Autobiographical memory in epileptic patients after temporal lobe resection or bitemporal hippocampal sclerosis

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ORIGINAL RESEARCH

Autobiographical memory in epileptic patients after temporal lobe resection or bitemporal hippocampal sclerosis

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Abstract

The human hippocampus is believed to be a crucial node in the neural network supporting autobiographical memory retrieval. Structural mesial temporal damage associated with temporal lobe epilepsy (TLE) provides an opportunity to systematically investigate and better understand the local and distal functional consequences of mesial temporal damage in the engagement of the autobiographical memory network. We examined 19 TLE patients (49.21 ± 11.55 years; 12 females) with unilateral mesial TLE (MTLE; 12 with anterior temporal lobe resection: 6 right MTLE, 6 left MTLE) or bilateral mesial TLE (7 BMTLE) and 18 matched healthy subjects. We used functional MRI (fMRI) with an adapted autobiographical memory paradigm and a specific neuropsychological test (Autobiographical Memory Interview, AMI). While engaged in the fMRI autobiographical memory paradigm, all groups activated a large fronto-temporo-parietal network. However, while this network was left lateralized for healthy participants and right MTLE patients, left MTLE and patients with BMTLE also showed strong activation in right temporal and frontal regions. Moreover, BMTLE and left MTLE patients also showed significant mild deficits in episodic autobiographical memory performance measured with the AMI test. The right temporal and extra-temporal fMRI activation, along with the impairment in autobiographical memory retrieval found in left MTLE and BMTLE patients suggest that alternate brain areas—other than the hippocampus—may also support this process, possibly due to neuroplastic effects.

Keywords Episodic memory · Temporal epilepsy · Bitemporal epilepsy · Functional MRI · Autobiographic network

Introduction

A core feature of episodic memory is our ability to retrieve personal experiences, referred to as autobiographical memory (AM) (Scoville and Milner 1957; Tulving 2002). These personal memories are usually accompanied by factual knowledge about a person's own past and rich perceptual information (Neisser et al. 1996), which form an autobiographical skeleton known as personal semantics (Renoult et al. 2012). The focus of the present paper is AM, or the ability to update and maintain a conscious record of our particular life events.

How autobiographical memories are represented in the human brain is still a central question in neuroscience memory research. Although the human hippocampus is thought to be a central node in the brain network subserving AM retrieval (Spiers et al. 2001), its exact function regarding the retrieval of long-term episodic memories remains controversial. It is worth noting that lesion-based neuropsychological and also neuroimaging studies with the presence of hippocampal and medial temporal lobe (MTL) damage usually show AM impairment (Addis et al. 2007; Gilboa et al. 2005; Steinvorth et al. 2005). Along this line, patients with temporal lobe epilepsy (TLE) or anterior temporal lobe resective epilepsy surgery (ATLR; Milner and Klein 2016; Noulhiane et al. 2007;

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Svoboda et al. 2006) provide an excellent opportunity to investigate the local and distal functional consequences of MTL damage in the engagement of the AM network. Indeed, hippocampal sclerosis (HS) is the most common cause of TLE and is a well-defined syndrome, often identified on MRI by hippocampal atrophy and signal abnormalities and on EEG as showing anterior temporal spikes (Rudie et al., 2015; Wieser 2004). It is also the most frequent surgically treated epilepsy syndrome, being a candidate for ATLR surgery with favorable prognosis (Wiebe et al. 2001). Strikingly, impairment in personal episodic AM in patients awaiting ATLR is similar to that of patients who have already undergone surgery (Noulhiane et al. 2007; St-Laurent et al., 2011; Viskontas et al. 2000), suggesting that removal of a nonfunctional hippocampus (i.e., already damaged) may not produce any additional memory deficits (Hermann et al. 1994; Vilà-Balló et al. 2017). Moreover, among TLE patients, those suffering from bilateral HS with seizures arising independently from each temporal lobe (BMTLE; just 14–23% of patients with refractory TLE; So et al. 1989) provide even a more unique (and uncommon) sample in which to study AM, as for these patients contralateral reliance is difficult and interhemispheric seizure transmission plays a notable role (Maguire et al. 2001; Mc Cormick et al., 2018; Scoville and Milner 1957; Steinvorth et al. 2005). However, we are not aware of previous attempts to investigate AM-functional related activity in a substantial BMTLE sample.

Albeit, TLE, ATLR and, especially, BMTLE patients provide an excellent framework to study AM, the neurofunctional and plastic AM-related changes elicited by these pathologies have been scarcely studied (Addis et al. 2007; Maguire 2001; Mc Cormick et al., 2018; Viskontas et al. 2000). Accordingly, the detection of AM problems in TLE is often missed in clinical practice. In addition and while, as aforementioned, lesion studies support the important role of the hippocampus in AM, there are many other factors that can influence the pattern and extent of retrograde memory loss after a temporal lobe lesion, such as the method of assessing and/or scoring memory performance.

In order to address these weaknesses and to answer the important question of which brain regions support AM retrieval after hippocampal damage, here, we examined AM functional MRI-related activity in a group of ATLR and BMTLE patients, and matched healthy subjects.

Material and methods

Participants

Nineteen patients with medically refractory TLE with unilateral or bilateral HS (49.21 ± 11.55 years; 12 females; mean epilepsy onset 11.53 ± 12.54 years; mean duration of epilepsy 36.00 ± 14.73 years; 6 with right and 6 with left unilateral HS; 7 with bilateral HS) and 18 healthy individuals matched for handedness (Edinburgh handedness test; Oldfield 1971), age (49.50 ± 11.93 years), gender (12 females) and education were included in the study. All unilateral TLE patients had already undergone epilepsy ATLR surgery (consisting of en bloc resection of the anterior 3.5 to 5.0 cm of the lateral temporal lobe, followed by removal of the mesial structures including the amygdala and more than 2.5 cm of the hippocampus). It is of note that the AM-related impairment in patients awaiting ATLR is similar to that of patients who have already undergone surgery (Viskontas et al. 2000). All patients were recruited during periodic clinical follow-up examination at the University Hospital of Bellvitge, and the diagnosis was established according to clinical, EEG and MRI data (Cendes et al. 2000). Long-term video-EEG monitoring was performed in all patients with all recorded seizures having the typical mesial TLE electroclinical phenotype. The seizures arose exclusively from one temporal lobe in presurgery unilateral TLE patients. All the results converged with MRI data. In contrast, in BMTLE patients with bilateral HS, seizure onsets arising independently from each temporal lobe were detected and recorded. In order to confirm bilateral epilepsy and rule out epilepsy surgery in this group, fluorodeoxyglucose positron emission tomography (FDG-PET) was performed showing bilateral temporal hypometabolism. There were no findings suggestive of extratemporal partial epilepsy in either group. We estimated the mean seizure frequency reported by the patient in the five years medical follow-ups preceding the assessment or surgery. There were no reports of patients having generalized seizures, except for 1 in a left MTLE patient. Patients had no previous history of status epilepticus. Potential precipitant injuries (initial precipitant injury; IPI) which might have contributed to the development of TLE included 3 febrile convulsions, 4 meningitis or encephalitis antecedent, 3 remote trauma, 2 birth prolonged exposure to anoxia, while 5 patients had no IPI, and the IPI was unknown in 2 patients. Postoperative seizure outcome was classified by the Engel outcome classification scale, which classifies postoperative seizures along a range from no epileptic activity to severe recurrent seizures: seizure-free or free of disabling seizures (class I), rare disabling seizures (class II), worthwhile improvement (class III), and no change (class IV). All patients that had undergone surgery were either seizure-free postoperatively or had occasional non-disabling seizures (Engel IA and IB respectively) with antiepileptic drug (AED) withdrawal or significant reduction. The histopathological findings confirmed HS in 10 patients, one patient had no pathologic diagnosis and in another patient no adequate surgical specimen was available for histopathologic evaluation. The seizure-related outcome and postoperative AEDs were collected during follow-up (which included an MRI session), at least

