APOE modifies the interaction of entorhinal cerebral blood flow and cortical thickness on memory function in cognitively normal older adults

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ABSTRACT

Objective: The ε4 allele of the apolipoprotein E (APOE) gene increases risk for cognitive decline in normal and pathologic aging. However, precisely *how* APOE ε4 exerts its negative impact on cognition is poorly understood. The present study aimed to determine whether APOE genotype (ε4+ vs. ε4-) modifies the interaction of medial temporal lobe (MTL) resting cerebral blood flow (CBF) and brain structure (cortical thickness [CT], volume [Vo]) on verbal memory performance.
Methods: Multiple linear regression models were employed to investigate relationships between APOE genotype, arterial spin labeling MRI-measured CBF and FreeSurfer-based CT and Vo in four MTL regions of interest (left and right entorhinal cortex and hippocampus), and verbal memory performance among a sample of 117 cognitively normal older adults (41 ε4+, 76 ε4-) between the ages of 64 and 89 (mean age = 73).
Results: Results indicated that APOE genotype modified the interaction of CBF and CT on memory in the left entorhinal cortex, such that the relationship between entorhinal CBF and memory was negative (*lower* CBF was associated with better memory) in non-carriers with higher entorhinal CT, positive (*higher* CBF was associated with better memory) in non-carriers with lower entorhinal CT, and negative (higher CBF was associated with *worse* memory) in ε4 carriers with lower entorhinal CT.
Conclusions: Findings suggest that older adult APOE ε4 carriers may experience vascular dysregulation and concomitant morphological alterations in the MTL that interact to negatively affect memory even in the absence overt clinical symptoms, providing potential insight into the mechanistic link between APOE ε4 and detriments in cognition. Moreover, findings suggest a distinct multimodal neural signature in ε4 carriers (*higher* CBF and *lower* CT in the entorhinal cortex) that could aid in the identification of candidates for future clinical trials aimed at preventing or slowing cognitive decline. Differential findings with respect to ε4 carriers and non-carriers are discussed in the context of neurovascular compensation.

1. Introduction

With a rapidly growing older population, identifying risk factors and mechanisms of age-related cognitive decline represents one of the greatest challenges to improving the health and overall independence of older adults. The ε4 allele of the apolipoprotein E gene (APOE) confers risk for pathologic and normal age-related cognitive decline (Bretsky et al., 2003; Richard J. Caselli et al., 2009; Schiepers et al., 2012; Tsuang et al., 2013). Precisely *how* APOE ε4 exerts its negative impacts on

cognition is still poorly understood, but is likely related to its role in a diverse range of biological processes including glucose metabolism, mitochondrial function, synaptic function, neurogenesis, tau phosphorylation, neuronal atrophy, neuroinflammation, and amyloid-β (Aβ) metabolism and aggregation (Kanekiyo et al., 2014; C.-C. Liu, Kanekiyo, Xu and Bu, 2013; Mahley and Rall, 2000). Interestingly, APOE ε4's effects on cognition appear largely dependent on age, with young ε4 carriers equal to or outperforming non-carriers on a wide range of cognitive abilities (Jochemsen, Muller, van der Graaf and Geerlings, 2012;

Marchant et al., 2010; Mondadori et al., 2007; Rusted et al., 2013), but older ε4 carriers demonstrating worse cognitive performance (Adamson et al., 2010; De Blasi et al., 2009; Honea et al., 2009; Kukolja et al., 2010; Tuminello and Han, 2011) and accelerated age-related cognitive decline, most notably in episodic memory (Bretsky et al., 2003; R. J. Caselli et al., 2004; Richard J. Caselli et al., 2009; Hayden et al., 2009; C.-C. Liu et al., 2013; Schiepers et al., 2012; Whitehair et al., 2010). Identifying and characterizing APOE-related brain changes could offer insight into the mechanistic link between APOE ε4 genotype and cognitive decline.

APOE ε4 carriers demonstrate alterations in cerebral blood flow (CBF), or the rate of delivery of arterial blood to the capillary bed in a volume of tissue. CBF is an indirect measure of neural function (Buxton, 2009) that has been implicated in both normal aging and AD-related cognitive decline (Bertsch et al., 2009; Hays et al., 2016; Heo et al., 2010), demonstrating reliable correlations with cognitive performance across the lifespan (Bangen et al., 2012; Bertsch et al., 2009; Okonkwo et al., 2014; Wierenga et al., 2012). APOE ε4 carriers demonstrate altered resting CBF across widespread medial temporal, frontal, and parietal regions (Tai et al., 2016; Wierenga et al., 2014) and the temporal staging of CBF alteration appears to resemble APOE-related changes in cognition, with ε4 carriers exhibiting higher resting CBF than non-carriers in early adulthood and middle-age, but lower resting CBF in old age (Thambisetty et al., 2010; Wierenga et al., 2013). It has been suggested that higher brain perfusion among ε4 carriers reflects cerebrovascular compensation for the deleterious effects of APOE ε4 (e.g., impaired repair mechanisms, neurovascular disruption) and that lower brain perfusion reflects a breakdown of these compensatory mechanisms (Dai et al., 2009; Hays et al., 2016; Koizumi et al., 2018; Luckhaus et al., 2008; Wierenga et al., 2012). Notably, cross-sectional investigations of cerebral perfusion in cognitively normal older adult ε4 carriers have produced mixed results, with reports of both increased (Bangen et al., 2009; Thambisetty et al., 2010) and decreased CBF (Filippini et al., 2011; Wierenga et al., 2013; Zlatar et al., 2016), relative to non-carriers. Similarly, findings from studies exploring associations between APOE-related CBF alteration and cognition have also been mixed, with reports of both positive and negative relationships between CBF and cognition in older adult ε4 carriers (Bangen et al., 2012; Wierenga et al., 2012; Zlatar et al., 2016). To the extent that some of these discordant findings are due to differences in sample characteristics (e.g., definitions of cognitively normal, middle age versus older adults) or methodology (e.g., imaging modality limitations, statistical or experimental control of confounding variables, regions of interest versus voxel wise analysis, differing methods of partial volume correction), it is important to extend these prior studies using cutting-edge methodologies within large, well-characterized samples to further clarify associations between APOE, CBF, and cognition.

