Neuroradiology (2016) 58:1143–1151
DOI 10.1007/s00234-016-1740-8

FUNCTIONAL NEURORADIOLOGY

Gender, apolipoprotein E genotype, and mesial temporal atrophy: 2-year follow-up in patients with stable mild cognitive impairment and with progression from mild cognitive impairment to Alzheimer's disease

M. V. Spampinato[1] · B. R. Langdon[2] · K. E. Patrick[1] · R. O. Parker[3] · H. Collins[1] · E. Pravata'[1,4] · For the Alzheimer's Disease Neuroimaging Initiative

Received: 24 May 2016 / Accepted: 10 August 2016 / Published online: 2 September 2016

Abstract
Introduction This study aimed to examine the relationship between gender, apolipoprotein E (APOE) genotype, and mesial temporal atrophy in mild cognitive impairment (MCI) with and without progression to Alzheimer's disease (AD).
Methods We evaluated 236 MCI patients with ($n = 121$) and without ($n = 115$) AD progression. Longitudinal MRI-based hippocampal volumes (HV) and entorhinal cortex (ERC) thickness were obtained. The Clinical Dementia Rating Sum of Boxes (CDR-SB) score was used to assess disease severity.
Results We found a significant effect of APOE, gender, and clinical course (stable MCI versus MCI-AD progression) on HV. There was a significant effect of clinical course and APOE, but not gender, on ERC. Baseline HV and APOE4 status predicted MCI-AD progression in women. Baseline ERC and APOE4 status predicted MCI-AD progression in men. There were significant differences in CDR-SB scores between patients with and without MCI-AD progression, but not between males and females, or APOE4 carriers and non-carriers.
Conclusions HV, but not ERC, is strongly influenced by gender in MCI. The effects of gender and APOE4 on neuroimaging biomarkers have potentially important implications in the prediction of MCI-AD progression and should be taken into account in clinical trials.

Keywords Mild cognitive impairment · Sex differences · Apolipoprotein E4 · Hippocampus · Entorhinal cortex · MRI

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.ucla.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in the analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

✉ M. V. Spampinato
spampin@musc.edu

For the Alzheimer's Disease Neuroimaging Initiative

[1] Department of Radiology and Radiological Science, Medical University of South Carolina, 96 Jonathan Lucas Street, MSC 323, Charleston, SC 29401, USA

[2] Department of Internal Medicine, Medical University of South Carolina, Charleston, SC, USA

[3] Department of Anesthesiology, Vanderbilt University, Nashville, TN, USA

[4] Department of Neuroradiology, Neurocenter of Southern Switzerland, Ospedale Regionale di Lugano, Lugano, Switzerland

Introduction

Mild cognitive impairment (MCI) is a prodromal state of Alzheimer's disease (AD) [1, 2]. Previous research has shown that MRI-based mesial temporal atrophy measures, especially entorhinal cortex (ERC) thickness and hippocampal volume (HV) can predict MCI-AD progression [3–13]. The ε4 allele of the apolipoprotein E (APOE4) is the strongest known genetic risk factor in sporadic AD [14–18]. Numerous studies have shown a relationship between APOE4 and the degree of hippocampal and entorhinal atrophy in MCI and AD [19–23].

In 2011, the Society for Women's Health Research made the recommendation to systematically analyze gender differences in AD and to integrate sex differences in the definition of biomarkers, diagnosis, and drug discovery [24]. Gender-specific differences in brain atrophy patterns have been demonstrated in MCI and AD [25–30]. The effect of gender on

brain volume loss may be at least as large as the APOE4 effect [31]. If atrophy patterns differ between men and women, then these differences should be taken into account when structural MR indices are used as AD biomarkers [32]. Although the relationship between gender and APOE has been previously evaluated in MCI and AD in a few studies using structural imaging [31, 33, 34], to our knowledge, none of these studies have evaluated the effects of gender and APOE4 on ERC and HV in MCI patients during the clinical transition from MCI to AD. Furthermore, it is imperative to integrate gender differences in mesial temporal atrophy in prediction models of MCI-AD progression.

Our primary objective was to assess whether gender and APOE4 have an influence on longitudinal patterns of ERC and HV in patients with stable MCI and MCI-AD progression. Furthermore, we evaluated whether gender has an influence on prediction models of MCI-AD progression, using as predictors the APOE4 status, ERC, and HV in a sample of MCI patients. Based on the prior literature, our hypothesis was that gender and APOE4 modulate structural MR biomarkers of AD.

Methods

Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database, launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD. For up-to-date information, see www.adni-info.org. The study was conducted according to the Good Clinical Practice guidelines, the Declaration of Helsinki, US 21 CFR part 50—Protection of Human Subjects—and part 56—Institutional Review Boards. Subjects were willing and able to undergo test procedures, including neuroimaging and follow-up, and written informed consent was obtained from participants. For details regarding the ADNI protocol procedures, see Appendix 1.

The ADNI1 cohort consisted of 819 subjects, of which 397 were with initial diagnosis of MCI [35]. Inclusion criteria were as follows:

1. MCI/AD progression: amnestic MCI at baseline, MCI-AD progression during the first 2 years of study participation, APOE genotyping results, and brain MRIs obtained 12 months prior to AD diagnosis (time 1) and at AD diagnosis (time 2). A third brain MRI obtained 12 months later was included when available (time 3).

