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ORIGINAL ARTICLE

Amyloid-independent functional neural correlates of episodic memory in amnestic mild cognitive impairment

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Abstract
Purpose Although amnestic mild cognitive impairment (aMCI) could have various biological characteristics, little attention has been given to the nature of episodic memory decline in aMCI with pathophysiologies other than Alzheimer's disease (AD), i.e., aMCI with low beta-amyloid (Aβ) burden. This study aimed to identify the functional neural basis of episodic memory impairment in aMCI with Aβ burden negative (aMCI-Aβ−) and to compare these results with aMCI with Aβ burden positive (aMCI-Aβ+).
Methods Individuals with aMCI (n=498) were selected from the Alzheimer's Disease Neuroimaging Initiative database. Based on the mean florbetapir standard uptake value ratio, participants were classified as aMCI-Aβ− or aMCI-Aβ+. Correlations between memory scores and regional cerebral glucose metabolism (rCMglc) were analyzed separately for the two subgroups using a multiple regression model.
Results For aMCI-Aβ−, significant positive correlations between memory and rCMglc were found in the bilateral claustrum, right thalamus, left anterior cingulate cortex, left insula, and right posterior cingulate. For aMCI-Aβ+, significant positive correlations between memory and rCMglc were found in the temporoparietal areas. These correlation patterns remained unchanged when clinical severity was added as a covariate
Conclusion Our findings indicate that memory impairment in aMCI-Aβ− is related to multimodal integrative processing and the attentional control system, whereas memory impairment in aMCI-Aβ+is related to the typical brain memory systems and AD signature. These results suggest that although the two subgroups are clinically in the same category as aMCI, the memory impairment process depends on completely different functional brain regions according to their Aβ burden level.

Keywords Amnestic mild cognitive impairment · Aβ burden · Episodic memory · Regional cerebral glucose metabolism

Introduction

Mild cognitive impairment (MCI) is the state of impairment of memory or other cognitive domains, but with preserved functional independence. However, biological characteristics of MCI are highly heterogeneous. For example, in a study using amyloid imaging and clinical diagnostics, the MCI group showed the lowest rate of concordance between molecular and clinical diagnosis [1]. Even the clinically homogeneous MCI group from the Alzheimer's Disease Neuroimaging Initiative (ADNI) showed four clusters with distinct biomarker patterns [2]. Furthermore, previous studies on MCI conversion to dementia showed that MCI is not always a prodromal form of Alzheimer's disease (AD), but can be any type of

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

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dementia [3] or a reversible case [2]. These serve as evidence that MCI likely arises from multiple etiologies.

The relationship between the brain function and cognition is important for the understanding of an underlying pathology. Given that memory impairment is the core cognitive characteristic of amnestic MCI (aMCI), functional and structural neuroanatomy of memory in aMCI has been investigated over the past few years [4–8]. Results suggest that the medial temporal lobe (MTL) volume and posterior cingulate and frontal functions correlate with memory scores. Particularly, one recent meta-analysis of functional imaging studies demonstrated that in addition to those brain memory systems, claustrum activity in healthy elderly individuals was observed during episodic memory retrieval [9]. Although a great deal of effort has been made to elucidate the neural correlates of memory in aging populations including aMCI and AD patients, little attention has been given to the nature of episodic memory failure especially in subjects with aMCI with etiologies other than AD, i.e., aMCI with low beta-amyloid (Aβ) burden. Apparently the aMCI group shows clinical homogeneity, such as episodic memory impairment; however, memory failure may include different mechanisms according to their own etiologies.

The relationship between memory and brain function has been assessed in vivo by the functional neuroimaging method. One commonly used methodology is [^{18}F]fluorodeoxyglucose positron emission tomography (FDG PET). Regional cerebral glucose metabolism (rCMglc), measured by FDG PET, is a reliable and a highly sensitive index of synaptic function [10, 11]. There is plenty of evidence showing that FDG PET imaging is a crucial tool for understanding underlying neurodegenerative pathology and for early diagnosis of AD and evaluating the brain-cognition relationship [12–15].

