

The Relationship of Brain Amyloid Load and APOE Status to Regional Cortical Thinning and Cognition in the ADNI Cohort

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Abstract.

Background: Both amyloid (A β) load and APOE4 allele are associated with neurodegenerative changes in Alzheimer's disease (AD) prone regions and with risk for cognitive impairment.

Objective: To evaluate the unique and independent contribution of APOE4 allele status (E4+ \ E4-), A β status (Amy+ \ Amy-), and combined APOE4 and A β status on regional cortical thickness (CoTh) and cognition among participants diagnosed as cognitively normal (CN, $n = 251$), early mild cognitive impairment (EMCI, $n = 207$), late mild cognitive impairment (LMCI, $n = 196$), and mild AD ($n = 162$) from the ADNI.

Methods: A series of two-way ANCOVAs with *post-hoc* Tukey HSD tests, controlling independently for A β and APOE4 status and age were examined.

Results: Among LMCI and AD participants, cortical thinning was widespread in association with Amy+ status, whereas in association with E4+ status only in the inferior temporal and medial orbito-frontal regions. Among CN and EMCI participants, E4+ status, but not Amy+ status, was independently associated with increased CoTh, especially in limbic regions [e.g., in the entorhinal cortex, CoTh was 0.123 mm greater ($p = 0.002$) among E4+ than E4- participants]. Among CN and EMCI, both E4+ and Amy+ status were independently associated with cognitive impairment, which was greatest among those with combined E4+ and Amy+ status.

¹Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (<http://adni.loni.usc.edu>). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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Conclusion: Decreased CoTh is independently associated with Amy+ status in many brain regions, but with E4+ status in very restricted number of brain regions. Among CN and EMCI participants, E4 + status is associated with increased CoTh, in medial and inferior temporal regions, although cognitive impairment at this state is independently associated with Amy+ and E4 + status. These findings imply a unique pathophysiological mechanism for E4 + status in AD and its progression.

Keywords: ADNI, Alzheimer's disease, amyloid, APOE, cortical thinning, memory, mild cognitive impairment

INTRODUCTION

According to the amyloid hypothesis [1], deposition of amyloid- β protein (A β) in the neocortex, is the initiating event in the pathophysiology of Alzheimer's disease (AD) and occurs 15 to 20 years before the first symptoms of the disease. This leads to downstream events including neurodegeneration and ultimately cognitive and functional impairment. Recent neuropathological diagnostic criteria for AD are based upon this hypothesis, incorporating the Thal phase schema of a stereotypic pattern of A β accumulation, anteceding Braak staging of neurofibrillary tangle pathology in the brain, with a continuous relationship existing between brain A β load and neurodegenerative changes [2]. There is also considerable evidence that APOE E4 (APOE4) carrier (E4+) status is associated with greater A β load in normal individuals as well as in all stages of AD, possibly as a result of the effect of APOE4 genotype on impaired clearance of A β protein [3, 4]. Aging and E4+ status are among the most strongly associated factors with increased risk for AD [3–5].

Deposition of A β *in vivo* is detectable with positron emission tomography (PET) scans, using an A β binding ligand, or by measuring A β levels in the cerebrospinal fluid (CSF), whereas downstream events such as neurodegeneration are detectable using volumetric measures of regional atrophy (especially hippocampal atrophy) and reduced cortical thickness (CoTh) on structural magnetic resonance imaging (MRI) scans, as well as deficits in regional cerebral glucose metabolism on PET scans. Recent clinical criteria for the diagnosis of AD dementia and Prodromal AD (NIA-AA and IWG criteria) rely on combinations of "positive biomarkers" in the presence of functional and/or cognitive impairment with high, intermediate or low levels of likelihood [6, 7] based on the presence of A β and neurodegenerative biomarkers. The presence of A β biomarkers in the absence of cognitive and functional impairment fulfills criteria for a diagnosis of preclinical AD.

Although it is well accepted that A β load, APOE4 status, and neurodegeneration are strongly interrelated [8], the presence and strength of the relationships between these factors and their independent effects on cortical thinning and cognition are not well understood at different stages of disease. As emerging treatments are developed, it is increasingly important to understand these independent relationships prior to developing appropriate disease modifying treatments for AD.

The relationship between E4+ status and higher A β load is well known, as is the relationship of both E4 + status and higher A β load to a greater risk for developing Alzheimer's disease and a greater degree of neurodegeneration [4, 9–11]. However, the relationship of APOE4 status to neurodegeneration and cognitive decline, independent of A β load, and the relationship of A β load to neurodegeneration and cognitive decline, independent of APOE4 status, are not known and to our knowledge have not been studied thus far.

In the present study, we examined both the combined and independent associations between global A β load, APOE4 status, and regional CoTh among four different diagnostic groups in the Alzheimer's Disease Neuroimaging Initiative (ADNI) sample, including cognitively normal (CN), early mild cognitive impairment (EMCI), late mild cognitive impairment (LMCI), or AD dementia participants. A unique aspect of this investigation was to determine the independent and combined effects of APOE4 status and A β load on regional CoTh and cognition among individuals presenting with minimal (EMCI) or no overt memory impairment (CN).

MATERIALS AND METHODS

Study data

Data used in the preparation of this article were obtained from the ADNI database (<http://adni.loni.usc.edu>). The ADNI was launched in 2003 as a public-private partnership, led by Principal

Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early AD.

Evaluations

Evaluations included: (1) Medical and neurological evaluation and routine labs; (2) Clinical Dementia Rating (CDR) scale, which was used as the index of functional ability [12]; (3) neuropsychological assessment, including the ADAS Cog 13 (ADAS13) and Mini-Mental State Exam (MMSE) subtests, used as the global index of cognitive ability [13], and the Rey Auditory Verbal Learning Test (RAVLT) and subtests, used as the index of memory performance [14]; (4) volumetric MRI; and (5) ^{18}F -AV45 amyloid PET scans. The time gap between MRI and PET scans was less than 3 months. A blood sample for assessment of APOE genotype was also obtained.

Baseline demographic, clinical, and APOE data were compared for 906 subjects, diagnosed as CN (251), EMCI (297), LMCI (196), or AD (162), as shown in Table 1. Subjects with one or more APOE4 alleles, i.e., APOE4 carriers, were classified as E4+, while those with no APOE4 alleles, i.e., APOE4 non-carrier, were classified as E4-.

