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As Time Goes By: Hippocampal Connectivity Changes With Remoteness of Autobiographical Memory Retrieval

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ABSTRACT: The hippocampus is crucial for episodic autobiographical memory retrieval. Functional neuroimaging evidence suggests that it is similarly engaged in recent and remote retrieval when memories are matched on vividness and personal importance. Far fewer studies have investigated the nature of hippocampal-neocortical coactivation in relation to memory remoteness. The purpose of this study was to examine hippocampal activity and functional connectivity as a function of memory age. Unlike most studies of autobiographical memory, we included autobiographical memories formed in the days and weeks before scanning, in addition to truly remote memories on the order of months and years. Like previous studies, we found that the hippocampus was active bilaterally regardless of memory age, with anterior activity increasing up to 1 yr and then decreasing, and with posterior activity being less sensitive to memory age. More importantly, hippocampal functional connectivity varied with memory age. Retrieving recent memories ($\leq$1 yr) showed a late coactivation of the hippocampus and areas of the autobiographical memory network, whereas retrieving remote memories (10 yrs) showed an early negative coactivation of the hippocampus and left inferior frontal gyrus followed by a positive coactivation with anterior cingulate. This finding may reflect that the hippocampus is more strongly integrated with the autobiographical memory network for recent than for remote memories, and that more effort is required to recover remote memories. © **2011 Wiley Periodicals, Inc.**

KEY WORDS: autobiographical memory; connectivity; hippocampus; memory age; retrieval

INTRODUCTION

Retrieving an autobiographical memory implicates a palette of cognitive processes that is mirrored by a broad pattern of brain activation (Maguire, 2001; Svoboda et al., 2006; Cabeza and St Jacques, 2007). For autobiographical memories that are episodic in nature, the hippocampal formation (including the CA fields, dentate gyrus, and subicular complex), hereafter referred to as the hippocampus, is a key structure. This is reflected in studies of patients with hippocampal damage (e.g., Kirwan, 2008; Rosenbaum, 2008). Similarly, hippocampal activity in healthy adults is associated with factors such as emotionality and vividness that are important to episodic recollection (Ryan et al., 2001; Addis et al., 2004b; Gilboa et al., 2004). There is disagreement, however, as to the necessity of the hippocampus in relation to the age of memories, with the Standard Model of Consolidation (Squire and Alvarez, 1995) holding that memories are temporarily stored in the hippocampus and later consolidated in the neocortex, and Multiple Trace Theory (Nadel and Moscovitch, 1997; Moscovitch et al., 2005) holding that the hippocampus is required for the retrieval of all vivid or detailed autobiographical memories regardless of age. The two theories also differ regarding hippocampal-neocortical connectivity: Standard Model of Consolidation predicts that connectivity diminishes with age, whereas Multiple Trace Theory maintains that it persists, though the structures implicated may change.

In fMRI studies of healthy adults, most have found hippocampal involvement regardless of memory age, supporting Multiple Trace Theory (Piolino et al., 2004; Rekkas and Constable, 2005; Steinvorth et al., 2006; Viard et al., 2007), especially when considering vividness (Ryan et al., 2001; Addis et al., 2004b; Gilboa et al., 2004). Where age effects were reported, these were confounded with vividness (Niki and Luo, 2002; Piefke et al., 2003) or time allowed for retrieval and activation (Maguire and Frith, 2003). Within the hippocampus, recent memories may engage the anterior region, whereas remote memories are more diffusely represented along the anterior-posterior plane (Gilboa et al., 2004; see also Rekkas and Constable, 2005).

The hippocampus, however, does not act in isolation. Its interaction with other brain structures, its "functional connectivity," during autobiographical memory retrieval has been explored in a few studies (Maguire et al., 2000; Addis et al., 2004a; Greenberg et al., 2005). For retrieval of memories a few years old, these studies suggested hippocampal connectivity with frontal areas (e.g., right inferior and left medial frontal gyrus), amygdala, parahippocampus, and cerebellum, among others (Maguire et al., 2000; Addis et al., 2004a; Greenberg et al., 2005). Comparing memories across different life periods, Viard et al. (2010) found that the strongest hippocampal-neocortical associations for vivid memories were from intermediate time periods. Significant correla-

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tions between the hippocampus and other brain structures throughout all time periods (except 18–30 yrs) were interpreted as support of the Multiple Trace Theory.

Many studies contrasting recent and remote memories designated events of 12–24 months in age as "recent" (for exceptions, see Maguire et al., 2001; Rekkas and Constable, 2005). However, assuming an exponential function of memory trace strength as found in behavioral studies (Rubin and Schulkind, 1997), and extrapolating from consolidation time in rats which ranges from a day to a month, and whose life span is about 2–3 yrs (Ghirardi et al., 1995), there may be more of a phenomenological and neural difference in humans between events that are 2 weeks old and 2 yrs old than between events that are 2 yrs old and 20 yrs old. Hence, studies that find similar activation in the hippocampus during retrieval of recent and remote events may do so because the so-called recent events have since long been consolidated and are not much different from the remote events.

