

# Consequences of hippocampal damage across the autobiographical memory network in left temporal lobe epilepsy

Donna Rose Addis,<sup>1,2,3</sup> Morris Moscovitch<sup>2,3</sup> and Mary Pat McAndrews<sup>1,2</sup>

<sup>1</sup>Toronto Western Research Institute, <sup>2</sup>Department of Psychology, University of Toronto and <sup>3</sup>Rotman Research Institute, Baycrest Centre for Geriatric Care, Toronto, ON, Canada

Correspondence to: Mary Pat McAndrews, Neuropsychology Clinic, 4F-409 Toronto Western Hospital, 399 Bathurst St., Toronto, ON, Canada M5T 2S8.

E-mail: mcandrws@uhnres.utoronto.ca

**Lesion and neuroimaging evidence suggests the hippocampus (HC) is a crucial node in the neural network supporting autobiographical memory (AM) retrieval, and thus focal damage to the HC may have functional consequences for structures throughout the network. Using fMRI, we examined the impact of hippocampal damage on the engagement and connectivity of the AM network in 11 patients with left temporal lobe epilepsy (mean age of onset of seizures, 24 years) with significant left hippocampal atrophy and a mild AM deficit. All investigations were completed pre-surgically. The fMRI paradigm comprised three conditions: (i) retrieving specific AMs in response to personalized cues obtained during a pre-scan interview; (ii) a sentence completion control task; and (iii) a size discrimination control task. AM-related activity (relative to the control tasks) was significantly reduced in patients compared to controls, in residual hippocampal tissue and across the AM network, including the medial prefrontal cortex, temporal poles, retrosplenial and lateral parietal cortex. Furthermore, the strength of connections involving the left HC was also reduced in patients. In contrast, connections between extra-hippocampal nodes, such as left retrosplenial and medial prefrontal cortex, were strengthened in patients, possibly reflecting a compensatory mechanism. Our findings confirm that the left HC is a crucial node in the AM network, possibly playing a dominant role in initiating the engagement of other network nodes, and its damage has significant consequences for the functional organization and connectivity of the neural network supporting AM retrieval.**

**Keywords:** autobiographical memory; hippocampus; temporal lobe epilepsy; effective connectivity; fMRI

**Abbreviations:** AI = autobiographical interview; AM = autobiographical memory; BOLD = blood-oxygenation level dependent; HC = hippocampus; ICS = inter-collicular sulcus; LMPFC = left medial prefrontal cortex; LTLE = left TLE; MPC = medial parietal cortex; MTL = medial temporal lobe; PHG = parahippocampal gyrus; ROI = region of interest; tPOLE = temporal pole; TPJ = temporoparietal junction; TLE = temporal lobe epilepsy.

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## Introduction

The neural effects of brain lesions are highly complex. Even when pathology is relatively circumscribed, it can alter or decrease functionality not only of the remaining tissue in the affected structure but also connected structures (Kopelman *et al.*, 2003). Therefore, while structural imaging can localize the lesion and characterize its extent, it does not impart information about the functional integrity of undamaged tissue. Functional neuroimaging techniques have contributed to a better understanding of how damage alters neural networks mediating cognitive processes such as memory retrieval.

Although some studies have shown that damage to the medial temporal lobe (MTL), including the hippocampus (HC), does not affect remote autobiographical memory (AM) (Bayley *et al.*, 2003; Bright *et al.*, 2006; Squire and Bayley, 2007), the majority of studies report that MTL damage is associated with impairments of AM (Westmacott *et al.*, 2001; Gilboa *et al.*, 2005; Steinworth *et al.*, 2005), even when MTL damage is unilateral (Barr *et al.*, 1990; Viskontas *et al.*, 2000; for a recent review, see Moscovitch *et al.*, 2006). Often, such damage affects retrieval of episodic aspects of AM, with relative sparing of semantic AM (Viskontas *et al.*, 2000; Squire and Bayley, 2007). Neuroimaging has revealed

that AM retrieval ubiquitously engages the MTL, as part of a network of structures (see Svoboda *et al.*, 2006 for a meta-analysis). To date, only one patient with HC damage has been studied using functional neuroimaging during AM retrieval (Maguire *et al.*, 2001). In comparison to the left-lateralized network evident in controls, this patient showed recruitment of homologous regions in the right MTL and cortex and altered connectivity in the network. Although this single result suggests that HC pathology alters the regions engaged by AM retrieval as well as interactions among them, this individual sustained his acute brain injury very early in development, and therefore it is not clear that those findings represent a generalizable model for alterations in cognitive networks later in life.

Temporal lobe epilepsy (TLE) provides a unique opportunity to investigate systematically the local and distal consequences of MTL damage on the engagement and connectivity of the AM network. Importantly, these patients do not typically perform at a 'floor' level with respect to AM retrieval (e.g. Viskontas *et al.*, 2000), which is crucial if one is to scan these patients (Price and Friston, 1999). Additionally, although some of the patients we studied had seizures beginning in childhood, the mean age of onset was 24 years. Furthermore, as these patients have unilateral damage, we can directly examine the possibility that reorganization involves greater recruitment of homologous regions in the unaffected hemisphere, which is an important general question in functional reorganization following brain injury.

In the present study, we examined AM-related activity in unilateral left TLE (LTLE) patients with significant left HC atrophy and a mild AM deficit. We predicted that activity in the damaged left HC would be reduced in patients relative to controls. We also expected group differences in other regions of the AM network, with the direction of effect helping to specify the nature of the reorganization and/or compensation. For example, if the left HC influences other regions (e.g. initiating engagement of other network nodes), then when damaged, activity of those functional targets will be reduced. Alternatively, other regions may activate more intensely to compensate for reduced activity in the dysfunctional HC, and additional regions may be recruited into the AM network in LTLE patients. Given the reliability of activity in this network and the compelling data regarding the impact of MTL damage on AM, we considered this an ideal situation to contribute to the developing literature on effective connectivity in patient populations.

## Methods

### Subjects

#### LTLE group

Eleven patients (five male) with LTLE were recruited for this study through the Epilepsy Program at Toronto Western Hospital. All subjects gave written informed consent for the study, approved

by the University Health Network Research Ethics Board. Each participant had a diagnosis of unilateral LTLE based upon localization of seizure focus to the left MTL (i.e. any MTL structure including HC, entorhinal, perirhinal or parahippocampal cortices) during extended EEG and video monitoring. Exclusion criteria included foci or lesions outside of the left MTL (e.g. frontal, lateral temporal or posterior cortical focus) and/or significant history of neurological or psychiatric impairment (other than that typically associated with TLE, including depression). At the time of pre-surgical assessment, patients ranged in age from 23 to 55 years ( $M = 39.50$ ,  $SD = 10.12$ ), had a mean age of seizure onset of 24.80 years ( $SD = 10.66$ ) and a mean duration of seizures of 16.92 years ( $SD = 11.32$ ); only two of 11 patients had childhood onset (i.e. before age 18) of seizures. Seven patients had left medial temporal sclerosis, defined by radiological criteria [i.e. evidence of atrophy in left HC (CA fields or dentate gyrus) on T1-weighted anatomical MRI scans and evidence of gliosis on T2-weighted anatomical MRI scans]. Nine LTLE patients were right-hand dominant. Although the other two patients were left-handed, sodium-amytal testing of language functions confirmed these patients were left-hemisphere dominant for language: neither showed disruption to language comprehension or production (i.e. comprehending and carrying out simple commands, naming, spelling, reading and repetition) during anaesthetization of the right hemisphere and both showed transient impairments in these functions during left hemisphere injections.

Neuropsychological testing was conducted during pre-surgical assessment of LTLE patients (Table 1; note for some measures, only 10 of 11 patients were tested due to extraneous circumstances). On average, this group had IQ scores in the normal range (Wechsler Abbreviated Scale of Intelligence Full Scale IQ, Verbal IQ and Performance IQ). Despite normal performances on average, there was some evidence of more impaired verbal functioning, consistent with a left MTL focus. While on Performance IQ, four of 11 patients performed at a level more than 1 SD *above* the normative mean and only two patients performed more than 1 SD *below* the mean, an opposite pattern was evident for Verbal IQ, where only one of 11 patients performed more than 1 SD *above* the mean and three performed more than 1 SD *below* the mean.

Also consistent with a left MTL focus, the majority of patients were impaired on measures of verbal memory (relative to norms from Spreen and Strauss, 1998). For instance, with respect to episodic learning and retrieval, eight of 11 patients were at or below  $z = -1$  on the Delayed Recall portion of the Rey Auditory Verbal Learning Test. Semantic verbal retrieval was also affected in the LTLE group, with 8 of 10 patients of patients at or below  $z = -1$  on the Boston Naming Test and 9 of 10 patients were at this level on phonemic oral fluency. In contrast, only 2 of 10 patients showed this same level of deficit on a test of visual memory, delayed recall of the Rey Osterreith Figure.