Neuroimaging acquisition

MRI scans were acquired from 1.5T or 3T scanners at multiple sites across the United States and Canada using MP-RAGE/IR-SPGR protocols for volumetric

analyses. ^{18}F -AV45 PET scans were acquired 50 minutes following administration of 370 MBq (10 mCi) bolus injection of ^{18}F -AV45, over a 20-min scanning period and images were reconstructed immediately afterwards. Details of MRI and AV45 PET imaging data acquisition and pre-processing can be found in the aforementioned ADNI website.

Image processing

MRI image processing

FreeSurfer pipeline (version 5.3.0) [15] was applied to the MRI scans under centos4_x86_64 Linux system to produce cortical and subcortical volumetric variables. The original MRI scan was first mapped to the standard MNI 305 space, yielding the image referred to as T1.mgz, which was used as the reference image in the following registration procedure. Based on the T1 image, the corresponding image file termed as aparc+ aseg.mgz provides the FreeSurfer parcellated and segmented cortical and subcortical regions. CoTh, surface area, and volume were then calculated as morphological variables on each of the 34 cortical regions for both hemispheres as well as the volume on each of the 45 subcortical regions of the whole brain.

In this study, regional CoTh in AD signature regions, previously identified by several groups [16, 17] was evaluated. These include the entorhinal cortex (ERC), parahippocampal gyrus (PHG), inferior temporal gyrus (ITG), temporal pole (TP), medial orbital frontal gyrus, superior temporal gyrus, rostral middle frontal gyrus, inferior parietal lobule (including angular gyrus), superior parietal lobule, supramarginal

Table 1
Participant demographic and clinical information

	CN (n=251)	EMCI (n=297)	LMCI (n=196)	AD (n=162)	F value
Female/Male	128/123	132/165	85/111	68/94	4.36 ^b
E4-/E4+	184/67	169/128	92/104	54/108	70.32*** ^c
Age	75.47 (6.54) ^a	71.53 (7.43)	73.83 (8.06)	74.94 (7.81)	14.85***
Education	16.43 (2.58)	15.99 (2.67)	16.31 (2.71)	15.76 (2.71)	2.71*
<i>Type of Cognitive Test</i>					
CDRSB	0.05 (0.2)	1.31 (0.78)	1.76 (1.06)	4.84 (2.07)	633.12***
ADAS13	9.09 (4.54)	12.72 (5.51)	17.9 (7.5)	31.55 (8.81)	434.53***
MMSE	29.04 (1.23)	28.32 (1.57)	27.61 (1.85)	22.77 (2.71)	448.73***
RAVLT_immediate	45.35 (10.58)	39.47 (10.8)	33.21 (10.82)	22.31 (7.03)	183.76***
RAVLT_learning	5.74 (2.44)	5.29 (2.45)	3.92 (2.58)	1.91 (1.77)	102.04***
RAVLT_% forgetting	36.22 (27.79)	46.98 (29.72)	67.37 (31.34)	90.1 (19.91)	142.34***

^aValues are represented as mean(sd), except gender and APOE gene status, which are frequencies instead. ^bSignificant group differences test (ANOVA for continuous and Chi-square test for categorical values, significance level is 0.05 by default). ^c $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

gyrus, precuneus, posterior cingulate gyrus, and the mean CoTh based on the aforementioned regions.

PET and MRI registration

In order to quantify the A β load from the PET scans, FMRIB Software Library (FSL) [18] was then used to co-register the PET image to the aforementioned T1 image. Considering the relatively low resolution of the PET image and to utilize as much information from PET as possible, the AV45 PET scan, with the skull, were co-registered linearly (i.e., trilinear interpolation) with 12 degrees of freedom onto the T1 image. Such a registration process guaranteed that the AV45 PET image had the same accurate segmentation and parcellation as in the MRI. Thus, the mean A β load of each of the FreeSurfer defined regions can be calculated, which was used later to calculate the global A β load value.

Global A β load calculation

The registered AV45 PET with the aparc+aseg image was first inspected to ensure appropriate calculations of the mean A β uptake value (SUV) of all the FreeSurfer-defined regions (ROIs) as expressed in (1).

$$SUV_{ROI_k} = \frac{\sum_{i=1}^{N_{ROI_k}} Val_i}{N_{ROI_k}} \quad (1)$$

where SUV_{ROI_k} represents the mean A β uptake value of the region ROI_k , with N_{ROI_k} representing the number of voxels labeled as region ROI_k in the aparc+aseg image, and Val_i represents the intensity of voxel i in the PET scan.

The SUV of the whole cerebellum, consisting of four subcortical regions (left/right cerebellum white matter and left/right cerebellum cortex), was then calculated using (2), accounting for the varying sizes of the subregions. The SUV of the global cortical was computed in the same way, i.e., volume-weighted mean of all 68 cortical ROIs as expressed in (2).

$$SUV_{CB} = \frac{SUV_{SR_1} \times V_{SR_1} + SUV_{SR_2} \times V_{SR_2} + \dots + SUV_{SR_N} \times V_{SR_N}}{V_{SR_1} + V_{SR_2} + \dots + V_{SR_N}} \quad (2)$$

where CB represents the combined region of N ROIs (4 and 68 for the cerebellum and global cortical, respectively), with SUV_{SR_i} representing the SUV of ROI_i , and V_{SR_i} represents the volume of ROI_i .

The standard uptake value ratio (SUVR), relative to the cerebellum, as given in Equation 3, was defined and considered as the global A β load representation.

$$SUVR = \frac{SUV_{globalcortical}}{SUV_{cerebellum}} \quad (3)$$

A widely-used threshold value of 1.10 is used here to delineate A β positive (Amy+, SUVR > 1.10) and A β negative (Amy-, SUVR \leq 1.10) status [19, 20].

Statistical methods

The statistical analysis was performed using R software (R 3.3.0) [21] and the default significant level was determined as 0.05. To examine the independent effect of A β load on regional CoTh, by controlling for the effects of APOE4 status, two-way analysis of covariance (ANCOVA), i.e., 4 (diagnosis: CN, EMCI, LMCI, AD) by 2 (A β load status: Amy+, Amy-) ANCOVA, was conducted per region, with APOE4 status (E4+, E4-) entered as categorical covariates.

Similarly, to investigate the individual effects of APOE4 status after controlling for global A β load, a series of 4 (diagnosis: CN, EMCI, LMCI, AD) by 2 (APOE4 status: E4+, E4-) ANCOVAs were conducted, with global A β load (SUVR) as an interval level covariate. As a complementary analysis, to assess the earliest individual effects of APOE4 status, a series of 2 (diagnosis: CN, EMCI) by 2 (APOE4 status: E4+, E4-) ANCOVAs were performed among 548 individuals diagnosed as CN or EMCI.

