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

Yu-Ling Chang[a], Christine Fennema-Notestine[b,c], Dominic Holland[d], Linda K. McEvoy[c], Nikki H. Stricker[e,f], David P. Salmon[d], Anders M. Dale[c,d], Mark W. Bondi[g,b,*]; for the Alzheimer's Disease Neuroimaging Initiative

[a]*Department of Psychology, National Taiwan University, Taipei, Taiwan*
[b]*Department of Psychiatry, University of California at San Diego, San Diego, CA, USA*
[c]*Department of Radiology, University of California at San Diego, San Diego, CA, USA*
[d]*Department of Neurosciences, University of California at San Diego, San Diego, CA, USA*
[e]*Veterans Affairs Boston Healthcare System, Boston, MA, USA*
[f]*Department of Psychiatry, Boston University School of Medicine, Boston, MA, USA*
[g]*Veterans Affairs San Diego Healthcare System, San Diego, CA, USA*

Abstract

Objective: To determine (1) whether age-standardized cognitive declines and brain morphometric change differ between Young-Old patients with Alzheimer's disease (YOAD) and Very-Old patients with Alzheimer's disease (VOAD), and (2) whether the 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 subjects and patients with AD. The two AD groups were divided further into subgroups on the basis of the presence of at least one *APOE* ε4 allele.

Results: The YOAD group showed more severe deficits and steeper declines in cognition than the VOAD group. Moreover, the presence of an *APOE* ε4 allele had a more deleterious effect on the YOAD group than the VOAD group 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.

Keywords: Alzheimer's disease; *APOE* genotype; Cognition; Morphometry; Magnetic resonance imaging; Longitudinal

1. Introduction

Dementia incidence increases exponentially between the ages of 65 years 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., older than 80 years) [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

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*Corresponding author. Tel.: +1-858-552-8585 ext. 2809; Fax: +1-858-642-1218.

E-mail address: mbondi@ucsd.edu

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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 regarding whether *APOE* allelic variants are associated with different cognitive and morphometric AD phenotypes [1,5,6]. Several cross-sectional studies have reported that AD *APOE* ε4 carriers have greater impairment in memory and executive function than AD non-*APOE* ε4 carriers [5]. Longitudinal studies have shown mixed results with AD *APOE* ε4 carriers demonstrating slower [7,8], faster [9–11], or equivalent [12,13] rates of cognitive decline as their non-*APOE* ε4 counterparts. Several studies have shown that the effects of the *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 subject 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 current 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 whether the *APOE* genotype affects these patterns differentially in the two cohorts. Based on 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 the *APOE* ε4 genotype on these cognitive functions [5]. With respect to morphometry, we predicted that interactive effects of age and *APOE* genotype would be apparent in the medial temporal lobe, and temporoparietal and frontal regions, given their well-documented roles in the pathology of early AD.

2. Methods

The raw data used in the current study were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database [15]. ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the U.S. Food and Drug Administration, private pharmaceutical companies, and nonprofit organizations as a $60 million, 5-year public–private partnership. The primary goal of ADNI is to test whether serial magnetic resonance imaging (MRI), positron emission tomography, 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 more than 50 sites across the United States and Canada [16]. 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 explained in full.

2.1. Participants

ADNI general eligibility criteria have been described elsewhere [17]. Participants included in the current study were healthy control (HC) participants or mildly demented patients with AD, 60 to 92 years old, not depressed, with a modified Hachinski score of 4 points 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 subjects had a Mini-Mental State Examination (MMSE) score between 24 points and 30 points (inclusive), a global Clinical Dementia Rating (CDR) [18] of 0, and did not meet criteria for MCI [19]. Mild AD participants had MMSE scores between 20 points and 26 points, a global CDR of 0.5 or 1.0, and met National Institute of Neurological and Communicable Diseases and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD [20]. The CDR-sum of boxes (CDR-SB) score was calculated for all participants to further estimate the level of clinical impairment.

