-C participants from several time points. With 3 or more time points nonlinearity can be detected. Finally, this study was limited by the nature of the methods employed to measure atrophy. Specifically, some variability in segmentation and extraction of ROIs is likely, based on the interaction between scan quality or other properties and specific image processing algorithms which may have resulted in variation in the accuracy of the annual change estimates. However, the largely automated methodology employed in these analyses provides for little or no rater bias inherent in manually-directed tools of volume extraction. Furthermore, other analysis techniques (e.g., TBM, BSI) may provide additional and complementary information to that extracted in the present study using VBM and automated parcellation. Although a comprehensive and direct comparison of the relative sensitivity and specificity of target MRI-based atrophy measures extracted using different methods has not been completed to our knowledge, ADNI provides an ideal cohort for investigating this issue. Finally, better methods for visualization and display of longitudinal changes on a voxel-wise basis would also be advantageous. Statistical parametric maps of time by group interactions, like those presented in the present study, do not illustrate the percent change at all significant locations. Development of improved tools for visualization of magnitude of changes as a function of diagnostic group would be useful.

In summary, this study used a combination of analysis methods to confirm that MRI-based morphometric markers

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<td>134</td>
<td>646</td>
<td>866</td>
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Key: AD, Alzheimer’s disease; APC, annual percent change; EC, entorhinal cortex; GM, gray matter; HC, healthy control; MCI-C, converters from mild cognitive impairment to probable AD; MCI-S, mild cognitive impairment-stable; MRI, magnetic resonance imaging; ROI, region of interest.
Fig. 5. Effect sizes of comparisons between AD and HC, and MCI-C and MCI-S for selected imaging biomarkers. The effect sizes for selected baseline and annual percent change (APC) values for the comparison of (A) AD and HC participants and (B) MCI-C and MCI-S participants are shown. Baseline medial temporal lobe (MTL) regions had the greatest effect sizes when comparing AD and HC, while APC in MTL regions demonstrated the greatest effect sizes in the MCI-C versus MCI-S comparison (n = 643 [30 participants removed due to failed image processing]; 143 AD, 57 MCI-C, 253 MCI-S, 190 HC). AD, Alzheimer’s disease; HC, healthy control; MCI-C, converters from mild cognitive impairment to probable AD; MCI-S, mild cognitive impairment-stable.
detect dynamic changes in rate of atrophy in patients with AD and MCI, compared with controls, and are highly sensitive to the likelihood of clinical progression within 1 year. Measures of GM density change within medial and lateral temporal regions have been employed less than volumetric measures to date but appear particularly promising and complementary to more standard measures such as hippocampal volumetry. The sensitivity of automated and unbiased methods for detecting differences in rate of neurodegenerative changes encourages their use in clinical trials of disease-modifying agents and in prevention trials.

Disclosure statement

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(ADNI) database (www.loni.ucla.edu/ADNI). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. For a complete list of investigators involved in ADNI see: http://www.loni.ucla.edu/ADNI/Data/ADNI_Authorship_List.pdf.

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The Freesurfer analyses were performed on a 112-node parallel computing environment called Quarry at Indiana University. We thank the University Information Technology Services at Indiana University and Randy Heiland, MA, MS, for their support.

Appendix. Supplementary data


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