On the other hand, neuropsychological measures of episodic memory are various and cover different aspects of memory function. Most previous studies applied a single memory measure to correlate brain function with it [5, 8, 9]. More representative measures for episodic memory obtained by combining results from multiple tests can be used to more precisely assess the neural basis of memory.

Therefore, the purpose of this study was to identify the functional neural basis of episodic memory impairment in aMCI with low Aβ burden using FDG PET. In addition, we compared these results with those obtained in aMCI with high Aβ burden.

Materials and methods

Study participants

Participants were selected from the ADNI database (adni.loni.usc.edu). For a detailed explanation and up-to-date information on ADNI, please see www.adni-info.org. We included individuals with aMCI only if [^{18}F]florbetapir PET and FDG PET had been conducted within 3 months of a clinical and cognitive assessment visit. In the final analysis, we included 498 individuals with aMCI who had received clinical evaluation and PET scans between April 2010 and December 2013. Detailed eligibility criteria for aMCI are described elsewhere [16]. Briefly, aMCI subjects had a clinical dementia rating (CDR) [17] of 0.5, Mini-Mental State Examination (MMSE) scores between 24 and 30, a memory complaint with objective memory loss but showing no impairment in other cognitive domains, preserved activities of daily living, and were nondemented. For comparison purposes, cognitively normal (CN) subjects with low Aβ burden were also selected from the ADNI. They had a CDR of 0, MMSE score between 24 and 30, and were not depressed, without MCI, and nondemented. Institutional Review Boards approved the study procedures across participating institutions in ADNI. Written informed consent to share data for scientific research purposes was obtained from each participant.

Memory measures and clinical information

We selected memory measures and basic clinical information from ADNI participants. For memory measures, the ADNI composite scores for memory (ADNI-Mem) [18] were selected. This score was developed by combining the Rey Auditory Verbal Learning Test (RAVLT; trials 1–5, interference trial, immediate and delayed recall, and recognition), AD Assessment Schedule–Cognition (ADAS-Cog; word list trials 1–3, recall, and recognition), MMSE (3 words recall), and logical memory (LM; immediate and delayed recall).

We included the CDR sum of boxes (CDR SOB) as a clinical severity measure. This measure covers six domains of cognitive and daily functioning with a possible score ranging from 0 to 18. It is a useful tool for staging clinical severity. For everyday functioning, we included the functional assessment questionnaire (FAQ). This assesses the instrumental activities of daily living with a score ranging from 0 to 30 [19]. This questionnaire is helpful for monitoring functional changes [20]. For global cognition, the MMSE score was included.

Florbetapir PET

We collected the mean florbetapir standardized uptake value ratio (SUVR) for each participant. A detailed description of florbetapir PET acquisition and processing can be found on the ADNI website (http://adni.loni.usc.edu/wp-content/uploads/2010/05/ ADNI2_PET_Tech_Manual_014201.pdf) or in previously published reports [21]. Briefly, the subject's first florbetapir image was coregistered to their MR image and segmented into Freesurfer (version 4.5.0)-defined cortical

regions (frontal, anterior/posterior cingulate, lateral parietal, and lateral temporal). Following this, the mean florbetapir uptake from those gray matter regions was extracted relative to uptake in the whole cerebellum. Participants were classified as Aβ burden positive (aMCI-Aβ+) or Aβ burden negative (aMCI-Aβ−), according to the SUVR cutoff of 1.11 for amyloid positivity [21].

FDG PET preprocessing

To investigate the relation between ADNI-Mem and rCMglc, we collected the most preprocessed form of FDG PET data from the ADNI. The ADNI PET protocol was strictly followed in each site. The ADNI preprocessing steps of FDG PET data have been previously described [22]. Briefly, a quality control process was applied to all scans. It includes assessment for image resolution and uniformity, checking for statistical noise, motion assessment across temporal frames, and visual checks for common artifacts. Then, with original raw PET images, the different temporal frames are coregistered. All image sets including a dynamic image set and a single-frame averaged image set are reoriented to a common spatial orientation and interpolated onto a uniform image grid. To reduce inter-scanner differences (17 different scanner models from 3 vendors), images are smoothed with a scanner-specific filter derived from each site's Hoffman phantom [23] and then provided a common isotropic resolution of 8 mm full-width at half-maximum resolution [22]. We further preprocessed for group-level analysis. These scans were adjusted for their origin and spatially normalized to the Montreal Neurological Institute (MNI, McGill University, Montreal, QC, Canada) space using Statistical Parametric Mapping 8 (SPM8) (Institute of Neurology, University College of London, UK) implemented on MATLAB. Then they were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum. Since we investigated within the aMCI group, intensity normalization to pons or cerebellum was not performed. Instead, global normalization using proportional scaling was performed because it has a higher signal to noise ratio compared with cerebellar count normalization [24].