To examine the earliest combined effects of both APOE4 status and A β load status on regional CoTh and on several cognitive variables (MMSE, RAVLT sub scores, and ADAS13 score), we focused on above-mentioned CN and EMCI participants ($n=548$), and divided them into four groups: E4-/Amy- ($n=241$), E4-/Amy+ ($n=112$), E4+/Amy- ($n=73$), and E4+/Amy+ ($n=122$). A series of one-way ANCOVAs were conducted, using age as a covariate, and with CoTh or cognitive scores as the dependent variables.

Multiple comparison correction was performed in all aforementioned ANCOVA analyses to control the false discovery rate (FDR). Statistically significant results (FDR-adjusted p value < 0.05) were further examined using *post hoc* Tukey HSD test.

RESULTS

E4+ status was associated with higher A β load across all diagnostic groups, as shown in Table 2 and Fig. 1.

Table 2

Effect of APOE4 status on global amyloid load (SUVR) in different diagnostic groups

	E4-	E4+	<i>t</i> test ^a	<i>p</i> value
CN	1.079(0.16)	1.178(0.2)	-3.65649	0.00021
EMCI	1.115(0.18)	1.246(0.21)	-5.76863	0
LMCI	1.147(0.23)	1.368(0.21)	-7.12632	0
AD	1.271(0.26)	1.439(0.16)	-4.32684	0.00002

^aH₀: SUVR(E4-) = SUVR(E4+) versus H₁: SUVR(E4-) < SUVR(E4+).

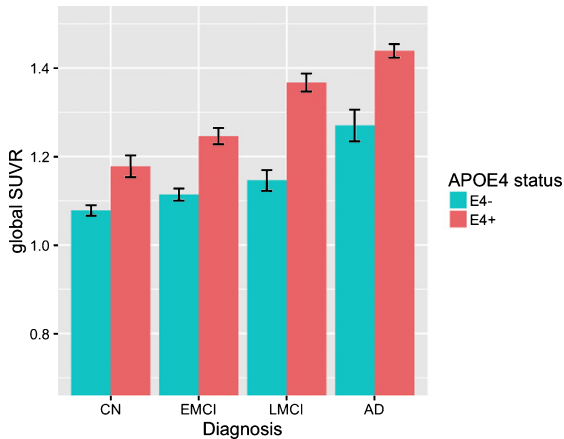


Fig. 1. Differences in mean amyloid load (¹⁸F-AV45) SUVR for each diagnostic group between E4- and E4+ participants.

Effect of Aβ load status on CoTh after controlling for APOE4 status

Results for the left hemisphere only are reported, since findings in both the left and right hemispheres were similar. As can be seen in Table 3 and Fig. 2, there was a statistically significant main effect for Aβ load, accounting for the effect of APOE4 status, on CoTh, for all brain regions examined, with the exception of the TP, superior frontal gyrus, and rostral middle frontal gyrus. The most significant effects were noted in the inferior temporal gyrus (ITG) ($F = 31.18$, $\text{diff} (\text{Amy}+ - \text{Amy}-) = -0.099$), inferior parietal lobule ($F = 20.82$, $\text{diff} = -0.068$), precuneus ($F = 16.55$, $\text{diff} = -0.058$), the mean CoTh for all regions ($F = 15.6$, $\text{diff} = -0.046$), ERC ($F = 14.59$, $\text{diff} = -0.159$), and supramarginal gyrus ($F = 10.98$, $\text{diff} = -0.051$). In all these regions Amy+ status was associated with reduced CoTh, adjusting for the effects of APOE4 status.

Table 3 also shows a strong main effect for diagnosis. Using *post hoc* tests (Tukey HSD), it was found that CoTh was reduced among AD participants compared to the three other diagnostic groups, and also

among LMCI participants, as compared to EMCI and CN participants. This pattern appeared to hold for every brain region included in these analyses, with the exception of the superior parietal lobule, where EMCI participants had greater CoTh than the other diagnostic groups, which did not statistically differ from each other. With rare exceptions, CoTh was equivalent between CN and EMCI participants. In the supramarginal gyrus and precuneus, CoTh was greater in EMCI than in CN participants. Statistically significant interaction terms (diagnosis with Aβ load status) were observed for the ITG and inferior parietal lobule, in which Amy+ status was associated with reduced CoTh only in the LMCI and the AD stages.

Effect of APOE4 status on CoTh after controlling for Aβ load

From Table 4, it can be seen that the diagnostic group effect was similar to the pattern observed in Table 3, i.e., AD patients had less CoTh than the other study groups and that LMCI participants had less CoTh than EMCI and CN participants, while CoTh was equivalent between CN and EMCI participants. An inspection of the regional CoTh by APOE4 status in Fig. 3 shows that for most brain regions analyzed, CoTh among CN and EMCI participants is numerically greater among those who are E4+ than E4-. However, the reverse is generally true among LMCI and particularly AD participants, for whom CoTh is generally lower among E4+ than E4- participants. After adjusting for global Aβ load (SUVR), there was a main effect for APOE4 status only in the ITG [$\text{diff}(\text{E4+} - \text{E4-}) = 0.048$ mm, $F = 9.99$, $p = 0.0016$] and medial orbitofrontal gyrus ($\text{diff} = 0.027$ mm, $F = 4.83$, $p = 0.028$), in which it can be observed that CoTh was overall greater among E4+ than among E4- participants (Fig. 3). Furthermore, the interaction term in Table 4 shows significant difference only in the ERC, where the CoTh is greater only among CN and EMCI participants who are E4+ as compared to those who are E4-, whereas among LMCI and AD participants, CoTh is greater among E4- as compared to E4+ participants (Fig. 3).

Importantly, when CN and EMCI subjects were analyzed independently (Table 5), E4+ status (controlling for Aβ load) was associated with increased CoTh in the ERC ($\text{diff} = 0.123$ mm, $F = 9.68$, $p = 0.002$), PHG ($\text{diff} = 0.082$ mm, $F = 6.02$, $p = 0.014$), ITG ($\text{diff} = 0.059$ mm, $F = 12.56$, $p = 0.0004$), and TP ($\text{diff} = 0.091$ mm, $F = 7.47$, $p = 0.006$).

