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Abstract

We previously demonstrated that Episodic Autobiographical Memories (EAMs) rely on a network of brain regions comprising the medial temporal lobe (MTL) and distributed neocortical regions regardless of their remoteness. The findings supported the model of memory consolidation which proposes a permanent role of MTL during EAM retrieval (Multiple-Trace Theory or MTT) rather than a temporary role (standard model). Our present aim was to expand the results by examining the interactions between the MTL and neocortical regions (or MTL-neocortical links) during EAM retrieval with varying retention intervals.

We used an experimental paradigm specially designed to engage aged participants in the recollection of EAMs, extracted from five different time-periods, covering their whole life-span, in order to examine correlations between activation in the MTL and neocortical regions. The nature of the memories was checked at debriefing by means of behavioral measures to control the degree of episodicity and properties of memories.

Targeted correlational analyses carried out on the MTL, frontal, lateral temporal and posterior regions revealed strong links between the MTL and neocortex during the retrieval of both recent and remote EAMs, challenging the standard model of memory consolidation and supporting MTT instead. Further confirmation was given by results showing that activation in the left and right hippocampi significantly correlated during the retrieval of both recent and remote memories. Correlations among extra-MTL neocortical regions also emerged for all time-periods, confirming the critical role of the prefrontal, temporal (lateral temporal cortex and temporal pole), precuneus and posterior cingulate regions in EAM retrieval. Overall, this paper emphasizes the role of a bilateral network of MTL and neocortical areas whose activation correlate during the recollection of rich phenomenological recent and remote EAMs.

Introduction

Autobiographical memory (AM) refers to information and memories of personal life events. It is composed of different types of representations, from general knowledge about oneself (semantic component, also referred to as "personal semantics") to very specific personal events (episodic component) (Tulving et al., 1988; Conway, 2001). The episodic component (EAM) is characterized by spatio-temporal specificity, mental visual imagery and emotion (Brewer, 1996; Conway and Pleydell-Pearce, 2000; Conway, 2001; Tulving, 2001), as well as by a particular self-reflective mental state, termed autonoetic consciousness, which implies that the subject recollects his memories with a sense of reliving (re-experiencing), by mentally "travelling back in time" (Wheeler et al., 1997; Tulving, 2001; Piolino et al., in press). Thus, the central tenet of episodic AM revolves around phenomenological re-experiencing and the sense of self in time. The semantic component is characterized by a state of consciousness, termed noetic consciousness, which enables one to retrieve general facts about a personal event without re-experiencing it.

Neuroimaging studies have detected an overall left-lateralized cerebral network associated with the retrieval of EAMs, including in particular prefrontal, medial and lateral temporal cortices, as well as posterior regions (Maguire, 2001; Moscovitch et al., 2005; Svoboda et al., 2006). Little is known, however, about interactions between these regions during autobiographical retrieval. Connectivity (Maguire et al., 2000; Addis et al., 2004a) or correlational (Greenberg et al., 2005) analyses can be used to address this issue. Maguire et al. (2000) showed increased connectivity between the hippocampus and the parahippocampal gyrus during the recognition of autobiographical events relative to other memory subtypes (autobiographical events, autobiographical facts, public events or general facts). Similarly, Addis et al. (2004a) showed that the left and right hippocampi were functionally connected during AM retrieval, as well as with the right parahippocampal gyrus. These findings suggest a role of the MTL in the retrieval of EAMs, but do not consider its involvement according to memory remoteness and the phenomenological properties of the memories retrieved.

A central debate today concerns the role over time of the MTL, in particular the hippocampus, in AM retrieval and two conflicting theories of memory consolidation have been proposed. The "standard model" suggests that the MTL is initially implicated in the encoding and consolidation of AMs, but with time, AM retrieval becomes independent of this region and relies only on neocortical regions (Squire and Alvarez, 1995; Bayley and Squire, 2005). Thus, the retrieval of recent memories relies on interactions between the MTL and

neocortical regions (or MTL-neocortical links), while the retrieval of remote memories depends solely on neocortical interactions. Moreover, this theory does not distinguish between the two components of AM (episodic and semantic) and assumes that both are subject to the same consolidation process. Alternatively, the "Multiple Trace Theory" (MTT, Nadel and Moscovitch, 1997; Moscovitch et al., 2005; Nadel et al., 2007) concurs with the standard model for the semantic AMs, but suggests that MTL-neocortical links are permanently required for the retrieval of EAMs. Of note, according to MTT, it is both the hippocampus and its related structures, including the parahippocampal gyrus, which are hypothesized to interact permanently with neocortical regions during the retrieval of both recent and remote EAMs.

In a continuation of our previous activation study (Viard et al., 2007) which favored MTT, we addressed these issues by exploring the patterns of co-activation between different MTL and neocortical regions during the retrieval of EAMs taken from five time-periods and covering the entire life-span of healthy aged adults. Our previous neuroimaging data had shown that a network, including mainly the left hippocampus, left superior frontal gyrus, bilateral precuneus and posterior cingulate gyrus, was commonly active for all time-periods. Behaviorally, all memories were characterized by specificity and a high level of details, hence were episodic (i.e. spatiotemporal uniqueness and details). However, some differences emerged among intermediate periods which were rated stronger than the most recent and most remote periods, in terms of the phenomenological attributes of memory (i.e. emotion, mental visual imagery, and autonoetic consciousness) and recruited additionally the right hippocampus.

In the present paper, using the same data set, we examined correlations in the activation of medial temporal and neocortical regions during the retrieval of recent and remote EAMs, in order to further test the two models of memory consolidation. In our analyses, we included *a priori* regions known to be particularly involved in the retrieval of EAMs (Cabeza and St Jacques, 2007), namely the MTL, prefrontal and, posterior regions (precuneus and posterior cingulate gyrus), as well as lateral temporal cortices. Indeed, substantial evidence implicates the MTL in the retrieval of EAMs, in particular the hippocampus and parahippocampal gyrus (Ryan et al., 2001; Maguire, 2001; Maguire and Frith, 2003 a, b; Piefke et al., 2003; Piolino et al., 2004; 2008; Gilboa et al., 2004; Addis et al., 2004b; Greenberg et al., 2005; Viard et al., 2007), as well as the amygdala which is known for its role in the processing of emotional AMs (Markowitsch et al., 2000, 2003; Daselaar et al., 2008; for review, see Phelps, 2004). A close link between memory and emotion is suggested by studies showing a preferential recall

of emotional events (Brewer, 1988; Dolan et al., 2000). The prefrontal cortex (PFC) is crucial for the reconstruction of EAMs from the initial search to the maintenance of a specific memory in mind and is thought to be involved in the controlled retrieval of information from posterior regions (Mayes and Roberts, 2001; Simons and Spiers, 2003; Gilboa, 2004; Cabeza and St Jacques, 2007; Piolino et al., 2008). Prefrontal regions are also hypothesized to play a role in the emergence of autonoetic consciousness, an essential characteristic of EAM retrieval (Levine et al., 1998; Piolino et al., 2005). Posterior regions, such as the precuneus or the posterior cingulate gyrus, have been associated with access to sensory-perceptual details, in particular via their role in mental visual imagery (Fletcher et al., 1995; Cavanna and Trimble, 2006). Lateral temporal activations are involved in semantic retrieval processes (Maguire, 2001; Piolino et al., 2007). Indeed, autobiographical retrieval is often initiated by first browsing through the general levels of autobiographical knowledge before accessing an episodic event (Conway and Pleydell-Pearce, 2000; Conway et al., 2001).

Concerning our main predictions and according to MTT, we expected activation in the MTL (hippocampus, parahippocampal gyrus, amygdala) and neocortical regions (frontal, temporal and posterior regions) to be correlated during the retrieval of EAMs, whether they belonged to recent or remote time-periods (Nadel and Moscovitch, 1997; Moscovitch et al., 2005; Nadel et al., 2007). Furthermore, we predicted that the more richly recollected intermediate periods (compared to the most recent and remote ones) would involve a larger bilateral MTL-neocortical correlational network.

