Received: 15 January 2021 | Revised: 3 June 2021 | Accepted: 21 July 2021

DOI: 10.1111/ejn.15399

RESEARCH REPORT

EJN European Journal of Neuroscience FENS WILEY

Asymmetric left–right hippocampal glutamatergic modulation of cognitive control in ApoE-isoform subjects is unrelated to neuroinflammation

Hui Zhang[1,2] | **Pui Wai Chiu**[1,3] | **Isaac Ip**[4] | **Tianyin Liu**[5] | **Gloria Hoi Yan Wong**[5] | **You-Qiang Song**[6] | **Savio Wai Ho Wong**[4] | **Karl Herrup**[7] | **Henry Ka Fung Mak**[1,2,3]

[1]Department of Diagnostic Radiology, The University of Hong Kong, Hong Kong

[2]Alzheimer's Disease Research Network, The University of Hong Kong, Hong Kong

[3]State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Hong Kong

[4]Department of Educational Psychology, Chinese University of Hong Kong, Hong Kong

[5]Department of Social Work and Administration, The University of Hong Kong, Hong Kong

[6]School of Biomedical Sciences, The University of Hong Kong, Hong Kong

[7]Alzheimer Disease Research Centre, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Correspondence
Henry Ka Fung Mak, Room 406, Block K, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong.
Email: makkf@hku.hk

Abstract

The glutamatergic cycle is essential in modulating memory processing by the hippocampal circuitry. Our combined proton magnetic resonance spectroscopy (^{1}H-MRS) and task-based functional magnetic resonance imaging (fMRI) study (using face-name paired-associates encoding and retrieval task) of a cognitively normal cohort of 67 healthy adults (18 ApoE4 carriers and 49 non-ApoE4 carriers) found altered patterns of relationships between glutamatergic-modulated synaptic signalling and neuronal activity or functional hyperaemia in the ApoE4 isoforms. Our study highlighted the asymmetric left–right hippocampal glutamatergic system in modulating neuronal activities in ApoE4 carriers versus non-carriers. Such brain differentiation might be developmental cognitive advantages or compensatory due to impaired synaptic integrity and plasticity in ApoE4 carriers. As there was no difference in myoinositol levels measured by MRS between the ApoE4 and non-ApoE4 subgroups, the mechanism is unlikely to be a response to neuroinflammation.

KEYWORDS
ApoE4, functional magnetic resonance imaging, glutamatergic system, magnetic resonance spectroscopy

Abbreviations: ACC, Accuracy rate; AD, Alzheimer's disease; APOE4, Apolipoprotein E ϵ4 allele; ASL MRI, Arterial spin labelling magnetic resonance imaging; BOLD, Blood-oxygenation-level-dependent; CA, Cornu ammonis; CBF, Cerebral blood flow; ^{11}C-PBR28, Peripheral-type benzodiazepine receptor; CSF, Cerebrospinal fluid; 3D-T1-FFE, 3D fast field echo; DARTEL, Diffeomorphic anatomical registration through Exponentiated lie algebra; DMN, Default mode network; EPI, Echo planar imaging; FDG, ^{18} F-fluorodeoxyglucose; FDR, Voxel-level false discovery rate; fMRI, Functional magnetic resonance imaging; FN-PA memory task, Face-name paired-associates encoding and retrieval task; FOV, Field of view; FWHM, Full width at half maximum; Glu, Glutamate; Glx, a combination of glutamate and glutamine; $[Glx]_{abs\_CSF\ corr.}$, Absolute concentrations of Glx with cerebrospinal fluid correction; HK-MoCA, Hong Kong Montreal Cognitive assessment; LH, Left hippocampus; MCI, Mild cognitive impairment; Ml, Myoinositol; $([ml]_{abs\_CSF\ corr.})$, Myoinositol with cerebrospinal fluid correction; MNI, Montreal Neurological Institute; MRI, Magnetic resonance imaging; MRS, Magnetic resonance spectroscopy; pCASL, Pseudo-continuous ASL; PCC, Posterior cingulate cortex; PET, Positron emission tomography; PI, Performance index; PRESS, Point resolved spectroscopy; QUEST, Quantification based on quantum estimation; RH, Right hippocampus; RT, Reaction time; SVS, Single voxel spectroscopy; TE, Echo time; TR, Repetition time; TSPO, Translocator protein.

Funding information
Research Grants Council of Hong Kong, Grant/Award Number: 17108315; University of Hong Kong

Edited by: Edmund Lalor

1 | INTRODUCTION

Besides increasing age (Herrup, 2010), genetic risk factors play an important role in the pathogenesis of Alzheimer's disease (AD). The apolipoprotein E ϵ4 allele (ApoE4), the most prevalent known genetic risk factor for AD, may account for up to half of all sporadic and familial late-onset cases (Caselli et al., 2009). The heterozygous and homozygous ϵ4 allele carriers are 3–4 times and 8–12 times more likely to progress into AD respectively (Heffernan et al., 2016). There are a myriad of mechanisms that link ApoE4 status with AD risks, such as synaptic dysfunction, abnormal amyloid aggregation and clearance and neuroinflammation (Kim et al., 2009; Liu et al., 2013).

Several volumetric magnetic resonance imaging (MRI) studies support a potential differential effect for ApoE genotypes in neurodevelopment (Wolf et al., 2013), but the findings have not been found consistently. Some studies suggested ApoE polymorphisms exert no significant effect on brain volume (Khan et al., 2014; Sidiropoulos et al., 2011). Other than structural MR imaging studies, functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have found preclinical functional brain changes in cognitively normal ApoE4 carriers. Using task-related paradigms, the brain activations in ApoE4 carriers were altered as compared to non-carriers in young (Filippini et al., 2009), middle (Johnson et al., 2006; Smith et al., 1999; Trivedi et al., 2006) and elderly (Bondi et al., 2000; Dickerson et al., 2005) age groups. Nevertheless, these studies on functional blood-oxygenation-level-dependent (BOLD) signals between ApoE4 carriers and non-carriers have been controversial (Fleisher et al., 2009). Some studies (Bondi et al., 2005; Bookheimer et al., 2000; Dickerson et al., 2005; Filippini et al., 2009; Fleisher et al., 2005; Shine et al., 2015) found that the high-risk (ApoE4) group demonstrates additional activations in both cerebral hemispheres. However, others have demonstrated decrease in brain activations (Fleisher et al., 2009; Johnson et al., 2006; Smith et al., 1999; Trivedi et al., 2006).

Glucose hypometabolism was seen in the same regions of the brain in at-risk ApoE4 carriers as in patients with probable AD using ^{18}F-fluorodeoxyglucose (FDG) PET, that is, based on studies in young (Reiman et al., 2004), middle age (Reiman et al., 1996) and elderly (Small et al., 2000) at-risk subjects. Notably, brain metabolism measured by FDG-PET largely reflects glutamatergic synaptic activity (Attwell & Laughlin, 2001; Hyder et al., 2006). The BOLD signal in fMRI is coupled to neural activity (Logothetis et al., 2001), and the process by which neural activity influences hemodynamic properties such as cerebral blood flow (CBF), cerebral blood volume and cerebral blood oxygen consumption is referred to as neurovascular coupling or 'functional hyperemia' (Attwell et al., 2010; D'Esposito et al., 2003). The discovery that functional hyperemia is driven largely by glutamate release indicates that fMRI images the neurovascular consequences of synaptic activity (Attwell et al., 2010). Hence, FDG metabolism (Small, 1995) and activated fMRI signal changes (Attwell et al., 2010; Cauli & Hamel, 2010) were correlated measures of synapse activity.

The synaptic regulatory functions of the ApoE receptors are differentially affected by ApoE isoforms (Lane-Donovan & Herz, 2017). ApoE4 promotes neuronal dysfunction by impairing the turnover of amyloid-β and weakening the ability of Reelin and ApoE receptors signalling to protect the deleterious effects of amyloid-β on the synapse. Recent proteomics studies revealed abnormal synaptic protein changes, such as accumulation of clusterin (Jackson et al., 2019) and neurogranin (Sun et al., 2016) and reduced expression of glutamate receptor proteins (Sweet et al., 2016). Glutamate (Glu) is the principal excitatory neurotransmitter (Shen, 2006) in the brain and mediates signalling in the glial/neuronal regulation of the neurovascular coupling (Hosford & Gourine, 2019). The impairment of the glutamatergic system heralded the presence of Alzheimer's-related neurodegenerative diseases (Revett et al., 2013; Zadori et al., 2014). Magnetic resonance spectroscopy (MRS) found decreased levels of glutamate/glutamine metabolites in AD (Antuono et al., 2001; Hattori et al., 2002). However, in a recent MRS study (Riese et al., 2015), reduced glutamate/glutamine in mild cognitive impairment was unrelated to the amyloid deposition and apolipoprotein E genotype.

The medial temporal lobe and the hippocampus, in particular, have been linked to different forms of memory (Brewer et al., 1998; Burgess et al., 2002; Nee & Jonides, 2008; Squire & Zola-Morgan, 1991). Face-name paired-associates encoding and retrieval task (FN-PA

memory task) has been used to study hippocampal activations across a large age-range of subjects (Haxby et al., 1996; Putcha et al., 2011; Sperling et al., 2001; Sperling et al., 2003; Zeineh et al., 2003). Nevertheless, glutamate played a salient role in frontal-hippocampal mechanisms of learning and memory. Hence, MRS study of the bilateral hippocampi provides a valuable neurochemical basis of the processes (Stanley et al., 2017).

By combining BOLD and ^{1}H-MRS techniques, one can examine the relationship between neurotransmitters and brain activation/deactivation at a system level (Hu et al., 2013). A review of previous studies demonstrated that neurotransmitters in specific brain regions orchestrated the neuronal changes during different cognitive activities (Duncan et al., 2014). To facilitate an understanding of the synaptic regulatory function of the ApoE isoforms on cognitive activity, we study the correlation between hippocampal glutamate and BOLD signal changes using a combination of MRS and task-based fMRI techniques.

We hypothesise in the current study that the synaptic signalling function might differ in ApoE4 carriers and non-carriers. Firstly, we compare the activated fMRI signal changes in low-risk (non-ApoE4) and high-risk (ApoE4) subjects using the FN-PA memory task. Secondly, we correlated activated fMRI signal changes in both subject groups with bilateral hippocampal glutamate. Mounting evidence (Chen et al., 2010; Liraz et al., 2013; Zadori et al., 2014) indicated that AD begins with subtle changes in synaptic function from the entorhinal cortex and hippocampus, which are the earliest regions of tau deposition and structural atrophy. As CBF could vary between individuals as well as among age groups and influence BOLD signals (D'Esposito et al., 2003), arterial spin labelling magnetic resonance imaging (ASL MRI) has been employed to measure CBF and used as covariate in the analysis. Finally, since neuroinflammation has been proposed as a pathogenic mechanism underlying ApoE4 genetic risk, the MRS metabolite marker of glial proliferation (myoinositol) was also measured and compared between the two subject groups. Our study offers insights in the neural mechanisms in cognitive control, pathogenesis of ApoE4 related cognitive decline and potentially therapy development in mild cognitive impairment and AD patients.

