Re-experiencing old memories via hippocampus: a PET study of autobiographical memory

Pascale Piolino,[a,b] Gaëlle Giffard-Quillon,[a] Béatrice Desgranges,[a] Gaël Chételat,[a] Jean-Claude Baron,[c] and Francis Eustache[a,d,*]

[a] Inserm E 0218-Université de Caen, France
[b] Institut de Psychologie, EA 1512, Université René Descartes, Paris 5, France
[c] Department of Neurology, University of Cambridge, UK
[d] Ecole Pratique des Hautes Etudes, CNRS 8581, Université René Descartes, Paris 5, France

The time-scale of medial temporal lobe (MTL) involvement in storage and retrieval of episodic memory is keenly debated. To test competitive theories of long-term memory consolidation, the present work aimed at characterizing which cerebral regions are involved during retrieval of recent and remote strictly episodic autobiographical memory. Using positron emission tomography (PET), we examined mental retrieval of recent (0–1 year) and remote (5–10 years) autobiographical memories, controlling for the nature of the autobiographical memories (i.e., specificity, state of consciousness, vividness of mental visual imagery, emotion) retrieved during scanning by behavioral measures assessed at debriefing for each event recalled. Cognitive results showed that specificity and emotion did not change with time interval although both autonoetic consciousness and mental image quality were significantly higher for recent memories, suggesting an underlying shift in the phenomenal experience of remembering with the passage of time. The SPM analysis revealed common activations during the recollection of recent and remote memories that involved a widespread but mainly left-sided cerebral network, consistent with previous studies. Subtraction analysis demonstrated that the retrieval of recent (relative to remote) autobiographical memories principally activated the left dorsolateral prefrontal cortex whereas the retrieval of remote (relative to recent) autobiographical memories activated the inferior parietal cortex bilaterally. ROIs analysis revealed more hippocampal activity for remote memories than for recent ones and a preferentially right-sided involvement of the hippocampal responses whatever the remoteness of autobiographical memories. New insights based on higher hippocampal response to the remoteness of episodic autobiographical memories challenge the standard model and are less discrepant with the multiple trace theory.
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* Corresponding author. Inserm E 0218-Université de Caen, Laboratoire de Neuropsychologie, CHU Côte de Nacre, 14033 Caen Cedex, France. Fax: +33-231065198.
E-mail address: neuropsycho@chu-caen.fr (F. Eustache).
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Introduction

Autobiographical memory is a multifaceted concept which concerns information and experiences of one's personal life that gives a sense of self-continuity. Tulving et al. (1988) distinguished a semantic component, which stores the general knowledge of one's past, and an episodic component, which contains the personal events situated in time and space. Several authors interested by the effect of time interval on autobiographical memory have demonstrated that there is a shift in the phenomenal experience of remembering with the passage of time (Conway et al., 1997). Many memories undergo a transition from episodic to semantic memory with time interval, repetition of similar events, or frequency of rehearsal (Barclay, 1986; Cermak, 1984; Conway et al., 1997; Linton, 1986; Neisser, 1986). Thus, given the multifaceted nature of autobiographical memory and its changes with time interval, it is necessary to have stringent methods of investigation, especially to control the nature of memory retrieved (Moscovitch et al., 1999), indicating not only the capacity to represent a specific event and locate it in time and space, but also the capacity to relive some specific feature of that event. The episodic and semantic components of memory are characterized by two different states of consciousness (Tulving, 1985, 2001, 2002; Wheeler et al., 1997). Noetic consciousness, which characterizes semantic memory, is the capacity that the subject has of being aware of the information about the world in the absence of recollection, while autonoetic consciousness is a feeling of re-experiencing or reliving the past and mentally travelling back in subjective time. Subjective reports of autobiographical memories can be assessed with the Remember/Know procedure (Gardiner, 1988, 2001; Tulving, 1985), which allows differentiating episodic and semantic autobiographical memory (Conway et al., 1997; Piolino et al., 2003a,b). A Remember judgment means that the subjects recollect a specific autobiographical event as a re-experiencing of the source of acquisition with details (i.e., feelings, perceptions, where and when). A Know judgment corresponds to a feeling of familiarity in the absence of recollection. Remembering is associated with autonoetic consciousness whereas knowing is associated with noetic consciousness. Several studies have shown that recall of visual imagery

about the context of an event is crucial to have a Remember experience. Hence, the subjective sense of remembering almost invariably involves some sort of visual re-experiencing of an event (Brewer, 1996; Conway, 2001; Dewhurst and Conway, 1994; Rubin and Greenberg, 1998). The assessment of visual imagery during autobiographical recollection can be based on the point of view associated with the mental representations called the "field/observer perspective" which permits to distinguish between the episodic and semantic aspects of autobiographical memory (Nigro and Neisser, 1983; Robinson and Swanson, 1993). In a "field perspective", the subject keeps the same point of view as in the original event, which is a characteristic of episodic autobiographical memory retrieval. Alternatively, in an "observer perspective", the subject sees himself in the event from the same point of view as an external observer. Subjective sense of remembering is prone to fading and decaying over time; we tend to re-experience more recent memories from something like the original perspective, whereas we tend to see ourselves as actors in the older memories.

Neuropsychological studies of autobiographical memory have considerably expanded this last decade and permitted to better identify the cerebral structures involved in the storage and retrieval of autobiographical memory (Conway and Fthenaki, 2000; Greenberg and Rubin, 2003; Kapur, 1999; Kopelman, 2002; Kopelman and Kapur, 2001). Retrograde amnesia refers to the loss of memory for information acquired before the onset of the cerebral pathology. Three different profiles of retrograde amnesia have been demonstrated depending on the locus of the lesion. Firstly, retrograde amnesia with Ribot's temporal gradient (Ribot, 1881), characterized by a better preservation of remote relative to recent memories, is observed after damage to the medial temporal lobe (MTL) (i.e., the hippocampus together with the adjacent entorhinal, perirhinal, and parahippocampal cortices). The extent of retrograde amnesia depends on the degree of hippocampal damage, ranging from the last 2 years when damage is limited to the CA1 field, to more than 15 years with extensive damage of the hippocampal formation (Rempel-Clower et al., 1996). Secondly, retrograde amnesia with reverse temporal gradient (impairment of remote memories with preserved recent ones) is observed in the early stages of semantic dementia where there is atrophy of the anterior temporal lobe with relative sparing of the hippocampal complex (Graham and Hodges, 1997; Murre et al., 2001; Piolino et al., 2003a,b). These patients show a progressive deterioration of their semantic memory but they keep a relatively well-preserved day-to-day (episodic) memory. Thirdly, retrograde amnesia without temporal gradient, characterized by a homogenous loss of the memories regardless of remoteness, is observed when the lesion concerns both the medial and the anterior temporal lobes (Kopelman, 2002; Kopelman and Kapur, 2001). These neuropsychological data have largely contributed to the elaboration of the theories of long-term memory consolidation. According to the "standard model", the MTL memory system serves as a temporary memory index of multiple aspects of the memory trace (episodic and semantic) stored in the neocortex (Bayley et al., 2003; Squire and Alvarez, 1995; Teng and Squire, 1999). This time-limited role of the MTL in memory retrieval has variable duration, ranging from few years (Graham and Hodges, 1997) to more than 10 years according to the authors (Reed and Squire, 1998; Rempel-Clower et al., 1996). However, several lesion studies demonstrated episodic retrograde amnesia without a temporal gradient with damage limited to MTL (Cipolotti et al., 2001; Fujii et al., 2000). Thus, an alternative theory termed the "Multiple Trace Theory" (MTT), which takes into account the episodic and semantic nature of the stored information, concurs with the "standard model" of consolidation for semantic memory, but proposes that the MTL has a permanent role in the storage and recovery of episodic memories (Nadel and Moscovitch, 1997; Nadel et al., 2000).

