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Changes in brain activity related to episodic memory retrieval in adults with single domain amnestic mild cognitive impairment

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ABSTRACT

The present fMRI study aimed to characterize the performance and the brain activity changes related to episodic memory retrieval in adults with single domain aMCI (sdaMCI), relative to cognitively unimpaired adults. Participants performed an old/new recognition memory task with words while BOLD signal was acquired. The sdaMCI group showed lower hits (correct recognition of old words), lower ability to discriminate old and new words, higher errors and longer reaction times for hits. This group also displayed brain hypoactivation in left precuneus and the left midcingulate cortex during the successful recognition of old words. These changes in brain activity suggest the presence of neural dysregulations in brain regions involved during successful episodic memory retrieval. Moreover, hypoactivation in these brain areas discriminated both groups with moderate sensitivity and specificity values, suggesting that it might constitute a potential neurocognitive biomarker of sdaMCI.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder in which several neuropathological changes that affect cognition take place. Recent research has shown that the onset of AD might appear 20 or even 30 years before the presence of clinical symptoms (Jansen et al., 2015). This, coupled with the lack of effective treatments for AD, has increased interest in the search for neurocognitive indices that enable early diagnosis of this disease. In this context, adults with amnestic mild cognitive impairment (aMCI) have become a target population for research. aMCI is defined as a clinical syndrome that often progresses to AD dementia and in which there is an objective memory disorder, with preserved activities of daily living and absence of dementia (Petersen, 2004, 2016; Petersen et al. 2014). In the search for neurocognitive indices of aMCI, the use of high spatial resolution techniques such as functional magnetic resonance imaging (fMRI) enables evaluation of the location of differences in brain activity in cognitively unimpaired adults and adults with aMCI. In this respect, fMRI studies have revealed that the most important effects of aMCI on brain activity occur in the medial temporal lobe (MTL), the frontal/prefrontal cortex, the posterior cingulate cortex (PCC) and inferior parietal cortex. These brain areas are functionally related to episodic memory (for recent reviews, see Bayram, Caldwell, & Banks, 2018; Chandra, Dervenoulas, Politis, & Initiative, 2019), a neurocognitive system that enables the conscious recollection of past experiences (Tulving, 2002). Episodic memory has typically been evaluated through an extensive variety of recognition memory tasks that consist of a memory encoding phase, in which participants are required to study and store new information in memory, and a retrieval phase, in which the participants have to respond whether an item was previously presented (correct recognition of an old stimulus, Hit) or not (correct identification of a new stimulus, Correct Rejection). Most previous fMRI studies evaluating aMCI have focused on encoding stages and have reported inconsistent findings (for a review, see Bayram et al., 2018) and the scarce studies focused on memory retrieval have also reported divergent results.

Regarding successful memory retrieval, it has been demonstrated that, relative to cognitively unimpaired controls, adults with aMCI showed brain hyperactivity in the lateral prefrontal cortex (Shu et al., 2021), the superior and inferior frontal gyrus (Heun et al., 2007; Trivedi et al., 2008), the superior temporal gyrus (Lenzi et al., 2011), the insula (Petrella *et al.* 2006) and sensorimotor areas such as the precentral gyrus and postcentral gyrus (Jin, Pelak, Curran, Nandy, & Cordes, 2012;

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Petrella et al., 2006). In addition, some studies have reported brain hypoactivity in frontal regions such as the superior, middle, inferior lateral and medial frontal gyrus (Mandzia, McAndrews, Grady, Graham, & Black, 2009), the ventrolateral prefrontal cortex and the medial frontal gyrus (Petrella et al., 2006; Shu et al., 2021; Trivedi et al., 2008), the parietal lobe and the posterior temporal lobe (Machulda et al., 2009), the parahippocampal gyrus/cortex (Jin et al., 2012; Trivedi et al., 2008), the hippocampus (Jin et al., 2012; Mandzia et al., 2009; Petrella et al., 2006; Shu et al., 2021), the cingulate gyrus (Mandzia et al., 2009), the angular gyrus and precuneus (Jin et al., 2012; Johnson et al., 2006; Machulda et al., 2009; Shu et al., 2021), the insula (Jin et al., 2012; Machulda et al., 2009) and the thalamus and occipital areas (Mandzia et al., 2009). In summary, there are important inconsistencies in the existing literature on fMRI findings in relation to aMCI. Thus, some studies have reported hyperactivity, others have reported hypoactivity and still others have reported hyperactivity and hypoactivity, suggesting that both fMRI activity patterns might coexist in aMCI (Jin et al., 2012; Petrella et al., 2006; Shu et al., 2021; Trivedi et al., 2008).

One important factor that may contribute to the discrepancies in findings is that the samples evaluated in some of the aforementioned fMRI studies include different aMCI subtypes (Machulda et al., 2009; Mandzia et al., 2009; Shu et al., 2021). According to Petersen et al. (2014). The aMCI can be differentiated into single-domain amnestic mild cognitive impairment (sdaMCI) and multiple-domain amnestic mild cognitive impairment (mdaMCI), depending on whether only memory (sdaMCI) or more (mdaMCI) cognitive domains are impaired. There is evidence showing differences in brain function and structure in adults with sdaMCI and adults with mdaMCI (for a review, see Li and Zhang, 2015). In particular, neuroimaging studies have demonstrated that, relative to adults with sdaMCI, adults with mdaMCI display (1) greater beta amyloid accumulation (Wolk et al., 2009), (2) greater grey matter atrophy in the superior frontal gyrus (Zhang et al., 2012) and reduced white matter integrity in temporal areas, the posterior parietal cortex, the frontal cortex and occipital lobe (Li et al., 2013) and (3) functional connectivity impairments in the default mode network (DMN) (Li et al., 2014).

It therefore seems that sdaMCI and mdaMCI represent two different levels of severity along a continuum between healthy aging and AD dementia (Brambati *et al.* 2009) and constitute two different cognitive stages with different brain activity patterns in the progression towards AD dementia.

In the case of those previous studies that compared sdaMCI and cognitively unimpaired adults (Heun et al., 2007; Jin et al., 2012; Johnson et al., 2006; Lenzi et al., 2011; Petrella et al., 2006; Trivedi et al., 2008) results are inconsistent probably due to the use of different analytical approaches (e.g. region of interest or whole brain analysis) and memory tasks with different types of stimuli that might require the involvement of different cognitive processes (Sevostianov et al., 2002). Importantly, none of these studies have evaluated whether the difference in brain activity between groups could represent a sensitive and specific neurocognitive marker of sdaMCI.

As far as we are concerned, the only fMRI study that used the same experimental paradigm (an old/new recognition task) and the same type of stimuli (words) as used in the present investigation was the study by Heun et al. (2007). This study revealed that, relative to cognitively unimpaired adults, adults with sdaMCI displayed hyperactivity in the right superior and inferior frontal gyrus during the successful recognition of old words and brain hyperactivity in the left middle frontal gyrus during the correct rejection of new words.

The scarcity and inconsistency of previous fMRI results and also the need to identify accurate neurocognitive indices of sdaMCI motivated that the main objective of the present study was to evaluate and compare the brain activity during the recognition phase of an old/new recognition task in adults with sdaMCI and cognitively unimpaired adults. The specific aims were as follows: (1) to characterize the brain areas that support successful recognition memory in cognitively unimpaired adults and adults with sdaMCI, and (2) to evaluate possible neural and behavioural changes in adults with sdaMCI by comparing the pattern of brain activity and task performance between both groups of participants.

