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Brain structural, functional, and cognitive correlates of recent versus remote autobiographical memories in amnestic Mild Cognitive Impairment

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ABSTRACT

Deficits in autobiographical memory appear earlier for recent than for remote life periods over the course of Alzheimer's disease (AD). The present study aims to further our understanding of this graded effect by investigating the cognitive and neural substrates of recent versus remote autobiographical memories in patients with amnestic Mild Cognitive Impairment (aMCI) thanks to an autobiographical fluency task. 20 aMCI patients and 25 Healthy elderly Controls (HC) underwent neuropsychological tests assessing remote (20-to-30 years old) and recent (the ten last years) autobiographical memory as well as episodic and semantic memory, executive function and global cognition. All patients also had a structural MRI and an FDG-PET scan. Correlations were assessed between each autobiographical memory score and the other tests as well as grey matter volume and metabolism. Within the aMCI, performances for the remote period correlated with personal semantic memory and episodic memory retrieval whereas performances for the recent period only correlated with episodic memory retrieval. Neuroimaging analyses revealed significant correlations between performances for the remote period and temporal pole and temporo-parietal cortex volumes and anterior cingulate gyrus metabolism, while performances for the recent period correlated with hippocampal volume and posterior cingulate, medial prefrontal and hippocampus metabolism. The brain regions related with the retrieval of events from the recent period showed greater atrophy/hypometabolism in aMCI patients compared to HC than those involved in remote memories. Recall of recent memories essentially relies on episodic memory processes and brain network while remote memories also involve other processes such as semantic memory. This is consistent with the semanticization of memories with time and may explain the better resistance of remote memory in AD.

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1. Introduction

Autobiographical memory is a multifaceted concept which concerns information and experiences of one's personal life and gives a sense of self-continuity (Conway, 2001; Piolino et al., 2009). The disturbance of autobiographical memory is well known in Alzeimer's disease (AD) (Addis et al., 2009; Addis and Tippett, 2004; Greene et al., 1995; Ivanoiu et al., 2004; Kopelman et al., 1989; Leyhe et al., 2009; M. Irish et al., 2011; Piolino et al., 2003) and has been described in patients with Mild Cognitive Impairment (MCI) as well (Irish et al., 2010; Leyhe et al., 2009; Murphy et al., 2008).

Interestingly, all memories are not affected in the same way in AD: recent memories are impaired first, whereas remote ones resist longer (Leyhe et al., 2009; Irish et al., 2010; Murphy et al., 2008). This is called the amnestic temporal gradient of Ribot or Ribot's law (Ribot, 1881). While the mechanisms underlying this gradient are not fully understood, it is thought to be related to the "semanticization" of episodic memories with time (Cermak, 1984; Eustache and Desgranges, 2008). Thus, remote

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autobiographical memories would tend to depend less on episodic memory function and related brain substrates and more on semantic memory compared to recent memories. As AD primary affects episodic memory function and brain substrates, this may explain why recent autobiographical memories are more sensitive and remote ones more resistant, especially in the earliest (predementia) stages where structural and functional brain changes are mainly confined to brain regions that belong to the episodic memory network such as the hippocampus and posterior cingulate cortex (Chételat et al., 2002, 2003; Stoub et al., 2006). A study assessing the brain substrates of autobiographical memory in AD tends to confirm this view, showing a relationship with the hippocampus for the recent, but not for the remote memories (Eustache et al., 2004) although conflicting findings have also been reported (Gilboa et al., 2005; Philippi et al., 2012). In patients with MCI, the results are inconclusive as the only study in MCI did not report any relationships with the hippocampus (Bastin et al., 2013).

The main objective of this study was thus to further our understanding of the gradient of Ribot in MCI patients, when brain changes are expected to be mainly confined to the episodic memory network. MCI represents a transitional state between the cognitive changes of normal aging and very early dementia and is recognized as a risk factor for AD. Epidemiologic studies have reported the annual progression rates of clinically diagnosed MCI to dementia to be in the 15–25% range (Petersen et al., 2009). This population is, therefore, particularly well-suited to assess the predementia stage of AD, although all MCI patients will not develop AD. For this purpose, the relationships between remote and recent autobiographical memory performances on the one hand, and cognitive and brain structural and functional measurements, on the other hand, were assessed in patients with MCI. We hypothesized that (i) MCI patients would have predominant deficits in recent episodic memory retrieval; (ii) these predominant recent memory deficits in MCI would reflect the involvement of cognitive processes and brain regions that are more sensitive to AD and (iii) remote episodic memory retrieval would be less affected as it would further depend on brain regions involved in semantic processing that are more preserved, as a reflect of the "semanticization" of episodic memories with time.