In recent years, a growing number of studies have described the neural substrates of autobiographical memory (for reviews, see Giffard-Quillon et al., 2002; Maguire, 2001) using Positron Emission Tomography (PET) or functional Magnetic Resonance Imaging (fMRI). These studies were interested in revealing the cerebral structures involved: (1) during autobiographical recollection regardless of the retention interval; (2) according to the nature of the information retrieved; and (3) according to the length of the retention interval.

Firstly, although some studies (Fink et al., 1996; Markowitsch et al., 1997, 2000) reported that the recollection of autobiographical memory involved a large right-lateralized network (including the prefrontal, temporoparietal, posterior cingulate, and temporolateral cortices, and the parahippocampal gyrus, hippocampus, and amygdala), most studies found widespread activation of left-sided structures (Andreasen et al., 1999; Conway et al., 1999; Maguire and Mummery, 1999; Maguire et al., 2000). The right-sided activation might reflect the emotional properties of memories studied (Fink et al., 1996), self-perspective during remembering personal past episodes (Piefke et al., 2003), utilization of a kind of task that emphasizes the recall of detailed episodic memories (Graham et al., 2003), or mechanisms of compensation in elderly (Maguire and Frith, 2003b). The left-sided activation might reflect the process of effortful recollection of episodic details (Conway, 2001; Maguire, 2001), or a bias toward producing semanticized instead of episodic memories depending on the paradigm used for eliciting memories under scanning session (Cabeza and Nyberg, 2000).

Secondly, studies interested in the influence of the nature of the information retrieved demonstrated differences in cerebral activation according to the type of memory that was assessed. Piefke et al. (2003) investigated the impact of emotional valence on the neural processes of autobiographical memory retrieval, showing a bilateral, but predominantly left-sided, neural activation. Positive (relative to negative) memories activated the orbito-frontal cortex, temporal pole, and medial temporal lobe (especially entorhinal cortex) bilaterally, whereas negative (relative to positive) memories increased neural activity in the right middle temporal gyrus only. Maguire and Mummery (1999) studied with PET the recognition (i.e., yes–no statement verification task) of four types of memories which differ according to the importance of personal relevance and temporal specificity: the autobiographical events (personal relevance, temporal specificity), the autobiographical facts or "personal semantics" (personal relevance, no temporal specificity), the public events (no personal relevance, temporal specificity), and the general knowledge (no personal relevance, no temporal specificity). A common memory retrieval network supporting all memory types was found to involve left cerebral structures such as the medial prefrontal cortex, medial and external temporal lobes, posterior cingulate cortex, and temporoparietal junction. Within this network, the recovery of specific autobiographical events activated the left hippocampus, the medial prefrontal cortex, and the left temporal pole, whereas the recovery of the autobiographical facts mainly activated the bilateral temporoparietal junction. Using an extended retrieval of memories in response to cue-words, Graham et al. (2003) have found in three recent PET studies that

episodic autobiographical memories relative to semantic facts produced bilateral activations in the middle temporal and medial frontal cortices. These findings document the necessity of controlling the episodic or semantic nature of the material retrieved during an autobiographical memory test, especially to test the models of memory consolidation.

Thirdly, several studies examined the hypothesis of a differential activation of the MTL according to the retention interval, but most were negative (Conway et al., 1999; Maguire and Frith, 2003a; Maguire et al., 2001; Nadel et al., 2000; Ryan et al., 2001; Tulving, 1989), conflicting with predictions from the "standard model". These results seemed at first glance to support the MTT theory but, as pointed out by some authors (Nadel et al., 2000), at the same time as the subjects recall old memories, they encode them once again (Buckner et al., 2001). Hence, the MTL activation for long retention interval would reflect the processing of encoding and not the access per se to old memories. Some studies, however, at least tried to control for this possibility by including a control condition that involved encoding (e.g., Conway et al., 1999). Moreover, specific aspects of the experimental design are likely to prevent a differential hippocampal involvement in recent and remote autobiographical memory retrieval. For example, Maguire's team uses a questionnaire that was proposed a few weeks before the scanning session to obtain the material to construct the sentence cues used during scanning to reactivate old memories traces. Moreover, during scanning, the autobiographical memory is tested by a decision task where the subject has to press a key to specify if each sentence cue presented auditorily is true or false, which is far from producing vivid recollection of personal past experiences. In contrast, three fMRI studies (Haist et al., 2001; Niki and Luo, 2002; Piefke et al., 2003) have provided evidence for a differential engagement of the hippocampal region in recent and remote autobiographical memory retrieval, arguing in favor of the standard model of memory consolidation. In fact, one of these studies concerned rather semantic than episodic remote memory, namely famous faces memory (Haist et al., 2001), and was therefore also compatible with the MTT model. The second study (Niki and Luo, 2002) involved topographical autobiographical memory controlled for details, but not for spatio-temporal specificity. However, detailed perceptual autobiographical remote memories might be generic rather than specific (Brewer, 1986). Interestingly, the third study concerned emotional-laden autobiographical memory (Piefke et al., 2003) and showed differential increases in neural activity in the hippocampal region bilaterally, associated with recent relative to remote memories (irrespective of emotional tone). Nevertheless, the study of Piefke et al. (2003) leaves open the possibility that the retrieval of remote memories tested (up to age 10 years) concerned rather semanticized memories than episodic ones (Cermak, 1984; Piolino et al., 2002). In sum, in experiments contrasting remote and recent autobiographical memory, differential activation of the MTL might depend on the degree to which a subject has refreshed old memories before the scanning session and the degree to which he is engaged in the retrieval of the details of the episode during the scanning session. Finally, recent studies illustrated that the issue of the hippocampal involvement in memory retrieval is very complex, depending not only on the remoteness of information but also on the age of subjects during encoding (Tsukiura et al., 2002) or retrieval (Maguire and Frith, 2003b). Interestingly, Maguire and Frith (2003a) demonstrated in a large group of young and older adults that the two hippocampi diverged in their responses to remoteness. The right hippocampus

decreased in activity with the passage of time, but not the left hippocampus.