Following an exponential function (Rubin and Shulkind, 1997), we included in this study events that were 1 week, 1 month, 1 yr, and 10 yrs old. We hypothesized that the hippocampus would be active throughout all time periods, but that its interaction with other brain structures would differ as a function of memory age. Crucially, we measured the temporal pattern of the brain connectivity across both life periods and epochs of autobiographical memory retrieval within each life period. Remote memories that are usually less vividly re-experienced may require more retrieval effort relative to the very recent memories utilized in this study, and may entail different neocortical-hippocampal interaction as compared to more recent memories. As such, more vividly re-experienced memories may also show a larger extent and greater sustenance of hippocampal interaction with neocortical areas that confer vividness within episodic autobiographical memory, such as those that mediate visual imagery.

MATERIALS AND METHODS

Participants

Participants were 12 healthy, right-handed subjects (33.7 ± 6.1 yrs old; 16.3 ± 3.1 yrs of education; five men), free of significant medical illnesses, including psychiatric disease (as determined by the Structured Clinical Interview for Diagnosis; SCID; First, 1995), neurological disease, and significant traumatic brain injury. These participants were scanned as part of a larger study on the effects of depression electroconvulsive therapy on autobiographical memory. Just like the depressed patients, these healthy controls were rescanned 6–10 weeks later. However, this report is restricted to the first scan in the healthy participants.

Scanning

Participants performed two tasks during scanning: autobiographical memory retrieval and odd/even number judgments, a recommended comparison task in studies of hippocampal function (Stark and Squire, 2001). The two tasks were randomly distributed within each run, with 10 trials of each task. Each run lasted ~11 min. Participants were familiarized with the tasks and performed two practice trials of each prior to scanning.

Autobiographical memory

Two days before scanning, while still at home, participants generated, dated, and gave titles to 10 events from each of four different time periods (i.e., 40 events in total, 10 events per time period): the last week (14 days, excluding the last 2 days; hereafter referred to as 1 w); the last month (3–7 weeks; 1 m); the last year (6–18 months; 1 yr); the last 10 yrs (5–10 yrs, 10 yrs). Participants were instructed to provide events that were specific to a single time and place. They were told that as such, "My vacation in Belize" was not acceptable, but that "My first surfing lesson in Belize" was. All event titles were randomized across the runs.

Each event title was presented for 18 s, preceded by a 1 s fixation and a 4 s cue of the upcoming task (i.e., "Autobiographical memory"). During the presentation of an autobiographical memory title, the participants were instructed to re-experience the event as vividly as possible, recalling thoughts, feelings, and visual images associated with the event. After 18 s, participants rated the amount of re-experiencing from 1 to 8 via fMRI-compatible response boxes. Eight seconds were provided for rating. Ten events were included in each run, with 2 from each of 2 time periods, and 3 from each of the other 2 time periods. Within each run, the events, and hence the time periods, were presented in a random order.

Immediately after scanning, participants rated each event on six different dimensions: visualization, emotional valence, emotional change at the time of the event, importance at the time of the event, importance at the time of scanning, and frequency of thinking about or talking about the event. Ratings ranged from 1 to 6, except the last dimension which was more finely grained (going from 0: never; to 11: constantly). Emotional valence ranged from negative (low) to positive (high) along the 6-point scale, but was transformed into 2 measures, going from 1 to 3. Ratings were performed after scanning rather than before to reduce potential contamination of recent recollection.

Odd/Even judgment

The odd/even number judgment (odd/even) task consisted of the presentation of nine numbers, one at a time, and was preceded by a 1 s fixation and a 4 s cue (i.e., "Odd/Even?"). Participants were instructed to determine whether the number was odd or even without making an overt response. Each number was presented for 1,900 ms, with a 100 ms interstimulus interval. After the presentation of the last number, participants rated the degree of re-experiencing, from 1 to 8 as described above. This rating was included as a manipulation check to determine the degree of contamination of the comparison task by any unbidden extraneous memories. Again, 8 s were provided for rating.

fMRI Data Acquisition

Scanning was conducted on a whole body 3.0T (Siemens Magnetom Trio Tim, Numaris/4Syngo MR B13; Siemens, Germany) with a standard quadrature bird-cage head coil. Participants were placed in the scanner in supine position, with their head firmly placed in a vacuum pillow to minimize head movement. Earplugs and headphones were provided to reduce the noise from the scanner, and sensors were placed on participants' left big toe and around the chest, to monitor heart rate and respiration. A volumetric anatomical MRI was performed before functional scanning, using a MP-RAGE sequence (TR/TE = 2,000/2.63 ms, 176 coronal slices perpendicular to the hippocampus, 256 × 256 acquisition matrix, voxel size = 1 mm^3, FOV = 25.6 cm). Functional imaging was performed to measure the blood oxygenation level-dependent (BOLD) effect (Ogawa et al., 1990). Scans were obtained using a single-shot T2*-weighted pulse with spiral in-out (TR/TE = 2,000/30 ms, flip angle 70°, 64 × 64 acquisition matrix, 32 coronal slices perpendicular to the hippocampus, 5 mm thick, voxel size = 3.1 × 3.1 mm, slice spacing = 0, FOV = 20 cm). To allow magnetization to reach equilibrium, stimulus presentation was delayed by 20 s at the start of each experimental run.

