APOE interacts with age to modify rate of decline in cognitive and brain changes in Alzheimer's disease

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Abstract

Background—To determine (1) whether age-standardized cognitive declines and brain morphometric change differ between Young-Old (YOAD) and Very-Old (VOAD) patients with Alzheimer's disease (AD) and (2) whether apolipoprotein E (APOE) genotype modifies these neuropsychological and morphometric changes.

Methods—Baseline and 12-month follow up neuropsychological and morphometric measures were examined for healthy control and AD individuals. The two AD groups were further divided into subgroups on the basis of the presence of at least one APOE ε4 allele.

Results—The YOAD showed more severe deficits andsteeper declines in cognition than the VOAD. Moreover, the presence of an APOE ε4 allele had a more deleterious effect on the YOAD than the VOAD on cognition and brain structure both cross-sectionally and longitudinally.

Conclusions—Results underscore the importance of integrating an individual's age and genetic susceptibility—and their interaction—when examining neuropsychological and neuroimaging changes in the early stages of Alzheimer's disease.

1. Introduction

Dementia incidence increases exponentially between the ages of 65 and 90 years. Although much progress has been made in identifying the typical cognitive deficits and brain morphometry changes associated with early Alzheimer's disease (AD), the boundaries between normal age-related functional and structural changes and early signs of AD remain especially difficult to delineate in the Very-Old (i.e., over the age of 80) [1]. A few studies have shown that AD-related cognitive [2–4] and morphometric [3, 4] changes observed in Young-Old patients are less salient in the Very-Old because brain and behavioral changes observed in normal aging overlap with indicators of AD to a greater degree in the Very-Old than in the Young-Old.

Another factor that may lead to differences in the cognitive deficit profiles of AD in the Young-Old and Very-Old is an age-related change in the influence of the ε4 allele of the apolipoprotein E (APOE) gene. Although it is well established that the APOE ε4 allele is the most common genetic risk factor for AD, controversy exists as to whether or not APOE allelic variants are associated with different cognitive and morphometric AD phenotypes [1, 5, 6]. Several cross-sectional studies have reported that AD ε4 carriers have greater impairment in memory and executive function than AD non-ε4 carriers [5]. Longitudinal studies have shown mixed results with AD ε4 carriers demonstrating slower [7, 8], faster [9–11], or equivalent [12, 13] rates of cognitive decline as their non-ε4 counterparts. Several studies have shown that the effects of APOE ε4 genotype on cognition appear to wane with advancing age in AD and in at-risk individuals [2, 5, 14]. This latter effect suggests that the cognitive phenotypic expression of the APOE ε4 allele may vary as a function of the age of patients. However, most of these studies were cross-sectional in design and incapable of ruling out cohort effects such as differences in subjects' age or severity of dementia. Furthermore, it is still largely unknown whether morphometric profiles differ by the patient's age at onset of disease and APOE status.

The present study compared baseline and longitudinal patterns of cognitive decline and regional brain atrophy in Young-Old and Very-Old patients with AD and sought to determine if APOE genotype differentially affects these patterns in the two cohorts. Based upon previous results [2–4], we predicted that, relative to Young-Old AD patients, Very-Old AD patients would exhibit less severe cognitive deficits and less atrophic regional brain changes at baseline, and the rate of cognitive and morphometric changes over time would be slower when using age-standardized cognitive and brain morphometric measures. We further predicted interactive effects of age and APOE genotype—with the presence of an APOE ε4 allele having a more deleterious effect on cognition and morphometry in the Young-Old with AD than in the Very-Old AD group. Specifically, we expected that

interactive effects of age and APOE genotype would be limited to memory and executive function given previous reports of the rather specific effect of APOE ɛ4 genotype on these cognitive functions [5]. With respect to morphometry, we predicted that interactive effects of age and APOE genotype would be apparent in medial temporal lobe, temporoparietal, and frontal regions given their well-documented roles in the pathology of early Alzheimer's disease.

2. Methods

The raw data used in the current study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.loni.ucla.edu/ADNI). ADNI was launched in 2003 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 non-profit organizations as a $60 million, 5-year public-private partnership. The primary goal of ADNI is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early AD. ADNI is the result of efforts of co-investigators from a broad range of academic institutions and private corporations. Subjects have been recruited from over 50 sites across the U.S. and Canada (see www.adni-info.org). The ADNI study was approved by an ethical standards committee on human experimentation at each institution. Written informed consent was obtained from all study participants, or their authorized representatives, after the procedures of the study were fully explained.

2.1 Participants

ADNI general eligibility criteria have been described elsewhere[15]. Participants included in the present study were Healthy Control (HC) participants or mildly demented patients with AD, 60–92 years old, non-depressed, with a modified Hachinski score of 4 or less, and with a study partner able to provide an independent evaluation of functioning. Participants with a history of stroke or neurological disorders other than AD were excluded from ADNI. HC had a Mini-Mental State Exam (MMSE) score between 24–30 (inclusive), a global Clinical Dementia Rating [16] score of 0, and did not meet criteria for MCI [17]. Mild AD participants had MMSE scores between 20–26, global CDR of 0.5 or 1.0, and met NINCDS/ADRDA criteria for probable AD [18]. The CDR-Sum of Boxes (CDR-SB) score was calculated for all participants to further estimate level of clinical impairment.

HC participants in ADNI were followed for 3 years, with assessments at 0, 6, 12, 24, and 36 months. AD patients were followed for 2 years, with assessments at 0, 6, 12, and 24 months. Participants who completed the baseline visit and at least the 1 year follow-up visit were included in this study. Seven HC participants (five in the Young-Old and two in the Very-Old) who converted to a diagnosis of MCI or AD during any of the ADNI follow-up visits were excluded from the analysis.

