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# Different neural routes to autobiographical memory recall in healthy people and individuals with left medial temporal lobe epilepsy

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ABSTRACT

Individuals with medial temporal lobe epilepsy (mTLE) are poor at recalling vivid details from autobiographical memories (AM), instead retrieving gist-like schematic memories. Recent research has suggested that this impoverished recall in comparison to controls may reflect (1) differential engagement of anterior vs posterior regions of the hippocampus (HC) and/or (2) differences between the engagement of the HC vs the ventromedial prefrontal cortex (vmPFC). Here we examined these hypotheses by comparing connectivity amongst hippocampal regions and between vmPFC and other brain regions during construction (retrieval of a particular event) vs elaboration (retrieval of perceptual detail) phases of AM recall in 12 individuals with left mTLE and 12 matched controls. Whereas functional connectivity amongst hippocampal regions changed from AM construction to elaboration in controls, the pattern of intra-hippocampal connectivity was unvarying in patients. Furthermore, patterns of connectivity from the vmPFC differed between phases in distinct ways in the two groups of participants. In patients, vmPFC activation was correlated with other prefrontal and lateral temporal cortices during construction and with visual-perceptual cortices during elaboration. While controls did not show a difference in whole-brain connectivity, they did uniquely show a dynamic shift from vmPFC connectivity to anterior HC during construction and to posterior HC during elaboration. Together, these findings suggest that impoverished AM recall in mTLE is a consequence of reduced activation and flexibility of bilateral hippocampal networks and greater reliance on neocortical contributions to memory retrieval.

## 1. Introduction

Recalling vivid, detail-rich events from one's own past (episodic autobiographical memory, AM) can encompass two distinct retrieval stages, first searching for and accessing specific life episodes (the construction stage), and second recollecting them by reassembling vivid episodic elements (the elaboration stage, Conway, 2009; Conway and Pleydell-Pearce, 2000). These complex mental processes appear to rely critically on the integrity of both hippocampi along their long-axis and their interhemispheric connectivity, together forming a critical hub to aid the coordination of transient neural networks underlying both AM phases (McCormick et al., 2015; St Jacques et al., 2011). In earlier work we found that the left anterior hippocampus showed stronger functional connectivity to the right anterior hippocampus (and a fronto-temporal network) during AM construction, and to both posterior hippocampi (and a wide-spread posterior neocortical network) during AM elaboration (McCormick et al., 2015). These findings agree with recent proposals that the networks including the anterior hippocampi are, amongst other functions, involved in event construction and those associated with the posterior segments in event elaboration (Poppenk et al., 2013; Sheldon and Levine, 2016; Zeidman and Maguire, 2016; but see Dede et al., 2016; Kirwan et al., 2008; Squire et al., 2010 for an alternative view that the hippocampus is not critical for retrieval of remote memories).

However, little is known about how these dynamic neural interactions are affected by damage to the hippocampus, such as is observed in patients with unilateral medial temporal lobe epilepsy (mTLE). Whereas unilateral mTLE typically does not lead to global AM amnesia, there is a clear difference in the phenomenological quality of AMs described by patients with mTLE and healthy controls (Addis et al.,

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2007a; St-Laurent et al., 2009, 2011; Viskontas et al., 2000; Voltzenlogel et al., 2006). That is, patients with mTLE have relatively little difficulty recalling the general story line or gist of an AM (potentially intact event construction), but they have great difficulty recalling specific episodic elements of an AM (potentially impaired event elaboration). Interestingly, this impoverished AM retrieval is commonly seen in both left and right hemisphere cases of mTLE (Addis et al., 2007a; St-Laurent et al., 2014, 2011; Viskontas et al., 2000), further emphasizing the above-mentioned importance of bilateral hippocampal integrity for specific, detail-rich AM retrieval. Together, these behavioural studies suggest that individuals with unilateral mTLE can construct the main organization of an AM (Conway, 2009; Conway and Pleydell-Pearce, 2000), but they are less able to retrieve the episodic elements embedded in this organizational structure as do healthy controls in the elaboration phase of AM retrieval. Because of the phenomenological dissociation between retrieval of gist or schematic AM information but not episodic AM information, these patients offer a unique opportunity to study neural networks separating these cognitive functions.

To our knowledge, no neuroimaging study has focussed on neural differences in AM construction and elaboration in patients with mTLE. In several studies that have averaged across the entire 10–20 s retrieval epoch, the epileptic and the healthy contralateral MTL typically show reduced activity (Addis et al., 2007a; McAndrews, 2012; St-Laurent et al., 2016) and reduced connectivity with other regions of the AM network (Addis et al., 2007a). Here, the damaged hippocampus appears disengaged from the broader AM network and we suspect it can no longer support the flexible intra- and interhippocampal connectivity that is required to coordinate transient neural networks underlying AM construction and elaboration. In agreement with this hypothesis, markers of the tissues' capability to form transient networks and respond to current task demands or process-specific alliances (Cabeza and Moscovitch, 2013; Moscovitch, 1992; Moscovitch et al., 2016), such as signal complexity and variability (Deco et al., 2011; McIntosh et al., 2010; Misic et al., 2010) are reduced in the affected hippocampus in patients with mTLE (Protzner et al., 2013, 2010). Here, we test the hypothesis that unilateral mTLE leads to reduced flexibility of intra- and inter-hippocampal functional connectivity and thus a diminished capacity for forming alliances with other brain regions to support shifting between construction and elaboration stages.

Hence, the bilateral hippocampal network that is so crucial to episodic AM retrieval in healthy controls may no longer be the critical hub for AM retrieval in individuals with mTLE. If true, then which brain region(s) supports the observed impoverished, schematic AM retrieval of these patients? Here, a candidate brain region is the ventromedial prefrontal cortex (vmPFC) which has strong structural and functional connections to the hippocampus (Andrews-Hanna et al., 2010; Catani et al., 2013, 2012; Eichenbaum, 2017), belongs to the primary AM retrieval network (Svoboda et al., 2006) and has been implicated as a key region for the re-organization or transformation of episodic, detail-rich memories into semantic, gist-like schema (Ghosh and Gilboa, 2013; Moscovitch et al., 2016; Winocur and Moscovitch, 2011; Winocur et al., 2010). For example, arguing for a potential role in supporting gist-like AM retrieval, the vmPFC seems to support general more than specific AMs (Addis et al., 2004), more remote than recent AMs (Bonnici et al., 2012; Bonnici and Maguire, 2017), and more impoverished AMs or narrative construction of patients with MTL damage than detailed AMs of healthy controls (Addis et al., 2007a; Maguire et al., 2001; Rabin et al., 2016; Keven et al., 2017). Recognizing that in the healthy brain, both vmPFC and MTL may play important roles in retrieving gist-like and episodically rich memories, respectively, we hypothesized that the vmPFC may be more critical in individuals with mTLE and that vmPFC connectivity might illustrate different neural networks underlying AM construction and elaboration in them.