Materials and Methods

Participants

Twelve right-handed (as measured by the Edinburgh handedness inventory) healthy females (mean age $\pm$ SD = 67.2 $\pm$ 5.2 years; ranging from 60 to 75 years old) with no history of psychiatric or neurological disorder were recruited through a university, a retirement association or a newspaper advertisement. To obtain a homogeneous group, we recruited only females. The study was approved by the Regional Ethics Committee and written informed consent was obtained from all subjects prior to their participation in the study. Participants had no abnormality on their T_1-weighted high-resolution magnetic resonance imaging (MRI). They underwent a battery of neuropsychological tests to assess their cognitive abilities and all performed in the normal range (see Viard et al., 2007, for a full description). Each participant resided at home and all were active in cultural pursuits, continuing education or with responsibilities in diverse associations.

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Task and Experimental Design

The experimental procedure was divided in two sessions (for more details, see Viard et al., 2007). A few weeks before the experimental phase, the first session was carried out with a close family member who was interviewed on the participant's specific life-events. In the second session, a training period preceded the functional scanning which was followed by a debriefing. Personal sentence-cues were elaborated from the family member's prior interview and cues were visually presented in white on a black background, using Superlab software (3.0 version, Cedrus). Participants were given precise instructions to recall "a personal event which occurred only once, at a particular place and date, and lasted several minutes or hours, but less than a day, with as many details as they could". The scanning period consisted of five functional runs, randomly intermixed across subjects, each corresponding to one time-period and composed of five intermixed experimental and control blocks. In the experimental condition, participants viewed sentence-cues presented for 5 seconds, followed by 19 seconds of blank screen during which they had to mentally retrieve the corresponding specific personal event (e.g., the wedding of Pierre; the visit to the Eiffel Tower). Since they could start their mental evocation while the cue was still on the screen, the maximum retrieval time was 24 seconds. They were asked to press on a button as soon as they gained access to the prompted event. Twenty-five sentences-cues were presented per subject, corresponding to the five different time-periods (P1: 0-17 years; P2: 18-30 years; P3: > 30 years old except for the last 5 years; P4: last 5 years except the last 12 months; P5: last 12 months). In the control condition, participants were asked to detect the presence of two consecutive letters ("mb") in pseudo-words of six letters (for example, "speugr" or "mbieha") and were instructed to press on a button when "mb" was present in the pseudo-word. This low-level task was chosen as a baseline condition in order to control for reading operations, mental processing of visual cues and motor processing, common to both experimental and control tasks.

Following the scanning session, a debriefing took place in which participants retrieved all events again and rated them on behavioral scales. We specifically assessed episodic AM, taking into account not only the objective specificity of the personal events that are recalled, (uniqueness, spatiotemporal location, details), but also the subjective experience of remembering the encoding context. Indeed, episodic AM relies not only on the ability to recall a specific event and locate it in time and space, but also on the ability to recollect specific details which distinguish that event from similar ones. As it is possible to rebuild a specific event from one's personal semantic AM without actually reliving sensory-perceptual

episodic details, it is vital to gauge the specificity of details from the encoding context through the sense of re-experiencing. The encoding context encompasses time and space (i.e. the specificity of event), sensory-perceptual-affective-cognitive details (i.e. the specificity of details), the subjective experience (i.e. autonoetic consciousness) and the visual experience (i.e. self-perspective) (Piolino et al., 2006, in press).

Participants were first given precise instructions to recall again the personal events from the five different time periods in the scan which were rated using strict objective criteria. The subjective reports of memories were then assessed using the Remember/Know procedure (Tulving, 1985; Gardiner, 1988), the quantification of mental visual imagery and the rememberer's self-perspective known as the Field/Observer perspective paradigm (Nigro & Neisser, 1983; Robinson & Swanson, 1993), which makes it possible to differentiate between episodic and semantic AM retrieval. In total, our procedure made it possible to measure episodic AM characterized by uniqueness, specificity and details, and as enabling someone to "travel back in time", relive specific events and view these events as they would originally have been seen through his or her own eyes (see also Crawley & French, 2005).

Accordingly, episodicity was estimated 1) with an "objective" measure using an episodic scale which takes into account uniqueness, specificity and details of each memory and 2) with "subjective" measures of remembering using analogical scales (see below). More precisely, the specificity of each evocation was measured by the investigators using a validated fine-grained five-point scale (Piolino et al., 2003; 2004; 2006; 2007, in press; Viard et al., 2007), taking into account the specificity of the content (single or repeated event), the spatiotemporal situation and the presence of details (perceptions, thoughts, feelings). A specific event with sensory details situated in time and space was given a score of 4. A specific event without any details but situated in time and space was scored 3. A repeated or extended event was scored 2 if it was situated in time and space or 1 if it was not. An absence of memory, or only general information about a theme, was scored 0. A total score (strictly episodic or EM score) was recorded per time period which took into account the number of specific and detailed memories scoring 4. Besides, in order to specify the different aspects of the recollective experience, participants were asked to rate their memories on several analogical scales (10-cm lines; subjective measurement), known to be crucial to control the degree of episodic re-experiencing (Piolino et al., 2004, in press; Viard et al., 2007). These scales evaluated the emotional intensity and state of consciousness at retrieval (as measured by the Remember/Know paradigm), as well as various attributes of mental visual imagery, such as

the mental strategy used during retrieval, the mental image quality and the number of mental images retrieved and the field viewpoint perspective.

As our previous study (Viard et al., 2007) showed that the objective measure of episodicity was comparable across the five time-periods and involved the hippocampus and neocortical regions whatever the time-periods, we did not focus the present analyses on this score. By contrast, since the subjective measures differed across the five time-periods, for the purpose of the present study, we calculated for each time-period an index of phenomenology (i.e. phenomenological score) that combines all behavioral subjective measures collected at debriefing (i.e. emotional intensity, state of consciousness, mental visual strategy, mental image quality and number of mental images, viewpoint perspective). Indeed, our interest was to answer the question of MTL-neocortical interaction over the course of time in episodic recollection which is based on the combination of three attributes, e.g. emotion, autonoetic consciousness and visual imagery (see results of Viard et al., 2007, and Piolino et al., in press for an extended theoretical account).

fMRI Data Acquisition

A blocked functional MRI design was used. Lying in the scanner, participants viewed the display via a mirror to an active matrix video projector. Stimulus onset was synchronized with the acquisition of the first slice. Anatomical and functional MRIs were acquired on a General Electrics Signa 1.5 tesla MRI scanner (GE, BUC, France). First, a high-resolution T1-weighted MRI scan (T1-MRI) was acquired with a three-dimensional inversion recovery spoiled gradient echo sequence (matrix size = 256 x 256 x 128; slice thickness = 1.5 mm). Second, a proton density/T2-weighted MRI scan (PD-MRI, T2-MRI) was acquired with 32 axial slices covering the entire brain and the superior part of the cerebellum (slice thickness = 3.8 mm). Finally, functional images were acquired with echo planar imaging blood oxygen level dependent (BOLD) sequence (repetition time = 6 s, echo time = 60 ms, flip angle = 90°, matrix size = 64 x 64 x 32, 50 volumes, 3.8-mm-thick slices) covering the same field of view as the T2-MRI acquisition.

Construction of an old-adult template

Using voxel-based morphometry (VBM; Good et al., 2001), each individual T1-MRIs were segmented according to the unified segmentation procedure (Ashburner and Friston, 2005) with spatial normalization included. Mean templates were calculated based on the individual segmented and normalized T1-MRIs, creating three separate old-adult templates

according to tissue type (e.g. grey and white matters, CSF) which were then spatially smoothed using an 8-mm FWHM Gaussian kernel.