The HC and AD participants were divided into subgroups on the basis of their age at baseline testing: (1) Young-Old groups comprised individuals aged 75 years or younger (range 60–75), and (2) Very-Old groups comprised individuals aged 80 years or greater

(ranged 80–91). The five-year age gap (i.e., participants were not studied if they fell between the ages of 76–80) resulted in an approximately 12-year age difference between the Young-Old and Very-Old groups. The subject pool was further restricted to those participants for whom adequately processed and quality checked MR baseline data existed. The final sample consisted of 227 participants: 83 Young-Old HC participants, 64 Young-Old AD patients, 40 Very-Old HC participants, and 40 Very-Old AD patients (see upper portion of Table 1). All participants were genotyped for apolipoprotein E (APOE) allele status using DNA extracted from peripheral blood cells. Participants with APOE genotype ε4/ε2 were excluded (n = 4) from the present study. To examine the impact of APOE ε4 allele on rate of decline in Young-Old and Very-Old AD patients, the patient groups were divided into subgroups on the basis of the presence of at least one APOE ε4 allele. The Young-Old ε4 AD group consisted of 49 participants; the Young-Old non-ε4 AD group consisted 15 participants; the Very-Old ε4 AD group consisted of 20 participants; the Very-Old non-ε4 AD group consisted 20 participants (see lower portion of Table 1).

2.2 Neuropsychological measures

The Participants were tested with a standardized battery of neuropsychological tests [15]. We assessed performance at baseline and at the one-year follow-up. Six neuropsychological domains were assessed with the following tests: (1) Language: 30-item Boston Naming Test and Category Fluency (animal and vegetable categories); (2) Attention/ Psychomotor Processing Speed: Trail Making Test Part A, and Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span Forward and Digit Symbol subtests; (3) Executive Function: Trail Making Test Part B and WAIS-R Digit Span Backward; (4) Immediate Recall: Rey Auditory Verbal Learning Test (RAVLT) Trials 1–5 Total Recall and Wechsler Memory Scale-Revised (WMS-R) Logical Memory (LM) Immediate Recall; (5) Delayed Recall: RAVLT Long-Delay Recall and WMS-R Logical Memory Delayed Recall; (6) Recall Savings: RAVLT Percent Long-Delay Savings and WMS-R Logical Memory Percent Delayed Recall Savings. The test scores achieved by the Young-Old and Very-Old AD patients on each measure were converted to z-scores based upon the mean and standard deviations of their respective HC group and summed to create the six neuropsychological domain composite scores. To ease interpretation, z-scores were modified to ensure that negative scores represented poorer performance.

2.3 MRI acquisition and analysis

Image acquisition and analysis methods were developed within the NIH/NCRR sponsored Morphometry Biomedical Informatics Research Network (mBIRN) and ADNI [19–22]. Data were collected across a variety of 1.5 T scanners. Protocols are described in detail at http://adni.loni.ucla.edu/research/protocols/mri-protocols/. Two T1-weighted volumes were acquired for each participant, one at baseline and one at follow-up approximately 1 year later. These raw DICOM MRI scans were downloaded from the public ADNI site (http://adni.loni.ucla.edu/about-data-samples/how-to-apply/). Locally, images were reviewed for quality, automatically corrected for spatial distortion due to gradient nonlinearity [21] and B1 field inhomogeneity [23], registered, and averaged to improve signal-to-noise. Volumetric segmentation [24, 25] and cortical surface reconstruction [25–28] used methods based on FreeSurfer software optimized for use on large, multi-site datasets. To measure

thickness, the cortical surface was reconstructed [26, 27] and parcellated into distinct regions of interest (ROIs) [25, 29]. FreeSurfer also provides estimates of white matter hypointensity (WMH) based on the automatic segmentation of the T1 weighted images. Details of the application of these methods to the ADNI data have been described in full elsewhere [30]. To limit the number of multiple comparisons, only regions assumed to be involved in early AD pathology [19–22] were included in the present analyses. These included volumetric measures of bilateral hippocampal formation, including dentate gyrus, CA fields, subiculum/ parasubiculum and the fimbria [31], and thickness measures of frontal, temporal, and parietal lobe cortical areas and bilateral cingulate cortex regions (see ROIs listed in Fig 3). To decrease the number of comparisons, the caudal and rostral anterior cingulate regions were combined as anterior cingulate cortex (ACC); the isthmus and posterior cingulate regions were combined as posterior cingulate cortex (PCC); and the pars opercularis and pars triangularis were combined as the frontal operculum. Following Buckner and colleagues [32], baseline volumetric data were corrected for individual differences in head size by regressing the estimated total intracranial volume (eTIV).

2.3.1 Longitudinal analysis of MRI scans—The longitudinal data was derived through Quarc (quantitative anatomical regional change, [33]). Dual 3-D follow-up structural scans for each participant were rigid-body aligned, averaged and affine aligned to the participant's baseline scan. Nonlinear registration of the images was then performed, where voxel centers were moved about until a good match was made between the images [33, 34]. This is achieved in the following way. The images are heavily blurred (smoothed), making them almost identical, and a merit or potential function is calculated. This merit function expresses the intensity difference between the images at each voxel, and depends on the displacement field for the voxel centers of the image being transformed; it is also regularized to keep the displacement field spatially smooth. The merit function by design will have a minimum when the displacement field induces a good match between the images. The displacement field in general will turn cubic voxels into displaced irregular hexahedra whose volumes give the volume change field. The merit function is minimized efficiently using standard numerical methods. Having found a displacement field for the heavily blurred pair of images, the blurring is reduced and the procedure repeated, thus iteratively building up a better displacement field. Two important additions to this are: 1) applying the final displacement field to the image being transformed, then nonlinearly registering the resultant image to the same target, and finally tracing back through the displacement fields thus calculated to find the net displacement field; and 2) restricting to regions of interest and zooming when tissue structures are separated by only a voxel or two. These additional features enable very precise registration involving large or subtle deformations, even at small spatial scales with low boundary contrast. Although large deformations are allowed by multiple nonlinear registration (or relaxation) steps, nonphysical deformations are precluded because at each level of blurring the image undergoing deformation is constrained to conform to the target. Note that calculating the deformation field does not depend on initially segmenting tissue. This deformation field was used to align scans at the sub-voxel level.

The follow-up aligned image underwent skull stripping and volumetric segmentations (subcortical structures, as well as hippocampus and cerebellum gray matter), with labels applied from the baseline scan. For the cortical reconstructions, surface coordinates for the white matter and pial boundaries were derived from the baseline images and mapped onto the follow-up images using the deformation field. Parcellations from the baseline image were then applied to the follow-up image. This resulted in a one-to-one correspondence between each vertex in the base image and the follow-up image. This procedure produced an estimate of the percent cortical volume loss at each vertex and within each ROI. To the extent that regional cortical areas are relatively stable across time points, the volume change is likely driven almost exclusively by changes in thickness. Atrophy rates were defined as the percent cortical volume loss over the course of one-year. These atrophy rates represent within-subject change over time and are independent of group differences in baseline measurements (e.g., eTIV). Because the procedure is fully automated, the test-retest reliability is 1. The method has been validated in model studies of complex spherical-shell geometries with low contrast and noise where a prescribed volume change is numerically estimated to accuracies of within 0.5% [33].