HC participants in ADNI were monitored for 3 years, with assessments at 0, 6, 12, 24, and 36 months. AD patients were monitored 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 of individuals age 75 years or younger (range, 60–75 years) and (2) Very-Old groups comprised of individuals age 80 years or older (range, 80–91 years). The 5-year age gap (i.e., participants were not studied if they fell between the ages of 76 years and 80 years) 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 MRI 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 *APOE* allele status using DNA extracted from peripheral blood cells. Participants with the *APOE* genotype ε4/ε2 were excluded (n = 4) from the current study. To examine the impact of the *APOE* ε4 allele on the 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 *APOE* ε4 AD group consisted of 49 participants, the Young-Old non-*APOE* ε4 AD group consisted 15 participants, the Very-Old *APOE* ε4 AD group consisted of 20 participants, and the Very-Old non-*APOE* 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 [17]. We assessed performance at baseline and at the 1-year follow-up. Six neuropsychological domains were assessed with the following tests: (1) language, which included the 30-item Boston Naming Test and Category Fluency (animal and vegetable categories); (2) attention/psychomotor processing speed, which included the Trail Making Test Part A and the Wechsler Adult Intelligence Scale-Revised Digit Span Forward and Digit Symbol subtests; (3) executive function, which included the Trail Making Test Part B and the Wechsler Adult Intelligence Scale-Revised Digit Span Backward; (4) immediate recall, which included the Rey Auditory Verbal Learning Test (RAVLT) Trials 1 through 5 Total Recall and Wechsler Memory Scale-Revised (WMS-R) Logical Memory Immediate Recall; (5) delayed recall, which included the RAVLT Long-Delay Recall and the WMS-R Logical Memory Delayed Recall; and (6) recall savings, which included the 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 on the mean and standard deviations (SDs) of their respective HC group and summed to create the six neuropsychological

Table 1
Demographic, global cognitive, clinical, and magnetic resonance imaging morphometric characteristics of Young-Old and Very-Old healthy control (HC) and Alzheimer's disease (AD) groups (upper portion) as well as of the four AD subgroups separated by apolipoprotein E (*APOE*) genotype (bottom portion) at baseline

Characteristic	Young-Old HC (n = 83)	Very-Old HC (n = 40)	Young-Old AD (n = 64)	Very-Old AD (n = 40)
Age, years	71.86 (2.30)	83.88 (2.55)	70.77 (3.21)	84.01 (2.66)
Education, years	15.37 (2.39)	15.95 (2.97)	14.69 (2.63)	14.80 (3.25)
Gender, % men	51	54	44	56
APOE ε4 carriers, %	25	28	77*	50†
MMSE score, points	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 score, points	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, mm^3	—	—	6852 (662)	11,970 (1765)‡
Blood homocysteine, μM/L	9.31 (2.91)§	11.25 (3.47)	9.99 (2.44)	10.92 (2.64)
HTN medications users, %	28	33	36	38
Loss to follow-up	10 (12%)	4 (10%)	12 (18.8%)	6 (15%)

Characteristic	Young-Old AD non-*APOE* ε4 (n = 15)	Young-Old AD *APOE* ε4 (n = 49)	Very-Old AD non-*APOE* ε4 (n = 20)	Very-Old AD *APOE* ε4 (n = 20)
Age, years	70.53 (3.44)	70.84 (3.17)	84.16 (3.10)	83.70 (2.18)
Education, years	16.07 (2.19)	14.27 (2.63)	14.90 (3.32)	14.80 (3.32)
Gender, % men	47	43	40	75
MMSE score, points	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 score, points	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, mm^3	7216.20 (1014.35)	6740.65 (811.35)	11,441 (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 medications users, %	40	35	30	45
Loss to follow-up	2 (13.3%)	10 (20.4%)	3 (15%)	3 (15%)

Abbreviations: APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; CDR, Clinical Dementia Rating; HIS, Hachinski Ischemia Scale; HTN, hypertension; WMH, white matter hypointensity (estimated from T1 image).

NOTE. Data presented as mean(SD) unless otherwise indicated.

*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 groups.

‡Indicates significant difference between the young-old AD group and the very old AD group.

§Indicates significant difference between the young-old HC group vs. the very old HC group and the very old AD group.

¶Indicates significant difference between the young-old AD *APOE* ε4 group and the very old AD *APOE* ε4 group.