APOE genotype is also associated with alterations in brain morphology. More specifically, ε4 carriers demonstrate reduced cortical thickness in youth relative to non-carriers (Alexander et al., 2012; Ringman et al., 2010; Shaw et al., 2007) and accelerated gray matter atrophy in old age, most notably in medial temporal lobe (MTL) regions (Cohen et al., 2001; den Heijer et al., 2002; Jak et al., 2007; Tohgi et al., 1997). Moreover, ε4 carriers who demonstrate APOE-related alterations in brain structure also exhibit cognitive deficits, compared to non-carriers (Honea et al., 2009; Lind et al., 2006), suggesting that APOE ε4 genotype might confer risk for cognitive decline through changes in brain structure, perhaps through its moderating role in myelination, brain plasticity, and repair functions (Zhong and Weisgraber, 2009). However, it is difficult to reconcile findings of reduced structural integrity in young ε4 carriers with evidence of increased cognitive performance in this same group. Thus, it has been suggested that lower cortical reserve in young carriers of the ε4 allele may represent a neural endophenotype that increases susceptibility to neurodegeneration later in life (Shaw et al., 2007). Therefore, rather than having direct effects on cognition, APOE ε4-related changes in brain structure may interact with concomitant alterations in CBF, exacerbating detrimental effects on cognition. If correct, this could help explain findings of both positive and

negative associations between CBF and cognition in ε4 carriers, as this relationship could vary as a function of structural integrity.

Together, this evidence suggests that cognitively normal APOE ε4 carriers experience alterations in CBF, brain structure, and memory, compared to non-carriers. Moreover, APOE-related alterations in MTL CBF and brain structure might interact to negatively impact memory performance in cognitively normal older adult carriers of the ε4 allele. No study, to our knowledge, has explored the interactions among these variables. To bridge this gap in the literature, the current study used arterial spin labeling (ASL) magnetic resonance imaging (MRI) and a high-resolution structural scan among a relatively large and well-characterized sample of cognitively normal older adults to determine whether APOE genotype (ε4+ vs. ε4-) modifies the interaction of MTL resting CBF and brain structure (cortical thickness [CT], volume [Vo]) on verbal memory performance. We predicted that the interaction of CBF and CT/Vo would differ by APOE genotype, such that increased CBF (reflecting neurovascular compensation) and reduced CT and/or Vo in MTL regions (entorhinal cortex [EC], hippocampus [Hc]) would interact to predict worse memory performance in APOE e4 carriers, but not in non-carriers. Exploratory analyses also investigated these same relationships in frontal brain regions implicated in memory encoding and retrieval (caudal anterior cingulate cortex [cACC], rostral middle frontal cortex [rMFC]). Such findings may help elucidate the underlying mechanisms of APOE ε4 effects on cognition and enable early intervention strategies aimed at preventing age-related cognitive decline.

2. Material and methods

2.1. Participants

See Table 1 for participant demographic and cognitive characteristics. Participants were community-dwelling older adult volunteers enrolled in a longitudinal study of normal aging at the VA San Diego Healthcare System (VASDHS). A total of 117 cognitively normal participants between the ages of 64 and 89 (mean age = 73.3, SD = 6.2) with available data were included in the current analyses. Forty-one participants were carriers of the APOE ε4 allele (ε3/ε4 = 37, ε4/ε4 = 4) and 76 were non-carriers (ε3/ε3 = 66, ε2/ε3 = 10). All participants were administered a full neuropsychological battery and an MRI scan (mean time interval between neuropsychological testing and MRI scan = 51 days). Normal cognitive function was determined based on a comprehensive neuropsychological test battery. Participants were excluded if performance on more than one measure within a cognitive domain was more than one standard deviation below age-appropriate norms, consistent with the empirically-derived criteria for diagnosis of mild cognitive impairment (MCI) developed by Jak and colleagues (Jak et al., 2009), or if overall performance on the Dementia Rating Scale (DRS) was more than 1 standard deviation below age-appropriate norms (see Sup Table S1 for specific cognitive tests, domains, and normative data; this resulted in the removal of 22 participants). Potential participants were also excluded if they had a history of severe head injury, uncontrolled hypertension, or a DSM-IV diagnosis of learning disability, attention deficit disorder, mood disorder, or substance abuse. In addition, participants were excluded if they had contraindications to MRI scanning such as ferrous implants or a pacemaker. All participants provided written informed consent prior to enrollment and data were collected in accordance with all ethical standards as stipulated by the UCSD and VASDHS institutional review board-approved procedures.

2.2. Verbal memory composite

All participants were administered a full neuropsychological battery. A verbal memory composite score was created using trials 1–5, short delay free-recall, and long delay free-recall raw scores from the California Verbal Learning Test – Second Edition (CVLT-II), measuring word list recall, and the Logical Memory immediate and delayed recall subtests of

Table 1

Participant demographic, cognitive, and brain characteristics. Note: APOE = Apolipoprotein E; SD= standard deviation; t or χ2= either t-statistic or χ2; df= degrees of freedom; NP= neuropsychological testing; DRS= Mattis Dementia Rating Scale; WMS-R= Wechsler Memory Scale-Revised; LM= Logical Memory; SS= scaled score; CVLT-II= California Verbal Learning Test-Second Edition; SD= short delay; LD= long delay; DKEFS= Delis-Kaplan Executive Function System; +tests that were included in the memory composite; *significance at p< 0.05; **significance at p< 0.01; ***significance at p< 0.001.

	APOE ε4- (n = 76)		APOE ε4+ (n = 41)		t or χ2	df	p-value
	Mean	SD	Mean	SD			
Age (years)	72.98	6.03	74.02	6.62	0.83	115	0.406
Gender (male/female)	26/50	–	13/28	–	0.08	1	0.784
Education (years)	16.52	2.27	15.90	2.2	1.44	115	0.151
NP and MRI time interval (days)	51.09	70.6	53.29	73.3	0.15	114	0.874
Stroke Risk %	9.78	6.77	9.78	6.84	0.00	114	0.999
Systolic Blood Pressure	130.2	15.9	124.5	11.6	2.20	112	0.029*
Diastolic Blood Pressure	76.97	8.51	71.66	9.23	2.97	109	0.004**
DRS Total Score	140.95	2.82	140.66	3.03	0.52	115	0.608
Memory Composite	0.148	0.79	−0.275	0.89	2.53	115	0.013*
WMS-R LM Immediate Recall+	31.92	6.27	28.63	5.83	2.77	115	0.007**
WMS-R LM Delayed Recall+	29.12	7.13	25.78	7.45	2.38	115	0.019*
CVLT-II List 1–5 total+	51.59	9.49	46.415	11.09	2.65	115	0.009**
CVLT-II SD Free Recall+	10.56	3.05	9.78	3.1	1.32	115	0.189
CVLT-II LD Free Recall+	11.57	2.89	10.41	3.09	2.03	115	0.045*
DKEFS CW Inhibition	58.55	10.78	67.68	14.29	3.87	114	<0.001***
DKEFS CW Inhibition Switch	64.27	14.98	72.90	21.92	2.50	113	0.014*
Trail Making Test-A	32.56	9.16	32.39	10.26	0.09	114	0.927
Trail Making Test-B	76.80	28.84	81.46	27.21	0.84	114	0.398
DKEFS Letter Fluency	46.12	13.83	49.12	12.13	1.16	115	0.245
WISC-R Block Design	47.07	7.93	45.22	6.901	1.25	114	0.213
R Hippocampal CBF	47.6	11.9	50.0	9.98	1.09	105	0.306
R Hippocampal Vo	3719	548	3670	474	0.47	115	0.633
L Hippocampal CBF	49.37	12.6	52.31	10.6	1.20	104	0.232
L Hippocampal Vo	3616	469	3529	492	0.93	114	0.350
R Entorhinal CBF	45.22	16.7	44.33	20.5	0.23	96	0.815
R Entorhinal CT	3.39	0.38	3.40	0.36	0.19	115	0.847
L Entorhinal CBF	45.69	13.6	39.55	15.8	2.01	94	0.047*
L Entorhinal CT	3.20	0.32	3.21	0.34	0.08	114	0.934
R Caudal Anterior Cingulate CBF	54.8	13.6	57.88	11.1	1.16	102	0.246
R Caudal Anterior Cingulate CT	2.67	0.29	2.70	0.32	0.62	115	0.530
L Caudal Anterior Cingulate CBF	55.31	15.7	58.53	11.9	1.08	104	0.282
L Caudal Anterior Cingulate CT	2.49	0.25	2.63	0.36	2.53	115	0.012*
R Rostral Middle Frontal CBF	61.11	14.7	62.78	10.1	0.61	106	0.541
R Rostral Middle Frontal CT	2.18	0.09	2.21	0.13	1.14	115	0.256
L Rostral Middle Frontal CBF	63.69	14.9	64.48	10.8	0.28	106	0.779
L Rostral Middle Frontal CT	2.25	0.13	2.22	0.14	1.11	115	0.266