2. Stable MCI: amnestic MCI at baseline and follow-up showing stable MCI for at least 36 months, APOE genotyping results, and brain MRIs obtained at the ADNI study baseline (time 1) and at the 12-month visit (time 2). A third brain MRI obtained at the 24-month visit was included when available (time 3).

Brain MRI included a 3D T1-weighted MPRAGE sequence collected using standardized protocols across 59 study sites in the USA and Canada with 1.5 Tesla MR scanners [36]. MCI subjects in the ADNI cohort were scheduled to undergo brain MRIs and clinical evaluations every 6 months for the first 2 years and then yearly. The MCI/AD progression group only included patients with progression to AD during the first 2 years of participation, when visits occurred every 6 months.

MR images were preprocessed using the following protocol: (a) gradient non-linearity correction via "GradWarp," (b) intensity non-uniformity by using B1 calibration, and (c) residual intensity non-uniformity by using "N3." The images also underwent scaling based on acquisitions of a phantom device. All acquisitions underwent quality-control evaluation and were performed by using a standardized protocol specifically developed for the ADNI, tailored for use with each model of MR scanner used at the different data collection sites [36]. Information on MR acquisition protocols can be found at http://adni.loni.usc.edu/ [37]. Bilateral HV, ERC, and intracranial volume (ICV) measurements were obtained using the FreeSurfer image analysis suite, which is documented and freely available for download online (FreeSurfer 4.4, http://surfer.nmr.mgh.harvard.edu/) [38], as previously described [33, 39–41]. To extract reliable volume and thickness estimates, images where automatically processed with the longitudinal stream in FreeSurfer [42]. Specifically, an unbiased within-subject template space and image is created using robust, inverse consistent registration [43]. Several processing steps, such as skull stripping, Talairach transforms, atlas registration, as well as spherical surface maps and parcellation, are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power [42]. All MR imaging data that did not pass the ADNI quality control evaluations, including segmentation quality control, were excluded.

Severity of symptoms of dementia was assessed using the Clinical Dementia Rating Sum of Boxes (CDR-SB) [44]. APOE genotype was determined from peripheral blood DNA [45, 46]. The cells were collected in plastic tubes (10 mL) coated with ethylenediaminetetraacetic acid and sent via overnight delivery to the University of Pennsylvania. Subjects were classified as APOE4 carriers (at least one ε4 allele) and non-carriers. For more detailed information, see the ADNI 1 Procedures Manual [45].

Individual HVs were normalized for intersubject variation in head size by dividing HV (in mm^3) by the estimated

baseline ICV (in cm^3). In the remainder of the manuscript, HV will indicate normalized HV. Mean HV and mean ERC measurements were calculated for each subject and time point.

Statistical analyses were conducted using SPSS 22.0. Results were considered significant when $p < 0.05$. First, we evaluated differences in patient characteristics using the Pearson χ^2 test (gender, race, APOE4) and ANOVA (age, years of education). Then, a mixed general linear model was used to assess longitudinal changes of CDR-SB, HV, and ERC. Gender, APOE genotype, and clinical course were included as between-subjects factors, and time (baseline, 12 months, 24 months) was the within-subjects factor. Bonferroni adjustment for multiple comparisons was applied across dependent variables and in the post hoc analyses. Effect sizes are reported using partial ETA-squared (η^2_p) with the guidelines of 0.01 for a small effect, 0.06 for a medium effect, and 0.14 for a large effect [47]. Effect size is the proportion of variance accounted for by an effect.

Stepwise linear discriminant analysis was used to identify whether APOE4, HV, and ERC measures obtained *at baseline* (time 1) could predict subsequent MCI-AD progression in this MCI patient sample. Leave-one-out cross-validation was used to minimize the increase in sensitivity and specificity associated with the use of the entire dataset to train the classifier.

Results

Clinical data

Two hundred thirty-six patients, 121 MCI-AD progression and 115 stable MCI subjects, were included in the study. One hundred sixty-one of the 397 individuals who had a diagnosis of MCI at the onset of the ADNI study were excluded: 56 with MCI-AD progression because baseline and/or 12-month MR images were not available or did not pass MR quality control screening; 86 subjects with stable MCI because baseline and/or 12-month MRI were not available, MR images did not pass MR quality control screening, or clinical follow-up of greater than 36 months was not available; and 19 subjects due to reversion from MCI to normal control status. Demographic and clinical characteristics of the study population are reported in Table 1. There was no significant difference in racial composition ($p = 0.13$), handedness ($p = 0.76$), age ($p = 0.20$), and years of education ($p = 0.07$) between males and females. The proportion of APOE4 carriers did not differ between males and females ($p = 0.23$); however, it significantly differed between stable MCI and MCI-AD converters ($p < 0.001$). The mixed general linear model with Huynh-Feldt correction for sphericity violation was performed to investigate the effects of gender, APOE4, and clinical course on longitudinal CDR-SB, a measure of dementia severity. We found a significant worsening over time of CDR-SB ($F = 100.8$, $\eta^2_p = 0.50$, $p < 0.001$), a significant time-by-clinical course (stable MCI versus MCI-AD progression) interaction on the trajectory of CDR-SB ($F = 79.4$, $\eta^2_p = 0.44$, $p < 0.001$), but no other significant interactions.