Statistical analysis

Demographic and clinical data were compared between groups using separate one-way analysis of variance (ANOVA) and χ^2 test for continuous and categorical variables, respectively. These analyses were performed using SPSS version 21.0 for Windows (SPSS Inc., Chicago, IL, USA); p values less than 0.05 were considered significant.

Voxel-based group comparisons in rCMglc were performed between CN and aMCI- Aβ− and between CN and aMCI-Aβ+. They were estimated on a voxel-by-voxel basis using a two-sample t test design with age as a covariate. We applied $p<0.05$ family-wise error (FWE) corrected for multiple comparisons, with an extent threshold of greater than 25 contiguous voxels. Second, correlation between the ADNI-Mem and rCMglc were analyzed separately for aMCI-Aβ− and aMCI-Aβ+groups using a multiple regression model with age, gender, and education as covariates, The statistical threshold was set at $p<0.001$, uncorrected for multiple comparisons, with an extent threshold of greater than 25 contiguous voxels. We did not apply corrections to control type I errors, because we aimed to explore the regional distribution patterns of memory neural correlates without a priori hypotheses. In additional analysis, to control clinical severity, CDR SOB was further added as a covariate to the multiple regression model. These analyses were performed using SPM8.

Results

Participant characteristics

Based on mean SUVR, the aMCI group was divided into aMCI-Aβ− (n=230) and aMCI-Aβ+(n=268). The demographic and clinical characteristics of the 498 subjects are presented in Table 1. No group differences in gender or education were found, whereas the aMCI-Aβ− group was younger than the aMCI-Aβ+. Apolipoprotein E (apoE) ε4 carriers were more frequent in aMCI-Aβ+subjects. Clinical severity

Table 1 Demographic and clinical characteristics of the participants

	aMCI-Aβ−	aMCI-Aβ+	Total
n	230	268	498
Age (SD), years	70.95 (8.32)	73.69 (7.14) [a]	72.43 (7.81)
Education (SD), years	16.34 (2.48)	15.94 (2.87)	16.12 (2.70)
Female, *n* (%)	127 (55.2)	154 (57.5)	281 (56.4)
apoE ε4 carriers, *n* (%)	54 (23.5)	173 (64.5) [a]	227 (45.6)
Aβ	1.00 (0.53)	1.37 (0.17) [a]	1.20 (0.22)
CDR SOB	1.32 (0.83)	1.63 (0.98) [a]	1.49 (0.93)
FAQ	1.97 (3.18)	3.29 (4.07) [a]	2.68 (3.74)
MMSE	28.52 (1.45)	27.64 (1.84) [a]	28.05 (1.73)
ADNI-Mem	0.55 (0.54)	0.19 (0.51) [a]	0.35 (0.55)
Hip volume	7326 (1146)	6777 (1055) [a]	7029 (1130)

Values are mean (standard deviation) for continuous variables or frequency (percentage) for gender and apoE genotype

aMCI-Aβ− amnestic mild cognitive impairment with low Aβ burden, *aMCI-Aβ+*amnestic mild cognitive impairment with high Aβ burden, *apoE* apolipoprotein E, *Aβ* average florbetapir mean SUVR of frontal, anterior cingulate, precuneus, and parietal cortex relative to the cerebellum, *CDR SOB* sum of boxes of the clinical dementia rating, *FAQ* functional assessment questionnaire, *MMSE* Mini-Mental State Examination, *ADNI-Mem* Alzheimer's disease neuroimaging initiative composite score for memory, *Hip volume* volume of the hippocampus

[a] Significant compared to aMCI-Aβ− ($p<0.001$)

and cognitive and everyday functioning were significantly worse in the aMCI-Aβ+than aMCI-Aβ− group.