2.4 Statistical analyses

Group comparisons for demographic, clinical (i.e., CDR sum of boxes scores, disease duration), and global cognitive (i.e., MMSE scores) variables were performed with analyses of variance (ANOVAs) and independent samples t tests or chi-square tests, as appropriate. Repeated measure GLMs were used for analyzing the longitudinal cognitive data with group as the between-subjects variable and, in separate analyses, each of the six cognitive variables (i.e., language, attention/psychomotor processing speed, executive function, immediate recall, delayed recall, and recall savings) as a within-subjects measures. ANOVAs and/or independent samples t tests were performed for follow-up pair-wise comparisons. Based on Bonferroni correction, α level was set to $p < .008$ for analyses of the 6 neuropsychological composite scores. Whenever the assumption of homogeneity of variance was not met, the t-value and significance of the comparison were reported according to the assumption that variances were unequal.

To assess group difference in baseline morphometric variables, effect of gender was first regressed from all thickness and volumetric measures. Bilateral hippocampal volumes were also corrected for differences in head size by regressing the estimated total cranial vault (eTIV) volume [32]. Next, the volumetric and cortical thickness measures of the two AD groups at baseline were z-transformed relative to their respective HC group such that negative values indicated smaller volume or thinner cortex. Regional atrophy rates were used in analyses of longitudinal morphometric differences. Because the current study did not pose specific hypotheses about hemispheric effects, the volumes and cortical thickness variables were averaged across right and left hemisphere values to decrease number of comparisons. Univariate ANOVAs were performed, followed by ANOVAs or independent samples t tests for post-hoc comparisons. Based on Bonferroni correction, the $α$ level was set to .0026 for assessment of baseline and longitudinal morphometry in the 19 ROIs. Effect sizes (Cohen's d) were calculated for neuropsychological and morphometric variables that reached statistical significance.

To rule out possible confounding effects driven by vascular risk factors separate analyses controlling for both modified Hachinski Ischemic Scale scores and blood homocysteine levels, were performed. Effects are reported when control for these factors changed the main results.

3. Results

3.1 Demographic and clinical data

The demographic and clinical characteristics for the two HC subgroups and the two AD subgroups are presented in Table 1. Consistent with the design of the study, the two Very-Old groups were older than the two younger groups ($F_{(3,223)}$ = 376.27, $p < .001$), although no significant age difference was observed between the two younger groups ($p = .17$) or the two older groups ($p = .98$). The four groups did not differ in educational attainment ($F_{(3,223)}$ = 2.28, $p = .08$), gender distribution ($\chi^2(3) = 2.01$; $p = .57$), modified Hachinski Ischemic Scale scores ($F_{(3,223)}$ = 1.38, $p = .25$), or percentage of people currently taking hypertension medications ($F_{(3,227)}$ = 1.67, $p = .65$). The four groups differed significantly on the blood homocysteine level ($F_{(3,223)}$ = 5.41, $p < .005$). Post-hoc analyses revealed that the Young-Old HC showed significantly lower homocysteine level compared to the Very-Old HC ($p < .005$) and the Very-Old AD ($p = .05$) groups, while the two AD groups showed comparable level of homocysteine ($p = .07$).

As expected, AD patients scored lower than HC participants on the MMSE ($F_{(3,223)}$ = 230.13, $p < .001$) and CDR-SB ($F_{(3,222)}$ = 280.07, $p < .001$). The two HC groups (MMSE: $p = .81$; CDR-SB: $p = .11$) and the two AD groups (MMSE: $p = .53$; CDR-SB: $p = .33$) did not differ significantly on the MMSE or the CDR-SB scores. The two AD groups did not differ significantly in the estimated years of disease duration ($t_{101} = -.12$, $p = .91$), but the Very-Old AD group showed greater volume of WMH than the Young-Old AD group ($t_{102} = -3.15$, $p = .002$). Both AD groups showed a higher frequency of APOE ε4 carriers compared to the two HC groups (all p-values < .005). The Young-Old AD group had a higher frequency of APOE ε4 carriers than their Very-Old AD counterparts ($\chi^2(1) = 7.78$; $p = .005$). The percentage of subjects lost to follow-up did not significantly differ between the four groups ($\chi^2(3) = 2.01$; $p = .57$).

We further compared the demographic and clinical variables for the four AD subgroups (APOE genotype x age). The four AD groups did not differ in educational attainment ($F_{(3,100)}$ = 1.55, $p = .21$), gender distribution ($\chi^2(3) = 6.83$; $p = .08$), CDR-SB scores ($F_{(3,100)}$ = .64, $p = .59$), MMSE scores ($F_{(3,100)}$ = .41, $p = .75$), modified Hachinski Ischemic Scale scores ($F_{(3,100)}$ = 0.51, $p = .68$), disease duration ($F_{(3,99)}$ = .35, $p = .79$), percentage of participants currently taking hypertension medications ($F_{(3,104)}$ = 1.14, $p = .77$), or blood homocysteine level ($F_{(3,100)}$ = 1.65, $p = .18$). As expected, the two Very-Old AD groups were older than the two younger AD groups ($F_{(3,100)}$ = 154.47, $p < .001$) whereas no significant age difference was observed between the two younger groups ($p = .75$) or the two older groups ($p = .60$). The Very-Old AD ε4 group had greater volume of white matter hypointensity than the Young-Old AD ε4 group ($F_{(3,100)}$ = 3.31, $p = .023$)

3.2 Neuropsychological assessment

Age main effects—Main effects for age using the age-normalized z-scores revealed significantly poorer performance in the Young-Old AD group than in the Very-Old AD group in the domains of executive function ($t_{92} = -3.83$, $p < .001$; Cohen's $d = 0.78$), attention/psychomotor processing speed ($t_{97} = -3.21$, $p = .002$; Cohen's $d = 0.68$), and immediate memory ($t_{101} = -2.77$, $p = .007$; Cohen's $d = 0.58$). The two AD groups had comparable performances on language ($t_{95} = 1.29$, $p = .20$), delayed memory ($t_{102} = 0.69$, $p = .50$), and recall savings ($t_{92} = -.82$, $p = .42$) (see Fig 1).