The main aim of the present study was to unravel the cerebral structures involved in the retrieval of episodic autobiographical memories according to their remoteness taking into account their specificity and phenomenal experience of remembering (state of consciousness, point of view and emotion). To this end, the experimental protocol was designed so as to be both more appropriate and more reliable than that used in previous autobiographical neuroimaging studies. Accordingly, remote and recent memories were not reactivated before the scanning session, and the nature of the autobiographical memories retrieved while scanning was controlled, using an up-to-date definition of episodic memory (Tulving, 2001, 2002), by specifying the different aspects of recollective experience. Thus, the episodic component of autobiographical memory retrieval was assessed with a fine-graded "episodic scale", and with the Remember/Know paradigm (Gardiner, 1988, 2001). We also used cognitive scales to characterize the vividness of the mental visual imagery (i.e., the strategy used—verbal or visual, the point of view—field or observer perspective, and the mental image quality) and the emotional intensity related to encoding or retrieval of personal events, which are both critical factors to episodicity of autobiographical memories.

To challenge the theories of long-term memory consolidation (namely, the "standard model" and "MTT"), we elaborated a paradigm of activation with PET in which healthy volunteers had to mentally retrieve strictly episodic autobiographical memories. We studied two retention intervals: a short retention interval (0–1 year; "Short") and a long retention interval (5–10 years; "Long"). The subtraction of these two conditions using voxel-based analysis should permit to identify the cerebral structures specifically involved during the retrieval of recent and remote episodic past. We also included a rest condition ("Rest") not only to disclose the cerebral regions activated during autobiographical retrieval regardless of the retention interval, but also to carry out the Short minus Rest and Long minus Rest comparisons. This paradigm should therefore allow us to assess both the common and differential neural mechanisms underlying recent and remote autobiographical memory retrieval. Moreover, to assess the putative central role of the hippocampus with respect to the theories of memory consolidation, we also used a parametric method with a region of interest (ROI) approach and a precise anatomical methodology to specifically assess the activity of this structure in the Short and Long conditions. To get around the issue of encoding during the retrieval task that we highlighted in the introduction, we were specially interested in the study of anterior–posterior axis of the hippocampus taking into account the HIPER model (Lepage et al., 1998) which suggests that the anterior hippocampus is involved during episodic memory encoding whereas the posterior hippocampus is more activated during episodic memory retrieval.

Materials and methods

Subjects

Seven right-handed (as measured by the Edinburgh handedness inventory) healthy young men were recruited among students of the University of Caen following approval by the Regional

Ethics Committee. They gave informed written consent after all procedures had been fully explained. Subjects ranged in age from 25 to 28 years were free from medication and from psychiatric and central nervous system disease or injury. They had no abnormality on their T_1-weighted high-resolution magnetic resonance imaging (MRI). For the purpose of the study, exclusion criteria included abnormal performance in a standard episodic memory test (California Verbal Learning Test; Delis et al., 1987) and two visual mental imagery tests (Mental Rotations test; Likert and Quasha, 1941; Minnesota Paper form Board: Vandenberg and Kuse, 1978). Moreover, the selection of subjects was based on their capacity to retrieve aloud episodic autobiographical memories from sentence cues (e.g., an event with one of your family members).

Protocol

The protocol was divided in three sessions. The first session had to do with a training to produce specific autobiographical memories with as much episodic details as they could such as time, location, perceptions, and feelings when they listened to sentences cues (e.g., a day when you attended a ceremony). This session was carried out few weeks before the PET experiment.

The second session concerned the experimental session, which was divided in two parts. In the activation part, during PET scanning, the subjects were verbally instructed to mentally relive personal episodes with as much detail as possible from 16 sentences cues according to two different retention intervals: Short (0–12 months) vs. Long (5–10 years). Eight sentences cues were proposed for each retention interval (e.g., recollect an event that occurred last summer for Short retention interval; e.g., recollect the day when you obtained your driving license for Long retention interval). Before scanning, subjects were familiarized with the experimental task by asking them to mentally retrieve four autobiographical memories with the same experimental conditions as while scanning. The sentences cues used during scanning were different from the first session and the familiarization stage. They were presented by a female voice. These sentences cues used in the first and second sessions were selected from a previous autobiographical memory experimental study on 52 healthy subjects aged 40 to 79 years (Piolino et al., 2002) and a pre-experimental study of the present protocol carried out on five young adults aged 25 to 28 years. Selection criteria for these cues consisted in the likelihood to produce specific detailed autobiographical memories in young subjects with the same ease of access regardless of time interval. Moreover, the sentences cues selected were as identical as possible between the two retention intervals, and differed only about the delay separating encoding and retrieval (e.g., a party with your friends since 1 year ago and a special party with your friends that took place when you were between 17 and 20 years of age).

In the debriefing part, and to identify the nature of the evocations achieved during scanning specifying the different aspects of recollective experience, the subjects were asked to retrieve these evocations again but this time aloud, and to rate them on analogical scales (10 cm lines) in terms of state of consciousness (from noetic to autonoetic), visual mental imagery (visual quality: from bad to very good; and strategy used: from verbal to visual) and emotion either during encoding or retrieval (from low to high). Regarding point of view, three choices were proposed: field, observer, or field/observer. Moreover, the speci-

ficity of each evocation was measured by the investigators using a fine-grained 6-half point scale rather similar to previous episodic scales used in normal subjects and patients with cerebral diseases (Graham and Hodges, 1997; Kopelman et al., 1989; Piolino et al., 2002, 2003a,b). This scale takes into account the specificity of the event: unicity, spatio-temporal situation, and richness of details (perceptions, thoughts, feelings) (see Appendix 1).

Finally, in the third session, performed 2 weeks later, the validity of the experimental session was assessed by checking the authenticity and the specificity of memories recollected during scanning (and tested at debriefing). At this re-test, the subject was asked to reproduce in random order their previous recollections from cues taken from the subject's original answers. The accuracy of the subject's recollections was assessed according to their consistency over the test–retest procedure. Comparison between the test and retest was designed to maintain, adjust, or reject the initial episodic score.

Neuroimaging investigations

Each subject underwent a high-resolution T_1-weighted volume MRI scan, which consisted of a set of 128 adjacent axial cuts parallel to the anterior commissure–posterior commissure line and with slice thickness 1.5 mm and pixel size 1×1 mm, using the SPGR gradient echo sequence (TR = 15.4 s; TE = 3.4 kHz; FOV = 24 cm; matrix = 256×256). All the MRI data sets were acquired on the same scanner (1.5 T Signa Advantage echospeed; General Electric) and with the same parameters. Standard correction for field inhomogeneities was applied.

Using PET, the rCBF was mapped 12 times, replicating four times each one of three conditions: (1) Rest; (2) Retrieval of recent autobiographical memories (Short); (3) Retrieval of remote autobiographical memories (Long). During the two conditions of activation, the subjects were instructed to mentally relive a specific episode of their past and to press a key when they started their recollection to note the absence of remembering after a sentence cue. Two sentence cues were proposed per scan belonging to the same retention interval. After the presentation of the first sentence cue, the subject recollected a memory for 45 s and stopped when he heard the word "stop", then the second sentence cue was presented and he recollected the next memory for 45 s. Moreover, this procedure permitted to measure the time of access to memory according to the time interval.