Table 3
Effect of amyloid status on regional CoTh, independent of APOE4 status (left hemisphere)

	CN		EMCI		LMCI		AD		F ^a	F ^a	post_hoc_Tukey	F ^a
	Amy- 165 Amy+ 86	Amy- 149 Amy+ 148	Amy- 66 Amy+ 130	Amy- 19 Amy+ 143	Amyloid	Diagnosis	(Diagnosis)	Diagnosis by Amyloid				
Age	74.51 (6.8) ^b 76.75 (5.7)	69.19 (7.4) 73.46 (6.8)	73.68 (9.4) 73.61 (7.3)	77.49 (8.2) 74.38 (7.7)	10.64*** ^c	15.79***	EMCI < All	4.78**				
Entorhinal	3.34 (0.38) 3.27 (0.37)	3.32 (0.46) 3.26 (0.43)	3.17 (0.52) 2.96 (0.52)	2.77 (0.74) 2.58 (0.49)	14.59***	42.18***	AD < All; LMCI < EMCI, CN	1.56				
Parahippocampal	2.67 (0.34) 2.58 (0.41)	2.66 (0.36) 2.67 (0.31)	2.52 (0.39) 2.5 (0.4)	2.44 (0.39) 2.31 (0.35)	6.74**	15.6***	AD < EMCI, CN LMCI < EMCI, CN	1.23				
Inferior temporal	2.66 (0.16) 2.61 (0.16)	2.66 (0.18) 2.61 (0.19)	2.61 (0.18) 2.57 (0.23)	2.57 (0.26) 2.39 (0.24)	31.18***	13.86***	AD < All; LMCI < EMCI, CN	3.13*				
Temporal pole	3.56 (0.33) 3.53 (0.36)	3.48 (0.37) 3.5 (0.34)	3.5 (0.35) 3.35 (0.45)	3.08 (0.63) 3.11 (0.51)	2.46	23.19***	AD < All; LMCI < CN	1.99				
Medial orbitofrontal	2.28 (0.15) 2.27 (0.18)	2.27 (0.14) 2.23 (0.16)	2.23 (0.17) 2.22 (0.17)	2.25 (0.2) 2.19 (0.16)	8.14**	4.57**	AD < CN; LMCI < CN	1.3				
Superior frontal	2.48 (0.17) 2.46 (0.17)	2.52 (0.15) 2.49 (0.15)	2.45 (0.17) 2.42 (0.16)	2.37 (0.17) 2.36 (0.18)	3.79	15.17***	AD < All; LMCI < EMCI	0.14				
Rostral Middle Frontal	2.15 (0.14) 2.15 (0.15)	2.18 (0.13) 2.15 (0.12)	2.14 (0.14) 2.11 (0.13)	2.09 (0.16) 2.07 (0.15)	1.87	8.2***	AD < EMCI, CN LMCI < EMCI	0.64				
Superior Parietal	1.96 (0.17) 1.96 (0.17)	2.01 (0.14) 2.01 (0.14)	1.97 (0.16) 1.94 (0.16)	1.95 (0.12) 1.86 (0.18)	6.08*	10.02***	EMCI > All	1.69				
Inferior Parietal	2.19 (0.16) 2.18 (0.17)	2.23 (0.14) 2.21 (0.15)	2.2 (0.14) 2.13 (0.16)	2.18 (0.18) 2.02 (0.2)	20.82***	10.67***	AD < All; LMCI < EMCI	4.78**				
Supramarginal	2.31 (0.18) 2.31 (0.18)	2.37 (0.15) 2.34 (0.16)	2.3 (0.17) 2.26 (0.17)	2.26 (0.19) 2.16 (0.18)	10.98***	16.51***	AD < All; EMCI > LMCI, CN	1.71				
Precuneus	2.14 (0.17) 2.12 (0.17)	2.19 (0.14) 2.15 (0.15)	2.14 (0.16) 2.1 (0.15)	2.11 (0.14) 1.99 (0.18)	16.55***	10.33***	AD < All; EMCI > LMCI, CN	1.92				
Posterior Cingulate	2.38 (0.18) 2.4 (0.18)	2.41 (0.17) 2.39 (0.17)	2.4 (0.17) 2.37 (0.17)	2.39 (0.22) 2.31 (0.18)	4.25*	1.7		1.66				
Mean CoTh.Left	2.30 (0.13) 2.29 (0.14)	2.33 (0.11) 2.31 (0.12)	2.28 (0.13) 2.24 (0.13)	2.23 (0.15) 2.15 (0.14)	15.6***	20.62***	AD < All; LMCI < EMCI, CN	1.54				

^aF value is adjusted for APOE4 Status (4 × 2 ANCOVA test). ^bValues are represented as mean(SD), upper is for Amy- group and lower is for Amy+ group. ^c $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Combined effect of APOE4 status and Aβ load status on CoTh among CN and EMCI groups

Among CN and EMCI groups, there were prominent age effects on CoTh in almost every brain region, each with a different combination of Aβ and APOE4 status. However, once such age effects were accounted for, there was no difference in CoTh measure in these two groups in any brain region.

Combined effect of APOE4 status and Aβ load status on cognitive variables among CN and EMCI groups

From Table 6 and Fig. 4, it can be seen that after accounting for age, there was a significant effect on all assessed cognitive scores: (a) the E4+/Amy+ group showed more impairment than the E4-/Amy- group on the MMSE score ($p < 0.001$); (b) the E4+/Amy+ group was more impaired than the E4-/Amy- ($p < 0.001$), as well as the E4-/Amy+ groups ($p = 0.005$) on the RAVLT (immediate) memory

test; (c) the E4+/Amy+ group was more impaired than the E4-/Amy- group on the RAVLT percent forgetting ($p = 0.018$); and (d) the E4+/Amy+ group had more impaired ADAS13 scores as compared to all other combinations of E4 +/- and Amy +/- (all $p < 0.001$).