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 National Institutes of Health/National Center for Research Resources–sponsored Morphometry Biomedical Informatics Research Network and ADNI [21–24]. Data were collected across a variety of 1.5-T scanners. Protocols have been described in detail [25]. Two T1-weighted volumes were acquired for each participant, one at baseline and one at follow-up approximately 1 year later. These raw Digital Imaging and Communications in Medicine (DICOM) magnetic resonance images scans were downloaded from the public ADNI site [26]. Locally, images were reviewed for quality, corrected automatically for spatial distortion resulting from gradient nonlinearity [23] and B1 field inhomogeneity [27], registered, and averaged to improve the signal-to-noise ratio. Volumetric segmentation [28,29] and cortical surface reconstruction [29–32] used methods based on FreeSurfer software (version 4.3.0) optimized for use on large, multisite data sets. To measure thickness, the cortical surface was reconstructed [30,31] and parcellated into distinct regions of interest (ROIs) [29,33]. 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 [34]. To limit the number of multiple comparisons, only regions assumed to be involved in early AD pathology [21–24] were included in the current analyses. These included volumetric measures of bilateral hippocampal formation, including dentate gyrus, Cornu ammonis (CA) fields, subiculum/parasubiculum, and the fimbria [35], and thickness measures of the frontal, temporal, and parietal lobe cortical areas and bilateral cingulate cortex regions (see ROIs listed in the results section). To decrease the number of comparisons, the caudal and rostral anterior cingulate regions were combined as the anterior cingulate cortex, the isthmus and posterior cingulate regions were combined as the posterior cingulate cortex, and the pars opercularis and pars triangularis were combined as the frontal operculum. Following Buckner and colleagues [36], baseline volumetric data were corrected for individual differences in head size by regressing the estimated total intracranial volume (eTIV).

The longitudinal data were derived through Quarc (quantitative anatomical regional change [37]). Dual three-dimensional follow-up structural images for each participant were rigid-body aligned, averaged, and affine aligned to the participant's baseline image. Nonlinear registration of the images was then performed, in which the voxel centers were moved about until a good match was made between the images [37,38]. 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 smooth spatially. The merit function, by design, has a minimum when the displacement field induces a good match between the images. The displacement field, in general, turns cubic voxels into displaced irregular hexahedra with volumes that 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 building up iteratively a better displacement field. Two important additions to this are (1) applying the final displacement field to the image being transformed, then registering nonlinearly 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 ROIs 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 segmenting tissue initially. This deformation field was used to align images at the subvoxel 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 image. 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, which resulted in a one-to-one correspondence between each vertex in the baseline 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 throughout the course of 1 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 one. The method has been validated in model studies of complex spherical shell geometries with low contrast and noise in which a prescribed volume change is estimated numerically to accuracies of within 0.5% [37].

2.4. Statistical analyses

Group comparisons for demographic, clinical (i.e., CDR-SB scores, disease duration), and global cognitive (i.e., MMSE scores) variables were performed with analyses of variance (ANOVAs) and independent samples *t* tests or χ^2 tests, as appropriate. Repeated-measure general linear models 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 pairwise comparisons. Based on the Bonferroni correction, the α level was set to $P < .008$ for analyses of the six neuropsychological composite scores. Whenever the assumption of homogeneity of variance was not met, the *t* value and the significance of the comparison were reported according to the assumption that variances were unequal.

To assess group differences 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 eTIV volume [36]. 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 the number of comparisons. Univariate ANOVAs were performed, followed by ANOVAs or independent samples *t* tests for post hoc comparisons. Based on the Bonferroni correction, the α level was set to .0026 for the 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 at baseline

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 group showed a significantly lower homocysteine level compared with the Very-Old HC ($P < .005$) and the Very-Old AD ($P = .05$) groups, whereas the two AD groups showed a comparable level of homocysteine ($P = .07$).

As expected, AD patients scored fewer points 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 with regard to the MMSE or the CDR-SB scores. The two AD groups did not differ significantly in the estimated years of disease duration ($t_{101} = -0.12$, $P = .91$), but the Very-Old AD group showed a 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 with 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 differ significantly among 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 × 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 ($F_{(3,\ 100)} = 0.64$, $P = .59$), MMSE scores ($F_{(3,\ 100)} = 0.41$, $P = .75$), modified Hachinski Ischemic Scale scores ($F_{(3,\ 100)} = 0.51$, $P = .68$), disease duration ($F_{(3,\ 99)} = 0.35$, $P = .79$), 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 *APOE* ε4 group had greater volume of WMH than the Young-Old AD *APOE* ε4 group ($F_{(3,\ 100)} = 3.31$, $P = .023$).