During Rest, subjects were instructed to relax, to keep their eyes closed and not to focus their mind on a precise thought. The three conditions (Rest = R, Short interval = S, and Long interval = L) were presented in a R, L, S, S, L, R, L, L, R, S, S, R sequence.

PET procedure

Subjects were scanned while lying supine in a darkened and quiet room. A black tent was set up all around the PET tomograph to ensure that the subjects were in total darkness. The subject's head was gently immobilized in a dedicated headrest. Head position was aligned transaxially to the orbito-meatal line with a laser beam. Measurements of regional distribution of radioactivity were performed with an ECAT HR + (SIEMENS) PET camera with full volume acquisition allowing the reconstruction of 63 planes (thickness: 2.4 mm; axial field-of-view: 158 mm; effective resolution is about 4.2 mm in all

Table 1

Behavioral measures: comparison between Short and Long retention intervals

Behavioral scales	Short retention interval	Long retention interval	P
Specificity	2.86 (± 0.28)	2.77 (± 0.36)	NS
Strategy used	6.78 (± 2.3)	7.23 (± 2.18)	NS
Point of view	7.00 (± 1.53)	6.71 (± 1.98)	NS
Autonoetic consciousness	8.48 (± 1.61)	6.85 (± 2.18)	0.04
Mental image quality	7.70 (± 2.32)	6.46 (± 2.30)	0.03
Emotion at encoding	6.08 (± 2.73)	6.81 (± 2.43)	NS
Emotion at retrieval	3.58 (± 3.03)	3.09 (± 2.40)	NS
Time of access to memory (s)	8.25 (± 6.03)	6.70 (± 5.04)	NS
Frequency of rehearsal	4.90 (± 3.21)	3.40 (± 2.50)	NS

The Wilcoxon two-sample test was used for the comparison between the two retention intervals. Means for each scale and each retention interval are indicated (M ± SD). Regarding specificity, the higher the score, the more specific the memory. Regarding strategy, the higher the score, the more visual the strategy. For the Point of View, we summed the number of "field" and "field/observer" responses. Regarding autonoetic consciousness, the higher the score, the more autonoetic the retrieval. Regarding mental image quality, the higher the score, the better the quality of the mental images. Regarding emotion, the higher the score, the more emotional the memory. Regarding time of access, the higher the score, the more rapid the access. Regarding frequency of rehearsal, the higher the score, the more frequent the rehearsal.
NS: non significant.

directions). Transmission scans were obtained with a ^{68}Ga source before emission scans. The duration of each scan was 90 s. About 7 mCi of H_2O^{15} were administered as a bolus in the left antecubital vein by an automated infusion pump. Each experimental condition was started 40 s before data acquisition and continued until scan completion. This process was repeated for each of the 12 scans, for a total injected dose of approximately 80 mCi. The interval between injections was 6 min 55 s; the position of the head was controlled with the laser beam before each injection.

Data analysis

Behavioral data were analyzed with non-parametric test (Wilcoxon two-sample test) to compare short and long retention intervals. Subsequently, those results were entered in a matrix of correlation (Spearman's rank correlation coefficient). Otherwise, all calculations and image transformations were performed on UNIX SYSTEM workstation. First, the 12 scans of each subject were realigned to each other, using the AIR 3.0 software (Automated Image Registration; Woods et al., 1997). For subsequent data analysis, the Statistical Parametric Mapping software (SPM99, Welcome department of Cognitive Neurology, UK) implemented in the MATLAB environment was used. The images were non-linearly transformed into standard space (MNI template), based on the atlas of Talairach and Tournoux (1988), and smoothed using a 12-mm Gaussian filter. The images were scaled to an overall CBF grand mean of 50 ml/100 g/min; we therefore refer to "adjusted rCBF" in what follows. We used a gray matter threshold of 80% of the whole brain mean.

Three types of analyses were performed. Firstly, we performed a Conjunction analysis of Short and Long minus Rest. For this analysis, we used the $P < 0.05$ corrected for multiple tests as cut-

off. Secondly, we performed direct comparisons between activation, that is, Long minus Short and Short minus Long. In these analyses, we used the uncorrected $P < 0.001$ for multiple comparisons (with cluster extent $k > 10$ voxels) because those contrasts were hypothesis-driven: with respect to the standard model of long-term memory consolidation, we predicted a selective activation of the MTL in Short retention interval (see Introduction). We furthermore performed comparisons between Long minus Short and Short minus Long activations. The results

Table 2

Results of the Conjunction analysis, tabulating for each peak the Brodmann areas, Talairach's coordinates, Z score, cluster size (k) and cluster-level P corrected

Regions	Brodmann areas	Talairach's coordinates			Z score	Cluster size	P corrected
		x	y	z			
Periaqueductal GM		2	−33	−5	5.38	6823	0.000
R. cerebellum		40	−64	−30	5.25		
		18	−79	−28	5.21		
		8	−63	−14	4.95		
		16	−43	−10	4.50		
		28	−51	−19	4.29		
L. cerebellum		−4	−53	−7	4.18		
		−2	−42	−18	3.97		
		−12	−37	−12	3.91		
		−2	−50	−33	3.31		
R. posterior cingulate	23/31	6	−55	21	4.84		
L. posterior cingulate	23/31	−6	−51	23	4.69		
R. retrosplenial cortex	30	18	−51	19	4.66		
R. fusiform/lingual gyrus	18	2	−58	5	4.74		
Anterior cingulate	32	0	18	40	5.07	1679	0.000
	32	0	21	34	5.03		
L. sup. frontal gyrus	6	−8	15	60	4.57		
L. mid. frontal gyrus	8	−32	16	45	3.61		
L. cerebellum		−32	−56	−36	4.22	450	0.003
		−36	−68	−37	3.89		
		−20	−40	−27	3.42		
L. mid temporal gyrus	39	−34	−57	23	3.37	385	0.005
L. angular gyrus	39	−42	−61	33	3.92		
L. parietooccipital J.	7/19	−34	−70	40	4.04		
L. sup frontal gyrus	10	−14	52	−8	4.26	358	0.008
	10	−8	59	12	3.73		
L. VL thalamus		−16	−9	8	4.41	337	0.01
L. caudate nucleus		−4	6	−5	3.70		
L. inf. frontal gyrus	47	−36	21	−1	4.27	325	0.01
L. orbitofrontal gyrus	11/47	−30	26	−25	4.09		
L. inf. frontal gyrus	47	−28	22	−16	3.80		
L. sup. temporal gyrus	38	−51	15	−16	5.26	224	0.04