Voxel-based group comparison of rCMglc

For comparison purposes, 219 CN subjects with Aβ burden negative from the ADNI data set were included (mean age 73.98, SD=6.65, range 56.2∼93.6; mean education 16.69, SD=2.58, range 8∼20). The aMCI-Aβ− group showed no significantly decreased or increased rCMglc regions, compared with the CN group. In contrast, the aMCI-Aβ+group showed significantly lower rCMglc in the bilateral temporal and posterior parietal regions compared with CN subjects (Fig. 1).

Relationship between ADNI-Mem and rCMglc

For the aMCI-Aβ− group, significant positive correlations between ADNI-Mem and rCMglc were found in the bilateral claustrum, right thalamus, left anterior cingulate cortex, left insula, and right posterior cingulate (Table 2 and Fig. 2).

On the other hand, in the aMCI-Aβ+group, significant positive correlations between ADNI-Mem and rCMglc were found in the left posterior cingulate cortex, left inferior parietal lobule, left middle temporal gyrus, left parahippocampal gyrus, left superior frontal gyrus, left fusiform gyrus, left thalamus, and right superior temporal gyrus (Table 2 and Fig. 3). These patterns of correlation remained unchanged when clinical severity was added as a covariate.

Discussion

This is the first study to our knowledge exploring the functional neural basis of episodic memory impairment in aMCI with Aβ burden negative using FDG PET. Our study revealed Aβ-independent positive associations between memory and rCMglc in the bilateral claustrum, right thalamus, left anterior cingulate, left insular, and right posterior cingulate in the aMCI-Aβ− subjects. On the other hand, positive associations were found mainly in the temporoparietal areas in the aMCI-Aβ+subjects.

The strong association between memory and claustrum in the aMCI-Aβ− group remained significant even controlled after clinical severity and multiple comparison corrections. This finding suggests that the claustrum is the key area for Aβ-independent memory failure. In line with our results, one meta-analysis on the relationship between episodic memory and functional imaging showed memory retrieval was related to claustrum activation in healthy subjects [9]. Until now, the function of the claustrum has been relatively poorly investigated and underestimated for its relevance in higher cognitive functions. The involvement of the claustrum in the memory process may be better understood in terms of brain connectivity. Recent diffusion tensor imaging (DTI) studies revealed that the claustrum has a central role in connecting multiple brain regions, and it showed the strongest probabilistic link with the MTL, particularly in the entorhinal cortex [25, 26] and connections with the superior frontal, precentral, postcentral, and posterior parietal cortices [27]. Based on this anatomical connectivity, the claustrum seems to receive input from multiple disparate parts of the brain, indicating it is a

