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RESEARCH ARTICLE

Regulating effect of CBF on memory in cognitively normal older adults with different ApoE genotype: the Alzheimer's Disease Neuroimaging Initiative (ADNI)

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Abstract
Apolipoprotein E (ApoE) ε4 allele and cerebral blood flow (CBF) changes are related to the increased risk of cognitive impairment independently. However, whether there are interactions between ApoE ε4 and CBF on memory performance in older adults with normal cognition remains unknown. This study determined whether the association between CBF and memory performance could be moderated by ApoE ε4 within a sample of cognitively normal older adults from the ADNI. 62 participants, including 23 with ApoE ε4 (ApoE ε4+) and 39 without ApoE ε4 (ApoE ε4−), underwent resting CBF measurement and memory testing. CBF was measured by arterial spin labeling MRI and memory performance was evaluated by the Rey Auditory Verbal Learning Test. By using linear regression models, CBF was negatively associated with memory function in ApoE ε4+ group, whereas positively in ApoE ε4− group by contrast. This study suggests that different CBF-memory relationships can be detected in cognitively normal ApoE ε4 carriers compared to ApoE ε4 non-carriers. Associations between hyperperfusion and worse memory performance in ApoE ε4 carriers may reflect vascular and/or cellular dysfunction.

Keywords Arterial spin labeling (ASL) · Cerebral blood flow (CBF) · ApoE ε4 · Memory function

Introduction

Cerebral blood flow (CBF) refers to the rate at which arterial blood delivers to the tissue capillary bed. It is a measure of neural function and brain metabolism. The precise measurement of CBF can be obtained by ASL, a novel MRI technique. CBF reduction (hypoperfusion) is related to cognitive impairment, indicating that cerebrovascular mechanisms are of great importance in the maintenance of cognitive performance (Knopman and Roberts 2010; Montagne et al. 2015b; Wierenga et al. 2014).

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The conclusions of previous studies determining the correlation between cognitive performance and CBF in cognitively normal older adults were inconsistent. Some reported positive correlation using arterial flow measurements of carotid and basilar (Rabbitt et al. 2006), while some showed negative association using ASL MRI (Bertsch et al. 2009). For instance, Heo et al. (2010) found that CBF of hippocampal was positively correlated with spatial memory function by using flow-enhanced signal intensity MRI. By contrast, another study by Steffener et al. (2013) found that memory performance was negatively associated with CBF in the posterior central gyrus, part of the temporal cortex and hippocampus, but positively associated with CBF in the orbital frontal lobe. Those results showed that associations between CBF and cognitive function may have clinical significance for the prevention of AD.

Whether the associations between CBF and cognitive function could be regulated by AD risks is still understudied. It is well established that cerebrovascular

dysfunction is related to mild cognitive impairment (MCI) and AD (Kelleher and Soiza 2013). ApoE ε4 is crucial to the integrity of cerebral vascular structure (Bell et al. 2012; Zlokovic 2011). The risk for AD is two to three folds higher in individuals carrying one ApoE ε4 allele (Corder et al. 1993) and 12-folds higher in those carrying two ApoE ε4 alleles (Corder et al. 1993; Roses 1996; Saunders et al. 1993). However, previous studies determining the association between ApoE ε4 and CBF showed mixed results. For example, compared to ApoE ε4− individuals, ApoE ε4+ individuals represented increased CBF in the medial temporal lobe, left lingual gyrus, precuneus and the right insular gyrus according to positron emission tomography (PET) studies (Bangen et al. 2012; Thambisetty et al. 2010; Wierenga et al. 2013). On the contrast, an ASL study showed that decreased regions of CBF in ApoE ε4+ group compared to ApoE ε4− group include right caudate, left middle temporal gyrus, right inferior parietal lobe, and right insula (Kim et al. 2013). Those studies seemed in contradiction with each other, which may be due to the different measurement methods of CBF (i.e., PET versus ASL MRI), but they all revealed the correlation between ApoE ε4 and CBF. However, those studies mainly concentrated on individuals with MCI or AD, and research on whether ApoE ε4 could modulate the association between CBF and memory function in cognitively normal older adults has been scanty.

This study investigated whether there was an association between regional ASL CBF and memory performance, and whether this association was modulated by ApoE ε4 in cognitively normal older adults.

Materials and methods

Participants

Data used in this study came from the ADNI database (adni.loni.usc.edu). The ADNI was launched by Principal Investigator Michael W. Weiner, MD in 2003. The primary goal of ADNI is to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessments can be combined to measure the progression of MCI and early AD. Following the establishment of the ADNI, ADNI-GO, ADNI-2 and ADNI-3 have been launched one after another. Participants included in this manuscript were cognitively normal older adults from the ADNI-2.