The data are local maxima detected with SPM99 software (see Materials and methods). Within these regions anatomical localization of the maxima Z voxels is based on Talairach and Tournoux's (1988) stereotactic atlas (using M. Brett's transform). Corrected significant level was set at $P < 0.05$ cluster size corrected for multiple comparisons (Z score > 3.09; GM = gray matter; R = right; L = left; VL = ventrolateral; J = junction; sup. = superior; inf. = inferior, mid. = middle).

of t statistic (SPM $\{t\}$) were then transformed into a normal standard distribution (SPM $\{z\}$). Thirdly, we used a region of interest (ROI) approach to specifically assess hippocampal activity during the Short and Long conditions (see Introduction). The ROIs were directly defined on the T_1-weighted MRI planes of these subjects, which were coregistered with PET plans by using SPM99. At first, each MRI data set was coregistered with its corresponding PET data set, and resliced at $x = 2.025$, $y = 2.025$, $z = 2.425$ mm, using an entirely automatic procedure implemented in SPM-99. We used the "mutual information" option for the coregistration, as recommended when images have been acquired in different modalities (Ashburner and Friston, 1997). Briefly, it is a three-step procedure, involving (i) simultaneous constraining affine registration of the images to template images of the same modalities; (ii) segmentation of both original images into homologous tissue classifications; and (iii) coregistration of the image partitions. Right and left hippocampal ROIs were then individually drawn by a single rater from contiguous T_1-weighted coronal sections obtained from the coregistered MRI data set. The border of the hippocampus was manually traced sequentially with a mouse-driven cursor on each slice from anterior to posterior. Since our aim was not to calculate the volume of this structure, but instead to assess its specific activity, we deliberately adopted a conservative approach, not trying to include the whole hippocampus but instead only the hippocampus. Therefore, doubtful voxels concerning their belonging to the hippocampus were excluded, as well as the most anterior or posterior hippocampal part when unclear. The hippocampal anatomic boundaries were defined as described in Watson et al. (1997), to include the CA1 to CA4 sectors, the dentate gyrus, the subicular complex, alveus, and fimbria. Briefly, on anterior-most sections, the head of the hippocampus was separated from the adjacent amygdala by either the inferior border of the temporal horn of the lateral ventricles of the alveus (when obvious) or by tracing a horizontal line connecting the plane of the temporal horn of the lateral ventricle to the surface of the uncus. The inferior margin of the hippocampus was outlined to include the subicular complex and the uncal cleft, but to exclude the parahippocampal gyrus, the crus of the fornix, and the isthmus of the cingulate gyrus. The tracing ended posteriorly in the section where the crus of the fornix departs from the lateral wall of the lateral ventricles. This left out a small portion of the tail of the hippocampus, but was preferred concerning our conservative approach.

The right and left hippocampal ROIs were also divided according to the antero-posterior axis, so that four ROIs per subject were studied, corresponding to the right Anterior (R-Ant), right posterior (R-Post), left anterior (L-Ant), and left posterior (L-Post) hippocampus. Once drawn on coregistered MRI, these ROIs were then superimposed onto their corresponding PET scans (obtained from the different activation conditions). For each ROI and across all

Table 3
Results of SPM contrasts (Short minus Long and Long minus Short retention conditions), tabulating for each peak the Brodmann's areas, Talairach's coordinates, Z score and cluster size

Regions	Brodmann areas	Talairach's coordinates			Z score	Cluster size
		x	y	z		
Short minus Long						
L. mid. frontal gyrus	46/10	−28	38	20	3.43	26
R. anterior cingulate	24/33	6	9	25	3.42	14
Long minus Short						
L. inf. parietal lobe	40/19	−30	−59	39	3.55	61
R. inf. parietal lobe	40/19/39	−40	69	30	3.26	16

See methodology and legend Table 1.

slices sampled, a value of mean relative perfusion, weighted by the number of voxels in the ROI, was calculated for each condition by averaging the values obtained for each of the four scans per condition. The statistical analysis of the data was processed with a repeated measure analysis of variance (ANOVA) to examine the influence of the time interval (Short vs. Long), the hemispheric laterality (Right vs. Left), and the antero-posterior axis (Anterior vs. Posterior) as within factors.

Results

Behavioral data

Means and standard deviations as well as the results of the analyses of differences between Short and Long are presented in Table 1. The results indicate no time interval effect for the specificity, the strategy used, the memory point of view, emotion during encoding or retrieval, time of access, and frequency of rehearsal. Not only the results showed that participants spent the same time trying to retrieve the episode for Short and Long interval, but also the participants indicated at debriefing that they spent actually all the time (45 s) reliving the episode. By separating the recalls into entirely different categories for "specific" events (score > 2) and "generic" events, the results did not differ between Short and Long: 91.07% specific events and 8.93% generic events for Short; 87.50% specific events and 12.50% generic events for Long. In contrast, autonoetic consciousness and mental image quality were significantly higher for Short as compared to Long. The study of the inter-correlation among the behavioral data for the Short retention interval showed a single significant correlation, concerning autonoetic consciousness and mental image quality ($r =$

Fig. 1. Short and Long retention conditions minus Rest: Statistical parametric "glass brain" maps showing the significant rCBF increases when subjects retrieve autobiographical memories compared to the Rest condition (Conjunction analysis). The volumes are thresholded at $P < 0.05$ corrected for multiple comparisons and projected in three orthogonal directions (sagittal, coronal and transverse). Stereotactic coordinates of local maxima are given in Table 1.