2 | MATERIALS AND METHODS

2.1 | Participants

Ninety-one healthy, cognitively normal subjects (age: range from 20 to 84, mean ± SD: 51 ± 16.6 years old, sex: 58F/33M) were enrolled. Subjects aged 20–60 years were recruited by advertisement on the campus of Hong Kong University recreation and sports service centres. Ambulatory community-living older adults (aged 60–80 years) were recruited from social centres for the elderly. In the community centres, these elderlies obtained social support and supervised exercises to maintain their well-being. Written informed consent was obtained from all subjects. The study logistics comply with the Declaration of Helsinki, and ethical approval of the research protocol was obtained from the Institutional Review Board of the University of Hong Kong and the Hospital Authority Hong Kong West Cluster.

2.2 | Inclusion and exclusion criteria

The subjects were being interviewed to gather sociodemographic data, self-reported smoking and alcohol history, drug or substance abuse, history of memory impairment and cognitive complaints, past medical history and related medications. The exclusion criteria included the followings: colour blindness, history of stroke, head injury, seizures, migraine or cancer within 5 years. Active infection, end-stage renal or other organ failure, non-ambulatory, psychiatric diseases, regular alcohol drinkers and drug abusers (Mazziotta et al., 2009) were also excluded. For the assessment, only right-handed subjects with normal blood pressure (less than 140/90 mmHg) and cognitive scores ≥ 26 in Hong Kong Montreal Cognitive Assessment (HK-MoCA) were included in the study (Wong et al., 2009).

2.3 | Experimental procedure

Each scanning session included a structural imaging sequence, ASL MRI, MRS acquisition and fMRI paradigms. There were only **67** subjects satisfying the above criteria in the final data analysis. In the fMRI part, 7 subjects were excluded because of head motion, and another 17 subjects were excluded because the fMRI pilot paradigm during set-up was shorter than the final optimised paradigm. In the MRS study, only 63 subjects were included (4 excluded because of head motion). In the behavioural part, only 66 subjects were included (1 excluded because of corrupted file).

2.3.1 | Structural sequence and ASL acquisition and analysis

All subjects underwent an MRI examination with a Philips-3T (Achieva) MR scanner using a standard 8-channel head coil. Structural images were acquired

with 3D fast field echo sequence (3D-T1-FFE sagittal, repetition time (TR) = 7 ms, echo time (TE) = 3.2 ms, Flip angle = 8°, voxel size = 1×1×1 mm^3, field of view (FOV) = 256). Details of the volumetric analysis were in the supporting information section.

Pseudo-continuous ASL (pCASL) acquired by 2D single-shot echo planar imaging (EPI): TR = 4000 ms, TE = 11 ms, labelling-duration = 1600 ms, post-labelling-delay = 1525 ms, 17 slices with spatial resolution of 3.5 × 3.5 × 7 mm. For the analysis of ASL data, the processing pipeline was from MRIcloud (https://braingps.mricloud.org/asl.v3) (Li et al., 2019).

2.3.2 | MRS data acquisition and analysis

Single voxel spectroscopy (SVS) was performed with the following parameters: TR/TE = 2000/39 ms, number of signals averaged = 128, phase cycles = 16, spectral width = 2000 Hz with spectral resolution of 1.95 Hz per point and free induction decay = 1024. Point resolved spectroscopy (PRESS) was used as the volume selection method for the region of interest and the excitation method for water suppression. For shimming, pencil-beam-auto was employed. Each voxel of size 2.5 × 1.5 × 1 cm^3 was placed in the left and right hippocampi (supporting information Figure S1).

Glx (a combination of glutamate and glutamine) processing was conducted using protocols described in detail in our previous publications (Chiu et al., 2014; Chiu et al., 2015; Chiu et al., 2018). In summary, absolute concentrations of Glx with cerebrospinal fluid (CSF) correction ($[Glx]_{abs\_CSF\ corr.}$) and myoinositol with CSF correction ($[ml]_{abs\_CSF\ corr.}$) were measured and quantified using internal water as reference by QUEST (quantification based on quantum estimation) in jMRUI (4.0) (supporting information section) with CSF, grey matter and white matter water content corrected (Chiu et al., 2018).

2.3.3 | fMRI scanning and behavioural tests protocol

This FN-PA memory task adopted a block-design from previously published papers (Putcha et al., 2011; Zeineh et al., 2003), and it comprised four blocks of memory encoding and four blocks of memory retrieval. During the encoding blocks, subjects viewed six face-name pairs (each face was viewed once per block), which were presented serially at a rate of 4 s per pair, with an inter-stimulus interval of 500 ms and instruction of 1.5 s, totally 28 s per block. During the presentation of each face-name pair, subjects were questioned whether they thought the name was matched with the face and pressed the button according to their opinion. This step was a purely subjective task designed to help enhance the associative encoding (Sperling et al., 2001). During recall blocks, subjects were shown faces without names and asked to respond whether they remembered the names or not without the need to name them. They were instructed to press the left button if they could recall the name of the face presented on the screen and press the right button if they forgot. The stimuli of encoding and recall were interspersed with the fixation blocks (a white crosshair on a black background, lasting for 20 s). In total, 24 face-name paired associations (12 males and 12 females) were used (supporting information Figure S2). Images were displayed within the IFIS System Manager 1.2/E-Prime environment (Psychology Software Tools, Inc., Pittsburgh, PA) in the scanner, and they presented to the participants on a screen visible via a mirror mounted on the head coil. After the scanning session, participants were asked to choose from two options as what the name of the person shown on a computer screen was.

2.3.4 | fMRI image acquisition and BOLD data analysis

Functional images were collected by using a gradient-echo echo planar sequence (parameters: TR = 2000 ms, TE = 30 ms, flip angle = 90°, voxel size = 3 ×3 ×4 mm^3) sensitive to BOLD contrast. The processing and statistical calculations were performed using Statistical Parametric Mapping (SPM12, Wellcome Department of Imaging Neuroscience, London, UK) based on MATLAB (The Mathworks Inc., Natick, MA, USA). Firstly, functional data were spatially realigned to the first volume of the first run to adjust for the head movement. Subjects with head movements more than 3 mm in any direction of *x*, *y* and *z* or over 3° were excluded. Then the data were co-registered to the anatomical images. The segmentation procedure was performed on the structural images to generate the tissue maps. In addition, the Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) tool (Ashburner, 2007) normalised the structural images and tissue maps to Montreal Neurological Institute (MNI) space and created transformation parameters. A standard EPI template was used for normalisation, and the images resampled into 3 × 3 × 3-mm^3 isotropic resolution in the MNI brain using the transformation parameters were estimated through DARTEL segmentation. Next, we smoothed the data using a Gaussian kernel of 8-mm full width at half

maximum (FWHM). In the first-level analysis, contrast images were generated for parameter estimates in the context of a general linear model based on three conditions: fixation, encoding and recall. Activation contrasts of interest were encoding versus fixation and recall versus fixation. We examined the activations of the whole group and genetic risk-related subgroups in the whole brain. One sample *t*-test was used respectively on the contrasts, and the results were considered to be statistically significant at $p < 0.01$ (voxel-level false discovery rate [FDR] adjusted). In addition, two sample *t*-tests were employed for genetic subgroup comparison (Alphasim correction, $p < 0.05$, cluster size>4158 mm^3).

2.4 | Genotyping

The blood samples were immediately collected after the neuropsychological examination and then were frozen and sent for ApoE genotype analysis using a polymerase chain reaction-based matter and divided into two groups based on the presence or absence of the ApoE4 allele. The ApoE Ɛ alleles of each subject were determined as described (Calero et al., 2009).

As in that publication, the primer sequences used were as follows:

ApoE_112C Forward CGGACATGGAGGACGTGT
ApoE_112R Forward CGGACATGGAGGACGTGC
ApoE_158C Reverse CTGGTACACTGCCAGGCA
ApoE_158R Reverse CTGGTACACTGCCAGGCG

2.5 | Statistical analysis

The statistical calculations were carried out with the SPSS package v. 24 (SPSS Inc., Chicago, USA). Two sample *t*-tests were applied to measure the group difference in demographic variables, the behavioural performance of FN-PA task, volumetric MRI, ASL MRI and MRS results, and sex was tested by Pearson's Chi-square test.

We defined performance index (PI) as follows:

$$\mathrm{PI} = \frac{1}{ACC} \times RT$$

ACC meant the accuracy rate of the face-name recognition task. RT was the reaction time. Lower PI scores indicated higher performance.

In order to explore any difference in the synaptic regulatory function of the ApoE isoforms on cognitive activity, we correlated the activated fMRI signal changes in both subject groups with bilateral hippocampal glutamate. Based on the activated regions obtained from the one sample *t*-test (FDR correction, $p < 0.01$, cluster size>810 mm^3) in each genetic risk subgroup (according to ApoE4 carrier status), the peak values of the activated regions were correlated with the $[Glx]_{abs.CSF\ corr.}$ in each hippocampus using age, CBF and sex as covariates (Pearson correlation, $p < 0.05$).

For a direct comparison between low-risk and high-risk groups, the Fisher *z* test ($p < 0.05$) was used to determine any significant difference between the correlation coefficients. The difference-test between correlation coefficients of regional activated fMRI signals and left hippocampal glutamate (LH) in the low-risk and high-risk groups and between correlation coefficients of regional activated fMRI signals and right hippocampal (RH) glutamate in the low-risk and high-risk groups was only made when one of the pairs had a significant correlation after the FDR correction.

3 | RESULTS

Supporting information Table S1 showed the demographic information, genetic and behavioural tests, cerebral blood flow, $[Glx]_{abs.CSF\ corr.}$ and $[mI]_{abs\_CSF\ corr.}$ and normalised grey matter volume of the ApoE subgroups. No significant difference was found between these two groups.