2. Methods

2.1. Participants

Forty five right-handed native French-speaking participants from the IMAP project (La Joie et al., 2013, 2012; Mevel et al., 2013) were included in the present study, including 20 patients with amnestic MCI (aMCI) and 25 Healthy elderly Controls (HC) matched for age, gender and education level (Table 1). All participants were aged over 50 years, had at least 7 years of education, had no clinical evidence of psychiatric or neurological disorders, no severe brain lesions on T2-weighted or FLAIR MRI images, no history of alcoholism or drug abuse, were free of medication that could affect cognitive functioning and reported being in good health. aMCI patients were recruited from local memory clinics and had memory complaint for less than 2 years. They were selected according to Petersen's criteria for aMCI (Petersen and Morris, 2005): isolated episodic memory deficits (1.5 SD of the normal mean for age and education notably for the Free and Cued Selective Recall Reminding Test), normal performances in other areas of cognition, in global cognition (assessed with MMSE and Mattis scales) and preservation of independence in functional abilities (see Fouquet et al., 2009, for further details). Clinical diagnosis was assigned by consensus under the supervision of senior neurologists and neuropsychologists. To further characterize the MCI patients included in this study, we assessed their profile of atrophy and hypometabolism compared to age- and education-matched controls with whole brain comparison analyses. MCI patients showed hippocampal atrophy and hypometabolism in the precuneus–posterior cingulate cortex and temporo-parietal areas. This profile is consistent with the pattern of alterations described in the literature in MCI patients as well as in the predemential stage of AD (Atiya et al., 2003; Chételat et al., 2002, 2003; Nestor et al., 2003a, 2003b).

HC participants were recruited from the community and performed in the normal range on a neuropsychological examination assessing multiple domains of cognition including episodic and semantic memory, executive and visuo-spatial functions, language and praxis.

Within a few days from recruitment, each participant underwent: 1) a detailed experimental neuropsychological battery, 2) a structural magnetic resonance imaging (MRI) study, and 3) a positron emission tomography (PET) study using [18F] fluoro-2-deoxy-D-glucose (^{18}FDG).

The IMAP Study was approved by regional ethics committee (Comité de Protection des Personnes Nord-Ouest III) and registered with ClinicalTrial.gov (number NCT01638949). All participants gave written informed consent to the study prior to the investigation.

2.2. Neuropsychological assessment

The task of interest in this study was an episodic autobiographical memory fluency task, inspired from Dritschel et al. (1992); see also Chételat et al. (2005), assessing two periods of life (recent and remote). The recent period corresponded to the 10 last years without the last year (to avoid very recent events — e.g. 1 h/day ago for the sake of comparativeness) while the remote period corresponded to the period when the participant was 20–30 years old. In this task, patients were given instructions to recall as many personal events of their life as possible for each period, during 2 min. The instructions were to recall

Table 1
Demographic and neuropsychological performances of the aMCI and control groups.

	aMCI (n = 20)	HC (n = 25)	Group effect
Age: years ± SD (range)	72.3 ± 7.2 (64–86)	70,5 ± 5.4 (61–81)	ns
Women /men	11/9	14/11	ns
Education: years ± SD (range)	10.0 ± 3.5 (7–20)	10.5 ± 3.2 (7–17)	ns
MMSE: score ± SD (range)	26.9 ± 1.5 (29–24)	28.9 ± 0.9 (30–27)	*
Mattis: score ± SD	135.1 ± 4.1	142.36 ± 1.9	*
Episodic memory :			
Recognition after superficial encoding ± SD	9.9 ± 2.9	13.4 ± 1.8	*
Free recall after deep encoding ± SD	5.15 ± 2.0	8.68 ± 2.3	*
Autobiographical memory remote period ± SD	3.05 ± 2.31	5.08 ± 2.99	*
Autobiographical memory recent period ± SD	2.00 ± 1.35	4.52 ± 2.21	*
Semantic memory :			
Category word fluency ± SD	23.8 ± 5.8	31.8 ± 7.3	*
Semantic autobiographical memory ± SD	14.8 ± 9.6	24.56 ± 8.7	*
Executive functions :			
Trail making test (B−A) ± SD	79.09 ± 54.2	55.36 ± 34.4	ns

Standard deviation appears in brackets. All variables were compared using t-tests. ns = non-significant.
*$p < 0.001$.

events situated in time and space, which lasted less than a day and happened only once, and to provide as many details as possible. An illustrative event with a set of examples of episodic details (e.g. time and place details, people, activities, conversations, emotion and thoughts) was given. In the first part of the trial, which was time-constrained, participants, had to remind as many events as possible that they just had to name in a few words. Predefined cues (e.g. a wedding, a birth or a Christmas day) were given to the participants if they stayed over 20 s without saying anything. In the second part of the test, participants were asked to provide as many details as possible for each event they mentioned in the first part. At the end of the task, the experimenter ensured with the participant that each event could be specifically re-experienced with details, assessing the specificity of the content (single or repeated event), the time and spatial location, and the presence of details (perception, thoughts or feelings) (Baddeley and Wilson, 1986). The rater quoted each event on a 5-point scale (single event = 1 point; lasting less than a day = 1 point; located in time = 1 point; situated in space = 1 point and at least 2 specific details = 1 point). Only specific events rated 5 were counted as an episodic event. For example "Every Wednesday with my grandmother we cooked cakes that we ate for afternoon snacks" is an event considered as a semantic event, whereas, " When I was 12 years old with my grandmother we had forgotten the cake in the oven, it was burnt and a lot of smoke spread in the house. My grandfather who was upstairs detected the burning smell, get off at full speed and tumbled in the stairs. I relive the scene as if I was there" is an event considered as an episodic event scored 5 in our scale. The number of episodic events within each period was used as "recent" and "remote" autobiographical episodic memory scores. The neuropsychological battery included 6 tests or subtests that evaluated a set of cognitive, mainly memory, functions. The battery is fully described in Mevel et al. (2013). The total score at the Mattis dementia rating scale (Mattis, 1976) was used to assess global cognitive function. Verbal episodic memory was assessed using the 'Encoding, Storage, Retrieval' (ESR) paradigm fully described elsewhere (Chételat et al., 2005). Briefly, participants had to recall as many words as possible from 2 distinct 16-word lists after either a superficial or a deep encoding phase. Performances in recognition after superficial encoding (maximum score = 16) are considered to reflect encoding capacity (and thus referred to as the encoding subtest in what follows), while free recall performances after deep encoding is thought to reflect retrieval capacity (and is thus referred to as the retrieval subtest in what follows). Semantic memory was assessed with the category word fluency task where patients were given instructions to list in 2 minutes as many words as possible which complied with the 'animals' semantic criteria (Cardebat et al., 1990). Personal semantic memory was evaluated with a semantic autobiographical fluency task similar to that described above for episodic autobiographical memory, but using names of individuals (excluding family members) that participants have personally met during each of the two periods of life instead of events (Dritschel et al., 1992). The sum of the number of names given for the two periods was used as a measure of personal semantic memory capacity. Finally, the Trail Making Test was used to assess executive functions (Greenlief et al., 1985) (Table 1). All resulting neuropsychological scores were transformed in z-scores [(aMCI value − average scores of controls) / standard deviation of controls] to be used in subsequent analyses. Z-scores were used so that the two scores of episodic autobiographical memory were expressed in a same scale and could be compared (as we were interested in comparing the degree of impairment between remote and recent memories).