the Wechsler Memory Scale-Revised (WMS-R), measuring story recall. These tests were selected based on results from a principal component analysis previously reported by our group on a similar sample of older adults (Wierenga et al., 2012). Verbal memory composite scores were derived by averaging the *z*-scores for each of the tests within the composite for the entire sample.

2.3. Vascular risk

All participants were administered the Framingham Stroke Risk Profile (FSRP), a common vascular risk index (D'Agostino et al., 1994; Wolf, D'Agostino, Belanger and Kannel, 1991) that is based on the following risk factors: age, systolic blood pressure, antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy. Risk of stroke (stroke risk %) is defined as the 10-year risk or predicted probability of incident stroke expressed as a percentage.

2.4. Apolipoprotein E genotyping

Genotyping was performed by the ADCS Biomarker Core at UCSD using real time PCR Restriction Fragment Length Polymorphism analysis. Genomic DNA was collected from participants using buccal swab and extracted using Qiamp DNA blood mini kit (Qiagen) followed by PCR amplification. Those with at least one ε4 allele (i.e., ε2/ε4, ε3/ε4, ε4/ε4) were classified as APOE e4 carriers (ε4+) and those without an ε4 allele (i.e., ε2/ε2, ε2/ε3, ε3/ε3) were classified as non-carriers (ε4-). Given that

the APOE ε2 allele is thought to have protective effects (Suri et al., 2013), we ran all analyses including and excluding ε2 carriers and results did not differ. Therefore, results from the entire sample are presented. An exact test of Hardy-Weinberg Equilibrium was not significant (*p* = 0.443), suggesting that the distribution of APOE genotype in the sample included in this manuscript does not differ significantly from the expected distribution in the general population.

2.5. MRI acquisition

Imaging data were acquired on a GE Discovery MR750 3T whole body system with a body transmit coil and an 8-channel receive-only head coil at the University of California San Diego Center for Functional MRI. The structural brain sequence consisted of a high-resolution T1-weighted Fast Spoiled Gradient Recall (3D FSPGR) scan: 172 1 mm contiguous sagittal slices, FOV = 25 cm, TR = 8 ms, TE = 3.1 ms, flip angle = 12, T1 = 600 ms, 256 x 192 matrix, Bandwidth = 31.25 kHz, frequency direction = S–I, NEX = 1, scan time = 8 min and 13 s. Resting CBF was acquired with the Multiphase Pseudocontinuous Arterial Spin Labeling (MPPCASL) sequence, which is optimized for robust CBF quantification (Jung et al., 2010): tagging duration = 2 s, post-labeling delay = 1.6 s, TR = 4.2 s, TE = 3 ms, reps = 64, FOV = 22 × 22 cm, 20 5 mm axial slices with a single shot spiral acquisition, collecting 8 cycles where each cycle consists of 8 images acquired with unique phase offsets, acquisition time = 4:46 min. A CSF calibration scan was also obtained using a spiral readout with TR = 4 s and TE = 3.4 ms and comprised nine 90° excitation pulses which were turned off for the first eight repetitions to generate

PD-weighted contrast (scan time: 36 s) to obtain an estimate of the equilibrium magnetization of cerebral spinal fluid, which is used to convert the perfusion signal into calibrated CBF units (mL blood/100 g tissue/min). Finally, a minimum contrast image was acquired to adjust for transmit and receive coil inhomogeneities. Two field map scans were also acquired and used for off-line field map correction to help correct for signal bunching and dropouts in the frontal/medial temporal lobes.

2.6. MRI pre-processing

2.6.1. CBF

ASL image processing was performed with Analysis of Functional NeuroImages (AFNI, afni.nimh.nih.gov)(Cox, 1996), FMRIB Software Library (FSL, Oxford, United Kingdom), and locally created Matlab scripts. Field map correction was applied to the ASL time series prior to co-registration to the middle time point to minimize the effects of participant motion. For each participant, a mean ASL difference image was formed from the average difference of the control and tag images and slice timing delays were accounted for in order to make the post-labeling delay time slice specific (T. T. Liu and Wong, 2005). This mean ASL image was then converted to absolute units of CBF (mL/100 g tissue/-min) using an estimate of the equilibrium magnetization of CSF as a reference signal (Chalela et al., 2000). This procedure resulted in a calibrated perfusion value for each voxel. Skull stripping of the high-resolution T1-weighted image was performed using AFNI's 3dSkullStrip. Tissue segmentation was performed using FSL's Automated Segmentation Tool (FAST) algorithm (http://fsl.fmrib.ox.ac.uk/fsl/) to define cerebrospinal fluid (CSF), gray matter (GM) and white matter (WM) regions. The high-resolution T1-weighted image and partial volume segmentations were registered to ASL space, and the CBF data were resampled to the same resolution as the T1-weighted image. The partial volume estimates were used to perform partial volume correction of the high-resolution CBF data using a linear regression approach with kernel size of 3 (Asllani et al., 2008; Zhao et al., 2017) as implemented by the ASL_file function in the BASIL toolset of FSL (Chappell et al., 2009). The partial volume corrected gray matter CBF data were then resampled back to their native resolution and registered to FreeSurfer space. CBF values were extracted from each anatomically defined FreeSurfer ROI (see below for FreeSurfer methods). Quality assurance of ASL data was performed prior to analysis using outlier detection, inspection of CBF histograms, and visual checks of the CBF maps, with removal of values for regions with poor CBF map coverage. This resulted in removal of 4% of the data.