3.1 | Encoding task

3.1.1 | BOLD results

Figure 1a,b showed the BOLD activations during the encoding-fixation contrast (one sample *t*-test) in the low-risk (non-ApoE4) and high-risk (ApoE4) subgroups. Activations involving bilateral superior, middle and inferior frontal gyrus; superior and inferior parietal such as angular, supramarginal gyri, middle and inferior; and medial temporal regions including amygdala, hippocampi and parahippocampal, occipital regions including fusiform and lingual gyri, anterior and middle cingulate, precuneus, insula, thalamus, precentral and postcentral gyri and supplementary motor cortex were seen in low-risk subgroup. In high-risk group, the activations were increased in bilateral superior, middle and inferior frontal gyri, superior and inferior parietal, right angular, right hippocampus, bilateral inferior temporal, occipital regions including bilateral fusiform and lingual gyri, bilateral insula, precentral and supplementary motor cortex in the encoding process. The overall cluster sizes appear larger in the low-risk group, likely due to a larger sample size (supporting information Tables S2 and S3)

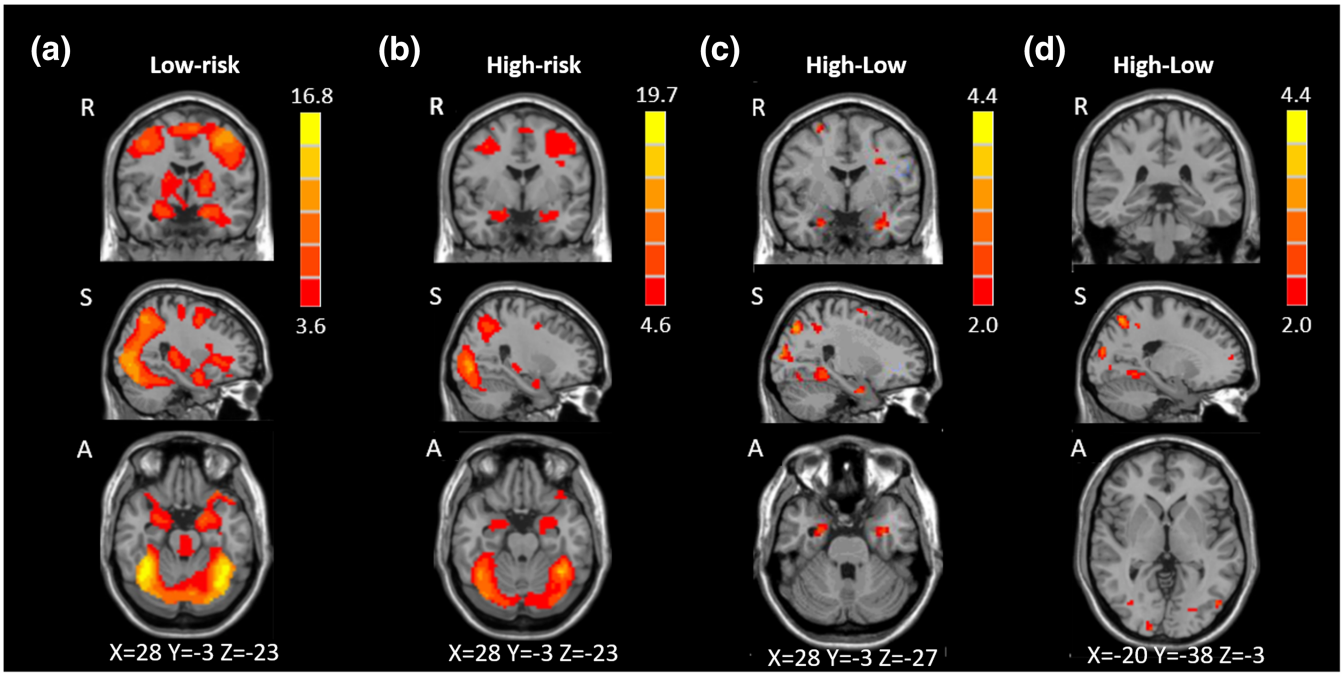

FIGURE 1 The imaging results of low risk ($N = 49$) and high risk ($N = 18$): (a) contrast: encoding-fixation with low risk, (b) contrast: encoding-fixation with high risk, (encoding: $p < 0.01$, false discovery rate [FDR] corrected, cluster size>810 mm^3). (c, d) The two sample *t*-test results between age-matched high-risk and low-risk (high-low) during encoding-fixation ($p < 0.05$, cluster size>270mm^3). R, right; S, superior; A, anterior

3.1.2 | Age-matched subgroups comparison

Since the group sizes were unequal, further analysis using age-matched low- and high-risk groups (18 subjects in each group with no significant difference in demographic, behavioural and neuropsychological tests, hippocampal glutamate concentration and CBF—data not shown) was performed, with BOLD results as in Figure 1c,d (two sample *t*-tests, alphasim correction, $p < 0.05$, as to size> 4158 mm^3). The high-risk group demonstrated more activations in both cerebral hemispheres including bilateral lingual, right fusiform, occipital gyri, bilateral superior parietal, left angular, left middle temporal, left inferior temporal, right parahippocampus and precuneus (supporting information Table S6).

Our findings showed stronger hippocampal, occipital and default mode network (DMN) activations, which reflected the extra cognitive effort by ApoE4 carriers to obtain the same level of performance as their non-carrier counterparts.

3.1.3 | Correlation of BOLD signals with glutamate

In order to explore any difference in the synaptic regulatory function of the ApoE isoforms on the cognitive task, we compare the correlation between activated fMRI signal changes in both subject groups with bilateral hippocampal glutamate.

Based on the regions (Figure 1a,b) obtained from one sample *t*-test of each group, the peak values of encoding-fixation were correlated with the $[Glx]_{abs.CSF\ corr.}$ in bilateral hippocampi with age, CBF and sex as covariates, and the results after the *p* value FDR adjustment were presented in Table 1.

In the 'low-risk' group, significant positive correlation ($p < 0.05$) of BOLD signal changes with $[Glx]_{abs.CSF\ corr.}$ in LH was found in left amygdala, left hippocampus, left inferior frontal, left inferior parietal, left insula and left parahippocampus. However, no statistical correlation was found between any activated region and $[Glx]_{abs.CSF\ corr.}$ in RH.

In the 'high-risk' group, BOLD signal changes showed no significant correlation ($p < 0.05$) with $[Glx]_{abs.CSF\ corr.}$ in LH. Contrary to the low-risk group, significant positive correlation ($p < 0.05$) of activations in right inferior parietal, left superior parietal and right middle frontal gyri with $[Glx]_{abs.CSF\ corr.}$ in RH.

For the comparison of correlation coefficients (using Fisher *z* test) between BOLD signal and left hippocampal glutamate, we found no significant difference between the low-risk and high-risk groups, except in the left amygdala ($p < 0.05$).

TABLE 1 The correlation results in activated regions (involved in the FN-PA task pathways) of low-risk and high-risk groups in the bilateral hippocampus during encoding (partial correlation: controlling for age, CBF and sex)

	Low-risk group_Glx_LH		High-risk group_Glx_LH		
Regions	***r***	**p_corrected**	***r***	**p_corrected**	**Significance**
Amygdala_L	0.353	0.036	−0.421	0.960	<0.05
Hippocampus_L	0.353	0.036	0.060	0.960	ns
Inferior Frontal_L	0.335	0.036	−0.045	0.960	ns
Inferior Parietal_L	0.316	0.041	0.090	0.960	ns
Insula_L	0.347	0.036	−0.017	0.960	ns
Parahippocampus_L	0.390	0.036	0.065	0.960	ns
	Low-risk group_Glx_RH		**High-risk group_Glx_RH**		
Regions	***r***	**p_corrected**	***r***	**p_corrected**	**Significance**
Inferior Parietal_R	−0.076	0.631	0.681	0.047	<0.05
Middle Frontal_R	−0.163	0.455	0.610	0.047	<0.05
Superior Parietal_L	−0.180	0.455	0.647	0.047	<0.05

Note: p_corrected indicated that the *p* values were adjusted with the FDR correction method. After Fisher *z* transformation, <0.05 in the significance column means the significant difference between the pair of correlation coefficients; ns means no significant difference.
Abbreviations: CBF, cerebral blood flow; FDR, false discovery rate.

For the comparison of correlation coefficients (using Fisher *z* test) between BOLD signal and right hippocampal glutamate, we found significant differences between the low-risk and high-risk groups in the right middle frontal, left superior parietal and right inferior parietal regions ($p < 0.05$).

The data showed that the glutamatergic synaptic modulation of neuronal activity (using the FN-PA task) during encoding was different in the ApoE isoforms, being modulated by left hippocampal glutamate in the low-risk group and by right hippocampal glutamate in the high-risk group.

3.2 | Recall task

3.2.1 | BOLD results

Figure 2a,b showed the BOLD activations during recall (one sample *t*-test) in the low-risk (non-ApoE4) and high-risk (ApoE4) subgroups. The regional activations in low-risk group during recall resembled encoding, though the activations were of different magnitudes. For the high-risk group, in addition to regions like bilateral superior, middle and inferior frontal; bilateral inferior temporal, superior and inferior parietal; and occipital regions including fusiform and lingual gyri, precentral, supplementary motor cortex and activations were also found in middle cingulate, precuneus, left supramarginal and angular gyri and bilateral thalami (supporting information Tables S4 and S5)

3.2.2 | Age-matched subgroups comparison

In the age-matched comparison during recall (Figure 2c, d, two sample *t*-tests, alphasim correction, $p < 0.05$, as to size> 4158mm^3), the high-risk group presented more activations in bilateral lingual, right fusiform, right superior parietal, right middle temporal, occipital gyri, left hippocampus and bilateral parahippocampus (supporting information Table S6).

3.2.3 | Correlation of BOLD signals with glutamate

Based on the regions (Figure 2a,b) obtained from one sample *t*-test of each group, the peak values of the contrast recall-fixation were correlated with the $[Glx]_{abs.CSF\ corr.}$ in bilateral hippocampi as demonstrated with age, CBF and sex as covariates, and the results after the *p* value FDR adjustment were presented in Table 2.

In the 'low-risk' group, no statistical correlation was found between any activated region and $[Glx]_{abs.CSF\ corr.}$ in LH and RH, but the correlation trend still existed in regions like left parahippocampus, bilateral precunei and left thalamus ($p = 0.06$) with $[Glx]_{abs.CSF\ corr.}$ in LH.