APOE genotype polymorphism effects—There were no significant main effects of APOE genotype on any of the cognitive domains in the AD groups.

Time main effects—Significant main effects for time were found on all six cognitive composite scores. Relative to their age-appropriate HC group, the AD patients as a whole demonstrated decline in performance over one year in all cognitive domains, including language ($F_{(1,79)} = 27.98$, $p < .001$), executive function ($F_{(1,70)} = 49.31$, $p < .001$), attention/psychomotor processing speed ($F_{(1,81)} = 8.14$, $p = .005$), immediate memory ($F_{(1,81)} = 35.26$, $p < .001$), delayed memory ($F_{(1,80)} = 9.43$, $p = .003$), and recall savings ($F_{(1,66)} = 8.42$, $p = .005$).

Age x APOE genotype interaction effects—Significant age x APOE genotype interaction effects were obtained for three of the baseline cognitive composite scores. Specifically, the presence of an APOE ε4 allele had a more deleterious effect on performance in the Young-Old AD group than in the Very-Old AD group on executive function ($t_{54} = -3.26$, $p = .002$; Cohen's $d = 0.82$), attention/psychomotor processing speed ($t_{61} = -3.74$, $p < .001$; Cohen's $d = 0.88$), and marginally for recall savings ($t_{52} = -2.32$, $p = .02$; Cohen's $d = 0.50$). In contrast, there were no significant differences on any of the cognitive domains between the two AD age groups for the non-ε4 carriers (all p-values > .05).

Age x time interactions effects—Significant age x time interaction effects were observed for four of the cognitive composite scores. The Young-Old AD group showed steeper declines over time than the Very-Old AD group on language ($F_{(1,81)} = 21.07$, $p < .001$, $\eta_p^2 = 0.21$), executive function ($F_{(1,72)} = 29.64$, $p < .001$, $\eta_p^2 = .29$), immediate recall ($F_{(1,83)} = 21.23$, $p < .001$, $\eta_p^2 = .20$), and delayed recall ($F_{(1,82)} = 33.43$, $p < .001$, $\eta_p^2 = .29$) composite scores.

APOE genotype x time interaction effects—Significant APOE genotype x time interactions were obtained only for the language domain ($F_{(1,81)} = 7.58$, $p = .007$, $\eta_p^2 = .09$) with the AD ε4 group, as a whole, showing steeper decline than the AD non-ε4 group over the one year follow-up interval.

Age x APOE genotype x time interaction effects—Significant age group x APOE genotype x time interaction effects were obtained on immediate recall. The Young-Old ε4 AD group showed steeper declines on immediate recall over one year than did the Very-Old

ε4 AD group ($F_{(3,81)}$ = 7.80, p < .001, η_p^2 = .22), whereas the two non-ε4 AD groups showed comparable rates of decline. The presence of an APOE ε4 allele also had a more deleterious effect on language function for the Young-Old AD group than for the Very-Old AD group ($F_{(3,79)}$ = 8.25, p < .001, η_p^2 = .24) (Fig 2).

3.3 Brain morphometry

Age main effects—The analyses were based on the age-normalized z-scores that also controlled for gender effects. The Young-Old AD group showed thinner baseline cortex than the Very-Old AD group in inferior parietal regions (t_{102} = −3.89, p < .001; Cohen's d = 0.80) (see Figure 3).

APOE genotype polymorphism effects—There were no significant main effects of APOE genotype on baseline morphometric measures in any of the ROIs in the AD groups.

Age x APOE genotype interaction effects—A significant age x APOE genotype interaction was obtained for the inferior parietal region ($F_{(3,100)}$ = 5.34, p = .002, η_p^2 = .14). The Young-Old ε4 AD group showed more cortical thinning than the Very-Old ε4 AD group in this cortical region, whereas the two non-ε4 AD groups showed comparable thickness (p >. 05).

Age x time interaction effects—Significant age x time (annual brain atrophy rate) interaction effects were found in both AD and HC groups. There was a greater rate of atrophy in the Young-Old AD group than in the Very-Old AD group for superior temporal (t_{64} = −5.04, p < .001; Cohen's d = 1.15), middle temporal (t_{64} = −6.70, p < .001; Cohen's d = 1.57), inferior temporal (t_{68} = −6.42, p < .001; Cohen's d = 1.48), caudal middle frontal (t_{60} = −3.18, p = .002; Cohen's d = 0.78), inferior parietal lobule (t_{68} = −5.64, p < .001; Cohen's d = 1.42), precuneus (t_{68} = −4.25, p < .001; Cohen's d = 0.99), superior parietal lobule (t_{64} = −4.31, p < .001; Cohen's d = 1.05), supramarginal (t_{68} = −5.69, p < .001; Cohen's d = 1.31), and posterior cingulate (t_{68} = −3.10, p = .002; Cohen's d = 0.72) regions. The two AD groups showed comparable rates of atrophy in hippocampus, but a marginally significant effect in entorhinal (p = .054) and parahippocampal (p = .04) regions with a greater rate of atrophy in the Young-Old AD group than in the Very-Old AD group. After controlling for both modified Hachinski Ischemic Scale scores and blood homocysteine level, the previously observed age x time effect on caudal middle frontal and posterior cingulate were no longer significant.

Age x time interaction effects were also obtained between the two HC groups, but these were in opposite direction to effects observed in the two AD groups. Specifically, the Very-Old HC group had a greater annual atrophy rate than the Young-Old HC group in hippocampal (t_{88} = −3.23, p = .002; Cohen's d = 0.75), entorhinal (t_{89} = 4.43, p < .001; Cohen's d = 1.09), supramarginal (t_{89} = 3.29, p = .001; Cohen's d = 0.76), and operculum (t_{89} = 3.19, p = .002; Cohen's d = 0.72) regions.

APOE genotype x time interaction effects—There were no significant APOE genotype effects on annual atrophy rate in the two AD groups in any of the ROIs.

