

Remembering Our Past: Functional Neuroanatomy of Recollection of Recent and Very Remote Personal Events

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Functional magnetic resonance imaging was used to study brain regions implicated in retrieval of memories that are decades old. To probe autobiographical memory, family photographs were selected by confederates without the participant's involvement, thereby eliminating many of the variables that potentially confounded previous neuroimaging studies. We found that context-rich memories were associated with activity in lingual and precuneus gyri independently of their age. By contrast, retrosplenial cortex was more active for recent events regardless of memory vividness. Hippocampal activation was related to the richness of re-experiencing (vividness) rather than the age of the memory *per se*. Remote memories were associated with distributed activation along the rostrocaudal axis of the hippocampus whereas activation associated with recent memories was clustered in the anterior portion. This may explain why circumscribed lesions to the hippocampus disproportionately affect recent memories. These findings are incompatible with theories of long-term memory consolidation, and are more easily accommodated by multiple-trace theory, which posits that detailed memories are always dependent on the hippocampus.

Keywords: autobiographical memory, fMRI, hippocampus, remote memory

Introduction

The capacity to reconstruct and re-experience personal events from the past is an ability that some think is unique to humans (Wheeler *et al.*, 1997; Tulving, 2002). There is considerable evidence that structures within the medial temporal lobe (MTL), most notably the hippocampal formation as well as parahippocampal, perirhinal and entorhinal cortices, are crucial for the formation and retrieval of new memories. The accepted view is that structures within the MTL guide the reinstatement of newly acquired memories by linking together patterns of cortical activation that were present during the original learning (Squire, 1992; McClelland *et al.*, 1995; Moscovitch, 1995; Nadel and Moscovitch, 1997). Far less is known about retention and retrieval of remote memories, and their representation in MTL and neocortex despite their importance for theories of memory consolidation and hippocampal-neocortical interaction. In this study, we use functional magnetic resonance imaging (fMRI) to investigate the effects of memory age and vividness on the brain regions implicated in retention and retrieval of remote memories cued by family photographs.

There is dispute in the functional neuroimaging literature, as in the lesion literature, about the extent of MTL activation during retrieval of recent and remote autobiographical memories. Evidence of greater activity in the MTL during retrieval of recent as compared to remote memories (Haist *et al.*, 2001; Niki and Luo, 2002; Piefke *et al.*, 2003) is consistent with

reports of temporally graded retrograde amnesia following damage to MTL and related structures (Squire, 1992; Rempel-Clover *et al.*, 1996; Milner *et al.*, 1998; Bayley *et al.*, 2003). These neuroimaging findings have been interpreted as supporting the view that memories become independent of the MTL with the passage of time. Leaving aside studies that examined semantic memory (Haist *et al.*, 2001), one of the problems with this interpretation is that recent memories tend to be more vivid than remote ones, and so vividness, rather than age, may determine the extent of MTL involvement. Attempts to control for this variable have been inadequate.

Other studies, however, found equivalent MTL activation for recent and remote memories (Conway *et al.*, 1999; Maguire and Mummery, 1999; Maguire *et al.*, 2001a; Ryan *et al.*, 2001; Maguire and Frith, 2003a), making them consistent with the observation that retrograde amnesia for detailed, personal memories (autobiographical re-experiencing) often is ungraded and may extend over many decades (Nadel and Moscovitch, 1997; Fujii *et al.*, 2000). These neuroimaging studies, however, have been criticized on the ground that events chosen for scanning were self-selected and based on pre-scan interviews, which may have contributed to this pattern of results (but see Conway *et al.*, 1999; Ryan *et al.*, 2001, *expt 2*).

We used functional neuroimaging to address and reconcile these issues and obtain more information about the representation of remote autobiographical memory in the brain. We focused on context-rich autobiographical memory because there is already general agreement that the MTL is not needed for retention and retrieval of well-rehearsed remote semantic memory, which includes memory for vocabulary, public events and famous people (but see Sanders and Warrington, 1971; Cipolotti *et al.*, 2001); nor is it needed for personal semantics, which includes facts about one's own past, and generic representations of recurring events and well-rehearsed personal 'folklore' (Cermak and O'Connor, 1983; Barsalou, 1988; Burgess and Shallice, 1996; Conway, 2001).

To prevent biased self-selection of well-rehearsed autobiographical memories, we used personal photographs that were collected from relatives and friends and were thus rarely or never viewed by the participants before scanning. The use of personal photos had several advantages. (i) It enabled us to impose external constraints on retrieval by providing specific cues from across the lifespan and thus obtain a more ecologically valid distribution of events to be recalled. Other investigators have used pre-selected remote and recent events that were very memorable and equivalent across time periods, and thus likely do not reflect a normal distribution of memory for past events. (ii) Since the stimuli were not self-selected, there was more variation in how well participants remembered the

events. Many events were remembered vividly while some remote events were not remembered at all. (iii) The procedure precluded re-encoding and reactivation of memories from pre-scan sessions from contributing to hippocampal activation, as may have been the case in previous studies. As well, to control for re-encoding during the scan itself, we compared brain activation while participants viewed their own photographs with activity while they viewed photos taken from other participants but matched in content and style to their own. To examine vividness as a confounding factor with age of the memory, we had subjects rate the vividness of their memories and used that, as well as age, as variables in our study.

Because the hippocampal complex does not act in isolation during reconstruction of past events, we investigated activations of other brain regions that were identified as constituting a network of regions implicated in autobiographical memory retrieval (Maguire, 2001a; Conway *et al.*, 2002). In particular, we examined anterior regions that mediate memory control processes (Wheeler *et al.*, 1997; Moscovitch and Winocur, 2002), or 'working with memory' (Moscovitch and Winocur, 2002), and posterior neocortex where presumably the information that formed the content of a past conscious experience is represented (Squire, 1992; McClelland *et al.*, 1995; Moscovitch, 1995; Nadel and Moscovitch, 1997). These regions are presumed to interact with MTL during retrieval. Frontal cortex involvement in retrieval of autobiographical memories in general is well established (Moscovitch, 1989; Kopelman, 1991; Kroll *et al.*, 1997; Moscovitch and Melo, 1997; Conway *et al.*, 2001; Kopelman and Kapur, 2001; Maguire, 2001b; Moscovitch and Winocur, 2002; Gilboa, 2004). It is difficult to predict clearly, however, whether frontal lobe activity is related to the age of the memory, as is the case for the MTL (but see Maguire *et al.*, 2001a; Conway *et al.*, 2002). With respect to posterior neocortex, those holding that memories become independent of the MTL as they age would predict greater activity in posterior regions for older memories because they should be retrieved directly from the neo-cortical representations, as cortico-cortical connections become more extensive and more stable with time. Alternatively, if retrieval of remote autobiographical memories continues to depend on the MTL, no difference in posterior neocortical activation is predicted, assuming that the quality of memories is the same. Three prominent posterior regions reported in neuroimaging studies of autobiographical memory are the retrosplenial cortex (Fink *et al.*, 1996; Andreasen *et al.*, 1999; Maguire and Mummery, 1999; Maguire *et al.*, 2001a; Ryan *et al.*, 2001), temporoparietal junction (Conway *et al.*, 1999; Fink *et al.*, 1996; Maguire and Mummery, 1999; Maguire *et al.*, 2001a; Ryan *et al.*, 2001) and lateral temporal cortex (Andreasen *et al.*, 1995; Fink *et al.*, 1996; Maguire and Mummery, 1999; Maguire *et al.*, 2001a; Ryan *et al.*, 2001). Of these, the temporal regions are considered likely sites for the representation of remote memories (Squire, 1992; Alvarez and Squire, 1994). In addition, an EEG study of autobiographical memory demonstrated that holding an autobiographical memory in mind, once it was retrieved, is associated with a late activation in the right temporal-occipital region (Conway *et al.*, 2001), suggesting retrieval of specific personal memories may be associated with more posterior neocortex than previously reported.