Functional Image Pre-processing

Functional images were processed and analyzed using the Statistical Parametric Mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spml). The first six volumes of the functional acquisition were discarded, allowing for signal stabilization, and differences in slice acquisition timing were corrected. Images were realigned to correct for interscan movement with creation of resliced mean functional volumes (mean-fMRI). For inter-modalities registration, rigid registration matrices (mean-fMRI onto T2-MRI and PD-MRI onto T1-MRI and T1-MRI onto the old-adult template) were computed, combined and then applied to fMRI volumes. Individual T1-MRIs were then segmented using the old-adult templates as priors (obtained previously, one for each tissue type; see above) and normalized. In order to set the fMRI volumes into our old-adult space, functional MRI images were resampled using the normalization parameters obtained in the segmentation step. Finally, data were spatially smoothed with an 8-mm^3 FWHM Gaussian kernel, leading to an image smoothness of approximately 11 mm in the 3 directions.

fMRI Data Analysis

A fixed-effect (within-subject) model was applied to the time-series of each subject. After filtering (high-pass filter: 96 s), t-statistic maps were generated for the contrasts "memory *minus* control", for each period. *A priori* ten bilateral anatomical VOIs selected from the aal template of SPM5 (Tzourio-Mazoyer et al., 2002; Piolino et al., 2008) were resampled to the old-adult template, resulting in twenty regions. The VOIs selected were the hippocampus, parahippocampal gyrus (BAs 30, 34, 35, 36), amygdala, superior frontal gyrus (approximately BAs 6, 8, 9, including the superior orbital and medial frontal gyri, BAs 10, 11; corresponding, in other terminologies, approximately to the ventro-medial PFC), middle frontal gyrus (approximately BAs 6, 8, 9, 10, 46, including the orbital middle frontal gyrus, BA 11; corresponding approximately to the dorso-lateral PFC), inferior frontal gyrus (including the orbital, opercular and triangular inferior frontal gyrus, BAs 44, 45, 47; corresponding to the ventro-lateral PFC), the precuneus (BA 7, 31), posterior cingulate gyrus (BAs 31, 30), as well as the lateral temporal cortex (including the superior, middle and inferior temporal gyri, BAs 20, 21, 22, 42) and temporal pole (including the superior and inferior temporal poles, BA 38).

For each participant, mean activation values corresponding to the difference in BOLD activation between the experimental and control tasks, were extracted within each VOI for each time-period using the "anatomical VOI analysis" of the fMRIroi SPM toolbox.

For the purpose of our study, we were mainly interested in identifying correlations between brain regions and used both simple univariate (see also Greenberg et al., 2005 who use a similar approach to ours) and multi-variate methods (see below). We performed correlational analyses between the twenty regions for each time-period independently. Bravais-Pearson coefficients were calculated for each VOI crossed with all other regions. The Bonferroni correction was applied to correct for multiple comparisons. Results were, thus, considered significant at $p < 0.000125$ (i.e. 0.05 divided by 20 x 20).

Additionally, we conducted two types of stepwise regression analyses (mutli-variate method) to study the relationships between activation in the different brain regions and the "phenomenological score" which combines various critical attributes of EAMs collected during the debriefing session (i.e. emotional intensity, autonoetic consciousness, mental visual strategy, mental image quality and number of mental images retrieved, viewpoint perspective) for each period separately. First, we conducted step-wise regression analyses to examine which brain regions best predicted the phenomenological score (combining all phenomenological attributes of episodic memories) taken as dependent variable, for each time-period. Second, we carried out other stepwise regression analyses to study the relationships between activation in both hippocampi and other brain regions, for each period separately, equated for their episodic characteristics. Mean activation values within both hippocampal VOIs were entered as dependent variables and those within the other VOIs as independent ones.

Results

Behavioral results

Behavioral results reported previously (Viard et al., 2007) showed that memories from all time-periods were characterized by specificity and detail (as measured by the EM score) attesting of their episodic nature, as well as by the use of a visual mental strategy and the retrieval of numerous mental images. Differences among periods included memories from P2, P3 and P4 which were emotionally more intense at encoding (for P2 and P3) or at retrieval (for P3 and P4), compared to memories from P1 and P5, and memories from P1 which were less autonoetic and mental image quality less clear than the other periods. Further analyses (ANOVA) carried out on the phenomenological score confirmed a significant effect of time-

periods (F(4,44) = 3.06, p < 0.05). Post hoc tests (PLSD Fisher) indicated that periods P1 and P5 were scored lower than the remote periods P2 and P3 and the recent period P4 (p < 0.05). Alternatively, the periods P2, P3 and P4 were equivalent (data not shown).

Correlational analyses

Results show similarities, as well as differences between periods. Of note, all significant correlations are positive at a very stringent threshold (p < 0.000125). For more clarity, results are separated, first, in terms of correlations in the activation between the MTL and neocortical regions and among subregions of the MTL (Table 1), then among extra-MTL neocortical regions (Table 2).

Correlations between activation in the MTL and neocortical regions and among subregions of the MTL

Results, depicted on Table 1 and Figure 1A, show that activation in the MTL correlates significantly with activation in neocortical regions (lateral temporal cortex, temporal pole, precuneus) or with other MTL regions, for the retrieval of both recent (P1, P2 and P3) and remote (P4 and P5) memories. More precisely, concerning interactions between the MTL and neocortical regions, activation in the MTL (hippocampus, parahippocampal gyrus) correlates significantly with activation in the lateral temporal cortex, on the left (for P3 and P4) and activity in the left amygdala correlates with that in the right temporal pole (for P1), left precuneus (for P1) or left lateral temporal cortex (for P4). Concerning interactions among MTL regions, activation in the left hippocampus correlates significantly with activation in the left parahippocampal gyrus (for P1, P3 and P5), in the left amygdala (for P3, P4 and P5) or right amygdala (for P3 and P4). On the right, activation in the hippocampus correlates significantly with activation in the amygdala for P3. Additionally, significant bi-hemispheric correlations emerge between both hippocampi (for P3 and P4), both parahippocampal gyri (for P2 and P4) and both amygdale (for P5). Thus, interactions between the MTL and neocortical areas are limited mainly to lateral temporal regions (temporal cortex or temporal pole). Altogether, there are as many intra-hemispheric as there are inter-hemispheric correlations between the MTL and neocortical regions or among MTL regions.

Correlations between activation in extra-MTL neocortical regions

Significant correlations involving the posterior regions are detected for memories from all time-periods: activations in the left and right precuneus correlate significantly for all periods

and activations in the left and right posterior cingulate gyri correlate for P1, P4 and P5. Additionally, activation in the precuneus correlates with activation in the posterior cingulate gyrus for P1 and P5, on the left and for P1 and P4, on the right. Significant results involving the frontal lobes also appear for all periods (subthresholded for P1): activation in the left and right superior frontal gyri correlate for P3 and P5 or between the superior and middle frontal gyri bilaterally for P4. Correlations involving the frontal lobes and posterior regions, in particular the precuneus, also emerge: significant interactions between the bilateral precuneus and either the superior, middle or inferior frontal gyri appear for P3 or P4. Finally, significant correlations between the frontal lobes and the lateral temporal areas, in particular the temporal pole, emerge significant for P2, P3 and P5, or between the posterior regions (posterior cingulate gyrus or precuneus) and the temporal poles for P1, P4 and P5. Findings are presented in Table 2 and Figure 1B. Overall, within extra-MTL neocortical areas, there are as many intra-hemispheric as there are inter-hemispheric correlations.

In order to account for the fact that neighboring VOIs might not be independent of each other and consequently bias the resulting correlations, we re-analyzed our data without smoothing the raw data. Results are very similar to the ones reported on the smoothed data and correlations between neighboring regions remained significant, both between the MTL and neocortex, within the MTL or within the neocortex. Thus, by not smoothing our data and hence by minimizing the possible "overlap" of regions on one another, the significant correlations among neighboring regions cannot be considered simple autocorrelations.