Table 1 Demographics and clinical characteristics

MCI-AD progression	Male ($N = 75$)	Female ($N = 46$)
Age range, median (SD)	75.9 (±6.2)	75 (±7.1)
Caucasian/Asian/African American	70/2/3	44/2/-
Handedness (right/left)	66/9	44/2
Median education (SD)	16 (±3) years	16 (±3) years
APOE4[a]	53/75	30/46
CSF $A\beta_{1–42}$[b]	153.6 (41.4)	139.7 (38.1)
CMRglc[c]	1.21 (0.22)	1.21 (0.10)
Stable MCI	Male ($N = 75$)	Female ($N = 40$)
Age range, median (±SD)	75.4 (±6.8)	73.6 (±8.3)
Caucasian/Asian/African American	70/2/3	38/2/-
Handedness (right/left)	70/5	35/5
Median education (±SD)	16 (±3) years	16 (±3) years
APOE4[a]	34/75	13/40
CSF $A\beta_{1–42}$[b]	143.4 (41.5)	178.6 (71.8)
CMRglc[c]	1.30 (0.10)	1.34 (0.12)

[a] APOE4: at least one copy of apolipoprotein E epsilon 4

[b] CSF $A\beta_{1–42}$: β-amyloid (Aβ 1-42) concentration in the cerebrospinal fluid (picograms/ml)

[c] CMRglc: 18-fluoro-deoxy-glucose (FDG)-PET cerebral metabolic rate of glucose consumption in the frontal, parietal, and temporal cortices normalized to pons

MR imaging

Time 1 and time 2 brain MRIs were available in all 236 subjects; time 3 brain MRIs were available in 196 subjects (88 MCI-AD progression patients, 51 males; 108 stable MCI patients, 72 males). The mixed general linear model with Huynh-Feldt correction for sphericity violation was performed to evaluate the effects of gender, APOE4, and disease course on longitudinal HV and ERC.

Hippocampus

HV was the dependent variable of interest in this analysis (Figs. 1 and 2). Please see Table 2 for a summary of HV measurements in patients stratified by gender and clinical course. We found a significant HV decline over time ($F = 223.1$, $\eta^2_p = 0.54$, $p < 0.001$), a significant time-by-APOE4 interaction on the trajectory of the HV ($F = 14.7$, $\eta^2_p = 0.07$, $p < 0.001$), with worse atrophy over time in APOE4-positive patients. There was also a significant time-by-gender ($F = 5.1$, $\eta^2_p = 0.03$, $p = 0.007$) and a significant time-by-clinical course interactions ($F = 5.3$, $\eta^2_p = 0.03$, $p = 0.006$). The interaction between gender and APOE and

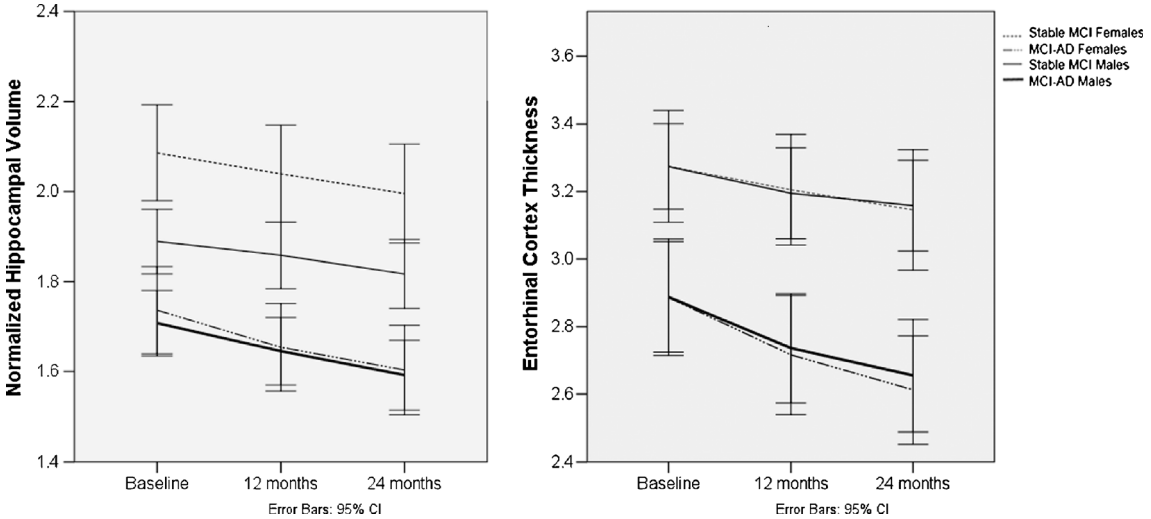

Fig. 1 Average (±95 % confidence interval) normalized hippocampal volume and entorhinal cortex thickness of patients stratified by gender and clinical course (*MCI* stable mild cognitive impairment over 4 years, *MCI-AD* progression from MCI to Alzheimer's disease)

between gender, APOE, and clinical course was not significant. Post hoc tests revealed that HVs were significantly lower in men than in women ($p = 0.03$). Evaluation of gender-by-APOE4 interaction revealed a trend toward lower HV in APOE4-positive men than women ($p = 0.08$). Evaluation of gender-by-clinical course interaction revealed significantly lower HV in men than in women with stable MCI ($p = 0.003$), but there were no significant differences between men and women with MCI-AD progression. HVs were also lower in men with MCI-AD progression than in men with stable MCI ($p = 0.001$) and in women with MCI-AD progression than in women with stable MCI ($p < 0.001$).