3.2. Neuropsychological assessment

3.2.1. 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

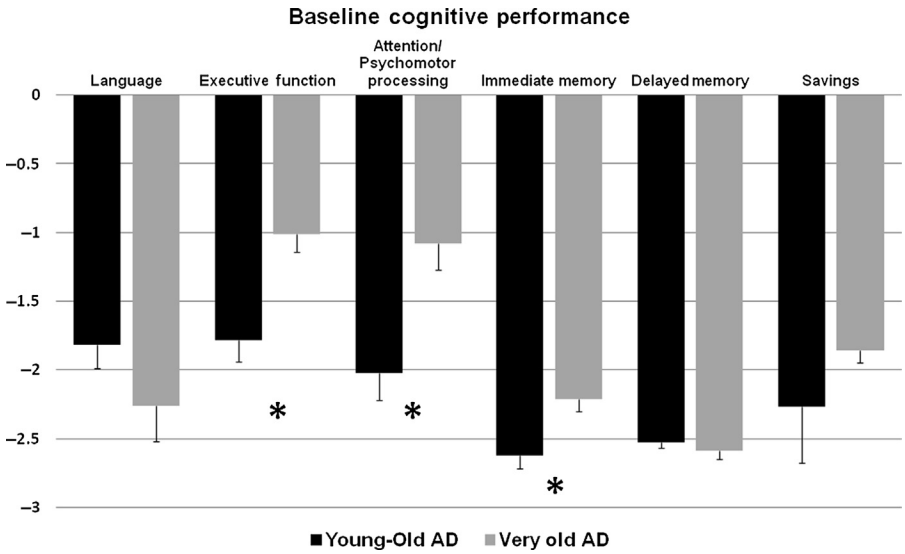

Fig. 1. Baseline performance of Young-Old patients with Alzheimer's disease (AD) vs. Very-Old patients with AD by cognitive domains computed by age-normalized z scores. * indicates significant difference at $P < .008$

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 ($t_{92} = -.82$, $P = .42$; Fig. 1).

3.2.2. APOE *genotype polymorphism effects*

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

3.2.3. *Time main effects*

Significant main effects for time were found for all six cognitive composite scores. Relative to their age-appropriate HC group, the AD patients as a whole demonstrated a decline in performance over 1 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 ($F_{(1, 66)} = 8.42$, $P = .005$).

3.2.4. *Age* × APOE *genotype interaction effects*

Significant age × *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-*APOE* ε4 carriers (all P values $>.05$).

3.2.5. *Age* × *time interactions effects*

Significant age × 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 ($F_{(1, 72)} = 29.64$, $P < .001$, $\eta_p^2 = 0.29$), immediate recall ($F_{(1, 83)} = 21.23$, $P < .001$, $\eta_p^2 = 0.20$), and delayed recall ($F_{(1, 82)} = 33.43$, $P < .001$, $\eta_p^2 = 0.29$) composite scores.

3.2.6. APOE *genotype* × *time interaction effects*

Significant *APOE* genotype × time interactions were obtained only for the language domain ($F_{(1, 81)} = 7.58$, $P = .007$, $\eta_p^2 = 0.09$), with the AD *APOE* ε4 group as a whole showing a steeper decline than the AD non-*APOE* ε4 group over the 1 year follow-up interval.

3.2.7. *Age* × APOE *genotype* × *time interaction effects*

Significant age group × *APOE* genotype × time interaction effects were obtained on immediate recall. The Young-Old *APOE* ε4 AD group showed steeper declines on immediate recall over 1 year than did the Very-Old *APOE* ε4 AD group ($F_{(3, 81)} = 7.80$, $P < .001$, $\eta_p^2 = 0.22$), whereas the two non-*APOE* 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 ($F_{(3, 79)} = 8.25$, $P < .001$, $\eta_p^2 = 0.24$) (Fig. 2).