Fig. 2. Statistical parametric glass brain maps showing the significant rCBF increases when subjects retrieve autobiographical memories (a: Short minus Long; b: Long minus Short). The volumes are thresholded at $P < 0.001$ (uncorrected for multiple comparisons) (cluster extent $k > 10$ voxels) and projected in three orthogonal directions (sagittal, coronal and transverse). Illustrative sections: anatomical localization of the left dorsolateral prefrontal cortex (A), left inferior parietal lobe (B) and right inferior parietal lobe (C) peaks (shown by the crossing lines), as projected onto a normal MRI set spatially normalized into MNI's template.
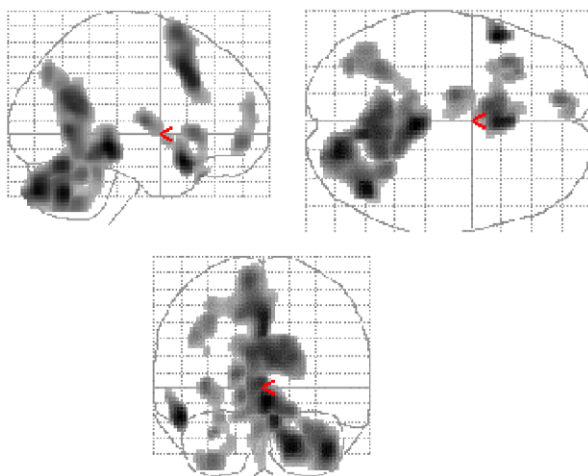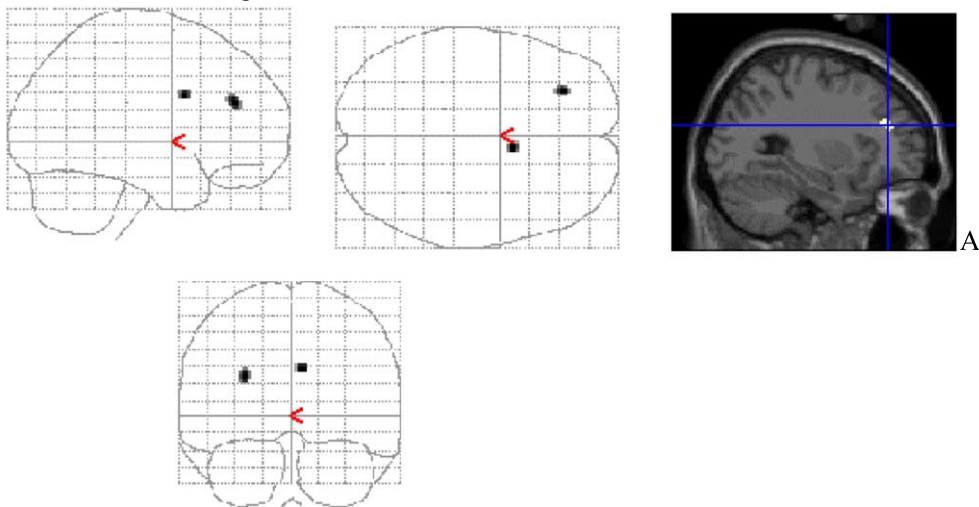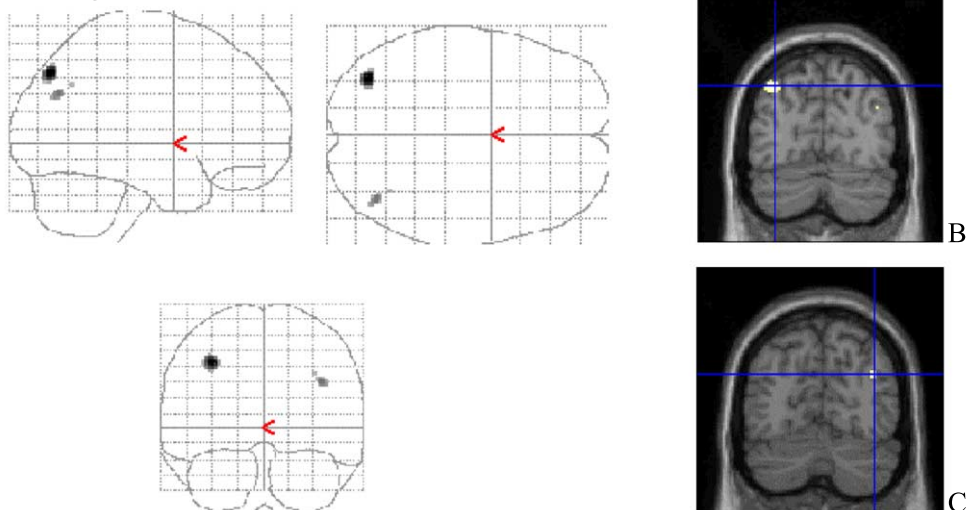
Fig. 1.

a: Short minus Long

b: Long minus Short

Fig. 2.

Table 4
ROI analysis: hippocampal values (Bq/cc) of relative perfusion (M $\pm$ SD) between the Short and Long conditions according to the hemispheric laterality and the antero-posterior axis

	Short	Long
R-Ant	47.1 $\pm$ 2.4	49.6 $\pm$ 2.5
R-Post	46.6 $\pm$ 1.6	49.5 $\pm$ 2.9
L-Ant	45.4 $\pm$ 3.9	47.1 $\pm$ 5.8
L-Post	42.7 $\pm$ 3.7	44.4 $\pm$ 3.7

R: right; L: left; Ant: anterior; Post: posterior.

0.75, $P \leq 05$). For the Long retention interval, autonoetic consciousness correlated principally with mental image quality ($r = 0.96$, $P < 0.01$), visual strategy ($r = 0.75$, $P \leq 0.05$), and sum of "field" and "field/observer" point of view ($r = 0.90$, $P \leq 0.05$). Otherwise, at debriefing, when asking the subjects what they were thinking about during the Rest intervals, two participants indicated they spent Rest time doing "nothing", whereas five others provided evidence they sometimes thought about their current personal activities and projects (i.e., going for shopping, preparing their lessons).

PET data

Conjunction analysis

Relative to Rest, activations common to both retention intervals involved an extensive network including the periaqueductal gray matter, bilateral cerebellum, bilateral posterior cingulate cortex, right retrosplenial cortex, anterior cingulate cortex, left fusiform gyrus, left subcortical areas, and left parietal, temporal and prefrontal cortices (Table 2 and Fig. 1). Comparing Short to Rest and Long to Rest showed results similar to the conjunction analysis (data not shown).

Short minus Long

The brain regions highlighted by this contrast were the left dorsolateral prefrontal cortex (junction of BA 46/10) and the right anterior cingulate cortex (BA 24/33) (Table 3 and Fig. 2A).

Long minus Short

This contrast revealed only the bilateral inferior parietal cortex (Table 3 and Fig. 2B).

ROIs analysis

The mean values of relative perfusion for the Short and Long conditions as a function of the hemispheric laterality and the antero-posterior axis are presented in Table 4. The three-way ANOVA (Short vs. Long, Right vs. Left, Anterior vs. Posterior) performed on these data revealed significant simple effects of Short vs. Long ($F(1,6) = 6.12$, $P = 0.04$; Long > Short 47.7 $\pm$ 4.3 > 45.4 $\pm$ 3.3) and Right vs. Left ($F(1,6) = 10.72$, $P = 0.01$; Right > Left: 48.2 $\pm$ 2.7 > 44.9 $\pm$ 4.4). The effect of Anterior vs. Posterior ($F(1,6) = 2.85$, $P = 0.14$; 47.3 $\pm$ 3.9 vs. 45.8 $\pm$ 3.9) and the interactions between factors were not significant ($P > 0.10$). This analysis showed that hippocampal activity was higher for Long relative to Short interval (regardless of anterior–posterior axis and laterality) and for right relative to left hemisphere (regardless of anterior–posterior axis and time interval).

Discussion

We examined the cerebral substrates implicated in mental retrieval of recent and remote episodic autobiographical memories using PET and a paradigm specially designed according to up-to-date concepts of episodic memory. The behavioral data (specificity, state of consciousness, vividness of the mental visual imagery, emotion) obtained at debriefing for each event recalled during scanning whatever the retention interval showed that recollection was characterized by specificity, autonoetic consciousness, visual imagery, and emotion. Nevertheless, recent memories were more autonoetic and had a better image quality than remote ones. The neuroimaging data showed firstly that common activations during recollection of memories (irrespective of remoteness) relative to Rest involved an extensive but preferentially left-sided cerebral network; secondly, that the retrieval of recent (relative to remote) autobiographical memories principally activated the left dorsolateral prefrontal cortex, whereas the retrieval of remote (relative to recent) autobiographical memories specifically activated the bilateral inferior parietal cortex; and thirdly, that no significant differential activation of the hippocampus according to the time period considered was demonstrated by SPM analysis, while ROIs analysis revealed more hippocampal activity for remote memories than for recent ones and for right relative to left hemisphere. These results will now be discussed in the light of recent concepts of autobiographical recollection and according to their relevance with models of long-term memory consolidation.