Table 1 Demographic characteristics of the TLE patients and control samples

	Gender	Age/surgery	Onset	Duration	MRI	N. AEDs	Seizure Frequency	PostOp AEDs	Engel Outcome Classification	IPI
B1	F	55	45	10	BHS	2	15–20	–	–	Yes
B2	M	64	7	57	BHS	3	3–4	–	–	Yes
B3	M	56	14	42	BHS	2	1–2	–	–	Yes
B4	F	43	12	31	BHS	2	10–16	–	–	Yes
B5	M	53	3	50	BHS	2	1	–	–	No
B6	F	35	3	32	BHS	2	8–16	–	–	Yes
B7	F	65	12	53	BHS	2	1–2	–	–	NK
B group	4F	53 (SD10.81)	13.71 (SD14.49)	39.29 (SD16.35)		2.14 (SD0.38)	7.14 (SD6.83)	–	–	
L1	F	37(35)	1	34	LHS	2	1–2	0	I	No
L2	F	63(61)	3	58	LHS	2	4–5	0	I	No
L3	F	34(32)	16	11	LHS	3	30–40	1	I	Yes
L4	F	57(54)	4	50	LHS	2	2–3	0	I	Yes
L5	F	45(44)	1	43	LHS	2	6–8	1	I	No
L6	F	41(39)	1	38	LHS	4	5–6	0	I	Yes
L group	6F	46.17(SD11.50)/ 44.16(SD11.30)	4.33 (SD5.85)	39.00 (SD16.17)		2.5 (SD0.84)	9.17 (SD12.81)	0–1	I	
R7	M	46(43)	1	42	RHS	3	10–12	0	I	Yes
R8	M	38(36)	18	18	RHS	3	4–6	0	I	Yes
R9	M	53(51)	11	40	RHS	3	3–4	1	I	Yes
R10	M	68(66)	41	25	RHS	2	3–4	0	I	Yes
R11	F	30(26)	9	17	RHS	2	14–16	0	I	No
R12	F	55(50)	17	33	RHS	3	3–4	1	I	NK
R group	2F	48.33(SD13.43)/45.33(SD13.76)	16.17 (SD13.63)	29.17 (SD10.83)		2.67 (SD0.52)	6.91 (SD4.91)	0–1	I	
Controls	12F	49.50 (SD11.93)	–	–	–	–	–	–	–	–

For controls the data represent the mean followed by the standard deviation in parenthesis. All unilateral TLE patients had undergone epilepsy surgery (anterior temporal lobe resection) at least 18 months before the MRI session. F, female; M, male; BHS: Bilateral Hippocampal Sclerosis LHS: Left Hippocampal Sclerosis RHS: Right Hippocampal Sclerosis; SD: standard deviation; Age/surgery: age at the MRI session/age at surgery in years; Onset: age at onset of epilepsy in years; Duration: epilepsy duration in years before surgery; Seizure frequency refers to the number of self-reported complex-partial seizures (CPS) per month before surgery; N. AEDs: Number of Antiepileptic Drugs before surgery; PostOp AEDs: postoperative antiepileptic drugs; IPI: initial precipitant injury. NK: not known. An Engel Outcome Classification of I, implies that patients were seizure free or with occasional non disabling seizures

18 months after ATLR (mean 27.3 ± 5.7 months). The exclusion criteria were evidence of MRI lesions other than HS or ATLR, psychiatric illness or impairment of general intellectual capacities. All the patients and controls were right-handed, as assessed with the Edinburgh handedness test (Oldfield 1971). The control group was composed of 18 subjects who had no record of neurological illnesses or psychiatric disorders. See Table 1 for demographic characteristics of the patients and control samples. The study was approved by the Ethical Committee of University Hospital of Bellvitge. Written informed consent was obtained from all the participants.

Neuropsychological assessment

All participants underwent a standardized neuropsychological examination before the MRI study. The evaluation was designed to explore a variety of mental operations with special emphasis on memory processing. In particular, a set of subtests from the Wechsler Memory Scale III (WMS III) and Wechsler Adult Intelligence Scale III (WAIS III) was employed to assess immediate and delayed verbal memory; immediate and delayed visual memory and working memory; and verbal comprehension (Wechsler 1997, 2004). Additionally, the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 1983), Semantic and Phonological fluency tests (Peña-Casanova, 2005) and the Trail Making Test (Reitan, 1992) were also carried out by all participants in order to explore their naming abilities, verbal fluency and processing speed, respectively (see Table 2). All these scores were compared to normative data, minimizing the possible bias of age and education in further statistical analysis. The Rey Auditory Verbal Learning test (RAVLT) was also performed, measuring the learning capability (total amount of correct responses) and delayed retrieval and recognition of the word list (results of RAVLT measures are all reported as a raw score due to a lack of normative data for the Spanish population). To compare clinical, demographic and neuropsychological data a Kruskal-Wallis test was used to test for between-subjects differences (RMTLE, LMTLE, BMTLE and Control). SPSS 18.0 software (SPSS Inc., Chicago, USA) was used for the analyses. Bonferroni correction was used to correct for the number of neuropsychological variables tested (13 tests, $p < 0.0038$). Differences between groups were further explored using Mann-Whitney U tests for variables showing significant and corrected group results. For these direct between-groups comparisons, Bonferroni correction was also used to control for multiple testing (6 between group comparisons). Differences in sex were assessed using a Chi-Squared test.

Table 2 Neuropsychological results of TLE patients and healthy participants

	RMTLE Mean ± SD	LMTLE Mean ± SD	BMTLE Mean ± SD	CONTROLS Mean ± SD
Years of education	11.2 ± 3.0.3	9.33 ± 4.84	9.86 ± 2.73	11.17 ± 2.99
Handedness	1.16 ± 0.36	1.67 ± 1.63	1.57 ± 1.51	1.45 ± 1.01
Immediate verbal memory	7.25 ± 3.1	7.5 ± 3.39	6.14 ± 2.41	6.28 ± 2.05
Delayed verbal memory	7.25 ± 2.06	7.83 ± 2.64	5.43 ± 2.76	9.78 ± 2.60
Immediate visual memory *	7.25 ± 1.26	8.17 ± 2.56	6.29 ± 2.98 #	11.72 ± 3.36
Delayed visual memory	7.25 ± 1.5	8.33 ± 2.42	5.14 ± 2.67	9.72 ± 2.16
WM: Digit Span	12 ± 3.16	7.5 ± 2.59	9 ± 3.1	9.28 ± 3.08
WM: L & N	10.25 ± 1.5	8.83 ± 4.22	7.14 ± 3.02	9.67 ± 3.34
VC: Vocabulary	10.67 ± 1.53	8.67 ± 1.37	8.86 ± 2.67	11.67 ± 2.00
BNT *	9.75 ± 0.5	6.0 ± 2.9 #	7 ± 2.58 #	10.50 ± 2.77
Fluency (Phonological - "p")	8.75 ± 2.75	5.4 ± 0.89	7.86 ± 5.46	10.78 ± 2.13
Fluency (Semantic-animals)	9.5 ± 1.91	5 ± 2.92	6.14 ± 3.13	9.89 ± 2.65
TMTA	6.5 ± 4.2	6.33 ± 3.39	6 ± 3.22	10.11 ± 3.32
TMTB	8 ± 1	8.5 ± 2.69	7.17 ± 3.43	8.78 ± 3.10
RAVLT	49.6 ± 13.79	40 ± 7.46	34.71 ± 9.66	44.72 ± 8.43