Age x APOE genotype x time interaction effects—The presence of an APOE ε4 allele was associated with a greater rate of atrophy in the Young-Old AD group than in the Very-Old AD group on several lateral temporal and parietal ROIs. Specifically, the Young-Old ε4 AD group showed a greater annual rate of atrophy in superior ($F_{(3,65)} = 6.69$, $p = .001$, $\eta_p^2 = .24$), middle ($F_{(3,65)} = 11.71$, $p < .001$, $\eta_p^2 = .35$), and inferior ($F_{(3,65)} = 11.43$, $p < .001$, $\eta_p^2 = .35$) temporal; superior ($F_{(3,65)} = 5.94$, $p = .001$, $\eta_p^2 = .08$) and inferior ($F_{(3,65)} = 10.21$, $p < .001$, $\eta_p^2 = .17$) parietal; precuneus ($F_{(3,65)} = 5.71$, $p = .002$, $\eta_p^2 = .12$), and supramarginal ($F_{(3,65)} = 9.71$, $p = .001$, $\eta_p^2 = .14$) regions than any of the other three AD groups. In contrast, the Very-Old ε4 AD group showed annual atrophy rates that were similar to those of the Very-Old non-ε4 AD and Young-Old non-ε4 AD groups in all ROIs, including medial temporal regions (all p-values $> .05$) (Fig 5).

4. Discussion

The present results extend our previous findings [3, 4] by demonstrating an interaction between APOE genotype and age in cross-sectional and longitudinal cognitive and morphometric manifestations of AD. We previously showed that when Young-Old and Very-Old patients with AD are compared to their respective age-appropriate HC subjects, the Very-Old AD patients exhibit less severe cognitive impairment and less regional brain atrophy than the Young-Old AD patients in a cross-sectional sample [3]. In the current study, we further found that the Very-Old AD patients also show a slower rate of cognitive decline in memory, executive function, and language, as well as a slower rate of atrophy in multiple temporal, parietal, and cingulate brain regions over time. These effects were partially explained by age-related decreases in cognitive performance and cortical thickness of the respective healthy control participants, which made the age-appropriate standard scores of the Very-Old AD patients less "abnormal" than those of the Young-Old AD patients.

In the present study, we also found that Young-Old AD patients with at least one APOE ε4 allele were more impaired (relative to age-appropriate HC participants) than Young-Old AD patients without an ε4 allele, or Very-Old AD patients with or without an ε4 allele, on baseline measures of executive function, attention, and psychomotor processing speed. Furthermore, the Young-Old ε4 AD patients had steeper declines in memory and language over a one-year interval than Young-Old non-ε4 or Very-Old ε4 and Very-Old non-ε4 AD patients. These results suggest that the effect of APOE genotype on cognition and rate of decline depend upon the patient's age at onset of disease. Variability in the results of previous studies that examined APOE-related differences in the cognitive phenotype of AD may be explained, in part, by this phenomenon. Previous studies that found APOE genotype effects on cognition or rate of cognitive decline typically studied patients in younger age ranges (i.e., mean ages less than 85)[10, 35], whereas studies that failed to find these effects may have included samples with wider or older age ranges[13].

The observed interaction between the effects of age and APOE genotype on cognition was also apparent in cortical thickness measures. Young-Old ε4 AD patients had greater thinning than Young-Old non-ε4 AD patients in inferior parietal cortex, whereas the Very-Old ε4 and non-ε4 AD patients did not differ. In addition, Young-Old ε4 AD patients had greater

atrophy over one-year than Young-Old non-ε4 AD and Very-Old ε4 and non-ε4 AD patients in a number of lateral temporal lobe and parietal cortical regions including precuneus cortex and the supramarginal gyrus. These findings are consistent with our hypothesis that decreased cortical thickness or accelerated rates of brain atrophy related to age and APOE ε4 genotype would be found in regions particularly susceptible to deposition of neurofibrillary tangles and neuronal loss such as the supramarginal gyrus.

However, not all brain regions usually affected by AD showed differential levels of volumetric or cortical thickness abnormality in the AD groups that were stratified by age and APOE genotype. For example, Young-Old ε4 AD patients showed only marginally more atrophy over the one-year interval than Young-Old non-ε4 AD and Very-Old ε4 and non-ε4 AD patients in hippocampus, entorhinal cortex and parahippocampal gyrus, and this was due largely to the fact that Very-Old HC participants showed more atrophy than Young-Old HC participants in these regions which skewed the AD patients age-adjusted atrophy scores. It should be noted, however, that while atrophy of the hippocampus and medial temporal gyrus increased with age and the presence of an APOE ε4 allele in the HC participants, the degree of difference between the HC and AD groups remained large. Thus, our findings do not contradict the position that early and severe atrophy of the hippocampus and medial temporal lobe cortex due to AD greatly eclipses normal age-related changes and allows atrophy in these regions to be a salient marker of AD. It should also be noted that, as with cognition, our findings of interactions between age and APOE genotype on morphometric brain changes related to AD may partially account for inconsistent findings across studies examining the effect of the APOE ε4 allele on brain atrophy in patients with AD.

The present findings have potential clinical implications because they imply that there are age and APOE genotype-related decrements in the sensitivity of cognitive and imaging measures for detecting AD. Because cognitive impairment (relative to age-appropriate HC) in Very-Old AD patients is less apparent than in Young-Old AD patients, the likelihood of false negative diagnostic errors is increased in very elderly patients. This could have important ramifications for diagnosis under the proposed Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) scheme, given that much of the distinction between 'major' and 'minor' neurocognitive disorder (i.e., analogous to dementia vs. mild cognitive impairment, respectively) rests on the severity of cognitive impairment. In this proposed scheme, −1 to −2 SDs below appropriate norms on cognitive testing defines minor neurocognitive disorder, whereas −2 or more SDs defines major neurocognitive disorder. Our findings suggest that application of this approach would likely give rise to greater numbers of false negative diagnostic errors (e.g., mis-assigning those who are demented as having a 'minor' neurocognitive disorder) in very elderly individuals than in younger elderly individuals. The common use of a −1.5 SD cutoff on memory testing for the identification of MCI may also need adjustment upward if it is to retain sensitivity for the detection of MCI in the Very-Old [2].

With respect to MR imaging, there may be less volumetric integrity (and more variability) in temporal lobe and other brain regions in the Very-Old. Consequently, imaging approaches that measure change in these structures as a diagnostic sign of AD may also be less useful in

this cohort because the change occurs against a backdrop of age-related change and increased variability in hippocampal and other regional atrophy [36]. Future empirical studies that define age-specific cutoff values for morphometric measures will be useful.