#### Control group

Fourteen healthy right-handed adults (six male) with no history of neurological or psychiatric impairment gave written informed consent prior to participation in this study. Controls ranged in age from 24 to 56 years ( $M = 34.14$ ,  $SD = 10.76$ ), and a non-parametric Mann–Whitney U-test confirmed they did not differ significantly in age from the LTLE group ( $U = 57.5$ ,  $P = 0.291$ ). The control

**Table 1** Performance of patients on neuropsychological measures of IQ, verbal and visuospatial functioning

| Neuropsychological measure      | Mean (SD)     | Range  | Number of subjects performing at |             |        |
|---------------------------------|---------------|--------|----------------------------------|-------------|--------|
|                                 |               |        | Z < -2                           | -1 < Z < -2 | Z > +1 |
| <b>IQ measures</b>              |               |        |                                  |             |        |
| Full scale IQ                   | 98.27 (16.70) | 67–118 | 1/11                             | 2/11        | 3/11   |
| Verbal IQ                       | 99.18 (13.93) | 76–117 | 0/11                             | 3/11        | 1/11   |
| Performance IQ                  | 98.00 (18.86) | 64–119 | 1/11                             | 1/11        | 4/11   |
| <b>Verbal functioning</b>       |               |        |                                  |             |        |
| RAVLT (delayed)                 | 7.54 (4.13)   | 1–14   | 6/11                             | 2/11        | 1/11   |
| Boston naming test              | 46.90 (10.17) | 23–56  | 7/10                             | 1/10        | 0/11   |
| Phonemic fluency                | 30.80 (11.55) | 14–50  | 5/10                             | 4/10        | 0/11   |
| <b>Visuospatial functioning</b> |               |        |                                  |             |        |
| Key figure (delayed)            | 20.90 (8.49)  | 8.5–35 | 2/10                             | 0/10        | 3/11   |

subjects did not undergo neuropsychological testing, unlike LTLE patients who completed these as part of pre-surgical assessment. fMRI data for 11 controls were taken from the study by Addis *et al.* (2004), with another three participants added to complete age-matching to the current patient group. This meant that the order and temporal proximity of the data collection for the fMRI task (pre-scan interview and scanning) and the behavioural measure of AM (Autobiographical Interview, AI) was different for patients and controls. Specifically, 12 controls completed the fMRI portion of the study an average of 1.76 years (SD = 0.78) prior to the AI. Furthermore, 6 of these 12 subjects completed the AI by telephone having moved out of area since the fMRI study. In contrast, the protocol for three controls and all of the patients involved completion of the AI immediately before beginning the fMRI study. Potentially, these differences in test administration could mean a stronger coupling between the behavioural measure (AI) and fMRI probes of AM in the patients than in the controls, although this source of variation did not have an impact on any of the principal analyses.

### Autobiographical interview (AI)

An adapted version of the AI (Levine *et al.*, 2002) was used to probe episodic and semantic AM. Using the standard AI instructions (Levine *et al.*, 2002), subjects were asked to retrieve four memories: two recent AMs, from the past 5 years (excluding the past 6 months) and two remote AMs of events occurring more than 10 years ago. General, non-specific probes (e.g. 'Could you tell me more about that?') were given if necessary to clarify instructions and encourage further description of details. Subjects were given a maximum time limit of 5 min per AM, thus administration took a total of ~20 min. After retrieving all four AMs, each memory was dated; if a range of years was given, the most recent was used. AMs were rated for frequency of rehearsal (either mental or verbal) on a six-point scale (1, once per week; 2, once a month; 3, once every few months; 4, once every 6 months; 5, once a year; 6, once every few years). All AMs were recorded and transcribed.

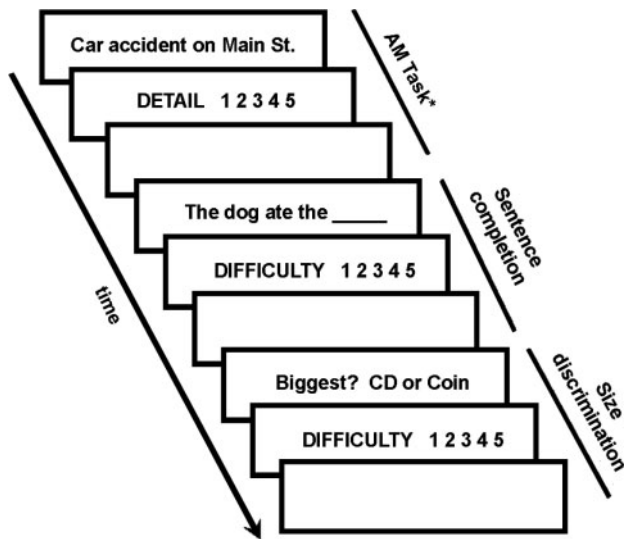
The standardized scoring procedure (Levine *et al.*, 2002) was used. Transcribed AMs were given a title (by researcher M.P.M.) that corresponded to the central event described; if more than one event was discussed, the event discussed in most detail that occurred over a brief timeframe was selected as the main event. Another two researchers then scored these AMs

independently: Rater 1 (the interviewer, D.R.A.) scored the entire set of AMs; Rater 2 (blind to group membership, M.J.), scored approximately half of the AMs (59 AMs). Scoring involved firstly segmenting each AM into distinct details, that is, chunks of information (e.g. a unique occurrence or thought). Details were then categorized as 'episodic' (i.e. details about the central event, including context, actions, thoughts) or 'semantic' (i.e. personal or general facts, extended events that are not specific in time, repetitions and other information irrelevant to the central event), and the number of each detail type was tallied. Inter-rater reliability for the half-set of AMs scored by both raters was high, as determined by an intraclass correlation (two-way mixed model; episodic, .953, semantic, .830), indicating an adequate level of consistency in scoring. Thus, the complete set of AM scores from Rater 1 was used in the present analyses. Finally, average AI episodic and semantic scores (i.e. the number of episodic or semantic details, averaged across the four AMs; note for one control this average comprised only three AMs due to a recorder failure) were computed for each participant and used in statistical analyses.

### fMRI paradigm

#### Pre-scan interview

At least 48 h prior to scanning, a 2 h interview was conducted to obtain AM stimuli to be presented during scanning. Subjects retrieved 20 AMs of events that were specific in time and place, had not occurred in the past year and were not recounted during prior administration of the AI (note, one patient could provide only 10 AMs). A list of cues was provided to facilitate retrieval, but AMs were not limited to these cues. Subjects dated each event and provided a brief 'title' to be used as a retrieval cue during scanning. Unlike the AI, they were not encouraged to recount details of the memories exhaustively but rather to provide a very brief description to ensure that it fit the criteria of a specific event. Each AM was rated on a five-point scale for the level of detail (from 'faint with few details' to 'exceptionally clear with great detail') and personal significance (i.e. how self-defining the event was; ranging from 'insignificant; made no difference to my life and how I view myself' to 'great personal significance, changing my life and how I view myself'). For each scale, examples of AMs which might be rated as high or low on these scales were included to help 'anchor' patients in their use of these scales.



**Fig. 1** Schematic illustration of fMRI paradigm: three types of trials were presented (AM task, sentence completion control task and size discrimination control task), each 16 s in total and comprised of three parts (stimulus presentation, rating and rest). Ten of each trial type were presented during a scanning sequence, and two sequences were completed. \*Note that for the AM task, the stimulus was a personalized AM cue obtained during a pre-scan interview, and the rating was either for the level of detail retrieved or the personal significance of the AM.

### Scanning protocol

This scanning protocol has been explained in detail elsewhere (Addis *et al.*, 2004; Fig. 1). Briefly, tasks and rating scales were explained to subjects immediately prior to scanning and AM titles produced in the pre-scan interview were presented to ensure there was no confusion during scanning. Furthermore, all subjects practised the rating responses to be made in the scanner (see below). Stimuli (black text) were presented using SuperLab Pro 2.0 (Cedrus Corporation, San Pedro, CA, USA), back-projected onto a screen and viewed through a mirror incorporated into the head coil. Each trial was 16 s, consisting of task presentation, rating and rest. In a single session, participants completed two scans during which 10 of each of three tasks (AM, sentence completion and size discrimination) were presented. The patient who provided only 10 specific AMs completed only one scan. For 11 controls, each scan also contained 10 trials of general AM retrieval for the purpose of another study (Addis *et al.*, 2004), but the functional images associated with these trials were removed before any pre-processing was implemented. This was appropriate given the length of each trial (16 s) in this study. Although it is possible that the subjects completing the longer version of the task may have experienced greater fatigue, the whole-brain pattern of activity evident in the two groups of controls (i.e. those completing the current protocol and those completing the lengthened protocol) did not differ.

### AM task

AMs titles were presented as retrieval cues for 6 s and subjects retrieved silently the relevant memory. A five-point rating scale (either detail or personal significance) was then presented for 4 s;

subjects responded by lifting the finger of the right hand corresponding to the rating (thumb = 1). This was recorded by a researcher in the MRI room. The dimension rated was constant across the entire scan, but differed between the two scans. Ratings were included during scanning to enable later correlations with ratings on the same dimensions obtained within more extensive post-scan ratings. A 6-s rest period followed, during which a blank screen was presented and subjects were instructed to rest.

### Control tasks

Two control tasks were included to control for various processes inherent in AM retrieval: (i) a sentence completion task controlled for narrative processes and semantic retrieval; and (ii) a size discrimination task controlled for visuospatial processing and retrieval of visuospatial information. Trials of each control task were randomly interspersed between AM trials during each scan. For sentence completion, a sentence missing the last word was presented (e.g. 'The dog ate a \_\_\_\_'); subjects completed the sentence silently with a word. For size discrimination, the names of two objects were presented (e.g. 'CD or coin') along with the word 'Biggest' to cue subjects to identify silently the larger of two items. Each control task was presented for 4 s. This was followed by the 4-s presentation of a five-point rating scale for task difficulty (to control for the AM rating scale) and an 8-s rest period.