2.6.2. CT and Vo

Cortical thickness and volume analysis were performed using Free-Surfer version 5.3 (http://surfer.nmr.mgh.harvard.edu), with the technical details of these procedures described in prior publications (Dale et al., 1999; Dale and Sereno, 1993; B. Fischl and Dale, 2000; B. Fischl, Liu and Dale, 2001; B. Fischl, Sereno, Tootell and Dale, 1999; Bruce Fischl et al., 2002; Bruce Fischl, Salat, et al., 2004; Bruce Fischl, van der Kouwe, et al., 2004; Reuter et al., 2010; Reuter et al., 2012). Of note, FreeSurfer derives measures of cortical thickness for cortical/surface regions, whereas volume is derived for subcortical regions. As such, cortical thickness was extracted from the left and right EC, cACC, and rMFC and volume was extracted from the left and right Hc. A quality assurance protocol was performed before analysis using the ENIGMA guidelines (http://enigma.usc.edu/protocols/imaging-protocols) and included visual checks of the cortical segmentations and region-by-region removal of values for segmentations found to be incorrect. Histograms of all regions' values were also computed for visual inspection. This resulted in removal of 1% of the data.

2.7. Statistical analyses

t-tests were used to compare groups on age, years of education,

continuous vascular risk factors, brain variables (CBF, CT/Vo), and cognitive variables. χ^2-tests were used to compare groups on sex and categorical vascular risk factors. CBF and CT/Vo were extracted from FreeSurfer-derived regions of interest (i.e., CT of the EC, cACC, and rMFC; Vo of the Hc) and multiple linear regression models were employed in R with the memory composite score as the dependent variable and APOE genotype and brain variables (CBF, CT/Vo) as independent variables. To test our a priori hypotheses, we explored the following 3-way interactions: 1) APOE genotype x EC CBF x EC CT, and 2) APOE genotype x Hc CBF x Hc Vo. A Bonferroni correction was applied to correct for multiple comparisons, and correlations were only considered significant at $p<0.0125$. Exploratory analyses also examined these same 3-way interactions in frontal regions: 1) APOE genotype x cACC CBF x cACC CT, and 2) APOE genotype x rMFC CBF x rMFC CT. Simples slopes analysis was utilized to determine the magnitude and direction of relationships at arbitrary values ($+/- 1SD$), whereas the Johnson-Neyman regions of significance method was applied to determine the magnitude and direction of relationships across a full range of values. Post hoc analyses explored two-way interaction models in regions that did *not* show a significant three-way interaction. Correlations between CBF and CT by region of interest (e.g., right EC CBF and right EC CT) were also examined post hoc. To assess model fit, post hoc analyses compared complex models including three-way interactions to simpler models including only two-way interactions.

All analyses statistically adjusted for the effects of age, sex, and education. Due to observed group differences, all analyses also adjusted for blood pressure (systolic blood pressure), and executive functioning performance (DKEFS color-word interference). Although groups did not differ on other measures of vascular risk (i.e., antihypertensive medication, diabetes, cigarette smoking status, history of cardiovascular disease, atrial fibrillation, and left ventricular hypertrophy), we ran additional models that included these variables given their potential impacts on brain structure and CBF. When added to the models, none of these additional variables predicted significant variance nor did any model including these variables demonstrate better fit than simpler models that did not include these variables (all $p > 0.05$). Moreover, all results remained the same whether these variables were included in the models or not. Thus, aiming at parsimony, we present results from simpler models that did not include these additional variables. Analyses including measures of Hc Vo adjusted for the effects of total intracranial volume.

Non-multicollinearity between all independent variables was confirmed by application of the multicollinearity index VIF (all VIF<2), linearity was confirmed by residuals versus fits plots, normality was confirmed by Q-Q plots, non-heteroskedasticity was confirmed by scale location plots, and no influential cases were identified through examinations of residuals versus leverage plots.

3. Results

3.1. Group differences in demographic and assessment variables

Groups (ε4+, ε4-) did not differ significantly on age, sex, or years of education, nor did they differ significantly in the time interval between neuropsychological testing and neuroimaging (all *ps* > 0.05; see Table 1). With regard to cardiovascular health, groups did not differ significantly on stroke risk percent based on the FSRP, nor did they differ on any of the variables that comprise this measure (i.e., history of smoking, cardiovascular disease, diabetes, stroke, atrial fibrillation, left ventricular hypertrophy, antihypertensive therapy), aside from significant differences in systolic and diastolic blood pressure ($t = 2.20$, $p = 0.029$; $t = 2.97$, $p = 0.004$; respectively; see Table 1). With regard to cognition, APOE ε4 carriers demonstrated worse performance on the memory composite than did non-carriers ($t = 2.53$, $p = 0.013$). They also performed worse on four of the five subtests that were used to create the memory composite (i.e., CVLT-II trials 1–5, long delay free recall; WMS Logical Memory

Immediate and Delayed Recall; see Table 1). With regard to tests in other cognitive domains, ε4 carriers performed worse on two subtests of the DKEFS Color Word Interference test (i.e., DKEFS Color Word Interference Inhibition and Inhibition Switching; all $ps < 0.01$; see Table 1), measuring cognitive flexibility and inhibitory control. No other group differences in cognitive performance were found (all $ps > 0.05$). With regard to measures of brain structure and function, APOE ε4 carriers exhibited lower left EC CBF than did non-carriers ($t = 2.01$, $p = 0.047$, see Table 1). No other significant group differences in resting CBF were found in brain regions of interest (i.e., Hc, cACC, rMFC; all $ps > .05$). APOE ε4 carriers demonstrated greater left cACC CT than did non-carriers ($t = 2.53$, $p = 0.012$; see Table 1). No other significant group differences in CT/Vo were found in brain regions of interest (i.e., EC, Hc, rMFC).

3.2. Three-way interaction of CBF, CT/Vo, and APOE, on memory performance

A priori analyses revealed a significant three-way interaction in the left EC, such that the interaction of left EC CBF and left EC CT on memory, differs by APOE genotype (see Table 2). Simples slopes revealed that the association between left EC CBF and memory was *positive* (for non-carriers with lower CT (-1SD) and *negative* for ε4 carriers with lower CT (-1SD, see Fig. 1). Johnson-Neyman intervals revealed that the relationship between entorhinal CBF and memory was *negative* (lower CBF was associated with better memory) in non-carriers with high EC CT (≥2.3SD), *positive* (higher CBF was associated with better memory) in non-carriers with low EC CT (≤−1.2SD), and *negative* (higher CBF was associated with worse memory) in ε4 carriers with low EC CT (≤-1.0SD see Fig. 1). Three-way interactions were not statistically significant in the right EC, left Hc, or right Hc (see Table 2); however, in the right EC and right Hc, there appeared to be slight trends toward the same three-way interaction (including directionality) found in the left EC (see Sup Fig. S1 and Fig. S2). Exploratory analysis of frontal regions (i.e., cACC, rMFC) revealed no statistically significant three-way interactions (see Table 3).