Regression analyses

Main results of the first step-wise regression analyses, depicted on Table 3, performed on the phenomenological score entered as the dependent variable and the mean activation values within each VOI entered as the independent ones, indicate that the best predictors for the phenomenological attributes of EAMs are the MTL (hippocampus, amygdala) for the intermediate periods (P2, P3 and P4) and neocortical regions (frontal or lateral temporal regions) for periods P1 and P5. Of note, the (left or right) frontal regions are significant predictors of the phenomenological score for all time-periods, accounting for 63% (P1), 31% (P2), 55% (P3), 13% (P4) and 70% (P5) of the variance.

Main results of the second step-wise regression analyses, depicted in Table 4, performed between both hippocampi as dependant variables and the other brain regions as independent variables, mainly show that activation in the (left or right) hippocampus is best predicted by activation in the MTL regions (parahippocampal gyrus and amygdala) and then

neocortical regions (frontal except for P5, temporal or posterior regions: precuneus and posterior cingulate cortex). Overall, the regression analyses show a pattern of significant MTL-neocortical interaction regardless of the time-period.

Discussion

In a continuation of our previous activation study (Viard et al., 2007) which demonstrated the permanent involvement of the hippocampus and neocortical regions in EAM retrieval regardless of remoteness, we investigated how functional integration between brain regions could be affected by memory remoteness. We examined correlations in the activation of brain regions known to play a crucial role in autobiographical retrieval, namely the MTL, frontal and posterior regions (precuneus and posterior cingulate gyrus), as well as lateral temporal regions during the retrieval of memories covering five time-periods in aged participants. Using a paradigm specifically designed to encompass up-to-date concepts of EAM (Tulving, 2001, 2002; Conway, 2001; Piolino et al., in press), we addressed the issue of episodic memory consolidation paying particular attention to the effect of time-interval on MTL-neocortical links.

Our previous findings had shown that the recollection of EAMs from the five time-periods triggered activation in a circumscribed network, including the left hippocampus and superior frontal gyrus, as well as the precuneus and posterior cingulate gyrus, bilaterally (Viard et al., 2007). Behavioral results indicated that regardless of the age of memories, recollection was characterized by specificity, attesting of their episodic nature (i.e. spatiotemporal uniqueness and details). Differences among periods included memories from P2, P3 and P4 which were rated stronger than the other periods (P1 and P5) in terms of the phenomenological attributes of memories and recruited, additionally, the right hippocampus.

New findings based on correlational and regression analyses show a pattern of significant MTL-neocortical or MTL-MTL interactions for all time-periods, as well as strong correlations within extra-MTL neocortical regions. These results will be discussed in light of the two conflicting models of long-term memory consolidation, first, in terms of activation between MTL and neocortical regions, then among subregions of the MTL and, finally, among neocortical regions.

Correlations between activation in the MTL and neocortical regions

Activations in the MTL and neocortex (lateral temporal cortex, temporal pole, precuneus) strongly correlate for both remote (P1 and P3) and recent (P4) periods, indicating that MTL-

neocortical links are still present during the retrieval of episodic memories whatever their remoteness. This result is concordant with the proposed permanent link between medial temporal and neocortical regions in the retrieval of EAMs irrespective of their remoteness (MTT; Nadel and Moscovitch, 1997; Nadel et al., 2007) and refutes the standard model which would have predicted greater MTL-neocortical correlations for recent compared to remote AMs. Instead, MTT postulates that the MTL as a whole (i.e. including the hippocampus, parahippocampal gyrus and amygdala) interacts permanently with neocortical regions during the retrieval of both recent and remote episodic AMs. Our results are also in line with an increasing number of studies using the voxel-based approach which have shown the permanent involvement of the MTL in the retrieval of EAMs whatever their remoteness (Ryan et al., 2001; Addis et al., 2004b; Gilboa et al., 2004; Piolino et al., 2004; Rekkas and Constable, 2005; Steinvorth et al., 2006; Nadel et al., 2007; Viard et al., 2007; Daselaar et al., 2008; Piolino et al., 2008). Further support to MTT is brought by recent patient studies which suggest that MTL damage impairs remote memory retrieval to a greater extent than was previously thought (Steinvorth et al., 2006; Noulhiane et al., 2007), although the importance of retrograde amnesia depends on the extent of the lesion (Hepner et al., 2007; Kirwan et al., 2008).

Interestingly, no significant correlations were detected between activation in the frontal and medial temporal regions, possibly due to the use of a stringent threshold, but consistent with previous findings (Markowitsch, 1995). Based on neuropsychological observations, Markowitsch (1995) proposed that prefrontal regions communicate with the lateral (and not the medial) part of the temporal lobes, in its polar area, and this is made possible via a bundle of fibers, the uncinate fasciculus, which unites the frontal and temporal lobes. Indeed, our results indicate that activation in the medial temporal regions significantly correlate with the lateral temporal areas, both for remote (P1 and P3) and recent (P4) periods. This is also consistent with previous connectivity findings which showed that the recollection of autobiographical events caused increased connectivity between the parahippocampal gyrus and the lateral temporal regions (lateral temporal cortex and temporal pole), relative to public events (Maguire et al., 2000). We can extrapolate these findings to pathology in which an interruption of circuits connecting frontal and temporo-polar regions produces a deficit in recall, even with intact MTL structures, resulting in a disconnection syndrome (Markowitsch, 1995; Levine et al., 1998; Piolino et al., 2005).

Correlations among subregions of the MTL

Activation in the hippocampus correlates significantly with activation in other MTL regions (parahippocampal gyrus, amygdala) during the retrieval of recent (P1 and P3) and remote (P4 and P5) EAMs. Additionally, we detected significant correlations in the activation of both hippocampi for remote (P3) and recent (P4) periods, suggesting that MTL-MTL links are permanently required for the retrieval of long-term EAMs regardless of memory age. These findings are thus concordant with MTT which would predict long-lasting interactions among MTL subregions (Nadel et al., 2007) and refute predictions of the standard model which would predict greater MTL-MTL interactions for recent than for remote memories (Squire and Alvarez, 1995). Results also showed significant correlations involving the parahippocampal gyrus, either bi-hemispheric correlations (for P2 and P4) or correlations with other MTL subregions (hippocampus or amygdala) for both remote (P1, P3) and recent (P4, P5) periods. Similarly, Addis et al. (2004a) showed that the left and right hippocampi were both functionally connected during AM retrieval, as well as with the right parahippocampal gyrus. While these findings support MTT and confirm the importance of the hippocampus in EAM retrieval whatever memory remoteness, they also underline the role of the parahippocampal gyrus and an interaction between both structures to support the recollection of personal past events (Maguire et al., 2000; Tsukiura et al., 2002; Okuda et al., 2003; St Jacques et al., 2008). Tsukiura et al. (2002) suggest that the parahippocampal gyrus, particularly on the right, may be implicated in the retrieval of topographical or spatial EAMs (Niki and Luo, 2002; Moscovitch et al., 2005). They propose that right parahippocampal activation could be related to the recruitment of posterior visual areas during the retrieval of older episodic memories. Although we did not detect a direct link between the parahippocampal gyrus and posterior areas, activation in the latter strongly correlated with other neocortical regions (see below).

Our results highlight the involvement of the amygdala and its interaction with the hippocampus and parahippocampal gyrus, particularly during the retrieval of memories from periods P3 and P4. Behaviorally, these periods were rated higher in terms of emotional intensity at retrieval compared to memories from the other periods. Emotion is an important phenomenological quality of persistent and vivid EAMs (Christianson, 1992; Talarico et al., 2004). Interestingly, our regressions analyses showed that the phenomenological attributes of EAMs (phenomenological score) are best predicted by the amygdala for P3, period which in our sample was rated the most intense emotionally, both at encoding and at retrieval. Much evidence suggests that the enhanced memory capability observed for emotional events is due,

at least in part, to the amygdala's influence on encoding and storage of hippocampal-dependent memories (for review, see Phelps, 2004), as suggested by many studies detecting amygdalar activation during EAM retrieval (Fink et al., 1996; Markowitsch et al., 2000, 2003; Maguire and Frith, 2003; Addis et al., 2004; Greenberg et al., 2005; Daselaar et al., 2008). Functional interactions have been detected between the amygdala and the hippocampus during encoding (Hamann et al., 1999; Dolcos et al., 2004), as well as during retrieval (Dolcos et al., 2005) especially if recall is accompanied by a sense of recollection (see also, Sharot et al., 2004). Thus, our results further highlight the role of the amygdala in phenomenological processes and the crucial role of emotion in the reviviscence of EAMs.