**Table 1**
Demographics.

| | Left mTLE | Controls |
|---|---|---|
| Group size | *(n = 12)* | *(n = 12)* |
| Sex, male/female | 6/6 | 8/4 |
| Handedness (right/left) | 11/1 | 10/2 |
| Age at scan, mean (SD) | 39.6 (11.4) | 39.9 (13.1) |
| Education years, mean (SD) | 15.2 (2.7) | 15.4 (5.2) |
| *Clinical parameters* | | |
| MTS (yes/no) | 7/5 | n.a. |
| Other MRI lesions (yes/no)[a] | 2/10 | |
| Age of onset, mean (SD) | 20.3 (15.9) | n.a. |
| Epilepsy duration | 20.9 (17.8) | n.a. |

MTS = Medial temporal lobe sclerosis.
[a] 1: single heterotopion in the left occipital lobe, 2: left temporal dysembryoplastic neuroepithelial tumor (DNET).

## 2. Material and methods

### 2.1. Participants

We included 12 individuals with left mTLE (L-mTLE) and 12 matched healthy controls in this study who gave written informed consent in accordance with a research protocol approved by the University Health Network Ethics Board. We focussed our study here on individuals with left mTLE, since our previous study (McCormick et al., 2015) indicated an important role of the left hippocampus in the early stages of AM retrieval. Each patient had a diagnosis of unilateral L-mTLE based on localization of seizure focus to the left MTL during extended video-EEG monitoring at our inpatient epilepsy monitoring unit. The presence of medial temporal lobe sclerosis (MTS) was determined by a neuroradiologist (see Table 1 for demographic and clinical information). The control participants were matched in age, sex, and education years; note that the current controls are a subset of the participants published in McCormick et al., 2015 that best matched the current patient cohort on these characteristics. All participants were fluent in English and had no history of significant psychiatric or neurologic disorder other than epilepsy in the patient group.

### 2.2. Autobiographical memory retrieval task

The experimental procedure was identical to our previously published paradigm (McCormick et al., 2015).

Before fMRI scanning, the experimental task was explained to the participants and they completed six practice trials of each condition. Then, the contents of these practice AMs were probed to confirm that participants understood the instructions (i.e., they could differentiate between the construction and elaboration phase and retrieved events were specific in time and place). Extra care was given to ensure that patients with L-mTLE understood the task properly by providing additional examples of AM construction and elaboration.

The experimental task consisted of two conditions, AM retrieval and math, with 22 trials of each condition. Each trial was 16.5 s long and trials were presented in a randomized fashion, with a jittered inter-stimulus interval (ISI) of 0.5, 1.0, or 1.5 s. During the AM retrieval condition, participants were visually presented with an event cue such as "a party". Then, the participants were asked to retrieve an event specific in time and place from their personal past that was coherent with the cue. Once they had retrieved a specific incident, they were instructed to press a response button. During the remaining seconds of the trial, they were asked to elaborate on the details of that particular memory, and to mentally relive the event in as much detail as possible. The button press indicated the end of the construction phase and the beginning of the elaboration phase (see Addis et al., 2007b for a similar paradigm). To mirror the AM condition, during the math condition,

participants were asked to covertly solve a simple math problem, for example 19 + 4. Once they had the solution in mind, they were instructed to press a response button. During the remaining seconds of the trial, participants were asked to mentally add three's to the solution (e.g. 23 + 3 + 3…). At the end of each trial, participants were asked to rate the memory as vivid or faint and the math problem as easy or hard. Due to technical difficulties with the button-box, the responses of two patients with L-mTLE and one control participant were not recorded during the task, but in a debriefing after the scan they confirmed that they followed the instructions throughout the task and we, therefore, included their fMRI data in the analyses.

### 2.3. MRI data acquisition and processing

Anatomical and functional data were acquired on a 3-T Sigma MR System (GE Medical Systems, Milwaukee). Anatomical scans, a T1-weighted sequence, were acquired first (120 slices, FOV = 220 mm, slice thickness = 1 mm, 0 gap, 256 × 256 matrix, resulting in a voxel size of 0.9 × 0.9 × 1.0). The functional scans were acquired in an interleaved order (EPI, TR = 2 s; 30–32 slices to cover the whole brain, FOV = 240 mm, slice thickness = 5 mm, 0 gap, 64 × 64 matrix, resulting in a voxel size of 3.75 × 3.75 × 5.0). Functional images were taken in an oblique orientation with each slice being perpendicular to the long-axis of the hippocampus to maximise the signal to noise ratio from the MTL. We acquired two functional sessions with 190 frames each. The first three frames of each session were dropped for signal equilibrium. The fMRI protocol also included two other experimental tasks (one before and one following the current AM task) that are not part of the current analysis.

All pre-processing of imaging data was performed using SPM8 (Statistical Parametric Mapping 8; Wellcome Department of Imaging Neuroscience, London). Functional images were co-registered to the subject's anatomical image, and temporally realigned and unwarped. The subject's anatomical image was segmented and spatially normalized to the T1-weighted Montreal Neurological Institute (MNI) template and the normalization parameters were then written to the functional data. Finally, fMRI data were smoothed using a Gaussian kernel of 8 mm full width half maximum (FWHM). SPM motion parameters were inspected for outliers (motion > 4 mm in any direction) but no subjects had to be excluded from the analysis. In addition, we visually inspected the overlap between the normalized patients' fMRI images and the SPM template to ensure that especially the hippocampi aligned properly.

### 2.4. Data analysis

#### 2.4.1. Behavioural analysis

Separate non-parametric Kruskal-Wallis analyses were used to assess: 1. Group differences in the total number of button presses that separated the AM construction from the elaboration phase, 2. Group differences in reaction times following the event cue (signalling the end of the AM construction and the beginning of the AM elaboration stage), and 3. Group differences in the vividness rating following the elaboration stage. Main effects and interaction effects were evaluated first, and a two-sided p-value of less than 0.05 was used to reject the null hypothesis in each case. Where there were significant main or interaction effects, post-hoc comparisons between groups and reaction times or vividness ratings were conducted using Sidak's multiple comparison tests, again using a two-sided p-value of less than 0.05 statistically significant.

#### 2.4.2. Univariate fMRI contrasts

As a first pass at the data, we conducted standard univariate contrasts to examine within-and between-group differences in activation levels during AM retrieval. Both AM and math conditions were modeled as mini blocks of 16 s duration. For each participant, the contrast AM activation > math activation was analysed as a fixed-effects model. The resulting contrast images were taken to the second level for each group separately and analysed as a random-effects one sample *t*-test in SPM8. On a whole brain level, we considered voxel cluster extending 20 adjacent voxels and the peak p-value less than 0.001 as significant. To explore differences between patients and controls, we used a two sample *t*-test (in both directions, i.e., controls > patients, and patients > controls) on the same contrast images. Due to the small sample size, we considered a slightly less stringent threshold, voxel cluster extending 50 adjacent voxels and the peak p-value less than 0.005 as significant.