3.3. Post hoc analyses

Post hoc analyses of two-way interaction models in regions that did *not* show a significant three-way interaction revealed an interaction of APOE genotype and right Hc CBF on memory performance ($t = 2.365$, $p = 0.020$), such that increased CBF in the right Hc was associated with worse memory in ε4 carriers but not in non-carriers (see Fig. 2). A significant two-way interaction of APOE and right cACC CT on memory performance was found ($t = 2.192$, $p = 0.030$), such that increased CT in the right cACC was associated with worse memory in ε4 carriers but not in non-carriers (see Fig. 3). No other significant two-way interactions were found (all $p > 0.05$). Post hoc analyses of correlations between regional CBF and CT showed no significant or marginal correlations by group (ε4-, ε4+) or when collapsing across the whole sample (all $ps > 0.2$). Post hoc model comparison of three-way and two-way interaction models showed that in the left EC, a three-way interaction model best fit the data (*Adjusted* $R^2 = 0.2298$, $p = 0.0006$) and demonstrated significantly better fit than a two-way interaction model ($F = 11.14$, $p = 0.0012$). In the right Hc, a three-way interaction model best fit the data (*Adjusted* $R^2 = 0.1926$, $p = 0.0006$) and demonstrated marginally better fit ($F = 2.05$, $p = 0.1556$) than a two-way interaction model (*Adjusted* $R^2 = 0.1833$, $p = 0.001$). Two-way interaction models best fit the data in the right EC (*Adjusted* $R^2 = 0.1342$, $p = 0.0145$) and the left Hc (*Adjusted* $R^2 = 0.1279$, $p = 0.0155$).

4. Discussion

Results showed that APOE genotype modified the interaction of MTL CBF and CT on cognitive performance among a sample of cognitively

Table 2

CBF, CT/Vo, APOE, and Memory. Note: Only variables of interest are included in table; All continuous independent variables were standardized; APOE= Apolipoprotein E gene; CBF= cerebral blood flow; CT= cortical thickness; Vo= volume; EC= entorhinal cortex; Hc= hippocampus; β= standardized regression coefficient; CI= confidence interval; bs= bootstrapped with 5000 replications; t= t-statistic. The 95% confidence interval of the coefficient was derived using the bootstrap bias-adjusted and accelerated bootstrap interval; +denotes significant at p<0.10; *denotes significance at p<0.05; **denotes significance at p<0.01

Independent Variable	β	95% CI (bs)	s.e. (bs)	t	p-value
APOE	−0.375	(-0.749, −0.019)	0.167	2.176	0.032*
Left EC CT	0.092	(-0.093, 0.280)	0.184	0.935	0.352
Left EC CBF	0.029	(-0.183, 0.197)	0.092	0.282	0.778
APOE*Left EC CT	−0.228	(-0.566, 0.084)	0.165	1.345	0.182
APOE*Left EC CBF	−0.115	(-0.482, 0.176)	0.156	0.705	0.482
Left EC CT*Left EC CBF	−0.241	(-0.423, −0.050)	0.092	2.302	0.023*
APOE*Left EC CT*Left EC CBF	0.488	(0.220, 0.761)	0.148	3.338	0.001**
APOE	−0.416	(-0.793, −0.064)	0.182	2.426	0.017*
Right EC CT	−0.039	(-0.219, 0.149)	0.092	0.409	0.683
Right EC CBF	0.038	(-0.166, 0.277)	0.114	0.357	0.722
APOE*Right EC CT	0.085	(-0.303, 0.467)	0.195	0.454	0.650
APOE*Right EC CBF	−0.266	(-0.590, 0.064)	0.168	1.557	0.123
Right EC CT*Right EC CBF	−0.117	(-0.346, 0.145)	0.124	0.970	0.334
APOE*Right EC CT*Right EC CBF	0.169	(-0.270, 0.526)	0.206	1.050	0.296
APOE	−0.303	(-0.645, 0.062)	0.178	1.821	0.071+
Left Hc Vo	−0.007	(-0.196, 0.171)	0.094	0.071	0.943
Left Hc CBF	0.024	(-0.172, 0.200)	0.094	0.260	0.795
APOE*Left Hc Vo	0.011	(-0.330, 0.371)	0.178	0.070	0.943
APOE*Left Hc CBF	−0.231	(-0.711, 0.158)	0.218	1.280	0.203
Left Hc Vo*Left Hc CBF	0.037	(-0.151, 0.214)	0.092	0.384	0.702
APOE*Left Hc Vo*Left Hc CBF	0.076	(-0.354, 0.552)	0.228	0.405	0.686
APOE	−0.290	(-0.786, 0.002)	0.182	1.717	0.089+
Right Hc Vo	−0.088	(-0.097, 0.268)	0.102	0.904	0.368
Right Hc CBF	0.079	(-0.101, 0.263)	0.092	0.864	0.390
APOE*Right Hc Vo	0.049	(-0.307, 0.415)	0.180	0.270	0.787
APOE*Right Hc CBF	−0.343	(-0.797, 0.032)	0.205	1.844	0.068+
Right HC Vo*Right Hc CBF	−0.152	(-0.369, 0.018)	0.096	1.784	0.077+
APOE*Right Hc Vo*Right Hc CBF	0.220	(-0.154, 0.669)	0.214	1.432	0.155