### Post-scan interview

Immediately following scanning, subjects completed a 30-min interview. Retrospective ratings of the detail and personal significance were made for each AM retrieved in the scanner. This included a re-rating of the one dimension rated in the scanner, which correlated highly with ratings obtained during the scan for controls ( $r_s = 0.783$ ,  $P < 0.001$ ) and LTLE patients ( $r_s = 0.689$ ,  $P < 0.001$ ). Thus, for all analyses, the post-scan rating for both detail and personal significance were used (Addis *et al.*, 2004). Subjects also reported whether they successfully retrieved the AM. Five LTLE subjects failed to recall one or more AMs within a scan (range = 1–3 failures), but for two patients this was due to a stimulus display error. Retrieval failures were excluded from analyses.

### Data acquisition

Anatomical images were acquired on a 1.5 Tesla Signa MR System (GE Medical Systems, Milwaukee, WI, USA) using a three-dimensional  $T_1$ -weighted sequence (FOV = 200) generating 60 axial slices (2.2-mm thick; except for one LTLE patient where 120 axial slices, 1.1-mm thick were generated). Functional data were acquired using single-shot spiral acquisition (TE = 40 ms, TR = 2 s, FOV = 220 mm). Twenty-five slices (5-mm thick, 1-mm gap) covering the entire brain were acquired in a coronal-oblique orientation, perpendicular to the long axis of the HC. The first three frames were dropped to allow for signal equilibrium.

### MTL width measurements

Hippocampal atrophy was assessed by a linear measurement of MTL width (Gao *et al.*, 2003). This does not measure MTL volume *per se*, but provides an accurate and sensitive index of hippocampal atrophy (Gao *et al.*, 2004). MTL widths were obtained using ANALYZE AVW Software (Biomedical Imaging

Resource, Mayo Foundation, Rochester, MN, USA). For each subject, the angle between the long axis of the HC and the AC-PC plane was measured for the left and right hemisphere. Anatomical images were reconstructed along the long axis of each HC at the hippocampal angle for that HC (i.e. two images were produced, one aligned to the left HC and one aligned to the right HC). For each, a slice passing through the inter-collicular sulcus (ICS) was generated. Although in the standard procedure MTL widths are taken at this slice (Gao *et al.*, 2003), pilot data from our lab indicate that more reliable HC measurements for TLE patients are obtained from the fourth slice above the ICS landmark slice. Thus, all measurements taken in this study were obtained from this slice.

Three measurements (in voxels) were made for each HC: (i) anterior MTL width, measured at the anterior boundary of the midbrain; (ii) posterior MTL width, measured at the posterior boundary of the midbrain; and (iii) midway MTL width, measured at the midway point between the anterior and posterior boundaries of the midbrain (Gao *et al.*, 2003). A linear measure of intracranial width (i.e. the distance from the most lateral aspect of the left temporal cortex to that on the right) was also taken at this slice, at the posterior boundary of the midbrain. To correct the HC measures for overall brain size, each MTL width was calculated as a proportion of the intracranial width measure. Measurements in voxels were converted to metric measurements (millimetres) by multiplication by voxel width (0.78 mm). The sum of the three MTL widths (anterior, midway and posterior), corrected for intracranial volume, was used as the measure of HC atrophy.

### Functional imaging pre-processing and analysis

Pre-processing and univariate analyses were performed using SPM2 (Wellcome Department of Cognitive Neurology, London, UK). Functional images were co-registered to a structural image, realigned and unwarped for motion correction, corrected for within-frame time of acquisition, spatially normalized and smoothed using a Gaussian kernel of 7.6 mm full-width half maximum. Data were high-pass filtered to account for low-frequency drifts. Each stimulus event was modelled by SPM2's canonical hrf (applied at task onset) and the six head-movement parameters were included as confounds. Data for each participant were analysed as a fixed-effects model with three conditions: AMs, sentence completion and size comparison. Contrast images were taken to the second level for relevant within-group and between-group random-effects analyses. Firstly, a within-group contrast of AM retrieval and control tasks (sentence completion and size comparison) was computed for each group. Secondly, two between-group contrasts were performed: (i) AM retrieval (relative to control tasks) in control relative to LTLE patients; and (ii) AM retrieval (relative to control tasks) in LTLE relative to control subjects. The AI episodic detail score for was included as a subject covariate to help explain variance in activity related to group differences in AM performance, as it is possible that activation differences are due to differences in the ability to perform the task. Although the AMs entered into these analyses were all successfully retrieved, other findings (and the current AI data) indicate group differences in the amount of episodic detail retrieved and it has been established that HC activation magnitude varies with detail (Addis *et al.*, 2004). Although the rating tasks were included for this reason, there unfortunately was considerable doubt as to the usefulness of these ratings from patients

(Results section). Thus, an objective measure of AM ability (the AI episodic detail score) was used as a covariate in an attempt to isolate better the effects due to the disorder (and damage) *per se*.

A significance threshold of  $P < 0.001$  (uncorrected for multiple comparisons), and an extent threshold of five contiguously active voxels ( $2 \times 2 \times 2 \text{ mm}^3$ ) was applied to these contrasts (Maguire *et al.*, 2001; Maguire and Frith, 2003; Rekkas and Constable, 2005; Vandekerckhove *et al.*, 2005). Region of interest (ROI) analyses were conducted in bilateral HC, based on *a priori* hypotheses that this region is active during AM retrieval (Fink *et al.*, 1996; Maguire, 2001; Ryan *et al.*, 2001; Piefke *et al.*, 2003; Addis *et al.*, 2004; Gilboa *et al.*, 2004), and that this should be a site of activation differences between patients and control subjects, given the location of pathology in patients. The ROI mask was created in MNI space using MARINA (Bertram Walter Bender Institute of Neuroimaging University of Giessen, Germany) and applied using the 'Small Volume Correction' option in SPM2 with a threshold of  $P < 0.05$  (corrected) and five contiguously active voxels ( $2 \times 2 \times 2 \text{ mm}^3$ ). For all analyses, MNI coordinates were converted to Talairach space and regions of activations were localized in reference to a standard stereotaxic atlas (Talairach and Tournoux, 1988).

### Effective connectivity analysis

An examination of how the effective connectivity of the AM network is altered by left HC damage in LTLE patients was accomplished using structural equation modeling (SEM, McIntosh and Gonzalez-Lima, 1994). This multivariate technique assesses the fit of a neuroanatomical model of connections with the interregional covariances observed in the blood-oxygenation level dependent (BOLD) signal.

### Region selection

Selection of regions for this analysis was based primarily upon Maguire *et al.*'s (2001) model of a left-lateralized AM retrieval network. In the current analysis, this was expanded to include homologous regions in the right hemisphere because the AM paradigm used in the present study resulted in bilateral activity and also as it was possible that patients with unilateral damage might show enhanced connectivity of unaffected right temporal regions involved in AM retrieval. The list of candidate nodes was then pared down to include only those which were significantly activated by control group in the contrast of AM and control tasks. Eleven regions comprised the final model (Table 2): left medial prefrontal cortex (LMPFC, BA10), bilateral temporal pole (tPOLE, BA21), bilateral HC, bilateral parahippocampal gyrus (PHG, BA35/36), bilateral medial parietal cortex (MPC, retrosplenial/posterior cingulate cortex, BA23/29/30) and left temporo-parietal junction (TPJ, BA40).

The peak voxel per group was selected for each of these regions on the basis of the relevant within-group contrast of AM retrieval and control tasks (Table 2). If a particular region was not significantly active in the LTLE group, the threshold was reduced and the peak voxel in that region was selected ensuring that the *peak* voxel for that region was used. Although extracting and averaging signal from all voxels comprising a region can provide a representative index of the region as a whole, here signal was extracted from the peak voxel as this represents the maximal index of the effect of interest (AM retrieval relative to control tasks) and

**Table 2** Peak voxels selected for the effective connectivity analysis from group-level parametric modulation analyses

| Region | Control group co-ordinates* |     |     |       |         | LTLE group co-ordinates |     |     |       |         |
|--------|-----------------------------|-----|-----|-------|---------|-------------------------|-----|-----|-------|---------|
|        | X                           | y   | z   | BA    | z-score | x                       | y   | z   | BA    | z-score |
| LMPFC  | −6                          | 56  | −15 | 10    | 5.28    | −10                     | 58  | −4  | 10    | 3.32**  |
| LHC    | −26                         | −20 | −14 | n/a   | 5.28    | −20                     | −14 | −14 | n/a   | 2.90    |
| RHC    | 28                          | −11 | −16 | n/a   | 5.45    | 20                      | −9  | −20 | n/a   | 2.73    |
| LPHG   | −26                         | −28 | −15 | 35/36 | 5.42    | −30                     | −28 | −17 | 35/36 | 1.41    |
| RPHG   | 28                          | −28 | −15 | 36    | 5.45    | 30                      | −24 | −12 | 35    | 1.94    |
| LtPOLE | −61                         | −9  | −16 | 21    | 5.64    | −63                     | −10 | −10 | 21    | 2.38    |
| RtPOLE | 57                          | 1   | −20 | 21    | 4.79    | 55                      | −5  | −15 | 21    | 3.80**  |
| LMPC   | −2                          | −55 | 21  | 23/30 | 6.26    | −8                      | −53 | 25  | 31    | 3.83**  |
| RMPC   | 12                          | −44 | 6   | 29/30 | 6.12    | 6                       | −44 | 13  | 29    | 3.44**  |
| LTPJ   | −40                         | −66 | 36  | 39    | 5.74    | −42                     | −66 | 31  | 39    | 2.70    |

\*All activations for control subjects were significant at a threshold of  $P < 0.05$  (corrected for multiple comparisons).