General discussion on the MTL-neocortical interactions

Overall, there are as many intra-hemispheric as there are inter-hemispheric correlations between the MTL and neocortical regions and the same is true within the MTL alone. This is concordant with a growing number of recent activation studies which detected bilateral MTL activation when participants were engaged in the retrieval of specific AMs (i.e. EAMs) rated strongly in terms of vividness, richness of detail, emotionality, re-experiencing or personal significance (Ryan et al., 2001; Piefke et al., 2003; Okuda et al., 2003; Gilboa et al., 2004; Mayes et al., 2004; Piolino et al., 2004; Greenberg et al., 2005; Steinvorth et al., 2006; Viard et al., 2007). Thus, combined with voxel-based studies, our results stress the idea that a bilateral interplay between MTL-neocortical regions characterizes rich EAM recollection (see also Piolino et al., 2008).

Our regression analyses provided further insights about the relationship between the phenomenological attributes of EAMs (via the phenomenological score which combines emotional intensity, autonoetic consciousness, mental visual strategy, mental image quality, number of mental images and viewpoint perspective) and certain brain regions. Interestingly, the phenomenological score was best predicted by the MTL (hippocampus and amygdala) for intermediate periods (P2, P3 and P4), while the score was best predicted by neocortical regions (frontal and lateral temporal regions) for periods P1 and P5. This might be explained by the fact that memories from intermediate periods were phenomenologically different compared to the very recent (P1) and very remote memories (P5). Indeed, although memories from all time-periods were specific (i.e. episodic, characterized by spatiotemporal uniqueness and details, as measured by the objective EM score), some memories showed modulations on certain subjective scales and were thus phenomenologically different according to the period considered (e.g. higher emotional intensity at retrieval for P3 and P4 compared to P1 and P5;

lower autonoetic consciousness and quality of mental images for P1). In fact, the objective EM score taps a different aspect of episodicity than the subjective recollective ratings. Indeed, one has to reach a certain threshold of episodicity, in order for an event to be episodic. Then, above the threshold, there are graduations or modulations on certain episodic qualities (Piolino et al., 2006; Viard et al., 2007).

Altogether, our results suggest that the retention interval (e.g. memory remoteness) is not the only factor which influences cerebral activity and interactions: richness of recollection (i.e. the quality of memories retrieved) has a crucial role on brain activity and brain interactions. This conclusion is actually in line with (and confirms) recent neuroimaging studies: beyond memory remoteness, richness of recollection (emotion, visual imagery, vividness, level of detail, personal importance) strongly influences patterns of brain activations (Ryan et al., 2001; Addis et al., 2004; Gilboa et al., 2005; for reviews, see Moscovitch et al., 2005; Cabeza and St Jacques, 2007). Overall, our results are very much in accordance with predictions of MTT which stress that all the phenomenological features of EAM retrieval are crucial for the continuous involvement of MTL-neocortical associations (see Moscovitch et al., 2005; Nadel et al., 2007).

Correlations between activation in extra-MTL neocortical regions

Our results indicate a continuous interaction between different neocortical sites for recent and remote periods, as predicted by both models of memory consolidation. Indeed, the standard model and MTT both suggest that cortico-cortical connections persist through time and will be strengthened as the memories are consolidated (Squire and Alvarez, 1995; Nadel and Moscovitch, 1997; Nadel et al., 2007). Here, we show that, for all time-periods, interactions among neocortical regions involve both anterior and posterior regions.

Strong correlations involving posterior regions are detected between the bilateral precuneus (for all time-periods) and between the precuneus and posterior cingulate gyrus (for P1, P4 and P5). Previous findings suggest a role of the precuneus, and the adjacent posterior cingulate cortex, in self-referential processes (Fink et al., 1996; Maddock et al., 2001). Along with other cortical midline structures (or CMS), both regions are hypothesized to play a role in generating a model of the self (Northoff and Bermpohl, 2004). In our study, the stimuli selected were highly self-relevant and targeted specific and unique AMs in the participants' lives. Furthermore, a role of the precuneus in visual mental imagery during episodic memory retrieval has previously been shown (Fletcher et al., 1995; Shallice et al., 1994; Cavanna and Trimble, 2006). Visual mental imagery increases the recall of EAMs: detailed memories are

often accompanied by strong imagery reports (Brewer, 1988, 1996; Dewhurst and Conway, 1994; Greenberg and Rubin, 2003). Indeed, our behavioral data indicate that, for all time-periods, the strategy used to retrieve memories was massively visual, possibly reflecting access to event-specific knowledge (ESK, Conway and Pleydell-Pearce, 2000).

Significant correlations involving frontal regions (superior, middle or inferior frontal gyri) are detected for all time-periods (subthresholded for P1), either fronto-frontal (for P3, P4 and P5) or between the frontal lobes and other neocortical regions (e.g. lateral temporal cortex or temporal pole for P1, P2, P3 and P5; precuneus for P3 and P4). Neuroimaging studies have provided extensive evidence that links episodic memory and AM to distinct functions of the frontal lobes, such as strategic retrieval processing, self referential processing, monitoring related to self processing (for reviews, see Cabeza and Nyberg, 2000; Gilboa, 2004; Svoboda et al., 2006; Cabeza and St Jacques, 2007). The prefrontal lobe is one of the critical regions for the emergence of autonoetic consciousness (Wheeler et al., 1997) and is also essential in self-awareness present at retrieval (Levine et al., 1998; Piolino et al., 2005). Lesion studies have shown that damage to the (right) prefrontal lobes can lead to disruption in the way individuals think about themselves: patients know what happened to them, but are unconcerned or indifferent, and their memories seem to lack personal significance (Wheeler et al., 1997). Our behavioral findings show that memories from all time-periods were recollected with an autonoetic state of consciousness. Moreover, strong correlations were detected among frontal regions probably supporting the rise of autonoetic consciousness in the retrieval process. Further confirmation was provided by the step-wise regression analyses which showed that, for all time-periods, (left or right) frontal regions were good predictors of the phenomenological score (which encompasses, in particular, autonoetic consciousness). Overall, our results highlight the crucial role of autonoetic consciousness in the reviviscence of EAMs and provide further evidence of a role of the frontal regions in accessing phenomenologically rich EAMs.

Finally, strong correlations involving the lateral temporal regions (temporal pole or lateral temporal cortex) emerged during the retrieval of memories from all time-periods, either correlations with frontal regions (for P2, P3 and P5) or with the precuneus (for P1, P4 and P5) or bi-hemispheric interactions between the left and right temporal poles (for P2, P3 and P5). Increased connectivity amongst lateral temporal areas has been detected during the recognition of general knowledge and public events (Maguire et al., 2000), both semantic in nature, suggesting a role of these regions in semantic processes. In fact, evidence has linked the functions of the lateral temporal lobes to personal semantic memory processes (Lee et al.,

2002; Mummery et al., 1996; Piolino et al., 2007; for review, see Svoboda et al., 2006). It has been hypothesized that the temporal pole acts as a convergence zone and integrates information from hippocampal structures and posterior association regions (Damasio, 1989; Maguire et al., 2000; Svoboda et al., 2006). Temporopolar activations are often reported in studies of AM retrieval and lesion to this region may cause focal retrograde amnesia (Wheeler and McMillan, 2001). Lateral temporal regions are also functionally connected with the hippocampus during the retrieval of both unique (specific) and repeated (general) autobiographical events (Addis et al., 2004a). Similarly, our regression analyses show that the lateral temporal regions are good predictors of hippocampal activation for all time-periods. Hence, these findings stress the role of semantic knowledge in accessing EAMs. More generally, our findings substantiate that episodic and semantic memory processes are integral parts of AM recollection and access to episodic events is often managed by first sifting through the general autobiographical knowledge (Conway and Bekerian, 1987; Conway and Pleydell-Pearce, 2000; Conway et al., 2001; Levine et al., 2004; Svoboda et al., 2006).