normal older adults. More specifically, relationships between left EC CBF and memory were negative in ε4 carriers with lower CT, positive in non-carriers with lower CT, and negative in non-carriers with higher CT. Moreover, the magnitude of the relationship between CBF and memory was increased in the context of high and low, versus intermediate, values
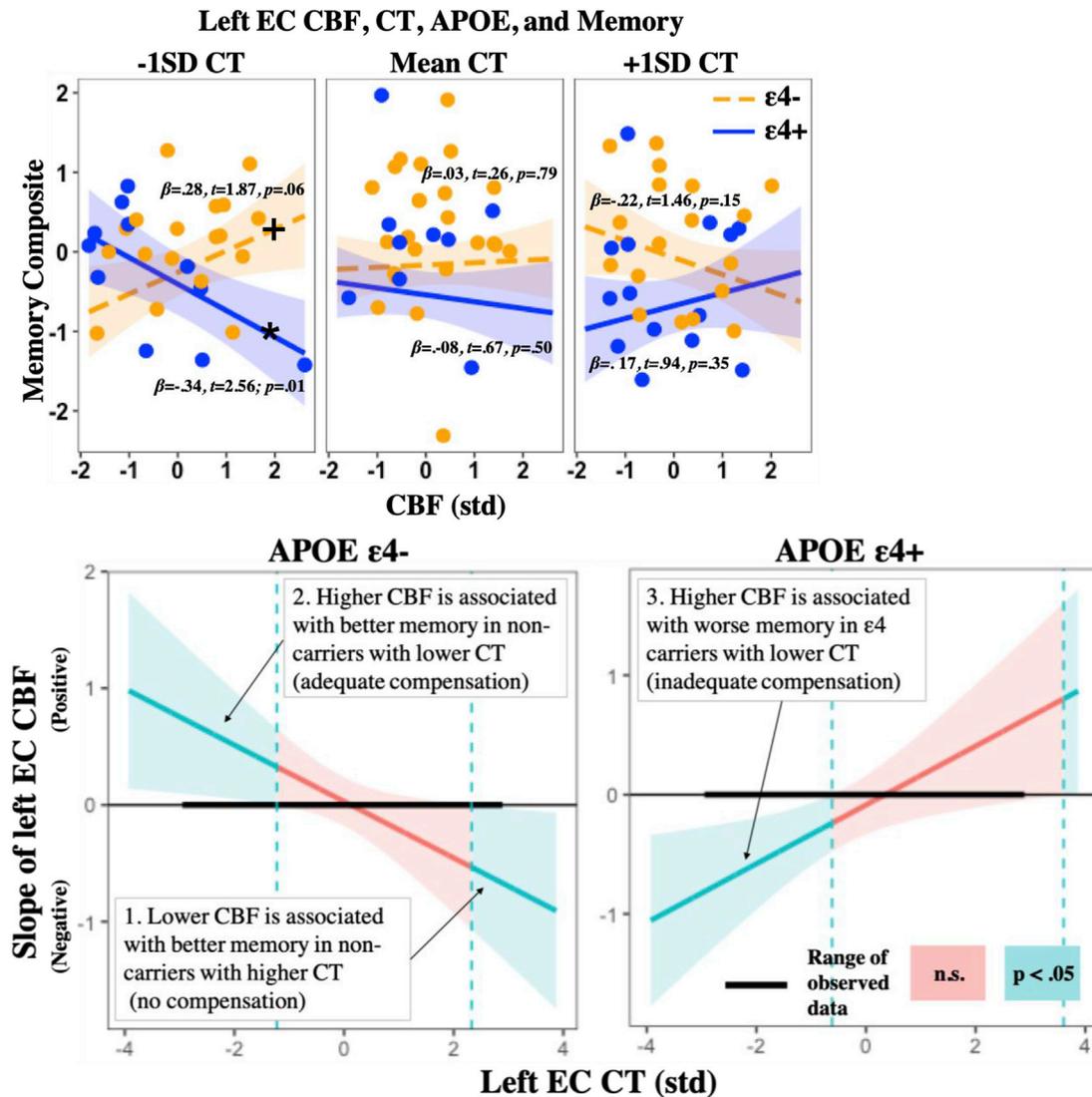
Fig. 1. Left EC CBF, CT, APOE, and memory. *Note: EC= entorhinal cortex; APOE= Apolipoprotein E gene; CBF= cerebral blood flow; CT= cortical thickness; std= Z-score standardization; SD= standard deviation; t= t-statistic; p= p-value; n.s.= not significant; +denotes significance at p<0.10; *denotes simple slope significance at p<0.05.*
Three-way interaction plot (top) with simple slopes (mean ±1SD) showing that the relationship between CBF and memory performance differs by APOE status and CT, such that the combination of higher left EC CBF and lower EC CT (-1SD) is associated with *better* memory performance for non-carriers and with *worse* memory performance for ε4 carriers.
Johnson-Neyman plot (bottom) showing that the direction and magnitude of the relationship between left EC CBF and memory performance differs across different values of CT (x-axis) and by APOE status. Intervals of left EC CT for which the relationship between CBF and memory is statistically significant are depicted in blue and non-significant intervals are depicted in red. Positive relationships between CBF and memory are depicted above the horizontal midline with greater positive values on the y-axis corresponding to increasing magnitude of the relationship in standard deviation units, whereas negative relationships are depicted below the horizontal line with greater negative values on the y-axis corresponding to increasing magnitude of the relationship. The thick aspect of the horizonal midline represents the range of observed data, whereas the thinner aspect represents the range of data that has been extrapolated beyond the observed data. Curved lines represent 95% confidence bands. **1.** There is a *negative* relationship between EC CBF and memory in non-carriers with higher EC CT (≥2.3SD) that increases in magnitude as CT increases, perhaps reflecting neural efficiency and no current need for compensation; **2.** There is a *positive* relationship between EC CBF and memory in non-carriers with lower EC CT (≤1.2SD) that increases in magnitude as CT decreases, perhaps reflecting compensatory increases in CBF that are supportive of memory function; **3.** There is a *negative* relationship between CBF and memory in ε4 carriers with lower EC CT (≤−0.62SD) that increases in magnitude as CT decreases, perhaps reflecting maximally invoked compensatory increases in CBF that are not fully supportive of memory function. Relationships between CBF and memory were non-significant in non-carriers with intermediate levels of EC CT and in ε4 carriers with intermediate or higher EC CT.
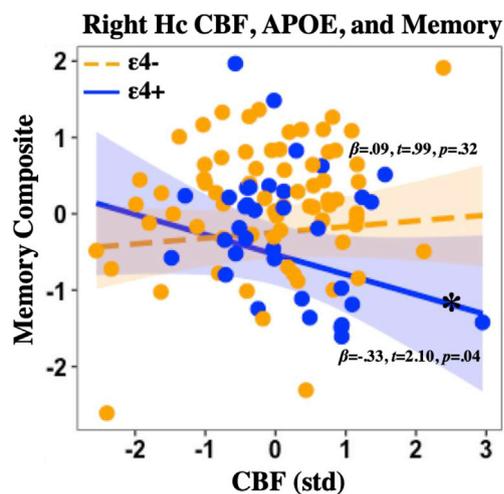
of CT. Although not statistically significant, there were slight trends toward this same three-way interaction in the right EC and the right Hc. Moreover, post hoc analyses demonstrated a modifying role of APOE genotype on the independent effects of both CBF and CT on memory, such that higher CBF in the right Hc predicted worse verbal memory performance in ε4 carriers, but not in non-carriers and higher CT in the right cACC predicted worse verbal memory performance in ε4 carriers, but not in non-carriers. APOE ε4 carriers also exhibited worse verbal memory performance, worse executive functioning performance, lower

left EC CBF, and higher right cACC CT. These findings are consistent with other APOE-related aging studies, supporting the notion that regionally specific perfusion and brain structure differences exist between ε4 carriers and non-carriers in areas that have been implicated in normal aging and AD-risk and that these differences are associated with worse cognitive function (Bangen et al., 2012; Dai et al., 2009; Hays et al., 2016; Meltzer et al., 2000; Wierenga et al., 2012; Zlatar et al., 2016). However, this is the first study, to our knowledge, to show that APOE genotype modifies the interactive relationship between MTL CBF and CT on

Table 3

cACC CBF, CT, APOE, and memory. Note: Only variables of interest are included in table; All continuous independent variables were standardized; cACC= caudal anterior cingulate cortex; APOE= Apolipoprotein E gene; CBF= cerebral blood flow; CT= cortical thickness; L= left; R= right; β= standardized regression coefficient; CI= confidence interval; bs= bootstrapped with 5000 replications; t= t-statistic. The 95% confidence interval of the coefficient was derived using the bootstrap bias-adjusted and accelerated bootstrap interval; +denotes significant at p<0.10; *denotes significance at p<0.05.