2.3. Neuroimaging procedure

2.4.1. MRI and PET data acquisition

For each participant, a high-resolution T1-weighted anatomical image was acquired on a Philips Achieva 3T scanner using a three-dimensional fast-field echo sequence (sagittal; repetition time = 20 ms; echo time = 4.6 ms; flip angle = 20°; 170 slices; slice thickness = 1 mm; field of view = 256 × 256 mm^2; matrix = 256 × 256).

^{18}FDG-PET images were acquired using the Discovery RX VCT 64 PET-CT device (GE Healthcare) with a resolution of 3.76 × 3.76 × 4.9 mm^3 (field of view = 157 mm). Forty-seven planes were obtained with a voxel size of 1.95 × 1.95 × 3.2 mm^3. A transmission scan was performed for attenuation correction before the PET acquisition. Participants were fasted for at least 6 h before scanning. After a 30 min resting period in a quiet and dark environment, 180 MBq of FDG was intravenously injected as a bolus. A 10 min PET acquisition scan began 50 min after injection.

2.4.2. MRI and PET data handling

MRI data were segmented, normalized and modulated using the VBM5.1 toolbox (http://dbm.neuro.uni-jena.de) implemented in the Statistical Parametric Mapping 5 software (SPM5; Welcome Trust Center for Neuroimaging, Institute of Neurology, London, England). To blur individual variations in gyral anatomy and to increase the signal-to-noise ratio, the spatially normalized GM data sets were smoothed with a 10 mm Gaussian filter. The resulting smoothed and spatially normalized GM data sets were used in the following analyses and processing.

^{18}FDG-PET data were first corrected for partial volume effects using the three-compartment method described by Giovacchini et al. (2004) and implemented in the PMOD software (PMOD Technologies). This method uses gray matter, white matter, and cerebrospinal fluid segments obtained from the VBM procedure to correct for both spill-in and spill-out effects. Resultant images were then coregistered onto corresponding MRI, normalized using the deformation parameters defined from the VBM procedure performed on the corresponding MRI and scaled using the mean PET value of the cerebellar gray matter. Resultant images were finally smoothed using a 12 mm FWHM Gaussian kernel.

2.4. Statistical analyses

2.5.1. Behavioural analyses

First, a one sample t-test was performed to compare each of the two episodic autobiographical memory z-scores (recent and remote) of aMCI patients to zero, to test whether aMCI performances significantly differed from those of the HC. Second, a paired t-test with the two z-scores of aMCI patients was performed to compare their degree of deficits in remote versus recent episodic autobiographical memory. Finally, to assess, within the aMCI, the cognitive correlates of these measures, the episodic autobiographical memory z-score for each period was entered as a dependent variable in separate partial correlation models with each z-score of the neuropsychological battery as an independent variable, correcting for age. Bonferroni correction was applied to control for multiple comparisons, so that a threshold of $p < 0.008$ (0.05/6) was required for results to be considered as significant.

2.5.2. Imaging analyses

Firstly, a multiple regression analyses were performed within the aMCI group, for each period of life and each neuroimaging modality with the autobiographical z-score as the variable of interest and age as a nuisance variable (4 models were performed). To address the issue of multiple comparisons, for each period and each imaging modality a cluster size was determined (Supplementary Table 1) combined with a voxel-level p (uncorrected) < 0.005 threshold to achieve a corrected statistical significance for multiple comparisons of $p < 0.05$ (as determined through Monte Carlo simulations using the AlphaSim program).

The significant clusters from these 4 regression analyses were defined as the clusters of interest in what follows, to be used in further analyses. In each of these clusters of interest, the corresponding values (mean grey matter volume or cerebral metabolism) were extracted and compared between HC and patients using a two sample t-test.

3. Results

3.1. Behavioural results

Firstly, within the HC, 80% of the remote events and 84.55% of the recent ones were considered as episodic, whereas within the aMCI, the proportions were 75.6% and 68.8%, respectively. aMCI patient z-scores were significantly lower than zero (i.e. significantly lower than the HC) for both the remote ($t(19) = -3.94$; $p < 0.001$) and the recent ($t(19) = 8.42$; $p < 0.001$) periods (Fig. 1). Moreover, the comparison between both z-scores revealed significantly greater deficits in aMCI patients for the recall of events from the recent period than from the remote period ($t(19) = -2.60$; $p = 0.02$).