Conclusions

Our main results indicate that activation in medial temporal and neocortical regions correlate during the retrieval of all EAMs, whether they are recent or remote, emphasizing a pattern of significant MTL-neocortical interaction regardless of the passage of time. We also show that MTL-MTL correlations remain constant for both recent and remote periods. Both sets of results are concordant with the proposed permanent link between MTL and neocortical regions and the persistence of MTL interactions for memories of all ages, as hypothesized by MTT. Our results also showed that richness of recollection (i.e. quality of memories retrieved) has a crucial role on brain activity and its interactions: richly recollected memories (from intermediate periods) recruited a larger bilateral MTL-neocortical correlational network. Our main results point that MTT, and more generally models of memory consolidation, could be complemented and possibly strengthened by considering more precisely the modulation of the MTL-neocortical interactions as a function of the phenomenological features of specific memories retrieved, such as emotion, mental visual imagery and, state of consciousness.

An aspect which we could not address in this study (due to design limitations) is the directionality of interaction. Effective connectivity methods, such as Dynamic Causal Modeling (DCM), are particularly appealing to determine causal outcomes. It would also be interesting, in future studies, to trace individualized ROIs to better delineate finer subregions in the medial temporal lobe, for example, in the parahippocampal gyrus (parahippocampal,

entorhinal and perirhinal cortices), in order to distinguish the separate contributions of each of these subregions in EAM retrieval, across time. Further research is, thus, needed to clarify the influence that the regions of the EAM network exert over one another and the contribution of the finer subregions of this system.

Acknowledgements

References

Addis DR, McIntosh AR, Moscovitch M, Crawley AP, McAndrews MP. 2004a. Characterizing spatial and temporal features of autobiographical memory retrieval networks: a partial least squares approach. Neuroimage 23:1460-1471.

Addis DR, Moscovitch M, Crawley AP, McAndrews MP. 2004b. Recollective qualities modulate hippocampal activation during autobiographical memory retrieval. Hippocampus 14:752-762.

Ashburner J, Friston KJ. 2005. Unified segmentation. Neuroimage 26:839-851.

Bayley PJ, Squire LR. 2005. Failure to acquire new semantic knowledge in patients with large medial temporal lobe lesions. Hippocampus 15:273-280.

Brewer W. 1986. What is autobiographical memory? In: Rubin DC, editor. Autobiographical Memory. Cambridge: Cambridge University Press. p. 25-49.

Brewer W. 1996. What is recollective memory? In: Rubin DC, editor. Remembering our past: studies in autobiographical memory. Cambridge: Cambridge University Press. p 19-66.

Cabeza R, Nyberg L. 2000. Imaging cognition II: An empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12:1-47.

Cabeza R, St Jacques P. 2007. Functional neuroimaging of autobiographical memory. Trends Cogn Sci 11:219-227.

Cavanna AE, Trimble MR. 2006. The precuneus: a review of its functional anatomy and behavioural correlates. Brain 129:564-583.

Conway MA. 2001. Sensory-perceptual episodic memory and its context: autobiographical memory. Philos Trans R Soc Lond B Biol Sci 356:1375-1384.

Conway MA, Bekerian DA. 1987. Organization in autobiographical memory. Mem Cognit 15:119-132.

Conway MA, Pleydell-Pearce CW. 2000. The construction of autobiographical memories in the self-memory system. Psychol Rev 107:261-288.

Conway MA, Pleydell-Pearce CW, Whitecross SE. 2001. The neuroanatomy of autobiographical memory: a slow cortical potentials (SCPs) study of autobiographical memory retrieval. J Mem Lang 45:493-524.

Conway MA, Pleydell-Pearce CW, Whitecross SE, Sharpe H. 2003. Neurophysiological correlates of memory for experienced and imagined events. Neuropsychologia 41:334-340.

Crawley SE, French CC. 2005. Field and observer viewpoint in remember-know memories of personal childhood events. Memory 13:673-81.

Damasio AR. 1989. Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. Cognition 33:25-62.

Daselaar SM, Rice HJ, Greenberg DL, Cabeza R, Labar KS, Rubin DC. 2008. The Spatiotemporal Dynamics of Autobiographical Memory: Neural Correlates of Recall, Emotional Intensity, and Reliving. Cerebral Cortex 18:217-229.

Dewhurst SA, Conway MA. 1994. Pictures, images, and recollective experience. J Exp Psychol Learn Mem Cogn 20:1088-1098.

Dolan RJ, Lane R, Chua P, Fletcher P. 2000. Dissociable temporal lobe activations during emotional episodic memory retrieval. NeuroImage 11:203-209.

Dolcos F, LaBar KS, Cabeza R. 2004. Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. Neuron 42:855-63.

Dolcos F, LaBar KS, Cabeza R. 2005. Remembering one year later: role of the amygdala and the medial temporal lobe memory system in retrieving emotional memories. Proc Natl Acad Sci USA 102:2626-31.

Fink GR, Markowitsch HJ, Reinkemeier M, Bruckbauer T, Kessler J, Heiss WD. 1996. Cerebral representation of one's own past: neural networks involved in autobiographical memory. J Neurosci 16:4275-4282.

Fletcher PC, Frith CD, Baker SC, Shallice T, Frackowiak RS, Dolan RJ. 1995. The mind's eye-precuneus activation in memory related imagery. Neuroimage 2:195-200.

Gilboa A. 2004. Autobiographical and episodic memory-one and the same? Evidence from prefrontal activation in neuroimaging studies. Neuropsychologia 42:1336-1349.

Gilboa A, Winocur G, Grady CL, Hevenor SJ, Moscovitch M. 2004. Remembering our past: functional neuroanatomy of recollection of recent and very remote personal events. Cereb Cortex 14:1214-1225.

Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. 2001 A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 14:21-36.

Greenberg DL, Rice HJ, Cooper JJ, Cabeza R, Rubin DC, Labar KS. 2005. Co-activation of the amygdala, hippocampus and inferior frontal gyrus during autobiographical memory retrieval. Neuropsychologia 43:659-674.

Greenberg DL, Rubin DC. 2003. The neuropsychology of autobiographical memory. Cortex 39:687-728.

Hepner IJ, Mohamed A, Fulham MJ, Miller LA. 2007. Topographical, autobiographical and semantic memory in a patient with bilateral mesial temporal and retrosplenial infarction. Neurocase 13:97-114.

Kirwan CB, Bayley PJ, Galvan VV, Squire LR. 2008. Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. Proc Natl Acad Sci USA 105:2676-2680.

Lee AC, Robbins TW, Graham KS, Owen AM. 2002. "Pray or Prey?" dissociation of semantic memory retrieval from episodic memory processes using positron emission tomography and a novel homophone task. Neuroimage 16:724-735.

Levine B, Black SE, Cabeza R, Sinden S, Meintosh AR, Toth JP, Tulving E, Stuss DT. 1998. Episodic memory and the self in a case of isolated retrograde amnesia. Brain 121:1951-1973.

Levine B, Turner GR, Tisserand D, Hevenor SJ, Graham SJ, McIntosh AR. 2004. The functional neuroanatomy of episodic and semantic autobiographical remembering: a prospective functional MRI study. J Cogn Neurosci 16:1633-1646.

Maddock RJ, Garrett AS, Buonocore MH. 2001. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience 104:667-676.

Maguire EA. 2001. Neuroimaging studies of autobiographical event memory. Philos Trans R Soc Lond B Biol Sci 356:1441-1451.