DISCUSSION

This study represents a first attempt to disentangle the complex inter-relationships between Aβ load, APOE4 genotype, regional CoTh, and cognition among well-defined diagnostic groups in ADNI. Previous studies have shown that: (1) higher global Aβ load and E4+ status are associated with a greater risk of progression from CN to MCI, and MCI to AD [22, 23]; (2) higher Aβ load is associated with reduced CoTh, but with subtle impairment of cognition in the CN and MCI stage [24–33]; (3) E4+ status is associated with an earlier age of onset of Aβ positivity and of AD, greater Aβ levels in the brain, reduced hippocampal volumes and CoTh in limbic

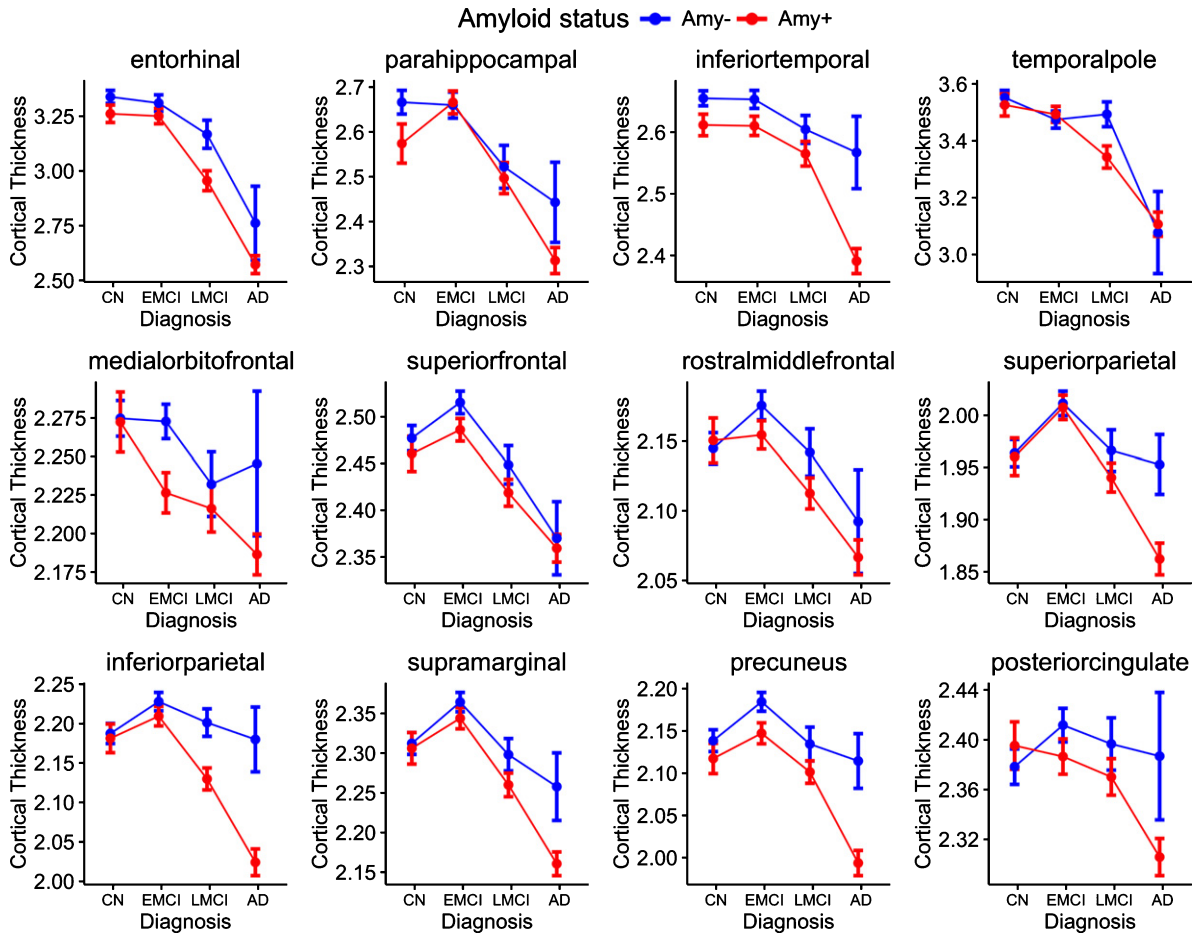


Fig. 2. Barplot of CoTh among Amy⁻ and Amy⁺ participants in 4 diagnostic groups for 12 brain regions.

and neocortical regions, and subtle cognitive deficits in CN individuals [4, 5, 34–43]; (4) further, irrespective of APOE4 status, reduced hippocampal volumes and CoTh in various brain regions, especially those regions characterized as AD signature regions, are associated with impaired memory and general cognition, as well as a greater risk for progression from CN to MCI and MCI to AD [44]. However, there is currently no consensus regarding the extent to which A β load status and APOE4 status, independently and in combination, are associated with neurodegenerative changes in AD prone regions and with cognitive impairment.

It is important to note that both trophic and toxic effects of A β peptide are known and they may not necessarily be mutually exclusive. The toxic effects may be mediated by different mechanisms, such as oxidative stress, inflammation, mitochondrial diffusion, alterations in membrane permeability, synaptic

dysfunction, and excitotoxicity through its interaction with neurotransmitter receptors. These effects contribute significantly to the neuronal damage seen in AD, which may be associated with A β itself, including high concentrations in fibrillar or aggregated states, interaction with free metals, interactions with previously injured or aged brain tissue and with decreased antioxidative mechanisms [45–48].

We devised our analytic strategy to investigate, among 906 participants in the ADNI-1/ADNI-Go and ADNI-2 cohorts, the unique and independent contributions of those elements, which are considered as upstream factors (i.e., A β load status and APOE4 status), on downstream factors (regional CoTh and cognitive measures tapping memory and general cognition). We also investigated the individual and additive effects of E4⁺ and Amy⁺ status on CoTh and cognitive performance, in the earliest stages of neurodegeneration, using different combinations

Table 4
Effect of APOE4 status on regional CoTh, independent of A β load (left hemisphere)