Although APOE genotype *per se* did not necessarily influence the rate of cognitive decline or brain morphometric change in patients with AD, the age by APOE genotype interaction effect is likely an important factor in determining and modulating decline. It is important to understand the role of APOE genotype and its interaction with age of onset in the progression of neurodegeneration to optimize treatment regimens, including therapies that target APOE function (see also [37]). Our results suggest, however, that less additional prognostic information would be provided by knowledge of APOE genotype in very elderly patients with AD.

Some limitations of the present study should be noted. First, histopathological verification of disease is not available so it is possible that some participants have a disorder other than AD or have AD with co-morbid pathologies (e.g., infarcts, Lewy bodies, etc.) that contribute to the cognitive and neuroimaging presentations. For example, the impact of white matter changes on the pattern of cognitive and regional brain changes in AD across different age groups may relate to some of the observed differences in cognitive profiles, as we noted a significantly greater amount of WMH in Very-Old AD relative to the Young-Old AD. However, ADNI exclusionary criteria ensure a low prevalence of vascular risk factors. Moreover, after controlling for the effects of select vascular risk factors (i.e., modified Hachinski Scale scores and blood homocysteine level), our findings of the distinct patterns in Young-Old versus Very-Old and their interaction with APOE status on the cognition and morphometry were retained. It suggested that the vascular factors were, for the most part, not driving these effects. Second, despite having a larger sample size than some previous studies, a sample size of 227 participants is relatively small, particularly once diagnostic groups were stratified on the basis of age and APOE status. This raises the issue of generalizability of the results. Thus, the study warrants replication in a larger and preferably autopsy-confirmed sample. Third, despite an effort made to ensure that none of the healthy control participants progressed to MCI or AD within three years after baseline evaluation, it is still possible that some participants with sub-clinical AD were misclassified into control groups (given the relatively short follow-up duration in the present study) potentially obscuring diagnostic group differences. Fourth, the relatively high number of men in the Very-Old group, though statistically non-significant, is inconsistent with studies that show female survival advantages [38]. Thus, the present sample may be biased towards a more physically healthy sample which limits the generalizability of results showing cognitive and morphometric differences between groups.

Despite these limitations, our results clearly argue against the simple application of our understanding of neuropsychological and neuroimaging changes in AD in the Young-Old to the detection of the disease in the Very-Old. Because there are normal age-related changes in cognitive performance and age-related changes in the influence of the APOE ε4 allele on cognition and morphometry, a multi-faceted approach that integrates neuropsychological assessment, APOE genotyping, and neuroimaging technologies [39, 40] may be needed to

characterize the early and preclinical stages of AD in this fastest growing and most vulnerable segment of our population.

Acknowledgments

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Research in Context

Systematic review

The cognitive phenotypic expression of the APOE ε4 allele may vary as a function of the age of patients. However, most of these studies were cross-sectional in design and it is still largely unknown whether morphometric profiles differ by the patient's age at onset of disease and APOE status.

Interpretation

Our results clearly argue against the simple application of our understanding of neuropsychological and neuroimaging changes in AD in the Young-Old to the detection of the disease in the Very-Old. A multi-faceted approach that integrates neuropsychological assessment, APOE genotyping, and neuroimaging technologies may be needed to characterize the early and preclinical stages of AD.