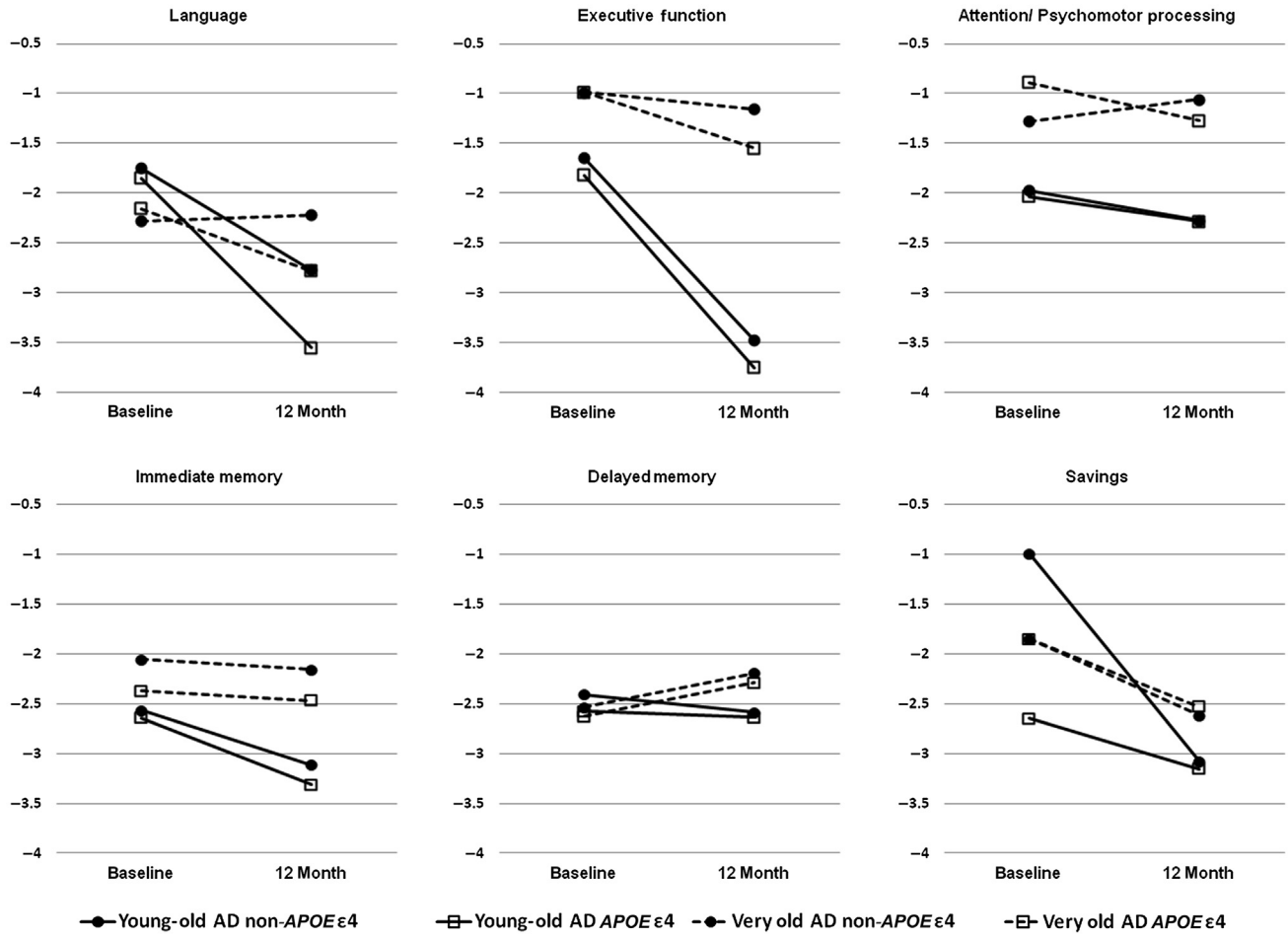

Fig. 2. Baseline and 12-month follow-up performance of the four Alzheimer's disease (AD) age × apolipoprotein E (*APOE*) genotype subgroups on the age-normalized z scores for the different cognitive domains.

3.3. Brain morphometry

3.3.1. 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 the inferior parietal regions ($t_{102} = -3.89$, $P < .001$; Cohen's $d = 0.80$; Fig. 3).

3.3.2. 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.

3.3.3. Age × APOE genotype interaction effects

A significant age × *APOE* genotype interaction was obtained for the inferior parietal region ($F_{(3,\ 100)} = 5.34$, $P = .002$, $\eta_p^2 = 0.14$). The Young-Old *APOE* ε4 AD group showed more cortical thinning than the Very-Old *APOE* ε4 AD group in this cortical region, whereas the two non-*APOE* ε4 AD groups showed comparable thickness ($P >. 05$).

3.3.4. Age × time interaction effects

Significant age × time (annual brain atrophy rate) interaction effects were found in both the 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 the 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 (Fig. 4). The two AD groups showed comparable rates of atrophy in the hippocampus, but a marginally significant effect in the entorhinal ($P = .054$) and parahippocampal ($P = .04$) regions, with