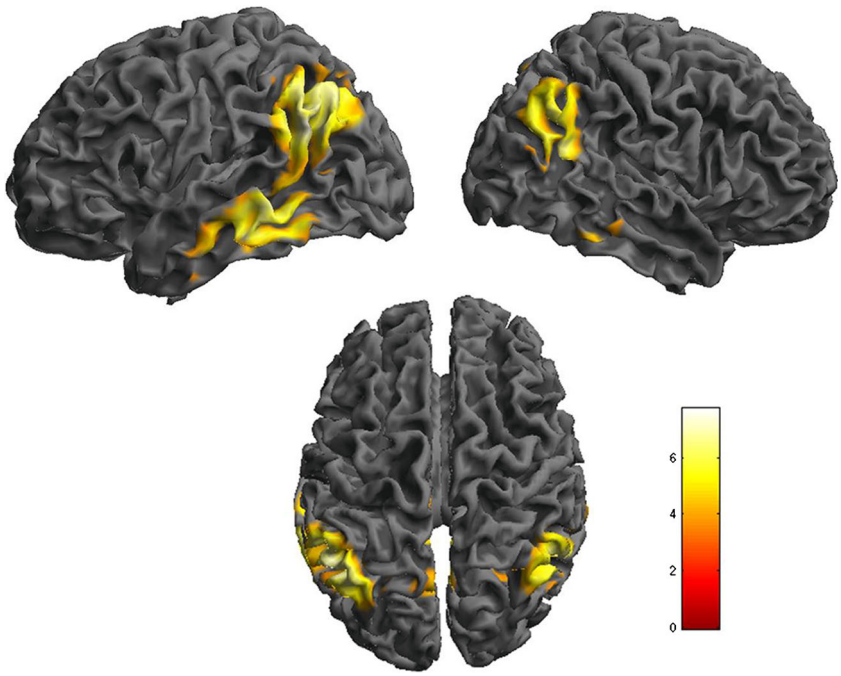

Fig. 1 Brain areas with reduced glucose metabolisms in aMCI with Aβ burden positive compared with the cognitively normal group. Group differences were estimated on a voxel-by-voxel basis using the two-sample *t* test design with age as a covariate. Significant regions are at $p<0.05$ FWE corrected for multiple comparisons, with an extent threshold of greater than 20 contiguous voxels

Table 2 Brain regions showing a significant positive correlation between memory score and glucose metabolism

Group	Brain region	BA	MNI coordinates			Voxels	Peak *t* value
			X	Y	Z		
aMCI-Aβ−	**R. claustrum**	–	**30**	**16**	**12**	**655**	**5.36**
	R. thalamus	–	30	−32	6		4.18
	L. claustrum	–	−24	18	6	459	4.25
	L. anterior cingulate	32	−26	34	14		4.01
	L. insula	13	−32	−6	20		3.80
	R. posterior cingulate	31	10	−28	42	26	3.41
aMCI-Aβ+	**L. posterior cingulate**	**31**	**−4**	**−53**	**27**	**3,752**	**8.96**
	L. parietal lobule	**40**	**−48**	**−62**	**36**	**2,962**	**6.46**
	L. middle temporal gyrus	**21**	**−64**	**−36**	**−10**	**2,058**	**5.69**
	L. hippocampus	–	**−26**	**−38**	**−8**		**5.07**
	L. parahippocampal gyrus	**35**	**−24**	**−16**	**−30**		**5.00**
	L. superior frontal gyrus	8	−26	40	48	57	4.47
	L. thalamus	–	−4	−12	8	68	3.90
	R. superior temporal gyrus	39	52	−62	32	222	3.88
	L. fusiform gyrus	20	−58	−6	−30	80	3.66

Bold=$p<0.05$ FWE corrected for multiple comparisons, otherwise $p<0.001$ uncorrected

aMCI-Aβ− amnestic mild cognitive impairment with low Aβ burden, *aMCI-Aβ+* amnestic mild cognitive impairment with high Aβ burden, *BA* Brodmann area, *R* right, *L* left

cornerstone of binding information from multimodal sources [26]. One event-related functional MRI study revealed that the claustrum was selectively activated when integrating conceptually related sounds and pictures [28]. Our aMCI-Aβ− group showed no cerebral glucose metabolic reductions compared with the CN group. Therefore, brain functions related to the typical memory system including the MTL seem to remain intact. Bearing the claustrum functions in mind, reductions