The comparison between the overall neuropsychological performance of patients versus controls is represented with the mean and standard deviation of the normalized test scores (normalization according to age and educational level in all the probes, except Rey Auditory Learning Test due to a lack of normative data for Spanish population). In order to detect possible differences between groups, a Kruskal-Wallis test was employed for each of the neuropsychological subtests. We used Bonferroni correction to take into account the 13 tests used. M: male; F: female; Handedness: 1 = right and 5 = left; WM, working memory; L & N, Letters and Numbers; VC, Verbal Comprehension; BNT, Boston Naming Test; TMT, Trail Making Test; RAVLT- Rey Auditory Verbal Learning test

**Significant, Bonferroni corrected group effect (Kruskal-Wallis)*

 # Significant Bonferroni corrected difference as compared to controls (Mann-Whitney U)

MRI scanning parameters

Images were acquired using a 3.0 Tesla Siemens Trio MRI system at the Hospital Clinic of Barcelona. A T1-weighted image (slice thickness = 1 mm; no gap; number of slices = 240; TR = 2300 ms; TE = 3 ms; matrix = 256 × 256; FOV = 244 mm; voxel size = 0.95 × 0.95 × 1 mm^3) was acquired. Two functional runs of 428 echo-planar images (EPI) were acquired using a single-shot T2*-weighted gradient-echo EPI sequence (slice thickness = 4 mm; no gap; number of slices = 32, interleaved order; TR = 2000 ms; TE = 29 ms; flip angle = 80°; matrix = 80 × 80; voxel size = 3 × 3 × 4 mm^3).

fMRI autobiographical memory task

We used an autobiographical memory task with two conditions: autobiographical memory retrieval (AMT, the experimental condition) and a go left/right arrow task with left/right key-press responses (control condition). Participants were tested for 16 remote and 16 recent memories, each of which contained half positive and half negative emotional valence. Considering previous AM neuroimaging studies (Maguire, et al., 2001) and the unconstrained nature of AM, we did not use rest as the baseline condition. The start of the AMT condition was visually presented with a title cue (e.g "think about your wedding day"). Subjects were instructed to close their eyes after reading the cue and to recollect the personal episode. The memories were cued using the St. Jacques and Levine (2007) autobiographic interview list of titles in order to avoid a pre-scan interview. The cues presented were chosen based on the patients' history and a previous family interview. These two methodological issues were considered because the aurally presented material and the data collection time for testing recollections have been described as naturally contributing to the predominantly left-lateralized activation pattern of the AM network (Addis et al. 2004; Maguire and Frith 2003). After 16 s of retrieval, a sound was aurally presented to signal the end of the retrieval phase, and the subjects were aurally instructed to open their eyes (Denkova et al. 2006; Gilboa 2004). Then a visual cue was presented to prompt subjects to rate the level of detail (1–5, from 'faint with few details' to 'exceptionally clear with great detail') of the AM just retrieved on a five-point scale, by using an MRI-compatible button pad. During the control condition, arrows pointing randomly to the left or the right were presented. In each control block, an arrow was presented every 2 s, for a total of 8 arrows per block. The subject had to select the spatially corresponding button (left or right) on a pad placed on his/her right hand. Each of the two functional runs encompassed 16 AMT blocks (i.e., total of 32 AMT trials) of 16 s of duration and 8 blocks also of 16 s of duration of the control condition. In each run, participants completed 2 control blocks for each 4 AMT trial (i.e., AMT, AMT, AMT, AMT, Control, Control, AMT, AMT, AMT, AMT, Control, Control, etc.). Participants were briefed on the task and completed a training block immediately prior to scanning.

fMRI preprocessing and statistical analysis

Data were analyzed using the Statistical Parameter Mapping software (SPM8, Wellcome Department of Imaging Neuroscience, University College, London, UK, www.fil.ion.ucl.ac.uk/spm/). Preprocessing included realignment, segmentation, normalization (to the MNI space) and smoothing with an 8 mm Gaussian kernel. Unified segmentation with medium regularization and cost function masking was applied for the patients (Ashburner and Friston 2005; Ripollés et al. 2012). The cost function masks were defined on the T1-weighted image for each patient using the MRIcron software package (http://www.cabiatl.com/mricro/mricron/index.html). The masks were depicted by an expert neurologist (J.M.) and encompassed the sclerotic areas (in the bilateral MTLE group) or the temporal resections (for left and right MTLE patients).

Smoothed and normalized functional images were submitted to a whole brain first level analysis based on a least-square estimation using the general linear model. A block-related design matrix was created including the two conditions of interest (AMT retrieval and control condition). Confounding factors due to head movement were also included in the model. After model estimation, the main effects for each condition were calculated. First level contrasts were entered into a 4 (Group: Healthy, RMTLE, LMTLE, BMTLE) × 2 (Condition: AMT, Control) mixed between-within ANOVA model. First, in order to show general AMT retrieval effects in each group of participants, paired t-tests were calculated to compute the AMT versus Control contrast. Interaction effects for the AMT versus Control condition contrast were calculated to show significant activation differences between groups. The following contrasts (searching for areas in which patients showed enhanced fMRI activation compared with controls) were calculated: [Right MTLE AMT – Control condition] > [Healthy AMT – Control]; [Left MTLE AMT – Control] > [Healthy AMT – Control]; [Bilateral MTLE AMT – Control] > [Healthy AMT – Control]. The reverse contrasts were also explored to assess which regions were more activated by the healthy participants compared with each group of patients. For only the areas showing a significant interaction (i.e.,regions showing significantly more engagement during AMT retrieval in patients compared to healthy participants), Spearman correlations were calculated between the mean activation within a given cluster and the scores on the AMI (for the total autobiographical and semantic scores, two correlations computed per significant cluster).

All statistics are reported at a $p < 0.001$ uncorrected threshold with 30 voxels of spatial extent (Lieberman and

Cunningham 2009). Only areas surviving a FDR correction at the voxel level (see Tables) are further discussed in the manuscript. Anatomical and cytoarchitectonical areas were identified using the Automated Anatomical Labeling and the Talairach Daemon data base atlases included in the xjView toolbox (http://www.alivelearn.net/xjview8/; Lancaster et al. 2000; Tzourio-Mazoyer et al. 2002).

Since the results for the five-point scale of the level of detail of the AMs retrieved during the scanning session follow an ordinal variable, a Kruskal-Wallis test was used to test for between-subjects differences using SPSS 18.0 software (SPSS Inc., Chicago, USA).

Post-scan autobiographical memory interview (AMI)

The AMI was administered and scored as described in the AMI test manual (Kopelman, et al., 1989) one week after the MRI study. The interview consisted of two types of questions administered concurrently: (i) autobiographical incident questions (e.g. specific memory of first day at first job with *where* and *when* statement), and (ii) personal semantic questions (e.g. name of firm and address of first job). These questions surveyed three distinct time periods: childhood (ages 0–18), early adulthood (ages 18–30), and recent (within the past 5 years). One RMTLE patient and 1 control did not complete the test. AMI scores were analyzed using two mixed between-within ANOVA models, one for each AM type (autobiographical vs. semantic information) with Time period (3 levels: childhood, early adulthood, recent) as within-subject factors, and Group (Healthy, RMTLE, LMTLE, BMTLE) as between-subject factors. For significant group effects, differences between groups were further explored using Mann-Whitney U tests after collapsing for time period.