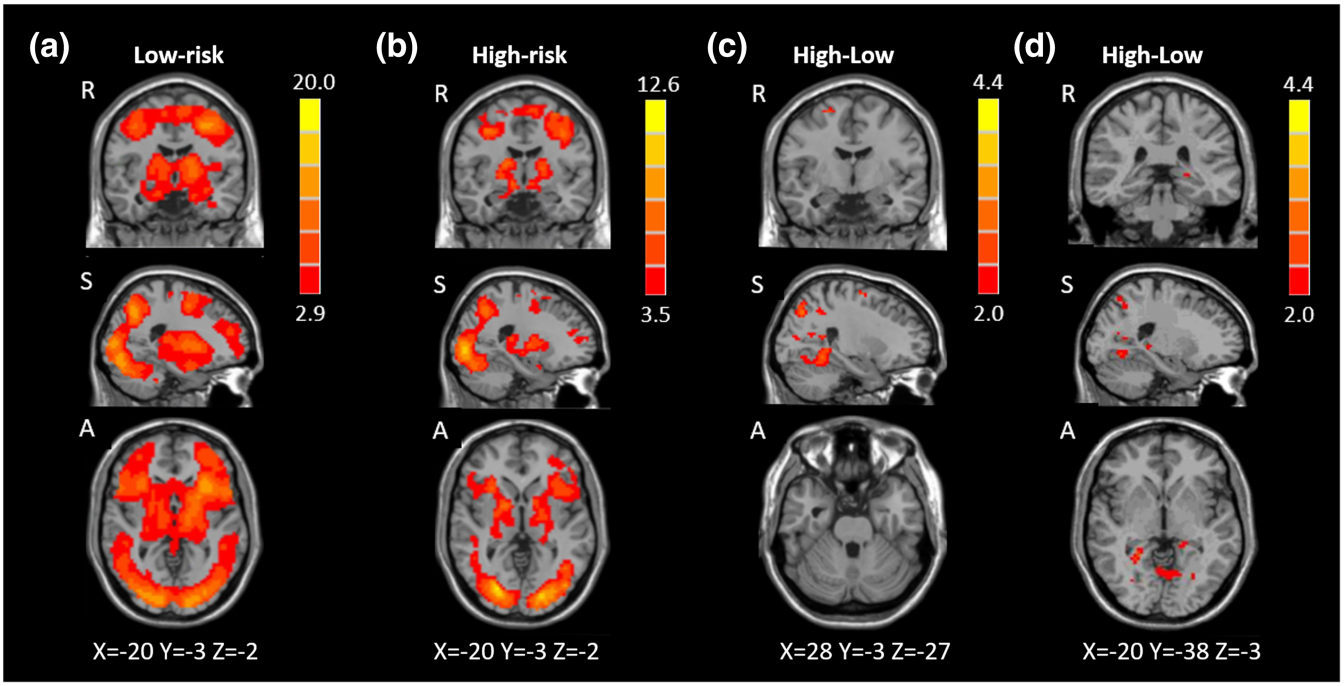

FIGURE 2 The imaging results of low risk ($N = 49$) and high risk ($N = 18$): (a) contrast: recall-fixation with low risk, (b) contrast: recall-fixation with high risk. (recall: $p < 0.05$, false discovery rate [FDR] corrected, cluster size>810 mm^3). (c, d) The two sample *t*-test results between age-matched high-risk and low-risk (High-Low) during recall-fixation ($p < 0.05$, cluster size>270mm^3). R, right; S, superior; A, anterior

In the 'high-risk' group, contrary to the low-risk group, significant positive correlation ($p < 0.05$) of activations in bilateral superior frontal gyri, bilateral inferior frontal, left superior parietal, bilateral inferior parietal, right middle temporal and left precuneus with $[Glx]_{abs.CSF\ corr.}$ in RH.

Comparison of correlation coefficients (using Fisher *z* test) between the BOLD signal and left hippocampal glutamate in the high- and low-risk groups was not performed since there was no significant correlation in both groups.

In the comparison of correlation coefficients (using Fisher *z* test) between the BOLD signal and right hippocampal glutamate, we found significantly higher correlation ($p < 0.05$) in the high-risk group in bilateral inferior frontal, bilateral inferior parietal, right middle temporal, left precuneus, bilateral superior frontal and left superior parietal.

The data showed that the glutamatergic synaptic modulation of neuronal activity during recall was different in the ApoE isoforms, that is, modulated by right hippocampal glutamate in the high-risk group but not modulated by either left (although a correlation trend existed) or right hippocampal glutamate in the low-risk group.

4 | DISCUSSION

4.1 | Neural pathways involved in face-name paired-associates encoding and retrieval tasks and a comparison of current fMRI findings with previous studies

The ability to form associations between names and faces is an essential aspect of episodic memory function, and the hippocampus and related structures are particularly critical. Research findings since late 1990s have consistently revealed distinctive neuropathways for memory encoding and retrieval. Haxby et al. (1996) found that the right hippocampus and adjacent cortex participated mainly in memory encoding but not recognition. In addition, there was lateralisation of prefrontal participation in encoding and recognition tasks that encoding activated left prefrontal cortex, whereas recognition activated right prefrontal cortex. Sperling et al. further distilled pathways engaged in successful associative encoding by comparing to activations during trials that were forgotten, and they concluded that the anterior regions of the hippocampal formation bilaterally and left inferior frontal cortex were crucial for successful encoding (Sperling et al., 2001; Sperling et al., 2003). Zeineh et al.'s (2003)

TABLE 2 The correlation results in activated regions (involved in the FN-PA task pathways) of low-risk and high-risk groups in the bilateral hippocampus during recall (partial correlation: controlling for age, CBF and sex)

	Low-risk group_Glx_LH		High-risk group_Glx_LH		
Regions	***r***	**p_corrected**	***r***	**p_corrected**	**Significance**
Hippocampus_R	0.235	0.135	0.667	0.125	-
Parahippocampus_L	0.307	0.060	0.263	0.434	-
Precuneus_L	0.339	0.060	0.403	0.346	-
Precuneus_R	0.325	0.060	0.436	0.346	-
Thalamus_L	0.307	0.060	0.360	0.346	-
	Low-risk group_Glx_RH		**High-risk group_Glx_RH**		
Regions	***r***	**p_corrected**	***r***	**p_corrected**	**Significance**
Inferior Frontal_L	−0.001	0.994	0.697	0.036	<0.05
Inferior Frontal_R	−0.034	0.994	0.734	0.036	<0.05
Inferior Parietal_L	−0.046	0.994	0.640	0.044	<0.05
Inferior Parietal_R	0.053	0.994	0.774	0.036	<0.05
Middle temporal_R	−0.079	0.994	0.611	0.049	<0.05
Precuneus_L	−0.077	0.994	0.684	0.036	<0.05
Superior Frontal_L	−0.104	0.994	0.603	0.049	<0.05
Superior Frontal_R	−0.046	0.994	0.639	0.044	<0.05
Superior Parietal_L	−0.011	0.994	0.689	0.036	<0.05

Note: p_corrected indicated that the *p* values were adjusted with the FDR correction method. After Fisher z transformation, <0.05 in the significance column means the significant difference between the pair of correlation coefficients; − means that the difference-test was not performed as there is no significant correlation in the low-risk and high-risk groups

Abbreviations: CBF, cerebral blood flow; FN-PA, Face-name paired-associates.

study found similar results that subdivisions within the hippocampus make distinct contributions to new memory formation; in addition, there was temporal decline in activations when new associations were learnt.

To sum up, in the encoding of novel face-name associations, the current level of evidence suggests that a distributed functional network is involved, including the hippocampal formation, dorsolateral prefrontal cortex, pulvinar nucleus of the thalamus, fusiform and adjacent areas of visual association cortex (Haxby et al., 1996; Sperling et al., 2001). In the recall of face-name associations, the anterior temporal lobe (Tsukiura & Cabeza, 2011) and the medial temporal lobe, especially the hippocampus and its adjacent parahippocampal cortex, entorhinal cortex and perirhinal cortex, are involved (Kirwan & Stark, 2004; Zeineh et al., 2003).

One important characteristic of the face-name association test is its reliance on associative memory and cross-modal association, which have been found to be especially sensitive to early stages of AD (Blackwell et al., 2004; Parra et al., 2010). For example, Vannini et al. (2012) observed a deterioration of the neuronal activity during the memorisation of face-name associations in people without clinical symptoms but with amyloid deposits (Sperling et al., 2009). The subregion changes in the activity observed in the current study by comparing the high-risk versus the low-risk group may pronounce underlying mechanism that is associated with cognitive decline.

Different fMRI memory activation tasks were used in prior studies, such as unrelated paired-word learning/recall (Bookheimer et al., 2000), picture encoding of scenes (Bondi et al., 2005), picture encoding of animals and landscapes (Filippini et al., 2009), verbal paired encoding (Fleisher et al., 2005) and face-name associative encoding (Dickerson et al., 2005). These studies showed greater hippocampal activations in the ApoE4 than non-ApoE4 carriers. In addition, activations were seen in parietal and prefrontal regions (Bookheimer et al., 2000); bilateral fusiform, prefrontal, superior parietal regions; and parahippocampus (Bondi et al., 2005), middle temporal, lingual, cingulate, frontal gyri and cerebellar vermis (Fleisher et al., 2005). Stronger BOLD responses elicited in the posterior cingulate cortex (PCC), precuneus and cingulate of ApoE4 carriers using a one-back visual working memory task (Shine et al., 2015).

In the current study, additional activations during encoding were in regions related to vision including

occipital (such as bilateral lingual and right fusiform gyri) and DMN including left inferior temporal and middle temporal gyri, right parahippocampus, bilateral superior parietal, left angular and precuneus (Figure 1c,d). The additional activations during recall in the high-risk versus low-risk group included occipital, bilateral lingual and right fusiform, left hippocampus and bilateral parahippocampus, right middle temporal and right superior parietal regions (Figure 2c,d).

Hence, our findings concurred with prior studies on ApoE genotypes that stronger hippocampal, occipital and default mode network activations reflect the cognitive effort by ApoE4 carriers to obtain the same level of performance as their non-carrier counterparts (Bondi et al., 2005; Bookheimer et al., 2000; Dickerson et al., 2005; Filippini et al., 2009). Interestingly, there was a higher activation during encoding in the precuneus of ApoE4 than non-ApoE4 carriers, which reflected decreased task-induced deactivation in the posteromedial cortex of ApoE4 carriers. The decline of task-based deactivation during encoding in posterior components of DMN including precuneus and PCC was also reported in amyloid positive older subjects using face-name association task (Sperling et al., 2009; Vannini et al., 2012) and in ApoE4 young healthy adults using one-back visual working memory task (Shine et al., 2015).

Since age might affect the resting cerebral blood flow and oxygen extraction fraction (Lu et al., 2011), the differences in BOLD signal changes between the two groups in current study were genuine since both groups have no significant difference in resting CBF and age.

BOLD response was primarily driven by cerebral blood flow changes, moderated by baseline deoxyhemoglobin and the ratio of fractional changes in CBF to cerebral metabolic rate of oxygen consumption (Ances et al., 2008). Hence, BOLD activations should not be directly interpreted as neuronal activities but reflect a complex relationship between vascular reactivity, cerebral blood flow, oxygen utilisation and baseline state (Fleisher et al., 2009). Therefore, the inconsistencies in prior fMRI studies in APOE isoforms more likely represent the dependence of BOLD signal changes on variables such as cognitive task used, brain region evaluated and age of the cohort. Controversies in interpretation will likely occur if such factors are not carefully considered.