#### 2.4.3. Dynamic intra- and inter-hippocampal transitions

Our previous study (McCormick et al., 2015) indicated that functional connectivity between different hippocampal segments (i.e., anterior and posterior, left and right) showed dynamic transitions between AM construction and elaboration. Therefore, using the exact hippocampal coordinates from that study, we tested the hypothesis that these intra- and inter-hippocampal transitions would be disrupted in individuals with L-mTLE. The four hippocampal nodes were located as follows (MNI coordinates in parentheses): bilateral anterior HC (ant lHC = −20 −10 −22; ant rHC = 28 −8 −16), bilateral posterior HC (post lHC = −24 −38 −2; post rHC = 26 −38 −2). We note these coordinates are compatible with our prior parcellation of hippocampus into anterior and posterior compartments based on diffusion tensor imaging (Adnan et al., 2016). For the current study, we extracted signal intensities from all participants for each hippocampal region for an early (4–6 s after onset) and a late (12–14 s after onset) time point. These time points fell securely within the construction and the elaboration phases for most trials and most participants; as reported below the average response time for the end of the construction phase for both groups was approximately 4 s. Further, we previously reported changes in hippocampal connectivity between AM construction and elaboration for these controls with these timings (McCormick et al., 2015). We then calculated correlation coefficients across participants, indicating functional connectivity, for four intra- and inter-hippocampal connections (i.e. 1. ant lHC – ant rHC; 2. ant lHC – post lHC; 3. ant rHC – post rHC; and 4. post lHC – post rHC). As a measure of the dynamic change in functional connectivity between the AM retrieval stages, we calculated the difference in these correlations (after Fisher's z-transformation) between the four connections for all participants. We took the absolute value of this difference because we aimed to examine the change of connectivity without a hypothesis about the direction of change. Therefore, the difference reflects the degree to which functional connectivity changed between AM construction and elaboration, so that the resulting value ranged from 0 to 1, where 0 indicated no change in connectivity strength between AM construction and elaboration and a value of 1 indicated maximal change of connectivity strength between both AM retrieval stages. Hence, each group contributed four difference scores, which were then averaged and compared between groups using the nonparametric version of a *t*-test, Mann-Whitney tests and considered a $p < 0.05$ significant.

#### 2.4.4. Seed partial least squares (PLS)

Since the hippocampal system seems to be disengaged during AM retrieval in the context of MTL damage, we aimed to examine different neural routes to AM construction and elaboration, focussing on the vmPFC as an important seed region in this patient population. We selected a seed within the anatomically-defined vmPFC that exhibited the greatest activation in the AM vs math condition in each group (MNI coordinates for controls: −4 30 −20 and patients: 4 30 −20). To examine broader patterns of regional interaction with the vmPFC, we conducted seed PLS analyses, a multivariate correlational technique which enabled us to examine functional connectivity i) between a vmPFC seed and voxels either of the whole brain or restricted to the hippocampi and ii) between subjects at two discrete time points (McIntosh et al., 1996, 2004). In the first instance, we explored

differential connectivity between the vmPFC and all voxels of the whole brain for patients with L-mTLE and healthy controls and in the second instance, focussed on connectivity between the vmPFC and all voxels of both hippocampi (without prescribing anterior and posterior segments). For the PLS analyses focussing on all voxels of the hippocampus, we used a bilateral hippocampal mask created in Marina (Walter et al., 2003). Therefore, we conducted two main seed PLS analyses: 1. vmPFC to whole brain, and 2. vmPFC to bilateral HC. In addition, we conducted these seed PLS analyses exploratory for both groups separately.

For detailed description of PLS please see elsewhere (Krishnan et al., 2011). Briefly, seed PLS examines the relationship between a target region (seed voxel) and signal intensities in all other brain voxels (or a region of interest) as a function of the experimental conditions over time without assumptions about the shape and time course of the hemodynamic response function (McIntosh et al., 2004; McIntosh and Lobaugh, 2004). The main tool of seed PLS is the singular value decomposition (SVD) which extracts ranked latent variables (LVs) from the covariance matrix of seed-to-voxel correlations and experimental conditions. Hence, these LVs express patterns of seed-to-voxel correlations associated with each condition. When applying seed PLS to event-related fMRI data, patterns of seed-to-voxel correlations are calculated for each lag (i.e., TR), providing a time course of seed-to-voxel correlations associated with the experimental conditions. Statistical significance of the LVs is usually assessed using permutation testing. In this procedure, each subject's data is randomly reassigned (without replacement) to different experimental conditions, and a null distribution is derived from multiple permutated solutions. In the current experiment, we used 500 permutations and considered LVs as significant if $p < 0.05$. Further, we assessed the reliability of each voxel that contributed to a specific LV's connectivity pattern using a bootstrapped estimation of the standard error (i.e., bootstrap ratio, BSR). For each bootstrapped solution (here 100 in total), subjects were sampled randomly with replacement and a new analysis was performed each time. In the current study, we considered clusters of 10 or more voxels with BSRs greater than 2.5 (roughly equal to a $p < 0.01$) to represent reliable patterns of vmPFC connectivity.

Further, to examine vmPFC connectivity we selected the seed vmPFC voxels based on the group's peak univariate contrast between AM and math, and extracted activity levels at an early time point (4 s after onset) of AM retrieval, at which participants were searching for a specific AM (construction), and a later time point (12 s after onset), at which participants continued recovery and mentally "replayed" episodic details of the event (elaboration). Activation levels were extracted with the multiple voxel extraction (1 voxel seed) tool in PLS based on mean-centered PLS analyses conducted for AM and math within each group separately. For all seed PLS, we used a non-rotated event-related version which allowed us to pre-specify a contrast between vmPFC functional connectivity at lag 2 (4 s after onset) and lag 6 (12 s after onset). This design allowed us to examine brain activation patterns that correlated with the activation during lag 2 in lag 2, and with activation during lag 6 in lag 6. Event-related PLS further calculates how lag 2 activations correlate with activation in all other lags, but these time bins are meaningless in our case. We therefore only report connectivity results from lag 2 and lag 6. Hence, we used seed PLS to differentiate brain regions whose activity correlate strongly with early versus late vmPFC during AM retrieval.

## 3. Results

### 3.1. Behavioural results

After each event cue, participants were asked to signal with a button press when they had successfully retrieved a memory, hence at the beginning of the elaboration phase. Healthy controls pressed the button on average for 19.5 out of 22 AM trials (SD 2.5) and 21.1 out of 22 math trials (SD 1.8), indicating that AM retrieval and math solving was successful for most of the trials. Individuals with L-mTLE made a button response on average for 18.1 (SD 3.8) AM trials and for 19.6 (SD 2.4) math trials. There was no group difference in the number of button presses ($KW = 1.3$, $p = 0.71$). Furthermore, controls took on average 3.7 s (SD 0.9 s) to retrieve an AM and 4.8 s (SD 0.7 s) to solve a math problem and individuals with L-mTLE took on average 4.1 s (SD 0.9 s) to retrieve an AM and 4.5 s (SD 1.5 s) to solve a math problem. Overall, there were no statistical differences between groups in reaction times ($KW = 4.8$, $p = 0.18$). These results support the following fMRI analyses, in which we examined the time point 4 s after onset as AM construction and 12 s after onset as AM elaboration.