Data Analysis

Univariate task analysis

Data processing and analyses were performed using Analysis of Functional NeuroImages software (AFNI; Cox and Hyde, 1997). Time series data were spatially co-registered (aligned volumetrically to a reference image within the run, using the 3dvolreg program in AFNI) to correct for small head motion using a 3D Fourier transform interpolation, and the linear trends were removed. Uncorrected head motion (spikes) was identified through visual inspection and reduced through averaging the two surrounding time points. Physiological motion (respiration and heart beat) was also removed through linear filtering. The data were normalized temporally and thereafter deconvolved, using the AFNI plugin 3dDeconvolve. T-statistics contrasting autobiographical memory retrieval for each time period and odd/even processing to a baseline consisting of all non-event time points (e.g., fixation) were calculated for each participant to create statistical maps. These activation maps were then transformed into stereotaxic space (Talairach and Tournoux, 1988; Cox and Hyde, 1997) and spatially smoothed with a Gaussian filter with a full width at half maximum value of 6.0 mm to minimize individual variation of the anatomical landmarks and to increase the signal-to-noise ratio. These last two steps were performed to facilitate the subsequent group analysis, which consisted of voxelwise, mixed effects (conditions fixed, participants random), two-way ANOVAs with time period as a within-subject factor.

Voxel of Interest (VOI) Analyses

Because of the theoretical importance of hippocampal activation in this study, we further interrogated the peak activation voxels within the right and left hippocampi. These voxels were selected from the overall autobiographical memory versus odd/even contrast (and therefore unbiased with respect to time period; see Supporting Information Table 1). These included right anterior and left posterior hippocampal peaks, supplemented by two most active voxels selected in the opposite locations (left anterior; right posterior) to ensure any hemispheric differences were not in fact effects of axis location. Hence, there were four VOIs, two per hemisphere; with one being anterior and one relatively posterior (−23, −10, −8; −26, −26, −1; 24, −17, −9; 21, −30, 4). The voxels were extracted from each subject's activation map, and entered into a repeated-measures 3-way ANOVA [Time (4) × Laterality (2) × Longitudinal axis (2: ant; post)].

Multivariate Functional Connectivity Analysis

The data were also analyzed with a multivariate method, spatiotemporal partial least squares (PLS; McIntosh et al., 1996). Generally speaking, spatiotemporal PLS assesses the relationship between patterns of whole brain activation across time to one or more other variables, such as behavior, experimental conditions (task PLS), or, of main interest here, co-activation in one or more seed voxel (seed PLS). These relationships are expressed as mutually orthogonal latent variables that describe differences and similarities in activation patterns in relation to the other selected variables. Each brain voxel has a particular weight ("salience") on each latent variable, and can be positive or negative depending on how this voxel is related to the pattern described by that latent variable.

We began with a task PLS assessing the patterns of whole-brain activation in relation to overall autobiographical memory retrieval. As expected, this replicated the findings of the univariate analysis and further provided a left anterior hippocampal peak from which a seed voxel was extracted. A seed PLS was subsequently run to examine whole-brain patterns of functional connectivity to this hippocampal peak as a function of memory age. Finally, a task PLS relating patterns of brain activation to memory ratings (e.g., vividness, personal importance, etc.) was attempted, but did not result in any clear associations and is not reported here. Possibly, there was not sufficient variation in the ratings or some of them (e.g., emotionality, vividness) may have worked against each other, reducing potential patterns. The ratings are nevertheless important in characterizing the retrieved memories, and are presented along with the brain imaging data.

The functional data that had been corrected for physiological and head motion were used for the PLS analyses. They were first spatially transformed to Talairach space (Talairach and Tournoux, 1988) using adwarp in AFNI, and then into voxels of 4 × 4 × 4 mm which is the format used by PLS. Thereafter, the data were spatially smoothed with an 8-mm full-width half-maximum Gaussian filter to reduce the effect of between-subject anatomical variation. The reliability of the identified voxels is assessed with a bootstrap estimation of the salience standard errors with 500 resamplings. The voxel salience was considered reliable when the salience-to-standard error

TABLE 1.

Ratings of Re-Experiencing During Retrieval and Memory Characteristics as a Function of Age of the Memory

Rating	1 Week	1 Month	1 yr	10 yrs
In-scanner rating				
Re-experiencing: AM data[a]	5.49 (1.23)	5.93 (1.22)	5.63 (1.06)	5.08 (1.43)
Post-scanner ratings				
Visualize[b]	5.10 (0.67)	4.76 (0.82)	4.67 (0.46)	4.31 (0.93)
Positive (1–3)	1.14 (0.60)	1.33 (0.74)	1.43 (0.58)	1.43 (0.66)
Negative (1–3)	0.48 (0.40)	0.57 (0.49)	0.53 (0.31)	0.61 (0.34)
Emotional change[c]	3.17 (1.28)	3.51 (1.00)	3.85 (1.04)	4.17 (0.85)
Important then[d]	3.83 (0.72)	4.34 (0.66)	4.67 (0.67)	4.97 (0.62)
Important now	2.34 (0.54)	2.52 (0.53)	2.60 (0.86)	2.71 (0.80)
Often think[e]	3.37 (1.77)	3.45 (1.88)	2.76 (1.17)	2.11 (1.08)
Average post-scanner ratings	2.78 (0.47)	2.92 (0.43)	2.93 (0.41)	2.90 (0.53)

All ratings were done on scales 1–6 with 6 being maximum, except re-experiencing which was 1–8, positive and negative, which were 1–3, and often think which was 0–11, going from never to constantly. Indicated differences between time periods were significant at $P < 0.05$, except important then, 1 w > 1 yr–10 yrs, which were significant at $P \leq 0.001$.

[a]1 w < 1 m; 1 m–1 yr > 10 yrs.

[b]1 w > 1 m–10 yrs.