\*\*Activations for LTLE subjects which were significant at a threshold of  $P < 0.001$  (uncorrected for multiple comparisons). All other coordinates represent the maximally activated sub-threshold voxel in the neural structure.

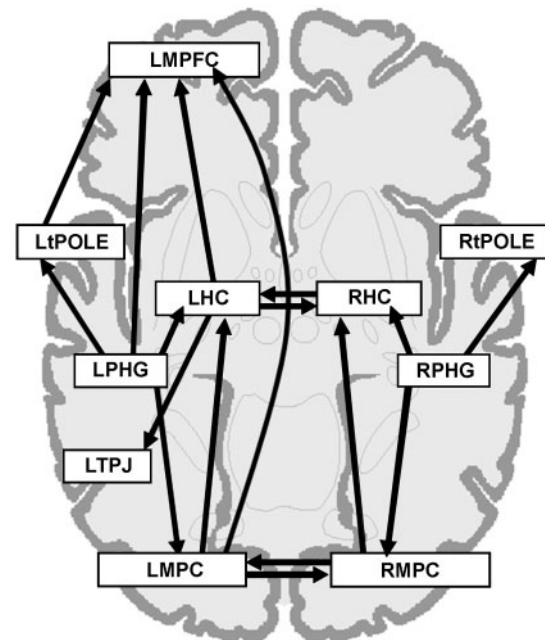
All co-ordinates reported in Talairach space. BA = Brodmann area; L = left, R = right, PHG = parahippocampal gyrus; tPOLE = temporal pole; MPC = medial parietal cortex.

also avoids dilution of this effect by less- or non-active voxels present within the region.

An additional constraint on voxel selection was the location of voxels within a region across the two groups. In some cases, the peak voxels from each of these group analyses were in different aspects of the same structure. Due to the fact that often subregions of a structure differ in function (Epstein and Kanwisher, 1998; Eldridge *et al.*, 2005), where possible peak voxels falling close to the same location (e.g. BA35/36 of the PHG) in both groups selected (see Table 2 for coordinates). Even so, there were some group differences in the exact spatial location of voxels (at most, 11 mm in the  $z$ -plane within LMPFC, BA 10). This likely reflects the fact that locations of functional regions can differ between individuals and groups, as has been established with respect to the fusiform face area (Spiridon *et al.*, 2005). Thus, we used the AM network evident in controls ( $P < 0.001$ , uncorrected) as a 'functional localizer' of the normal AM network to ensure that every peak voxel selected for patients was also active as part of the normal AM network. For each individual, the signal intensity (i.e. the relative difference between BOLD activity during AM retrieval and control tasks) was extracted from each of the 11 peak voxel locations in that participant's relevant SPM contrast image.

### Model construction

An anatomical model of connections between the 11 regions was generated based upon known primate neuroanatomy (Van Hoesen, 1982; Vogt and Pandya, 1987; Cavada and Goldman-Rakic, 1989; Lavenex *et al.*, 2002; Kobayashi and Amaral, 2003; Kondo *et al.*, 2003) and restricted to those used by Maguire *et al.* (2001; Fig. 2). This model pre-specifies where multi-synaptic connections may exist and the potential direction of these connections, and thus ensures that any significant connections found between regions are anatomically viable (Addis and McAndrews, 2006; McIntosh, 1999). One connection from Maguire *et al.*'s model (left tPOLE to TPJ) was excluded from the present model as its inclusion in preliminary analyses resulted in model instability. The final model was stable, with stability indices  $< 1$ . A functional model for each group was constructed



**Fig. 2** Anatomical model for the effective connectivity analysis. Arrows represent the anatomical connections included in the model, based on known primate neuroanatomy. Note that the connections included in the model do not necessarily reflect monosynaptic connections (i.e. neuron to neuron) but rather multi-synaptic relays. Locations of the structures on the brain schematic are not accurate and are placed to maintain clarity. For Talairach coordinates of peak voxels, refer to Table 1. L = left, R = right; PHG = parahippocampal gyrus; tPOLE = temporal pole; MPC = medial parietal cortex.

using the signal intensity data from the relevant contrast images of each participant within that group. The extracted signal intensities for all regions were correlated, and the resulting correlation matrix constituted the functional model for that group.

### Path analysis

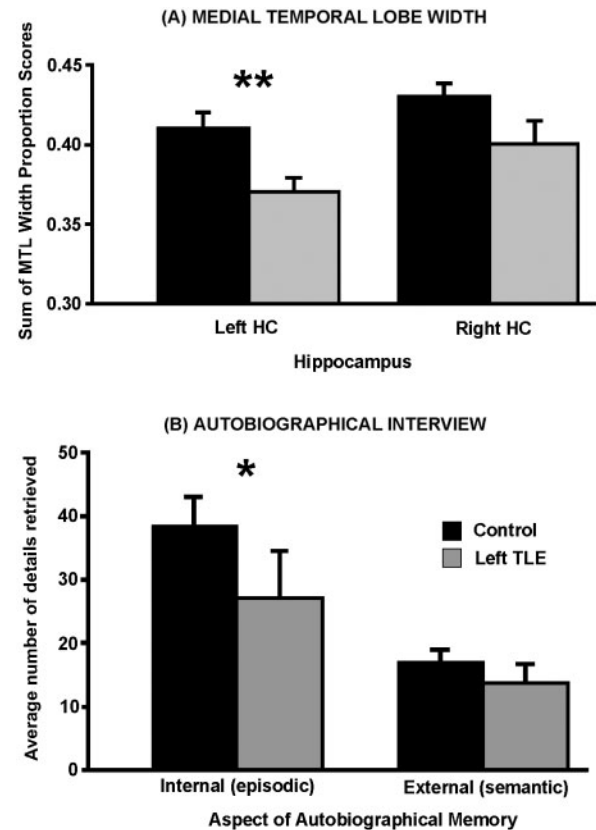
All SEM calculations were performed using Lisrel 8.30 (Joreskog and Sorbom, 1993). Firstly, estimates of path coefficients were calculated based upon correlations of signal intensity values within group and across subjects from the regions in the anatomical model. The resulting coefficients indicate the strength and direction of the effect of that link in the model. Unlike simple correlations, path coefficients are asymmetric (e.g. the path coefficient for the influence of region A upon B can be different from the path coefficient for the influence of region B upon A), thus providing information about the directionality of inter-regional interactions. Significant differences across the groups were then assessed using the stacked-model approach (McIntosh and Gonzalez-Lima, 1994). In an omnibus test, a null model was first constructed in which the path coefficients from both groups were set to be equal across groups. This was compared with a second, alternative model in which all path coefficients were allowed to vary. The differences between the models were assessed by subtracting their goodness-of-fit  $\chi^2$  values to obtain a  $\chi^2_{\text{diff}}$ . A significantly lower  $\chi^2$  value for the alternative model (i.e. a greater  $\chi^2_{\text{diff}}$  between the models) indicated there were significant group differences ( $P < 0.05$ ). Statistical significance of the  $\chi^2_{\text{diff}}$  was determined taking into account the difference of degrees of freedom between the null and alternative models. This approach has been shown to be sensitive for detecting differences in effective connections within an anatomically-defined network even if the absolute model fit is poor (Protzner and McIntosh, 2006).

Next, the connections which contributed significantly to the differences between the null and alternative model were ascertained by allowing connections to vary in a stepwise manner. Significantly different connections (i.e. that contributed to the significance of the difference across groups as evident by any decrease of the  $P$ -value associated with the  $\chi^2_{\text{diff}}$ ) were then set to vary for the remainder of the analysis. Any connection which did not contribute to the significance of the difference across groups ( $P < 0.05$ ) was set to be equal across group as the analysis progressed to the next connection. As this was a stepwise analysis, the order that the connections were entered in to the analysis could potentially affect the results, that is, whether a particular connection was found to be significant. Thus, four orders of connections were used: connections involving anterior to posterior regions; posterior to anterior; subcortical, then anterior to posterior cortical; subcortical, the posterior to anterior cortical (Addis and McAndrews, 2006). The stepwise analysis which resulted in the largest difference between the null and alternate chi-square values was posterior to anterior and this was used to determine significant connections.

## Results

### Hippocampal atrophy

HC atrophy in patients with LTLE was assessed using the sum of three linear width measurements (corrected for intracranial width; Figs 3A and 4). Mann–Whitney  $U$ -tests revealed significant atrophy in the left ( $U = 28.00$ ,  $P = 0.006$ ) but not right ( $U = 49.00$ ,  $P = 0.134$ ) HC in patients relative to healthy control subjects, consistent with the laterality of epileptic foci in these patients. A Wilcoxon signed rank test revealed a significant main effect of laterality with the



**Fig. 3** (A) Average sum of MTL width measurements (anterior, midway and posterior widths, proportional to intracranial width) of the left and right hippocampi of control and LTLE subjects. (B) Average number of episodic and semantic details produced by control and LTLE subjects during AM retrieval in the AI. Bars indicate SEM. \*Trend towards a significant group difference,  $P = 0.058$ . \*\*Significant group difference,  $P = 0.006$ .

right HC being significantly wider than the left ( $Z = -2.51$ ,  $P = 0.012$ ).