Lastly, controls rated on average 13.5 (SD 5.1) AMs as vivid and 15.1 (SD 4.5) math problems as easy to solve. Patients rated their AMs equally often vivid (Avg 13.7, SD 5.1) and math problems as equally easy (Avg 12.5, SD 7.9). Again, there was no statistical difference between both groups ($KW = 2.8$, $p = 0.96$). Whereas these results seem surprising at first glance, previous research has found that patients' rating of AM vividness to be a poor indicator of memory deficits (St-Laurent et al., 2014, 2016).

### 3.2. Brain activation during AM retrieval

Examining the univariate contrast AM versus math in healthy controls first, we found that controls showed activation of all brain regions commonly associated with AM retrieval (see Supplementary Table S1 for MNI coordinates), including bilateral hippocampal (both anterior and posterior segments), parahippocampal gyri, bilateral lateral parietal cortices, bilateral lateral temporal cortices, PCC/Retrosplenial cortex, and medial prefrontal cortex, including vmPFC (Svoboda et al., 2006).

Examining the same contrast in patients with L-mTLE, we found that patients did not show any MTL activation in either hemisphere (see Supplementary Table S2 for MNI coordinates). All other neocortical regions commonly associated with AM retrieval (mentioned above) were activated in patients as well.

Further, the between-group contrast revealed that healthy controls showed greater activation of the left hippocampus with the peak being on the border between anterior and posterior segments (MNI: −32 −24 −14) during AM retrieval in comparison to patients with L-mTLE (see Fig. 1 and Table S3 for MNI coordinates). Controls also showed greater activation in the left posterior cingulate cortex and right cerebellum. Although patients with L-mTLE did not show greater right hippocampal activation during the AM retrieval than the math condition whereas controls did, this difference was not significant in the between-group contrast.

Interestingly, we found that the L-mTLE group showed greater activation in bilateral temporal cortices and in right prefrontal cortices, including the vmPFC (see Fig. 1 and Table S3 for MNI coordinates). These findings suggest greater reliance on alternate neocortical regions, including the vmPFC, for individuals with L-mTLE.

### 3.3. Dynamic hippocampal transitions during AM retrieval stages

We next examined variability in intra- and inter-hippocampal functional connectivity as a function of AM retrieval stage in the two groups. We found that functional connectivity within and between both hippocampi changed markedly in healthy controls, with connections strongest between anterior hippocampal segments during construction and between posterior hippocampal segments during elaboration (see Fig. 2). In contrast, there was little distinction in connectivity strength between AM retrieval stages in individuals with L-mTLE. Indeed, intra- and inter-hippocampal connectivity changes from one AM stage to the other was significantly greater in healthy controls than in patients with L-mTLE (MWU, $p = 0.028$). As shown in Fig. 2 (and in correlation graphs in S1 and patient activation at a liberal threshold in S2), this was

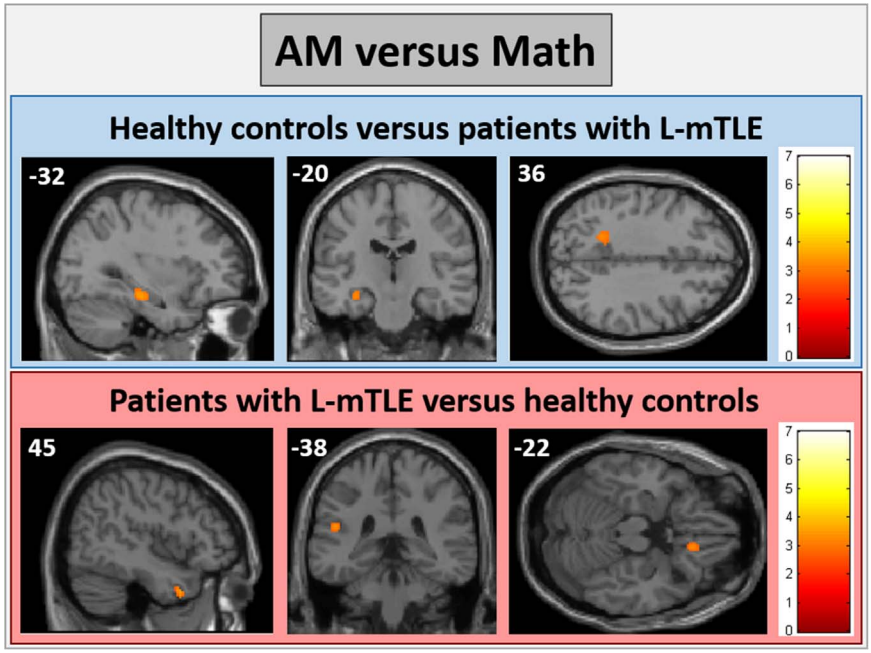


**Fig. 1. Differences in brain activation between AM retrieval in healthy controls and patients with L-mTLE.** The upper panel illustrates brain regions that show greater activation for the univariate contrast AM > Math in healthy controls than patients with L-mTLE. The lower panel shows brain regions with greater activation related to AM > Math in patients with L-mTLE than in healthy controls. Both panels are displayed at a threshold of $p < 0.005$ unc., and cluster > 50 adjacent voxels. Colour bar describes t-values; Activation is displayed on a standard T1-weighted MRI template. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

not simply due to overall impoverished HC activation or connectivity in the patient sample. Rather, the shift from anterior to posterior connectivity that appears to undergird retrieval of episodic detail is defective in the context of left MTL damage.

### 3.4. vmPFC-neocortex connectivity during AM retrieval stages

We next explored how vmPFC connectivity with other brain regions might differ between construction and elaboration. We therefore conducted a seed PLS analysis examining vmPFC to whole brain connectivity contrasting patients with L-mTLE and healthy controls. This interaction analysis revealed a significant vmPFC connectivity pattern separating AM construction and elaboration (LV 1, $p = 0.01$, see Fig. 3, Table S4). Interestingly, vmPFC connectivity differentiated AM construction from AM elaboration in patients with L-mTLE, whereas controls did not contribute to this pattern. Here, during AM construction, the vmPFC was most strongly connected to regions in ventromedial prefrontal cortex as well as bilateral lateral temporal cortex. In contrast, during AM elaboration, vmPFC connectivity now included occipital and parietal cortices, as well as bilateral insula and right lateral temporal cortex.

In exploratory post-hoc analyses, we examined both groups separately. In patients, the whole brain seed PLS revealed a highly significant pattern separating AM construction and elaboration (LV 1, $p < 0.001$, Fig. S3, see Table S5 for MNI coordinates). These results mainly reflected the differences also seen in the between-group PLS.

In controls, on the other hand, vmPFC connectivity did not differ between AM construction and elaboration (LV 2, $p = 0.11$). There was, however, a robust pattern of vmPFC connectivity that was similar for AM construction and elaboration (LV 1, $p = 0.04$, Table S6 for MNI coordinates). During both AM retrieval stages, the vmPFC in controls was connected to a brain-wide network spanning medial and lateral temporal cortices, perceptual-visual areas, and dorsolateral prefrontal cortices. This finding suggests that, in controls, the vmPFC communicates with the same brain regions during event construction and elaboration.