Materials and Methods

Nine middle-aged adults (mean age = 50.75 years; range = 38–58 years; three males) who reported no history of neurological or psychiatric disorder, major medical illness or substance abuse were paid \$75 for their participation.

The stimuli consisted of five photographs (resized and grayscaled) from each of five time periods (25 in all), ranging from when the participant was 5 years old until the present time. Pictures were collected from relatives and friends of each participant, to ensure that the participants would have no prior knowledge of which events were to be used during scanning, and to prevent the possibility of reactivation of memories from the pre-scan session. Only photos depicting events (as opposed to portraits) were selected, and photos likely to be associated with well-rehearsed events were avoided based on consultation with the confederate. Participants appeared in all photos selected, to control for the effects of self-related processing. During scanning, each picture was presented for 30 s to allow participants to reconstruct and fully re-experience the memory. Pilot data indicated that shorter durations (20 s) did not allow subjects enough time for full re-experiencing, particularly for the remote events. It is important to note two ways in which the stimuli used in the present study differ from those used in other studies, thereby necessitating longer recollection times. First, the use of specific events selected by the experimenter may have made it more difficult for participants to retrieve or reconstruct the events. On the other hand, events pre-selected by the participants, as is typical in other studies, lead to direct or 'spontaneous' retrieval. Second, once a memory is retrieved, a photograph provides additional cues, which allow for rich detailed recollections that evolve over time as more and more details become apparent or meaningful, in contrast to minimal cues provided by a sentence or a single word, as in other studies. In a debriefing session following the scan, participants indicated that they had either never seen the photos or that they hadn't seen them in many years.

Twenty-five photos from people unknown to the participant, matched for content and perceptual detail, were used as control stimuli. For control photos, participants were asked to imagine detailed scenarios of what the people in the photo might be doing, what they were doing before, what they will be doing after, what they are thinking, feeling, etc. This baseline resembles the target memory task in that they both require generation of detailed scenarios embellished by visual imagery and are based on retrieval of script-based knowledge or representations (e.g. Mandler, 1984). What distinguishes the baseline from the target task is that the latter is related to specific events, whereas the former is based on general knowledge. In addition, we used another fortuitous 'baseline' condition of personal photographs for which subjects were unable to retrieve event-specific details. This baseline offers a tighter comparison to re-experiencing of autobiographical events as it includes similar aspects of perceptual input, orientation to past events, reference to self-related ideation and schemata, retrieval of personal semantic and generic information, and so forth. The primary difference between these two 'conditions' is that the baseline condition is not accompanied by the retrieval of detailed experiential aspects of the specific events and lacks the subjective phenomenon of re-experiencing. In short, it is akin to a personal generic, or personal semantic, memory in terms of what is retrieved, and to retrieval attempt, in terms of what is not retrieved.

Instructions were given regarding the differences between episodic, generic (e.g. repeated experiences, extended events) and semantic autobiographical memory. Participants were asked to recall and re-live the event depicted in the picture to the best of their ability and to retrieve as much episodic information as possible. Participants were trained prior to scanning on both tasks with photos that were not used during the scan.

Five runs corresponding to five time periods were conducted. The five time periods corresponded to ages 5–11, 11–20, 20–30, 30–40 and recent, which included photos of events up to 5 years old. For the one participant who was younger than 40 (age 38), the age ranges were: 5–11, 11–20, 20–26, 26–32 and past 5 years. A 5 year period for recent events was selected because it has been suggested that retrograde amnesia following damage restricted to the hippocampus proper may last only a couple of years (Rempel-Clower *et al.*, 1996;

Reed and Squire, 1998; Kapur and Brooks, 1999; Manns *et al.*, 2003). It was hypothesized that hippocampal activation observed for events older than a few years would thus be difficult to explain within the framework of current consolidation theories. Stimuli were presented using E-prime software and presentation order of runs was randomized.

Following the scanning session, participants viewed the photos in the same order and rated them for vividness, arousal, personal significance (a scale of 0 to 6) and pleasantness (a scale of -3 to +3). Here we report the data based on the vividness ratings as these most directly applied to the question at hand, namely, the involvement of the hippocampus in retrieval of context-rich memories. For this sub-scale participants were asked to give high ratings only to photographs for which they were able to retrieve specific episodic details. They were asked to distinguish in their ratings between context-rich recollections and highly visual but not context specific memories such as generic memories. Only the former were rated high on vividness. Ten of the photos, two from each time period, were later selected for a further extensive semi-structured autobiographical interview. The data from the interview are not presented here, and instead these were used to verify that the subjective vividness ratings indeed reflected episodic recollections rather than generic representations. All subjects indicated during post-scan debriefing that they found the control task equally difficult across age blocks and that they thought their made-up scenarios were at least as detailed as the real memories they retrieved. A subset of subjects ($n = 4$) was also required to complete the vividness scale for the twenty-five imaginary scenarios, corroborating the verbal report.

fMRI Data Acquisition

Images were collected using a GE Sigma 1.5T MR scanner with a standard head coil (CVyi hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI). Functional scans were performed using a single shot T2*-weighted pulse sequence with spiral readout. Twenty-seven axial slices, 5 mm thick, were obtained [$T_R = 2000$, $T_E = 40$ ms, flip angle 80° , FOV 20 cm with a functional scan matrix of 64×64 (3.12 mm \times 3.12 mm)]. Scan sequences were blocked, and consisted of five 30 s presentations of 'self' photos alternating with five 30 s presentations of 'other' photos, with 6 s fixation in-between photos, making a total of 190 images per run. For each participant, standard volumetric anatomical MRI was performed before functional scanning by using a 3-D T1-weighted pulse sequence ($T_R = 12.4$ ms, $T_E = 5.4$ ms, flip angle 35° , 22×16.5 field of view, 256×192 acquisition matrix, 124 axial slices 1.4 mm thick).

fMRI Data Analysis

Data were analyzed using Analysis of Functional NeuroImaging software (AFNI; Cox, 1996). Time series data were spatially realigned to correct for head motion using a 3-D Fourier transform Interpolation, and detrended to a constant reference scan by using a fifth-order polynomial. Time-series data from the three earliest time periods were concatenated and treated as 'remote' photos (>15 years old; mean \pm SD = 32.3 ± 10.28 years), which is well beyond the few years thought to be required for complete consolidation of memories. The recent time-period consisted of photos from within the previous 5 years (1.75 ± 1.61 years). To ensure that differences in statistical power do not account for findings in the remote versus recent conditions, we also selected five photos from the remote condition that were rated highest on vividness, making them roughly equivalent (although still lower) to the recent events in terms of vividness. For each of these events, the corresponding 'other' photo was selected to serve as baseline, and the same analyses were performed (see below) using these photos.