	CN	EMCI	LMCI	AD	F ^a	F ^a	post_hoc_Tukey	F ^a
	E4- 184	E4- 169	E4- 92	E4- 54	APOE4	Diagnosis	(Diagnosis)	Diagnosis
	E4+ 67	E4+ 128	E4+ 104	E4+ 108	Status			by APOE4
Age	75.77 (6.3) ^b	72.07 (7.3)	74.96 (8.6)	76.43 (8.6)	29.12***	12.89***	EMCI < All	0.44
Entorhinal	73.93 (7.0)	70.33 (7.5)	72.46 (7.4)	73.90 (7.3)	0.02	68.18***	AD < All; LMCI < EMCI, CN	4.84**
	3.30 (0.38)	3.22 (0.46)	3.11 (0.54)	2.69 (0.60)				
Parahippocampal	3.35 (0.37)	3.37 (0.41)	2.96 (0.51)	2.55 (0.48)	1.71	25.56***	AD < All; LMCI < EMCI, CN	1.08
	2.62 (0.38)	2.64 (0.32)	2.50 (0.39)	2.37 (0.38)				
Inferior temporal	2.68 (0.34)	2.70 (0.34)	2.52 (0.39)	2.31 (0.34)	9.99**	32.41***	AD < All; LMCI < CN	0.5
	2.63 (0.15)	2.62 (0.19)	2.57 (0.21)	2.42 (0.27)				
Temporal pole	2.68 (0.17)	2.65 (0.19)	2.59 (0.22)	2.41 (0.24)	1.55	32.87***	AD < All; LMCI < CN	1.1
	3.53 (0.35)	3.45 (0.37)	3.42 (0.40)	3.11 (0.53)				
Medial orbitofrontal	3.60 (0.32)	3.53 (0.34)	3.38 (0.44)	3.10 (0.52)	4.83*	4.78**	AD < EMCI, CN	0.53
	2.27 (0.15)	2.25 (0.15)	2.22 (0.16)	2.17 (0.18)				
Superior frontal	2.28 (0.18)	2.25 (0.15)	2.22 (0.18)	2.21 (0.15)	2.01	22.2***	AD < All; LMCI < EMCI	1.49
	2.46 (0.18)	2.51 (0.14)	2.44 (0.17)	2.33 (0.15)				
Rostral Middle Frontal	2.50 (0.16)	2.50 (0.16)	2.42 (0.16)	2.37 (0.19)	0	14.73***	AD < All; LMCI < EMCI	1.8
	2.14 (0.15)	2.18 (0.12)	2.13 (0.14)	2.05 (0.16)				
Superior Parietal	2.15 (0.14)	2.15 (0.13)	2.11 (0.12)	2.08 (0.15)	0.57	18.66***	AD < All; LMCI < EMCI	1.7
	1.95 (0.16)	2.02 (0.14)	1.96 (0.16)	1.88 (0.18)				
Inferior Parietal	2.00 (0.17)	2.00 (0.14)	1.94 (0.16)	1.87 (0.18)	0.1	25.75***	AD < All; LMCI < EMCI	2.11
	2.18 (0.16)	2.22 (0.15)	2.18 (0.16)	2.06 (0.20)				
Supramarginal	2.21 (0.18)	2.22 (0.15)	2.13 (0.15)	2.03 (0.21)	2.08	30.71***	AD < All; LMCI < EMCI	0.99
	2.30 (0.18)	2.35 (0.15)	2.29 (0.17)	2.17 (0.19)				
Precuneus	2.34 (0.17)	2.36 (0.16)	2.26 (0.17)	2.17 (0.18)	0.36	22.49***	AD < All; LMCI < EMCI	1.39
	2.12 (0.16)	2.17 (0.14)	2.12 (0.16)	2.03 (0.17)				
Posterior Cingulate	2.16 (0.17)	2.16 (0.15)	2.10 (0.16)	2.00 (0.18)	0.16	5.47***	AD < All	2.03
	2.37 (0.18)	2.41 (0.17)	2.38 (0.16)	2.33 (0.20)				
MeanCoTh_left	2.42 (0.18)	2.38 (0.17)	2.38 (0.18)	2.31 (0.18)	2.31	38.84***	AD < All; LMCI < EMCI, CN	1.25
	2.29 (0.14)	2.32 (0.11)	2.27 (0.14)	2.16 (0.15)				
	2.32 (0.13)	2.32 (0.12)	2.25 (0.13)	2.16 (0.14)				

^aF value is adjusted for global A β load (4 × 2 ANCOVA test). ^bValues are represented as mean(SD), upper is for E4- group and lower is for E4+ group. ^c $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

of APOE4 status and A β load status (E4-/Amy-, E4+/Amy-, E4-/Amy+ and E4+/Amy+) among CN and EMCI participants.

Our results confirmed previous reports showing that E4+ status is associated with increased A β load among all stages of AD (Table 2). Amy+ status, among all participants, was found to be associated with reduced CoTh in many AD vulnerable regions, independent of the effects of E4+ status (Table 3) [28, 29, 49, 50], but E4+ status was associated with reduced CoTh in restricted brain regions, and only among LMCI and AD participants (Table 4). Unexpectedly, E4+ status was associated with *increased* CoTh in some of the most vulnerable brain regions to AD pathology (i.e., the ERC, PHG, and ITG) in the preclinical and very early stages of AD (i.e., among CN and EMCI participants) (Table 5).

Even though we found there was no observed cortical thinning in association with Amy+ status, and there was cortical thickening in association with E4+ status, among CN and EMCI participants, there was impairment on all cognitive tests among these

participants, in association with either Amy+ and E4+ status, independently and to the greatest extent with combined Amy+ and E4+ status (Table 6). Global cognitive scores (ADAS13), among CN and EMCI participants, were significantly impaired among E4+/Amy+ groups as compared to all other groups, including those who were E4-/Amy-, suggesting that the presence of Amy+ status is independently associated with greater impairment of global cognitive scores. Further, memory impairment, on the RAVLT immediate test, was greater among those who were E4-/Amy+, as compared to those who were E4+/Amy+, suggesting that the presence of E4+ status is independently associated with greater immediate memory impairment. These results demonstrate that in the earliest stages of AD, in the absence of cortical thinning, there is impairment in cognitive performance attributable to combined E4+ and Amy+ status, as well as independently to E4+ status and to Amy+ status. Given that there is a known relationship between CoTh and cognitive scores [44, 51, 52], the finding among CN and EMCI