Inclusion criteria

1. Age between 55 and 90 years old;
2. Years of education > 6;
3. Mini-mental state examination (MMSE) score ≥ 24;
4. Clinical Dementia Rating (CDR) score = 0;
5. Participants who have completed RAVLT.

Exclusion criteria

1. A history of cerebral infarction or brain injury;
2. Existence of other neurological diseases that may cause cognitive impairment such as severe depression, brain tumor, Parkinson's Disease, brain trauma and normal pressure hydrocephalus, etc.;
3. Existence of other systemic diseases that may lead to cognitive impairment, such as impairments of liver or kidney function, thyroid dysfunction, folate and/or vitamin B12 deficiency, specific infections (e.g. syphilis and HIV), etc.;
4. Consumption of drugs that may affect cognitive function, including sedatives, anxiolytics, nootropics or cholinergic drugs;
5. Systemic disease with significant symptoms, such as heart failure, tumor, drug dependence, drug addiction, etc.;

A total of 70 participants were selected in accordance with the above criteria, of whom 25 carried with ApoE ε4 and 45 without ApoE ε4. We further excluded participants who were diagnosed as cognitively normal but met criteria for MCI, with scores of neuropsychological measures one standard deviation lower than normative expectations within a cognitive domain (Bondi et al. 2014; Edmonds et al. 2015; Jak et al. 2009). A final sample of 62 participants were included.

Neuropsychological assessment

Memory function was evaluated by the RAVLT. The detailed procedures were as follows: first, the participants were required to learn 15 words (list A) for 5 times and recall freely (trials 1–5). Then, the participants were asked to learn 15 interfered words (list B) and recall list B freely, followed by recalling list A immediately (trial 6) and 30 min later (trial 7). We calculated total scores of the trials 1–5 as memory performance.

MRI data acquisition

MRI was conducted on a Siemens MAGNETOM Verio 3.0 Tesla scanner. Structural images and ASL images were downloaded. The structural MRI data were acquired utilizing a three-dimensional (3D) magnetization-prepared rapid acquisition with gradient echo (MPRAGE) T1-weighted sequence. Pulsed ASL (Wong et al. 1997) data were acquired by QUIPS II with thin-slice TI1 periodic

saturation sequence (Luh et al. 1999). The acquisition parameters of 3D_T1 were: repetition time (TR) = 2300 ms, echo time (TE) = 2.98 ms, inversion time (TI) = 900 ms, field of view (FOV) = 256 mm × 240 mm, slice number: 176 (sagittal) and flip angle (FA) = 9°. The acquisition parameters of pulsed ASL were: TR = 3400 ms, TE = 12 ms, TI1 = 700 ms, TI2 = 1900 ms, FOV = 256 mm × 256 mm, slice number: 24 (axial), thickness = 4 mm and image matrix = 64 × 64.

MRI data processing

ASL data processing was conducted by SPM8. To minimize the effect of head motion, ASL images were aligned to the intermediate time point. Perfusion weighted images were calculated from the difference between control and labeled images. ASL images were normalized to the Montreal Neurological Institute (MNI) space. Then, each participant's brain was spatial smoothed with a Gaussian kernel at full-width-at-half-maximum (FWHM) of 8 mm × 8 mm × 8 mm. Finally, to correct CBF in the gray matter, partial volume effect (PVE) correction was performed.

The following cerebral regions which are closely related to aging and AD were selected as regions of interest (ROI) in this study: medial temporal lobe (hippocampus, parahippocampal gyrus and uncus), parietal lobe (supramarginal gyrus, angular gyrus, precuneus and posterior cingulate), and frontal lobe (anterior cingulate gyrus, middle and medial frontal gyrus). Average CBF was extracted for each ROI.

Statistical analysis

In order to compare intergroup differences in demographic data and cognitive function scores, the continuous variables in this study were analyzed by the independent sample *t* test and categorical variables were analyzed by the Chi-squared test. A hierarchical linear regression model was employed to investigate whether there are interactions between ApoE genotype and CBF on memory function. CBF of ROIs, ApoE genotype and the interaction term were chosen as independent variables and memory performance was the dependent variable. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 19.

Results

There were no significant differences between the two groups with respect to age, sex, education and cognitive performers (Table 1). Significant interactions of CBF and ApoE genotype on memory performance were found in three ROIs by regression analyses. Spearman's correlation showed that memory scores were negatively associated with CBF of the medial temporal lobe ($r = -0.45$, $p = 0.03$), parietal lobe ($r = -0.56$, $p = 0.007$), and frontal lobe ($r = -0.51$, $p = 0.02$) in the ApoE ε4+ group. Contrarily, memory scores were positively associated with CBF of the medial temporal lobe ($r = 0.48$, $p = 0.002$), parietal lobe ($r = 0.37$, $p = 0.02$), and frontal lobe ($r = 0.38$, $p = 0.03$) in the ApoE ε4− group (Fig. 1).