Autobiographical Retrieval

Percent changes in signal intensity of 'self' with respect to 'other' were determined by using the highest voxel-wise correlations from one of five ideal waveforms that varied in T_R offset (modeling 0-4 T_R offset) to account for the delay in haemodynamic response. Activation maps were transformed into Talairach coordinates and smoothed using a Gaussian filter of 6 mm FWHM to facilitate group analysis.

Group analysis consisted of a voxel-wise mixed model two-factor analysis of variance (ANOVA) with subjects as a random factor and picture age (remote and recent) as a fixed factor. Statistically significant brain activity was established using a voxel-cluster threshold technique for a whole brain corrected level of significance of 0.05 (voxel $P < 0.001$; minimum cluster size, 320 mm³). Because of our prior hypothesis regarding the role of the MTL, we also corrected for a reduced search volume that included all MTL structures, i.e. hippocampus, parahippocampal, perirhinal and entorhinal cortices ($P < 0.05$ corrected; voxel $P < 0.005$; minimum cluster size of 90 mm³).

To test differences between recent and remote memories, the activity in five target regions was studied. These regions are consistently reported in the literature to be involved in autobiographical memory tasks (medial prefrontal, retrosplenial, temporoparietal cortices and hippocampus) as well as the inferolateral temporal-occipital cortex that was intensely activated in the present study. For each of these regions the center of activation from the remote versus other contrast was selected as a centroid: medial prefrontal cortex (BA 10; $x = -9$, $y = 55$, $z = 15$; $t = 19.25$), extended retrosplenial cortex (BA 31; $x = -5$, $y = -58$, $z = 22$; $t = 17.97$), temporoparietal junction (BA 39; $x = 40$, $y = -55$, $z = 25$; $t = 10.52$) and hippocampus ($x = -33$, $y = -19$, $z = -15$; $t = 5.41$), as well as inferolateral temporo-occipital cortex (BA 19/37; $x = 50$, $y = -62$, $z = -3$; $t = 12.46$). Differences between recent and remote autobiographical memory were thresholded at $P < 0.05$ corrected for five 10 mm radius spherical search volumes centered at the peaks of activation foci of the target regions.

We also looked at individual subjects' hippocampal activations to explore patterns of activation related to remote and recent events. The hippocampus was defined by visual inspection of structural MRI data based on published anatomical guidelines (Shenton *et al.*, 1992), guided by the Talairach atlas (Talairach and Tournoux, 1988). Centroids of hippocampal activations for recent versus other, and remote versus other, contrasts were identified on non-smoothed images and plotted on a sagittal plane taken from the atlas. The significance of differences in variability of distribution of activations along the y -axis was tested using an F -test for differences in variance.

To explore further the distribution of activation along the rostro-caudal axis of the left hippocampus, two region of interest (ROI) masks corresponding to the anterior and posterior halves of the hippocampus were created. The mid-section of the hippocampus was determined at the coronal slice where the posterior commissure first appears. The averages of percent change for anterior and posterior hippocampal ROIs were calculated for recent and remote conditions separately. These data were subjected to repeated measures ANOVA with time (recent versus remote) and location (anterior versus posterior) as within-subject factors.

Autobiographical Re-experiencing

This analysis was carried out on the remote events only following reports by participants that they were unable to recall many of the events depicted in the photographs. Such reports were rare for recent events, only occurring once in three subjects, reflecting the ease with which recent memories are retrieved. Based on participants' vividness ratings of the memories they had in the scanner, remote memories were defined as 'high' (4, 5 or 6) or 'low' (0, 1 or 2) on vividness. As described above, low ratings referred to photographs where subjects were either unable to recall anything about the event or where only generic recollections came to mind. Each 'low' or 'high' rated photo was matched with one 'high' or 'low' rated photo within the same run and pair-wise difference in vividness rating between the photographs had to be >2 . Overall, there were 27 event-pairs that matched these criteria; seven participants contributed three pairs each, one participant only had two pairs and another had four pairs that matched these criteria. The average rating for 'low' and 'high' photos was 1.48 and 4.91, respectively. A square-wave reference vector was constructed based on this division, and voxel-wise correlations were calculated for this contrast. The contrasts were thresholded at $P < 0.05$ corrected for five 10 mm radius spherical search volumes centered at the peaks of activation foci of the target regions (see above). Group analysis consisted of a voxel-wise t -test against a null hypothesis of no difference in activation between the vividly recollected and non-recol-

lected events ($P < 0.05$ corrected; voxel $P < 0.005$; minimum cluster size of 90 mm^3).

Differences between recent events and remote events that were vividly re-experienced were explored. For each vividly re-experienced remote event, the following 'other' block was selected as baseline, and a square-wave reference vector was created. The mean activation maps of the two conditions were then subtracted as described above for the general remote versus recent comparison with the same statistical thresholds applied.

Results

Remote and Recent Autobiographical Retrieval

The hippocampus was active both for remote and for recent photos (Fig. 1c). Remote events consisted of pictures fifteen years and older with an average of 32.5 ± 10.28 years ago and recent events consisted of photos from within the previous five years, an average of 1.75 ± 1.61 years. Eight out of nine subjects showed left hippocampal activity for remote events. Of the eight subjects, five also showed significant right hippocampal activity. For recent events, all subjects showed hippocampal activation, four on the left, two on the right and three bilaterally. The participants had not viewed the photographs for many years, up to decades for the remote photos, and so the activation is unlikely to be the result of reactivation of a previous viewing occasion. Additionally, the baseline condition included unfamiliar photos, which would recruit encoding processes at least to the same degree as familiar photos, suggesting that residual hippocampal activation is

likely related to retrieval rather than (re-)encoding. Similar results were obtained when only five events were used in the remote condition, with significant activation appearing in the left hippocampus ($x = -24, y = -16, z = -16; t = 4.41$).

An inspection of the distribution of individual activations along the rostrocaudal axis of the left hippocampus across subjects (Fig. 2) revealed that the variability of activations related to remote events was significantly greater than the variability of activations related to recent events [$F(17,14) = 6.04; P < 0.001$]. This was also true for right hippocampal activations [$F(12,9) = 9.32; P < 0.001$], although there were fewer foci of activation, and the overall mean activation did not reach our statistical cut-off either for remote or recent events. We performed the same analysis for the left hippocampus using only the five most vivid memories from the remote period. There was significantly more variation along the y -axis for remote memories in this analysis too [$F(9,14) = 6.62; P < 0.001$]. We also performed the analysis using only voxels that were significantly active at $P < 0.001$; the result of the differences in variance was still significant [$F(6,8) = 6.32; P < 0.02$]. This effect could be due to a more variable distribution of activity associated with the age of the memory (within-subject variability). Alternatively, it could be that different subjects tend to show activations in different regions along the hippocampus (between-subject variability). For subjects with more than one hippocampal activation in remote events ($n = 5$) the between-subject variability was not greater than the within-