The correlations between each episodic autobiographical z-score and each of the other cognitive z-scores from the neuropsychological battery showed a significant relationship between performances for the remote period and semantic autobiographical fluency, verbal episodic memory retrieval, and a trend was found for the Mattis (Table 2). For the recent period, a significant correlation was found only for verbal episodic memory retrieval.

3.2. Correlations between autobiographical memory and brain imaging data (grey matter volume and metabolism)

Significant correlations between episodic autobiographical memory z-score for the remote period and normalized grey matter volume were found in the left temporal pole, inferior temporal neocortex and fusiform gyrus (cluster 1_MRI_remote), and in a right temporo-parietal area encompassing the angular and middle occipital cortices (cluster 2_MRI_remote; Fig. 2). For the recent period, significant correlations with grey matter volume were found in anterior medial temporal structures, including the anterior hippocampus and parahippocampal gyrus and the amygdala, in both right (cluster 1_MRI_recent) and left (cluster 2_MRI_recent) hemispheres.

The correlations with FDG-PET data revealed significant association between episodic autobiographical memory z-scores for the remote period and metabolism in the left anterior cingulate gyrus (cluster 1_FDG_remote; Fig. 3). Autobiographical z-scores for the recent period correlated with metabolism in four clusters, including the medial orbitofrontal, ventro-lateral prefrontal cortex and hippocampal region (i.e. hippocampus, amygdala, parahippocampal and fusiform gyrus extending to the temporal neocortex) in the left (cluster 1_FDG_recent) and right (cluster 2_FDG_recent) hemispheres, the posterior cingulate cortex (cluster 3_FDG_recent) and a small cluster encroaching the anterior parahippocampal, fusiform and inferior temporal gyrus (cluster 4_FDG_recent). Table 3 summarizes the coordinates of the peak voxels within each significant cluster as well as the corresponding statistics.

Note that the findings remained essentially unchanged when including as an additional covariate in the model either the score for the other period (i.e. the remote score for the recent one and reversely), or another fluency score, to account for global generative search capacity.

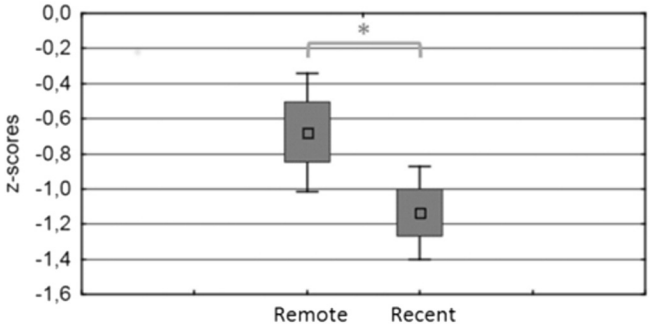

Fig. 1. Autobiographical memory performances in aMCI patients expressed in z-scores using the matched controls as reference.

Table 2
Results of the partial correlation analyses between neuropsychological measures (z-scores) and episodic autobiographical memory z-scores for the two time periods, correcting for age.

Episodic autobiographical memory	Neuropsychological measures	R	p
Remote period	Verbal episodic memory retrieval	0.62	0.004*
	Verbal episodic memory encoding	0.27	0.25
	Semantic memory	0.26	0.29
	Personal semantic autobiographical memory	0.76	0.002*
	Executive functions	0.50	0.08
	Global cognitive function	0.50	0.03
Recent period	Verbal episodic memory retrieval	0.59	0.008*
	Verbal episodic memory encoding	0.29	0.23
	Semantic memory	0.07	0.77
	Personal semantic autobiographical memory	0.26	0.29
	Executive functions	0.09	0.71
	Global cognitive function	0.36	0.13

* Correlations are considered as significant at $p < 0.008$ to account for multiple testing.

3.3. Comparison between HC and aMCI patients in grey matter volume and metabolism in the clusters of interest

The comparison of the grey matter volume between HC and aMCI patients revealed no significant difference in the two clusters from the remote period (left temporal cortex — cluster 1_MRI_remote: $t(43) = 1.44$, $p = 0.16$; right temporo-parietal cortex — cluster 2_MRI_remote: $t(43) = -0.62$, $p = 0.54$). In contrast, a significant decrease was found in aMCI compared to HC in both clusters from the recent period (right medial temporal lobe — cluster 1_MRI_recent: $t(43) = 2.32$, $p = 0.03$; left medial temporal lobe — cluster 2_MRI_recent: $t(43) = 2.52$, $p = 0.02$; see Fig. 2).

As for the comparison of FDG metabolism, no difference was found between HC and aMCI patients in the left anterior cingulate gyrus (cluster 1_FDG_remote: $t(43) = 0.44$, $p = 0.44$). By contrast a significant decrease in aMCI compared to controls was found in two out of the four clusters for the recent period (right fronto-hippocampal region — cluster 2_FDG_recent: $t(43) = 4.84$, $p > 0.001$; posterior cingulate cortex — cluster 3_FDG_recent: $t(43) = 2.40$, $p = 0.02$; see Fig. 3).