We expected that, relative to cognitively unimpaired adults, the sdaMCI adults would show brain activity changes in MTL and posterior parietal regions due to the important functional role of these regions in episodic memory retrieval and their high vulnerability to showing early structural and functional changes in the progression towards AD dementia (for recent reviews, see Bayram et al., 2018; Chandra et al., 2019). In addition, considering the results of, to our knowledge, the only previous fMRI study in sdaMCI adults that have used a similar memory task with words as stimuli (Heun et al., 2007), we expected that adults with sdaMCI would show brain hyperactivity in the right superior and inferior frontal gyrus during the correct recognition of old words.

2. Materials and method

2.1. Participants

Twenty-four cognitively unimpaired (CU) old adults (mean age: 66 years, SD: 9.1) and twenty-four adults diagnosed with sdaMCI (mean age: 67.96 years, SD: 9.5). Participants were randomly selected from a larger sample participating in the longitudinal Compostela Aging Study (CompAS), referred to our research group from Primary Care Health Centres in Santiago de Compostela, Galicia (Spain). Both groups were matched with regard to age, sex and years of education, although the latter presented a statistical trend to significant differences between groups ($p = 0.06$).

The differences between groups for the demographic and neuropsychological measures (see Table 1) were evaluated via two sample *t*-tests and, for all continuous variables, the Coheńs D effect sizes were estimated (Lenhard & Lenhard, 2016). The research project was approved by the Galician Clinical Research Ethics Committee (Xunta de Galicia, Spain) and was performed in accordance with the ethical standards established in the 1964 Declaration of Helsinki (Lynöe, Sandlund, Dahlqvist, & Jacobsson, 1991). Participants gave their written informed consent prior to taking part in the study. All of them reported no previous diagnosis of any neurological disorder or psychiatric disturbances or history of clinical stroke, motor-sensory deficit or substance abuse/-dependence (alcohol or drug). Forty-five of the participants were right-handed and three were left-handed, as evaluated by the Edinburgh Handedness Inventory (Oldfield, 1971). All participants had normal audition and normal or corrected-to-normal vision. Participants were excluded if they had any of the following: prior diagnosis of depression or other psychiatric disturbances, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria (DSM-5 - American Psychiatric Association, 2013); prior diagnosis of neurological disease, including probable Alzheimer's Disease (AD) or other types of dementia, according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) and DMS-5 criteria; previous brain damage or brain surgery; previous chemotherapy; prior diagnosis of diabetes type II; sensory or motor disturbances; and consumption of substances that might affect normal performance of the tasks. The participants underwent clinical, neurological and neuropsychological examination conducted respectively by general practitioners, cognitive neurologists and neuropsychologists specialized in aging and dementia. MCI was diagnosed in accordance with Petersen's criteria (Albert et al., 2011; Petersen, 2004): (a) evidence of concern, corroborated by an informant about a change in cognition, relative to the previous level; (b) evidence of poorer performance in one or more cognitive domains that is greater than expected for the patient's age and educational background; (c) preservation of independence in functional abilities; and (d) non-fulfilment of diagnostic criteria for dementia (NINCDS-ADRDA and DSM-5 criteria). For criterion (b) we considered

Table 1
Mean values and standard deviations (SD, in brackets) of demographic and neuropsychological measures of CU adults and sdaMCI adults.

	CU	sdaMCI	p = *	Cohen's d effect sizes
	$N = 24$	$N = 24$		
Age	66 (9.1)	67.96 (9.5)	0.47	0.21
Years of education	13.96 (6.0)	10.88 (5.1)	0.06	0.55
Gender (Female/Male)	9/15	9/15		
General functioning				
MMSE	28.58 (1.98)	27.33 (2.46)	0.06	0.56
Attention				
TMT-A (seconds)	47.54 (33.63)	53.42 (24.65)	0.49	0.20
CAMCOG-R (Attention and Calculation)	8.04 (1.55)	7.79 (1.38)	0.56	0.17
Executive Function				
TMT-B (seconds)	121.96 (83.54)	156.44 (104.14)	0.22	0.37
Phonological Verbal Fluency	16.17 (5.65)	12.58 (4.30)	0.02	0.72
CAMCOG-R (Executive Function)	21.42 (4.76)	19.13 (4.86)	0.11	0.48
Memory				
CVLT (Long-delay free recall)	11.46 (2.19)	5.38 (3.26)	<0.001	2.19
CVLT (List A total recall)	50.63 (8.56)	34.92 (8.60)	<0.001	1.83
CAMCOG-R (Memory)	22.83 (2.67)	19.63 (3.72)	0.001	0.99
Language				
BNT	51.08 (8.06)	47.13 (6.34)	0.07	0.55
Semantic Verbal Fluency (animals)	20.04 (5.95)	17.25 (3.19)	0.05	0.58
CAMCOG-R (Language)	26.88 (2.69)	26.67 (1.40)	0.74	0.10

Two sample *t*-test;
* Results are significant at $p < 0.05$. MMSE: Mini-Mental State Examination; TMT-A/B: Trail Making Test (version A/B); CVLT: California Verbal Learning Test, CAMCOG-R: Cambridge Cognitive Examination; BNT: Boston Naming Test; CU: cognitively unimpaired old adults; sdaMCI: single-domain amnestic mild cognitive impairment.

evidence of poorer performance scoring 1–2 standard deviation range (between the 3rd and 16th percentiles) below norms by age and education (DSM-5, American Psychiatric Association, 2013).

All participants underwent the Spanish version (Lobo et al., 1999) of the Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) in order to evaluate their general cognitive functioning. In addition, the following cognitive domains were evaluated: (a) attention, with Trail Making Test A (Reynolds, 2002) and the Attention and Calculation CAMCOG-R subscale (Cambridge Cognitive Assessment-Revised, CAMCOG-R, Roth, Tym, & Mountjoy, 1986), (b) executive functioning, with Trail Making Test B (Reynolds, 2002), Phonological verbal fluency (Lezak, Howieson, Loring, Hannay, & Fischer, 2004) (say words starting with "p" in one minute) and the Executive Function CAMCOG-R subscale, c) memory, with the Spanish version (Benedet & Alejandre, 2014) of the California Verbal Learning Test (CVLT) (Delis, Kramer, & Kaplan, 1987), which measures List A Total Recall, and Long-Delay Free Recall) and the Memory CAMCOG-R subscale and (d) language, with the Spanish version of the Boston naming test (BNT) (Williams, Mack, & Henderson, 1989), Semantic verbal fluency (animals) (Lezak et al., 2004) and the Language CAMCOG-R subscale. Participants were diagnosed as having single domain amnestic MCI when the impairment only affected episodic memory. One domain is considered impaired when performance in two different tests for that domain (Clark et al., 2013; Klekociuk, Summers, Vickers, & Summers, 2014) lies in the 1–2 standard deviation range below appropriate norms.

2.2. Task and fMRI procedures

2.2.1. Stimuli

Participants performed an old/new recognition memory task with fifty words that were randomly selected from the EsPal Spanish word database (Duchon, Perea, Sebastián-Gallés, Martí, & Carreiras, 2013) as stimuli, using constrains for lexical frequency, familiarity and number of letters. Then, lists of old and new words were built and *t*-tests were performed to contrast that no differences were found on valence, arousal, familiarity of the word in the context of Spanish speech, degree of concretion, frequency of use and length. Words were displayed in lowercase and Chicago font (size 80) and, from the 50 words selected for the task, 31 referred to living beings and 19 referred to non-living things. Two lists of words were created: one list of 20 words that was presented during the study and retrieval phases (old words) and a list of 30 words presented only during the retrieval phase (new words). The word lists did not differ in any of the variables mentioned above.