[c]1 w < 1 yr–10 yrs; 1 m < 10 yrs.

[d]1 w < 1 m–10 yrs; 1 m < 10 yrs.

[e]1 w–1 yr > 10 yrs.

ratio, corresponding to a z score, was above 3.3 ($P < 0.001$). No correction for multiple comparisons is required as image-wide statistical assessment is performed in a single analytic step. The reliability of the extracted latent variables is assessed through a permutation test, which was also run 500 times. The brain response is described across the event at different lags that each last 1 TR. In our case, there were 8 lags, each lasting 2 s, beginning at 4 s post stimulus onset.

RESULTS

Behavioral Findings

There was an overall effect of time period on the amount of re-experiencing as rated following each memory in the scanner (as a within-subject effect, and as a quadratic but not linear within-subject contrast), $F_{(3,\ 33)} = 4.76$; $P = 0.007$, due to significant differences between time periods: 1 w < 1 m > 10 yrs, and 1 yr > 10 yrs. Re-experiencing of potential extraneous memories during the odd/even task was significantly lower than that during autobiographical memory retrieval at all time periods (Ps $< 0.000-0.01$), showing that this manipulation was effective in having participants not engage in autobiographical memory retrieval during the control task [through runs 1 to 4 the M and (SD) of re-experiencing during odd/even were 2.81 (1.34); 3.40 (1.26); 3.37 (1.28); 3.36 (1.17)]. For the post-scanner measures, there were main effects of time for the measures visualize [$F_{(3,\ 27)} = 3.57$, $P < 0.05$], emotional change [$F_{(3,\ 27)} = 5.93$, $P < 0.005$], important then [$F_{(3,\ 27)} = 13.2$, $P < 0.0001$], and often think [$F_{(3,\ 27)} = 4.38$, $P < 0.05$]. In general (see Table 1 notes for specifics), the extent to which participants could visualize the event and how often they thought of it decreased with remoteness, whereas emotional change and importance of the event when it happened increased with remoteness.

Functional Neuroimaging Findings

Overall autobiographical memory activity

In comparison to the odd/even task, autobiographical memory retrieval (regardless of time period) activated the thalamus, prefrontal areas, anterior and posterior cingulate, middle temporal gyrus, the hippocampus and parahippocampus, precuneus and cerebellum (see Supporting Information Table 1). Most activations were bilateral, except that of the lingual gyrus which was left-lateralized. This pattern corresponds to the core network of autobiographical memory activation as reported in previous studies (Maguire, 2001; Svoboda et al., 2006). Deactivations (odd/even > autobiographical memory retrieval) were observed bilaterally in the pre- and post-central gyri and the inferior parietal lobule, and unilaterally in the left middle occipital/inferior temporal gyrus, the right middle temporal gyrus, and the right claustrum.

Autobiographical memory activation as a function of time period

A modulation of brain activity as a function of memory remoteness would be reflected in a main effect of time period. Such an effect was indeed observed bilaterally in the cuneus and posterior cingulate, unilaterally in the left precuneus, the right anterior cingulate, and the left cerebellar tonsils (ts: 9.7–16.9).

Direct comparisons contrasting all time periods (see Table 2) showed that recency was most frequently associated with the precuneus bilaterally, with greater activation in 1 w versus 1 yr,

TABLE 2.

Brain Areas Differing in Activity Between Time Periods (P < 0.001)

Region	Cluster size (ml)	BA	X	Y	Z	t
1 w < 1 m						
R med fro gyr/ant cing	183	32	18	9	47	6.64
R parahippocampus/hippocampus*	125	30	25	−38	−1	5.79
1 w > 1 yr						
R inf par lob	202	40	48	−43	29	9.40
R precuneus	1,330	7	6	−69	38	7.23
L precuneus	347	7	−13	−73	35	7.16
1 w > 10 yrs						
BL cingulate gyr	457	23	−8	−22	31	12.44
R thal	199		23	−27	0	8.16
R precuneus	672	7	6	−68	38	5.80
1 m > 1 yr						
R paracentral lobule	295	4	8	−39	67	4.73
L precuneus	165	7	−22	−58	49	6.10
L precuneus	154	7	−24	−65	28	5.23
R precuneus	299	31	12	−66	23	6.45
1 m > 10 yrs						
L fusiform	197	37	−38	−53	−6	6.07
R cing gyr	234	31	13	−55	27	6.52
R midd temp	166	19	34	−60	11	5.45
R midd temp gyr	330	37	48	−66	7	6.55
L cerebellar tonsil	599		−5	−47	−37	7.00
L cerebellum	331		−19	−50	−37	5.83
R declive	200		19	−55	−14	6.40
1 yr > 10 yrs						
R cing gyr	218		16	−3	27	6.60
R parahippocampus*	99	35	16	−23	−17	5.27
1 yr < 10 yrs						
L inf par lobule	185	40	−42	−61	42	5.56

Coordinates are in standardized space of Talairach and Tournoux (1988). *T* values > 4.8 are significant at $P = 0.005$; *T* values > 5.8 at $P = 0.0001$. Positive *t* values suggest greater activity for the first of the two compared time periods, and negative *t* values suggest greater activity for the second.

BA, Brodmann area; L, left; R, right; med, medial; fro, frontal; gyr, gyrus; ant, anterior; cing, cingulate; inf, inferior; par, parietal; BL, bilateral; thal, thalamus; midd, middle; temp, temporal.