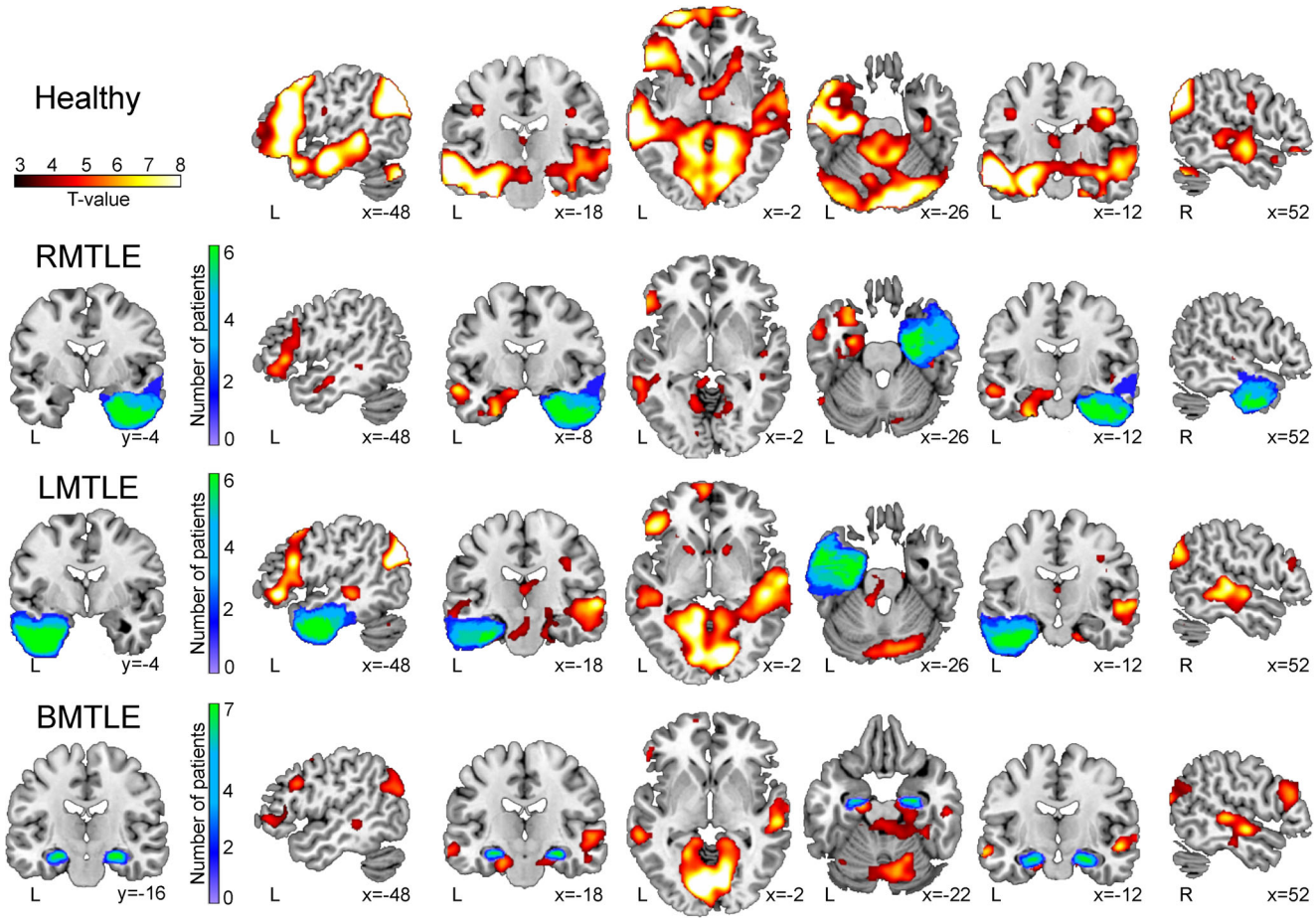

Fig. 1 Enhanced group-level fMRI-signals for the Autobiographical Memory task. Neurological convention is used with MNI coordinates at the bottom right of each slice. All statistical maps are thresholded at a $p < 0.001$ uncorrected threshold with 30 voxels of cluster extent (the main labeled areas of the AM network survived a $p < 0.001$ FDR-corrected threshold, see Table 3). In red-yellow, results for the AM > Control contrast are shown for the healthy subjects (first row), RMTLE (second row), LMTLE (third row) and BMTLE patients (fourth row). For patients, in blue-green, an overlap map shows, for each voxel, the number of patients with lesion in a particular area. L, left hemisphere; R, right hemisphere

Table 3 Group effects of Autobiographical Memory

Anatomical Area	Size	Coordinates	t- value
Healthy subjects			
R Angular Gyrus	94,450	48-74 38	14.85
L Sup/Mid/Inf Temporal Gyrus		-58 -10 -14	14.02
L Angular Gyrus		48-72 40	13.92
L Sup/Mid Occipital Gyrus		-44 -76 38	13.72
L Sup/Inf Parietal Gyrus		-34 -76 48	13.38
L Calcarine		-2 -58 10	12.95
L Precuneus		-4 -58 12	12.83
R Sup/Mid Occipital Gyrus		46-78 32	12.52
L Sup/Mid/Inf Frontal Gyrus		-52 28 14	12.30
R Lingual Gyrus		10-76 -10	12.26
B Cerebellum/Brainstem		8-84 -26	12.17
L Lingual Gyrus		-2 -56 6	11.85
L Fusiform Gyrus		-30 -14 -24	11.61
B SMA		-8 22 44	11.51
R Precuneus		4-58 16	11.48
L Hippocampus		-28 -10 -22	11.41
L Parahippocampal Gyrus		-28 -14 -26	11.25
L Ant/Mid/Post Cingulate Gyrus		-8 22 38	10.89
R Calcarine Gyrus		14-82 4	10.82
R Cuneus		4-62 20	10.76
L Cuneus		-2 -64 22	10.76
L Precentral Gyrus		-44 10 50	10.38
R Ant/Mid/Post Cingulate Gyrus		2-54 30	9.78
R Caudate		20 22 10	9.28
R Parahippocampal Gyrus		20-44 -4	8.38
R Sup/Mid/Inf Temporal Gyrus		52-12 -10	8.33
R Hippocampus		38-14 -18	8.31
R Sup/Mid/Inf Frontal Gyrus		22 30 54	8.05
L Insula		-34 24-2	7.46
L Caudate		-16 6 22	7.41
R Fusiform Gyrus		24-70 -6	7.39
R Insula		42-18 4	5.68
R Putamen		22 22 2	6.57
L Putamen		-26 14-8	6.25
R Mid Frontal Gyrus	55	54 28 34	4.15
RMTLE			
L Sup/Mid/Inf Temporal Gyrus	6444	-58 -4 -14	7.59
L Parahippocampal Gyrus		-22 -14 -34	7.27
L Fusiform Gyrus		-24 -14 -36	7.05
L Sup/Mid/Inf Frontal Gyrus		-50 28 2	6.73
L Hippocampus		-24 -10 -26	6.26
L SMA		-6 20 56	5.54
L Sup Frontal Gyrus	735	-16 60 36	6.32
R Lingual Gyrus	4590	12-74 -12	6.13
B Cerebellum/Brainstem		12-74 -14	5.99
L Calcarine		-4 -58 4	5.73
L Lingual Gyrus		-2 -58 6	5.64
L Precuneus		-6 -80 46	5.38
L Post Cingulum		-6 -40 6	5.36
R Precuneus		8-40 4	5.12
R Calcarine		16-56 4	4.94
L Sup Occipital Gyrus		-8 -82 44	4.92
L Cuneus		-4 -82 40	4.55
L Mid Temporal Gyrus	1402	-60 -40 -4	5.86
L Mid Occipital Gyrus		-38 -72 34	4.91
L Angular Gyrus		-58–64 22	4.55
L Inf Parietal Gyrus		-36-80 40	4.23
R Fusiform Gyrus	94	40-28 -28	5.81
R Sup/Mid/Inf Temporal Gyrus	808	46-14 -4	4.70
R Sup Occipital Gyrus	125	16-90 36	4.19
R Cuneus		18-88 38	3.97
R Angular Gyrus	59	56-66 32	3.98
LMTLE			
R Lingual Gyrus	50,245	14-80 -4	10.92
L Calcarine		-10 -64 10	10.84
R Calcarine		14-84 0	10.37
L Sup/Mid Occipital Gyrus		-24 -86 42	10.18
L Cuneus		2-92 14	10.13
L Lingual Gyrus		-8 -64 6	9.97
L Angular Gyrus		-48 -74 30	9.86
L Sup/Inf Parietal Gyrus		-26 -84 42	9.32
R Cuneus		6-92 16	9.30
B SMA		-6 28 64	9.27
L Sup/Mid/Inf Frontal Gyrus		-40 12 58	9.13
L Precuneus		-8 -58 8	9.06
L Sup/Mid/Inf Temporal Gyrus		-54 -66 22	8.92
R Precuneus		8-52 10	8.91
B Cerebellum/Brainstem		-8 -46 -2	8.70
L Ant/Mid/Post Cingulate Gyrus		-6 -52 22	8.36
R Sup/Mid/Inf Temporal Gyrus		50-26 0	8.34
R Sup Parietal Gyrus		32-76 52	7.55
R Angular Gyrus		54-70 32	7.52
R Mid/Post Cingulate Gyrus		2-54 30	7.12
R Sup/Mid Occipital Gyrus		52-68 28	7.08
R Sup/Mid/Inf Frontal Gyrus		14 42 48	6.70
L Precentral Gyrus		-38 8 48	6.32
L Fusiform Gyrus		-18 -40 -12	6.23
L Parahippocampal Gyrus		-16 -38 -10	6.03
R Fusiform Gyrus		34-42 -4	5.82
R Parahippocampal Gyrus		32-42 -4	5.78
R Post Hippocampus		32-40 -4	5.65
R Caudate		4 8-6	5.42
L Post Hippocampus		-12 -38 4	5.37
L Caudate		-2 8-8	5.25
L Putamen		-18 12-4	4.98
R Putamen		16 12-2	4.87
R Ant Hippocampus		26-18 -18	3.54