4. Discussion

In the present study, we aimed at assessing the cognitive and neural correlates of remote versus recent episodic autobiographical memory so as to better understand the gradient of Ribot in early AD. In patients with aMCI, we found that the performances for the remote period correlated with i) personal semantic performances, verbal episodic memory retrieval (and global cognition as a trend); ii) temporo-parietal and temporal pole volumes and anterior cingulate metabolism, which were all found to be preserved in MCI compared to HC. By contrast, performances for the recent memories only correlated with anterograde episodic memory performances, and the neural substrates included medial temporal (including hippocampal), medial and lateral prefrontal and posterior cingulate areas, most of which being significantly impaired in MCI patients compared to HC.

4.1. Recent autobiographical memory correlates

The involvement of the hippocampal volume and metabolism in recent episodic autobiographical memories is consistent with three previous studies in AD that reported a link with hippocampal (or medial temporal lobe) volume (Gilboa et al., 2005; Philippi et al., 2012) and metabolism (Eustache et al., 2004) for recent periods. The hippocampus is known as a key region for episodic memory processing (Squire and Zola-Morgan, 1991) and also as the main structural substrate for episodic memory deficits in AD (Desgranges et al., 2002; Eustache et al.,

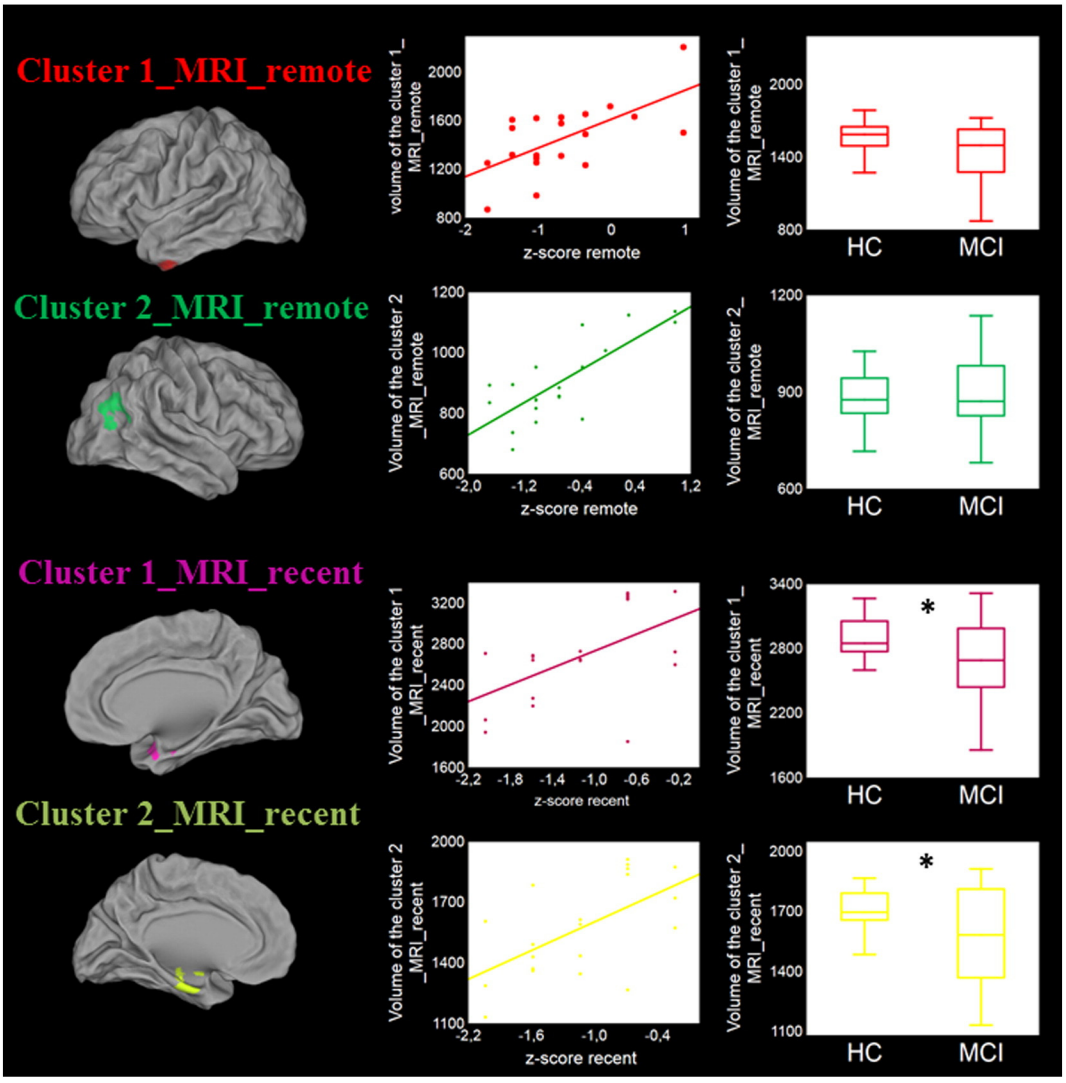

Fig. 2. Positive correlations between remote versus recent episodic autobiographical memory z-scores and grey matter volume, and boxplots of the comparison of grey matter volumes in each corresponding cluster between healthy controls and aMCI patients.

2001) and even in aMCI patients (Chételat et al., 2003; Fouquet et al., 2012; Stoub et al., 2006). Its implication here thus suggests that recent autobiographical memory retrieval mainly relies on episodic memory processes, consistently with the results of the correlation analyses with neuropsychological performances. Note that the only study that assessed this question in patients with aMCI did not find an association with hippocampal volume or metabolism (Bastin et al., 2013). The specific reason for this discrepancy is difficult to identify as there are many differences between this previous paper and ours. Indeed, the autobiographical task (they assessed the degree of episodicity while we assessed the number of episodic events, and the periods differed), and neuroimaging data processing (in our study we applied PVE correction of FDG-PET data and performed cerebellum instead of proportional scaling, two factors known to have a strong influence on the results especially for hippocampal metabolism measurement in early AD; see Mevel et al. 2007) are differents.