Entorhinal cortex

ERC was the dependent variable of interest in this analysis. Please see Table 2 for a summary of ERC measurements in patients stratified by gender and clinical course. We found a significant longitudinal decrease in ERC ($F = 131.3$, $\eta^2_p = 0.44$, $p < 0.001$), a significant interaction between time and clinical course on the trajectory of the ERC W scores ($F = 10.8$, $\eta^2_p = 0.06$, $p < 0.001$). There was also a significant time-by-APOE4 interaction ($F = 7.1$, $\eta^2_p = 0.04$, $p = 0.001$), with worse atrophy over time in APOE4-positive patients, but no significant time-by-gender interaction. The interactions between gender and APOE; gender and clinical course; and gender, APOE, and clinical course were not significant. Post hoc analyses revealed that ERC was significantly lower in individuals with MCI-AD progression than in those with stable MCI ($p < 0.001$).

Next, we tested the hypothesis that prediction models of MCI-AD progression differ between men and women. For this purpose, we performed a stepwise discriminant analysis with HV, ERC thickness, and APOE4 status as predictors of

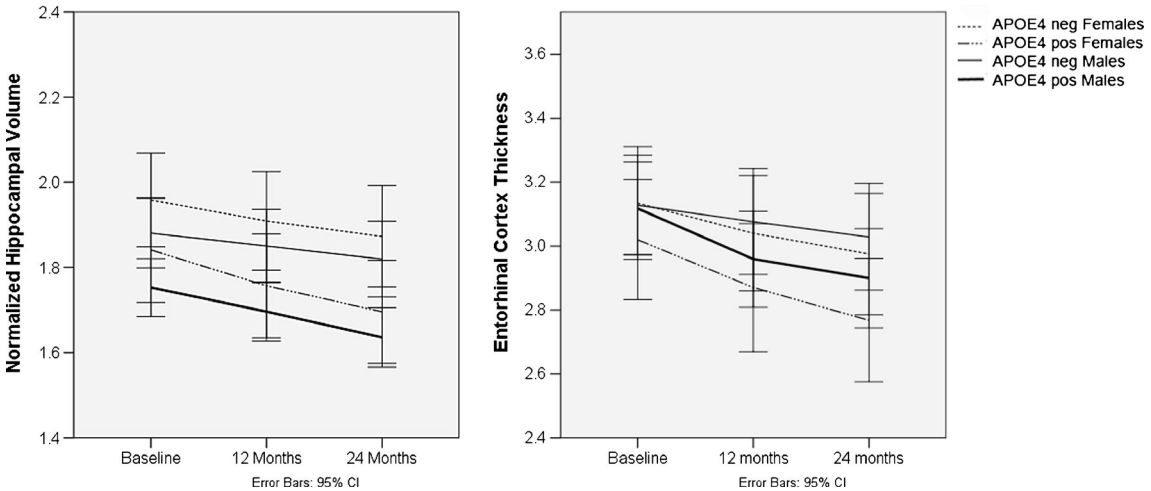

Fig. 2 Average (±95 % confidence interval) hippocampal volume and entorhinal cortex thickness of patients stratified by gender and apolipoprotein E ε4 status (*APOE4 neg* no apolipoprotein E ε4 allele, *APOE4 pos* at least one apolipoprotein E ε4 allele)

Table 2 Average hippocampal volume (HV) and entorhinal cortex thickness (ERC) (standard deviation) in stable MCI and MCI-AD progression

MCI-AD conversion	Male ($N = 75$)	Female ($N = 46$)	
	Time 1/time 2/time 3	Time 1/time 2/time 3	p value[a]
HV	1.71 (0.26)/1.65 (0.27)/1.59 (0.28)	1.74 (0.29)/1.65 (0.29)/1.60 (0.30)	0.867
ERC	2.89 (0.54)/2.74 (0.54)/2.66 (0.55)	2.89 (0.47)/2.71 (0.48)/2.61 (0.43)	0.821
Stable MCI	Male ($N = 75$)	Female ($N = 40$)	
	Time 1/time 2/time 3	Time 1/time 2/time 3	p value[a]
HV	1.89 (0.31)/1.86 (0.32)/1.81 (0.33)	2.09 (0.31)/2.04 (0.31)/2 (0.32)	0.003
ERC	3.27 (0.53)/3.20 (0.56)/3.16 (0.56)	3.27 (0.46)/3.20 (0.45)/3.14 (0.50)	0.922
Females	MCI-AD progression ($N = 46$)	Stable MCI ($N = 40$)	
	Time 1/time 2/time 3	Time 1/time 2/time 3	p value[a]
HV	1.74 (0.29)/1.65 (0.29)/1.60 (0.30)	2.09 (0.31)/2.04 (0.31)/2 (0.32)	<0.001
ERC	2.89 (0.47)/2.71 (0.48)/2.61 (0.43)	3.27 (0.46)/3.20 (0.45)/3.14 (0.50)	<0.001
Males	MCI-AD progression ($N = 75$)	Stable MCI ($N = 75$)	
	Time 1/time 2/time 3	Time 1/time 2/time 3	p value[a]
HV	1.71 (0.26)/1.65 (0.27)/1.59 (0.28)	1.89 (0.31)/1.86 (0.32)/1.81 (0.33)	0.001
ERC	2.89 (0.54)/2.74 (0.54)/2.66 (0.55)	3.27 (0.53)/3.20 (0.56)/3.16 (0.56)	0.001