2.2.2. Procedure

The old/new recognition memory task consisted of a study and a test phase (see Fig. 1). The study phase took place while structural magnetic resonance imaging (MRI) scans were acquired. During this phase of the task, participants had to study a list of twenty words (old stimuli), which were randomly and sequentially displayed three times, while they simultaneously made (pressing one of two different buttons with the thumb or the index finger of the right hand) a living/non-living judgment. At the end of the study phase, participants rested for 30 min while other sequences of the MRI protocol were acquired. The retrieval phase then began while BOLD fMRI data were recorded. In this phase of the task, the 20 words of the study list (old words) were presented twice in a pseudo-random order and mixed with the 30 new words. Participants were required to press one of two different buttons, with the thumb or the index finger, to make the old/new recognition judgment about the words. The response buttons used during the study and retrieval phases were counterbalanced among participants. A practice block with four words not employed in the task was performed before the start of the study phase of the task, to ensure that participants had understood the task correctly.

All subjects listened the task instructions through a compatible headphone system, and words were displayed using an MRI-compatible Visual HD System (NordicNeuroLab, Inc, Milwaukee, WI). The presentation of each word was interspersed with a variable duration baseline fixation cross whose duration was designed, with the Optseq 2.0 tool, to optimize the recovery of the BOLD response (Dale, 1999) (Optseq 2.0 https://surfer.nmr.mgh.harvard.edu/optseq/). In particular, during the study phase, each word was presented for 2500 ms, and the presentation of each word was interspersed with a fixation cross (null trials) whose duration ranged from 800 to 1200 ms. During the retrieval phase, each word was presented for 2000 ms. In this phase of the task, the presentation of each word was interspersed with a fixation cross (null trials) whose duration ranged from 0 to 14000 ms. Responses were collected via a fibre-optic response box (NordicNeuroLab, Inc, Milwaukee, WI) that participants held in their right hand. Behavioural data were handled by a PC running Presentation ® software (Version 12.2, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

2.3. Data acquisition

Magnetic resonance imaging was performed with a Philips 3 T Achieva scanner (Philips Medical System, Best, The Netherlands) at the University Hospital Complex of Santiago de Compostela, Galicia (Spain). A sagittal T1-weighted 3D Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) sequence (repetition time/echo time = 7.45 ms / 3.40 ms, flip angle = 8°; 180 slices, voxel size = 1 ×1 x 1 mm, field of view = 240 ×240 mm^2, matrix size = 240 ×240 mm) was obtained while participants studied the word list (Study phase). The

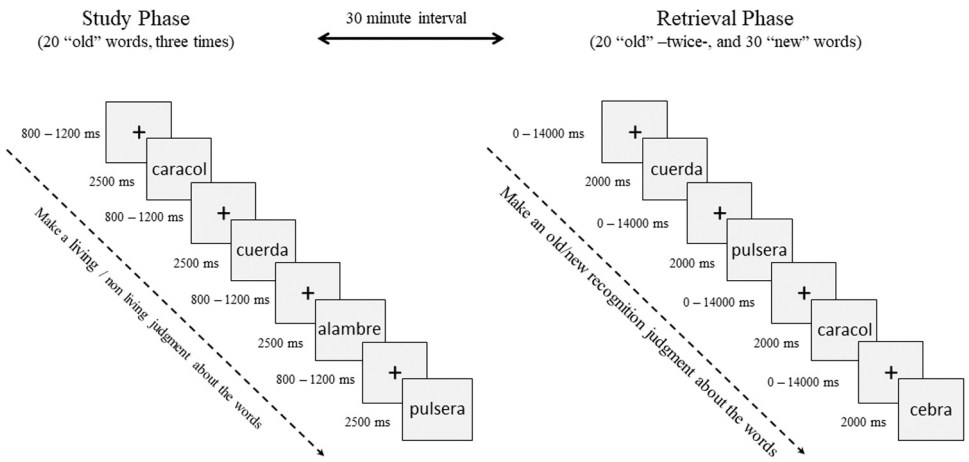

Fig. 1. Old/New recognition memory task design. Words were displayed in Spanish language (word translation: caracol: snail, cuerda: string, alambre: wire, pulsera: bracelet, cebra: zebra).

retrieval test began 30 min later, and functional magnetic resonance images were acquired with a gradient echo-planar imaging (EPI) sequence sensitive to blood oxygen level-dependent (BOLD) contrast (repetition time/echo time = 2000 ms / 30 ms, flip angle = 87°; 37 interleaved slices, voxel size = 3 ×3 x 3.5 mm, gap between slices = 3.5 mm, field of view = 240 ×240 mm^2, matrix size = 80 ×80 mm). Four dummy scans were automatically discarded before image acquisition to prevent signals arising from progressive saturation. A vacuum cushion was used to minimize the subject́s head movements during the acquisition.

2.4. Statistical analysis: behaviour

The Shapiro-Wilk normality test was conducted in order to test the assumption of normality over all the evaluated dependent variables: percentage of responses and the reaction times (RTs) in the correct recognition of old words (Hit), the correct rejection (identification) of new words (CR), errors during the recognition of old words (respond "new word" when an old word was presented), false alarms (FA, respond "old word" when a new word was presented) and the percentage of misses (response omissions) for old and new words. The parametric two sample *t*-test was performed in those variables with a normal distribution and the non-parametric Mann-Whitney *U* test was conducted in those variables that did not met the normality assumption. Since the percentage of hits and false alarms had not a normal distribution (see Table 2), the non-parametric discriminability (*A prime: A*) and response bias (*B double prime D: B''$_D$*) measures were calculated (Snodgrass, Levy-Berger, & Haydon, 1985). The *A´* varies from 0 to 1, those *A´* values above 0.5 indicate high ability to discriminate old and new stimulus (0.5 indicates chance performance). In the case of *B''$_D$* scores, values greater than 0 indicate conservative bias (i.e. responding "old" infrequently) and values less than 0 indicate liberal bias (i.e. responding "old" frequently). Finally, for all continuous variables, the Coheńs D effect sizes were estimated (Lenhard & Lenhard, 2016).

2.5. fMRI processing and data analysis

2.5.1. fMRI preprocessing

Image preprocessing and statistical analysis of fMRI data was performed in Matlab R2016a (Mathworks, Inc, Sherborn, MA, USA) using the Statistical Parametric Mapping software SPM12 (Wellcome Centre for Human Neuroimaging, University College London, http://www.fil.ion.ucl.ac.uk/spm). Visual quality control of all images was performed in order to detect excessive motion and signal artefacts. Structural and functional images were then reoriented to the anterior-posterior commissure. Functional images were then slice-timed corrected and

Table 2
Mean values and standard deviations (SD, in brackets) of CU adults and sdaMCI adults in A´score, B''$_D$ score, the percentage of responses (%) and reaction times (RT, ms) in each condition (Hit, CR, Errors, False Alarms) and misses. Mean ranks are also reported for non-parametric variables.