Table 3 (continued)

Anatomical Area	Size	Coordinates	t- value
R Inf Frontal Gyrus	269	54 28 22	4.59
BMTLE			
L Lingual Gyrus	19,738	-6 -78 -6	9.47
R Calcarine		14-86 8	9.44
R Lingual Gyrus		10-74 -4	9.24
L Calcarine		-8 -82 0	8.80
R Cuneus		4-90 14	7.96
B Cerebellum/Brainstem		-10 -76 -12	7.14
L Sup/Mid Occipital Gyrus		-10 -90 8	7.75
L Cuneus		-4 -70 24	6.96
L Precuneus		-4 -52 8	6.81
R Sup Occipital Gyrus		16-88 32	6.75
L Mid/Post Cingulate Gyrus		-6 -42 8	6.38
R Fusiform Gyrus		24-70 -14	6.34
R Precuneus		6-52 10	6.24
L Parahippocampal Gyrus		-18 -16 -24	5.74
R Mid Cingulate Gyrus		8-42 8	5.72
L Hippocampus		- 20 -14 – 22	5.45
L Fusiform Gyrus		-22 -76 -6	5.25
L Sup/Inf Parietal Gyrus		-14-82 46	5.06
L Angular Gyrus		-56 -64 30	5.05
R Parahippocampal Gyrus		18-14 -22	4.35
R Sup/Mid/Inf Temporal Gyrus	1407	58-24 2	7.31
R Sup/Mid Frontal Gyrus	513	26 36 54	7.27
L Sup/Mid/Inf Frontal Gyrus	2766	-34 6 66	6.37
L Precentral Gyrus		-42 12 32	5.63
B SMA		-6 16 52	5.03
L Sup/Mid Temporal Gyrus	348	-62 -12 -12	5.87
L Mid Temporal Gyrus	620	-60 -36 -2	5.63
R Inf Frontal Gyrus	659	48 26 18	5.49
R Mid Occipital Gyrus	266	50–76 18	5.08
R Angular Gyrus		56-66 30	3.91
L Inf Frontal Gyrus	356	-54 30 12	4.55
R Fusiform Gyrus	35	42-8 -26	3.65

fMRI local maxima for the AB > Control contrast for Healthy subjects, LMTLE, RMTLE and BMTLE patients (see also Fig. 1). Results are reported at a $p < 0.001$ uncorrected threshold with 30 voxels of spatial extent. All peak values survived an FDR $p < 0.001$ correction at the voxel level. MNI coordinates are used. L, left; R, right; B, bilateral

Results

Demographic and neuropsychological data

Tables 1 and 2 show the demographic, clinical and out of scanner neuropsychological variables for the unilateral TLE (right and left), bilateral TLE patients and the control group. We found no statistically significant differences in sex [$\chi(1) = 4.88$, $p = 0.180$], age [$H(3) = 0.99$, $p = 0.803$], years of education [$H(3) = 0.91$, $p = 0.803$] or handedness [$H(3) = 0.468$, $p = 0.926$] between TLE patients and healthy subjects. Between the patient groups there was no statistically significant difference in onset [$H(2) = 4.43$, $p = 0.109$] or duration [$H(2) = 2.13$, $p = 0.344$] of epilepsy, number of antiepileptic drugs [$H(2) = 3.15$, $p = 0.206$] or seizure frequency [$H(2) = 0.443$, $p = 0.801$], nor in the age at surgery [$H(2) = 1.12$, $p = 0.570$] .

Regarding the neuropsychological variables tested, no between-group effects were found for immediate verbal memory [$H(3) = 1.51$, $p = 0.679$], learning capability [RAVLT: $H(3) = 7.76$, $p = 0.051$], working memory [Digit Span: $H(3) = 4.60$, $p = 0.203$; Letters and Numbers: $H(3) = 3.78$, $p = 0.285$], or the TMTB [$H(3) = 1.27$, $p = 0.736$]. Several measures showed a trend for between-group differences (not corrected for multiple comparisons; 13 tests, Bonferroni $p < 0.0038$), including delayed verbal memory [$H(3) = 10.87$, $p = 0.012$], vocabulary comprehension [$H(3) = 11.61$, $p = 0.009$], semantic fluency [$H(3) = 12.66$, $p = 0.005$], phonological fluency [$H(3) = 10.17$, $p = 0.017$], and delayed visual memory [$H(3) = 13.44$, $p = 0.004$] and processing speed [TMTA: $H(3) = 9.06$, $p = 0.028$]. Importantly, significant Bonferroni corrected differences between groups were found for immediate visual memory [$H(3) = 14.48$, $p = 0.002$] and for naming abilities [Boston Naming Test; $H(3) = 17.22$, $p = 0.001$]. Mann-Whitney U tests (Bonferroni correction was at 0.0083 due to the 6 comparisons made) showed that healthy participants performed better than BMTLE patients in the two aforementioned tests (all ps < 0.002), better than LMTLE patients in naming abilities ($p < 0.001$; immediate visual memory did not survive the correction, $p = 0.022$) and presented the same level as RMTLE individuals for both neuropsychological variables (naming abilities: $p = 0.195$; visual memory, $p = 0.019$ not corrected for multiple comparisons).