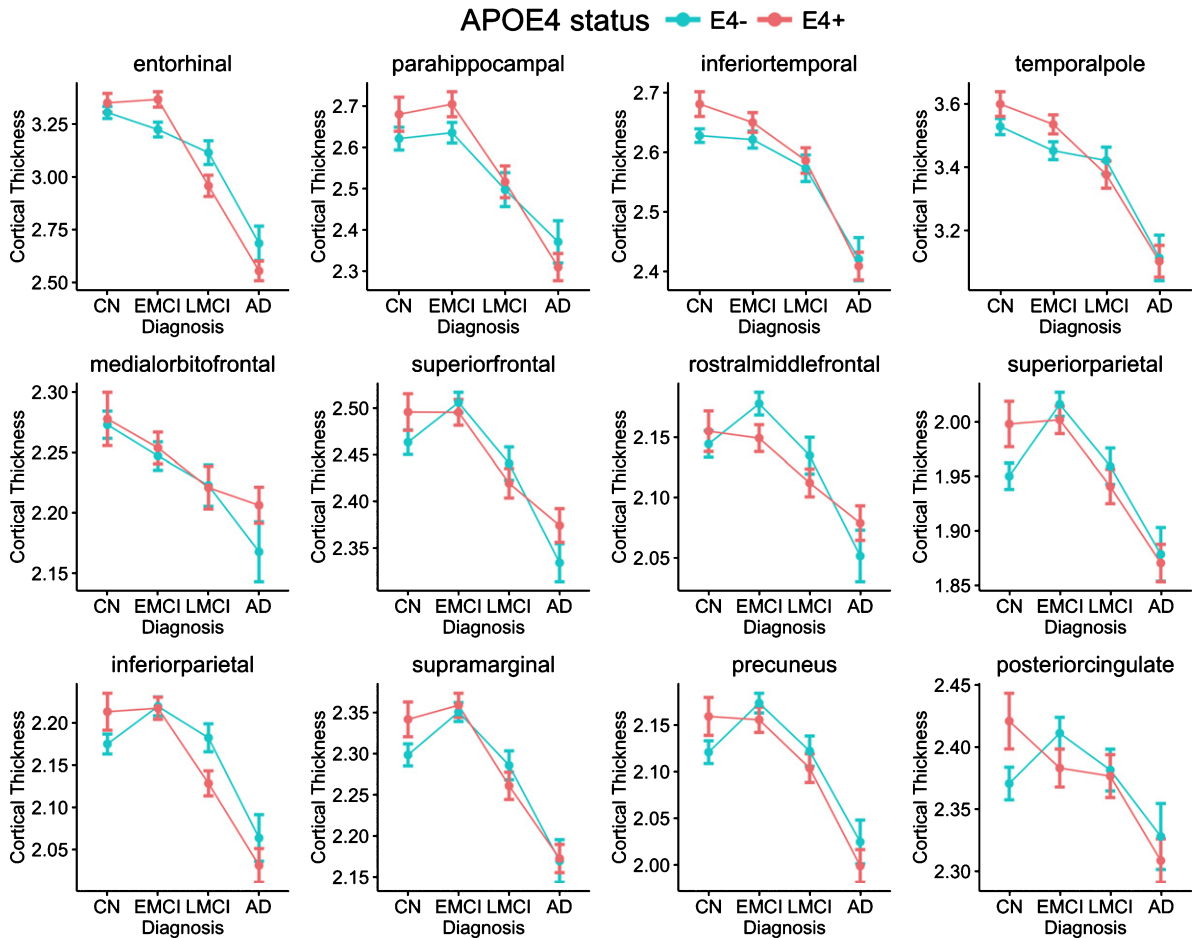


Fig. 3. Barplot of CoTh among E4- and E4+ participants in 4 diagnostic groups for 12 brain regions.

participants, who are E4+, of an association with increased CoTh in the most vulnerable regions to AD pathology, suggests that the mechanism underlying neurodegeneration associated with E4+ status is distinct from that of Amy+ status.

Biological processes, such as metabolic activation, increased blood flow and inflammation [53, 54], may result in increased volume of the cortical ribbon in brain regions, in which the neurodegenerative process begins, with subsequent cortical thinning as neurodegeneration becomes more advanced [55–57]. It is apparent that APOE4 is a contributing factor to neurodegeneration, and is strongly linked to AD pathology, alone and particularly in combination with the A β peptide. APOE4 may increase A β deposition in plaques and impair its clearance, and also may act independently through pathways that may not involve A β [52]. The pathophysiological effects of APOE4 may be mediated at a molecular level in

the process of redistribution of lipids in normal lipid homeostasis, repairing injured neurons, maintaining synapto-dendritic connections, and scavenging toxins. These pathophysiological effects result in adverse outcomes in various neurological conditions and in “normal” aging. E4+ status is associated with adverse outcomes, acceleration of progression, worsening overall prognosis in response to head injury, oxidative stress, ischemia, and inflammation, as well as lowering of the age of onset of neurodegenerative disease [55].

A weakness of this study is that it is cross-sectional and so any inferences about progression from the CN to AD stage must be considered tentative. A major strength of the current investigation is that it utilizes a well-characterized ADNI cohort, including large numbers of subjects who are cognitively normal or in the earliest stages of disease, to power the analyses. These large numbers of subjects that are

Table 5
Effect of APOE4 status on regional CoTh in CN and EMCI, independent of A β load (left hemisphere)

	CN		EMCI		F ^a	F ^a	F ^a
	E4- 184 E4+ 67	E4- 169 E4+ 128	APOE4 Status	Diagnosis	Diagnosis by APOE4		
Entorhinal	3.30 (0.38) ^b	3.22(0.46)					
Parahippocampal	3.35 (0.37)	3.37 (0.41)	9.68*** ^c	0.26	1.92		
	2.62 (0.38)	2.64 (0.32)					
Inferior temporal	2.68 (0.34)	2.70 (0.34)	6.02*	0.71	0.06		
	2.63 (0.15)	2.62 (0.19)					
Temporal pole	2.68 (0.17)	2.65 (0.19)	12.56***	0.45	0.37		
	3.53 (0.35)	3.45 (0.37)					
Medial orbitofrontal	3.60 (0.32)	3.53 (0.34)	7.47**	3.88*	0.06		
	2.27 (0.15)	2.25 (0.15)					
Superior frontal	2.28 (0.18)	2.25 (0.15)	1.71	1.72	0.04		
	2.46 (0.18)	2.51 (0.14)					
Rostral Middle Frontal	2.50 (0.16)	2.5 (0.16)	1.21	2.56	1.93		
	2.14 (0.15)	2.18 (0.12)					
Superior Parietal	2.15 (0.14)	2.15 (0.13)	0.45	1.23	2.46		
	1.95 (0.16)	2.02 (0.14)					
Inferior Parietal	2.00 (0.17)	2.00 (0.14)	1.68	6.29*	4.65*		
	2.18 (0.16)	2.22 (0.15)					
Supramarginal	2.21 (0.18)	2.22 (0.15)	2.7	3.56	1.81		
	2.30 (0.18)	2.35 (0.15)					
Precuneus	2.34 (0.17)	2.36 (0.16)	3.81	5.71*	1.17		
	2.12 (0.16)	2.17 (0.14)					
Posterior Cingulate	2.16 (0.17)	2.16 (0.15)	1.6	3.89*	3.58		
	2.37 (0.18)	2.41 (0.17)					
Mean CoTh_left	2.42 (0.18)	2.38 (0.17)	0.56	0.02	5.87*		
	2.29 (0.14)	2.32 (0.11)					
	2.32 (0.13)	2.32 (0.12)	3.55	2.52	2.72		