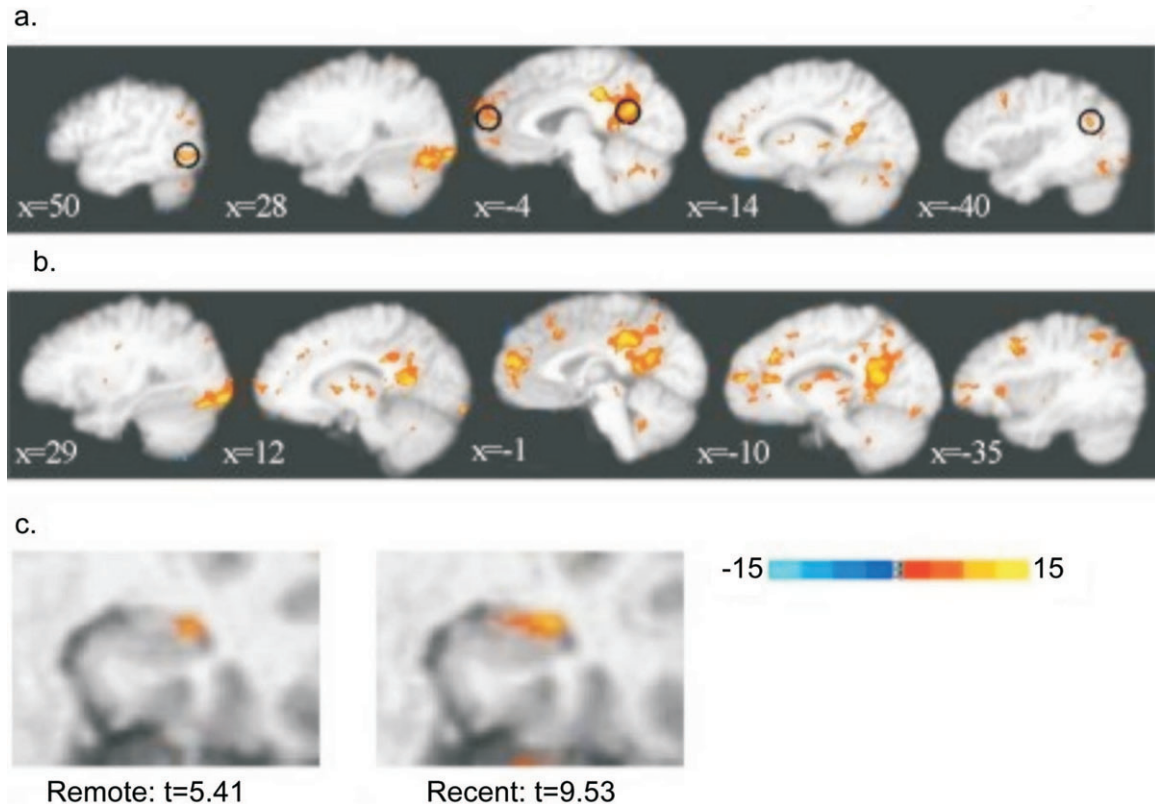


Figure 1. Activations for 'self' versus 'other' conditions. Activations shown include only areas of minimum cluster size 320 mm^3 ($P < 1.0 \times 10^{-5}$). The functional maps are overlaid on an average anatomical image from all participants. The colors used in the functional maps denote t -values shown in the bar. (A) Remote events (mean = 32.5 years ago). Black circles mark the centroids of activation used for the contrast of vividly versus non-vividly recalled events. (B) Recent events (mean = 1.75 years ago). (C) Sagittal view of left hippocampal activation for remote ($x = -33, y = -19, z = -15$) and recent ($x = -32, y = -18, z = -15$) events. Minimum cluster size = 90 mm^3 ($P < 5.0 \times 10^{-3}$).

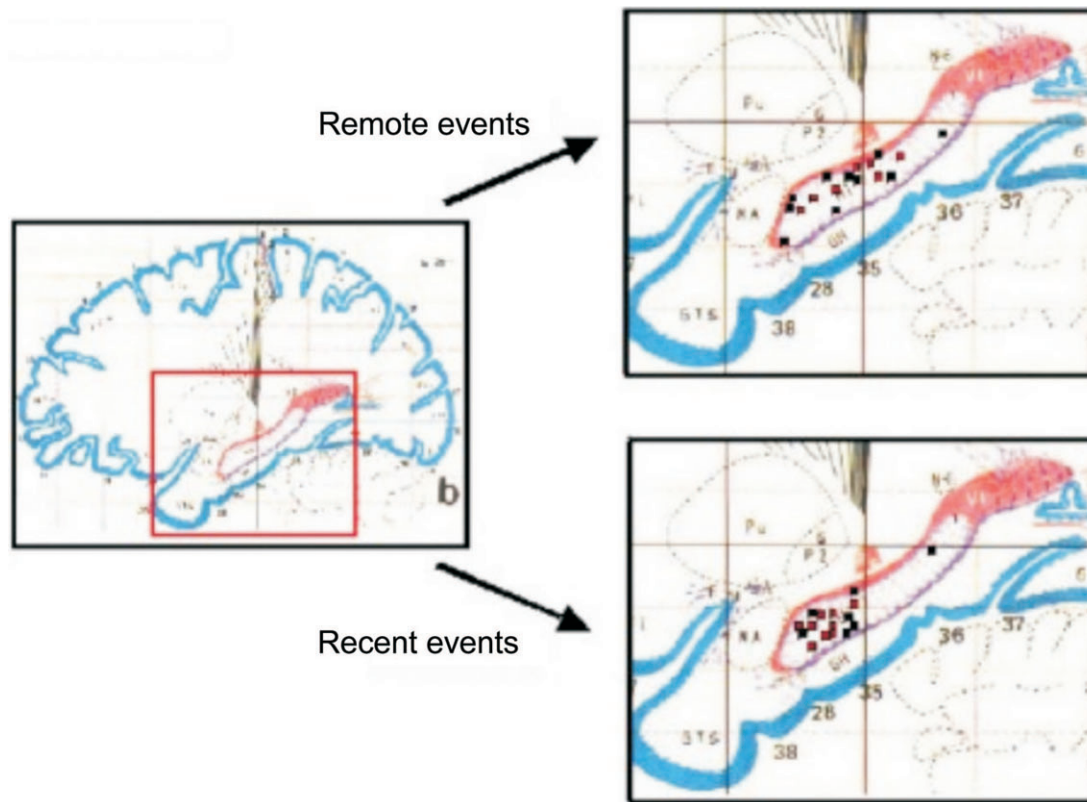


Figure 2. Schematic renderings of remote and recent activations. Each point corresponds to a statistically significant activation from within the left hippocampus in either remote (top; $n = 18$) or recent (bottom; $n = 16$) conditions. Red and black squares represent activations at a significance level of $P < 0.001$ and $P < 0.01$ uncorrected, respectively. Activations are shown on a single sagittal plane taken from the Talairach and Tournoux (1988) atlas (25 mm lateral to the midline). Overlapping activations were offset slightly in the recent condition. Differences in the lateral displacement of the activations from the midline (along the x -axis of the Talairach atlas) are not represented in the figure. The lateral and vertical dimensions did not show any obvious systematic variability and therefore are not considered as a part of the overall pattern of interest.