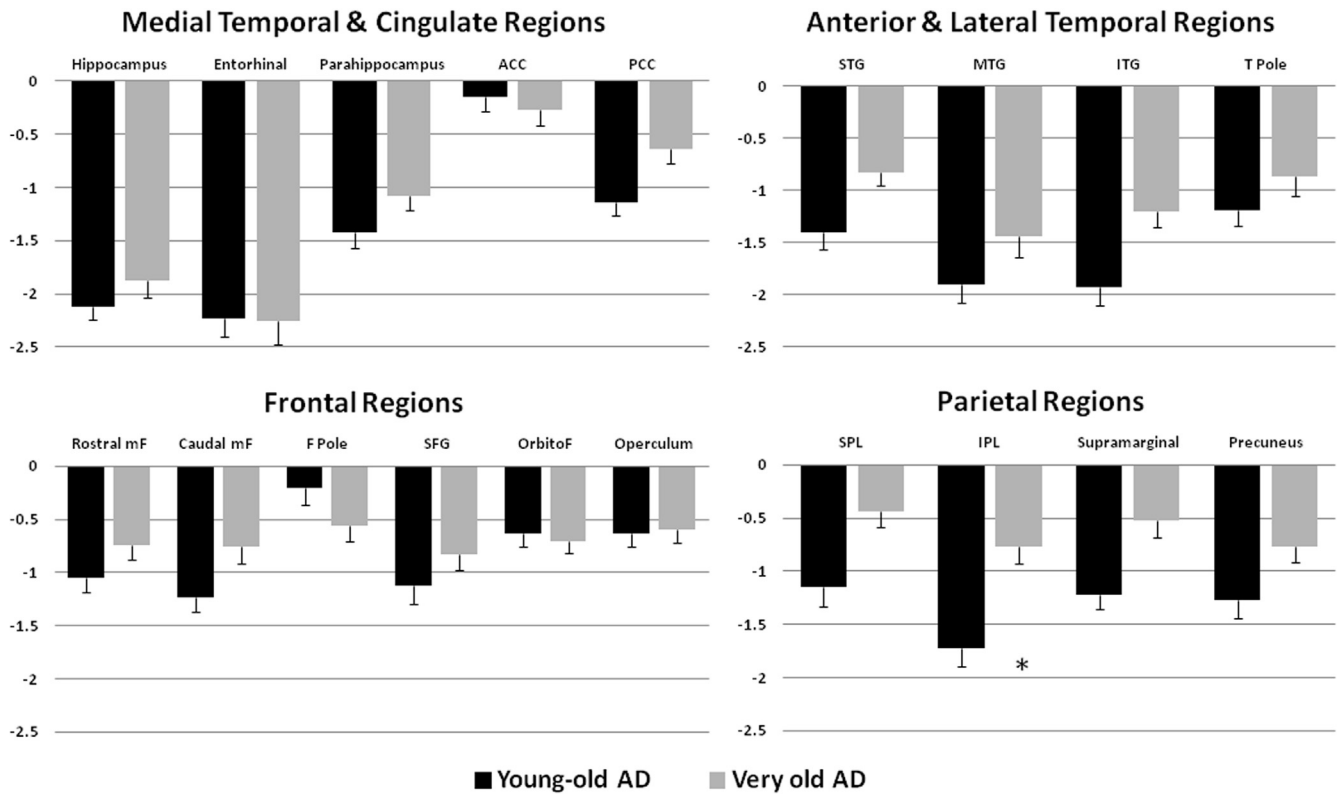

Fig. 3. Regional brain atrophy in the Young-Old and Very-Old Alzheimer's disease (AD) patients using standardized z scores derived from their age-appropriate healthy control counterparts at baseline. Error bars denote standard error of the mean. * $P < .001$. ACC, anterior cingulate cortex; PCC, posterior 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.

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 levels, the previously observed age × time effect on the caudal middle frontal and posterior cingulate were no longer significant.

Age × time interaction effects were also obtained between the two HC groups, but these were in the 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 the 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 opercular ($t_{89} = 3.19$, $P = .002$; Cohen's $d = 0.72$) regions.

3.3.5. APOE *genotype* × *time interaction effects*

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

3.3.6. *Age* × APOE *genotype* × *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 *APOE* ε4 AD group showed a greater annual rate of atrophy in the superior ($F_{(3, 65)} = 6.69$, $P = .001$, $\eta_p^2 = 0.24$), middle ($F_{(3, 65)} = 11.71$, $P < .001$, $\eta_p^2 = 0.35$), and inferior ($F_{(3, 65)} = 11.43$, $P < .001$, $\eta_p^2 = 0.35$) temporal regions; the superior ($F_{(3, 65)} = 5.94$, $P = .001$, $\eta_p^2 = 0.08$) and inferior ($F_{(3, 65)} = 10.21$, $P < .001$, $\eta_p^2 = 0.17$) parietal regions; the precuneus ($F_{(3, 65)} = 5.71$, $P = .002$, $\eta_p^2 = 0.12$); and the supramarginal ($F_{(3, 65)} = 9.71$, $P = .001$, $\eta_p^2 = 0.14$) region than any of the other three AD groups. In contrast, the Very-Old *APOE* ε4 AD group showed annual atrophy rates that were similar to those of the Very-Old non-*APOE* ε4 AD and Young-Old non-*APOE* ε4 AD groups in all ROIs, including the medial temporal regions (all P values, >.05; Fig. 5).