[a] Post hoc analyses results of patients stratified by gender and clinical course after Bonferroni correction for multiple comparisons

MCI-AD progression. For these analyses, we used structural imaging metrics obtained *at baseline*, when all patients were deemed to have mild cognitive impairment but did not meet diagnostic criteria for dementia. In the female cohort, HV (discriminant function coefficient = 0.89) and APOE4 (discriminant function coefficient = 0.42), but not ERC, contributed to the prediction model ($\chi^2 = 37.3$, $p < 0.001$), with correct classification of 71.7 % of MCI-AD converters. In the male cohort, ERC (discriminant function coefficient = 0.84) and APOE4 (discriminant function coefficient = 0.57), but not HV, contributed to the prediction model ($\chi^2 = 29.8$, $p < 0.001$), with correct classification of 72 % of MCI-AD converters.

Discussion

We evaluated the longitudinal course of HV and ERC thickness in stable MCI and MCI-AD progression over 2 years. We found a significant effect of gender, APOE4 status, and clinical course on HV. HVs were lower in MCI-AD converters, APOE4 carriers, and in men. On the other hand, only the clinical course and APOE4, but not gender, were found to have an effect on ERC.

Gender dimorphism occurs in AD in multiple domains, including incidence, cognition, language ability, behavior, and brain structure [24, 48]. The reasons for gender differences in AD remain incompletely understood and may be related to postmenopausal estrogen reduction, differences in brain reserve capacity, cortical cytoarchitecture, brain size, neuron count, or sex differences in AD pathology [24, 49–51]. We found that gender had a significant effect on the degree of mesial temporal atrophy in MCI and early AD. Longitudinal HV measurements were greater in women with stable MCI than in all the other groups, including men with stable MCI. While sex differences in HV existed in the stable MCI cohort, HV was comparable between women and men with MCI-AD progression. Conversely, ERC was not influenced by the gender. Our results show that HV measurements obtained at the clinical disease stage of MCI may be a stronger structural predictor of MCI-AD progression in women than in men. Conversely, only ERC and APOE4, but not HV, were found to be strong predictors of MCI-AD progression in the male group. This suggests that there is a stronger association between hippocampal atrophy and clinical manifestations of AD in women than in men.

Few longitudinal studies have assessed sex differences in brain atrophy in aMCI and AD [29, 31]. Hua et al. evaluated the progression of whole-brain atrophy and temporal lobe atrophy over 12 months in a large sample of elderly controls, aMCI, and AD patients and found greater brain atrophy rate in aMCI females than in males [29]. Hua et al. did assess subgroups of aMCI patients with and without progression and found greater brain atrophy in converters than in non-converters, but the gender-by-clinical course interaction was not evaluated or reported. Skup et al. evaluated gender differences in brain volume between stable aMCI and AD patients using longitudinal structural MRI data [30]. In the aMCI cohort, Skup et al. found greater atrophy of the caudate nuclei, thalami, and right middle temporal gyrus in men than in women and greater atrophy of precunei in females than in males, but there were no reported gender differences in hippocampal atrophy. The discrepancy between our results and those of Skup el al. may be explained by the use of different postprocessing

techniques. In this prior study, voxel-wise comparisons across the entire brain and 24 brain regions of interest were performed [30]. As a result, any differences in hippocampal atrophy between aMCI men and women may have been obscured by the use of corrections for multiple comparisons across the entire brain or large cerebral volumes. Furthermore, Skup et al. only evaluated clinically stable aMCI patients and specifically excluded MCI-AD converters. The novelty of our approach compared to these previous studies is twofold. First, our analysis focused on the longitudinal effects of gender and APOE4 on two practical and clinically relevant structural imaging metrics, widely used in clinical trials. Secondly, we evaluated amnestic MCI patients who were clinically stable and MCI-AD converters, a group who may theoretically benefit from early therapeutic interventions, and we studied the gender-by-clinical course interaction.

Figure 2 shows longitudinal HV and ERC W scores in males and females with and without the APOE4 allele. There was a significant effect of APOE4 on HV and ERC thickness, with lower HV and ERC in APOE4 carriers than non-carriers. These findings are in agreement with prior studies on the effect of APOE4 on hippocampal and ERC atrophy in MCI and AD [21, 23, 31, 52–59]. Despite a large number of studies that examined the effect of APOE4 on imaging biomarkers of AD, the effects of the gender-by-APOE4 interaction on the manifestations of AD remain not well understood [60]. An autopsy study found that female APOE4 carriers are at higher risk of greater amyloid plaque and neurofibrillary tangle pathology [61]. Another autopsy study revealed an interaction between APOE4 and gender on amyloid plaque formation in females between the ages of 60 and 79, but not in older women, while an association between APOE4 and greater amyloid plaque formation in men of all ages [62]. While the pathology literature provides evidence of a gender-by-APOE4 interaction and it is known from epidemiology reports that women are at greater risk for AD dementia, the mechanisms of the gender-by-APOE4 interaction remain unknown. The interaction between gender, APOE, and pathophysiology of AD may certainly be sex hormone mediated, and hormone replacement therapy may play a role [60]. Fleischer et al. have evaluated the relationship between HV, gender, and numbers of copies of the APOE allele ε4 in MCI [33]. In agreement with our results, the authors also reported significantly smaller normalized HV in homozygote APOE4-positive males than females, although there were no significant gender-related differences between heterozygote APOE4-positive MCI patients. Liu et al. explored the effect of APOE4 on regional cortical thickness and brain volume in MCI and AD using cross-sectional MRI data [34]. In the female MCI group, the volume of the amygdala was smaller in APOE4-carriers than non-carriers. Furthermore, in the male MCI group, more widespread volumetric differences were found between carriers and non-carriers, with lower volumes of the hippocampi, amygdala, deep gray nuclei, as well as regions of the occipital, temporal, and frontal lobes [50]. Although we did not find a significant effect of the gender-by-APOE4 interaction on HV and ERC thickness, we also found a trend toward lower HV in APOE4-positive men than women. Holland et al. examined the effect of age, APOE4, and gender on annual brain atrophy rates and clinical decline [31]. They found that the annual atrophy rates of ERC and HV were higher in MCI and AD women and in APOE4 carriers. Although we did not assess annual atrophy rates in our cohort, our results imply faster HV declines in women along the MCI-AD continuum. In fact, we found that HV was greater in women than in men with mild cognitive symptoms. However, gender differences were attenuated in more severely impaired subjects with early AD dementia. Overall, evidence from the literature and our findings suggest that APOE4 and gender may independently and cooperatively influence the AD phenotype.