Maguire EA, Frith CD. 2003a. Lateral asymmetry in the hippocampal response to the remoteness of autobiographical memories. J Neurosci 23:5302-5307.

Maguire EA, Frith CD. 2003b. Aging affects the engagement of the hippocampus during autobiographical memory retrieval. Brain 126:1511-1523.

Maguire EA, Mummery CJ, Buchel C. 2000 Patterns of hippocampal-cortical interaction dissociate temporal lobe memory subsystems. Hippocampus 10:475-482.

Markowitsch HJ. 1995. Which brain regions are critically involved in the retrieval of old episodic memory? Brain Res Rev 21:117-127.

Markowitsch HJ, Thiel A, Reinkemeier M, Kessler J, Koyuncun A, Heiss WD. 2000. Right amygdalar and temporofrontal activation during autobiographic, but not fictitious memory retrieval. Behav Neurol 12:181-190.

Markowitsch HJ, Vandekerckhove MM, Lanfermann H, Russ MO. 2003. Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. Cortex 39:643-665.

Mayes AR, Roberts N. 2001. Theories of episodic memory. Philos Trans R Soc Lond B Biol Sci 356:1395-1408.

Mayes AR, Montaldi D, Spencer TJ, Roberts N. 2004. Recalling spatial information as a component of recently and remotely acquired episodic or semantic memories: an fMRI study. Neuropsychology 18:426-441.

Moscovitch M, Rosenbaum RS, Gilboa A, Addis DR, Westmacott R, Grady C, McAndrews MP, Levine B, Black S, Winocur G, Nadel L. 2005. Functional neuroanatomy of remote episodic, semantic and spatial memory: a unified account based on multiple trace theory. J Anat 207:35-66.

Mummery CJ, Patterson K, Hodges JR, Wise RJ. 1996. Generating 'tiger' as an animal name or a word beginning with T: differences in brain activation. Philos Trans R Soc Lond B Biol Sci 263:989-995.

Nadel L, Moscovitch M. 1997. Memory consolidation, retrograde amnesia and the hippocampal complex. Curr Opin Neurobiol 7:217-227.

Nadel L, Campbell J, Ryan L. 2007. Autobiographical memory retrieval and hippocampal activation as a function of repetition and the passage of time. Neural Plast 2007:90472.

Niki K, Luo J. 2002. An fMRI study on the time-limited role of the medial temporal lobe in long-term topographical autobiographic memory. J Cogn Neurosci 14:500-507.

Northoff G, Bermpohl F. 2004. Cortical midline structures and the self. Trends Cogn Sci 8:102-107.

Noulhiane M, Piolino P, Hasboun D, Baulac M, Samson S. 2007. Autobiographical memory after temporal lobe resection: neuropsychological and MRI volumetric findings. Brain 130:3184-3199.

Okuda J, Fujii T, Ohtake H, Tsukiura T, Tanji K, Suzuki K, Kawashima R, Fukuda H, Itoh M, Yamadori A. 2003. Thinking of the future and past: the roles of the frontal pole and the medial temporal lobes. Neuroimage 19:1369-1380.

Phelps EA. 2004. Human emotion and memory: interactions of the amygdala and hippocampal complex. Curr Opin Neurobiol 14:198-202.

Piefke M, Weiss PH, Zilles K, Markowitsch HJ, Fink GR. 2003. Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. Brain 126:650-668.

Piolino P, Chételat G, Matuszewski V, Landeau B, Mézenge F, Viader F, de la Sayette V, Eustache F, Desgranges B. 2007. In search of autobiographical memories: A PET study in the frontal variant of frontotemporal dementia. Neuropsychologia 45:2730-2743.

Piolino P., Desgranges B., Eustache F. Episodic autobiographical memory over the course of time: cognitive, neuropsychological and neuroimaging findings. Special Issue on Episodic memory and the brain [theoretical review paper]. Neuropsychologia, in press.

Piolino P, Desgranges B, Benali K, Eustache F. 2002. Episodic and semantic remote autobiographical memory in ageing. Memory 10:239-257.

Piolino P, Desgranges B, Clarys D, Guillery-Girard B, Taconnat L, Isingrini M, Eustache F. 2006. Autobiographical memory, autonoetic consciousness and self-perspective in aging. Psychol Aging 21:510-525.

Piolino P, Desgranges B, Hubert V, Bernard F, Chételat G, Baron JC, Eustache F. 2008. Reliving lifelong episodic autobiographical memories via the hippocampus: a correlative resting PET study in healthy middle-aged subjects. Hippocampus 18:445-459.

Piolino P, Giffard-Quillon G, Desgranges B, Chételat G, Baron JC, Eustache F. 2004. Re-experiencing old memories via hippocampus: a PET study of autobiographical memory. Neuroimage 22:1371-1383.

Piolino P, Hannequin D, Desgranges B, Girard B, Beaunieux H, Giffard B, Lebreton K, Eustache F. 2005. Right ventral frontal hypometabolism and abnormal sense of self in a case of disproportionate retrograde amnesia. Cogn Neuropsychol 22:1005-1034.

Rekkas PV, Constable RT. 2005. Evidence that autobiographic memory retrieval does not become independent of the hippocampus: an fMRI study contrasting very recent with remote events. J Cogn Neurosci 17:1950-1961.

Robinson JA, Swanson KL. 1993. Field and observer modes of remembering. Memory 1:169-184.

Rubin DC, Schrauf RW, Greenberg DL. 2003. Belief and recollection of autobiographical memories. Mem Cognit 31:887-901.

Ryan L, Nadel L, Keil K, Putnam K, Schnyer D, Trouard T, Moscovitch M. 2001. Hippocampal complex and retrieval of recent and very remote autobiographical memories: evidence from functional magnetic resonance imaging in neurologically intact people. Hippocampus 11:707-714.

Shallice T, Fletcher P, Frith CD, Grasby P, Frackowiack RSJ, Dolan R. 1994. Brain regions associated with acquisition and retrieval of verbal episodic memory. Nature 121:561-579.

Sharot T, Delgado MR, Phelps EA. 2004. How emotion enhances the feeling of remembering. Nat Neurosci 7:1376-80.

Simons JS, Spiers HJ. 2003. Prefrontal and medial temporal lobe interactions in long-term memory. Nature Rev Neurosci 4:637-648.

Squire LR, Alvarez P. 1995. Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr Opin Neurobiol 5:169-177.

St Jacques P, Rubin DC, LaBar KS, Cabeza R. 2008. The short and long of it: neural correlates of temporal-order memory for autobiographical events. J Cogn Neurosci 20:1327-1341.

Steinvorth S, Corkin S, Halgren E. 2006. Ecphory of autobiographical memories: an fMRI study of recent and remote memory retrieval. Neuroimage 30:285-298.

Svoboda E, McKinnon MC, Levine B. 2006. The functional neuroanatomy of autobiographical memory: a meta-analysis. Neuropsychologia 44:2189-2208.

Talarico JM, LaBar KS, Rubin DC. 2004. Emotional intensity predicts autobiographical memory experience. Mem Cognit 32:1118-32.

Tsukiura T, Fujii T, Okuda J, Ohtake H, Kawashima R, Itoh M, Fukuda H, Yamadori A. 2002. Time-dependent contribution of the hippocampal complex when remembering the past: a PET study. Neuroreport 13:2319-2323.

Tulving E. 2001. Episodic memory and common sense: how far apart? Philos Trans R Soc Lond B Biol Sci 356:1505-1515.

Tulving E. 2002. Episodic Memory: from mind to brain. Annual Review of Psychology 53:1-25.

Tulving E, Schacter DL, McLachlan DR, Moscovitch M. 1988. Priming of semantic autobiographical knowledge: a case study of retrograde amnesia. Brain Cogn 8:3-20.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, Mazoyer B, Joliot M. 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15:273-289.