^aF value is adjusted for global A β load (2 × 2 ANCOVA test). ^bValues are represented as mean(SD), upper is for E4- group and lower is for E4+ group. ^c $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Table 6
Combined effect of APOE4 status and A β load status on cognitive scores among CN and EMCI groups

	E4-Amy- (241)	E4-Amy+ (112)	E4+ Amy- (73)	E4+ Amy+ (122)	F_age	F_E4Amy ^a
MMSE	28.93 (1.35) ^b	28.54 (1.39)	28.73 (1.28)	28.16 (1.73)	8.48*** ^c	7.86***
RAVLT immediate	44.00 (10.98)	41.61 (11.2)	43.73 (10.8)	38.13 (10.3)	36.85***	E4+ Amy+ <E4-Amy- ^d 8.23***
RAVLT Percent forgetting ^e	38.79 (29.8)	43.67 (28.5)	39.8 (26.94)	48.37 (29.74)	8.5**	E4+ Amy+ <E4- Amy-; E4+ Amy+ <E4- Amy+ 2.86*
ADAS13 ^e	10.00 (4.82)	11.45 (5.61)	9.70 (5.17)	13.58 (5.56)	21.9***	E4+ Amy+ >E4- Amy- 13.51*** E4+ Amy+ >All

^aF value is adjusted for age (One-way ANCOVA test). ^bValues are represented as mean(SD). ^c $p < 0.1$; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

^dPost Hoc Tukey results with significant difference. ^eHigher scores indicate worse performance.

available in the ADNI cohort provide the statistical power required to tease apart independent effects of upstream biological processes, such as A β load and APOE4 status as they relate to downstream effects on CoTh and cognition. Future analyses should attempt to confirm these findings using longitudinal analyses of the data, and to further evaluate the effects of regional, rather than global deposition of A β , on CoTh and cognition.

In conclusion, our findings suggest that both A β load and APOE4 status are highly associated with progressive neurodegeneration, as measured by cortical thinning, especially in the LMCI and AD stages, and especially in brain regions which are vulnerable to AD pathology. Even though there is no significant cortical thinning noted in CN and EMCI stages, associated with E4+ or Amy+ status, there is measurable cognitive impairment present. The association

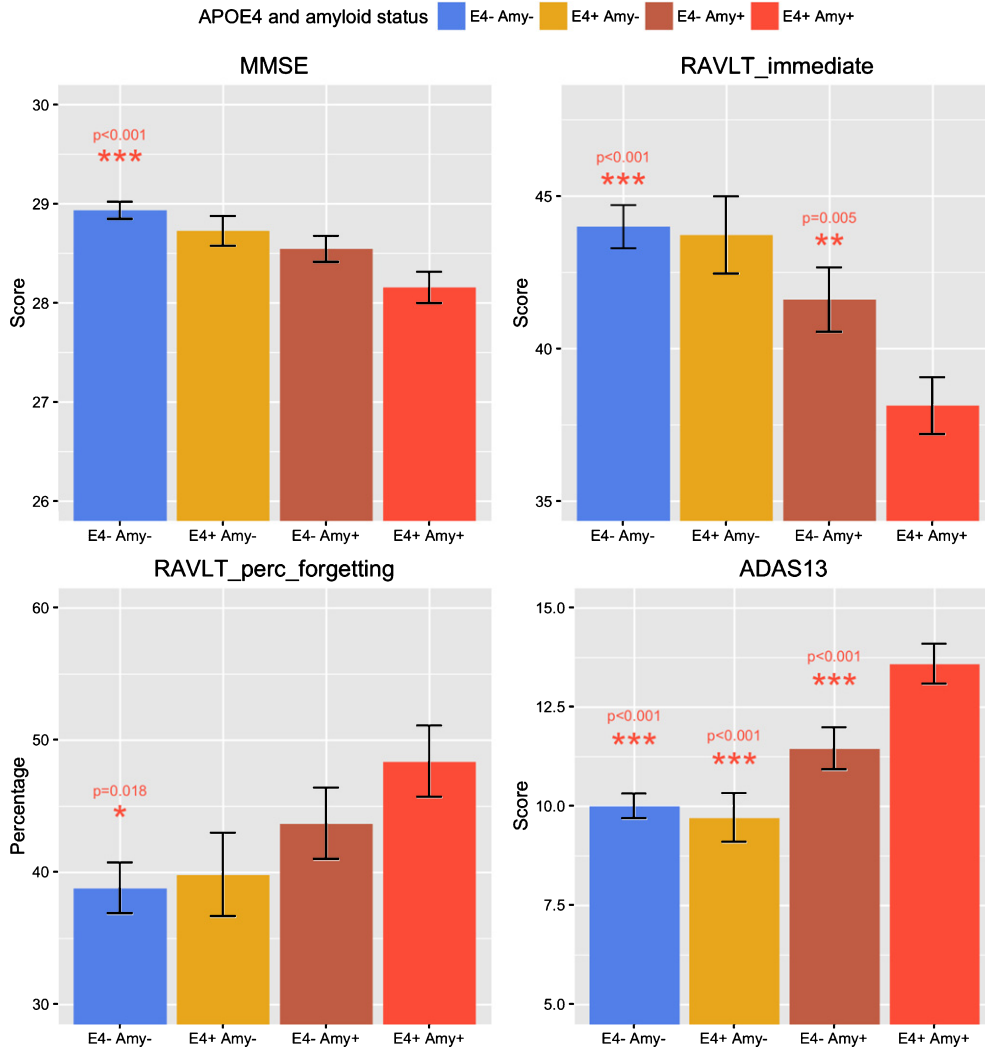


Fig. 4. Bar graph of scores on following cognitive tests: MMSE, RAVLT (immediate), RAVLT (% forgetting) and ADAS13. Individual bars represent the following groups of participants: E4-/Amy-; E4+/Amy-; E4-/Amy+ and E4+/Amy+. The colored asterisk (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$) on the E4-/Amy- indicates a significant difference in score from the score for the corresponding color bar, i.e., E4+/Amy+ group, same as E4-/Amy+ bars in RAVLT (immediate) and ADAS13, as well as E4+/Amy- in ADAS13. There was no significant difference among E4-/Amy-, E4+/Amy-, E4-/Amy+ group.

of E4+ status with cortical thickening, rather than thinning, suggests the possibility of a very different pathophysiological role for E4+ from that of A β deposition in the progression of AD.

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