Independent Variable	β	95% CI (bs)	s.e. (bs)	t	p-value
APOE	0.371	(-0.762, 0.016)	0.201	2.136	0.035*
R cACC CT	−0.236	(-0.168, 0.393)	0.141	2.039	0.044*
R cACC CBF	−0.088	(-0.211, 0.292)	0.126	0.461	0.646
APOE* R cACC CT	0.369	(-0.739, −0.019)	0.184	3.655	0.031*
APOE* R cACC CBF	0.118	(-0.558, 0.299)	0.220	2.312	0.586
R cACC CT* R cACC CBF	−0.062	(-0.560, 0.103)	0.166	1.443	0.599
APOE* R cACC CT* R cACC CBF	0.041	(-0.468, 0.338)	0.207	2.178	0.804
APOE	−0.305	(-0.786, 0.002)	0.193	1.745	0.084+
L cACC CT	−0.089	(-0.294, 0.101)	0.098	0.884	0.378
L cACC CBF	−0.003	(-0.235, 0.218)	0.114	0.032	0.974
APOE* L cACC CT	−0.017	(-0.330, 0.345)	0.175	0.110	0.912
APOE* L cACC CBF	−0.149	(-0.668, 0.230)	0.220	0.713	0.477
L cACC CT* L cACC CBF	−0.112	(-0.322, 0.086)	0.104	1.153	0.251
APOE* L cACC CT* L cACC CBF	0.130	(-0.288, 0.612)	0.237	0.647	0.519

Fig. 3. Right cACC CT, APOE, and memory. *Note: cACC= caudal anterior cingulate cortex; APOE= Apolipoprotein E gene; CBF= cerebral blood flow; CT= cortical thickness; std= Z-score standardization; p= p-value; R= right;*Denotes simple slope significance at p < 0.05.*
Two-way interaction plot showing a significant interaction of right cACC CT and APOE on memory performance, such that higher CT in the right cACC is associated with *worse* memory performance in ε4 carriers but not in non-carriers.
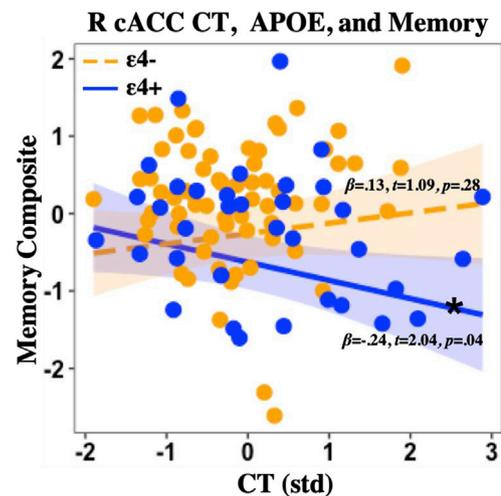

Fig. 2. Right Hc CBF, APOE, and memory. *Note: Hc= hippocampus; APOE= Apolipoprotein E gene; CBF= cerebral blood flow; std= Z-score standardization; p= p-value; *denotes simple slope significance at p < 0.05.*
Two-way interaction plot showing a significant interaction of APOE and right Hc CBF on memory, such that higher CBF in the right Hc is associated with *worse* memory performance in ε4 carriers but not in non-carriers.

cognitive function, providing a more complete accounting of the relationships among these variables.

The complex three-way interaction of left EC CBF, CT, and APOE on verbal memory performance may be appreciated in the context of regional compensatory brain activity, reflecting efforts to maintain adequate brain oxygenation in the face of vascular aging and/or neuropathological damage. For example, the observed negative relationship between EC CBF and cognition (*lower* CBF being associated with better memory) in non-carriers with higher CT may reflect neural efficiency, such that non-carriers with higher cortical reserve have no need to invoke compensatory increases in CBF. In contrast, the observed positive relationship between EC CBF and cognition (*higher* CBF being associated with better memory) in non-carriers with lower CT may reflect successful cerebrovascular compensation, such that non-carriers with lower cortical reserve are invoking compensatory increases in CBF that are adequately supporting current memory function. In this same context, the observed negative relationship between EC CBF and cognition (higher CBF being associated with *worse* memory) in ε4 carriers with lower CT may reflect a relative breakdown of cerebrovascular compensation, such that compensatory increases in CBF among ε4 carriers with lower cortical reserve are maximally invoked and not fully supportive of current memory function (see the Johnson-Neyman plot in Fig. 1 for a visual depiction), though future research is needed to determine if they adequately support memory function over *time* (e.g., memory stability). Overall, these findings are largely consistent with the Capillary Dysfunction Hypothesis of Alzheimer's disease, which posits that ε4 carriers experience increased heterogeneity of capillary blood flow, which reduces the amount of oxygen that can diffuse into tissue. This reduction in oxygen diffusion necessitates a compensatory increase in CBF to maintain adequate brain oxygenation (Østergaard et al., 2013). However, progressive increases in this heterogeneity of flow is thought to result in low tissue oxygen tension, a state which paradoxically benefits (due to increased blood-tissue oxygen concentration gradients) from *suppression* of CBF (Jespersen and Østergaard, 2012; Østergaard et al., 2013). Although essential for the maintenance of oxygen availability, this compensatory reduction in cerebral perfusion may ultimately lead to oxidative stress, activation of inflammatory pathways, and increased amyloid levels in the brain (Ostergaard et al., 2013). Taken together, this suggests that cognitively normal ε4 carriers with higher EC CBF and lower EC CT may be at elevated risk for cognitive decline due to inadequate/maximally invoked cerebrovascular compensatory mechanisms. It is also possible, that ε4 carriers with lower cortical reserve who do *not* demonstrate compensatory increases in CBF could be at even greater risk for cognitive decline, though future longitudinal research is needed to test this hypothesis. Moreover, non-carriers showing this same

compensatory pattern (higher CBF and lower CT) may also be at elevated risk for cognitive decline, as this may signal some degree of vascular aging and/or neuropathological damage. Interestingly, the results of the current study may help explain mixed findings in the literature with regard to relationships between MTL CBF and cognition (findings of both positive and negative associations), as the direction and magnitude of this relationship appears to vary as a function of both CT and APOE genotype. As such, future studies exploring the relationship between CBF and cognition among older adults should consider accounting for these additional variables.