4.2 | Correlative study of fMRI activations and bilateral hippocampal glutamate in the low-risk and high-risk groups

The novel finding in current study is the striking difference between the two groups in the side of hippocampus being involved in glutamatergic modulation of neuronal activities, that is, being lateralised to left hippocampus in the low-risk group during encoding, while being lateralised to the right hippocampus in the high-risk group during encoding and recall (Tables 1 and 2).

Interestingly, in the low-risk group during encoding, although multiple regions had significant correlation with left hippocampal glutamate after FDR correction, only correlation of BOLD signal with left hippocamapal glutamate in left amygdala was significantly different from high-risk group. This might be due to the following: (1) lower r values between BOLD and left hippocampal glutamate (unlike the much values seen in the high-risk group) and (2) small sample size of high-risk group. Indeed, sample size calculation (supporting information) revealed that the power of the correlative study is suboptimal for the high-risk group.

During recall in low-risk group, no significant correlation of neuronal activations with left hippocampal glutamate after FDR correction can be explained by the 'priming' effect; that is, reintroduced learned 'or familiarised' face-name pairs during recall required a lower cognitive effort (Hu et al., 2013; Squire et al., 1992; Zeineh et al., 2003).

Significant advances have been made in understanding how ApoE might contribute to AD disease risk for the past two decades, but it is important to recognise that early functional and morphologic changes reported in ApoE4 carriers might not reflect progressive disease-related changes but rather ApoE-related neurodevelopmental alterations (Wolf, Caselli, et al., 2013).

Previous molecular and optogenetic animal studies reported left–right asymmetry of the hippocampal synapses (Kohl et al., 2011; Shinohara et al., 2008; Shipton et al., 2014). The dissociated role of Glx in left versus right hippocampus in modulating neuronal activities during episodic memory is in concordance with recent molecular and optogenetic animal studies. Shinohara et al. found that postsynaptic spines at cornu ammonis (CA) synapses (CA3-CA1) differed in glutamate receptor composition according to the hemispheric origin of CA3 afferents. Kohl et al. used optogenetic tools to selectively stimulate axons of CA3 pyramidal cells originating in either left or right mouse hippocampus and found that left CA3 input produced more long-term potentiation at CA1 synapses than right CA3 input as a result of differential expression of N-Methyl-D-aspartate receptor subunits. Shipton et al. suggested that hippocampal long-term memory processing was lateralised in mice. We therefore hypothesised that such hippocampal synaptic lateralisation could occur in human ApoE4 isoforms and such divergence of function between equivalent

structures in each hemisphere might make optimal use of the nervous system (Shipton et al.).

In current study, the cause of the asymmetrical left–right correlation between hippocampal synaptic glutamate and neuronal activity is unknown. This could be developmental or compensatory. Our study was based on a cohort with a mean age in the late 40s. We studied different age groups including the young (20–39 years: $N = 22$), middle-aged (40–59 years: $N = 23$) and elderly (60 and above years: $N = 22$). This would allow a thorough evaluation of hippocampal synaptic signalling of neuronal events in the ApoE isoforms across the adult age span.

Previous studies showed that young ApoE4 carriers might perform better than non-carriers (Han & Bondi, 2008), such as in IQ scores (Yu et al., 2000), education, temperament, memory performance (Mondadori et al., 2007) and visuospatial skill (Bloss et al., 2010). Such studies corroborated the developmental cognitive superiority of ApoE4 carriers.

The Nun Study identified a connection between literacy in early life and memory decline in late life (Snowdon, 1996). Linguistic ability in early life found to be a marker of cognitive ability, neurocognitive development and neurologic reserve. Subsequent studies revealed a link between decreased propositional density or p-density and neuropsychological deficits and AD neuropathology later in life (Riley et al., 2005). Medina et al. also found that the presence of ApoE4 allele was significantly associated with a lower p-density among persons at risk for Familial AD (Medina et al., 2011). Alleles of the apolipoprotein E gene were found to have distinct neuroanatomic signatures, identifiable in childhood (Shaw et al., 2007) and young adults (Alexopoulos et al., 2011). These studies suggested that thinner entorhinal cortex and smaller hippocampal volumes in ApoE4 carriers might contribute to the latter development of AD due to lower cognitive reserve.

Taken together, our study might provide another piece of evidence of the hypothesised role of ApoE4 as an example of antagonistic pleiotropy (Han & Bondi, 2008). A pattern of hippocampal glutamatergic signalling of neuronal activities in ApoE4 allele carriers distinctive from non-ApoE4 carriers (lateralised to the right hippocampus) could represent diversity in neuronal development. This might confer neurocognitive benefit very early in life but might exert an adverse effect on survival later in age.

Synaptic failure is an early pathological feature of AD. The present finding of the asymmetric synaptic responses in ApoE isoforms could be explained from a compensatory perspective. Prior studies demonstrated that ApoE likely in an isoform-dependent manner modulates synaptic integrity and plasticity (Ji et al., 2003; Love et al., 2006; Sweet et al., 2016). ApoE4 was found to suppress the expression of synaptic proteins (including synaptophysin and glutamate receptors) and impair dendritic morphology, synaptic transmission and plasticity in an age-dependent manner (Zhao et al., 2018). We postulated that due to ApoE4-induced synaptic impairment of left hippocampal glutamatergic modulation, neural compensation in ApoE4 carriers might occur to maintain brain functional resilience by shifting to the right side (Barulli & Stern, 2013).

Although dose-dependent AD risk of ApoE isoforms was related to amyloid load (Reiman et al., 2009), the influence of amyloid deposition leading to asymmetric hippocampal glutamatergic modulation in the current study would be unlikely. Prior clinical amyloid imaging studies by PET showed that amyloid positivity tends to appear earlier in cognitively intact ApoE 4 carriers (near 56 years of age) than non-ApoE4 carriers (at 76 years of age) (Zhao et al., 2018). The average age of our cohort was in the late 40s, and the effect would be minimal. However, the impact of oligomeric amyloid β, potentially the most toxic species, could not be eliminated since oligomer-positivity could occur for even longer than plaque-positivity (Herrup, 2015).

Since neurotoxic reactive astrocytic response mediated by microglia has been implicated in AD (Liddelow et al., 2017; Tai et al., 2015), it is prudent to search for any glial proliferation in ApoE isoforms. Emerging data also showed their role in regulating multiple facets of the innate immune response (Keene et al., 2011). Myoinositol (mI) is generally assumed to be a marker of gliosis based on the fact that higher myoinositol levels being present in the cultured astrocytes as compared to neurons in vitro (Duarte et al., 2012). Furthermore, ample evidence suggested that mI might potentially be useful as a biomarker for glial activation in neurodegenerative diseases including AD and mild cognitive impairment (MCI) (Kantarci, 2013). As there was no difference in mI as measured by MRS between the ApoE4 and non-ApoE4 subgroups, the mechanism is unlikely to be a response to neuroinflammation.

Nevertheless, neuroinflammatory PET markers such as ^{11}C-PBR28 (a radioligand for translocator protein, TSPO, overexpressed by activated microglia and reactive astrocytes) might be more sensitive to neuroinflammation (Kreisl et al., 2016). ^{11}C-PBR28 was shown to have greater binding in AD patients than controls, particularly in temporal and parietal cortices (Kreisl et al., 2013), and the annual rate of TSPO binding in the temporo-parietal regions being five times higher in patients with clinical progression (Kreisl et al., 2016). Further study by such a biomarker might be helpful to exclude such a possibility.

5 | LIMITATIONS

Firstly, for the MRS methodology:

Glx was measured instead of the individual metabolites because the current study was aimed at evaluating the glutamatergic system of healthy individuals with tight coupling between glutamate and glutamine (Ramadan et al., 2013). In the situation whereby impairments in glutamate-glutamine cycling seemed to occur, these metabolites should be separately measured (Taylor et al., 2015). Another drawback of steady state MRS technique was the unknown composition of synaptic and intracellular glutamate and glutamine. With recent high field MRS systems, functional MRS might track glutamate modulations during cognitive tasks with high temporal resolution directly (Stanley & Raz, 2018).

The ROI selection for MRS is specific and could influence the results. Since the entorhinal cortex and hippocampus are the earliest regions of tau deposition and structural atrophy, our current ROI selection was optimal. Inclusion of other ROIs such as posterior cingulate/precuneus (Antuono et al., 2001; Hattori et al., 2002; Riese et al., 2015) would be ideal but lead to prolongation of the study time.

Secondly, for the study cohort:

The final cohort consisted of only 67 instead of 91 subjects (due largely to wastage of 17 subjects for optimising the pilot fMRI FN-PA paradigm). As a result, the even smaller sample size in the ApoE4 subgroup might limit the power of the correlative results. Hence, our findings are exploratory and await validation by a larger cohort of ApoE4 subjects.

While this study has documented changes between the high-risk (ApoE4+) and low-risk (ApoE4-) groups, the stage of changes cannot be defined given the wide age range of the participants (20 to 84 years). A dedicated study of specific age ranges is useful to evaluate any age-related effect on the phenomenon.

6 | CONCLUSIONS

The task-based fMRI findings concurred with prior studies on ApoE genotypes that stronger hippocampal, occipital and default mode network activations reflected the cognitive effort by ApoE4 carriers to obtain the same level of performance as their non-carrier counterparts. Our study highlighted the asymmetric left–right hippocampal glutamatergic system in modulating neuronal activities, that is, significant unilateral (left) hemispheric correlation with left hippocampal glutamate in APOE4 non-carriers during encoding and bilateral hemispheric correlation with right hippocampal glutamate in APOE4 carriers during encoding or recall. Such brain differentiation might reflect developmental cognitive advantages in ApoE4 carriers or be compensatory due to impaired synaptic integrity and plasticity in ApoE4 carriers. Nonetheless, the mechanism is unrelated to neuroinflammation in our study.