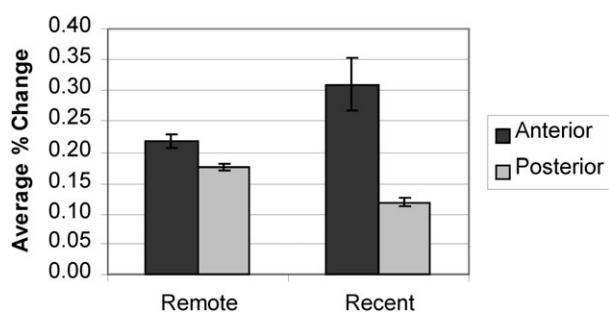


Figure 3. A histogram displaying the average percent BOLD signal change for the anterior and posterior left hippocampus ROIs as a function of remoteness of memory.

subject variability [$F(4,14) = 0.27$; $P > 0.1$], suggesting the effect indeed is related to memory age.

To investigate this effect further, we compared the average percent change of the anterior and posterior portions of the hippocampus for recent and remote events separately (Fig. 3). Repeated measures ANOVA revealed a main effect of location [anterior versus posterior; $F(1,8) = 8.36$, $P < 0.05$] no main effect of time [remote versus recent; $F(1,8) = 0.369$, $P > 0.05$] and an interaction of time by location [$F(1,8) = 6.68$, $P < 0.05$]. Post-hoc paired sample t -test for the difference between anterior and posterior hippocampal activity in remote versus recent events revealed a significantly larger difference in recent than remote [$t(8) = -2.58$, $P < 0.05$], supporting the original observation.

With regard to whole-brain activation, remote and recent photograph conditions yielded patterns of activation that were similar to those reported by others (Fig. 1). These included limbic/paralimbic memory-related structures comprising the Papez circuit: left hippocampus, anterior thalamus and retrosplenial cortex (BA 29/30/31) as well as the left temporal pole (BA 38) and the right parahippocampal gyrus (BA 28/35).

Other regions active in both conditions were the ventrolateral PFC (BA 10/47) and the cerebellum, which mediate strategic aspects of retrieval, or 'working with memory', as well as the medial and polar prefrontal cortex (BA 9/10), which are thought to be involved in the processing of self-related memories and cognition. Additionally, activation was seen in the bilateral precuneus (BA 31/7) and temporo-parietal junction (angular gyrus, BA 39), regions often implicated in imagery and spatial processing in the context of episodic memory. Prominent areas of activation that were seen in the present study but were not reported in previous studies of remote memory included a very large bilateral activation in the lingual and fusiform gyri (BA 19/37). This may be related to the complex visual stimuli (photos) used in the present study and the extended period for re-experiencing, which likely induced more sensory perceptual memory-related activation than the verbal materials used in previous studies.

Comparisons between Remote and Recent Events

There were no statistically significant differences between recent and remote events after correction for whole-brain

multiple comparisons. Within the five target regions of interest, it was found that recent events showed higher activity in retrosplenial cortex ($x = -13, y = -54, z = 14; t = -6.35$) and remote events showed higher activity in the inferolateral temporo-occipital cortex (BA 19/37; $x = 51, y = -62, z = -3; t = 7.33$). The left hippocampus showed only a trend towards higher activity for recent events ($x = -32, y = -19, z = -14; t = -3.49 P < 0.05$ uncorrected). Though showing only a trend towards greater hippocampal activation for recent events and greater neocortical activation for remote ones, these differences may be interpreted as evidence supporting the standard model of consolidation theory. Alternatively, this effect could be related to subjects' inability to retrieve vivid episodic memories which are remote, as suggested by self-reports and the autobiographical interview following the scan session. That is, memory for remote events was generally poorer than

for recent events, so what appears to be an effect of memory age may simply be an effect of memory quality. Indeed, whereas almost all recent events were recalled vividly, this was true of only a portion of the remote events.

The Effect of Vividness in Remote Events

To determine whether it is the vividness of the memory, rather than its age, that is associated with greater hippocampal activation, we compared the quality of the remotely retrieved events, since it was only among those that any great variability existed. We contrasted remote events that were recollected with rich episodic details and those that were not. This direct comparison showed significant activation within the left hippocampus ($x = -27, y = -21, z = -16; t = 5.41$; Fig. 4) that was associated with vivid recollection of remote events. When remote events