### 3.5. vmPFC-HC during AM retrieval stages

Our previous analyses indicated that the vmPFC might be more important in supporting retrieval of AM in individuals with L-mTLE but that its interactions with the hippocampi does not differentiate between AM stages in this group. Therefore, we conducted a seed PLS analysis to evaluate whether functional connectivity between the vmPFC and hippocampus (using a whole hippocampal mask) differs for the AM retrieval stages. The between-group seed PLS did not reveal a significant LV ($p = 0.57$).

However, the exploratory seed PLS in controls revealed one significant pattern separating AM construction and elaboration (LV 1, $p = 0.04$, Fig. 4, see Table S7 for hippocampal MNI coordinates). During AM construction, controls showed stronger connectivity between the vmPFC and bilateral anterior hippocampi than during elaboration. In contrast, during AM elaboration, the vmPFC was more strongly connected to both posterior hippocampal segments than during construction. A similar PLS analysis in the L-mTLE group yielded no significant effects (LV1, $p = 0.39$), showing that hippocampal connectivity with the vmPFC did not vary as a function of AM stage. The control results are in line with previous studies (McCormick et al., 2015; Poppenk and Moscovitch, 2011; Zeidman et al., 2014) that point to a crucial role of the anterior hippocampus in event construction and the posterior segments to event elaboration. We extend these findings by adding that the connection with the vmPFC may facilitate this flexible back- and forward interaction between the AM retrieval stages in the context of healthy MTL function.

## 4. Discussion

Autobiographical memory (AM) retrieval relies on a variety of mental processes, each of which is supported by interacting transient neural networks (Addis et al., 2007b; Daselaar et al., 2008; McCormick et al., 2015; St Jacques et al., 2011). Foremost, in the healthy brain, these are hippocampal-centered process-specific alliances (PSAs) that enable one to construct and elaborate on vivid, detail-rich AMs from the personal past. On the other hand, patients with unilateral left mTLE have difficulty recalling these episodic AMs, instead describing more gist-like or schematic AMs, possibly relying more heavily on personal semantic information such as facts about oneself or typical events associated with the retrieval cue. By focussing on these two different stages of AM retrieval, we identified different patterns of network engagement and flexibility in control and L-mTLE groups involving

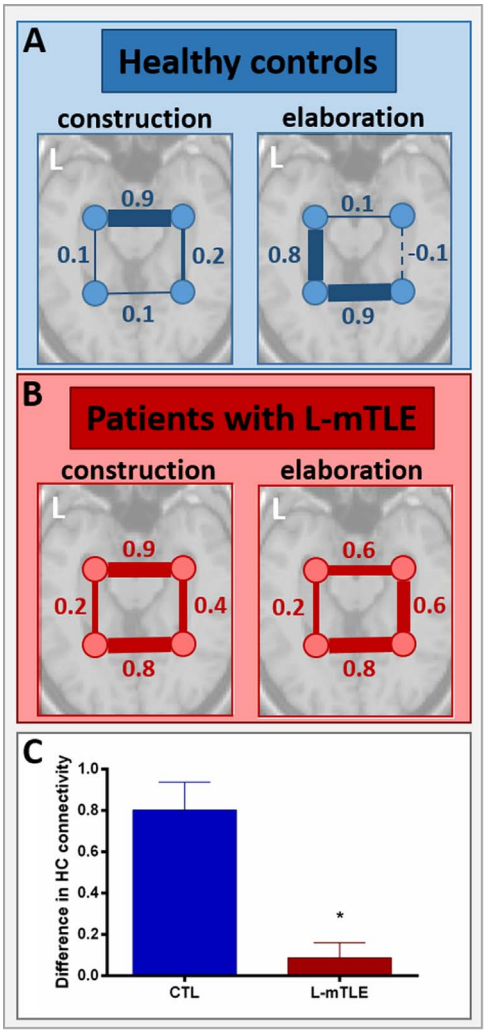


**Fig. 2. Dynamic hippocampal fluctuations during AM construction and elaboration.** This figure displays functional connectivity between four hippocampal nodes (bilateral anterior and posterior) during AM construction and elaboration in healthy controls (CTL, blue, panel A) and patients with L-mTLE (red, panel B). Thickness of the lines correspond to connectivity strength (connectivity values displayed next to the lines); dotted lines indicate negative and solid lines positive correlations; L = left, functional connectivity is superimposed on a standard T1-weighted MRI template. Nodes are shown in approximate positions to the MNI coordinates for display purposes only. Panel C summarises the difference in intra- and interhippocampal (HC) connectivity between AM construction and elaboration shown in panels A and B. * = $p < 0.05$ (Mann-Whitney-*U* test). Whereas functional connectivity strength between hippocampal nodes changes from AM construction to elaboration in controls, connectivity is unvarying in patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

regions associated with retrieval of specific episodic detail (MTL) and general event schemas (vmPFC).

### 4.1. Bilateral hippocampal interactions during AM construction and elaboration

A main goal of this study was to examine how unilateral damage to the MTL affects the critical intra- and inter-hippocampal interactions that allow healthy controls to construct and elaborate vividly specific events from their past. Previous studies document impairments in the amount of episodic detail associated with AM retrieval in patients with unilateral (Addis et al., 2007a; St-Laurent et al., 2009, 2016, 2011; Viskontas et al., 2000) or bilateral (Maguire et al., 2001; Scoville and Milner, 1957; Steinvorth et al., 2005) MTL damage, indicating that the integrity of both hippocampi is important for vivid AM retrieval. There is little information, however, on how the two hippocampi interact with one another and with other cortical structures to enable vivid AM retrieval beyond our previous study showing greater interactions between lateral frontal cortex and anterior left hippocampus during construction and between bilateral posterior hippocampi and visual association areas during elaboration (McCormick et al., 2015). Here, we report that intra- and inter-hippocampal functional connectivity changes dynamically between AM construction and elaboration in healthy controls, but not in patients with left mTLE. Specifically, left MTL damage disrupts dynamic patterns of connectivity that support PSAs (Cabeza and Moscovitch, 2013; Moscovitch et al., 2016) that are the norm during healthy AM retrieval. Further, our group and others have previously proposed that the right hippocampus might play a key role in contributing perceptual richness to retrieved AMs (St-Laurent et al., 2016) whereas the left hippocampus may be mainly involved in searching and assessing specific AMs (Gilboa et al., 2004; Maguire, 2001a, 2001b). While there may indeed be important distinctions between left and right hippocampal contributions, the current study stresses the importance of the functional interactions of both hippocampi during AM construction and elaboration.