ACKNOWLEDGEMENTS

This work was supported by Research Grants Council of Hong Kong (GRF grant number: 17108315) and the State Key Laboratory of Brain and Cognitive Sciences, the University of Hong Kong.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

Conceptualisation: HKFM and KH; Investigation: HZ, PWC, TL and YS; Formal analysis: HZ and PWC; Visualisation: GHYW and SWHW; Writing: HZ, TL and KH, HKFM; Funding acquisition: HKFM.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15399.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Gloria Hoi Yan Wong https://orcid.org/0000-0002-1331-942X

Henry Ka Fung Mak https://orcid.org/0000-0002-2007-0650

REFERENCES

Alexopoulos, P., Richter-Schmidinger, T., Horn, M., Maus, S., Reichel, M., Sidiropoulos, C., Rhein, C., Lewczuk, P., Doerfler, A., & Kornhuber, J. (2011). Hippocampal volume differences between healthy young apolipoprotein E epsilon2 and epsilon4 carriers. *Journal of Alzheimer's Disease*, *26*(2), 207–210. https://doi.org/10.3233/JAD-2011-110356

Ances, B. M., Leontiev, O., Perthen, J. E., Liang, C., Lansing, A. E., & Buxton, R. B. (2008). Regional differences in the coupling of cerebral blood flow and oxygen metabolism changes in response to activation: Implications for BOLD-fMRI. *NeuroImage*, *39*(4), 1510–1521. https://doi.org/10.1016/j.neuroimage.2007.11.015

Antuono, P. G., Jones, J. L., Wang, Y., & Li, S. J. (2001). Decreased glutamate + glutamine in Alzheimer's disease detected in vivo with (1)H-MRS at 0.5 T. *Neurology*, *56*(6), 737–742. https://doi.org/10.1212/wnl.56.6.737

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007

Attwell, D., Buchan, A. M., Charpak, S., Lauritzen, M., Macvicar, B. A., & Newman, E. A. (2010). Glial and neuronal control of brain blood flow. *Nature*, *468*(7321), 232–243. https://doi.org/10.1038/nature09613

Attwell, D., & Laughlin, S. B. (2001). An energy budget for signaling in the grey matter of the brain. *Journal of Cerebral Blood Flow and Metabolism*, *21*(10), 1133–1145. https://doi.org/10.1097/00004647-200110000-00001

Barulli, D., & Stern, Y. (2013). Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. *Trends in Cognitive Sciences*, *17*(10), 502–509. https://doi.org/10.1016/j.tics.2013.08.012

Blackwell, A. D., Sahakian, B. J., Vesey, R., Semple, J. M., Robbins, T. W., & Hodges, J. R. (2004). Detecting dementia: Novel neuropsychological markers of preclinical Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *17*(1–2), 42–48. https://doi.org/10.1159/000074081

Bloss, C. S., Delis, D. C., Salmon, D. P., & Bondi, M. W. (2010). APOE genotype is associated with left-handedness and visuospatial skills in children. *Neurobiology of Aging*, *31*(5), 787–795. https://doi.org/10.1016/j.neurobiolaging.2008.05.021

Bondi, M. W., Houston, W. S., Eyler, L. T., & Brown, G. G. (2005). fMRI evidence of compensatory mechanisms in older adults at genetic risk for Alzheimer disease. *Neurology*, *64*(3), 501–508. https://doi.org/10.1212/01.WNL.0000150885.00929.7E

Bookheimer, S. Y., Strojwas, M. H., Cohen, M. S., Saunders, A. M., Pericak-Vance, M. A., Mazziotta, J. C., & Small, G. W. (2000). Patterns of brain activation in people at risk for Alzheimer's disease. *The New England Journal of Medicine*, *343*(7), 450–456. https://doi.org/10.1056/NEJM200008173430701

Brewer, J. B., Zhao, Z., Desmond, J. E., Glover, G. H., & Gabrieli, J. D. (1998). Making memories: Brain activity that predicts how well visual experience will be remembered. *Science*, *281*(5380), 1185–1187. https://doi.org/10.1126/science.281.5380.1185

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, *35*(4), 625–641. https://doi.org/10.1016/s0896-6273(02)00830-9

Calero, O., Hortiguela, R., Bullido, M. J., & Calero, M. (2009). Apolipoprotein E genotyping method by real time PCR, a fast and cost-effective alternative to the TaqMan and FRET assays. *Journal of Neuroscience Methods*, *183*(2), 238–240. https://doi.org/10.1016/j.jneumeth.2009.06.033

Caselli, R. J., Dueck, A. C., Osborne, D., Sabbagh, M. N., Connor, D. J., Ahern, G. L., Baxter, L. C., Rapcsak, S. Z., Shi, J., Woodruff, B. K., Locke, D. E. C., Snyder, C. H., Alexander, G. E., Rademakers, R., & Reiman, E. M. (2009). Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *The New England Journal of Medicine*, *361*(3), 255–263. https://doi.org/10.1056/NEJMoa0809437

Cauli, B., & Hamel, E. (2010). Revisiting the role of neurons in neurovascular coupling. *Frontiers in Neuroenergetics*, *2*, 9. https://doi.org/10.3389/fnene.2010.00009

Chen, Y., Durakoglugil, M. S., Xian, X., & Herz, J. (2010). ApoE4 reduces glutamate receptor function and synaptic plasticity by selectively impairing ApoE receptor recycling. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(26), 12011–12016. https://doi.org/10.1073/pnas.0914984107

Chiu, P. W., Lui, S. S. Y., Hung, K. S. Y., Chan, R. C. K., Chan, Q., Sham, P. C., Cheung, E. F. C., & Mak, H. K. F. (2018). In vivo gamma-aminobutyric acid and glutamate levels in people with first-episode schizophrenia: A proton magnetic resonance spectroscopy study. *Schizophrenia Research*, *193*, 295–303. https://doi.org/10.1016/j.schres.2017.07.021

Chiu, P. W., Mak, H. K., Chan, Y., Chan, T., & Ho, K. M. (2015). Hippocampal MR spectroscopic abnormalities in a cohort of syphilitic patients with HIV and neurosyphilis infection. *Am J Nucl Med Mol Imaging*, *5*(1), 83-94. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/25625030

Chiu, P. W., Mak, H. K., Yau, K. K., Chan, Q., Chang, R. C., & Chu, L. W. (2014). Metabolic changes in the anterior and posterior cingulate cortices of the normal aging brain: Proton magnetic resonance spectroscopy study at 3 T. *Age (Dordrecht, Netherlands)*, *36*(1), 251–264. https://doi.org/10.1007/s11357-013-9545-8

D'Esposito, M., Deouell, L. Y., & Gazzaley, A. (2003). Alterations in the BOLD fMRI signal with ageing and disease: A challenge for neuroimaging. *Nature Reviews. Neuroscience*, *4*(11), 863–872. https://doi.org/10.1038/nrn1246

Dickerson, B. C., Salat, D. H., Greve, D. N., Chua, E. F., Rand-Giovannetti, E., Rentz, D. M., Bertram, L., Mullin, K., Tanzi, R. E., Blacker, D., Albert, M. S., & Sperling, R. A. (2005). Increased hippocampal activation in mild cognitive impairment compared to normal aging and AD. *Neurology*, *65*(3), 404–411. https://doi.org/10.1212/01.wnl.0000171450.97464.49

Duarte, J. M., Lei, H., Mlynarik, V., & Gruetter, R. (2012). The neurochemical profile quantified by in vivo 1H NMR spectroscopy. *NeuroImage*, *61*(2), 342–362. https://doi.org/10.1016/j.neuroimage.2011.12.038

Duncan, N. W., Wiebking, C., & Northoff, G. (2014). Associations of regional GABA and glutamate with intrinsic and extrinsic neural activity in humans-a review of multimodal imaging studies. *Neuroscience and Biobehavioral Reviews*, *47*, 36–52. https://doi.org/10.1016/j.neubiorev.2014.07.016

Filippini, N., MacIntosh, B. J., Hough, M. G., Goodwin, G. M., Frisoni, G. B., Smith, S. M., Matthews, P. M., Beckmann, C. F., & Mackay, C. E. (2009). Distinct patterns of brain activity in young carriers of the APOE-epsilon4 allele. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(17), 7209–7214. https://doi.org/10.1073/pnas.0811879106

Fleisher, A. S., Houston, W. S., Eyler, L. T., Frye, S., Jenkins, C., Thal, L. J., & Bondi, M. W. (2005). Identification of Alzheimer disease risk by functional magnetic resonance imaging. *Archives of Neurology*, *62*(12), 1881–1888. https://doi.org/10.1001/archneur.62.12.1881

Fleisher, A. S., Podraza, K. M., Bangen, K. J., Taylor, C., Sherzai, A., Sidhar, K., Liu, T. T., Dale, A. M., & Buxton, R. B. (2009). Cerebral perfusion and oxygenation differences in Alzheimer's disease risk. *Neurobiology of Aging*, *30*(11), 1737–1748. https://doi.org/10.1016/j.neurobiolaging.2008.01.012

Han, S. D., & Bondi, M. W. (2008). Revision of the apolipoprotein E compensatory mechanism recruitment hypothesis. *Alzheimers*

Dement, *4*(4), 251–254. https://doi.org/10.1016/j.jalz.2008.02.006

Hattori, N., Abe, K., Sakoda, S., & Sawada, T. (2002). Proton MR spectroscopic study at 3 tesla on glutamate/glutamine in Alzheimer's disease. *Neuroreport*, *13*(1), 183–186. https://doi.org/10.1097/00001756-200201210-00041

Haxby, J. V., Ungerleider, L. G., Horwitz, B., Maisog, J. M., Rapoport, S. I., & Grady, C. L. (1996). Face encoding and recognition in the human brain. *Proceedings of the National Academy of Sciences of the United States of America*, *93*(2), 922–927. https://doi.org/10.1073/pnas.93.2.922

Heffernan, A. L., Chidgey, C., Peng, P., Masters, C. L., & Roberts, B. R. (2016). The neurobiology and age-related prevalence of the epsilon4 allele of Apolipoprotein E in Alzheimer's disease cohorts. *Journal of Molecular Neuroscience*, *60*(3), 316–324. https://doi.org/10.1007/s12031-016-0804-x

Herrup, K. (2010). Reimagining Alzheimer's disease—An age-based hypothesis. *The Journal of Neuroscience*, *30*(50), 16755–16762. https://doi.org/10.1523/JNEUROSCI.4521-10.2010

Herrup, K. (2015). The case for rejecting the amyloid cascade hypothesis. *Nature Neuroscience*, *18*(6), 794–799. https://doi.org/10.1038/nn.4017

Hosford, P. S., & Gourine, A. V. (2019). What is the key mediator of the neurovascular coupling response? *Neuroscience and Biobehavioral Reviews*, *96*, 174–181. https://doi.org/10.1016/j.neubiorev.2018.11.011

Hu, Y., Chen, X., Gu, H., & Yang, Y. (2013). Resting-state glutamate and GABA concentrations predict task-induced deactivation in the default mode network. *The Journal of Neuroscience*, *33*(47), 18566–18573. https://doi.org/10.1523/JNEUROSCI.1973-13.2013

Hyder, F., Patel, A. B., Gjedde, A., Rothman, D. L., Behar, K. L., & Shulman, R. G. (2006). Neuronal-glial glucose oxidation and glutamatergic-GABAergic function. *Journal of Cerebral Blood Flow and Metabolism*, *26*(7), 865–877. https://doi.org/10.1038/sj.jcbfm.9600263