	CU	sdaMCI	*t / Z*	Shapiro-Wilk	*p*=*	Cohen's d effect sizes
	***N* =24**	***N* =24**	***value***			
Hit (%)	82.29 (20.39) /29.40	75.31 (14.75) /19.60	-2.43	<0.001	0.01[b]	0.75
CR (%)	75.69 (22.51) / 26.58	71.53 (19.93) / 22.42	-1.03	<0.001	0.31[b]	0.30
A´score	0.874 (0.19) / 29.15	0.866 (0.07) / 19.85	-2.30	<0.001	0.02[b]	0.70
B''$_D$ score	-0.087 (0.55)	0.238 (0.50)	-2.15	0.196	0.04[a]	0.62
Errors (%)	12.81 (17.04) / 19.23	16.67 (7.79) / 29.77	-2.62	<0.001	0.008[b]	0.81
False Alarms (%)	17.36 (16.56) / 23.58	16.94 (11.20) / 25.42	-0.46	<0.001	0.66[b]	0.13
RT Hit	1026.25 (172.18)	1122.46 (148)	-2.08	0.079	0.04[a]	0.60
RT CR	1167.41 (213.69)	1262.16 (194.02)	-1.61	0.332	0.12[a]	0.46
RT Errors[c]	1149.75 (404.21) / 21	1336.17 (197.61) / 25.79	-1.21	<0.001	0.23[b]	0.48
RT False Alarms[c]	1206.83 (266.45)	1304.33 (231.84)	-1.32	0.700	0.19[a]	0.39
Misses to old words (%)	4.9 (7.71) / 22.06	8.02 (11.59) / 26.94	-1.26	<0.001	0.21[b]	0.35
Misses to new words (%)	6.94 (11.75) / 22.15	11.53 (15.91) / 26.85	-1.18	<0.001	0.22[b]	0.34

CU: cognitively unimpaired old adults; sdaMCI: single-domain amnestic mild cognitive impairment.
A´score: A prime discriminability measure; B''$_D$ score: B double prime response bias measure.
[a] : Parametric variables: Two sample *t*-test. Degrees of freedom were 46.
[b] : Non-parametric variables: Mann-Whitney *U* test.
[c] : Two subjects did not have errors and false alarms. Thus, degrees of freedom were 44.
* Results are significant at $p < 0.05$.

realigned, and a mean realigned functional image was also calculated for each subject by averaging all realigned functional scans. Total displacement and scan to scan displacement measures were estimated for all participants and compared between both groups not revealing significant differences in both head motion metrics [*CU group* mean: 0.20; SD: 0.09; *sdaMCI group* mean: 0.34; SD: 0.44; $t(46) = -1.53$; $p = 0.132$] and scan to scan displacement [*CU group*: 0.19; SD: 0.11; *sdaMCI group*: 0.23; SD: 0.15; $t(46) = -1.00$; $p = 0.321$]. Then, structural T1-weighted images and the realigned functional images were coregistered. Grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) were segmented by applying the unified segmentation algorithm (Ashburner & Friston, 2005) to the structural T1-weighted image of each subject. Functional images were normalized (3 ×3 x 3 mm voxel size) to the Montreal Neurological Institute (MNI) space using the 4th degree B-spline interpolation method and then were spatially smoothed using a Gaussian kernel of 8 mm full-width at half maximum (FWHM). Further preprocessing was carried out in order to remove artifacts. Specifically, an Independent Component Analysis was conducted with MELODIC (Beckmann & Smith, 2004) to decompose the BOLD signal in spatiotemporal components. Components identified as potential artifacts were regressed out from the BOLD signal.

Since cerebrovascular changes associated with healthy and pathological aging may alter the coupling between the BOLD signal and neural activity (D'Esposito, Deouell, & Gazzaley, 2003; Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Mcdonough, Letang, & Stinson, 2019), we estimated the Resting State Functional Amplitude (RSFA) of each subject in order to account for differences in cerebrovascular reactivity. For that purpose, we firstly preprocessed resting-state fMRI scans of all subjects following the same preprocessing protocol employed for task-fMRI data (both sequences had the same acquisition parameters). These resting-state fMRI scans were further processed for estimating the RSFA using the AFNI software (Cox, 1996). The Afni_proc.py was employed to despike the time series, remove the first 3 TRs, apply a bandpass filter to the time series between 0.01 and 0.08 Hz, demean the time series and to regress out motion parameters, their derivatives, and also the white matter signal from the time series. RSFA is computed as the standard deviation of the BOLD time series (Kalcher et al., 2013; Kannurpatti, Motes, Biswal, & Rypma, 2014; Kannurpatti & Biswal, 2008).

2.5.2. Task-based fMRI statistical analyses

The spatially normalized and smoothed functional images of each subject were analyzed with the general linear model (GLM) approach implemented in SPM12 in order to model the BOLD signal at each voxel. All statistical analyses were performed only for the brain activity evoked during successful recognition trials in order to reduce the contribution of error-related processes in fMRI results. Thus, onsets and durations (corrected by RTs) of event-related responses during the correct recognition of old words (Hit condition) and the correct rejection of new words (CR condition) were included in the GLM. Next, we employed the Optimized Censoring Toolbox to detecting and censoring (i.e. including as regressors) outlying datapoints due to movement or signal intensity spikes (Wilke & Baldeweg, 2019). Thus, six movement parameters (three translations, three rotations) and the outlying scans were included in the GLM as regressors in order to control residual movement and artifact-related effects. The hemodynamic response of each event type was modelled with the canonical hemodynamic response function (HRF) and a high pass filter with a cut-off period of 128 s was applied in order to filter out the low-frequency variations from the time series. The model parameters were estimated and linear contrasts were calculated using two-sample *t*-test to estimate the brain activity evoked during the Hit condition, the brain activity evoked during the CR condition and also to estimate those brain regions that showed an old-new effect, that is, significant higher brain activity in the Hit condition relative to the CR condition (Hit > CR contrast). Finally, before conducting the group analyses, contrast images of each subject were rescaled by dividing each contrast image by the RSFA image in order to account for cerebrovascular reactivity differences within the BOLD signal.

Within-group analysis was performed using the individual contrast images. An exploratory analysis was carried out on the brain regions involved during the Hit and CR conditions as well as on those brain regions that showed an old-new effect (Hit > CR contrast) in each group. For this purpose, significant brain activation was estimated for both conditions and also for the Hit > CR contrast in each group (CU and sdaMCI) with one-sample *t*-tests. Between-group analysis was performed using the Hit > CR contrast images of each subject by a one-way analysis of variance (ANOVA) in order to compare between groups the brain activity related to successful memory retrieval and including the years of education and the number of hits of each participant as covariates. Both types of analysis were performed considering the whole brain as the volume of interest. Finally, for both statistical analyses, a voxel-wise permutation testing (10000 permutations) with Threshold Free Cluster Enhancement (TFCE) correction (Smith & Nichols, 2009) was conducted with the TFCE toolbox implemented in SPM12 (http://www.neuro.uni-jena.de/tfce/). Results were considered as significant at $p < 0.05$ Family-Wise Error (FWE).