In addition, our data complement new computational and empirical research indicating that the capacity to explore different transient network configurations might be an important parameter of functional integrity of neuronal systems (Deco et al., 2011; Garrett et al., 2010; Ghosh et al., 2008; Honey et al., 2007; McIntosh et al., 2010; Misic et al., 2010). This research commonly focuses on brain signal variability, as indexed by entropy or standard deviation in EEG or fMRI data, as an indicator of the tissues' capability to explore different network constellations. For example, we have shown in mTLE that such variability is reduced in the epileptogenic hippocampus and that it relates to individual differences in cognitive performance (Protzner et al., 2013, 2010). Another indicator of the flexibility of brain networks is the capacity to shift between task-negative or default mode and task-positive network configurations during memory encoding, which has been shown to correlate with the clinical status in individuals with varying degrees of cognitive impairment related to Alzheimer's disease pathology (Petrella et al., 2007). Our current data provide another example of that general principle by showing reduced flexibility in functional connectivity of the hippocampus during different mental states (i.e., construction and elaboration) in individuals with mTLE. We suggest that flexibility may be fundamental to the capacity to form distinctive PSAs that enable vivid AM recall.

### 4.2. vmPFC connectivity during AM construction and elaboration

We were particularly interested in connectivity with the vmPFC for several reasons. The medial prefrontal cortex, including the ventral portion, has strong structural and functional connections to the hippocampi and is typically considered part of the primary AM network (Andrews-Hanna et al., 2010; Catani et al., 2013, 2012; Svoboda et al., 2006). With respect to connectivity during AM retrieval, there are strong reciprocal interactions between MTL and medial PFC networks during both construction and elaboration, and this connectivity increases when memories are easily accessed and vividly recollected (St Jacques et al., 2011). Further, there are indications that this connectivity is stronger with anterior compared to posterior hippocampus at rest (Adnan et al., 2016) and during AM construction but not elaboration (McCormick et al., 2015). We note that the vmPFC region selected for the current analyses, while based on the peak differences between AM and Math conditions in each group, was somewhat inferior and caudal to the more 'canonical' anterior medial PFC region that we and others have typically reported in studies of AM retrieval. Nonetheless, it does fall within the boundaries described for the ICA-derived MTL component of AM retrieval networks (St Jacques et al., 2011). Furthermore, the vmPFC seed, as well as the corresponding region showing greater activity in L-mTLE patients than in controls, falls

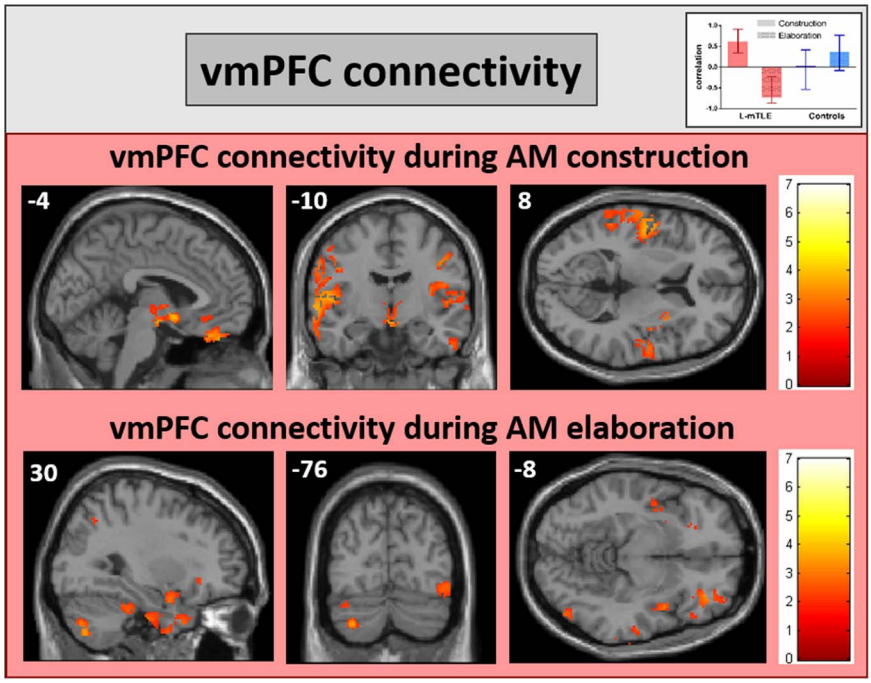


**Fig. 3. vmPFC connectivity during both AM retrieval stages in healthy controls and patients with L-mTLE.** The inset displays the correlation bar graph of the significant LV1 of the seed PLS analysis. Patients are depicted in red and controls in blue. The smooth bars refer to the construction stage and the textured bars to the elaboration stage. Of note, the fMRI data from healthy controls do not contribute to this pattern (i.e. their confidence intervals cross the zero line). The figure therefore displays functional connectivity of patients with L-mTLE between the vmPFC seeds and other brain regions during construction (4 s after onset) and elaboration (12 s after onset). Connectivity patterns are displayed on a standard T1-weigthed MRI template. The colour bar graph indicates boot strap ratios (BSR). BSR > 2.5 and clusters of more than 10 contiguous voxels were considered significant. Whereas the vmPFC is strongly connected to other prefrontal and lateral temporal cortices during AM construction, the vmPFC is further connected to posterior neocortical regions during AM elaboration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

squarely within the region identified by van Kesteren and colleagues to be involved in schema activation in memory (van Kesteren et al., 2013, 2010b).

Whereas the between-group PLS contrasting vmPFC-hippocampal connectivity during AM construction and elaboration did not reveal significant differences, the specific connectivity patterns separating both AM stages in controls was significant. Here, we found the vmPFC was more strongly connected to anterior hippocampi during AM construction and to posterior hippocampi during AM elaboration. In contrast, in the seed PLS analysis for the vmPFC with the rest of the brain, controls showed a stable pattern of connectivity across construction and elaboration stages. Here, widespread bilateral regions of cortex showed significant functional interactions, including medial and lateral frontal, lateral temporal, and occipital gyri. While some of these regions are typically activated in AM retrieval, it did not recapitulate the full AM network. Given that our seed was based in the posterior vmPFC, we suspect that this stable AM construction and elaboration pattern may reflect schema-related processes. Research has emphasized the role played by this region in monitoring and evaluating the subjective relevance of existing schemas to current task demands (Gilboa and Moscovitch, 2016; Hebscher and Gilboa, 2016). In learning new material, greater congruence between elements (e.g., object-scene pairs, typical associations amongst features or items, coherent vs scrambled movie scenes) can engage schemas, resulting in increased mPFC activity, enhanced mPFC-HC connectivity, and better subsequent memory (van Kesteren et al., 2013, 2010a, 2010b). Interestingly, emerging