*Even though cluster threshold is 150 ml, these areas are included since the hippocampal region is a primary focus in this study.

1 w versus 10 yrs, 1 m versus 1 yr. Additional areas showing "recency effects" were the posterior cingulate gyrus (1 w > 10 yrs bilaterally; 1 m > 10 yrs in the right), inferior parietal lobe (1 w > 1 yr in the right; 1 yr > 10 yrs in the left), the right paracentral lobule (1 m > 1 yr), the right middle temporal gyrus and the cerebellum (1 m > 10 yrs). The only exceptions to the overall finding of greater activation with recency were in the right medial frontal gyrus, which was more activated in 1 m than in 1 w, accompanied by the right posterior hippocampal cluster, which fell short of the cluster size threshold. Also, the left inferior parietal gyrus was more activated in 1 yr than in 10 yrs.

Hippocampal activity as a function of time period (VOI analyses)

Hippocampal activity was significantly greater in the memory condition than in the control condition across all VOI's, as indicated by analysis of 95% confidence intervals around each VOI (see Supporting Information Table 2). Variation in hippocampal activity across time period, laterality, and the anterior–posterior axis was assessed by a three-way repeated measures ANOVA. There were main effects of Laterality (left > right) and Axis (anterior > posterior), and interactions between Time and Axis, and Laterality and Axis. As can be seen in Figure 1, the Time × Axis interaction was due to increased activation with remoteness in the anterior hippocampus bilaterally, except for Time 4, and slightly decreasing activation with remoteness in the posterior hippocampus. In the anterior hippocampus, the left hemisphere showed significant differences between time periods: 1 w < 1 m = 1 yr (Ps ≤ 0.05), and the right between time periods: 1 w < 1 yr > 10 yrs (Ps < 0.05). In the posterior hippocampus, there was a slight but non-significant decrease in the left hemisphere ($P = 0.09$), and a significant decrease in the right hemisphere [$F_{(1, 11)} = 6.7$, $P < 0.05$], although none of the pair-wise comparisons between time periods was significant, suggesting a weak effect of time overall.

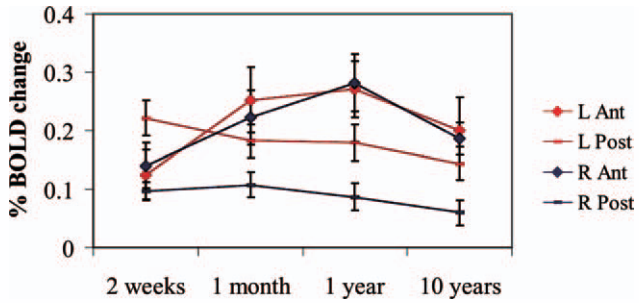

FIGURE 1. BOLD % change (mean and SD) in the hippocampus during autobiographical memory retrieval as compared to the odd/even task, as a function of memory age and hippocampal location. L, Left; Ant, Anterior; Post, Posterior; R, Right. Activity was strikingly similar within location across hemispheres, whereas it differed along the hippocampal axis within the same hemisphere. In the anterior hippocampus, most significantly in the right, activity increased somewhat for memories up to 1 yr back and then decreased, whereas there were no significant differences in the posterior hippocampus between time periods.

The Laterality × Axis interaction was due to more activity in the left than the right posterior hippocampus [$F_{(1,\ 11)} = 15.7$, $P < 0.005$], but similar activity in the left and right anterior hippocampus ($F < 1$). Overall, there was a striking resemblance in activation patterns across hemispheres, suggesting a more crucial role of anterior–posterior axis location than laterality in terms of memory remoteness.

Functional connectivity of the hippocampus during autobiographical memory retrieval (PLS)

A task PLS yielded a single latent variable that distinguished between autobiographical memory retrieval across all time periods and the odd/even task ($P < 0.0001$; it accounted for 68% of the cross-correlation variance). This pattern corresponded to the main effect of autobiographical memory retrieval reported above for the univariate analysis. There were no further latent variables. Our main goal in applying PLS was to examine differences in hippocampal-neocortical coactivation, functional connectivity, as a function of time period, which may be independent from level of hippocampal activity across time periods. The most reliable active hippocampal voxel derived from the task PLS was noted in the left hemisphere (−28, −12, −16; bootstrap ratio: −7.2), in the anterior sector of the hippocampus. This served as the seed voxel (see Fig. 2A) in the seed PLS, assessing functional connectivity between this hippocampal voxel and the rest of the brain.

The first significant latent variable showed overall similarities between time periods ($P < 0.0001$; 43% of cross-correlation variance), including functional connections between the hippocampal voxel and various areas of the autobiographical memory network, such as mainly left prefrontal structures (e.g., insula, middle frontal cortex) and mediotemporal areas (hippocampus, parahippocampus). Of greater theoretical interest, an additional significant latent variable showed differential connectivity patterns across the 4 time periods of this voxel, dissociating time periods 1–3 (1 w – 1 yr) and time period 4 (10 yrs; $P = 0.006$; 6% of cross-correlation variance). Figure 2 shows the correlations between activity in the seed and the rest of the brain during retrieval from the 4 time periods as a function of lag (i.e., scanning epoch), with 95% CIs yielded by the bootstrap procedure. There were significant associations between time period and patterns of hippocampal connectivity, but these differed according to lag. There were no significant correlations at lag 3 (6 s), so these data are not reported. For time periods