2.6. Receiver operating characteristic analysis

A receiver operating characteristic (ROC) curve analysis was conducted in order to evaluate the sensitivity and the specificity of those brain activity changes revealed by the between-group analysis. For that purpose, we firstly obtained the functional beta values by extracting the mean signal from a sphere with 5 mm of radius size centered on the x, y, z MNI coordinates of the brain regions that showed significant activation differences in the between-group analysis. These functional beta values were extracted using the MARSeille Boîte À Région dîntérêt (Marsbar) (http://marsbar.sourceforge.net/) and then entered in a ROC curve analysis to determine the sensitivity and specificity. ROC curves were performed in the IBM SPSS Statistical package v.26 for Windows and were considered suitable when the area under the curve (AUC) was greater than 0.7.

3. Results

3.1. Behavioural data

As can be observed in Table 2, relative to CU adults, the sdaMCI group had a significantly lower percentage of hits (medium-large effect size, $d = 0.75$), lower ability to discriminate old and new words (Áscore) (medium-large effect size, $d = 0.70$), higher B''_D scores (medium-large effect size, $d = 0.62$), higher percentage of errors during the recognition of old words (large effect size, $d = 0.81$) and longer reaction times during the correct recognition of old words (medium-large effect size, $d = 0.60$). The groups did not differ in the percentage of correct rejections, false alarms, misses (omissions responses) for old and new words as well as the reaction times of correct rejections, false alarms and errors during the correct recognition of old words.

3.2. fMRI results

3.2.1. Within group analysis

Brain regions that were significantly activated for the Hit and CR conditions, as well as in the Hit > CR contrast, in each group are shown in Table 3 and Table 4, respectively. Both groups showed a similar distribution of brain activity in both conditions of the task.

During the Hit condition (see Table 3 and Fig. 2), the CU group displayed significant brain activity in left frontal regions (triangular part of the inferior frontal gyrus, middle frontal gyrus and superior frontal gyrus including its orbital part), sensorimotor areas (left precentral and postcentral gyrus and right supplementary motor area) and also in the anterior cingulate. The CU group also displayed similar brain activity

Table 3
Brain regions that showed significant activation in CU adults in the Hit and CR conditions.

Brain region	Combined peak-cluster level					
	Cluster size	L/R	MNI Coordinates (x, y,z)			TFCE-FWE p value
CU – HIT Condition						
Precentral Gyrus	20213	L	-48	5	38	<0.001
Supplementary Motor Area		R	3	8	56	<0.001
Postcentral Gyrus		L	-42	-13	47	<0.001
Inferior Frontal Gyrus (triangular part)		L	-39	23	29	<0.001
Middle Frontal Gyrus		L	-36	32	29	<0.001
Superior Frontal Gyrus		L	-24	-1	53	<0.001
Anterior Cingulate	12	L	-15	47	-4	0.041
Superior Frontal Gyrus (orbital part)		L	-24	47	-7	0.041
CU – CR Condition						
Supplementary Motor Area	4365	L/R	0/3	14/5	53/65	<0.001/<0.001
Precentral Gyrus		L	-48	5	41	<0.001
Postcentral Gyrus		L	-39	-28	53	<0.001
Inferior Frontal Gyrus (triangular part)		L	-36	23	26	<0.001
Superior Frontal Gyrus		L	-24	-10	56	<0.001
Fusiform Gyrus	1979	L	-27	-73	-13	<0.001
Inferior Occipital Gyrus		L/R	-33/33	-79/−82	-4/−4	0.001/0.002
Calcarine Sulcus		L	-12	-88	-4	0.001
Lingual Gyrus		L/R	-9/21	-82/−85	-7/−4	0.001/0.003
Middle Occipital Gyrus		L	-24	-88	11	0.003
Superior Occipital Gyrus		L	-21	-76	23	0.004
Inferior Temporal Gyrus		R	45	-67	-4	0.008
Precentral Gyrus	393	R	54	-1	44	0.021
Postcentral Gyrus		R	57	-13	47	0.024
Inferior Frontal Gyrus (triangular part)		R	48	32	26	0.029
Middle Frontal Gyrus		R	39	35	29	0.030
Superior Parietal Lobule		R	27	-52	59	0.038
Inferior Parietal Lobule		R	30	-49	56	0.039
Inferior Frontal Gyrus (opercular part)		R	42	11	32	0.046
Thalamus	127	L/R	-6/15	-16/−13	-1/2	0.030/0.039
Superior Frontal Gyrus	1	R	18	-13	77	0.041
Supramarginal Gyrus	2	L	-45	-37	26	0.046
CU – Old-New Effect (HIT > CR)						
Cerebellum	196	R	33	-49	-22	0.030
Fusiform Gyrus		R	24	-46	-13	0.038
Lingual Gyrus		R	18	-52	-4	0.040
Precentral Gyrus	122	L	-36	-4	56	0.032
Postcentral Gyrus		L	-45	-13	53	0.032
Superior Frontal Gyrus		L	-24	-7	56	0.048
Supplementary Motor Area	237	L/R	-3/9	-1/−19	53/56	0.033/0.032
Paracentral Lobule		L	0	-31	56	0.041
Precuneus		L	-3	-34	59	0.044
Midcingulate Cortex		L/R	-6/3	14/11	38/41	0.048/0.046
Cerebellum	55	L	-18	-37	-19	0.033
Parahippocampal Gyrus		L	-18	-28	-16	0.049
Precuneus	44	R	15	-55	23	0.038
Inferior Temporal Gyrus	9	R	48	-58	-16	0.048

Keywords: CU: Cognitively unimpaired old adults; L/R: Left or right hemisphere; Cluster size: numbers of voxels in each cluster; MNI: Montreal Neurological Institute coordinates.

Table 4
Brain regions that showed significant activation in the adults with single-domain amnestic mild cognitive impairment in the Hit and CR conditions.

Brain region	Combined peak-cluster level					
	Cluster size	L/R	MNI Coordinates (x,y, z)			TFCE-FWE p value
sdaMCI – HIT Condition						
Lingual Gyrus	12685	L/R	-12/24	-79/−82	-13/−7	<0.001/<0.001
Inferior Frontal Gyrus (opercular part)		L	-36	11	29	<0.001
Inferior Temporal Gyrus		R	45	-58	-10	<0.001
Fusiform Gyrus		R	33	-73	-13	<0.001
Inferior Occipital Gyrus		L/R	-33/39	-76/−79	-7/−1	<0.001/<0.001
Middle Occipital Gyrus		L	-24	-82	11	<0.001
Calcarine Sulcus		L	-6	-85	-7	<0.001
Supplementary Motor Area		L/R	0/9	11/8	53/56	<0.001/<0.001
Superior Temporal Gyrus	60	L	-45	-43	20	0.026
Middle Temporal Gyrus		L	-48	-49	11	0.038
Rolandic Operculum	14	L	-48	-19	20	0.046
Anterior Cingulate	9	L	-3	32	23	0.048
sdaMCI – CR Condition						
Lingual Gyrus	11992	R	21	-85	-7	<0.001
Fusiform Gyrus		R	27	-79	-7	<0.001
Precentral Gyrus		L	-36	-7	59	<0.001
Middle Occipital Gyrus		L/R	-27/36	-82/−79	11/8	<0.001/<0.001
Inferior Occipital Gyrus		L / R	-30/45	-79/−73	-7/−10	<0.001/<0.001
Postcentral Gyrus		L	-42	-25	47	<0.001
Cerebellum		L	-9	-79	-13	<0.001
Calcarine Sulcus		L	-6	-85	-7	<0.001
Middle Temporal Gyrus		R	45	-70	2	<0.001
sdaMCI – Old-New Effect (HIT > CR)						
NS						

Keywords: sdaMCI: Single-domain amnestic mild cognitive impairment; L/R: Left or right hemisphere; Cluster size: numbers of voxels in each cluster; MNI: Montreal Neurological Institute coordinates; NS: Not significant.

distribution in the CR condition (see, Table 3 and Fig. 2). In particular, significant brain activity was located in frontal regions (bilateral triangular part of the inferior frontal gyrus, right opercular part of the inferior frontal gyrus, right middle frontal gyrus and bilateral superior frontal gyrus), parietal regions (right inferior/superior parietal lobule and left supramarginal gyrus), temporal areas (right inferior temporal gyrus), sensorimotor areas (bilateral precentral/postcentral gyrus and bilateral supplementary motor area), occipital or occipito-temporal areas (bilateral inferior occipital gyrus, left middle and superior occipital gyrus, bilateral lingual gyrus, left fusiform gyrus and left calcarine sulcus). This group also displayed significant brain activity in the bilateral thalamus.