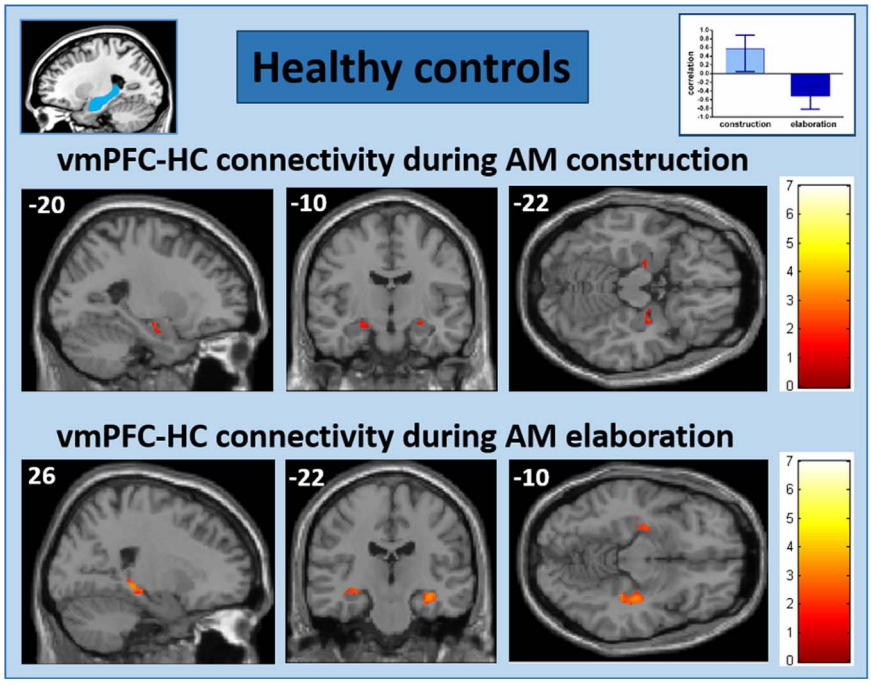


**Fig. 4. Post hoc vmPFC-HC connectivity during both AM retrieval stages in healthy controls.** Functional connectivity between the vmPFC seed and a region-of-interest mask of bilateral hippocampi (rendered in blue) during construction (4 s after onset) and elaboration (12 s after onset) displayed on a standard T1-weigthed MRI template. The colour bar graph indicates boot strap ratios (BSR). BSR > 2.5 and clusters of more than 10 contiguous voxels were considered significant. The inset displays the correlation bar graph of the significant LV1 of the seed PLS analysis. Whereas the vmPFC is strongly connected to bilateral anterior hippocampi during AM construction, the vmPFC is strongly connected to bilateral posterior hippocampi during AM elaboration. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

directional connectivity evidence suggests that the vmPFC might guide hippocampal processes (Cansino et al., 2017, see McCormick et al., 2017), albeit that has not been studied in autobiographical memory.

A quite different pattern emerged for individuals with L-mTLE. Consistent with the current findings regarding intra-hippocampal connectivity, they showed equivalent connectivity between vmPFC and hippocampal segments during both AM retrieval stages. At the current moment, detailed characterisation of pathology differences between anterior and posterior hippocampal segments in mTLE is missing. Nonetheless, the principle new finding here is that there is again no dynamic variation in the MTL-based networks (even when involving the vmPFC) when patients are retrieving what are generally quite impoverished autobiographical memories. Conversely, unilateral MTL damage resulted in different patterns of connectivity between the vmPFC and other regions of cortex during AM construction and elaboration. During construction, the vmPFC showed stronger connectivity to other ventromedial and dorsolateral prefrontal and lateral temporal cortices. Connectivity of the vmPFC during elaboration was more widespread, involving bilateral parietal, temporal and occipital cortices. Of interest, this pattern of connectivity is more similar to what we had observed in an earlier seed-PLS centered on the left hippocampus in controls (McCormick et al., 2015), suggesting that patients were attempting to retrieve memories using an alternate access point into the AM network, centered on vmPFC rather than the hippocampus as a 'hub'. These results are also in keeping with our previous study of L-mTLE patients, in which effective connectivity analyses demonstrated that they did not rely on vmPFC-HC interactions during AM retrieval but rather on long range neocortico-neocortical interactions including between medial prefrontal and retrosplenial cingulate cortices (Addis et al., 2007a).

### 4.3. The quality of AM memories supported by typical and aberrant retrieval networks

Unfortunately, our scanning protocol did not allow for collection of detailed verbal descriptions that would enable us to classify retrieved AMs as schematic or vivid, and we have found that ratings of vividness that we did collect are not particularly reliable in patients with memory dysfunction due to mTLE. Nonetheless, previous reports, including several from our group, show stark phenomenological differences between descriptions of AMs of patients with unilateral mTLE and healthy controls (Addis et al., 2007a; St-Laurent et al., 2009, 2011; Viskontas et al., 2000; Voltzenlogel et al., 2006), demonstrating that patients are able to retrieve the general story line or gist of an AM. This is further supported by recent evidence from individuals with bilateral MTL damage who are able to construct a coherent narrative from picture books (Keven et al., 2017) and recall most of their past life chapters (Grilli et al., 2017). On the other hand, patients with either unilateral or bilateral MTL damage seem not able to recall the episodic elements that add to the perceptual richness of the experience. In addition, research with healthy controls indicates that engaging the hippocampus and associated MTL networks to a greater degree is associated with more vivid and detailed memories (Addis et al., 2004; St Jacques et al., 2011). Further, when schemas are involved during retrieval of associative information, better recall of schema-congruent information appears to rely on vmPFC engagement whereas recall of unique or incongruent material is biased toward MTL engagement (van Kesteren et al., 2012). Here we reflect on what insights might be gleaned regarding the quality of AM retrieval from the current findings based on distinctions and interactions between brain regions involved during memory construction versus elaboration of event details, with the caveat that we do not have qualitative AM data for the specific participants in this study. To facilitate the discussion, we stipulate the following operational definitions of episodic detail (perceptual, spatio-temporal details associated with a specific AM), gist (key facts or principle narrative elements of a specific AM), and schema (a network of common associations amongst similar AMs typically built up over multiple episodes).

First, findings for controls support our and others earlier findings that networks centered around the anterior hippocampi are especially engaged during event construction and networks around the posterior hippocampi during event elaboration (McCormick et al., 2015; Zeidman and Maguire, 2016). Here, we add to the picture by showing that flexible interactions between these hippocampal compartments and the vmPFC across retrieval stages are a correlate of healthy, and presumably more vivid and specific, AM. Our interpretation of these results brings together two somewhat disparate lines of research. Regarding the anterior-posterior distinction within the hippocampus, there is considerable recent interest in dissociations of memory processes. As outlined in a recent review, the connectivity patterns differ, with the anterior hippocampus linking to entorhinal cortex, fusiform cortex, temporal pole and vmPFC whereas the posterior hippocampus connects to parahippocampal gyrus, visual association areas, inferior parietal cortex, and cingulate (Poppenk et al., 2013). As the review documents, both rodent and human functional imaging data indicate that the anterior compartment is more specialized toward global representations and the posterior toward more local details. In addition, recent studies have shown the importance of vmPFC-hippocampal interactions (without specifying the compartment but generally shown to be anterior) specifically when prior knowledge is called upon for construction of new episodic memories (Liu et al., 2016; Preston and Eichenbaum, 2013; van Kesteren et al., 2010b). Moreover, we have shown that as details of naturalistic episodic memories are lost over a 7-day study-test delay, but gist is retained (Sekeres et al., 2016), there is a shift in activation at retrieval from the entire hippocampus to only the anterior hippocampus accompanied by greater activation in the vmPFC (Sekeres et al., 2017).