A study limitation was the uneven gender balance between groups, a bias present in the ADNI MCI cohort. Also, despite the ADNI study including a large patient cohort, sample size in certain subgroups is suboptimal. Specifically, the inclusion of only 13 APOE4-positive women with stable MCI is not ideal when trying to assess the effect of the female gender, APOE4, and clinical course on mesial temporal atrophy. History of hormone replacement therapy and menopausal age was not available. We were unable to investigate in detail the relationship between structural MR metrics and other established AD biomarkers because CSF and PET data were available only for about half of the patients. Future investigations will clarify whether current AD biomarker models should be modified to take into consideration gender differences and the gender-by-APOE interaction.

Conclusions

We found that the severity of mesial temporal atrophy during the progression from MCI to AD, especially hippocampal atrophy, is strongly influenced by gender and APOE genotype. Furthermore, there may be a role for gender-specific imaging paradigms to predict MCI-AD progression. In fact, the MCI-AD progression prediction model for the female group included HV and APOE4 status. Conversely, ERC and APOE4, but not HV, were predictors of AD progression in males. Gender- and APOE-related differences should be taken into account when using structural MR indices, specifically HV and ERC, as markers of AD diagnosis, to monitor progression and treatment response. Future studies should

investigate whether gender differences in AD warrant gender-specific preventive or therapeutic strategies.

Acknowledgments Data collection and sharing for this project were funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Disease Cooperative Study at the University of California, San Diego. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Compliance with ethical standards We declare that all human and animal studies have been approved by the Medical University of South Carolina Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. We declare that all patients gave informed consent prior to inclusion in this study.

Conflict of interest We declare that we have no conflict of interest.

Appendix 1

ADNI study protocol summary Enrolled subjects were between 55 and 90 (inclusive) years of age, had a study partner able to provide an independent evaluation of functioning, and spoke either English or Spanish. All subjects were willing and able to undergo all test procedures including neuroimaging and agreed to longitudinal follow up. Between 20 and 50 % must have been willing to undergo two lumbar punctures, spaced 1 year apart. Specific psychoactive medications were excluded. General inclusion/exclusion criteria for the MCI subjects enrolled in the ADNI 1 study were as follows:

MCI subjects MMSE scores between 24 and 30 (inclusive), a memory complaint, have objective memory loss measured by education-adjusted scores on Wechsler Memory Scale Logical Memory II, a CDR of 0.5, absence of significant levels of impairment in cognitive domains other than memory, essentially preserved activities of daily living, and an absence of dementia.

All subjects underwent clinical/cognitive assessments and 1.5 T structural MRI at specified intervals (6 or 12 months) for 2–3 years. Approximately 50 % of the subjects also had FDG PET scans at the same time intervals. MCI subjects at high risk for conversion to AD ($n = 400$) were studied at 0, 6, 12, 18, 24, and 36 months. All MRI and PET scans were rapidly assessed for quality so that subjects may be rescanned if necessary. All clinical data were collected, monitored, and stored by the Coordinating Center at the ADCS. University of Pennsylvania collected biomarker samples. All raw and processed image data were archived at LONI.