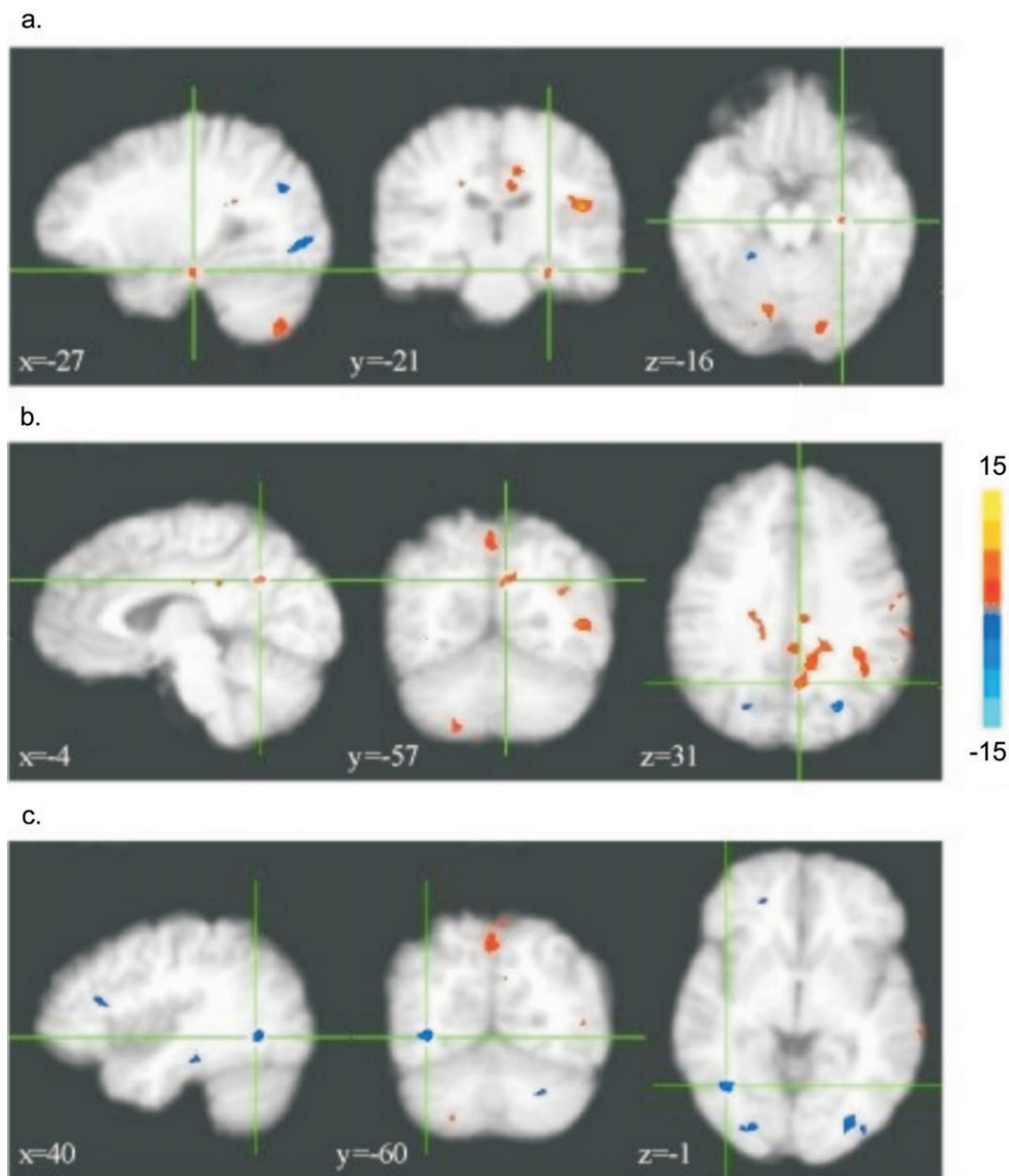


Figure 4. Activation from vividly (red) versus non-vividly (blue) recalled events. The cross hairs on the images are centered at activations within the spherical search regions of: (A) hippocampus ($x = -27, y = -21, z = -16$); (B) retrosplenial cortex ($x = -4, y = -57, z = 31$); and (C) inferior temporal gyrus ($x = 40, y = -60, z = -1$). Activations shown include areas of minimum cluster size 90 mm^3 ($P < 5.0 \times 10^{-3}$). Colors used in the functional maps denote t -values shown in the bar to the right of the figure.

that were re-experienced vividly were compared with recent events, no differences in MTL regions were detected.

Of the other four target regions (see Fig. 1 and Materials and Methods), one showed higher activity for vivid memories and one, for events that were not recollected. Higher activity for events that were vividly recollected was found in the posterior cingulate/precuneus region (BA 31; $x = -4$, $y = -57$, $z = 31$; $t = 7.44$) in proximity to the retrosplenial cortex (Fig. 4). This suggests that the hippocampus and the posterior cingulate/precuneus cortex are more directly related to the actual experience of remembering a remote event in great detail.

The greater inferotemporal activation for events that were not vividly recalled (BA 37, $x = 38$, $y = -59$, $z = -1$; $t = -6.12$) is harder to interpret. It should be kept in mind, however, that subjects could recognize all of the people and places depicted in non-recollected events, and could reproduce many generic and personal semantic facts about them. It could thus be hypothesized that this region is related to greater analysis devoted to photos of familiar people and places in a failed effort to extract detailed autobiographical knowledge. No significant differences were found in the other two regions that were searched (medial prefrontal cortex and temporo-parietal junction).

Regions outside the search area that showed activation related to events that were re-experienced and events that were not ($P < 0.001$, uncorrected; minimum cluster size

100 mm³) are presented in Table 1. These regions did not survive the strict statistical correction for whole-brain multiple comparisons that we used in the present study, so they will not be discussed or interpreted further. These results are presented, however, at a significance level comparable to that used by most other studies in the field because there is a close correspondence between the conditions being compared (events vividly recalled versus events that were not). These comparisons provide the reader with the opportunity to observe patterns of activation that contrast actual re-experiencing and failure to retrieve specific events in autobiographical memory, which has never been demonstrated before.

Remote and Recent Memories Comparable for Vividness

In the comparison of vividly recollected remote memories and recent memories, two regions displayed activations that survived correction for whole-brain multiple comparisons (voxel $P < 0.001$; minimum cluster size, 320 mm³). One of these regions was the lingual gyrus (BA 18: $x = 12$, $y = -73$, $z = -10$; $t = 14.17$), which showed greater activation for vividly recollected remote memories, both when compared with recent memories and when compared to poorly recollected remote memories. The other was the retrosplenial cortex (BA 29/30: $x = -14$, $y = -53$, $z = 19$; $t = -11.85$), which showed greater activation for recent memories compared with vividly recollected remote memories. Importantly, there was not even

Table 1
Locations of significant fMRI activity for vividly and non-vividly recollected events, outside the five ROIs

	Region		x	y	z	t-value
Higher activation for vividly re-experienced events						
Frontal	Anterior cingulate (32)	L	-19	33	19	9.41
Parietal	Precuneus (19)	L	-35	-66	40	5.77
	Insula (13)	L	-46	-20	18	20.26
	Pre-central gyrus (4)	L	-62	-7	23	9.47
	Precuneus (7)	R	1	-64	40	8.44
	Posterior cingulate (23/31)	L	-10	-31	27	8.95
Temporal	Superior temporal sulcus (21)	L	-45	-54	7	8.21
	Superior temporal sulcus (21)	L	-55	-9	-4	5.80
	Superior temporal sulcus (22)	R	58	-50	14	5.61
	Perirhinal cortex (34)	R	27	0	-12	5.23
Occipital	Lingual gyrus (18)	L	-14	-81	-14	5.43
	Lingual (19)	R	9	-73	-9	9.67
	Cuneus	R	11	-83	28	7.94
Other	Caudate	R	9	7	16	6.10
	Putamen	R	25	-2	9	10.12
	Cerebellum	L	-27	-67	-59	5.83
Higher activation for non-vividly recollected events						
Frontal	Superior frontal gyrus (10)	R	27	49	17	-6.44
Parietal	Precuneus (lateral) (19)	L	-24	-71	35	-9.54
Temporal	Inferior temporal gyrus (20)	R	41	-26	-14	-7.32
occipital	Inferior occipital gyrus (18)	L	-28	-77	-3	-8.63
	Middle occipital gyrus (19)	L	-39	-68	14	-6.87
Other	Cerebellum	R	24	-40	-15	-6.91

a trend towards a significant hippocampal difference between recent and remote memories once we corrected for vividness.

Discussion

We report three main findings concerning the functional neuroanatomy of remote memory. First, the hippocampus participates equally in retrieval of both remote and recent memories which are vivid. Second, there is greater distribution of activation along the hippocampus in remote memories than in recent memories. Third, retrieving detailed vivid autobiographical experiences, as opposed to personal semantic information, is a crucial mediating feature that determines the involvement of hippocampus and two posterior neocortical regions, precuneus and lingual gyrus, in remote autobiographical memory.

Our participants demonstrated significant left hippocampal activation for both recent and remote events when compared to the imaginary scenarios baseline and even to personal pictures for which the participants had no specific memories. These findings indicate that hippocampal activation is associated more with retrieval of detailed specific memories than with retrieval of detailed imaginary events or of personal semantic or generic memories. These data challenge traditional consolidation theories, which posit that the MTL, and particularly the hippocampus, are temporary memory structures needed only until memories are consolidated elsewhere in the brain. It can be argued, however, that the observed MTL activation is not needed for retrieval, but merely accompanies it. To be consistent, one would also have to apply the same reasoning to account for the hippocampal activation that we observed during the retrieval of recent memories, and that others have observed for anterograde memories. The association of hippocampal activation with vividness on tests of remote memory is compatible with evidence from neuroimaging and lesion studies on anterograde memory that hippocampal activation is associated with recollection of context-bound memories rather than with simple familiarity (Eldridge *et al.*, 2000; Moscovitch and McAndrews, 2002). In particular, our results are consistent with those of Maguire *et al.* (2001b), whose single-case study showed that even in a person with large bilateral hippocampal lesions, activation of the remaining viable tissue is observed only when the person recollects and re-experiences an autobiographical episode, rather than simply knowing that it occurred. Finally, hippocampal activation is not obtained for retrieval of remote semantic memories (e.g. Haist *et al.*, 2001), which suggests that the hippocampus is specifically associated with retrieval of detailed autobiographical episodes. Collectively, these data are consistent with the idea that hippocampal activation during remote memory signifies the same necessary recollective processes as are implicated during retrieval of recent and of anterograde memories.