More broadly, observation of an interaction between CBF, CT, APOE, and memory performance in the MTL among cognitively normal adults supports the hypothesis that the APOE ε4 isoform confers risk for cognitive decline through altered MTL perfusion, and that concomitant altered cortical morphology in the same region may further exacerbate the detrimental effects of CBF alteration on cognition. The concept of APOE-related alterations in MTL CBF (rather than MTL CT) being more tightly linked to cognitive function is further supported by our observation of an independent association between CBF and cognitive performance in ε4 carriers in MTL regions (i.e., right hippocampus), but no independent association between CT and cognition in MTL regions. Moreover, the localization of the interaction between APOE, CBF and CT on verbal memory in the left entorhinal cortex suggests the presence of AD-related neuropathological processes, rather than an exacerbation or speeding up of normal aging processes, as the EC is one of the first regions to be affected by AD pathology (Braak and Braak, 1991), but is relatively spared in normal aging (Fjell et al., 2009; Good et al., 2001; Raz et al., 2005; Raz et al., 2007). It is also important to note that the three-way interaction of APOE, CBF, and CT on memory in the entorhinal cortex was observed in the context of uncorrelated regional CBF and CT (e.g., no correlation between left EC CBF and left EC CT). The notion that alterations in regional CBF may be independent from alteration in brain structure is supported by previous literature (Chen et al., 2011) and taken together with the current results, suggests that although perhaps dissociable (e.g., not occurring concurrently; reflecting different underlying pathological processes), these brain indicators demonstrate associations in the MTL when accounting for APOE genotype and cognitive performance. While the current study did not test laterality directly, it may be important to note that we found a statistically significant three-way interaction of CBF, CT, APOE, and memory in the left, but not the right, EC. Although our observation of a slight non-significant trend toward this same interaction in the right EC suggests that statistical power may have played a role, prior studies have also shown that ε4 carriers demonstrate lower left than right EC CT (Donix et al., 2013), suggesting that the left EC may be more vulnerable to APOE-related neuropathological damage compared to the right EC. Similarly, our finding of a significant two-way interaction of CBF and APOE on memory in the right, but not the left, Hc could reflect low power or could suggest that APOE-related neurovascular alteration in MTL regions may be less left-localized than structural alteration.

Exploratory analyses of prefrontal regions and memory function revealed a rather unexpected finding: *higher* right cACC CT among ε4 carriers compared to non-carriers was associated with worse verbal memory performance. Although counterintuitive, given that most studies report widespread cortical thinning in ε4 carriers, this finding may be better understood in the context of the normal aging cortical morphology literature. Against the backdrop of widespread age-related cortical thinning and volume reduction, there is accumulating evidence suggesting that there may be isolated areas of age-related cortical thickening in the prefrontal cortex, including the ACC (Abe et al., 2008; Fjell et al., 2009; Salat et al., 2004). As such, it is possible that the APOE ε4 isoform may lead to an exaggeration or speeding up of normal age-related morphological changes in the ACC. This concept is supported by recent studies showing that ε4 carriers do indeed exhibit higher CT and/or volume in prefrontal regions (including the ACC) compared to non-carriers (Dowell et al., 2016; Espeseth et al., 2008, 2012). The

current results are similar to those reported on an event related potential study of attention and cortical thickness by APOE status. This 2012 study found that higher prefrontal CT in APOE ε4 carriers was associated with worse selective attention. Our results extend these prior findings to other cognitive domains, showing that higher CT in prefrontal regions (i.e., cACC) in ε4 carriers, compared to non-carriers is also associated with worse verbal memory performance. The observed negative association between CT and cognition lends support to the concept of higher relative thickness of the prefrontal cortex as part of a dysfunctional process associated with the ε4 allele, perhaps due to impaired repair mechanisms (Sundstrom et al., 2004; Teter et al., 2002).

Limitations of the current study include the use of a cross-sectional design, which restricted our ability to draw causal conclusions and limited our ability to determine whether associations among APOE, CBF, and CT, and cognition represent normal aging or pathologic processes. It is also important to note that our sample had relatively high levels of education, and although this demographic factor was not associated with APOE genotype, its limited range may reduce the generalizability of these findings. Although groups (ε4+/ε4-) did not differ significantly in the average time interval between cognitive testing and fMRI scanning (53 and 51 days, respectively), decreasing the time interval between cognitive testing and MRI may improve accuracy of brain-behavior associations. Moreover, our sample of 117 only included 41 APOE ε4 carriers, which may have limited our ability to detect statistically significant three-way interactions in other regions. It may also be important to note that the confidence bands for the intervals of significance in the Johnson-Neyman plot approached (but did not include) zero, particularly with respect to non-carriers. Future investigations should include longitudinal designs with larger, more diverse samples to replicate and extend the current findings. Furthermore, the inclusion of additional markers of AD, such as CSF biomarkers may help better characterize APOE ε4 carriers.

The strengths of the current study include the use of non-invasive ASL MRI to measure partial volume corrected CBF, and the use of a high-resolution structural MRI scan to examine CT and Vo. Furthermore, use of FreeSurfer offers advantages over traditional voxel-based morphometry methods, as it also allows for examination of the components of volume separately (thickness and surface area), as it has been found that these two do not necessarily track with one another. Moreover, the extraction of CBF from FreeSurfer-derived brain regions represents a strength, allowing us to directly investigate CBF (and brain structure) in regions that are defined by each individual's anatomy, rather than atlas-defined regions which are less sensitive to individual anatomical differences because they require that data are first aligned and warped to a generic anatomic template. Lastly, the current study benefited from the inclusion of a well-controlled and well-characterized sample of cognitive normal older adults, which included the use of several cognitive test performances to characterize cognitive status.

5. Conclusions

In conclusion, our findings support the notion that APOE ε4 carriers may be experiencing vascular dysregulation and concomitant morphological alterations in the MTL that interact to negatively affect cognition prior to the onset of overt clinical symptoms, providing potential insight into the mechanistic link between APOE ε4 and detriments in cognition. Although future longitudinal research is needed to determine whether these relationships also predict future cognitive decline, the current observed pattern of *higher* CBF and *lower* CT in the EC predicting worse memory performance suggests a novel multimodal neural signature with the potential to detect ε4 carriers who are at elevated risk for cognitive impairment. Such early detection could inform candidate selection and study design for future clinical trials. On a broader scale, the current results add to accumulating evidence supporting the early role of vascular dysregulation in AD risk and could lead to the identification of vasoprotective treatments with the potential to delay or prevent the onset of age-related cognitive decline and/or AD.

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Appendix A. Supplementary data

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