4. Discussion

The current 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 showed previously that when Young-Old and Very-Old patients with AD are compared with their respective age-appropriate HC subjects, the Very-Old AD patients exhibit less severe cognitive impairment and less regional

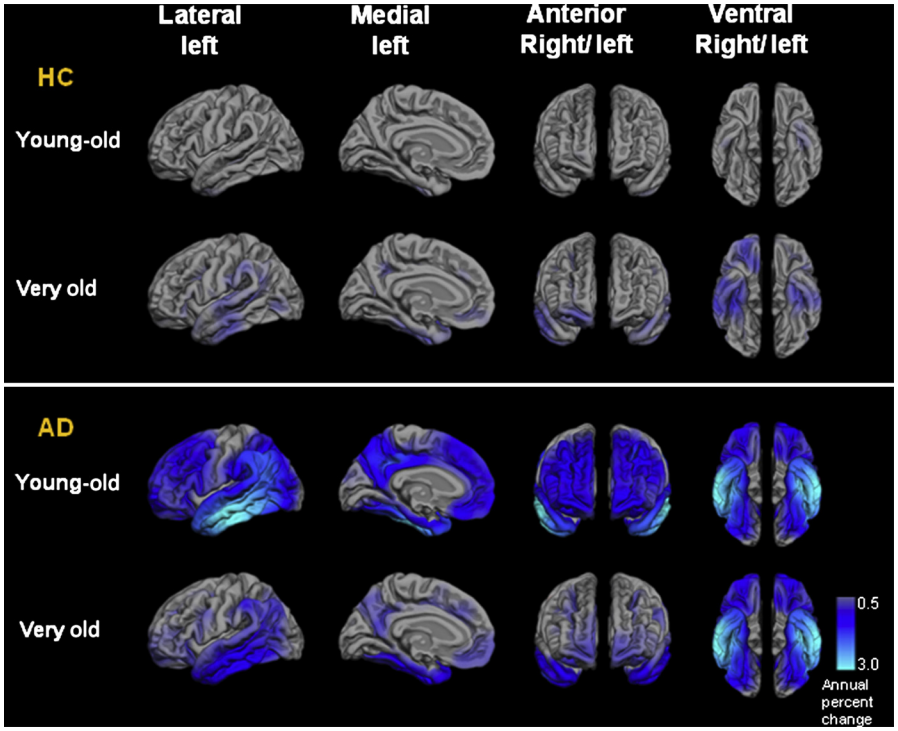

Fig. 4. Annual neocortical atrophy rates (as measured by percent volume change) in regions of interest in the Young-Old healthy control (HC), Very-Old HC, Young-Old Alzheimer's disease (AD), and Very-Old AD groups.

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 explained in part by age-related decreases in cognitive performance and cortical thickness of the respective HC 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 current 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 *APOE* ε4 allele, or Very-Old AD patients with or without an *APOE* ε4 allele, on baseline measures of executive function, attention, and psychomotor processing speed. Furthermore, the Young-Old *APOE* ε4 AD patients had steeper declines in memory and language over a 1-year interval than Young-Old non-*APOE* ε4 or Very-Old *APOE* ε4 and Very-Old non-*APOE* ε4 AD patients. These results suggest that the effect of *APOE* genotype on cognition and rate of decline depend on 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 age younger than 85) [10,39], 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 *APOE* ε4 AD patients had greater thinning than Young-Old non-*APOE* ε4 AD patients in the inferior parietal cortex, whereas the Very-Old *APOE* ε4 and non-*APOE* ε4 AD patients did not differ. In addition, Young-Old *APOE* ε4 AD patients had greater atrophy over 1 year than Young-Old non-*APOE* ε4 AD, Very-Old *APOE* ε4, and non-*APOE* ε4 AD patients in a number of lateral temporal lobe and parietal cortical regions, including the 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