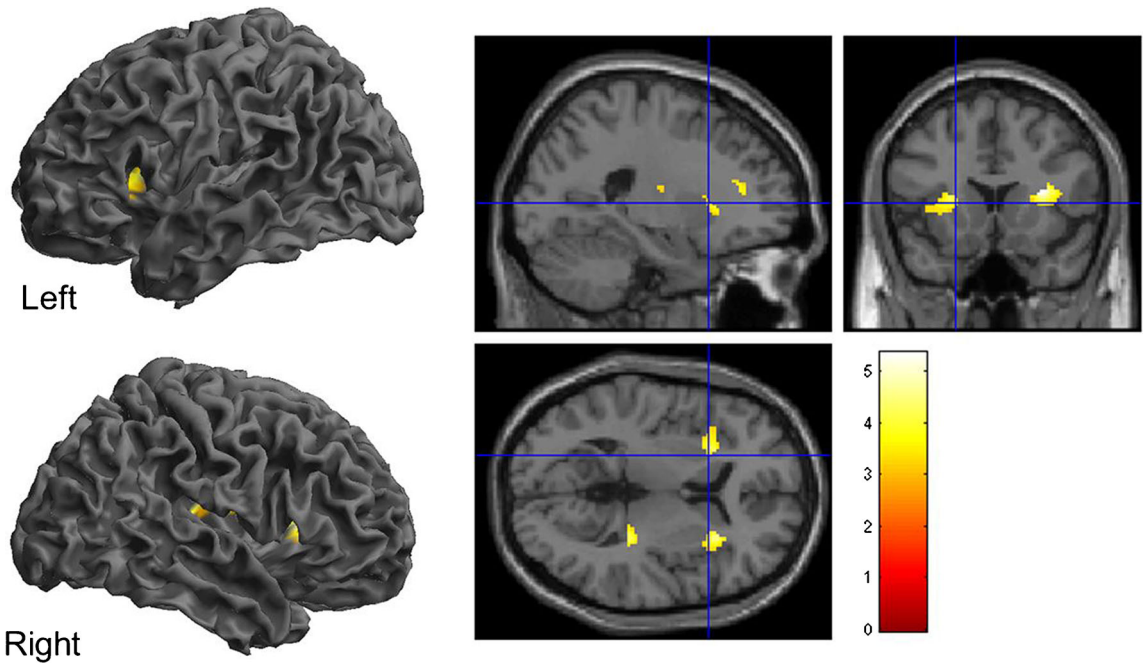

Fig. 2 Brain areas with significant positive correlations between rCMglc and memory in aMCI with Aβ burden negative. Statistical parametric maps showing the results of positive correlations between the ADNI memory composite score and rCMglc using a multiple regression model with age, gender, and education as covariates in aMCI with Aβ burden negative. Significant regions are at $p<0.001$ (uncorrected for multiple comparisons) with an extent threshold of greater than 20 contiguous voxels. The significant peak voxels of clusters are presented in Table 2