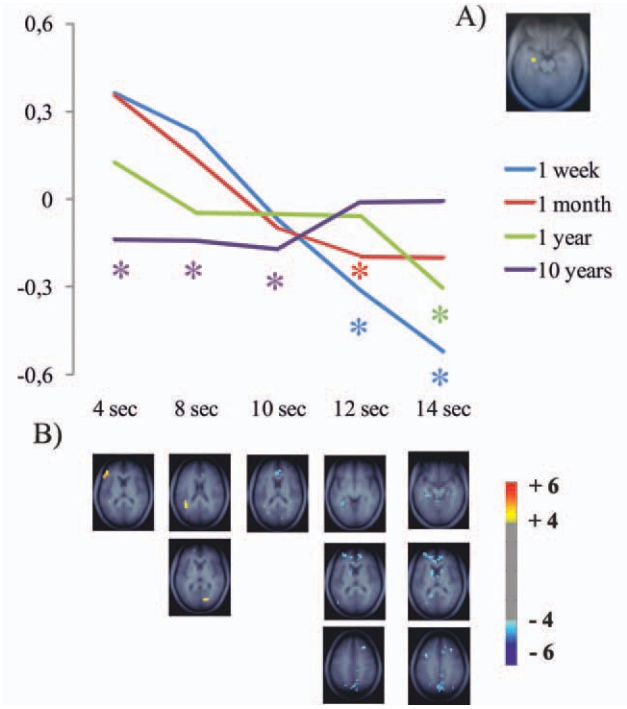

FIGURE 2. Results of seed PLS indicating coactivations between (A) the left anterior hippocampal seed and (B) the rest of the brain as a function of memory age. The line figure indicates correlations between seed activity and activity in other brain regions across lags (time in seconds) as a function of memory age. The correlations are represented on brain bootstrap plots (below), with yellow voxels indicating positive bootstrap ratios, and blue voxels indicating negative bootstrap ratios. The right side of the brain images represents the right hemisphere. The sign of the correlation or bootstrap ratio alone is arbitrary; the direction of the association between activity in the seed voxel and other regions is determined by the correspondence of the sign of the correlation with the sign of the bootstrap ratio. At 4 and 8 s, there was a negative coactivation (i.e., negative correlation; positive bootstrap ratios) between the left anterior hippocampus and the left inferior frontal gyrus, the left superior temporal gyrus and the right cuneus for the 10 yrs condition. This coactivation was positive for the more recent time periods, but it did not reach significance. At 10 s for the 10 yrs condition, there was a positive coactivation (i.e., negative correlation, negative bootstrap ratios) with the anterior cingulate bilaterally. During retrieval of the more recent memories, the left hippocampus showed later (12–14 s) coactivations with prefrontal areas, the precuneus, and caudate (see Table 3 for a summary of all areas). *Significant correlation where the 95% CI does not include 0.

TABLE 3.

Brain Structures Functionally Connected to the Left Hippocampal Seed as a Function of Lag and Bootstrap Ratio Direction

Brain structure	Number of voxels	*X*	*Y*	*Z*	Bootstrap ratio
Lag 2: 4 s: positive ratio					
L inferior frontal gyrus	43	−48	23	14	6.02
Lag 4: 8 s: positive ratio					
L superior temporal gyrus	12	−39	−47	18	4.02
R cuneus	18	13	−73	8	4.44
Lag 5: 10 s: negative ratio					
Anterior cingulate (BL)	10	2	34	12	−4.38
Lag 6: 12 s: negative ratio					
R precuneus, BA 7	11	6	−76	39	−5.63
L middle frontal gyrus, BA 8	14	−32	27	37	−4.89
R precuneus, BA 7	20	10	−64	37	−4.81
R cingulate gyrus, BA 31	13	6	−28	40	−4.76
L precuneus, BA 31	12	−24	−74	23	−4.75
R medial frontal gyrus, BA 9	21	5	50	15	−4.65
L superior/middle frontal gyrus, BA 10	21	−27	47	15	−4.55
R anterior cingulate, BA 32	15	3	37	14	−4.46
Lag 7: 14 s: negative ratio					
L hippocampus	22	−33	−24	−8	−6.03
L superior/medial frontal gyrus, BA 10	103	−18	49	2	−5.98
R precuneus, BA 7	77	6	−64	35	−5.57
L precuneus	35	−26	−57	30	−5.17
R caudate body	13	7	16	11	−4.87
L caudate body	24	−10	−0	16	−4.76
R superior frontal gyrus	48	19	11	48	−4.63

Coordinates are reported in Talairach space.
The bootstrap ratio is the parameter estimate for that voxel over its standard error and is proportional to a *z* score.
L, left; R, right; BA, Brodmann area; BL, bilateral.

1–3 (1 w to 1 yr), at 12–14 s into retrieval, the hippocampus was functionally connected to several midline posterior and frontal structures (see negative saliences in lags 6 and 7 in Table 3/ blue areas in Fig. 2B), including the anterior and posterior cingulate, precuneus, and anteromedial prefrontal regions as well as the bilateral caudate and the hippocampus itself. This pattern was not observed for time period 4 (10 yrs), where hippocampal activation was negatively correlated with activation in the left inferior frontal gyrus, the left superior temporal gyrus, and the right cuneus at early lags (4–8 s). At 10 s, the pattern for this time period shifted such that there was a positive hippocampal/anterior cingulate coactivation. These results suggest that the hippocampus has different functional connections when retrieving events from 1 week and up to 1 yr ago as compared to 10 yrs ago.