The results are more compatible with the Multiple Trace Theory (MTT; Nadel and Moscovitch, 1997), which considers hippocampal neurons to be an integral part of context-rich autobiographical memory traces and which assigns the hippocampus a permanent role in retrieval of such memories. This theory posits that neurons within the hippocampal complex act as part of hippocampal-neocortical ensembles to index the different neocortical areas that need to be activated to produce the full content of an episodic memory. The literature on remote autobiographical memory of patients with amnesia

following MTL lesions suggests that when the lesion extends to the whole hippocampal complex, retrograde amnesia can extend for decades and even encompass a lifetime. Some very remote memories may survive (Rempel-Clower *et al.*, 1996; Reed and Squire, 1998), though only in gist form that lacks the episodic specificity that characterizes similar memories in intact subjects (Hirano and Noguchi, 1998; Viskontas *et al.*, 2000; Cipolotti *et al.*, 2001; Westmacott *et al.*, 2001; but for contrary evidence, see patient EP in Bayley *et al.*, 2003).

The present study provides converging evidence that the hippocampus is involved in retrieval of episodic details in very remote memories. When vividly re-experienced remote events were contrasted with events where no re-experiencing occurred, the left hippocampus was one of a handful of regions that showed significant activation, suggesting a specific role for the hippocampus in the phenomenology of episodic re-experiencing. The right entorhinal cortex showed a similar pattern of activation. By comparison, retrieval of general semantic self-related information such as knowledge regarding the people portrayed in a photo or the place where it was taken, does not implicate the MTL regions to a similar extent.

Nadel and Moscovitch (1997, 1998) have noted that when the lesion is restricted to part of the hippocampal complex there may be a gradient of retrograde amnesia with recent memories being affected more than remote ones. This is in line with MTT, which suggests that the extent of hippocampal damage in amnesic patients corresponds to the extent of retrograde memory loss, with only complete damage causing a flat gradient of episodic memory loss. Individual analysis of foci of activation within the hippocampus in the present study demonstrated that, for recent events, activations were clustered, whereas for remote events, they tended to be more dispersed along the rostrocaudal axis of the hippocampus. These results are consistent with one of the main postulates of MTT, i.e. the repeated reinstatements of a memory lead to the formation of new, distributed traces within the MTL that would index the network of neocortical regions that represent the event. Remote, detailed memories should, therefore, be more widely distributed in MTL than recent memories, and may survive minimal damage to the MTL. Our neuroimaging data suggest that partial hippocampal damage could affect recent memories more; however, there is no direct evidence that multiple traces formed during multiple reinstatements is the underlying mechanism of the difference in distribution of activations, though the results are consistent with this idea.

An alternative explanation for this finding is that there is a qualitative difference between the way memories are encoded during adolescence and early adulthood, and memories encoded later in life. Most of the events in the remote period occurred when our participants were younger than thirty years of age, a life period that is characterized by preferential recall of memories under certain testing conditions, known as the reminiscence bump (Rubin *et al.*, 1986; Fitzgerald, 1996; Rubin and Schulkind, 1997; Conway and Haque, 1999). One explanation of the reminiscence bump is that highly self-relevant novel experiences, which characterize this period (Fitzgerald, 1996), may be encoded preferentially and distinctively ('privileged encoding'; Conway and Haque, 1999). Another possibility is that enhanced encoding is independent of self-relevance, but instead is fueled by a collection of other biological, cognitive, and environmental variables that operate on memories of personal events, as well as on factual and

semantic ones (Rubin and Schulkind, 1997). Either way, it could be that the finding from the present study represents a neural correlate of such privileged encoding which would give rise to increased accessibility of memories from that age and possibly also to their increased resistance to partial neurological insult.

Some imaging studies have also reported hippocampal activity during retrieval of remote memories (Fink *et al.*, 1996; Maguire and Mummery, 1999; Maguire *et al.*, 2001a; Ryan *et al.*, 2001; Maguire and Frith, 2003a). It has been argued that these activations might be related either to the retrieval of a more recent event, namely the pre-scan interview, or to (re-)encoding of information in the context of the experimental task itself. The present results cannot be explained by the former alternative, as subjects only viewed the photos once, in the magnet, and the photos themselves had not been viewed for many years, and in some cases subjects had never seen them before. The re-encoding alternative is also unlikely. The present study controlled for the encoding hypothesis by using a baseline task in which subjects imagined scenarios associated with unfamiliar photos. Complex visual scenes reliably produce encoding-related activation in the hippocampus (Stern *et al.*, 1996; Stark and Squire, 2001) that tends to be stronger for unfamiliar pictures (Stark and Squire, 2001). Despite this, retrieval of information about personal episodes led to greater hippocampal activity in the present study, even though vividness ratings were similar for imagined scenarios and personal memories, and even higher for the former compared with remote memories.

Viewed from our perspective, that the hippocampus is invariably implicated in retention and retrieval of context-rich autobiographical memories, the present data are not incompatible with previous reports of time-limited involvement of the MTL in retrieval of remote memories (Haist *et al.*, 2001; Niki and Luo, 2002; Piefke *et al.*, 2003). Studies reporting time-limited effects either are concerned with semantic memory or do not sufficiently address the possible confounding of memory quality with memory age. Haist and colleagues (Haist *et al.*, 2001) demonstrated a decreasing gradient in the activation of the entorhinal cortex during retrieval of semantic information (famous faces), as would be predicted by both traditional consolidation theories and MTT. These results, therefore, do not speak to the critical issue of context-specific memories, such as vividly recalled autobiographical episodes. An alternative interpretation of the findings of Haist *et al.* (2001) could be that the gradient observed is related to a greater degree of vivid *personal* memories that are associated with the famous people. This interpretation is consistent with recent studies by Westmacott and her colleagues (Westmacott and Moscovitch, 2003; Westmacott *et al.*, 2004), who found that merely reading names of famous people can automatically trigger an autobiographically significant memory in addition to the semantic memory associated with that individual. Such autobiographically significant memories likely are mediated by the MTL, in that they are severely impaired in patients with MTL damage. People who became famous recently are more likely to trigger such autobiographical memories than those who achieved their fame long ago. It is interesting to note that the right entorhinal cortex in the present study showed a similar pattern of activation as the left hippocampus; namely, stronger activation for recent events that is mediated by the vividness of remote memories retrieved.

The results of two other studies that show greater hippocampal activation in recent than remote memories for specific places (Niki and Luo, 2002) or events (Piefke *et al.*, 2003) are difficult to interpret for two reasons. There is no report of activation levels of events from each time period against an independent baseline, so it is hard to know whether the difference reported is due to lack of activation in the remote period or due to weaker activation, as in the present study. In addition, the obvious confounding of age of memory with the amount of detail that is retrieved and the extent to which the event is re-experienced is not adequately addressed in these two studies. Piefke and colleagues (Piefke *et al.*, 2003) found that recent memories were rated by participants as being higher than remote ones on re-experiencing, richness of details and emotionality. They did not attempt, however, to control for these variables, leaving open the possibility that any differences in hippocampal activation they report are due to one of these confounding factors rather than age of the memory *per se*. Niki and Lou (2002) attempted to use the level of detail retrieved as a variable in studying differences between remote and recent memories. They only used categorical classes ('high' versus 'low') to rate the amount of detail retrieved about places, which may not be sensitive enough to capture qualitative differences between remote and recent memories.