In the case of the old-new effect (Hit > CR contrast), the CU group displayed significant brain activity in frontal brain regions (left superior frontal gyrus), parietal regions (bilateral precuneus), sensorimotor areas (bilateral supplementary motor area, left precentral/postcentral gyrus and left paracentral lobule), temporal areas (right inferior temporal gyrus and left parahippocampal gyrus), occipital or occcipito-temporal areas (right fusiform and lingual gyrus). This group also displayed a significant old-new effect in the bilateral cerebellum and the bilateral midcingulate cortex (see, Table 3 and Fig. 2).

In the Hit condition, the sdaMCI group (see Table 4 and Fig. 2) displayed significant brain activity in frontal areas (left opercular part of

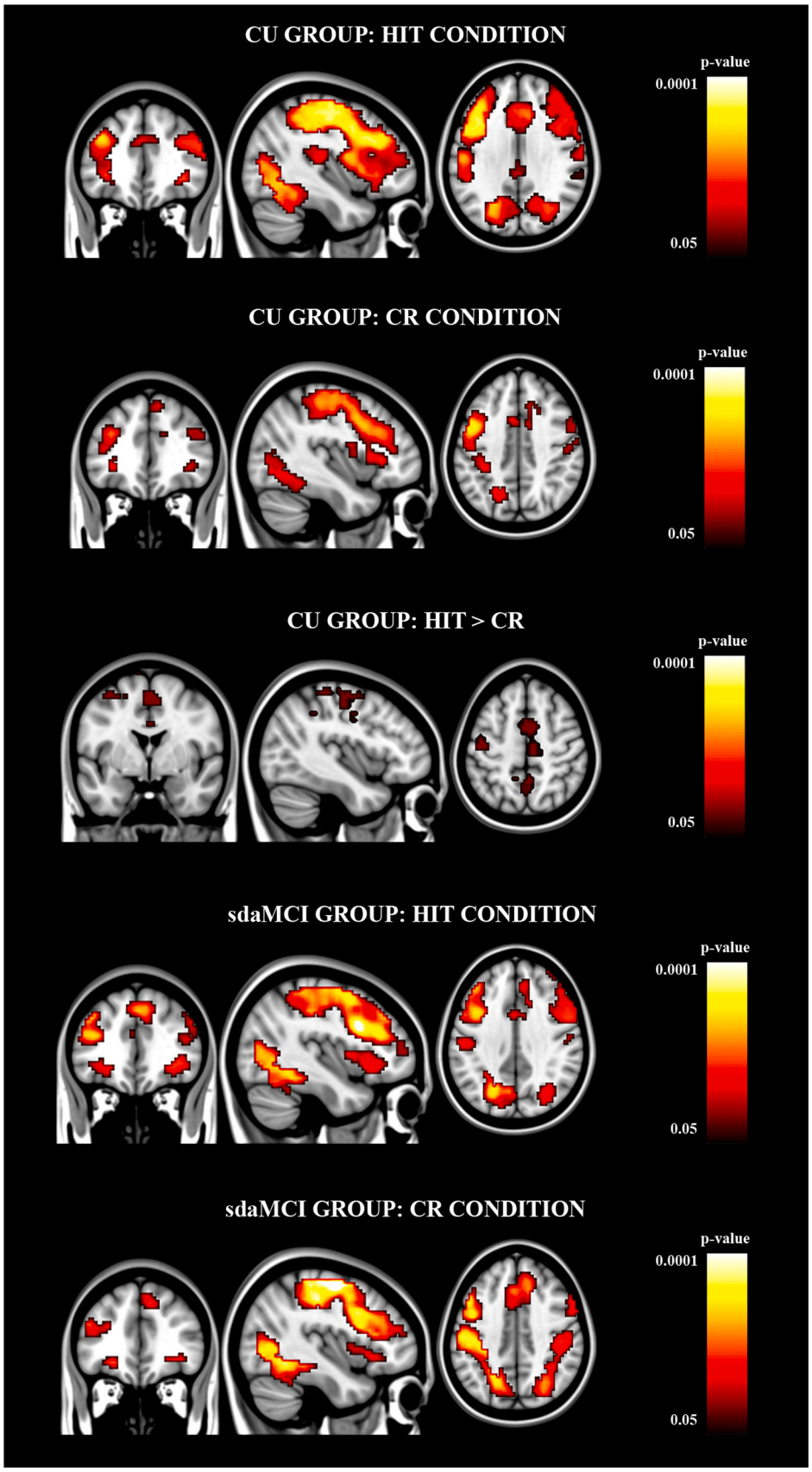

Fig. 2. Brain areas showing significant activation in the CU and the sdaMCI groups for the Hit and CR conditions, as well as in the CU group for the Hit>CR contrast.

the inferior frontal gyrus), temporal areas (right inferior temporal gyrus, left middle/superior temporal gyrus), sensorimotor areas (bilateral supplementary motor area), occipital or occipito-temporal regions (bilateral inferior occipital gyrus, left middle occipital gyrus, bilateral lingual gyrus, right fusiform gyrus and left calcarine sulcus). Significant brain activity was also observed in the left rolandic operculum and the anterior cingulate of the left hemisphere. In the CR condition, the sdaMCI group (see Table 4 and Fig. 2) displayed significant brain activity in temporal regions (right middle temporal gyrus), sensorimotor areas (left precentral/postcentral gyrus), occipital or occipito-temporal areas (bilateral inferior/middle occipital gyrus, left calcarine sulcus and right fusiform/lingual gyrus) and also in the left cerebellum. The sdaMCI group did not show a significant old/new effect.

3.2.2. Between group analysis

The between-group analysis revealed that, in comparison to the sdaMCI group, CU adults displayed a significantly higher brain activity in the Hit condition relative to the CR condition in the left midcingulate cortex and the left precuneus (see Table 5 and Fig. 3). No further significant differences between both groups were found in the Hit > CR contrast.

In addition, the ROC curves (see Table 6) revealed the following area under the curve (AUC), sensitivity, and specificity values for discriminating between CU and sdaMCI adults in the left midcingulate cortex (AUC = 0.81; sensitivity = 0.79 and specificity = 0.71) and the left precuneus (AUC = 0.76; sensitivity = 0.71 and specificity = 0.71).