Behavioral data on autobiographical memory retrieval

The present behavioral findings based upon an experimental investigation, which uses tight criteria for episodicity, and a checking procedure permitted to confirm that the data obtained during scanning really concerned verified episodic recollection whatever the time period considered. Indeed, recollections were characterized by spatiotemporal specificity, autonoetic consciousness, visual imagery, and emotion, which are critical features of episodic memories (Brewer, 1996; Conway, 2001; Conway and Pleydell-Pearce, 2000; Tulving, 2001). These findings may have some reliable implications, as they are based on an experimental investigation which explores strictly episodic recent and remote memory using checking procedure which have shown that the two-time intervals tested were well matched on numerous characteristics. Nevertheless, as recent relative to remote recollections were more autonoetic and vivid, our findings outline the fact that autobiographical memory retrieval is modulated by time-related processes (Barclay, 1986; Conway et al., 1997; Linton, 1986; Rubin and Schulkind, 1997). These findings are consistent with Piefke et al. (2003) who have recently shown, with an fMRI study of autobiographical memory, that recent relative to remote memories were higher rated for behavioral characteristics such as picture likeness as well as the richness of details (see also, Niki and Luo, 2002) and the degree the subjects re-experienced their personal past events. Interestingly, our behavioral data pointed to an increase of the link between the feeling of remembering (autonoetic consciousness) and mental visual imagery in the remote time period. This finding is consistent with the idea that mental visual imagery would become active in episodic remembering when sensory perceptual knowledge of the past dominates (Conway, 2001). Moreover, visual imagery is a particularly efficient cue to retrieve episodic autobiographical memories since

images are economic representations that contain the contextual details of an event such as the actors, actions, and locations as well as some temporal information (Conway, 1988; Dewhurst and Conway, 1994; Williams et al., 1999). In sum, as emphasized by Piefke et al. (2003), our behavioral data highlight that "time interval is not a kind of formal temporal criterion", but has differential effects on many dimensions of memories that may interact with the brain regions and the neural processes involved (see also Tsukiura et al., 2002).

Activations at autobiographical memory retrieval regardless of the remoteness

The neuroimaging data showed that regardless of time interval, the retrieval of autobiographical memories involved an extensive network predominantly comprising left-sided neocortical regions, especially the prefrontal cortex. Many regions of this network have previously been found to be implicated in autobiographical recollection, such as the right lateral cerebellum (Andreasen et al., 1999; Maguire et al., 2000), the bilateral posterior cingulate cortex (particularly during successful retrieval of autobiographical memories, Maddock et al., 2001), the retrosplenial cortex (especially in affect-laden memories; Fink et al., 1996; Maddock, 1999; Maguire et al., 2001; Piefke et al., 2003), the left temporal neocortex (Maguire and Mummery, 1999), and the left prefrontal cortex (Andreasen et al., 1999; Conway et al., 1999; Maguire and Mummery, 1999; Maguire et al., 2000; but see Fink et al., 1996; Markowitsch et al., 1997, 2000). In particular, functional neuroimaging studies have confirmed that the medial frontal cortex is particularly responsive to retrieval of autobiographical episodic memories (Maguire and Mummery, 1999; Maguire et al., 2001; Graham et al., 2003). Conway and Pleydell-Pearce (2000) have proposed a neurocognitive model, which takes into account this preferentially left-sided widespread network, implicated in autobiographical memory. According to this model, the reconstruction of memories requires the activation of a network involving the prefrontal lobe (for strategic processes) and the lateral temporal lobe (for personal semantic memory), as well as posterior, essentially occipital, regions (for sensory/perceptual episodic details). Nevertheless, preferential left-sided frontal activation was also in a way unexpected, considering that numerous studies have stressed a right hemispheric predominance in episodic non-autobiographical memory retrieval and a left hemispheric predominance in semantic memory retrieval (Cabeza and Nyberg, 2000, for a review). Several authors (Conway, 2001; Piefke et al., 2003) have underlined that the left prefrontal activation in autobiographical memory is related to the complexity of retrieved information (see Nolde et al., 1998), whereas rather simple episodic memory tasks yield right prefrontal activation. The other cerebral structures highlighted in our study correspond to the results of more classical activation studies of memory using a laboratory material supporting either episodic non-autobiographical memory or other sets of memories. Thus, the retrosplenial cortex, thalamus, anterior and posterior cingulate cortex are all known to be involved in episodic memory retrieval (see for reviews Cabeza and Nyberg, 2000; Desgranges et al., 1998). Noteworthy, these further regions—and especially the retrosplenial cortex—are closely connected with the hippocampal formation and other structures of the MTL subserving memory function (Insausti et al., 1987; Piefke et al., 2003). In addition, parietal regions have been related to semantic memory, fusiform gyrus to visual imagery (Cabeza and Nyberg, 2000) and periaqueductal gray matter to emotion since this region belongs to the rostral limbic system which is engaged in executive functions including those associated with affect (Devinsky et al., 1995).

Activations at autobiographical memory retrieval according to the remoteness

Specific activations were found for each retention interval (Short or Long) relative to the other. This could be explained by the involvement of different cognitive processes during the recovery of recent and remote autobiographical memories as stressed by our behavioral data. Differences between Short and Long interval do exist that are associated with behavioral differences.

During the retrieval of recent memories characterized by their higher autonoetic and mental image quality, the main activation was in the left dorsolateral prefrontal cortex (BA 46/10) and, at a lesser degree, in the right anterior cingulate cortex (BA 24/33). This finding indicates specific activations during the recollection of recent (relative to remote) memory (see also Conway et al., 1999; Maguire et al., 2001; Niki and Luo, 2002; Piefke et al., 2003). It could reflect the involvement of "REMO sites" (Lepage et al., 2000) given the implication of autonoetic consciousness for the recent memories. Accordingly, Tulving (2001), (2002) and Wheeler et al. (1997) suggested that one of the functions of the frontal lobes concerns self-awareness (i.e., the ability to introspect on one's own thoughts) intimately related to autonoetic consciousness, which is particularly characteristic of recent autobiographical memories (see Behavioral data). Prefrontal activation could also reflect the reconstruction of specific autobiographical memories subtended by effortful and strategic processes (Conway et al., 1999), as well as the retrieval of specific perceptual information (Piefke et al., 2003; Ranganath et al., 2000). Conway (2001) suggested that the left prefrontal cortex is predominantly activated when the complexity of the memory task strongly engages working memory concerning the self, and consequently implicates the autonoetic state of consciousness.