DISCUSSION

This study examined the neural correlates of retrieving autobiographical memories of varying remoteness, including a finer grained analysis of recent memories than in previous studies. We found that, in addition to activation of the autobiographical memory network for all time periods, the hippocampus was activated bilaterally regardless of memory age. A dissociation was observed between the anterior and posterior parts of the hippocampus bilaterally, with activity in the anterior part increasing for memories up to 1 yr old, and then decreasing (but not below the level of the 1-week old memories), and activity in the posterior hippocampus showing a slight but non-significant decrease over time. This dissociation along the hippocampal axis was strikingly similar across hemispheres. Finally, the hippocampus showed a different pattern of coactivation with other brain areas when retrieving remote (10 yrs) as compared to more recent autobiographical memories (1 week to 1 yr back).

This study extends previous findings of hippocampal activation regardless of memory age (Ryan et al., 2001; Gilboa et al., 2004; Piolino et al., 2004; Rekkas and Constable, 2005; Steinvorth et al., 2006; Viard et al., 2007) to a fuller autobiographical time course extending from the very recent past (1 week) to the remote past (10 yrs). Previous research suggests hippocampal activation can be expected during memories this recent (2 weeks; Hassabis et al., 2007). The only other study comparing memories as recent as ours to remote memories (2.5 days old

vs. 8 yrs old; Rekkas and Constable, 2005) observed left-lateralized hippocampal activation for the recent memories, and bilateral activation for the remote. This was interpreted as support of Multiple Trace Theory, since more remote memories should have more traces and thus provoke a larger activation. Variation in laterality has been observed in a few studies with the left hippocampus active throughout and the right varying in activity as a function of memory age (Maguire and Frith, 2003; Addis et al., 2004b; Viard et al., 2007). We did not observe such a laterality effect, but instead observed a bilateral activation across time-periods with an anterior–posterior differentiation of activation intensity within the hippocampus that was similar across hemispheres.

A functional differentiation between the anterior and posterior hippocampus has previously been suggested using laboratory materials as a function of stimulus novelty (Strange et al., 1999; Poppenk et al., 2010), stimulus material/modality (Small et al., 2001), memory function (Moser and Moser, 1998), and memory process (Lepage et al., 1998). Similarly, for autobiographical memory, we found that both sectors are activated during retrieval, but there may be differences in the characteristics of that retrieval that engage them differently. The anterior part showed an increase in activity with remoteness up to 1 yr back in time, which thereafter decreased (although not below the level of the 1-week-old memories). This finding corresponds to the sensitivity of the anterior, but not posterior, hippocampus to reduced activation with repetition of autobiographical memories that are matched for age (Svoboda and Levine, 2009). Similarly, Gilboa and colleagues (2004) found that hippocampal activation associated with recent memories (up to 5 yrs old;1.75 $\pm$ 1.61 on average) was clustered in the anterior sector of the hippocampus, whereas hippocampal activation associated with remote memories (mean years of age = 32.3) was distributed throughout the anterior-posterior axis. Our results of anterior hippocampal activity increasing for up to 1-yr-old memories and then decreasing somewhat for 10-yr-old memories are consistent with these findings.

For very recent memories, our findings also correspond to those of Rekkas and Constable (2005), who observed left posterior hippocampal activity (-22, -24, -9) for 2.5 days old memories, as we found greater posterior than anterior activity for the 1 week old memories in the left hemisphere. For more remote memories (10 yrs) we observed, on average, greater anterior than posterior activity, although posterior activity was also present. This is in accordance with Rekkas and Constable (2005) where remote memories (from childhood and teenage years) activated the anterior hippocampus bilaterally (y: -13/-12). These findings may, however, appear contradictory to Gilboa et al. (2004) who suggested anterior activation for recent memories, but what they call "recent" (up to 5 yrs) partly overlap with what we call "remote" (10 yrs). It is in general difficult to compare these studies and ours to each other as they differ on several dimensions such as memory age, retrieval cues and duration, control conditions, and pre-scan procedures. What can be concluded, nevertheless, is that the hippocampus is activated during retrieval from all time periods, but that there may be regional variation as a function of memory age, and, as with retrieval of memories for laboratory materials, with other aspects of the retrieval process and the memory that is retrieved.