### Autobiographical memory performance

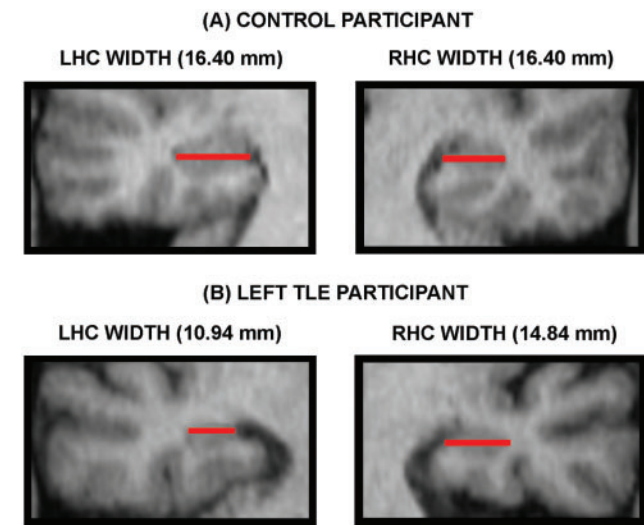
#### Autobiographical interview

From the adapted AI (Levine *et al.*, 2002), two AM scores were derived: the episodic detail score (i.e. average number of episodic details, including context, actions, thoughts, per AM) and the semantic detail score (i.e. average number of semantic details, including personal or general facts, repetitions, irrelevant details, per AM). Analyses of these scores revealed a mild deficit of episodic AM in LTLE patients, with a trend towards a significant reduction relative to the control group (effect size = 0.378; Fig. 3B). In contrast, there was no evidence of a group difference in semantic AM (effect size = 0.279). This mild episodic AM impairment was not directly related to reduced fluency or verbal output (as measured by phonemic FAS fluency test; Table 4). A Wilcoxon Signed Rank Test revealed a main effect of detail type, with subjects producing significantly

more episodic than semantic details ( $Z = -3.94, P < 0.001$ ). The groups did not differ in subjective ratings of rehearsal frequency or the recency of the AMs retrieved (i.e. the number of years since the event occurred; Table 3).

**AMs recalled during scanning**

The characteristics of AMs retrieved during scanning are also presented in Table 3. There were no significant group differences with respect to the recency of these AMs or subjective ratings of detail. However, LTLE patients rated their AMs higher in personal significance relative to controls.



**Fig. 4** Examples of left and right MTL width measurements in a (A) control and (B) LTLE participant. For each participant, a left and right coronal section of the medial temporal lobe is shown where the thinnest width measurement between the anterior and posterior boundaries of the midbrain was made. A red line representing the measurement is also shown. Note in this display, no corrections for intracranial width have been made. LHC = left HC; RHC = right HC; mm = millimeters.

This difference could represent an important confound; our earlier work shows that HC activity in controls is modulated by personal significance (Addis et al., 2004). To evaluate whether patients and controls used the rating scales in a similar manner, we correlated ratings of detail and personal significance (a ‘subjective’ index of memory) and the AI episodic detail score (an ‘objective’ measure of memory). Although these correlations were expected to be weak, given the different instructions for the AI (discuss AMs in detail for 5 min) and AM retrieval during scanning (recall cued AMs within 6 s), we could at a minimum examine the direction of the relationship between objective and subjective measures of AM performance. The groups differed with controls showing weak positive correlations while patients exhibited negative correlations, such that patients with more severe AM deficits (based on objective measures) tended to rate their own retrieval as higher in these AM qualities (Table 4). This suggests that patients lack insight into their memory

**Table 4** Spearman rank correlations between autobiographical interview (AI) episodic detail score and (1) neuropsychological measures and (2) subjective ratings of AMs retrieved during scanning

|   | Spearman correlation with AI episodic detail score |                         |
|---|--|-------------------------|
|   | Controls   | Patients                |
| (1) Neuropsychological measures   |  |                         |
| Phonemic (FAS) fluency  | n/a  | 0.200 ( $P = 0.580$ )   |
| (2) Subjective ratings of AMs retrieved during fMRI scanning <sup>a</sup> |  |                         |
| Detail  | 0.193 ( $P = 0.51$ )                               | -0.297 ( $P = 0.37$ )   |
| Personal significance   | 0.183 ( $P = 0.53$ )                               | -0.789 ( $P = 0.004$ )* |

<sup>a</sup>Subjective rating on a 5-point scale (1 = low, 5 = high) provided during the post-scan interview.

\*Significant correlation.

**Table 3** Characteristics of AMs retrieved by control and LTLE subjects

| Memory characteristic                               | Control group | LTLE group    | Mann–Whitney U-Test <sup>a</sup> |
|---|---------------|---------------|----------------------------------|
| Autobiographical interview                          |               |               |                                  |
| Mean rehearsal (SD)                                 | 2.29 (0.604)  | 3.13 (1.23)   | U = 43.00 ( $P = 0.066$ )        |
| Mean recency in years (SD)                          | 9.71 (2.70)   | 12.34 (6.36)  | U = 57.00 ( $P = 0.291$ )        |
| Range of recency                                    | 0.5–29 years  | 0.5–34 years  |                                  |
| Mean number of episodic details                     | 38.58 (16.04) | 27.58 (24.38) | U = 42.50 ( $P = 0.058$ )*       |
| Mean number of semantic details                     | 17.04 (7.57)  | 13.77 (9.79)  | U = 51.50 ( $P = 0.166$ )        |
| Autobiographical memory fMRI task                   |               |               |                                  |
| Mean recency in years (SD)                          | 14.42 (7.27)  | 13.93 (4.62)  | U = 77.00 ( $P = 1.00$ )         |
| Mean detail rating <sup>b</sup> (SD)                | 3.10 (0.65)   | 3.44 (0.94)   | U = 60.50 ( $P = 0.373$ )        |
| Mean personal significance rating <sup>b</sup> (SD) | 2.68 (0.40)   | 3.40 (0.78)   | U = 25.00 ( $P = 0.003$ )**      |

<sup>a</sup>Mann–Whitney U-score from non-parametric independent samples test.

<sup>b</sup>Subjective rating on a 5-point scale (1 = low, 5 = high) provided during the post-scan interview.

\*Marginally significant group difference.

\*\*Significant group difference.

deficits (Banos *et al.*, 2004) and are unable to accurately rate their memory performance. Alternatively, they may rate the AMs retrieved relative to other memories they have, which, on the whole, are poorer than those of controls. Due to the uncertainty about the validity of AM ratings made by patients, these data were not used for any further analyses.

### Neural substrates of AM retrieval

A random-effects contrast of BOLD signal associated with AM retrieval relative to the two semantic control tasks (Table 5 and Fig. 5A) confirmed that controls engaged the standard AM retrieval network, ( $P < 0.001$ , uncorrected for multiple comparisons, Maguire *et al.*, 2000, 2001; Piefke *et al.*, 2003) including LMPFC, anterior cingulate, lateral temporal cortex and TPJ and bilateral thalamus, posterior cingulate, HC and PHG. Although MTL activity was bilateral, it was more spatially extensive and greater in magnitude on the left (Fig. 5Ai). Note that engagement of this network was so robust and extensive at our standard whole-brain threshold (i.e.  $P < 0.001$ , uncorrected), all reported results are based on a more conservative threshold of  $P < 0.05$  (corrected).

The contrast of the AM and control tasks for LTLE patients (Table 5 and Fig. 5B) revealed this group did not significantly activate residual HC tissue during AM

retrieval, using either the standard threshold for whole-brain analysis or ROI analysis. However, there was evidence of subthreshold HC activity ( $P < 0.005$ ), more extensively in the right HC which is contralateral to the seizure focus and atrophy. Despite their poor engagement of the HC, LTLE patients did show significant activation in other regions of the AM retrieval network, specifically bilateral retrosplenial/posterior cingulate cortex, left precuneus and right tPOLE. Furthermore, a very weak (subthreshold) increase relative to the control tasks was seen in the LMPFC. Overall, the intensity and spatial extent of all activations in patients was considerably reduced relative to controls.

Between-groups random-effects contrasts of AM-related activity were performed with the AI episodic detail score included as a subject covariate to control for differences in episodic AM ability. There were no regions that patients engaged to a level greater than that observed in control subjects. In contrast, controls engaged numerous regions more than LTLE patients; (Table 6 and Fig. 6), including bilateral HC, which survived correction for multiple comparisons in an ROI analysis. This difference was more spatially extensive and of higher magnitude in the left HC. Other regions in which controls exhibited greater activity included bilateral retrosplenial/posterior cingulate cortex and TPJ, left precuneus, right thalamus and tPOLE.