References

1. Petersen RC (2004) Mild cognitive impairment as a diagnostic entity. J Intern Med 256:183–194
2. Ganguli M, Dodge HH, Shen C, DeKosky ST (2004) Mild cognitive impairment, amnestic type: an epidemiologic study. Neurology 63:115–121
3. Devanand DP, Pradhaban G, Liu X et al (2007) Hippocampal and entorhinal atrophy in mild cognitive impairment: prediction of Alzheimer disease. Neurology 68:828–836
4. Fan Y, Batmanghelich N, Clark CM, Davatzikos C (2008) Spatial patterns of brain atrophy in MCI patients, identified via high-dimensional pattern classification, predict subsequent cognitive decline. Neuroimage 39:1731–1743
5. Fennema-Notestine C, Hagler DJ Jr, McEvoy LK et al (2009) Structural MRI biomarkers for preclinical and mild Alzheimer's disease. Hum Brain Mapp 30:3238–3253
6. Jack CR Jr, Wiste HJ, Vemuri P et al (2010) Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. Brain 133:3336–3348
7. Karas G, Sluimer J, Goekoop R et al (2008) Amnestic mild cognitive impairment: structural MR imaging findings predictive of conversion to Alzheimer disease. AJNR Am J Neuroradiol 29:944–949
8. Jack CR Jr, Vemuri P, Wiste HJ et al (2011) Evidence for ordering of Alzheimer disease biomarkers. Arch Neurol 68:1526–1535
9. Pennanen C, Kivipelto M, Tuomainen S et al (2004) Hippocampus and entorhinal cortex in mild cognitive impairment and early AD. Neurobiol Aging 25:303–310
10. Tapiola T, Pennanen C, Tapiola M et al (2008) MRI of hippocampus and entorhinal cortex in mild cognitive impairment: a follow-up study. Neurobiol Aging 29:31–38
11. Risacher SL, Saykin AJ, West JD et al (2009) Baseline MRI predictors of conversion from MCI to probable AD in the ADNI cohort. Curr Alzheimer Res 6:347–361
12. Velayudhan L, Proitsi P, Westman E et al (2013) Entorhinal cortex thickness predicts cognitive decline in Alzheimer's disease. J Alzheimers Dis 33:755–766
13. Ewers M, Walsh C, Trojanowski JQ et al (2012) Prediction of conversion from mild cognitive impairment to Alzheimer's disease dementia based upon biomarkers and neuropsychological test performance. Neurobiol Aging 33:1203–1214
14. Verghese PB, Castellano JM, Holtzman DM (2011) Apolipoprotein E in Alzheimer's disease and other neurological disorders. Lancet Neurol 10:241–252
15. Mahley RW, Huang Y (2006) Apolipoprotein (apo) E4 and Alzheimer's disease: unique conformational and biophysical properties of apoE4 can modulate neuropathology. Acta Neurol Scand Suppl 185:8–14
16. Mahley RW, Weisgraber KH, Huang Y (2006) Apolipoprotein E4: a causative factor and therapeutic target in neuropathology, including Alzheimer's disease. Proc Natl Acad Sci U S A 103:5644–5651
17. Tiraboschi P, Hansen LA, Masliah E, Alford M, Thal LJ, Corey-Bloom J (2004) Impact of APOE genotype on neuropathologic and neurochemical markers of Alzheimer disease. Neurology 62:1977–1983