4. Discussion

Recent fMRI evidence on the effects of aMCI on episodic memory retrieval has revealed divergent results. As stated in the Introduction section, one of the factors attributed to this discrepancy is the evaluation of heterogeneous samples in which different aMCI subtypes are mixed. In this respect, the need to evaluate more homogeneous samples with better defined aMCI subtypes has been highlighted in recent reviews (Bayram et al., 2018; Li & Zhang, 2015). Following these suggestions, the present event-related fMRI study was aimed at detecting and characterizing the location of changes in brain activity during successful episodic memory retrieval in adults with sdaMCI in comparison with CU adults. For this purpose, adults with sdaMCI and CU adults performed an old/new recognition memory task using words as stimuli. Performance and the BOLD hemodynamic response, related to neural activity in response to the correct recognition of old words (Hit condition) and those evoked during the correct rejection of new words (CR condition), were evaluated for each group. Moreover, neural correlate of successful episodic memory retrieval (i.e. the old-new effect) was compared between groups.

4.1. Within group analysis

The exploratory analysis of the brain activity evoked during performance of the task revealed that, during the Hit and CR conditions, there was a wide distribution of brain activity involving frontal, parietal, temporal and occipito-temporal areas. This distribution of brain activity is consistent with observations made in a previous study that used a recognition memory task with words in CU and sdaMCI adults (Heun et al., 2007).

The brain activity observed in frontal and midcingulate brain areas may be related to decision-making and information goal-oriented and manipulation processes (Fletcher & Henson, 2001; Holroyd, Ribas-Fernandes, Shahnazian, Silvetti, & Verguts, 2018). The prefrontal cortex also has important functional connections with lateral and medial portions of the posterior parietal lobe (e.g. inferior/superior parietal lobe, PCC/precuneus) as well as with MTL regions (e.g. hippocampus and parahippocampal cortical areas), forming a brain network involved in recognition memory tasks (for reviews, see Dickerson and Eichenbaum, 2010; Scalici, Caltagirone, & Carlesimo, 2017). Moreover, the brain activity observed in occipital, occipito-temporal areas (e.g. lingual gyrus, fusiform gyrus), in lateral temporal areas and the insular cortex may be related, respectively, to visual and linguistic processing of words (Machielsen, Rombouts, Barkhof, Scheltens, & Witter, 2000; Oh, Duerden, & Pang, 2014). Brain activity in sensorimotor brain areas (e.g. precentral gyrus, postcentral gyrus, paracentral lobule and the supplementary motor area) and cerebellum may not only be associated with the selection of the relevant information and the identification of the target, but also with voluntary control of motor movement (Chung, Han, Jeong, & Jack, 2005; D'Angelo, 2018; Lanciego, Luquin, & Obeso, 2012; Wang et al., 2015).

4.2. Between group analysis

Regarding the comparison between groups, behavioural data revealed that adults with sdaMCI had a significantly lower percentage of hits and lower ability to discriminate old and new words, higher percentage of errors during the recognition of old words (old words recognized as new words), longer reaction times during the correct recognition of old words, and displayed a conservative response bias (i.e. responding "old" infrequently). No significant differences between groups were observed in the percentage of correct rejections, false alarms, misses for old and new words as well as in the reaction times of correct rejections, false alarms and errors during the recognition of old words. These results are consistent with those obtained in previous studies, in which adults with sdaMCI showed a lower percentage of correct responses or showed a poorer old/new discrimination ability than CU adults (Heun et al., 2007; Lenzi et al., 2011; Trivedi et al., 2008) and longer reaction times during the correct recognition of stimulus that were previously studied (Lenzi et al., 2011; Trivedi et al., 2008). This pattern of behavioural results may indicate that, relative to CU adults, the sdaMCI group display deficits not only in the ability to discriminate between old and new stimuli but also they show a slowing in the retrieval of information stored in memory and probably also in the preparation or the selection of the appropriate response for its subsequent execution.

Moreover, comparison of brain activity related to successful episodic memory retrieval between both groups revealed that, in comparison to the sdaMCI group, the CU group displayed a higher brain activity in the Hit condition relative to the CR condition in the left midcingulate cortex and the left precuneus. Evidence from different neuroimaging modalities have demonstrated the vulnerability of the precuneus in aMCI, a brain region functionally involved in the episodic memory retrieval (Dickerson & Eichenbaum, 2010). In this sense, it has been reported that, on the course towards AD dementia, aMCI adults show several pathophysiological changes relative to CU adults in the precuneus, such as reduced glucose metabolism (Bailly et al., 2015), reduced cortical thickness (Csukly et al., 2016) and connectivity dysfunctions within the default mode network (DMN), in which the precuneus is an important functional node (Bai et al., 2011).

Table 5
Brain regions that showed significant differences in brain activity between CU adults and adults with sdaMCI in the Hit > CR contrast.

Brain region	Combined peak-cluster level					
	Cluster size	L/R	MNI Coordinates (x,y,z)			TFCE-FWE p value
CU > sdaMCI						
Midcingulate Cortex	120	L	-15	-25	41	0.030
Precuneus	95	L	-9	-49	41	0.039

Keywords: CU: Cognitively unimpaired adults; sdaMCI: single-domain amnestic mild cognitive impairment group; L/R: Left or right hemisphere; Cluster size: numbers of voxels in each cluster; MNI: Montreal Neurological Institute coordinates.