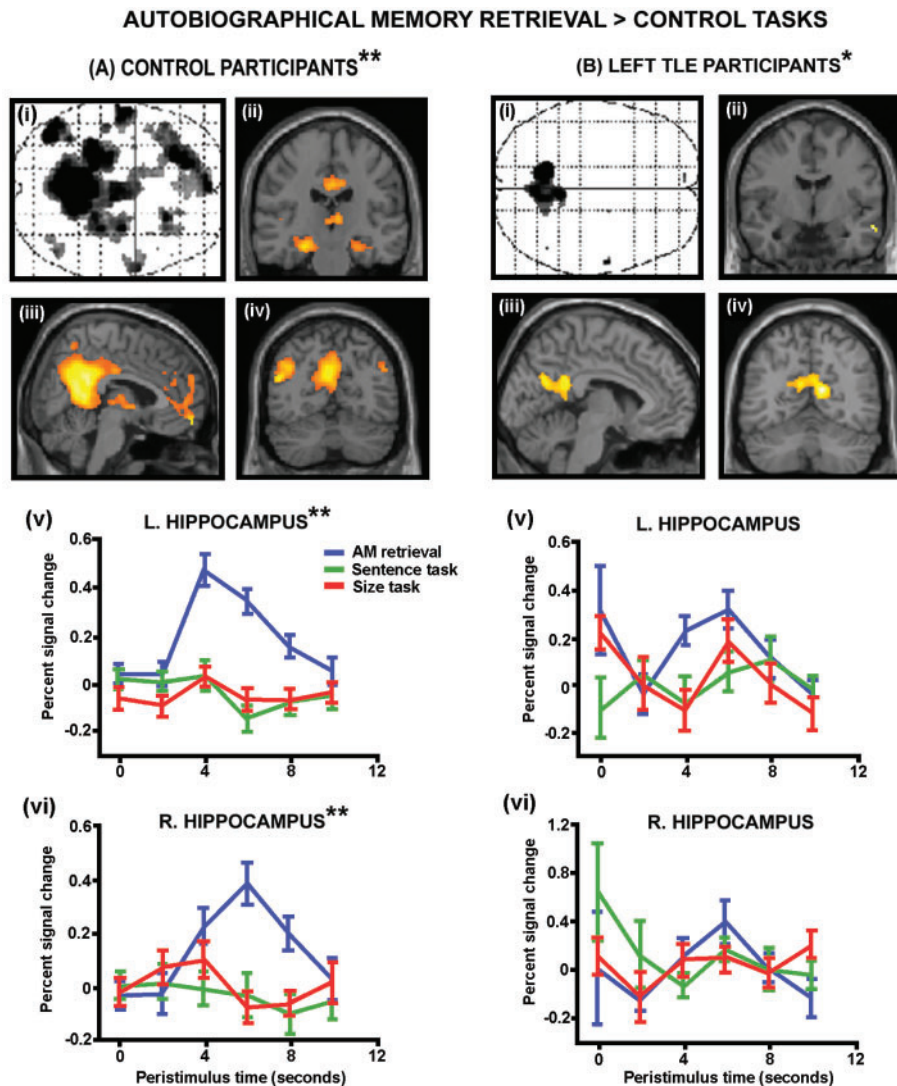
**Table 5** Brain regions activated in control and LTLE subjects during AM retrieval compared to control tasks (sentence completion and size discrimination)

| Brain region   | Coordinates |     |     | Z-score |
|--|-------------|-----|-----|---------|
|  | X           | y   | z   |         |
| <b>Control group*</b>                                  |             |     |     |         |
| L. Superior/middle frontal gyrus (BA 8/9)              | -22         | 40  | 31  | 5.58    |
| L. Medial frontal gyrus (BA 10/11)                     | -6          | 56  | -15 | 5.28    |
| L. Anterior cingulate cortex (BA 23)                   | -2          | -16 | 32  | 4.91    |
| L. Thalamus (dorsomedial nucleus)                      | -2          | -11 | 6   | 5.12    |
| R. Thalamus (dorsomedial nucleus)                      | 6           | -17 | 6   | 5.21    |
| L. Hippocampus   | -26         | -20 | -14 | 5.28    |
| R. Hippocampus   | 28          | -11 | -16 | 5.45    |
| L. Parahippocampal gyrus (BA 35/36)                    | -26         | -28 | -15 | 5.42    |
| R. Parahippocampal gyrus (BA 36)                       | 28          | -28 | -15 | 5.15    |
| L. Middle temporal gyrus (temporal pole; BA 21)        | -61         | -9  | -16 | 5.64    |
| R. Middle temporal gyrus (temporal pole; BA 21)        | 57          | 1   | -20 | 4.79    |
| L. Retrosplenial/posterior cingulate cortex (BA 23/30) | -2          | -55 | 21  | 6.26    |
| R. Retrosplenial/posterior cingulate cortex (BA 29/30) | 12          | -44 | 6   | 6.12    |
| L. Angular gyrus (BA 39)                               | -40         | -66 | 36  | 5.74    |
| R. Cerebellum  | 18          | -34 | -13 | 4.97    |
| <b>LTLE group**</b>                                    |             |     |     |         |
| R. Middle temporal gyrus (temporal pole; BA 21)        | 55          | -5  | -15 | 3.80    |
| L. Retrosplenial/posterior cingulate cortex (BA 23/31) | -14         | -54 | 14  | 4.95    |
| R. Retrosplenial/posterior cingulate cortex (BA 23/30) | 4           | -42 | 24  | 4.01    |
| L. Precuneus (BA 7)                                    | -2          | -63 | 27  | 3.84    |

For each region of activation, the co-ordinates of the maximally activated focus within each different structure are reported, as indicated by the highest Z-score. BA = Brodmann area.

\*All activations in the control group are significant at  $P < 0.05$  (corrected for multiple comparisons).

\*\*All activations in the LTLE group are significant at  $P < 0.001$  (uncorrected for multiple comparisons).



**Fig. 5** (A) Activity associated with AM retrieval relative to control tasks (sentence completion and size discrimination) in control subjects ( $P < 0.05$ , corrected; shown at  $P < 0.001$ , uncorrected). (i) The glass brain demonstrates the extensive nature of activity across the AM network, including activity in (ii) bilateral HC, (iii) LMPFC and parietal cortex (including precuneus, retrosplenial and posterior cingulate) and (iv) bilateral medial parietal cortex and TPJ. Average BOLD response for AM and control tasks exhibited in peak HC voxels are shown: (v) left HC ( $xyz = -28 - 35 - 8$ ); (vi) right HC ( $xyz = 28 - 11 - 16$ ). (B) Activity associated with AM retrieval relative to the control tasks in LTLE subjects ( $P < 0.001$ , uncorrected; shown at  $P < 0.005$ , uncorrected). (i) The glass brain shows the overall reduction in activity across the AM network. Activity was limited to: (ii) right temporal pole and (iii, iv) medial parietal cortex. Average BOLD responses exhibited in peak sub-threshold HC voxels are shown: (v) left HC ( $xyz = -20, -14, -14$ ); (vi) right HC ( $xyz = 20, -9, -20$ ). Bars indicate SEM. L = left; R = right. \*Significant at  $P < 0.001$ , uncorrected. \*\*Significant at  $P < 0.05$ , corrected for multiple comparisons.

### Effective connectivity of the AM retrieval network

SEM was used to assess group differences in the effective connectivity of the AM network. The omnibus SEM analysis revealed significant group differences in the effective connectivity of the AM retrieval network [ $\chi^2_{diff}(7) = 59.17, P < 0.0001$ ]. A stepwise assessment of connections was conducted to determine which connections differed significantly across groups ( $P < 0.01$ ). This revealed numerous connections centred on the left HC that behaved differently in the context of hippocampal pathology

(Fig. 7, Table 7). Firstly, there was a weakening of several positive connections evident in controls. Specifically, the influence of left MPC (retrosplenial/posterior cingulate) on left HC, as well as that of left HC on LMPFC, was dramatically weaker in LTLE. Interestingly, patients also showed a strengthening of the direct effective connection between left MPC and LMPFC cortices, bypassing the left HC. In other words, the influence of the left MPC upon LMPFC, which is expressed indirectly via the left HC node in the control group model, became more direct in the context of left HC damage. Another pattern of group

**Table 6** Brain regions in which control subjects showed greater activation than LTLE subjects during AM retrieval with AM performance (AI episodic detail score) as a covariate

| Brain region   | Coordinates |     |     | Z-score |
|--|-------------|-----|-----|---------|
|  | x           | y   | z   |         |
| R. Medial prefrontal cortex (BA 8/9)                   | 8           | 38  | 29  | 3.51    |
| R. Superior frontal gyrus (BA 8)                       | 22          | 8   | 51  | 3.94    |
| L. Middle frontal gyrus (BA 9)                         | 44          | 27  | 32  | 3.71    |
| R. Middle frontal gyrus (BA 46)                        | 46          | 36  | 17  | 3.57    |
| R. Middle frontal gyrus (BA 11)                        | 44          | 44  | −14 | 3.60    |
| R. Thalamus (dorsomedial nucleus)                      | 6           | −11 | 6   | 3.71    |
| L. Basal ganglia (putamen)                             | −28         | −18 | −4  | 3.88    |
| L. Hippocampus*  | −32         | −31 | −7  | 3.59    |
| R. Hippocampus*  | 22          | −33 | −4  | 4.15    |
| L. Parahippocampal gyrus (BA 36)                       | −30         | −32 | −12 | 4.10    |
| R. Parahippocampal gyrus (BA 35)                       | 20          | −32 | −9  | 3.93    |
| L. Superior temporal gyrus (temporal pole; BA 38)      | 50          | 15  | −7  | 3.33    |
| L. Superior temporal gyrus (BA 22)                     | −50         | 37  | 7   | 3.58    |
| L. Retrosplenial/posterior cingulate cortex (BA 29)    | −12         | −44 | 8   | 3.56    |
| R. Retrosplenial/posterior cingulate cortex (BA 29/30) | 12          | −42 | 6   | 3.48    |
| L. Precuneus (BA 7)                                    | −2          | −50 | 39  | 3.17    |
| L. Inferior parietal lobule (BA 40)                    | −38         | −50 | 45  | 3.94    |
| R. Inferior parietal lobule (BA 40)                    | 36          | −53 | 38  | 4.14    |
| R. Fusiform gyrus (BA 19)                              | 32          | −76 | −13 | 4.16    |
| L. Middle occipital gyrus (BA 19)                      | −44         | −76 | −6  | 4.08    |
| L. Cerebellum  | −26         | −68 | −39 | 3.99    |
| R. Cerebellum  | 30          | −42 | −18 | 3.30    |

All activations are significant at  $P < 0.001$  (uncorrected). For each region of activation, the coordinates of the maximally activated focus within each different structure are reported, as indicated by the highest Z-score. BA = Brodmann area.