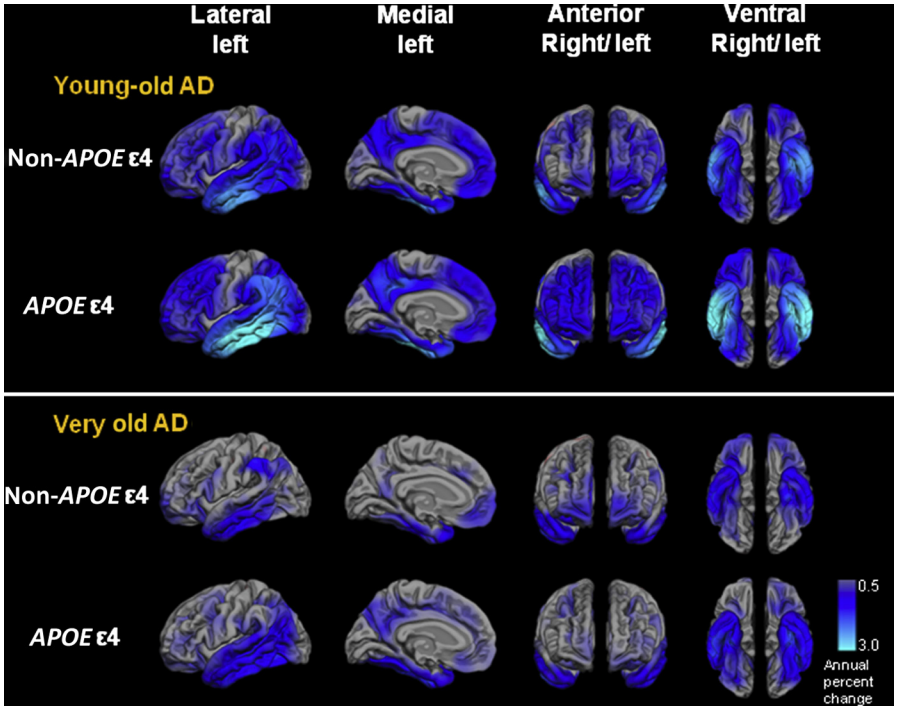

Fig. 5. Annual neocortical atrophy rates (as measured by percent volume change) in regions of interest for each of the four early Alzheimer's disease (AD) groups: Young-Old nonapolipoprotein (non-*APOE*) ε4, Young-Old *APOE* ε4, Very-Old non-*APOE* ε4, and Very-Old *APOE* ε4 AD groups.

APOE ε4 AD patients showed only marginally more atrophy during the 1-year interval than Young-Old non-*APOE* ε4 AD and Very-Old *APOE* ε4 and non-*APOE* ε4 AD patients in the hippocampus, entorhinal cortex, and parahippocampal gyrus, and this was largely a result of 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 although 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 resulting from 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 account in part for inconsistent findings across studies examining the effect of the *APOE* ε4 allele on brain atrophy in patients with AD.

The current 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 subjects) 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-Old patients. This could have important ramifications for diagnosis under the proposed *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition [40] scheme, given that much of the distinction between major and minor neurocognitive disorders (i.e., analogous to dementia vs. MCI, respectively) rests on the severity of cognitive impairment. In this proposed scheme, −1 to −2 SDs below appropriate norms on cognitive testing define minor neurocognitive disorder, whereas −2 or more SDs defines a 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., misassigning 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 MRI, there may be less volumetric integrity (and more variability) in the 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 [41]. 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 × *APOE* genotype interaction effect is likely an important factor in determining and modulating decline. It is important to understand the role of the *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 [42]). 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 current 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 comorbid pathologies (e.g., infarcts, Lewy bodies, and so on) 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 patients relative to the young-old AD patients. 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 levels), our findings of the distinct patterns in Young-Old vs. Very-Old and their interaction with *APOE* status on cognition and morphometry were retained. They 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 after 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 the effort made to ensure that none of the HC participants progressed to MCI or AD within 3 years after baseline evaluation, it is still possible that some participants with subclinical AD were misclassified into control groups (given the relatively short follow-up duration in the current study), potentially obscuring diagnostic group differences. Fourth, the relatively high number of men in the Very-Old group, although statistically nonsignificant, is inconsistent with studies that show female survival advantages [43]. Thus, the current sample may be biased toward a more physically healthy sample that 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 multifaceted approach that integrates neuropsychological assessment, *APOE* genotyping, and neuroimaging technologies [44,45] may be needed to characterize the early and preclinical stages of AD in this fastest growing and most vulnerable segment of our population.

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RESEARCH IN CONTEXT

1. Systematic review: The cognitive phenotypic expression of the apolipoprotein E (*APOE*) ε4 allele may vary as a function of the age of patients. However, most of studies have been cross-sectional in design and it is still largely unknown whether morphometric profiles differ by patient age at onset of disease and *APOE* status.
2. Interpretation: Our results clearly argue against the simple application of our understanding of neuropsychological and neuroimaging changes in Alzheimer's disease in the Young-Old to the detection of the disease in the Very-Old. A multifaceted approach that integrates neuropsychological assessment, *APOE* genotyping, and neuroimaging technologies may be needed to characterize the early and preclinical stages of Alzheimer's disease.
3. Future directions: Future studies should explore the role of the *APOE* genotype and its interaction with age of onset in the progression of neurodegeneration to optimize treatment regimens, including therapies that target *APOE* function.

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