Although many functional neuroimaging studies, including this one, have shown similarity in hippocampal activation associated with episodic autobiographical memory across recent and remote time periods, functional neuroimaging studies can only be regarded as complementary to lesion studies concerning the necessity of a given region to a given function. On the other hand, a human lesion study cannot address questions concerning real-time functional connectivity that also is crucial to the understanding of autobiographical memory retrieval. The pattern of hippocampal engagement with neocortical elements of the autobiographical memory network likely modulates the phenomenological experience associated with retrieving an autobiographical memory (cf. Addis et al., 2004b; Viard et al., 2010). Consistent with Multiple Trace Theory, we found that both the hippocampus and the autobiographical memory network were active regardless of memory age, but the nature of the hippocampal-neocortical interactions was not invariant across time periods. Autobiographical memory retrieval is extended over time and consists of retrieving the memory and then elaborating on it. Generally, retrieval is initially associated with mainly (left) frontal activity and then with posterior temporal and occipital activity during elaboration and maintenance of the memory (Conway et al., 2001). We found that during retrieval of memories from 1 w to 1 yr old, the hippocampus was coactivated with both midline frontal and posterior elements of the autobiographical memory network late into the retrieval process (12–14 s). Similar areas (i.e., precuneus, left prefrontal) peaked around 12 s in an autobiographical memory retrieval study of Daselaar et al. (2008) during the elaboration phase of the memory, and it is possible that hippocampal coactivation with these areas reflects a higher extent of elaboration and reliving of the more recent autobiographical memories than of the most remote memories. By contrast, for the 10 yrs old memories, the hippocampus showed negative interaction with the left inferior frontal, left superior temporal, and right precuneus at the early epochs, followed by positive coactivation with the anterior cingulate, perhaps reflecting an initial absence of memory recovery, and thereafter increased retrieval effort (Schacter et al., 1996) and reliving during the elaboration of the memory (Daselaar et al., 2008). Negative functional connectivity between the hippocampus and areas of the autobiographical memory network has been observed in previous research where memories older than 1 yr were used (Addis et al., 2004a). The dissociation in functional connectivity of the hippocampus between the most remote time period and the others was paralleled by decreasing visualizability and re-experiencing of autobiographical memories over time. This is in line with Viard et al. (2010) who observed more interaction between medial temporal lobe regions and neocortical areas during retrieval of currently emotional memories from intermediate time periods, than during less emotional memories from the most recent and most remote time periods.

The functional connectivity of the hippocampus in relation to autobiographical memory remoteness, and changes in the

quality of those memories with time and other factors, provide new information about the relation of memory age to hippocampal-neocortical interactions. Evidence of continued connectivity between the hippocampus and neocortical structures across time argues against the Standard Model of Consolidation which predicts reduced connectivity with increasing memory age. Although the sustained connectivity with time is consistent with Multiple Trace Theory, variations in the pattern of connectivity indicate that the process of retrieving remote memories involves hippocampal-neocortical interactions that are more complex than had previously been observed. Whereas functional connectivity between the hippocampus and cortical areas for the more recent memories was positive throughout the retrieval period, the connectivity for remote memories changed direction, from negative at the beginning, to positive at the end. A possible interpretation of these findings is that for recent memories, the cue (i.e., event title) activates the hippocampally mediated memory from the very beginning, whereas for the more remote memories, the cue may not be as effective immediately; first, it may be necessary to determine precisely which event the cue specifies without interference from hippocampally-mediated memories. Once that has been settled, the process proceeds in a similar fashion as for recent events. Further studies are needed to test this interpretation and, more broadly, to determine whether the differences in pattern of connectivity observed in this study are a reliable distinguishing feature between recent and remote memories.

Turning to other regions, the autobiographical memory network (Maguire, 2001; Svoboda et al., 2006) was activated throughout all time periods, although there was some variation in areas and extent. Midline posterior regions, including the precuneus and posterior cingulate, were more activated with recent memories. A positive association between precuneus activation and recency is in line with earlier research (Niki and Luo, 2002; Rekkas and Constable, 2005; Viard et al., 2007). This structure has been associated with imagery (Fletcher et al., 1995), vivid and context-rich retrieval, re-experiencing (Gilboa et al., 2004) and retrieval success (Kapur et al., 1995), all of which are likely higher for recent memories than for remote ones. The posterior cingulate has previously been associated with recency (Niki and Luo, 2002; Piefke et al., 2003), and is thought to be involved in integrating self-referential stimuli into a person's autobiographical context (Northoff and Bermpohl, 2004). Less frequently, recency effects were also observed in the inferior parietal lobe, the right paracentral lobule, the right middle temporal gyrus and the cerebellum. The right medial frontal/paracingulate region was more active for 1-month-old memories as compared to 1-week old memories. The 1-month old memories were personally salient, as reflected in ratings of re-experiencing and importance at the time of the event. This finding is difficult to accommodate within the autobiographical memory literature as this region is not strongly associated with autobiographical memory importance or vividness and is in fact more strongly activated in conjunction with laboratory than autobiographical materials (Cabeza et al., 2004).

The memory stimulus generation in this study consisted of participants generating events 2 days before scanning rather than only once in the scanner, which may have contaminated recollection during scanning. Earlier functional neuroimaging studies, however, suggest that hippocampal activation associated with autobiographical stimuli holds in spite of pre-scan rehearsal (Maguire et al., 2001; Ryan et al., 2001; Levine and Svoboda, 2009). The same holds for re-encoding in retrieval studies. Each time a memory is retrieved it may also be re-encoded, which would give rise to encoding-related hippocampal activity regardless of memory age. Confronting similar problems, Gilboa et al. (2004) showed that such effects are small relative to retrieval effects. Likewise, in our study, if re-encoding accounted for the observed hippocampal activation that accompanied retrieval of recent and remote memories, no differences between them should have emerged since re-encoding would be quite similar for all events.

Our data indicate that the hippocampus is active during episodic autobiographical memory retrieval for events occurring one week and up to 10 yrs ago. Although both the hippocampus and the rest of the autobiographical memory network are active across all time periods when considered in isolation, the way different parts of the network interact with one another differs as a function of memory remoteness and variations in the quality of those memories with time. Studying the hippocampus alone is an initial step in determining how memory is consolidated in the brain, but exploring its interactions with the rest of the brain is the next necessary step to understand fully a memory's journey from inception to retrieval.

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