fMRI autobiographical memory task (AMT)

For the AMT > Control condition contrast, all groups activated a large network comprising visual regions (mainly occipital and parietal gyri and the precuneus), frontal and parietal areas and the MTL, including the hippocampus, the parahippocampus and the fusiform gyrus (see Fig. 1 and Table 3). While this network was left lateralized for the healthy group and RMTLE patients, LMTLE and BMTLE patients also showed strong activations on right temporal and frontal regions. Although both controls and LMTLE patients activated portions of the right hippocampus and parahippocampus, BMTLE patients only engaged spared areas of the left hippocampus and the parahippocampal gyrus bilaterally. However, healthy participants consistently showed enhanced fMRI activity in several regions when compared with each of the patient groups during AMT retrieval (see Fig. 2 and Table 4). Specifically, controls showed more

activity than LMTLE patients especially in the left (but also right) hippocampal and temporal regions, not only within the lesion site (which is obviously expected), but also in regions adjacent to the lesioned areas. As expected, and taking into account that the pattern of AM-related activity is commonly left lateralized, RMTLE patients showed a less severe pattern of reduced activity. Finally, disrupted MTL activity was even more evident in BMTLE patients, who showed reduced activity in bilateral temporal and hippocampal regions as well as in the left frontal areas.

Despite this pattern of reduced activation around the lesioned regions, both the BMTLE and LMTLE groups showed enhanced, potentially compensatory, activity in several areas. Indeed, while no differences were found for the RMTLE > Healthy contrast, for LMTLE patients, significant interactions (FDR-corrected) were found in the right superior and middle temporal, superior parietal and lingual/calcarine areas, and in the left spared fusiform gyrus (see Table 5 and Fig. 3a). In addition, BMTLE patients exhibited greater activity than controls in the right inferior frontal gyrus (IFG) and the left occipital gyrus (again, FDR-corrected; see Table 5 and Fig. 3b). Finally, in BMTLE patients, the mean fMRI activity within the aforementioned left occipital and right inferior frontal clusters correlated with the post-scan AMI scores for autobiographical incidents ($r = 0.81$, $p < 0.035$ and $r = 0.82$, $p < 0.028$, respectively; Fig. 3b), but not for the semantic memory schedules. These results suggest that LMTLE and BMTLE patients recruit spared temporal and frontal regions to compensate for the loss of function in left MTL areas.

The five-point scale measuring the level of detail of the AMs retrieved during scanning revealed non-significant differences between groups [$H(3) = 1.1$, $p = 0.776$].

Post-scan autobiographical memory interview performance

For the AMI autobiographical scores, no effect of Time period [$F(2,62) = 0.041$, $p > 0.96$] or Time x Group interaction was found [$F(6,62) = 0.586$, $p > 0.740$]. However, there was a significant effect of Group [$F(3,31) = 6.061$, $p < 0.002$; see Fig. 4a]. After collapsing by time period, Mann-Whitney U tests (Bonferroni correction was $p < 0.0083$, for the 6 comparisons computed) showed that healthy participants scored higher than LMTLE ($p < 0.001$) and BMTLE ($p < 0.001$) patients. However, no differences were found between RMTLE patients and healthy subjects ($p = 0.058$). Finally, no significant differences among the scores of any of the groups of patients were found at the corrected significance level.

Regarding the semantic scores for the AMI, significant main effects of Time [subjects remembered recent better than older semantic items; $F(2,62) = 5.45$, $p < 0007$] and Group [$F(3,31) = 3.52$, $p < 0.026$, see Fig. 4b] were found. The Group x Time interaction was not significant [$F(6,62) = 0.776$, $p > 0.59$]. After collapsing for time period, Mann-Whitney U tests showed that healthy subjects ($p < 0.001$), RMTLE ($p < 0.004$) and LMTLE patients ($p < 0.008$) scored significantly higher than BMTLE patients. No other differences were found among groups (all $p > 0.1$).

Discussion

This is, to the best of our knowledge, the first study investigating neuropsychological and functional MRI AM-related activity patterns in patients with ATLR and a selected group

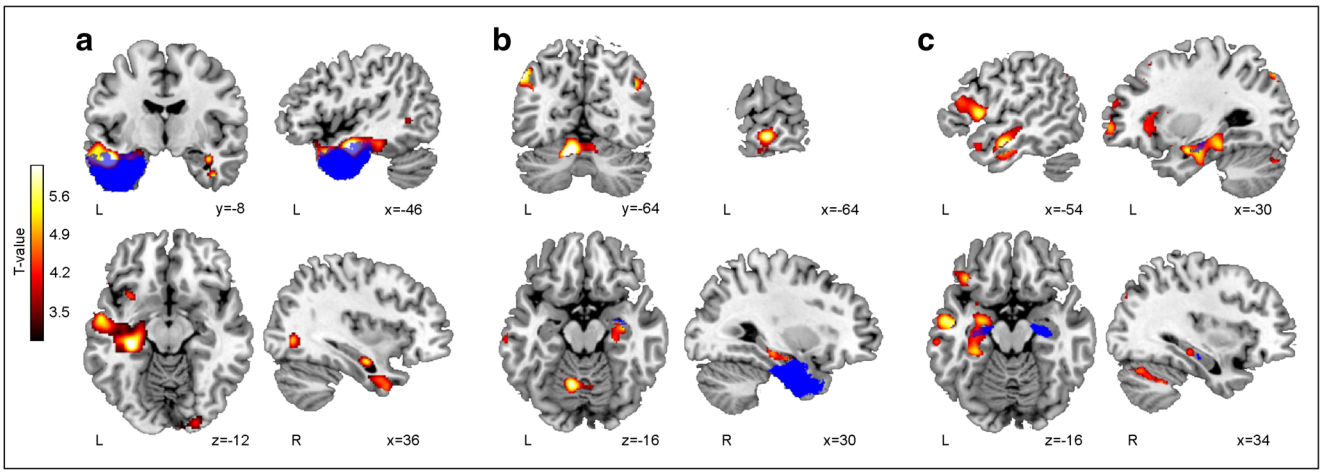

Fig. 2 Areas showing enhanced fMRI activity in healthy participants compared with patients for the AM > Control contrast. Neurological convention is used with MNI coordinates at the bottom right of each slice. All statistical maps are thresholded at a $p < 0.001$ uncorrected threshold with 30 voxels of cluster extent (main peak values within the majority of the shown clusters survived a $p < 0.05$ FDR corrected threshold, see Table 4). In red-yellow, areas showing enhanced fMRI activity in healthy participants when compared with patients. In blue, an overlap map shows lesioned regions in at least 50% of the patients of each group. **A.** Healthy participants vs. LMTLE. **B.** Healthy participants vs. RMTLE. **C.** Healthy participants vs. BMTLE L, left hemisphere; R, right hemisphere

Table 4 Areas showing enhanced fMRI activity in healthy participants compared with patients