Viard A, Piolino P, Desgranges B, Chételat G, Lebreton K, Landeau B, Young A, de la Sayette V, Eustache F. 2007. Hippocampal activation for autobiographical memories over the entire lifetime in healthy aged subjects: An fMRI study. Cereb Cortex 17:2453-2467.

Wheeler MA, McMillan CT. 2001. Focal retrograde amnesia and the episodic-semantic distinction. Cogn Affect Behav Neurosci 1:22-36.

Wheeler MA, Stuss DT, Tulving E. 1997. Toward a theory of episodic memory: the frontal lobes and autonoetic consciousness. Psychol Bull 121:331-354.

Table 1: Patterns of significant correlations between subregions of the MTL and neocortical regions and between subregions of the MTL ($p_{corr} < 0.000125$).

Period 1	r²
L Hcp - L Para	0.85
L Amg - R T pole	0.88
L Amg - L Prec	0.85
Period 2	
R Para - L Para	0.85
Period 3	
L Hcp - L Para	0.94
L Hcp - L Amg	0.87
L Hcp - R Amg	0.85
R Hcp - R Amg	0.92
R Hcp - L Hcp	0.85
L Para - L T lat	0.84
L Para - R Amg	0.90
R Para - R Amg	0.85
Period 4	
L Hcp - R Amg	0.92
L Hcp - L T lat	0.92
L Hcp - L Amg	0.87
L Hcp - R Hcp	0.85
L Amg - L T lat	0.90
L Para - R Para	0.91
L Para - R Amg	0.87
Period 5	
L Hcp - L Para	0.87
L Hcp - L Amg	0.86
L Amg - R Amg	0.90

Abbreviations: Amg = amygdala, Hcp = hippocampus, L = left, MTL = medial temporal lobe, Para = parahippocampal gyrus, Prec = precuneus, r = Bravais-Pearson coefficient, R = right, T lat = lateral temporal gyrus, T pole = temporal pole.

Table 2: Patterns of significant correlations between extra-MTL neocortical regions ($p_{corr} <$ 0.000125).

Period 1	r²
L PCC - R PCC	0.95
L PCC - L Prec	0.86
R PCC - L Prec	0.86
L Prec - R Prec	0.89
L Prec - R T pole	0.90
L F mid - R T pole	0.77*

Period 2	
L F mid - L T pole	0.90
R F inf - R T pole	0.85
L Prec - R Prec	0.89
L T pole - R T pole	0.87

Period 3	
R F sup - L F sup	0.90
R F mid - L F mid	0.89
R F sup - R Prec	0.88
L F mid - L Prec	0.90
R F inf - R Prec	0.85
R F mid - R T pole	0.88
L F inf - L T pole	0.95
L F inf - R T pole	0.91
L Prec - R Prec	0.91
L T pole - R T pole	0.95

Period 4	
L F sup - L F mid	0.93
R F sup - R F mid	0.86
L F mid - L F inf	0.89
L F sup - L Prec	0.87
L F sup - R Prec	0.87
L PCC - R PCC	0.97
R PCC - L Prec	0.89
L Prec - R Prec	0.92
R PCC - R Prec	0.85
R PCC - L T pole	0.87
L Prec - L T pole	0.91
L Prec - R T pole	0.88
R Prec - R T pole	0.87

Period 5	
R F sup - L F sup	0.88
L F inf - L T pole	0.90
L PCC - R PCC	0.95
L PCC - L Prec	0.89
L Prec - R Prec	0.92
R Prec - R T pole	0.86
L T pole - R T pole	0.87

Abbreviations: F sup = superior frontal gyrus, F mid = middle frontal gyrus, F inf = inferior frontal gyrus, L = left, MTL = medial temporal lobe, PCC = posterior cingulate gyrus, Prec = precuneus, r = Bravais-Pearson coefficient, T lat = lateral temporal gyrus, T pole = temporal pole, R = right.

* p<0.0025

Table 3: Results of the regression analyses between the phenomenological score (combining emotional intensity, autonoetic consciousness, mental visual imagery) as dependent variable and each VOI as independent variables for the five time-periods.

	Step	predictors	r^2	Total r^2
Period 1				
	1	L F mid	0.63**	-
	2	L T lat	0.10*	0.74**
Period 2				
	1	L Hcp	0.24*	-
	2	L F inf	0.31*	0.55*
	3	R T pole	0.15*	0.70*
Period 3				
	1	L Amg	0.36*	-
	2	L F inf	0.55**	0.51*
	3	L T pole	0.05^{ns}	0.68*
Period 4				
	1	R T pole	0.57**	-
	2	R Hcp	0.15*	0.72**
	3	L F sup	0.13*	0.85**
Period 5				
	1	R F sup	0.49*	-
	2	R F mid	0.21*	0.70**

Abbreviations: Amg = amygdala, F sup = superior frontal gyrus, F mid = middle frontal gyrus, Hcp = hippocampus, L = left, Para = parahippocampal gyrus, T = lateral temporal gyri, T pole = anterior/middle temporal pole, R = right.

r^2 is the total proportion of variance mediated by each predictor and the total r^2 is the total r^2 for the selected predictors with associated significance probability (* $p<0.005$ ** $p<0.01$, *** $p<0.05$, ^{ns} non significant).

Table 4: Final multiple regression model performed on the predictive significant variables selected by the stepwise regression using BOLD measures of both hippocampi as dependent variables and the other brain regions as independent variables scores for the five time-periods.

Dependent variable	Step	predictors	r^2	Total r^2
Period 1				
L Hcp		L Para	0.71***	-
		L T lat	0.17**	0.88***
		L F mid	0.06*	0.94***
		R F inf	0.02*	0.97***
R Hcp		L Amg	0.58**	-
		R F inf	0.27**	0.85**
		R F sup	0.06*	0.91***
		R Para	0.04*	0.95***
Period 2				
L Hcp		L Para	0.41*	-
		L PCC	0.21*	0.62*
R Hcp		R T lat	0.23$^\$$	-
Period 3				
L Hcp		L Para	0.87***	-
		L F mid	0.04$^\$$	0.91***
		L F sup	0.04*	0.95***
R Hcp		R Amg	0.85***	-
Period 4				
L Hcp		R Amg	0.84***	-
		L T lat	0.07*	0.91***
		R F mid	0.05**	0.96***
		R T lat	0.01*	0.98***
R Hcp		R Para	0.70***	-
		R Prec	0.12*	0.82***
Period 5				
L Hcp		L Para	0.75***	-
		L Prec	0.17**	0.92***
		R T pole	0.02$^\$$	0.94***
		L T pole	0.02*	0.97***
R Hcp		R Para	0.59**	-
		L PCC	0.17*	0.76**

Abbreviations: Amg = amygdala, F sup = superior frontal gyrus, F mid = middle frontal gyrus, Hcp = hippocampus, L = left, Para = parahippocampal gyrus, PCC = posterior cingulate gyrus, Prec = precuneus, r = Bravais-Pearson coefficient, T = lateral temporal gyri, T pole = temporal pole, R = right.

r^2 is the total proportion of variance mediated by each predictor and the total r^2 is the total r^2 for the selected predictors with associated significance probability ($^\$$ p=0.005, * p<0.005 ** p<0.01, *** p<0.001, ^{ns} non significant).

Note: The table shows the regression coefficient (B) and associated significance probability (p) of each independent variable.

Figure 1: Schematic illustration of results from the correlational analyses between (A) subregions of the MTL and neocortical regions and among MTL regions and (B) extra-MTL neocortical regions, for each time-period. Numeric values represent significant correlational coefficients (r^2) between the two subregions connected by arrows ($p_{corr} < 0.000125$).

Abbreviations: Amg = amygdala, F sup = superior frontal gyrus, F mid = middle frontal gyrus, F inf = inferior frontal gyrus, Hcp = hippocampus, L = left; Para = parahippocampal gyrus, PCC = posterior cingulate gyrus, Prec = precuneus, R = right; T lat = lateral temporal gyrus, T pole = Temporal pole.