Beyond the hippocampus, our analyses demonstrated the involvement of other brain areas in recent memories, such as the amygdala (both in terms of volume and metabolism), and the posterior cingulate, medial orbitofrontal, ventrolateral prefrontal and inferior temporal cortex. The amygdala as well as the orbitofrontal cortex are well-known for their role in the processing of emotional information notably in relation with memory (LeDoux, 1998; Roberts et al., 2004); our finding may thus reflect the emotional content associated with vivid recent memories, and its contribution to the retrieval of these memories. The posterior cingulate cortex is described as a part of the core autobiographical network [for review Svoboda et al., 2006]; it is also known to have a role in episodic memory processes, and to be at least partly responsible for early anterograde episodic memory deficits in AD and aMCI (Bastin et al., 2010; Chételat et al., 2003). The ventrolateral prefrontal activity has been associated with strategic retrieval, monitoring, and selection of relevant information from posterior cortical association areas (Fletcher and Henson, 2001; Henson et al., 1999; Petrides, 2002). Finally, the inferior temporal cortex is part of the "semantic system" (Binder et al., 2009) known to be involved in semantic memory. More specifically, it is considered as an area of high-level integration that stores abstract representations of entity and event knowledge (Binder and Desai, 2011).

Interestingly, all of these regions are part of the Default Mode Network (DMN), a set of brain regions that are consistently more activated during a resting or passive baseline condition than during active, goal-directed analyses of environmental stimuli (Raichle et al., 2001). Some of these regions, such as the posterior cingulate, medial orbitofrontal and ventrolateral prefrontal cortex, are DMN hubs, while others are not always included in the DMN, but all are often co-activated and show correlated activity (Buckner et al., 2009; Tomasi et al., 2010).

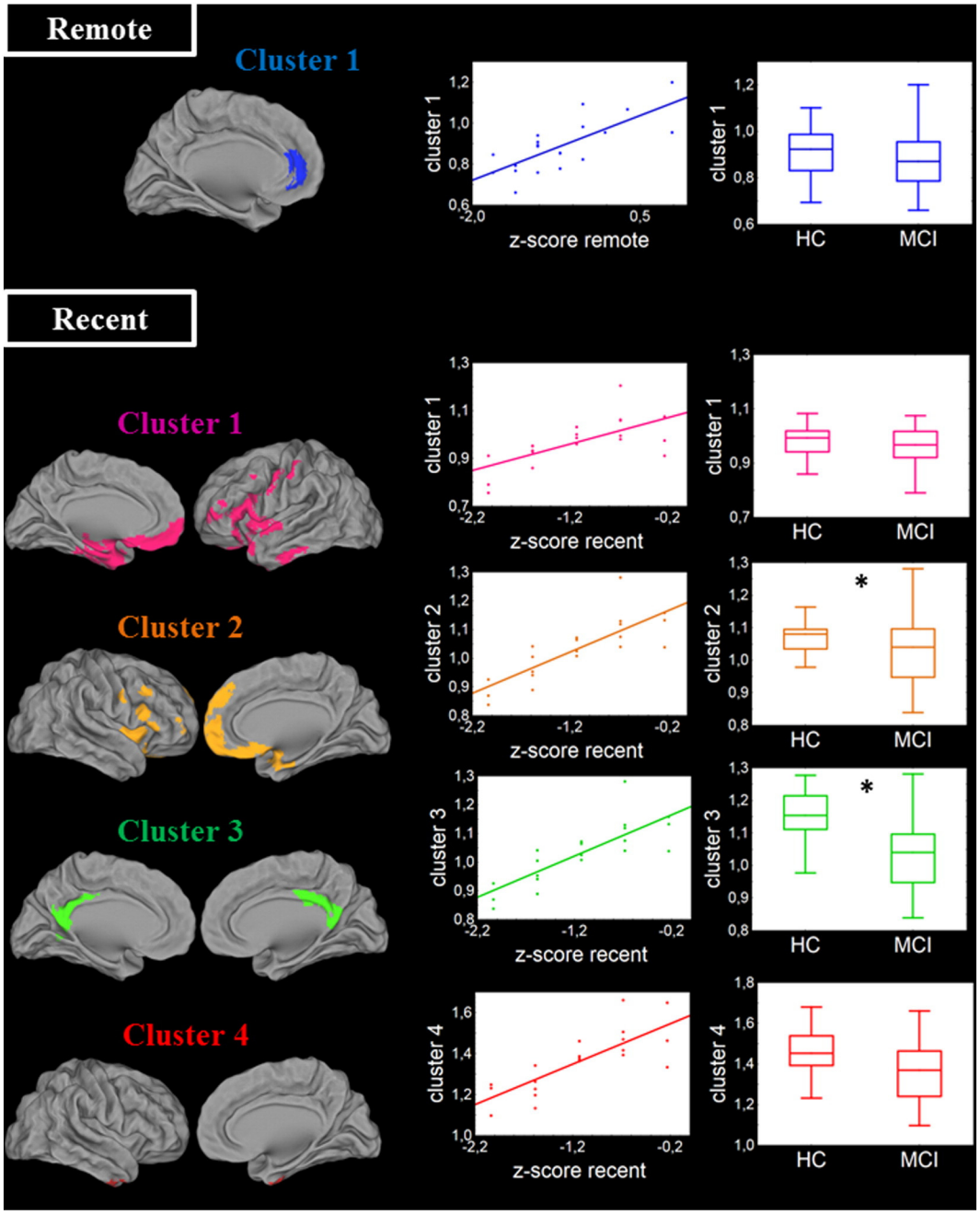

Fig. 3. Positive correlations between episodic autobiographical remote versus recent memory z-scores and brain metabolism, and boxplots of the comparisons of FDG metabolism in each corresponding cluster between healthy controls and aMCI patients.