Discussion

Our study explored whether there were interactions between regional CBF and ApoE genotype on memory function in older adults with normal cognition. In specific, results suggested that among ApoE ε4+ individuals, memory function was negatively associated with CBF of regions relating to AD and aging. Contrarily, among ApoE ε4− individuals, memory function was positively associated with CBF. The study indicated that for individuals who are without genetic risk of AD, hyperperfusion maintains memory performance, however, for individuals with the ApoE ε4, heightened CBF may not maintain memory performance any more.

Typically, decreased regional CBF are explained as representing decreases of cognitive function, while increased CBF in preclinical AD are often thought to reflect a compensatory strategy to pathologic process (Dai et al. 2009). Indeed, previous studies demonstrated that increased CBF was significantly correlated to better memory function in MCI with AD risk factors, and it was explained as a compensatory response since higher CBF can provide more oxygen and glucose to support neuronal activity (Fleisher et al. 2009; Bangen et al. 2012; Zlatar et al. 2014), as the case for the ApoE ε4− participants in this study. Contrarily, for cognitively normal older adults with ApoE ε4, heightened CBF may not support better cognitive function any more. Unlike previous studies that focused on MCI or AD patients, we chose cognitively normal older adults as participants and, crucially, there was no significant difference in cognitive function between the ApoE ε4+ and ApoE ε4− group. In ApoE ε4+ group, increased CBF may indicate that these participants' RAVLT performance is decreasing (although still normal), and more CBF are needed to maintain the decreasing memory function. It has been showed that early MCI was characterized by hyperperfusion and later MCI by hypoperfusion when transiting to dementia (Wierenga et al. 2014) and it is possible that ApoE ε4+ participants in our study are more vulnerable to develop MCI. To further determine

Table 1 Demographic statistics and cognitive characteristics of the participants

	ApoE ε4− (n = 39)		ApoE ε4+ (n = 23)		F/X^2	*p*
	Mean	SD	Mean	SD		
Age	71.08	6.87	73.27	5.94	F = 2.8	0.24
Sex (female/%)	30/76%	–	16/70%	–	X^2 = 0.7	0.62
Years of Education	15.87	2.32	16.02	2.14	F = 2.47	0.33
MMSE	27.3	1.3	26.7	1.5	F = 1.03	0.51
RAVLT trials 1–5 total	49.74	10.74	47.04	10.62	F = 3.12	0.47

ApoE ε4 apolipoprotein E ε4 allele, *RAVLT* Rey Auditory Verbal Learning Test, *MMSE* mini-mental state examination, *SD* standard deviation