Anatomical area	Cluster Size	Coordinates	t-value
Healthy > LMTLE			
Left Middle Temporal Gyrus (BA 21)	3285	-46 -8 -20	6.84***
Left Hippocampus		-30 -28 -12	6.36***
Left Inferior Temporal Gyrus (BA 20)		-44 -12 -22	5.61***
Left Middle Occipital Gyrus (BA 19)	303	-34-70 0	5.85***
Left Middle Temporal Gyrus		54-46 -8	4.20
Right Hippocampus	431	38-10 -20	5.62***
Right Inferior Temporal Gyrus (BA 20)		42-8 -34	5.33**
Right Middle Temporal Pole (BA 21)		32 8-40	5.17**
Right Middle Occipital Gyrus (BA 19)	182	38-72 0	5.48***
Left Superior Frontal Gyrus (BA 10)	149	-26 62 2	5.25**
Right Lingual Gyrus (BA 17)	366	22-96 -16	4.67*
Healthy > RMTLE			
Left Cerebellum	690	-12-64 -24	5.98***
Left Middle Temporal Gyrus (BA 21)	216	-66 -22 -10	5.45*
Left Inferior Parietal Gyrus (BA 39, 40)	421	-50 -66 40	5.44*
Right Inferior Parietal Gyrus (BA 39, 40)	239	44-70 38	4.98
Right Hippocampus	152	34-14 16	4.47
Left Middle Cingulate Gyrus (BA 32)	268	-10 8 42	4.16
Right Anterior Cingulate Gyrus (BA 10)	128	10 48 14	4.10
Healthy > BMTLE			
Right Inferior Parietal Gyrus (BA 39, 40)	283	44-74 38	6.74***
Left Middle Temporal Gyrus (BA 21)	792	-50 -10 -18	5.93***
Left Inferior Temporal Gyrus (BA 20)		-44 -14 -22	5.30**
Right Inferior Parietal Gyrus (BA 39, 40)	561	-44 -80 30	5.47**
Left Inferior Frontal Gyrus (BA 44,45,47)	2326	-52 12 6	5.41**
Left Superior Frontal Gyrus (BA 10)		-32 58 0	4.81*
Left Middle Frontal Gyrus (BA 9,46)		-46 28 34	4.67*
Left Insula (BA 13)		-36 10 14	4.51
Left Hippocampus	761	-28 -8 -20	5.33**
Left Fusiform Gyrus		-32 -16 -24	5.14*
Left Parahippocampal Gyrus		-30 -32 -14	4.94*
Left Anterior Cingulate Gyrus (BA 24)	573	-2 30 16	5.27**
Right Cerebellum	399	48-66 -32	5.04*
Right Anterior Cingulate Gyrus (BA 24)	557	4 32 16	4.92*
Left Cerebellum	178	-48 -70 -32	4.34
Right Superior Temporal Pole (BA 38)	139	-46 16-22	4.25
Right Hippocampus	36	34-28 -12	4.01

fMRI local maxima for the Healthy AB > Control vs. LMTLE, RMTLE, BMTLE AB > Control contrasts (see also Fig. 2). Results are reported at a $p < 0.001$ uncorrected threshold with 30 voxels of spatial extent. Peak values surviving FDR correction are indicated with an asterisk using MNI coordinates. BA, Brodmann Area

***p < 0.005 FDR-corrected

**p < 0.01 FDR-corrected

*p < 0.05 FDR-corrected

of BMTLE patients (compared with well-matched healthy participants). Using an adapted AMT fMRI paradigm, we found that AMT retrieval engaged a large network encompassing not only the MTL, but also prefrontal, parietal and occipital areas. The study findings evidence that healthy participants consistently showed enhanced fMRI activity in several regions, when compared with each of the patient groups during AMT retrieval. The network pattern observed was left lateralized for healthy participants and RMTLE patients. However, LMTLE and BMTLE patients also showed

strong activations in the right temporal and prefrontal regions. In addition, the AMI revealed a mild deficit of episodic AM in TLE patients (St-Laurent et al. 2009; Viskontas et al. 2000), with significant differences in BMTLE and LMTLE patients compared to controls (Herfurth et al. 2010; St-Laurent et al. 2011). Moreover, the AMI scores for AM revealed no effect of time. This absence of temporal gradient might lend support to the view that retention and recovery of memory for autobiographical episodes depend on the hippocampal complex for as long as the memory exists (Moscovitch and Nadel, 1998). This is contrary to the classic view of a time-limited role for the hippocampus in memory formation and consolidation before neocortical areas assume responsibility for storage and retrieval (Squire 1992).

Due to the multi-modal nature of AM retrieval, several cognitive processes are engaged during AMT recollection. In accordance with previous neuroimaging literature (Maguire 2001; Maguire and Frith 2003; Svoboda et al. 2006), healthy participants and RMTLE patients in the present study primarily activated—with a left-lateralized pattern—the core neural AM network, which includes the MTL, the retrosplenial cortex, and medial and prefrontal cortices, as well as the temporoparietal junction and the cerebellum. Nevertheless, like previous work with pre-operative patients reductions in AM-associated activation were widespread, and the functional integrity of the left HC in LMTLE and bilateral HC in BMTLE appeared particularly compromised(Addis et al., 2007; Maguire et al., 2001). And yet, this network was left lateralized for the healthy group and RMTLE patients, while both LMTLE and BMTLE patients showed strong activations on right temporal and frontal regions (Maguire et al., 2001; Mc Cormick et al., 2018). Moreover, LMTLE and BMTLE patients when compared with controls (and besides from right temporal activation in LMTLE), also showed engagement in areas described as secondary or tertiary in AM recall studies, due to their less frequent activation. These regions included parietal and visual areas and the left spared fusiform gyrus for LMTLE patients (Addis et al. 2007; Gilboa 2004; Levine et al. 2004; Maguire and Frith 2003; Markowitsch et al. 2000; Piefke et al. 2003; Ryan et al., 2001), and the right inferior frontal gyrus and left occipital gyrus for the BMTLE sample (Gilboa 2004; Maguire et al. 2001; Piefke et al. 2003). Although AM retrieval literature on fMRI in TLE is scarce, at least two studies have shown a similar pattern with strong activations in right-hemispheric, extratemporal areas and also spared regions within the left hemisphere (Addis et al. 2007; Maguire et al. 2001), and also our results are consistent with those of other healthy participant functional studies with activation of other areas than those at the central core of AM (Andreasen et al., 1995; Gilboa et al., 2004; Markowitsch et al., 2003; Svoboda et al., 2006). As the work presented here, most of the cited studies used a cueing slide with key words presented to evoke an event specific in time and place from their personal past.

The present study—examining a sample of BMTLE and also MTLE patients—provides further and stronger evidence for the existence of secondary and tertiary activation areas which may reflect a compensatory effect: in the context of hippocampal damage, more posterior memory areas as well as extratemporal healthy regions might take a dominant role (Addis et al. 2004; Gilboa 2004; Maguire and Frith 2003). There might also be striving on the part of the patient, with greater use of working memory in order to adhere to the task instructions, which would be reflected in the frontal activations found in BMTLE patients and their relationship with AMI scores (Gilboa 2004; Maguire and Frith 2003; Maguire

Table 5 Areas showing enhanced fMRI activity in patients compared with healthy participants

Anatomical area	Coordinates	Cluster Size	t-value
LMTLE > Healthy			
Left Fusiform Gyrus (BA 19)	-34 -54 -6	55	4.51***
Right Superior Parietal Gyrus (BA 7)	24-74 54	87	4.39***
Right Lingual Gyrus; Right Calcarine (BA 17)	18-82 -4	52	4.31**
Right Superior Temporal Gyrus (BA 22)	52-26 0	90	4.16**
Right Middle Temporal Gyrus (BA 21)	54-46 -8	47	3.95*
BMTLE > Healthy			
Left Superior/Middle Occipital Gyrus (BA 31)	-24 -80 20	127	4.44***
Right Inferior Frontal Gyrus (BA 46)	50 20 20	162	4.36***

fMRI local maxima for the LMTLE AB > Control vs. Healthy AB > Control contrast (top) and the BMTLE AB > Control vs. Healthy AB > Control contrast (bottom; see also Fig. 2). Results are reported at a $p < 0.001$ uncorrected threshold with 30 voxels of spatial extent. Peak values surviving FDR correction are indicated with an asterisk using MNI coordinates. BA, Brodmann Area