The DMN is thought to have a role in introspection processes including mind-wandering, prospective thoughts and recollection of autobiographical memories. Our findings as a whole thus reveal the implication of brain areas often co-implicated not only in episodic memory tasks and related processes - especially in autobiographical memory such as introspection, self and emotional processes - but also in semantic processes.

4.2. Remote autobiographical memory correlates

The autobiographical memory score for the remote period was found to correlate not only with anterograde episodic memory, but also with other cognitive functions, i.e. personal semantic memory and, as a trend, global cognitive functions. This is consistent with the view that remote memories tend to be less episodic in nature as they "semantize" with time (Cermak, 1984; Martinelli et al., 2013; Schmidtke and Vollmer, 1997). Thus, as mentioned in the Introduction section, the retrieval of remote autobiographical memory is expected to depend less on the episodic network structures (medial temporal lobe structures) and more on neocortical structures compared to recent memories (Eustache et al., 2004). Consistent with this interpretation, the neuroimaging analysis did not show a relationship between remote autobiographical memory and the hippocampus (neither to the structure nor to the metabolism). Similarly, Eustache et al. (2004) did not find a link between remote memories and metabolism in the hippocampus but with frontal and posterior regions. Other structural and functional studies in AD however reported a link between remote autobiographical memory performances and the medial temporal volume (Gilboa et al., 2005; Irish et al., 2014; Philippi et al., 2012). The involvement of the hippocampus for both recent and remote memories has also been shown in functional

Table 3
Statistics of the correlations between grey matter volume or metabolism and remote versus recent autobiographical z-scores correcting for age.

	Regions	Coordinates (mm) of the peak voxels within significant clusters			T-value	Cluster size	MCI vs HC		
		x	y	z			t	dl	p
Cluster 1_MRI_remote	L temporal pole L inferior temporal neocortex L fusiform gyrus	−38	−4	−37	4.84	1519	−0.62	43	0.54
Cluster 2_MRI_remote	R temporo-parietal area R angular gyrus R middle occipital gyrus	45	−68	30	5.21	2142	1.44	43	0.16
Cluster 1_MRI_recent	R anterior hippocampus R parahippocampal gyrus R amygdala	13	−5	−23	3.96	1875	2.52	43	0.02
Cluster 2_MRI_recent	L anterior hippocampus L parahippocampal gyrus L amygdala	−12	−7	−23	4.98	3173	2.32	43	0.03
Cluster 1_FDG_remote	L anterior cingulate gyrus	−8	42	2	5.70	316	0.44	43	0.66
Cluster 1_FDG_recent	L medial orbitofrontal Lventro-lateral prefrontal cortex L hippocampal region (i.e. hippocampus, amygdala, parahippocampal and fusiform gyrus extending to the temporal neocortex)	−6	32	−22	6.70	6479	0.27	43	0.79
Cluster 2_FDG_recent	R medial orbitofrontal R ventro-lateral prefrontal cortex R hippocampal region (i.e. hippocampus, amygdala, parahippocampal and fusiform gyrus extending to the temporal neocortex)	6	28	−20	5.88	4279	1.61	43	0.11
Cluster 3_FDG_recent	L posterior cingulate cortex	−6	−56	16	5.70	1001	4.84	43	<0.001
Cluster 4_FDG_recent	R anterior parahippocampal gyrus R fusiform gyrus R inferior temporal gyrus	44	−2	−36	3.54	276	2.40	43	0.02

neuroimaging studies performed in healthy subjects (Addis et al., 2004; Conway et al., 1999; Gilboa, 2004; Maguire, 2001; Maguire and Frith, 2003b; Rekkas and Constable, 2005; Ryan et al., 2001; Steinvorth et al., 2006; Viard et al., 2010). Our results may appear as contradictory; however, the hippocampus was also found to be related to remote memories when lowering the statistical threshold ($p < 0.05$ uncorrected) but the relationships were stronger for recent memories. In addition, the involvement of the hippocampus is likely to depend on the task and measures used to assess remote memory. In the present study, despite the fact that only episodic memory events (i.e. recalled with details and situated in time and space) have been counted, it is likely that the events were less episodic in nature for the remote than for the recent period. This probably reflects the ecological situation where individuals rely more on semantic (and other) processes to retrieve remote events than on strictly episodic processes (Cermak, 1984; Martinelli et al., 2013; Schmidtke and Vollmer, 1997) and this is reinforced by the fact that the remote events have been repeated over time since they occurred. It seems yet that, in specific conditions where the subjects are guided and supported to retrieve remote events mostly relying on episodic memory, the hippocampus is significantly involved (Viard et al., 2007; Addis et al., 2004; Conway et al., 1999; Gilboa et al., 2004; Maguire and Frith, 2003a, 2003b; Rekkas and Constable, 2005; Ryan et al., 2001; Steinvorth et al., 2006; Viard et al., 2010).