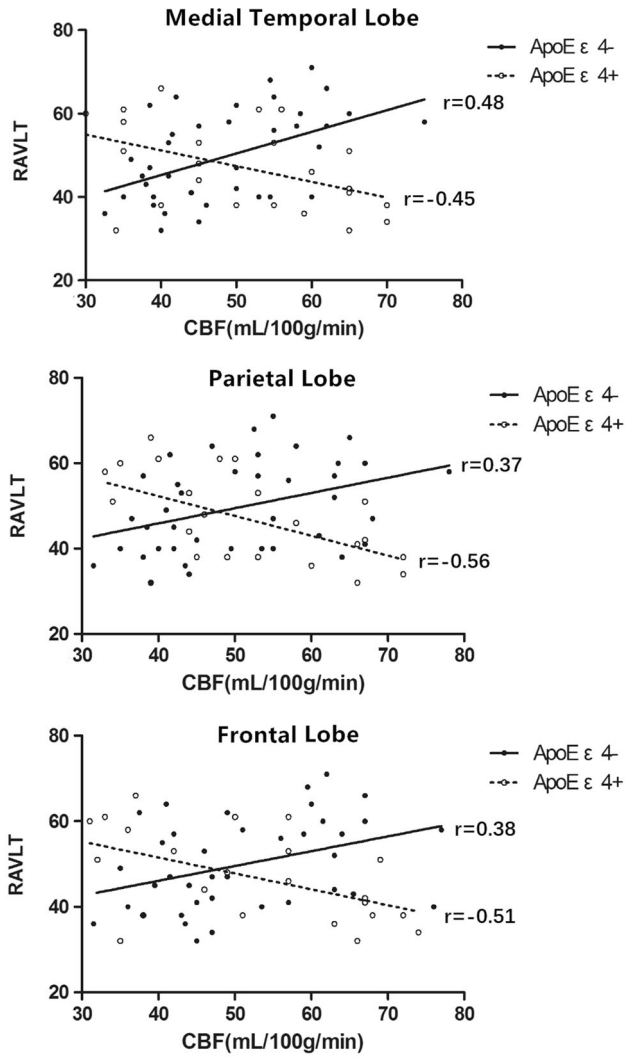

Fig. 1 Scatterplots of interaction of ApoE ε4 and CBF on memory performance (RAVLT trials 1–5 total) for 3 regions of interest. Medial temporal lobe includes: hippocampus, parahippocampal gyrus and uncus; parietal lobe includes: supramarginal gyrus, angular gyrus, precuneus and posterior cingulate; frontal lobe includes: anterior cingulate gyrus, middle and medial frontal gyrus. Solid line represents the ApoE ε4+ group, dotted line represents the ApoE ε4− group. *ApoE ε4* apolipoprotein E ε4 allele, *CBF* cerebral blood flow, *RAVLT* Rey Auditory Verbal Learning Test

the role of increased CBF, a longitudinal study is in need to explore CBF differences across the trajectory of AD.

Normal neuronal computation and information processing requires sophisticated regulation of the chemical composition of the neuronal environment maintained by the blood–brain barrier (BBB) (Iadecola 2004, 2013; Zlokovic 2008). BBB limits the entry of neurotoxic blood-derived products and macromolecules into the brain (Zlokovic 1995; Zlokovic et al. 1985, 1987). It also plays a critical role in removing neurotoxic products from brain such as amyloid β (Aβ). BBB is composed of endothelial cells, perivascular mural cells and pericytes, of which pericytes plays a key role in maintaining the integrity of BBB. ApoE4, the corresponding protein of ApoE ε4, is associated with neurovascular dysfunction in patients with neurological disorders (Kim et al. 2009; Verghese et al. 2011) (e.g. AD, traumatic brain injury and haemorrhage) as well as in individuals with normal cognition (Reiman et al. 2004; Thambisetty et al. 2010; Sheline et al. 2010). The mechanisms may be due to toxic effects of ApoE4 on cerebrovascular and/or neurons. First, ApoE4 can lead to pericyte loss via cyclophilin A (Bell et al. 2012), and reduction of pericytes can result in a long-term BBB leakage and microvascular changes contributing to neurodegenerative diseases (Armulik et al. 2010; Bell et al. 2010; Daneman et al. 2010). For instance, accelerated pericyte degeneration and BBB breakdown have been reported in ApoE ε4 carriers with AD (Halliday et al. 2016). Moreover, using contrast MRI, subtle BBB leakages can be detected during normal aging in the medial temporal lobe, which worsens with MCI (Montagne et al. 2015a). Second, it is well established that ApoE4 is associated with increase of Aβ in brain (Kim et al. 2009; Zlokovic 2013) and impairment of Aβ removal across the BBB (Bell et al. 2007; Castellano et al. 2011). Finally, ApoE4 has direct toxic effects on neurons which may be mediated by its role in tau phosphorylation, synaptic plasticity and neuroinflammation (Zlokovic 2013; Kim et al. 2009; Mahley et al. 2009). Therefore, for ApoE ε4+ individuals, although the CBF does increase during the preclinical phase of cognitive

function disorder, this increase can no longer help to maintain their memory function because of the various pathological neurovascular changes caused by ApoE4. Taken together, the discussion above may help to interpret why heightened CBF in ApoE ε4+ group was correlated with worse memory function compared to that in the APOE ε4− group.

An increasing number of studies have demonstrated that ASL CBF can be considered as a useful biomarker in individuals with AD risks as this technique can distinguish the vulnerable from normal participants (Fleisher et al. 2009; Bangen et al. 2012). Furthermore, ASL CBF can predict progression from the preclinical phase to AD sensitively (Beason-Held et al. 2013; Chao et al. 2010). Our present research underlined the vital correlation between CBF and memory performance. Moreover, it further demonstrated that ASL CBF is a reliable biomarker of genetic risk of AD (i.e. ApoE ε4) and is associated with memory function in cognitively normal older adults. Additionally, our research highlighted the potential value of detecting vascular factors in the pathogenesis of AD.

The strength of our study was that we included a well-matched sample of cognitively normal older adults who have completed ASL MRI and multiple cognitive assessments. Our research has several limitations. First, the sample size was small and the distribution of ApoE groups was unbalanced (62.9% ApoE ε4− versus 37.1% ApoE ε4+). Second, A longitudinal study should be conducted in the future to richen the research. It is possible that some of the ApoE ε4+ participants remain cognitively normal and, likewise, some of the ApoE ε4− participants may develop cognitive impairment over time. Despite these limitations, ASL CBF may prove to be a sensitive biomarker in terms of very early AD.

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Author contributions JYW designed the experiment, analyzed the data and drafted this manuscript. GPP, PL, XFT are responsible for revising this manuscript. BYL is responsible for designing this experiment, revising and finalizing this manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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