\*Bilateral HC ROI analysis indicated group difference in left and right hippocampal activity was significant at  $P < 0.05$  (corrected).

differences in effective connectivity was a change in the sign of connections involving left PHG. The positive connections between this structure and the left tPOLE and HC in control subjects became strikingly negative in patients. Additionally, the negative connection between left PHG and LMPFC became positive.

## Discussion

### Autobiographical memory retrieval

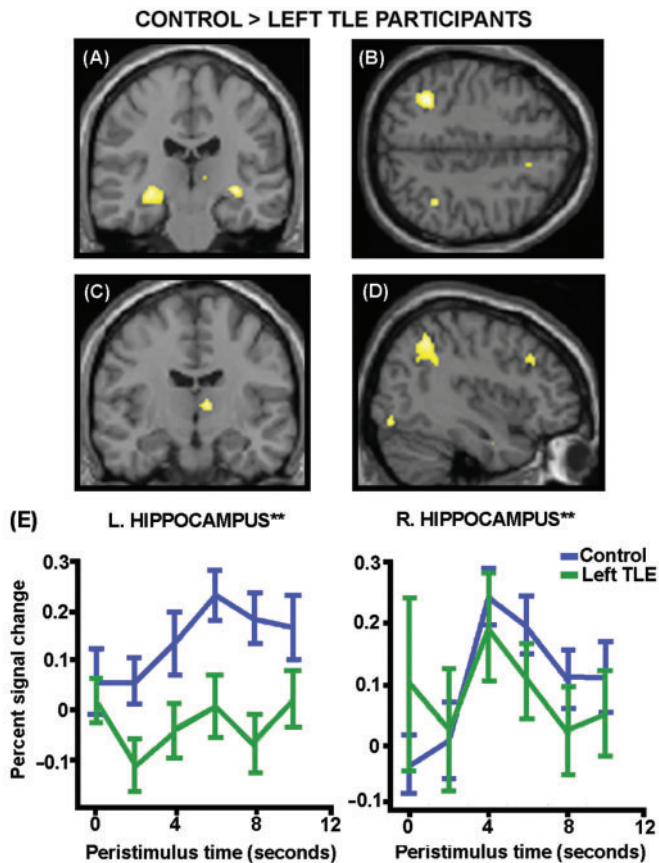
The AI revealed that LTLE patients have a mild impairment of episodic but not semantic AM. This is consistent with other reports of AM deficits in patients with TLE (Barr *et al.* 1990; Viskontas *et al.*, 2000) and other patients with MTL damage (Gilboa *et al.*, 2005; Steinvorth *et al.*, 2005; Squire and Bayley, 2007). The specificity of this deficit supports Multiple Trace Theory and the premise that the MTL supports retrieval of AMs containing episodic detail and is not engaged in recovery of remote semantic information (Nadel and Moscovitch, 1997; Moscovitch *et al.*, 2005, 2006). As the episodic AM deficit was not associated with either semantic AM or verbal fluency performance, it does not appear to merely reflect a general impairment in verbal output (Martin *et al.*, 1990; Barnett *et al.*, 2000). Furthermore, there were no group differences in either levels of rehearsal or recency of the AMs retrieved, eliminating important possible confounds that might

explain observed differences in the amount of episodic details produced (e.g. Piefke *et al.*, 2003).

### Activation of the AM network in LTLE

The contrast of AM retrieval to the control tasks in control subjects revealed robust activation of the standard AM network documented in many previous studies (see Svoboda *et al.*, 2006, for a meta-analysis). Here, the HC was engaged bilaterally, though more extensively and to a slightly greater magnitude on the left as has been demonstrated repeatedly (e.g. Fink *et al.*, 1996; Ryan *et al.*, 2001; Maguire and Frith, 2003; Piefke *et al.*, 2003; Rekkas and Constable, 2005; but see Viard *et al.*, in press). In striking contrast, engagement across the AM retrieval network was notably reduced in LTLE patients, even at an uncorrected statistical threshold. This observation was confirmed in all regions across the AM network by the direct group contrast of AM-related activity.

Although reductions in AM-associated activation were widespread, the functional integrity of the left HC appeared particularly compromised, consistent with their pathological profile. Examination of subthreshold ( $P < 0.005$ , uncorrected) HC activity revealed that rather than the typical greater left-than-right pattern seen in controls here and elsewhere (Fink *et al.*, 1996; Ryan *et al.*, 2001; Maguire and Frith, 2003; Piefke *et al.*, 2003;), patients exhibited more spatially extensive activity in the intact right HC than the



**Fig. 6** Regions in which control subjects show greater activation than LTLE subjects during AM retrieval (AI episodic detail score as a covariate;  $P < 0.001$ ; shown at  $P < 0.005$ , uncorrected): (A) bilateral HC; (B) bilateral TPJ; (C) right thalamus; and (D) right fusiform and TPJ. Average BOLD response for AM tasks exhibited by control and LTLE subjects in the peak voxel within the (E) left and right HC are shown (left,  $xyz = -32, -31, -7$ ; right,  $xyz = 22, -33, -4$ ; bars indicate SEM). L = left; R = right. \*\*Significant at  $P < 0.05$ , corrected for multiple comparisons.

damaged left HC. Furthermore, the reduction in HC activity was more profound in the left HC, where the magnitude of activation was equivalent in AM and control tasks. Although there was a significant group difference in right HC, examination of the timecourse data (Fig 5Bvi) indicates high variability in the LTLE group, with some subjects clearly showing close to normal levels of activation. The comparable nature of activity in this right hippocampal voxel is important to note, as it suggests that the lower activity levels in other parts of the network do not simply reflect a generalized inability to activate tissue in response to cognitive tasks. Other patient studies, notably a positron emission tomography study by Eustache and colleagues (2004), have shown that integrity of the right HC appears to be of importance in AM. Specifically, in patients with Alzheimer's disease, AM deficits significantly correlated with reduced metabolism in the right HC. This highlights the need for studies examining the impact of unilateral

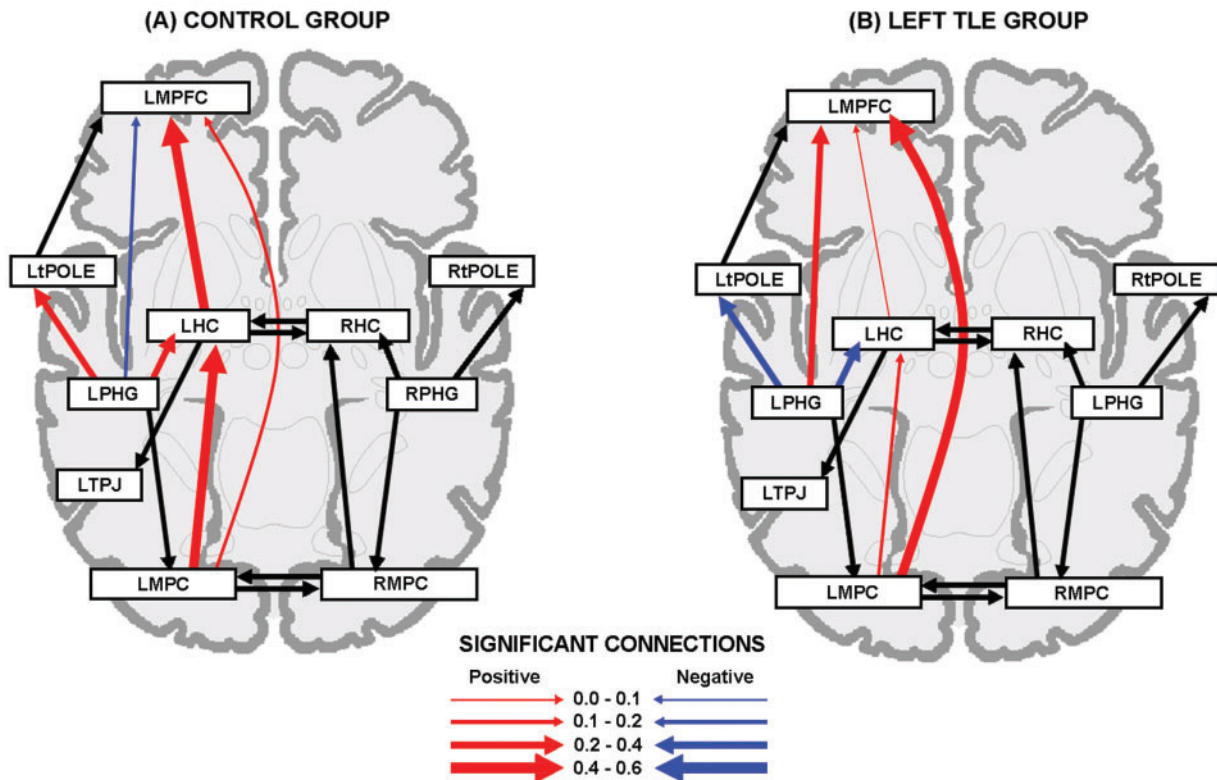
right MTL damage on AM retrieval and the engagement of the AM network.