Recently, using event-related fMRI, Maguire and Frith (2003) reported ungraded activation in the left hippocampus but 'temporally graded' activation of the right hippocampus in a mixed group of younger and older adults. They propose that this difference may be related either to the right hippocampal role in spatial processing, or that recent memories may be more salient in terms of visual-perceptual qualities. The latter interpretation fits in nicely with the interpretation presented in the present paper, adding the important aspect of type of detail, which may influence laterality. We note, however, that in the present study, with middle-aged participants, right hippocampal activation was inconsistent across individuals, and consequently was not significant at the group level.

An alternative interpretation of the intriguing right hippocampal gradient of Maguire and Frith (2003) is that the time course for recovering remote memories is different in the left and right hippocampi. Ryan *et al.* (2001) also report bilateral hippocampal activity using similar stimuli to Maguire and Frith's (pre-selected events, verbal stimuli, similar detail levels for recent and remote events) but allowing longer for re-experiencing (20 s). The time course data from Ryan's study reveals that while the left hippocampus peaks after 2 s for both recent and remote events, the right hippocampus peaks after 6 s for recent and 8 s for remote events. Participants in Maguire and Frith's study had ~4–5 s for retrieval after stimulus presentation (Maguire and Frith, 2003b). This duration may have been too short to capture the peak of the BOLD response in the right hippocampus, particularly for remote memories in the older adult sub-group, which seems to drive the effect. In addition, although the amount of detail associated with recent and remote memories was equated outside of the magnet during a pre-scan interview (Maguire and Frith, 2003b), it is not clear whether the same amount of detail was retrieved in the magnet, particularly for the remote events. Our pilot data suggested that reconstruction of remote memories takes considerably longer than reconstruction of recent ones [cf. Conway *et al.* (2002) for a discussion of imaging studies that may not be associated with full re-experiencing]. Thus, it may

be that the asymmetry observed by Maguire and Frith (2003b) occurred because old memories take longer to reconstruct and because the right hippocampus takes longer to reach a peak response.

Contribution of Extra-MTL Structures

Although the hippocampus is central to retrieval of episodic autobiographical memories, it acts within the context of many other frontal and posterior neocortical regions, some of which are directly related to the re-experiencing component and others of which participate in more general memory strategic retrieval processes.

Posterior Cingulate/Precuneus and Lingual Gyrus (Re-experiencing)

Retrieval of both recent and remote memories was associated with neural activity in the retrosplenial cortex that extended into the posterior cingulate and the precuneus, as well as extensive regions within the lingual and fusiform gyri. Retrosplenial/posterior cingulate activity is consistently reported in imaging studies of autobiographical memory (Maguire, 2001b) and damage to this region is known to cause severe amnesia (Bowers *et al.*, 1988; Heilman *et al.*, 1990). The direct comparison of events that were re-experienced and those that were not, yielded activation in the precuneus/posterior cingulate, but not the retrosplenial cortex proper (Vogt *et al.*, 2001), suggesting these regions should not be treated as part of the same functional system (see below a discussion of the pattern of activation associated with retrosplenial proper). The precuneus has been labeled the 'mind's eye' (Fletcher *et al.*, 1995) and its involvement in imagery and episodic memory is well established (Cabeza and Nyberg, 2000). The posterior cingulate is involved in topokinetic and topographical processing, including retrieval of spatial context and assessment of retrieved spatial representations (Burgess *et al.*, 2001; Vogt *et al.*, 2001), and thus may be performing a similar function in the visuospatial domain.

The lingual and fusiform gyri are active in encoding (Stern *et al.*, 1996; Machielsen *et al.*, 2000) and recall (Roland and Gulyas, 1995; Kohler *et al.*, 1998) of complex visual stimuli, and have also been shown to be responsive to emotional salience at recognition (Taylor *et al.*, 1998). Interestingly, these regions are not reported in other studies of autobiographical memory, possibly because the verbal material and shorter duration used in those studies is not as conducive to visual re-experiencing. An EEG study of autobiographical memory (Conway *et al.*, 2001) showed posterior activity which apparently emanated from temporal-occipital cortex which was associated with later stages of the retrieval process when memories were held in mind. The present study also provides evidence that this activation is specifically related to the re-experiencing component of autobiographical retrieval, as bilateral lingual activation was associated with remote memories that were re-experienced, i.e. where sensory-perceptual episodic memories were attained.

Retrosplenial Cortex (Generic Memory)

In contrast to the above areas, the retrosplenial cortex [a region within the bank of the callosal sulcus (Vogt *et al.*, 2001)] was significantly more active in recent memories than in remote memories, even in the comparison that included only the remote memories that were vividly re-experienced. The

data from the present study are consistent with the hypothesis that this structure is needed to activate, integrate and construct generic visual representations in posterior neocortex (Conway and Pleydell-Pearce, 2000) which may be more plentiful for recent than for remote memories. Highly detailed generic and semantic information may support or provide a framework for the construction of specific episodic memories (Burgess and Shallice, 1996). Such a function contrasts with that of the posterior cingulate/precuneus, which is apparently directly associated with retrieval of vivid specific memories, displaying a similar pattern of activation as the hippocampus.

The Frontal Lobes (Strategic Processes)

Three prefrontal regions were related to retrieval of recent and remote memories, namely left dorsolateral, medial, primarily on the left, and right ventrolateral prefrontal cortex. The medial aspect of the PFC was one of the major regions to differentiate 'self' from 'other' conditions, but was not differentially activated in remote memories that were vividly retrieved when compared with those that were not. This is in accordance with evidence suggesting that this region is generally important in the cognitive processing of self-related stimuli (Craig *et al.*, 1999; Gusnard *et al.*, 2001; Kelley *et al.*, 2002). The right ventrolateral PFC participates in memory control processes, possibly through the specification of retrieval cues in a reiterative fashion (Fletcher and Henson, 2001; Moscovitch and Winocur, 2002), which would be required given the richness of the cue that we used (Moscovitch and Winocur, 2002; Gilboa, 2004).

Conclusion

We show that the hippocampus is active in the retrieval of both recent and very remote memories that are rich in detail, even when we controlled for alternative explanations such as reactivation and re-encoding of the retrieved memories. Furthermore, there is evidence that representation of remote memories may be more distributed along the hippocampus, which is compatible with the lesion literature on retrograde amnesia that suggests recent memories are more vulnerable to partial hippocampal lesions than remote memories. Finally, we present evidence for the importance of vividness or re-experiencing in determining the participation of both the hippocampus and posterior neocortical regions in retrieval of autobiographical memories, and of the PFC in working with those self-related memories.

Notes

This research was supported by a Canadian Institutes of Health Research (CIHR) grant to G.W. and M.M. A.G. is supported by an Ontario Graduate Scholarship.

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