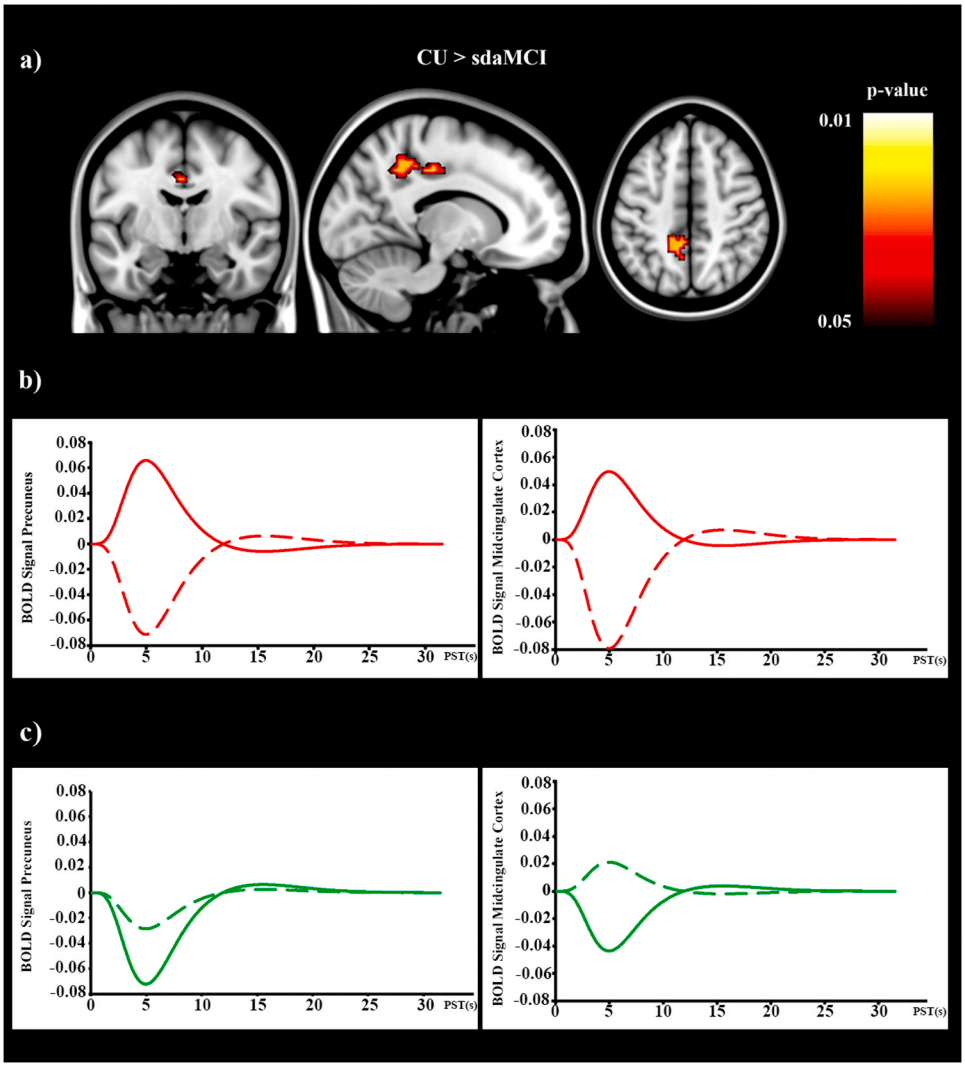

Fig. 3. a) Significant brain activity differences between CU adults and the sdaMCI group in the Hit > CR contrast in the precuneus (sagittal and axial views) and the midcingulate cortex (coronal and sagittal views) of the left hemisphere. **b)** Peristimulus time (PST) and average of best-fitted responses of left precuneus (left panel) and left midcingulate cortex (right panel) in the CU group in the Hit (solid lines) and CR condition (dashed lines). **c)** Peristimulus time (PST) and average of best-fitted responses of left precuneus (left panel) and left midcingulate cortex (right panel) in the sdaMCI group in the Hit (solid lines) and CR condition (dashed lines).

Table 6
Receiver Operating Characteristic (ROC) curve results.

Brain region	AUC	Sensitivity	Specificity
Left Midcingulate Cortex	0.81 (0.68–0.94)	0.79 (0.58–0.93)	0.71 (0.49–0.87)
Left Precuneus	0.76 (0.62–0.90)	0.71 (0.49–0.87)	0.71 (0.49–0.87)

AUC: Area Under the Curve.
Lower and Upper limits of 95% Confidence Intervals in brackets.

Taking into account the task-based fMRI evidence, our results are consistent with those of previous studies reporting brain hypoactivity in adults with sdaMCI in the right precuneus during the correct recognition of previously learned line drawings (Johnson et al., 2006) and hypoactivity in the right cuneus/precuneus activity during the recognition of pair of faces and occupations (Jin et al., 2012). Precuneus hypoactivation in aMCI adults was also recently reported (Shu et al.,2021) in a combined EEG-fMRI study in which an old/new recognition memory task similar to ours (although using nouns in Chinese characters as stimuli) was utilized to characterize the neural dysfunctions of successful recognition in aMCI adults. They observed that compared with the CU group, the aMCI group displayed hypoactivity in ventrolateral prefrontal cortex, precuneus and hippocampus and brain hyperactivity in lateral prefrontal cortex. In the case of precuneus, the hypoactivation took place in the temporal window of event-related potential (ERP) components related to familiarity judgments.

In the present study, the hypoactivation of the left precuneus could be related to the left lateralization of brain function in word retrieval (Riès, Dronkers, & Knight, 2016). Moreover, taking into account the previous task-based fMRI evidence, the precuneus hypoactivity found in the sdaMCI group, would represent neural dysfunction that could be affecting familiarity-based judgments, such as those that might be involved in our recognition memory task in which recollection-based judgments (i.e. retrieval of contextual details about the words such as their location on screen or its colour) are not required.

In addition, the sdaMCI group showed hypoactivity in the left midcingulate cortex, which is a part of the cingulate system involved in anticipating and signaling motivationally targets, encoding reward values, signaling errors, and influencing motor responses. The midcingulate area is functionally involved in the Frontoparietal Network (FPN) (Gilmore, Nelson, & McDermott, 2015; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008), a frontoparietal control system with a critical role in coordinating goal-oriented behaviors in a rapid and flexible manner (Cole, Bassett, Power, Braver, & Petersen, 2014; Marek & Dosenbach, 2018). Functional connectivity deficits in FPN were recently demonstrated in adults with MCI compared with CU adults (Cera, Esposito, Cieri, & Tartaro, 2019) and also in patients with AD dementia (Zhao, Lu, Metmer, Li, & Lu, 2018). Previous studies had pointed that regions of the cingulate system were involved in retrieval monitoring

using an associative memory task by contrasting the neural activity elicited during weak versus strong memory signals (that is, associative misses > associative hits) (de Chastelaine, Mattson, Wang, Donley, & Rugg, 2016). However, taking into account that the fMRI results in the present study are derived from a contrast that isolates the neural correlates of successful recognition (i.e. Hit > CR), the hypoactivity of the midcingulate cortex found in the sdaMCI group could be only attributed to neural dysregulations of this brain area that would be affecting successful episodic memory retrieval processes in adults with sdaMCI.

Despite using the same kind of stimuli and similar old/new recognition memory task, we did not replicate the significant differences observed by Heun et al. (2007) between both groups in the neural activity of frontal brain regions during the correct recognition of old (right superior and inferior frontal gyrus). We did not observe differences between groups in these frontal regions but we found hypoactivity in the left precuneus and the left midcingulate cortex, suggesting that episodic memory retrieval processes would be functionally affected in the sdaMCI group. Differences in task design (the memory task used in Heun et al.'s study had two Study-Test-Test sequences, with 90 different old words to memorize in each sequence, and one half of the 90 old words were presented in each test phase), task difficulty (in Heun et al.'s study, participants had to memorize a higher number of words, a total of 180 old words), and the cognitive decline of the sdaMCI adults evaluated (unlike Heun et al.'s study, we did not find significant differences in the general cognitive functioning -MMSE score-) could explain the discrepancies in results between both studies.

Given that all participants fulfilled strictly the diagnosis of sdaMCI, the present fMRI results would indicate that memory impairment of these participants is related to brain hypoactivity in the precuneus and the midcingulate cortex of the left hemisphere. However, given that the neuropsychological battery revealed reduced performance in one neuropsychological test about executive function and other about language, it cannot be ruled out that some significant effects may be mediated by the premorbid deficits in other related cognitive processes such as executive functions necessary to cope with task requirements and/or also language since the participants performed a verbal task.

In addition, the sensitivity and specificity values revealed by ROC curve analysis suggest that these brain activity changes could be relevant in the development of cognitive decline in the AD continuum. This question should be addressed in future investigations with larger samples of sdaMCI, and including a mdaMCI sample to contrast their validity as neurocognitive markers in the progression from sdaMCI towards more severe cognitive impairment stages such as mdaMCI or even AD dementia. Moreover, considering the scaffolding theory of aging and cognition (STAC) model postulations, the hypoactivity of these brain regions together with the lower performance in the sdaMCI group would represent the undermine of brain efficiency of some components of neural processing such as the signal to noise ratio, the fidelity of representations and the speed of neural transmission (Reuter-Lorenz & Park, 2014).

To sum up, compared with CU group, adults with sdaMCI display hypoactivation in the left precuneus and the left midcingulate suggesting neural dysfunctions in successful episodic memory retrieval. These brain activity changes during the successful recognition of old words might constitute a potential neurocognitive marker of sdaMCI in clinical settings.

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Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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