Overall, the ability of this AM paradigm to lateralize according to the side of the TLE seizure focus indicates it is sensitive to HC atrophy and dysfunction. Even so, it is possible that the finding of reduced AM-related activity in the left HC in a group analysis is related, at least in part, to inter-subject inconsistencies in the exact location of hippocampal activity. Thus, even if patients engage residual hippocampal tissue, the varying location of this tissue across subjects likely reduces the inter-subject overlap in activity needed to achieve a significant effect. However, the presence of structural damage is not the only factor to be considered given there were group differences even in structurally intact regions outside the MTL.

There were no regions in which LTLE patients exhibited more activity than controls, suggesting there was no evidence of compensatory activity supporting AM retrieval in patients. This is contrary to the fMRI findings in patient Jon (Maguire *et al.*, 2001), who recruited a number of right hemispheric regions not engaged by the control subjects. This is perhaps not surprising given the early time-point and bilaterality of Jon's HC damage and the severity of his AM deficit. However, it may also reflect a more general concern in interpreting functional imaging data in patients relative to controls when level of performance is not matched. Here, we attempted to statistically control for group differences in task ability by using the AI episodic detail score as a covariate. Had there been a better strategy to titrate performance, it may have been possible to identify compensatory activity (Stern *et al.*, 2005). We attempted to use the subject-provided ratings for each memory as an approach to identify equivalent levels of 'performance'. Unfortunately, we concluded patients and controls were not using these rating scales in the same way, with subjective ratings by patients during scanning being inversely correlated with the AI episodic detail score. Whatever the source of this difference, it rendered use of subjective ratings as a potential 'matching' variable inappropriate. In future studies of AM in patient populations, it would be useful to collect an objective recollection rating during the post-scan interview (e.g. AI episodic detail score as a measure of level of detail) for each AM retrieved in the scanner. Despite the lack of compensatory levels of activation in these patients, there is evidence from our effective connectivity analyses suggesting that re-routing of interactions between neural regions may be an important, and potentially compensatory, mechanism.

### Connectivity of the AM network in LTLE

Overall, the reduction of activity across the brain in LTLE patients suggests that when the left MTL is damaged, the ability of other regions in the AM network to become activated is affected. An effective connectivity analysis also revealed distal effects of left MTL damage, with striking



**Fig. 7** Diagrammatic representation of the effective connections within the neural network mediating AM retrieval in **A** control and **B** LTLE subjects. Connections which differed significantly between the groups are depicted in colour (red = positive influence, increasing activity in the target node, blue = negative influence decreasing activity in the target node). Arrow thickness represents the strength of the connection (i.e. the value of the path coefficient), as described in the key (see Table 7 for exact value of path coefficients). Connections which did not differ significantly between groups are depicted in black.

**Table 7** Path coefficients for effective connections that differed significantly between control and LTLE groups

| Connection            | Path Coefficient |               |
|-----------------------|------------------|---------------|
|                       | Controls         | LTLE Patients |
| Left MPC → Left HC    | 0.52             | 0.13          |
| Left HC → LMPFC       | 0.57             | 0.05          |
| Left MPC → LMPFC      | 0.13             | 0.56          |
| Left PHG → Left tPOLE | 0.38             | −0.38         |
| Left PHG → Left HC    | 0.33             | −0.28         |
| Left PHG → LMPFC      | −0.10            | 0.28          |

PHG = parahippocampal gyrus; tPOLE = temporal pole; MPC = medial parietal cortex.

group differences in the AM network, particularly in those connections involving the left HC. Firstly, the strongly positive influence of left MPC (retrosplenial/posterior cingulate) on left HC in controls was substantially weakened in patients. Medial parietal regions support visuospatial imagery inherent in episodic AMs, and thus in controls, this pattern of connectivity likely reflect

retrieval of such information and its subsequent integration with other aspects of the AM by the HC. Given that visuospatial information is a dominant type of detail in AMs (Greenberg and Rubin, 2003), this weakened connectivity might, in part, explain the reduction of episodic details in the AMs of LTLE patients. This finding, however, is in contrast to that seen in Patient Jon, who exhibited significantly more connectivity between left MPC and HC. While this disparity might reflect the fact that, unlike the patients in this study, Jon's left HC was significantly engaged during AM retrieval relative to control tasks, this may be related to a host of other factors, including differences in paradigm (autobiographical recognition versus retrieval).

In controls, the left HC interacted strongly with LMPFC. Furthermore, the left MPC was able to influence LMPFC indirectly via this path. This strong posterior-to-anterior interaction may reflect verification by prefrontal regions of visuospatial memory elements reactivated by posterior cortex (Moscovitch and Winocur, 2002). In patients, this left HC to LMPFC connection was significantly weakened, akin to that evident for the left MPC influence upon HC.

Thus, left HC pathology disrupted both segments of the interaction between left MPC and LMPFC. However, the direct positive influence between left MPC and PFC was significantly stronger in patients, effectively bypassing the compromised left HC node. In fact, a strengthening of this same connection was evident in Patient Jon (Maguire *et al.*, 2001). It is not surprising that this potentially compensatory mechanism in the LTLE patients involves left MPC and LMPFC, given that these are two of the only regions engaged by AM retrieval in these patients (albeit LMPFC region was sub-threshold), suggesting that a reasonable level of functionality may be required for regions to support AM retrieval in a compensatory manner. This finding also indicates that the influence of left MPC regions on LMPFC, whether direct or via the left HC, is an important interaction mediating AM retrieval. Indeed, when the 'preferred' route via the HC is disrupted, an alternate, and possibly suboptimal, route emerges. Finally, the presence of a strengthened interaction between nodes which were engaged in patients, albeit at a reduced or sub-threshold level, suggests that activity in these regions reflects task relevant activity.

An interesting pattern of results was evident for connections involving the left PHG. In controls, this structure positively influenced the left HC and tPOLE, a finding concordant with the findings of (Maguire *et al.*, 2000). Furthermore, left PHG negatively influenced LMPFC, albeit moderately. In LTLE patients, however, the sign of all three connections reversed. Thus, in the network mediating AM retrieval in patients, the left PHG negatively influenced the HC and tPOLE, but positively influenced LMPFC. In patient Jon, PHG–HC connectivity was also different from controls, but rather than becoming negative, this influence was absent. Here, it appears that the left PHG is no longer acting in synchrony with other left temporal structures. Rather than these three regions being positively connected and PHG activity resulting in increased HC and temporopolar activity, in patients PHG activity negatively influences these other two regions. This could reflect the PHG taking a dominant role in the context of HC damage, and suppressing the activation of any residual HC tissue. At the same time, this suppression has a more generalized effect within the left temporal lobe, inhibiting undamaged regions such as the tPOLE. Further, the fact that the connectivity between the left PHG and LMPFC becomes positive when the HC input into LMPFC is substantially weakened could also be taken to support this hypothesis that patients are retrieving different types of episodic detail during AM retrieval. For example, in associative recognition tasks, it has been demonstrated that the PHG region is sufficient to support retrieval of unitized information whereas the HC is required for binding of memory elements (Quamme *et al.*, 2007).

It is striking to note that with a left-lateralized seizure focus and left HC atrophy there are no changes to the pattern of effective connectivity in the right hemisphere.

One might expect the spared hemisphere to compensate for damage in the left hemisphere, for example, with the strengthening of connections between nodes homologous to those forming critical connections in the left hemisphere. It is of particular interest that connections involving the right HC were not strengthened, especially given that patients showed more extensive activity in the right than left HC, albeit at a sub-threshold level. Furthermore, the only temporal region significantly engaged in patients during AM retrieval, the right tPOLE, showed no changes in its effective connectivity. These findings are, however, consistent with observations from our earlier unilateral lesion (Viskontas *et al.*, 2000) and functional imaging (Addis *et al.*, 2004) findings which suggest that the right and left medial temporal regions may contribute to AM retrieval in different ways or via different attributes and thus full compensation for focal damage is improbable.

## Conclusions

The findings presented here revealed that the effects of damage within the MTL and AM network are complex and varied, characterized by both reductions of activation and changes in connectivity. This study provides clear evidence for an important role of the HC within the AM network, possibly as the 'hub' of the network. When this node is damaged, a cascade of effects appears on multiple levels. Behaviourally, the episodic quality of AMs is diminished, while at the neural level, activity is decreased not only in the damaged HC but the entire AM network is down-regulated. Effective connectivity analyses revealed that the successful retrieval of AMs in these patients was supported by an altered network that bypasses the damaged hippocampal node, and shows increased reliance on other components of the AM network. This included the emergence of a strong direct connection between left MPC (retrosplenial/posterior cingulate) and medial PFC, as well as an increased role of the left PHG. This latter finding, along with the reduction in the number of episodic details comprising the residual AMs of LTLE patients, may reflect the fact that successful retrieval of such AMs is more dependent on other forms of associative binding specifically supported by the PHG, such as the retrieval of unitized information, rather than the online reintegration of episodic details supported by the HC.

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