Future directions

Future studies should explore the role of APOE genotype and its interaction with age of onset in the progression of neurodegeneration to optimize treatment regimens, including therapies that target APOE function.
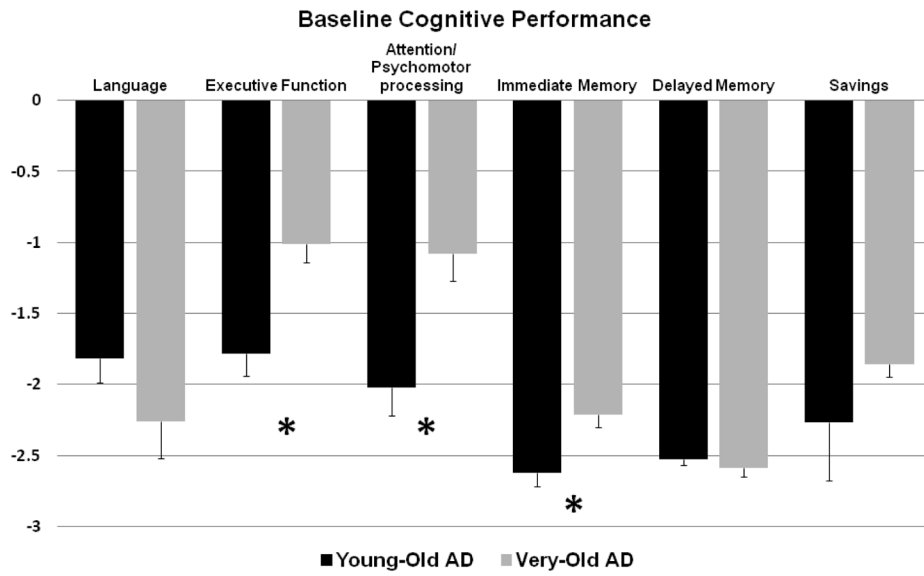
Figure 1.
Baseline performances of Young-Old AD vs. Very-Old AD by cognitive domains computed by age-normalized z-scores.
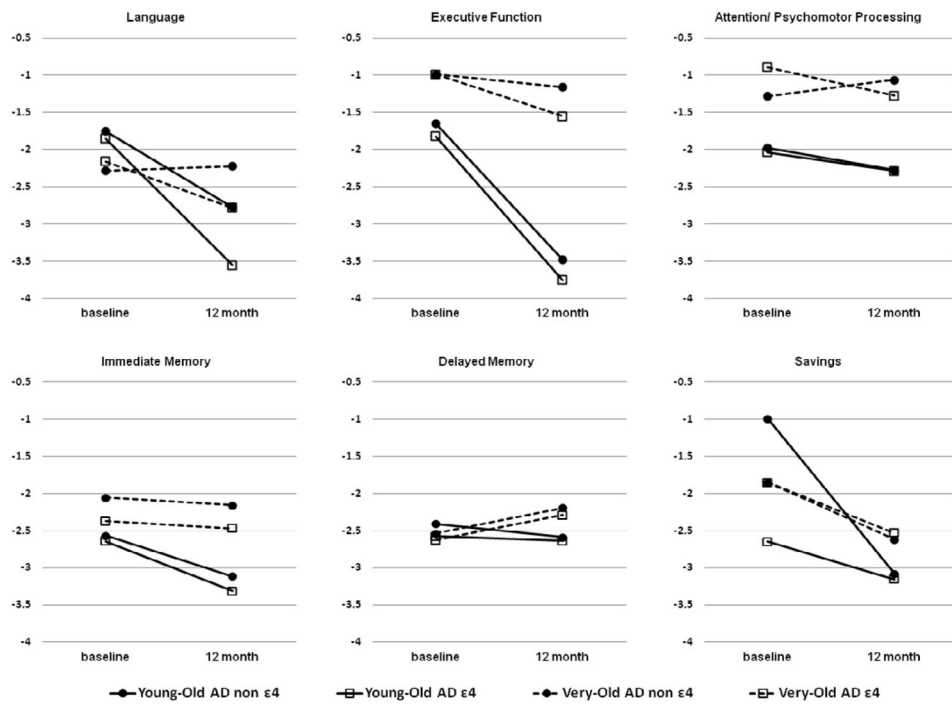
Figure 2.
Baseline and 12-month follow-up performances of the four AD age x APOE genotype subgroups on the age-normalized z-scores for the different cognitive domains.
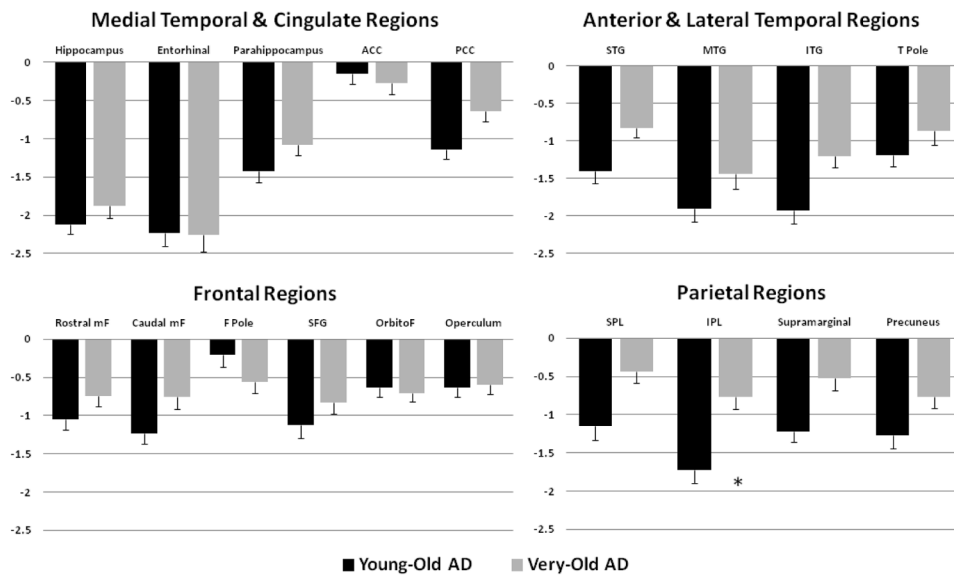
Figure 3.
Regional brain atrophy in the Young-Old and Very-Old Alzheimer's disease (AD) patients utilizing standardized z-scores derived from their age-appropriate healthy control counterparts at baseline. Error bars denote SEM. * $p < .001$. Abbreviations: ACC, anterior cingulate cortex; PCC, posterior cingulate cortex; STG, superior temporal gyrus; MTG, middle temporal gyrus; ITG, inferior temporal gyrus; T pole, temporal pole; mF, middle frontal; F pole, frontal pole; SFG, superior frontal gyrus; orbitoF, orbitofrontal; SPL, superior parietal lobule; IPL, inferior parietal lobule.
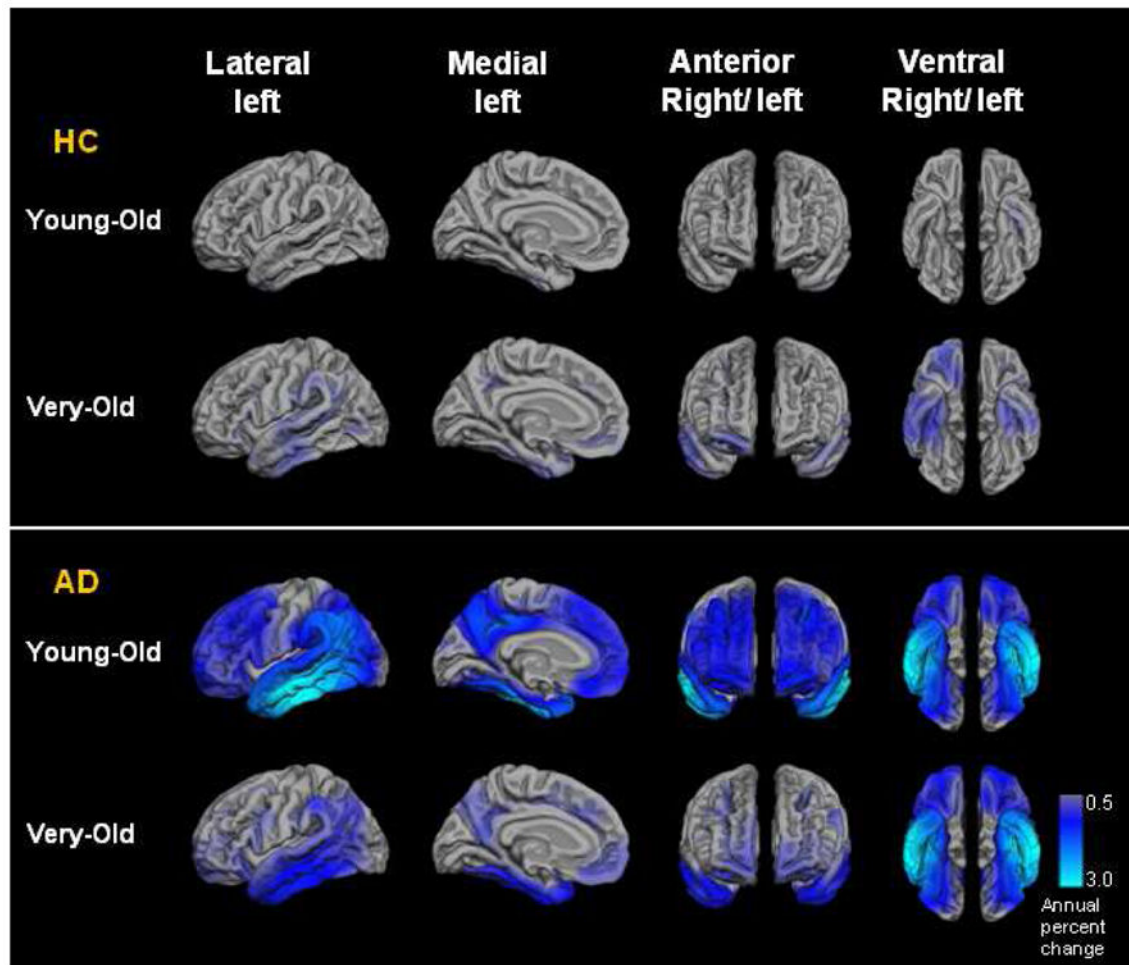
Figure 4.
Annual neocortical atrophy rates (as measured by percent volume change) in regions of interest in the Young-Old healthy control (HC), Very-Old HC, Young-Old Alzheimer's disease (AD), and Very-Old AD groups.
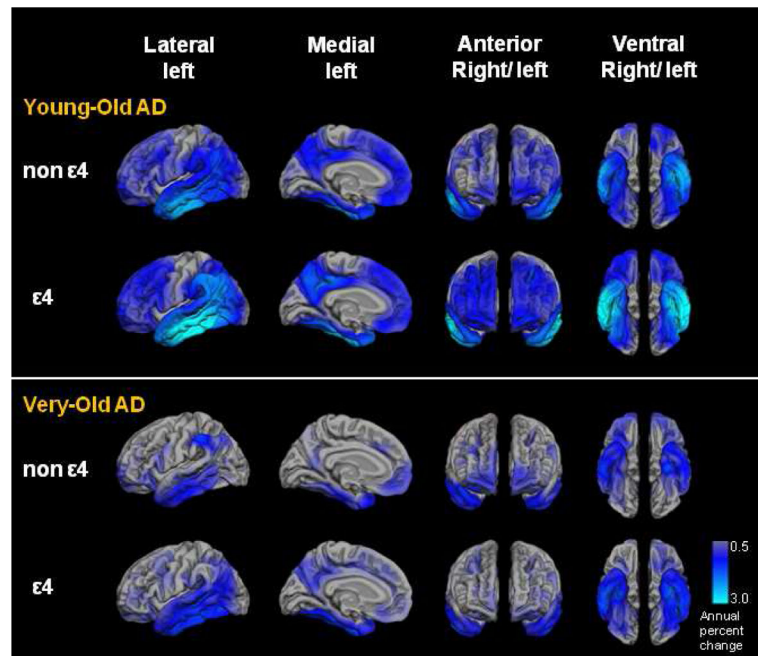
Figure 5.
Annual neocortical atrophy rates (as measured by percent volume change) in regions of interest for each of the four early Alzheimer's disease (AD) groups: Young-Old non-ε4, Young-Old ε4, Very-Old non-ε4, and Very-Old ε4 AD groups.