Jackson, R. J., Rose, J., Tulloch, J., Henstridge, C., Smith, C., & Spires-Jones, T. L. (2019). Clusterin accumulates in synapses in Alzheimer's disease and is increased in apolipoprotein E4 carriers. *Brain Commun*, *1*(1), fcz003. https://doi.org/10.1093/braincomms/fcz003

Ji, Y., Gong, Y., Gan, W., Beach, T., Holtzman, D. M., & Wisniewski, T. (2003). Apolipoprotein E isoform-specific regulation of dendritic spine morphology in apolipoprotein E transgenic mice and Alzheimer's disease patients. *Neuroscience*, *122*(2), 305–315. https://doi.org/10.1016/j.neuroscience.2003.08.007

Johnson, S. C., Schmitz, T. W., Trivedi, M. A., Ries, M. L., Torgerson, B. M., Carlsson, C. M., Asthana, S., Hermann, B. P., & Sager, M. A. (2006). The influence of Alzheimer disease family history and apolipoprotein E epsilon4 on mesial temporal lobe activation. *The Journal of Neuroscience*, *26*(22), 6069–6076. https://doi.org/10.1523/JNEUROSCI.0959-06.2006

Kantarci, K. (2013). Proton MRS in mild cognitive impairment. *Journal of Magnetic Resonance Imaging*, *37*(4), 770–777. https://doi.org/10.1002/jmri.23800

Keene, C. D., Cudaback, E., Li, X., Montine, K. S., & Montine, T. J. (2011). Apolipoprotein E isoforms and regulation of the innate immune response in brain of patients with Alzheimer's disease. *Current Opinion in Neurobiology*, *21*(6), 920–928. https://doi.org/10.1016/j.conb.2011.08.002

Khan, W., Giampietro, V., Ginestet, C., Dell'Acqua, F., Bouls, D., Newhouse, S., ... consortium, I. (2014). No differences in hippocampal volume between carriers and non-carriers of the ApoE epsilon4 and epsilon2 alleles in young healthy adolescents. *Journal of Alzheimer's Disease*, *40*(1), 37–43. https://doi.org/10.3233/JAD-131841

Kim, J., Basak, J. M., & Holtzman, D. M. (2009). The role of apolipoprotein E in Alzheimer's disease. *Neuron*, *63*(3), 287–303. https://doi.org/10.1016/j.neuron.2009.06.026

Kirwan, C. B., & Stark, C. E. (2004). Medial temporal lobe activation during encoding and retrieval of novel face-name pairs. *Hippocampus*, *14*(7), 919–930. https://doi.org/10.1002/hipo.20014

Kohl, M. M., Shipton, O. A., Deacon, R. M., Rawlins, J. N., Deisseroth, K., & Paulsen, O. (2011). Hemisphere-specific optogenetic stimulation reveals left-right asymmetry of hippocampal plasticity. *Nature Neuroscience*, *14*(11), 1413–1415. https://doi.org/10.1038/nn.2915

Kreisl, W. C., Lyoo, C. H., Liow, J. S., Wei, M., Snow, J., Page, E., Jenko, K. J., Morse, C. L., Zoghbi, S. S., Pike, V. W., Turner, R. S., & Innis, R. B. (2016). (11)C-PBR28 binding to translocator protein increases with progression of Alzheimer's disease. *Neurobiology of Aging*, *44*, 53–61. https://doi.org/10.1016/j.neurobiolaging.2016.04.011

Kreisl, W. C., Lyoo, C. H., McGwier, M., Snow, J., Jenko, K. J., Kimura, N., ... Biomarkers Consortium, P. E. T. R. P. T. (2013). In vivo radioligand binding to translocator protein correlates with severity of Alzheimer's disease. *Brain*, *136*(Pt 7), 2228–2238. https://doi.org/10.1093/brain/awt145

Lane-Donovan, C., & Herz, J. (2017). ApoE, ApoE receptors, and the synapse in Alzheimer's disease. *Trends in Endocrinology and Metabolism*, *28*(4), 273–284. https://doi.org/10.1016/j.tem.2016.12.001

Li, Y., Liu, P., Li, Y., Fan, H., Su, P., Peng, S. L., Park, D. C., Rodrigue, K. M., Jiang, H., Faria, A. V., Ceritoglu, C., Miller, M., Mori, S., & Lu, H. (2019). ASL-MRICloud: An online tool for the processing of ASL MRI data. *NMR in Biomedicine*, *32*(2), e4051. https://doi.org/10.1002/nbm.4051

Liddelow, S. A., Guttenplan, K. A., Clarke, L. E., Bennett, F. C., Bohlen, C. J., Schirmer, L., Bennett, M. L., Münch, A. E., Chung, W. S., Peterson, T. C., Wilton, D. K., Frouin, A., Napier, B. A., Panicker, N., Kumar, M., Buckwalter, M. S., Rowitch, D. H., Dawson, V. L., Dawson, T. M., ... Barres, B. A. (2017). Neurotoxic reactive astrocytes are induced by activated microglia. *Nature*, *541*(7638), 481–487. https://doi.org/10.1038/nature21029

Liraz, O., Boehm-Cagan, A., & Michaelson, D. M. (2013). ApoE4 induces Abeta42, tau, and neuronal pathology in the hippocampus of young targeted replacement apoE4 mice. *Molecular Neurodegeneration*, *8*, 16. https://doi.org/10.1186/1750-1326-8-16

Liu, C. C., Kanekiyo, T., Xu, H., & Bu, G. (2013). Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nature Reviews. Neurology*, *9*(2), 106–118. https://doi.org/10.1038/nrneurol.2012.263

Logothetis, N. K., Pauls, J., Augath, M., Trinath, T., & Oeltermann, A. (2001). Neurophysiological investigation of the

basis of the fMRI signal. *Nature*, *412*(6843), 150–157. https://doi.org/10.1038/35084005

Love, S., Siew, L. K., Dawbarn, D., Wilcock, G. K., Ben-Shlomo, Y., & Allen, S. J. (2006). Premorbid effects of APOE on synaptic proteins in human temporal neocortex. *Neurobiology of Aging*, *27*(6), 797–803. https://doi.org/10.1016/j.neurobiolaging.2005.04.008

Lu, H., Xu, F., Rodrigue, K. M., Kennedy, K. M., Cheng, Y., Flicker, B., Hebrank, A. C., Uh, J., & Park, D. C. (2011). Alterations in cerebral metabolic rate and blood supply across the adult lifespan. *Cerebral Cortex*, *21*(6), 1426–1434. https://doi.org/10.1093/cercor/bhq224

Mazziotta, J. C., Woods, R., Iacoboni, M., Sicotte, N., Yaden, K., Tran, M., ... Members of the International Consortium for Brain, M. (2009). The myth of the normal, average human brain—The ICBM experience: (1) subject screening and eligibility. *NeuroImage*, *44*(3), 914–922. https://doi.org/10.1016/j.neuroimage.2008.07.062

Medina, L. D., Rodriguez-Agudelo, Y., Geschwind, D. H., Gilbert, P. E., Liang, L. J., Cummings, J. L., & Ringman, J. M. (2011). Propositional density and apolipoprotein E genotype among persons at risk for familial Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders*, *32*(3), 188–192. https://doi.org/10.1159/000333023

Mondadori, C. R., de Quervain, D. J., Buchmann, A., Mustovic, H., Wollmer, M. A., Schmidt, C. F., ... Henke, K. (2007). Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. *Cerebral Cortex*, *17*(8), 1934–1947. https://doi.org/10.1093/cercor/bhl103

Nee, D. E., & Jonides, J. (2008). Neural correlates of access to short-term memory. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(37), 14228–14233. https://doi.org/10.1073/pnas.0802081105

Parra, M. A., Abrahams, S., Logie, R. H., Mendez, L. G., Lopera, F., & Della Sala, S. (2010). Visual short-term memory binding deficits in familial Alzheimer's disease. *Brain*, *133*(9), 2702–2713. https://doi.org/10.1093/brain/awq148

Putcha, D., O'Keefe, K., LaViolette, P., O'Brien, J., Greve, D., Rentz, D. M., Locascio, J., Atri, A., & Sperling, R. (2011). Reliability of functional magnetic resonance imaging associative encoding memory paradigms in non-demented elderly adults. *Human Brain Mapping*, *32*(12), 2027–2044. https://doi.org/10.1002/hbm.21166

Ramadan, S., Lin, A., & Stanwell, P. (2013). Glutamate and glutamine: A review of in vivo MRS in the human brain. *NMR in Biomedicine*, *26*(12), 1630–1646. https://doi.org/10.1002/nbm.3045

Reiman, E. M., Caselli, R. J., Yun, L. S., Chen, K., Bandy, D., Minoshima, S., Thibodeau, S. N., & Osborne, D. (1996). Preclinical evidence of Alzheimer's disease in persons homozygous for the epsilon 4 allele for apolipoprotein E. *The New England Journal of Medicine*, *334*(12), 752–758. https://doi.org/10.1056/NEJM199603213341202

Reiman, E. M., Chen, K., Alexander, G. E., Caselli, R. J., Bandy, D., Osborne, D., Saunders, A. M., & Hardy, J. (2004). Functional brain abnormalities in young adults at genetic risk for late-onset Alzheimer's dementia. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(1), 284–289. https://doi.org/10.1073/pnas.2635903100

Reiman, E. M., Chen, K., Liu, X., Bandy, D., Yu, M., Lee, W., Ayutyanont, N., Keppler, J., Reeder, S. A., Langbaum, J. B. S., Alexander, G. E., Klunk, W. E., Mathis, C. A., Price, J. C., Aizenstein, H. J., DeKosky, S. T., & Caselli, R. J. (2009). Fibrillar amyloid-beta burden in cognitively normal people at 3 levels of genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(16), 6820–6825. https://doi.org/10.1073/pnas.0900345106

Revett, T. J., Baker, G. B., Jhamandas, J., & Kar, S. (2013). Glutamate system, amyloid ss peptides and tau protein: Functional interrelationships and relevance to Alzheimer disease pathology. *Journal of Psychiatry & Neuroscience*, *38*(1), 6–23. https://doi.org/10.1503/jpn.110190

Riese, F., Gietl, A., Zolch, N., Henning, A., O'Gorman, R., Kalin, A. M., ... Michels, L. (2015). Posterior cingulate gamma-aminobutyric acid and glutamate/glutamine are reduced in amnestic mild cognitive impairment and are unrelated to amyloid deposition and apolipoprotein E genotype. *Neurobiology of Aging*, *36*(1), 53–59. https://doi.org/10.1016/j.neurobiolaging.2014.07.030

Riley, K. P., Snowdon, D. A., Desrosiers, M. F., & Markesbery, W. R. (2005). Early life linguistic ability, late life cognitive function, and neuropathology: Findings from the Nun study. *Neurobiology of Aging*, *26*(3), 341–347. https://doi.org/10.1016/j.neurobiolaging.2004.06.019