The retrieval of remote (relative to recent) autobiographical memories activated inferior parietal areas bilaterally. These regions are involved in storage of semantic information and spatial processing (Persson and Nyberg, 2000). Burgess et al. (2001a,b) have highlighted the role of parietal areas in imaging, manipulating and re-experiencing the products of real-life events retrieval, which is in accordance with our behavioral data showing the importance of visual imagery, especially for remote memories. As far as the issue of differential patterns of activation according to the remoteness of autobiographical memories is concerned, the findings from previous studies are diverse. The decline of activation in prefrontal cortex with the increasing remoteness of autobiographical memory is not unprecedented (Maguire et al., 2001). By contrast, Piefke et al. (2003) observed that the retrieval of remote relative to recent memories (regardless of their emotional valence) did not yield any specific activation. Previous activation studies on autobiographical memory (irrespective to the remoteness) have emphasized the involvement of parietal structures (Maguire and Mummery, 1999).

Besides the above differences of activation between remote and recent memories, our results revealed no differential activation of the MTL whatever the contrast studied using SPM approach. Previous studies (Conway et al., 1999; Maguire et al., 2001; Nadel et al., 2000; Ryan et al., 2001) alike did not show differential activation of the MTL, which may suggest a more permanent role of the MTL in the recovery of autobiographical memories as proposed by the MTT theory (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1999). In most of these studies, however, the MTL was activated both in recent and remote memories, by opposition to our results. Nevertheless, the ROIs analysis based on a three-way ANOVA (Short vs. Long, Right vs. Left, Anterior vs. Posterior), clearly showed that the involvement of hippocampus was more important in long retention interval than short one. Two studies have demonstrated a differential involvement of the hippocampal region with time interval but unlike the present study, to the disadvantage of the remote past in accordance with the standard model predictions (Niki and Luo, 2002; Piefke et al., 2003 see Introduction). Maguire and Frith (2003a) have recently found that the right, but not the left, hippocampus decreased in activity with remoteness suggesting an asymmetrical time-dependent contribution of the hippocampal complex with time interval. Our results, interestingly, emphasize that higher hippocampal response to the remoteness of episodic autobiographical memories concerned the whole hippocampus (i.e., anterior and posterior). Based on the HIPER model (Lepage et al., 1998), which proposes that the anterior hippocampus is involved during the episodic memory encoding whereas the posterior hippocampus is more implicated during retrieval, our result reveals that hippocampal activation reflects not only the processing of re-encoding of old memories (as pointed out in the introduction), but also retrieval per se. The higher hippocampal activity regardless of the anterior posterior axis we observed for long (relative to short) retention interval is consistent with the idea that remote memories, more than recent memories, imply a phenomenon of re-encoding (anterior region) and retrieval processes (posterior region). More encoding-related activity for remote memories than for recent memories might be compatible with both models of long-term memory consolidation. One reasonable hypothesis is that if the hippocampus has a time-limited role, it might show more encoding-related activity for remote memories, which are relatively "novel" to it than for recent memories, which are familiar to it. This result may also fit well with the MTT that argues in favor of a role of hippocampal complex in reactivating old memory traces. By contrast, more retrieval-related activity for remote episodic memories than for recently learned ones is more compatible with the MTT. As the retrieval of episodic details of memories becomes more difficult with the passage of time (Moscovitch et al., 1999; Piolino et al., 2002), the engagement of MTL component would be more important to provide the context of old experience (relative to recent experience) as a pointer or index to neocortical elements. Pulling together the results of the SPM and ROIs analyses, our data demonstrate the role of hippocampus and parietal regions for retrieving remote autobiographical memories where visual imagery is particularly important for ensuring sense of remembering. This observation is consistent with the involvement of a temporoparietal pathway for visuospatial processing, and more specially for retrieving the spatial context of lifelike events (Burgess et al., 2001a,b).

The remaining question is the issue of the bilateral, but preferentially right-sided, involvement of the hippocampal responses whatever the remoteness of autobiographical memories. By contrast, regardless of time interval, the majority of previous autobiographical neuroimaging studies have shown preferentially left-sided hippocampal activations (Maguire and Mummery, 1999; Maguire et al., 2000, 2001; Ryan et al., 2001). As suggested by Burgess et al. (2002), the right hippocampus would appear particularly involved in memory for locations within an environment whereas the left hippocampus would be more involved in context-dependent episodic or autobiographical memory. Nevertheless, these neuroimaging studies might not succeed to tap aspects of autobiographical memories that depend on right structures (see Conway et al., 2002; Graham et al., 2003 for a similar view). Few authors have demonstrated like the present study right-sided hippocampal activations in autobiographical memory (Fink et al., 1996; Tsukiura et al., 2002). In particular, using ROIs analysis, Tsukiura et al. (2002) demonstrated an increasing of hippocampal complex responses (right-sided parahippocampus) in a group of young adults during the recall of episodes from the childhood and the recent period. As pointed in Introduction, our bilateral but preferentially right-sided activations might reflect the emotional properties of memories recalled, self-perspective during remembering personal episodes or the retrieval of spatial details. More specially, our finding may reflect the employment of a task providing long time for retrieval (i.e., 45 s) to stress the recall of richly detailed episodic memories (i.e., specific details such as time, location, perceptions, and feelings; see Graham et al., 2003 for related data). In effect, the majority of studies that showed left-sided hippocampal activations used short retrieval period. Moreover, Maguire et al. (2000, 2001) used a recognition paradigm, which is more likely to involve retrieval of semantic autobiographical knowledge instead of episodic details. Specific aspects of the experimental designs (i.e., age of subjects and retrieval task) and data analysis (i.e., SPM or ROIs comparisons) in the studies are likely to explain differences concerning the laterality. It is, finally, worth noting that our results highlight the role of right (or at least bilateral, Eslinger, 1998) temporal structures including hippocampus in autobiographical memories which is in keeping with some findings from the neuropsychological literature (Kopelman and Kapur, 2001; Kopelman et al., 1999).

In summary, our results show differential behavioral characteristics as well as differential cerebral activations according to the remoteness of memories (prefrontal vs. inferior parietal cortex) consistent with underlying changes in phenomenal experience of remembering. Thus, autobiographical memory retrieval may depend on time-related mechanisms that interact with the brain regions and the neural processes involved. Moreover, we emphasize a largest involvement of hippocampus to the remoteness of episodic memories, which bolsters the MTT theory relative to the "standard consolidation" theory.

Appendix A. Specificity scoring chart of event recall task performed after scans (Piolino et al., 2002)

3	Specific event (isolated, situated in time and space) with details (thoughts, emotions, images etc.)
2.5	Specific event (isolated, situated in time and space) without detail
2	Detailed generic event (repeated or continuous, situated in time and space)
1.5	Generic event (repeated or continuous situated in time and space), not very detailed
1	Vague event (repeated or continuous with little detail of time or space)
0.5	Vague personal impression (content and circumstances very vague)
0	Absence of an answer or general information

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