Table 1

Demographic, global cognitive, clinical, and MRI morphometric characteristics of Young-Old and Very-Old healthy control and Alzheimer's disease groups (upper portion) as well as of the four AD subgroups separated by apolipoprotein E genotype (bottom portion) at baseline.

	Young-Old HC (n=83)	Very-Old HC (n=40)	Young-Old AD (n=64)	Very-Old AD (n=40)
Age	71.86 (2.30)	83.88 (2.55)	70.77 (3.21)	84.01 (2.66)
Education	15.37 (2.39)	15.95 (2.97)	14.69 (2.63)	14.80 (3.25)
Gender (% men)	51%	54%	44%	56%
% APOE e4 carriers	25%	28%	77% *	50% **
MMSE	29.00 (1.08)	29.02 (1.06)	23.52 (2.05)	23.20 (2.19)
CDR sum of boxes	0.02 (0.11)	0.07 (0.18)	4.07 (1.31)	4.43 (1.92)
Modified HIS scores	0.51 (0.72)	0.45 (0.55)	0.59 (0.66)	0.73 (0.72)
Disease duration (years)	--	--	3.16 (2.29)	3.23 (2.20)
WMH volume (mm³)	--	--	6852 (662)	11970 (1765) §
Blood homocysteine, µM/L	9.31 (2.91) †	11.25 (3.47)	9.99 (2.44)	10.92 (2.64)
% HTN meds users	28%	33%	36%	38%
Loss to follow-up	10 (12%)	4 (10%)	12 (18.8%)	6 (15%)

	Young-Old AD non-e4 (n=15)	Young-Old AD e4 (n=49)	Very-Old AD non-e4 (n=20)	Very-Old AD e4 (n=20)
Age	70.53 (3.44)	70.84 (3.17)	84.16 (3.10)	83.70 (2.18)
Education	16.07 (2.19)	14.27 (2.63)	14.90 (3.32)	14.80 (3.32)
Gender (% men)	47%	43%	40%	75%
MMSE	23.27 (2.34)	23.59 (1.97)	23.00 (2.03)	23.50 (2.37)
CDR sum of boxes	3.90 (1.35)	4.12 (1.31)	4.23 (1.97)	4.60 (1.94)
Modified HIS scores	0.53 (0.52)	0.61 (0.70)	0.65 (0.75)	0.80 (0.70)
Disease duration (years)	3.21 (2.61)	3.14 (2.22)	2.85 (1.97)	3.58 (2.44)
WMH volume (mm³)	7216.20 (1014.35)	6740.65 (811.35)	11441 (2437)	8820.63 (824) †‡
Blood homocysteine, µM/L	10.59 (2.13)	9.81 (2.52)	10.63 (2.46)	11.21 (2.85)
% HTN meds users	40%	35%	30%	45%
Loss to follow-up	2 (13.3%)	10 (20.4%)	3 (15%)	3 (15%)

Abbreviations: CDR, Clinical Dementia Rating Scale; HIS, Hachinski Ischemia Scale; HTN, hypertension; WMH, white matter hypointensity (estimated from T1 image)

† indicates significant difference between the Young-Old HC group versus the Very-Old HC group and the Very-Old AD group

*
indicates significant difference between the Young-Old AD group and the two HC groups

**
indicates significant differences between the Very-Old AD group and the other three group

§
indicates significant difference between the Young-Old AD group and the Very-Old AD group

‡
indicates significant difference between the Young-Old AD e4 group and the Very-Old AD e4 group