Shaw, P., Lerch, J. P., Pruessner, J. C., Taylor, K. N., Rose, A. B., Greenstein, D., Clasen, L., Evans, A., Rapoport, J. L., & Giedd, J. N. (2007). Cortical morphology in children and adolescents with different apolipoprotein E gene polymorphisms: An observational study. *The Lancet Neurology*, *6*(6), 494–500. https://doi.org/10.1016/s1474-4422(07)70106-0

Shen, J. (2006). 13C magnetic resonance spectroscopy studies of alterations in glutamate neurotransmission. *Biological Psychiatry*, *59*(10), 883–887. https://doi.org/10.1016/j.biopsych.2005.07.042

Shine, J. P., Hodgetts, C. J., Postans, M., Lawrence, A. D., & Graham, K. S. (2015). APOE-epsilon4 selectively modulates posteromedial cortex activity during scene perception and short-term memory in young healthy adults. *Scientific Reports*, *5*, 16322. https://doi.org/10.1038/srep16322

Shinohara, Y., Hirase, H., Watanabe, M., Itakura, M., Takahashi, M., & Shigemoto, R. (2008). Left-right asymmetry of the hippocampal synapses with differential subunit allocation of glutamate receptors. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(49), 19498–19503. https://doi.org/10.1073/pnas.0807461105

Shipton, O. A., El-Gaby, M., Apergis-Schoute, J., Deisseroth, K., Bannerman, D. M., Paulsen, O., & Kohl, M. M. (2014). Left-right dissociation of hippocampal memory processes in mice. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(42), 15238–15243. https://doi.org/10.1073/pnas.1405648111

Sidiropoulos, C., Jafari-Khouzani, K., Soltanian-Zadeh, H., Mitsias, P., Alexopoulos, P., Richter-Schmidinger, T., Reichel, M., Lewczuk, P., Doerfler, A., & Kornhuber, J. (2011). Influence of brain-derived neurotrophic factor and apolipoprotein E genetic variants on hemispheric and lateral ventricular volume of young healthy adults. *Acta Neuropsychiatr*, *23*(3), 132–138. https://doi.org/10.1111/j.1601-5215.2011.00546.x

Small, G. W. (1995). Apolipoprotein E type 4 allele and cerebral glucose metabolism in relatives at risk for familial Alzheimer disease. *JAMA: The Journal of the American Medical Association*, *273*(12), 942–947. https://doi.org/10.1001/jama.1995.03520360056039

Small, G. W., Ercoli, L. M., Silverman, D. H., Huang, S. C., Komo, S., Bookheimer, S. Y., ... Phelps, M. E. (2000). Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(11), 6037–6042. https://doi.org/10.1073/pnas.090106797

Smith, C. D., Andersen, A. H., Kryscio, R. J., Schmitt, F. A., Kindy, M. S., Blonder, L. X., & Avison, M. J. (1999). Altered brain activation in cognitively intact individuals at high risk for Alzheimer's disease. *Neurology*, *53*(7), 1391–1396. https://doi.org/10.1212/wnl.53.7.1391

Snowdon, D. A. (1996). Linguistic ability in early life and cognitive function and Alzheimer's Disease in late life. *JAMA*, *275*(7), 528–532. https://doi.org/10.1001/jama.1996.03530310034029

Sperling, R. A., Bates, J. F., Cocchiarella, A. J., Schacter, D. L., Rosen, B. R., & Albert, M. S. (2001). Encoding novel face-name associations: A functional MRI study. *Human Brain Mapping*, *14*(3), 129–139. https://doi.org/10.1002/hbm.1047

Sperling, R. A., Chua, E., Cocchiarella, A., Rand-Giovannetti, E., Poldrack, R., Schacter, D. L., & Albert, M. (2003). Putting names to faces: Successful encoding of associative memories activates the anterior hippocampal formation. *NeuroImage*, *20*(2), 1400–1410. https://doi.org/10.1016/s1053-8119(03)00391-4

Sperling, R. A., Laviolette, P. S., O'Keefe, K., O'Brien, J., Rentz, D. M., Pihlajamaki, M., ... Johnson, K. A. (2009). Amyloid deposition is associated with impaired default network function in older persons without dementia. *Neuron*, *63*(2), 178–188. https://doi.org/10.1016/j.neuron.2009.07.003

Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., & Raichle, M. E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences of the United States of America*, *89*(5), 1837–1841. https://doi.org/10.1073/pnas.89.5.1837

Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, *253*(5026), 1380–1386. https://doi.org/10.1126/science.1896849

Stanley, J. A., Burgess, A., Khatib, D., Ramaseshan, K., Arshad, M., Wu, H., & Diwadkar, V. A. (2017). Functional dynamics of hippocampal glutamate during associative learning assessed with in vivo (1)H functional magnetic resonance spectroscopy. *NeuroImage*, *153*, 189–197. https://doi.org/10.1016/j.neuroimage.2017.03.051

Stanley, J. A., & Raz, N. (2018). Functional magnetic resonance spectroscopy: The "new" MRS for cognitive neuroscience and psychiatry research. *Frontiers in Psychiatry*, *9*, 76. https://doi.org/10.3389/fpsyt.2018.00076

Sun, X., Dong, C., Levin, B., Crocco, E., Loewenstein, D., Zetterberg, H., ... Alzheimer's Disease Neuroimaging, I. (2016). APOE epsilon4 carriers may undergo synaptic damage conferring risk of Alzheimer's disease. *Alzheimers Dement*, *12*(11), 1159–1166. https://doi.org/10.1016/j.jalz.2016.05.003

Sweet, R. A., MacDonald, M. L., Kirkwood, C. M., Ding, Y., Schempf, T., Jones-Laughner, J., Kofler, J., Ikonomovic, M. D., Lopez, O. L., Garver, M. E., Fitz, N. F., Koldamova, R., & Yates, N. A. (2016). Apolipoprotein E*4 (APOE*4) genotype is associated with altered levels of glutamate signaling proteins and synaptic Coexpression networks in the prefrontal cortex in mild to moderate Alzheimer Disease. *Molecular & Cellular Proteomics*, *15*(7), 2252–2262. https://doi.org/10.1074/mcp.M115.056580

Tai, L. M., Ghura, S., Koster, K. P., Liakaite, V., Maienschein-Cline, M., Kanabar, P., Collins, N., Ben-Aissa, M., Lei, A. Z., Bahroos, N., Green, S. J., Hendrickson, B., van Eldik, L. J., & LaDu, M. J. (2015). APOE-modulated Abeta-induced neuroinflammation in Alzheimer's disease: Current landscape, novel data, and future perspective. *Journal of Neurochemistry*, *133*(4), 465–488. https://doi.org/10.1111/jnc.13072

Taylor, R., Neufeld, R. W., Schaefer, B., Densmore, M., Rajakumar, N., Osuch, E. A., ... Theberge, J. (2015). Functional magnetic resonance spectroscopy of glutamate in schizophrenia and major depressive disorder: Anterior cingulate activity during a color-word Stroop task. *NPJ Schizophrenia*, *1*, 15028. https://doi.org/10.1038/npjschz.2015.28

Trivedi, M. A., Schmitz, T. W., Ries, M. L., Torgerson, B. M., Sager, M. A., Hermann, B. P., Asthana, S., & Johnson, S. C. (2006). Reduced hippocampal activation during episodic encoding in middle-aged individuals at genetic risk of Alzheimer's disease: A cross-sectional study. *BMC Medicine*, *4*, 1. https://doi.org/10.1186/1741-7015-4-1

Tsukiura, T., & Cabeza, R. (2011). Remembering beauty: Roles of orbitofrontal and hippocampal regions in successful memory encoding of attractive faces. *NeuroImage*, *54*(1), 653–660. https://doi.org/10.1016/j.neuroimage.2010.07.046

Vannini, P., Hedden, T., Becker, J. A., Sullivan, C., Putcha, D., Rentz, D., Johnson, K. A., & Sperling, R. A. (2012). Age and amyloid-related alterations in default network habituation to stimulus repetition. *Neurobiology of Aging*, *33*(7), 1237–1252. https://doi.org/10.1016/j.neurobiolaging.2011.01.003

Wolf, A. B., Caselli, R. J., Reiman, E. M., & Valla, J. (2013). APOE and neuroenergetics: An emerging paradigm in Alzheimer's disease. *Neurobiology of Aging*, *34*(4), 1007–1017. https://doi.org/10.1016/j.neurobiolaging.2012.10.011

Wolf, A. B., Valla, J., Bu, G., Kim, J., LaDu, M. J., Reiman, E. M., & Caselli, R. J. (2013). Apolipoprotein E as a beta-amyloid-independent factor in Alzheimer's disease. *Alzheimer's Research & Therapy*, *5*(5), 38. https://doi.org/10.1186/alzrt204

Wong, A., Xiong, Y. Y., Kwan, P. W., Chan, A. Y., Lam, W. W., Wang, K., ... Mok, V. C. (2009). The validity, reliability and clinical utility of the Hong Kong Montreal cognitive assessment (HK-MoCA) in patients with cerebral small vessel disease. *Dementia and Geriatric Cognitive Disorders*, *28*(1), 81–87. https://doi.org/10.1159/000232589

Yu, Y. W. Y., Lin, C.-H., Chen, S.-P., Hong, C.-J., & Tsai, S.-J. (2000). Intelligence and event-related potentials for young female human volunteer apolipoprotein E ε4 and non-ε4 carriers. *Neuroscience Letters*, *294*(3), 179–181. https://doi.org/10.1016/s0304-3940(00)01569-x

Zadori, D., Veres, G., Szalardy, L., Klivenyi, P., Toldi, J., & Vecsei, L. (2014). Glutamatergic dysfunctioning in Alzheimer's disease and related therapeutic targets. *Journal of Alzheimer's Disease*, *42*(Suppl 3), S177–S187. https://doi.org/10.3233/JAD-132621

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science*, *299*(5606), 577–580. https://doi.org/10.1126/science.1077775

Zhao, N., Liu, C. C., Qiao, W., & Bu, G. (2018). Apolipoprotein E, receptors, and modulation of Alzheimer's Disease. *Biological Psychiatry*, *83*(4), 347–357. https://doi.org/10.1016/j.biopsych.2017.03.003

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Zhang, H., Chiu, P. W., Ip, I., Liu, T., Wong, G. H. Y., Song, Y.-Q., Wong, S. W. H., Herrup, K., & Mak, H. K. F. (2021). Asymmetric left–right hippocampal glutamatergic modulation of cognitive control in ApoE-isoform subjects is unrelated to neuroinflammation. *European Journal of Neuroscience*, *54*(4), 5310–5326. https://doi.org/10.1111/ejn.15399