18. Liu CC, Kanekiyo T, Xu H, Bu G (2013) Apolipoprotein E and Alzheimer disease: risk, mechanisms and therapy. Nat Rev Neurol 9:106–118
19. den Heijer T, Oudkerk M, Launer LJ, van Duijn CM, Hofman A, Breteler MM (2002) Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. Neurology 59: 746–748
20. Moffat SD, Szekely CA, Zonderman AB, Kabani NJ, Resnick SM (2000) Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. Neurology 55:134–136
21. Spampinato MV, Rumboldt Z, Hosker RJ, Mintzer JE (2011) Apolipoprotein E and gray matter volume loss in patients with mild cognitive impairment and Alzheimer disease. Radiology 258:843–852
22. Burggren AC, Zeineh MM, Ekstrom AD et al (2008) Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers. Neuroimage 41:1177–1183
23. Hostage CA, Choudhury KR, Murali Doraiswamy P, Petrella JR, Alzheimer's Disease Neuroimaging I (2014) Mapping the effect of the apolipoprotein E genotype on 4-year atrophy rates in an Alzheimer disease-related brain network. Radiology 271:211–219
24. Carter CL, Resnick EM, Mallampalli M, Kalbarczyk A (2012) Sex and gender differences in Alzheimer's disease: recommendations for future research. J Womens Health (Larchmt) 21:1018–1023
25. Apostolova LG, Dinov ID, Dutton RA et al (2006) 3D comparison of hippocampal atrophy in amnestic mild cognitive impairment and Alzheimer's disease. Brain 129:2867–2873
26. Ballmaier M, O'Brien JT, Burton EJ et al (2004) Comparing gray matter loss profiles between dementia with Lewy bodies and Alzheimer's disease using cortical pattern matching: diagnosis and gender effects. Neuroimage 23:325–335
27. Callen DJ, Black SE, Caldwell CB, Grady CL (2004) The influence of sex on limbic volume and perfusion in AD. Neurobiol Aging 25: 761–770
28. Liu Y, Paajanen T, Westman E et al (2010) APOE epsilon2 allele is associated with larger regional cortical thicknesses and volumes. Dement Geriatr Cogn Disord 30:229–237
29. Hua X, Hibar DP, Lee S et al (2010) Sex and age differences in atrophic rates: an ADNI study with *n*=1368 MRI scans. Neurobiol Aging 31:1463–1480
30. Skup M, Zhu H, Wang Y et al (2011) Sex differences in grey matter atrophy patterns among AD and aMCI patients: results from ADNI. Neuroimage 56:890–906
31. Holland D, Desikan RS, Dale AM, McEvoy LK (2013) Higher rates of decline for women and apolipoprotein E epsilon4 carriers. AJNR Am J Neuroradiol 34:2287–2293
32. Jack CR Jr (2011) Alliance for aging research AD biomarkers work group: structural MRI. Neurobiol Aging 32(Suppl 1):S48–57
33. Fleisher A, Grundman M, Jack CR Jr et al (2005) Sex, apolipoprotein E epsilon 4 status, and hippocampal volume in mild cognitive impairment. Arch Neurol 62:953–957
34. Liu Y, Paajanen T, Westman E et al (2010) Effect of APOE epsilon4 allele on cortical thicknesses and volumes: the AddNeuroMed study. J Alzheimers Dis 21:947–966
35. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease., pp 939–944
36. Jack CR Jr, Bernstein MA, Fox NC et al (2008) The Alzheimer's Disease Neuroimaging Initiative (ADNI): MRI methods. J Magn Reson Imaging 27:685–691
37. ADNI (2008) MRI protocols. http://adni.loni.usc.edu/methods/documents/mri-protocols/.2016
38. McDonald CR, McEvoy LK, Gharapetian L et al (2009) Regional rates of neocortical atrophy from normal aging to early Alzheimer disease. Neurology 73:457–465
39. Fischl B, Liu A, Dale AM (2001) Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. IEEE Trans Med Imaging 20:70–80
40. Fischl B, Salat DH, Busa E et al (2002) Whole brain segmentation: automated labeling of neuroanatomical structures in the human brain. Neuron 33:341–355
41. Han X, Jovicich J, Salat D et al (2006) Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage 32: 180–194
42. Reuter M, Schmansky NJ, Rosas HD, Fischl B (2012) Within-subject template estimation for unbiased longitudinal image analysis. Neuroimage 61:1402–1418
43. Reuter M, Rosas HD, Fischl B (2010) Highly accurate inverse consistent registration: a robust approach. Neuroimage 53:1181–1196
44. Juva K, Sulkava R, Erkinjuntti T, Ylikoski R, Valvanne J, Tilvis R (1995) Usefulness of the Clinical Dementia Rating scale in screening for dementia. Int Psychogeriatr 7:17–24
45. Petersen R, Aisen P, Beckett L et al (2010) Alzheimer's Disease Neuroimaging Initiative (ADNI): clinical characterization. Neurology 74:201–209
46. Saykin AJ, Shen L, Foroud TM et al (2010) Alzheimer's Disease Neuroimaging Initiative biomarkers as quantitative phenotypes: genetics core aims, progress, and plans. Alzheimers Dement 6:265–273
47. Cohen J (1988) Statistical power analysis for the behavioral sciences, 2nd edn. L. Erlbaum Associates, Hillsdale, N.J
48. Lin KA, Doraiswamy PM (2014) When Mars versus Venus is not a cliche: gender differences in the neurobiology of Alzheimer's disease. Front Neurol 5:288
49. Irvine K, Laws KR, Gale TM, Kondel TK (2012) Greater cognitive deterioration in women than men with Alzheimer's disease: a meta analysis. J Clin Exp Neuropsychol 34:989–998
50. Damoiseaux JS, Seeley WW, Zhou J et al (2012) Gender modulates the APOE epsilon4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. J Neurosci 32:8254–8262
51. Lehmann DJ, Refsum H, Nurk E et al (2006) Apolipoprotein E epsilon4 and impaired episodic memory in community-dwelling elderly people: a marked sex difference. The Hordaland Health Study. J Neurol Neurosurg Psychiatry 77:902–908
52. Schuff N, Woerner N, Boreta L et al (2009) MRI of hippocampal volume loss in early Alzheimer's disease in relation to ApoE genotype and biomarkers. Brain 132:1067–1077
53. Agosta F, Vossel KA, Miller BL et al (2009) Apolipoprotein E epsilon4 is associated with disease-specific effects on brain atrophy in Alzheimer's disease and frontotemporal dementia. Proc Natl Acad Sci U S A 106:2018–2022
54. Lehtovirta M, Laakso MP, Soininen H et al (1995) Volumes of hippocampus, amygdala and frontal lobe in Alzheimer patients with different apolipoprotein E genotypes. Neuroscience 67:65–72
55. Mori E, Lee K, Yasuda M et al (2002) Accelerated hippocampal atrophy in Alzheimer's disease with apolipoprotein E epsilon4 allele. Ann Neurol 51:209–214
56. Manning EN, Barnes J, Cash DM et al (2014) APOE epsilon4 is associated with disproportionate progressive hippocampal atrophy in AD. PLoS One 9:e97608
57. Yaffe K, Haan M, Byers A, Tangen C, Kuller L (2000) Estrogen use, APOE, and cognitive decline: evidence of gene-environment interaction. Neurology 54:1949–1954
58. Hashimoto M, Yasuda M, Tanimukai S et al (2001) Apolipoprotein E epsilon 4 and the pattern of regional brain atrophy in Alzheimer's disease. Neurology 57:1461–1466
59. Pievani M, Galluzzi S, Thompson PM, Rasser PE, Bonetti M, Frisoni GB (2011) APOE4 is associated with greater atrophy of the hippocampal formation in Alzheimer's disease. Neuroimage 55:909–919

60. Ungar L, Altmann A, Greicius MD (2014) Apolipoprotein E, gender, and Alzheimer's disease: an overlooked, but potent and promising interaction. Brain Imaging Behav 8:262–273
61. Corder EH, Ghebremedhin E, Taylor MG, Thal DR, Ohm TG, Braak H (2004) The biphasic relationship between regional brain senile plaque and neurofibrillary tangle distributions: modification by age, sex, and APOE polymorphism. Ann N Y Acad Sci 1019:24–28
62. Ghebremedhin E, Schultz C, Thal DR et al (2001) Gender and age modify the association between APOE and AD-related neuropathology. Neurology 56:1696–1701