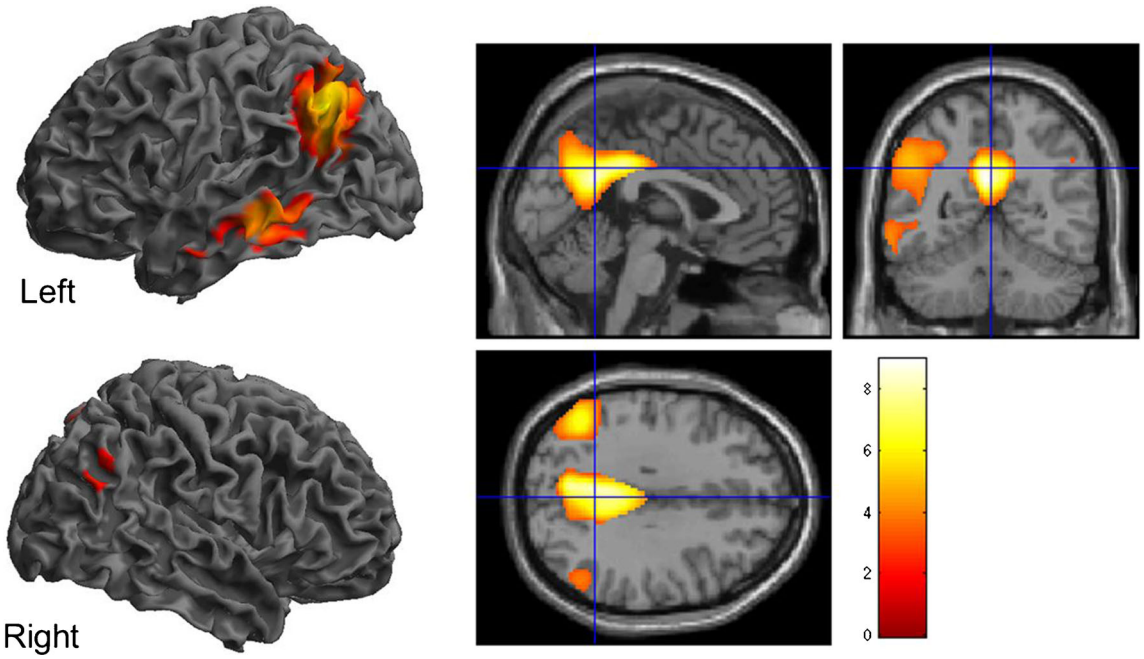

Fig. 3 Brain areas with significant positive correlations between glucose metabolism and memory in aMCI with Aβ burden positive. Statistical parametric maps showing the results of positive correlations between the ADNI memory composite scores and rCMglc using multiple regression model with age, gender, and education as covariates in aMCI with Aβ burden positive. Significant regions are at $p<0.001$ (uncorrected for multiple comparisons) with an extent threshold of greater than 20 contiguous voxels. The significant peak voxels of clusters are presented in Table 2

in cerebral glucose utilization in the claustrum in our aMCI-Aβ− subjects might reflect that their episodic memory decline could be related to inefficient integration from different information sources, rather than direct dysfunction of the memory-related brain system itself. Other positively correlated cerebral regions in the aMCI-Aβ− group are the anterior and posterior cingulate gyri that have been implicated in attentional control tasks [29–31]. Our findings suggest that although the MTL is the key area in episodic memory, the claustrum and cingulate gyrus play important roles in multimodal integration and attentional control that contribute to successful episodic memory functioning, particularly in aMCI with no AD pathology.

In the aMCI-Aβ+group, our results regarding associations between episodic memory performance and rCMglc in the left temporoparietal areas including the posterior cingulate, hippocampus, and parahippocampal gyrus are largely in accordance with the results from a number of previous studies investigating the relationship of brain function and memory that suggest those brain regions are crucial for memory [32–34]. Furthermore, these brain areas are closely in agreement with typical patterns of reduced brain metabolism in early AD [35]. Therefore, episodic memory failure in the aMCI-Aβ+group may be the consequence of AD pathology and dysfunctions in memory-related brain systems.

Another point worth noting is that we used the recently developed ADNI memory composite score [18] instead of conventional single memory measures. According to the original definition by Tulving et al., episodic memory involves receiving and storing new information about what is happening at a particular time and place, and re-experiencing it (retrieval) [36]. Because "successfully remembering" encompasses adequate encoding, storage, and retrieval [37], memory measures should include all these components. In this context, the ADNI memory composite score contains such episodic components. More specifically, the composite score includes several levels of episodic memory function with various difficulties such as encoding (new learning) and a retrieval procedure (delayed free recall and recognition) for both a simple word list and story. It also includes both auditory (three words from MMSE, RAVLT, and LM) and visually presented words (ten-word list from ADAS-Cog). Most previous neural correlate studies on memory used a single memory measure tapping only one of these features. The ADNI memory composite score is valid and better at detecting memory changes as well as a more representative measure for episodic memory by combining results from multiple tests [18]. However, it should be noted that nonverbal memory measures were excluded in the composite score. That is the reason why neural correlates of memory were strongly left lateralized, especially for the aMCI-Aβ+group.

Although our study has significant implications, there were some limitations and future directions to be discussed. First, involvement of the claustrum in the Aβ-independent episodic memory function is a relatively new finding in this research field. Therefore, additional studies with independent samples are needed to replicate our results. Second, we investigated the

neural basis for memory in terms of a localizationist view. Given that the claustrum has massive connectivity with the MTL, further network-based neural correlate studies using functional and structural imaging in an aMCI-Aβ+group are warranted for extending our knowledge of the mechanisms of underlying memory problems.

In conclusion, the current study is the first to separately explore the functional neural basis of episodic memory impairment in aMCI with and without Aβ pathology. In-depth understanding of the various pathophysiologies and the nature of memory failure in aMCI is crucial for prognosis and treatment. Our findings indicate that memory impairment in aMCI depends on different functional brain regions according to Aβ burden level. Memory impairment in aMCI-Aβ− group is related with multimodal integrative processing and the attentional control system, whereas memory impairment in the aMCI-Aβ+group is related with the typical brain memory systems and AD signature. These results suggest the possibility that although the two subgroups were clinically in the same aMCI category, the memory impairment process depends on completely different functional brain regions according to their Aβ burden level.

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Compliance with ethical standards

Conflicts of interest None.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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