Considering the current data for controls, the strong vmPFC-anterior HC connectivity during AM construction could carry information on how one specific AM relates to a more general schema activated by the cue word. Of interest, in a previous study we found the hippocampus to be equally engaged in retrieving unique memories (e.g., "first kiss") and equally vivid repeated events (e.g., "Thanksgiving dinner at grandma's house"), but that the vmPFC was activated to a greater extent in the latter (Addis et al., 2004). In the current context, the cue "a party' might engender a search for a particular AM that results in retrieval of a friend's birthday party several months ago that was especially fun. We might consider the vmPFC to be key to retrieving memory schema and the hippocampus to engage in binding and reintegration of the global elements for a specific event. Thus, one might speculate that the anterior HC-vmPFC interaction enables one first to activate a generic schema of a party via the vmPFC (Gilboa and Moscovitch, 2016; Hebscher and Gilboa, 2016), and then, via the anterior hippocampus, to retrieve the general scene of the party venue, who was there, and what was so especially fun about it, as well as how this specific party fits into the overall relationship to this particular friend. During elaboration, there is a switch to connectivity involving posterior hippocampus and vmPFC, possibly important for retrieving some specific episodic details that help to highlight what was distinct about this specific memory from other more generic schemas about birthday parties. The retrieval of those fine-grain episodic details relies on posterior hippocampal connections with other cortical regions that are evident during the elaboration phase (McCormick et al., 2015) or during retrieval of other specific types of information associated with recollection (Poppenk and Moscovitch, 2011). Our current findings highlight the importance of flexible switching between anterior and posterior compartments, and by extension their related networks, in retrieving vivid AMs. Of interest, vmPFC connectivity with a number of other neocortical regions, including some of those known to be involved in memory retrieval, did not vary across retrieval states, suggesting those interactions may have more to do with instantiation of schema elements than with defining particular episodes (Gilboa and Moscovitch, 2016; Hebscher and

Gilboa, 2016).

Turning to the case of L-mTLE patients, previous studies suggest that they are typically able to generate memories, but these have sparser, more gist-like quality that is lacking in perceptual and experiential detail (St-Laurent et al., 2009, 2011; Viskontas et al., 2000; Voltzenlogel et al., 2006). The reduced activation in the damaged hippocampus is typically reflected in diminished engagement and connectivity with the rest of the AM network (Addis et al., 2007a; Dupont et al., 2000; Jokeit et al., 2001), suggesting the impoverished AM recall is more reliant on alternate neocortical networks for either construction, elaboration, or both processes. That hypothesis is consistent with the current findings with respect to the absence of normative changes in intra- and brain-wide connectivity patterns of the hippocampus across AM retrieval stages. In contrast, activation and connectivity with the vmPFC was more central to these retrieval operations in the context of left MTL dysfunction and this was the region supporting differential network connectivity. During construction, there was stronger interaction with left lateral and temporal cortices, regions that are often engaged during retrieval of semantic information (Binder et al., 2009; Burianova and Grady, 2007; Lambon Ralph, 2014). In contrast, the vmPFC showed stronger functional connections with bilateral fusiform, parietal and visual-perceptual cortices during AM elaboration than construction. This constellation of brain regions has been implicated in semantic retrieval but also visual perception (Binder et al., 2009; Grill-Spector and Weiner, 2014; Kanwisher et al., 1997). While various neocortical regions have been shown to be more strongly activated for general or less vivid memories in controls (Addis et al., 2004; Sekeres et al., 2017), there are no data of which we are aware that can help determine whether this pattern of 'abnormal' connectivity is a correlate of less vivid memory in general or is a consequence of reorganization due to neurological damage. It is also important to note that the different patterns of connectivity we observed in patients and controls are constrained by the choice of PLS seed regions, and other mapping strategies could reveal alternate network configurations associated with MTL damage and/or less vivid memory. In sum, our results suggest that both construction and elaboration phases engage different neocortical networks that are distinct from those associated with the normative hippocampal networks, resulting in AMs that may contain more semantic content and elaborations compared to the rather vivid perceptual experience tied to that specific episode. In line with this speculation, patients with bilateral MTL damage cannot imagine unique, detail-rich events but they are able to retrieve semantically-related content to these events (Hassabis et al., 2007).

One might question whether the relatively preserved gist recall in AM in unilateral mTLE patients relies exclusively on processes of schema activation supported by the vmPFC. That is, are the event-specific elements somehow constructed out of personal semantics and multiple relevant events? It is not possible to answer that question based on the present data, but we can offer the following relevant observations. First, recall of semantic details for AM events, as well as retrieval of elements of common scripts (e.g., washing the dishes), is not impaired in mTLE patients (St-Laurent et al., 2009); these are not particular to a specific event. Second, for newly learned laboratory events, mTLE patients are equally impaired at retrieving story elements or gist whether the material was presented in the form of a simple narrative or a more perceptually-elaborate film clip, yet both are considerably poorer than gist recall for AMs (St-Laurent et al., 2014). Here, too, it should be noted that gist recall is relatively preserved compared to memory for perceptual details. Last, it is interesting to note that the neocortical regions we found to be differentially connected to anterior vs posterior hippocampus in controls (McCormick et al., 2015) are quite similar to those connected to the vmPFC at different retrieval stages in mTLE patients in the current study. While these findings suggest that schema activation and coordination processes instantiated by vmPFC may be the primary driver of event gist recall in these patients, it is also important to note that we do see evidence of some (albeit greatly reduced) hippocampal activity in both epileptogenic and healthy hippocampi that may contribute to retrieval of what are clearly distinct elements of a specific memory (e.g., an unexpected guest at the friend's party). As discerning subtle differences between the types of global AM details that may be based on hippocampal versus vmPFC engagement is likely to be quite difficult, studies that utilize the previously discussed schema-congruent and incongruent associative learning methods of van Kesteren and colleagues may provide better insight into the relative roles of these structures and their associated networks in mTLE.

## 5. Limitations

We acknowledge that our sample size is small and thus we directed our hypotheses specifically at hippocampal and vmPFC activation and connectivity. However, it is possible that some genuine group differences have been missed due to low power, such as an overall group difference in vmPFC-HC connectivity. Nonetheless, there are very few studies examining functional connectivity during autobiographical memory in patients with medial temporal lobe damage, and therefore, we believe our positive findings represent a valuable contribution to our understanding of the neural mechanisms of autobiographic retrieval.

## 6. Conclusions

Our findings provide evidence that the phenomenological differences in the descriptions of autobiographical memories in patients with unilateral left mTLE are associated with retrieval by alternative neural routes from those typically used by healthy controls. In the healthy brain, a flexible neural system that relies on the integrity of both hippocampi enables the coordination of transient neural networks underlying episodic AM construction and elaboration. In patients with left MTL dysfunction, the vmPFC is more engaged during AM retrieval, coordinating with distinct neocortical regions during the two phases of recall. This proposal aligns with the hypothesis that memories which have been transformed from detail-rich to schematic in the normal course of changes over time may center on neocortical networks including vmPFC and no longer on the hippocampus (Moscovitch et al., 2016; Winocur and Moscovitch, 2011).

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2017.08.014.

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