Remote autobiographical memory was found to relate to temporo-parietal and temporal pole volume and anterior cingulate metabolism. The anterior cingulate cortex is known to play a role in attention processes including divided attention (Nebel et al., 2005), and in episodic memory (Martinelli et al., 2013) while the temporal pole is thought to be involved in semantic (naming) tasks and emotional integration of highly processed perceptual inputs (Olson et al., 2007; Semenza, 2011). As for the temporo-parietal junction, this region is included in the DMN and is thought to be involved in episodic and semantic components of autobiographic memories (Renoult et al., 2012) Altogether, our findings suggest that not only multiple processes are involved in the retrieval of remote memories, including semantic and attention but also episodic processes.

4.3. Recent versus remote memories: an interplay between episodic and semantic memory components

Our results suggest that the retrieval of recent memories not only is essentially based on episodic memory abilities but also relies on brain regions involved in semantic processes. This highlights the relevance of semantic processes in the retrieval of autobiographical events. Indeed, even if these recent memories are still very detailed and contextualized, episodic memory requires binding of contextual elements within existing frameworks of conceptual knowledge (Reder et al., 2009). On the other hand, the retrieval of remote memories was found to rely mainly on semantic processes and network. However, behavioural and imaging results also reveal the presence of an episodic component in remote memory retrieval. This is consistent with the fact that remote memories are not expected to be independent from episodic memory structures, but to rely less on these structures, and more on other (neocortical) structures, as compared to recent memories (Moscovitch et al., 2005; Nadel et al., 2007a, 2007b). Moreover, the involvement of the temporal neocortex for both remote and recent memories likely reflects the semantic component associated with autobiographical memories (Svoboda et al., 2006; Holland et al., 2011; Addis et al., 2004; Maguire and Frith, 2003, Gilboa et al., 2005; Renoult et al., 2012). As a whole, our results agree with the idea that autobiographical memories cannot be considered from a binary perspective (i.e. either episodic or semantic in nature) but rather as involving both components to a variable degree. Consistent with this view, several authors have highlighted the existence of an interplay between the episodic and semantic components of memories (Greenberg and Verfaellie, 2010; Irish and Piguet, 2013; Renoult et al., 2012).

4.4. Differential impairment of remote versus recent memory performances and neural substrates in MCI

Consistent with the gradient of Ribot, aMCI patients showed significantly greater impairment for recent than for remote memories in the

present study. This report is consistent with previous studies in AD (Addis and Tippett, 2004; Greene et al., 1995; Irish et al., 2011; Ivanoiu et al., 2004; Kopelman et al., 1989; Leyhe et al., 2009; Piolino et al., 2003) and aMCI patients (Irish et al., 2010; Leyhe et al., 2009; Murphy et al., 2008).

Moreover, showing that most brain regions involved in recent memories are impaired in aMCI patients compared to controls while those involved in remote memories are relatively preserved, the present study furthers our understanding of the brain mechanisms of the gradient of Ribot, i.e. the fact that recent autobiographical memories are more sensitive while remote ones are more resistant in MCI. Thus, in early AD, atrophy is known to concern firstly the hippocampus before extending to the temporal neocortex and other polymodal association areas (Atiya et al., 2003; Chetelat et al., 2003); the former was related with the events from the recent period while the latter were involved in the retrieval of remote memories. Similarly for metabolism, earliest changes in AD are known to concern the posterior cingulate (involved in the recent period) and temporo-parietal cortex, before extending to medial and lateral prefrontal regions (found for the remote period). In sum, the Ribot gradient is likely to reflect the fact that the neural substrates for remote versus recent memories are distinct, and differentially sensitive to the pathological processes underlying MCI.

4.5. Limitation

A limitation of our autobiographical memory task is that it only assesses a limited number of life periods. It has been shown that a lower number of periods were associated with a greater chance of demonstrating a temporal gradient (Barnabe et al., 2012). It is possible that the assessment of a greater number of epochs (e.g. 5 life periods) would reduce this gradient effect and impacts on our neuroimaging findings. Another limitation relates to the time granted for autobiographical memory recollection. As the participants were asked to give as many events as possible in a limited time (2 min), the performances may have been influenced by initiative search abilities which may be impaired in patients. To ensure that our findings, and more specifically autobiographical memory performances, were not merely the reflect of generative search processes, we used another independent time-limited fluency task as a covariate to control for this factor; the results were essentially unchanged (data not shown). Moreover, the autobiographical fluency task is not as specific as other tasks such as those using specific probing (Autobiographical Interview, Levine et al., 2002; TEMPau, Piolino et al., 2000). Indeed, the richness in episodic details and contextual specificity might influence the results and more specifically the implication of the hippocampus. Future studies using other autobiographical episodic memory tasks would allow further understanding the impact of the task.

4.6. Conclusion

In conclusion, this study contributes to our understanding of the Ribot gradient in aMCI considered as the early (predementia) stage of AD. It would be interesting to further explore this question from a network perspective to highlight the role of connectivity disruption within specific networks. Task-related functional MRI also appears as a complementary approach to grasp a more complete picture of the mechanisms of recent versus remote memory deficits in early AD, allowing to unravel not only regions of impaired activity in aMCI in each condition, but also potential areas of increased activity.

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.nicl.2015.05.010.

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