***$p < 0.005$ FDR-corrected

**$p < 0.01$ FDR-corrected

*$p < 0.05$ FDR-corrected

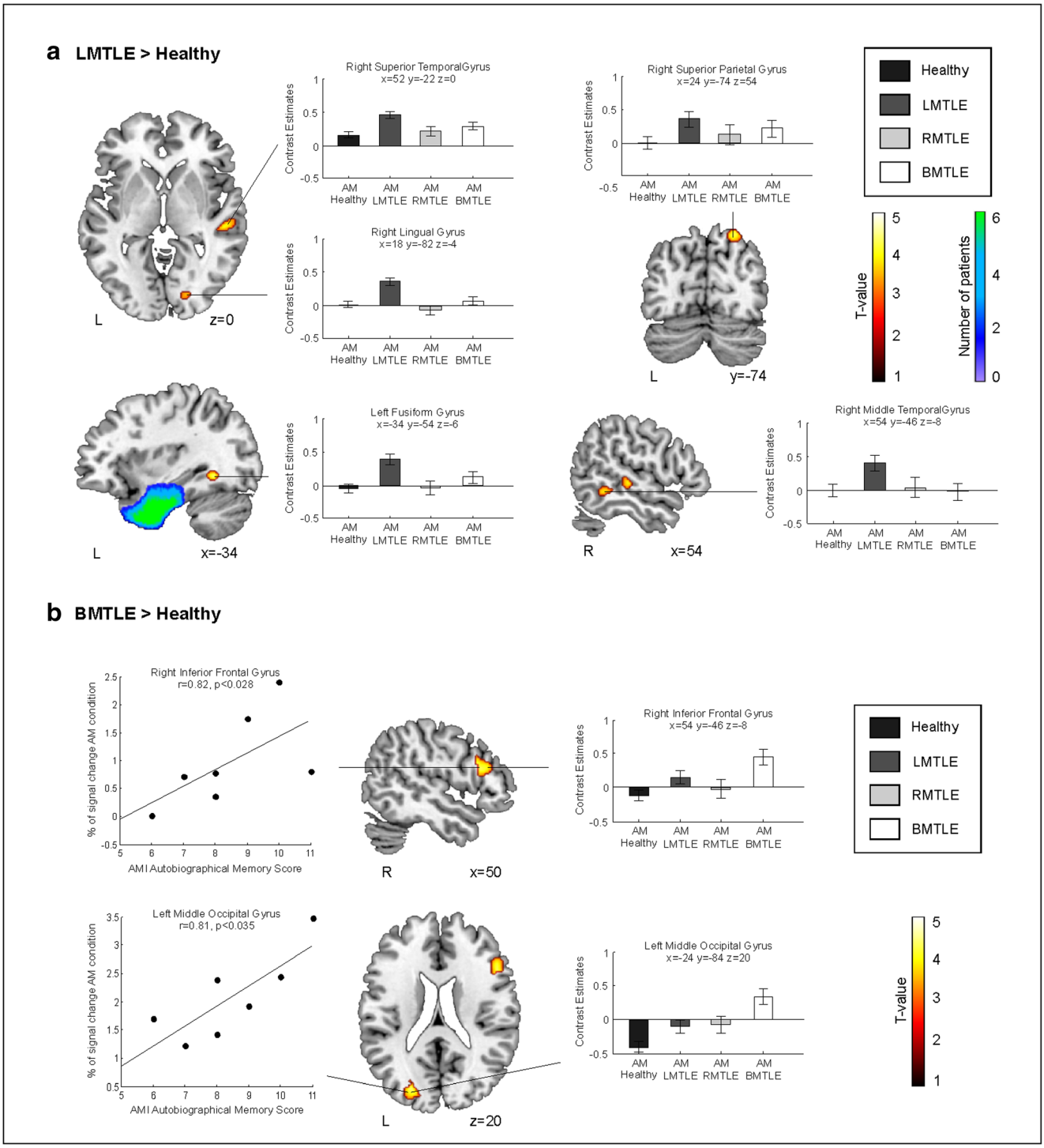

Fig. 3 Areas showing enhanced fMRI activity in patients compared with healthy participants for the AM > Control contrast. Neurological convention is used with MNI coordinates at the bottom right of each slice. All statistical maps are thresholded at a $p < 0.001$ uncorrected threshold with 30 voxels of cluster extent (main peak values within the shown clusters survived a $p < 0.05$ FDR-corrected threshold, see Table 4). Bar graphs indicate contrast estimates (proportional to percent of signal change; black for controls, dark grey for LMTLE patients, light grey for the RMTLE group and white for BMTLE patients) with standard error of the mean. **A.** In red-yellow, areas showing enhanced fMRI activity in LMTLE patients when compared with healthy participants. In blue-green, an overlap map shows, for each voxel, the number of patients with a particular area lesioned. **a** In red-yellow, areas showing enhanced fMRI activity in BMTLE patients when compared with healthy participants. The scatter plots show the correlation between the mean percent of signal change in fMRI activity within each cluster of interest and the AMI score for autobiographical incidents. L, left hemisphere; R, right hemisphere; AM, Autobiographical Memory condition

et al. 2001). However, it should be noted that anatomical reorganization of memory-related structures is often observed due to the chronicity of TLE and its frequently early onset. A well-known model of plasticity proposes that reorganization of memory may occur due to functional reserve: the ability of the nonepileptic, contralateral MTL to adapt and provide spare memory capacities (Levine et al. 2004; Maguire et al. 2001; Mc Cormick et al., 2018). Alternatively, functional adequacy (the memory capacity of undamaged ipsilesional temporal lobe structures) may substitute primary for secondary memory areas (Bonelli et al. 2010). Despite showing more functional damage (diminished left activation and lower scores in the AM interview), the extra-temporal and right-lateralized activation found in LMTLE and BMTLE patients indicates that these regions have the potential for great adaptive neuroplasticity. Furthermore, BMTLE patients were the only group showing deficits in semantic memory compared to controls, suggesting that: i) conceptual representations are supported by an interconnected, bilateral, temporal widespread network; and that ii) it may take damage to both hemispheres to produce an unequivocal deficit of semantic memory (Lambon et al. 2010; Mc Cormick et al., 2018; Viskontas et al. 2000).

Although both hemispheres are undoubtedly involved in AM recollection, there is evidence for left hemispheric dominance (Maguire 2001; Svoboda et al. 2006). Neuropsychological lesion studies also show that left-lateralized damage to the MTL region is more often associated with severe episodic memory impairment than right-lateralized damage (Spiers et al. 2001). A possible interpretation of the left-lateralized pattern in healthy and RMTLE participants is that the time course for recovering memories is different in the two hemispheres (Ryan et al. 2001). The time course data of Ryan et al. (2001) reveal that the right hippocampus takes longer than the left to reach fMRI activation peak response during AMT retrieval. These functional differences suggest that although the left hemisphere may assume a dominant role in retrieving and organizing memories, AM still draws on information supplied by both hemispheres (Addis et al. 2004, 2007; Mc Cormick et al., 2018; Ryan et al. 2001). Therefore, while LMTLE and BMTLE patients show less activation and worse AMI results, they still present greater right compensatory activation.

The interpretation of AM findings has often been criticised due to the heterogeneity of methodological factors. In our particular case, we tried to minimize the possible influence of language-induced AMT retrieval by presenting very short written sentences as AMT cues, followed by 16 s of eyes-closed retrieval. Moreover, a five-point scale measuring the level of detail of the AMs retrieved during scanning (Gilboa 2004; Piefke et al. 2003; Ryan et al. 2001) revealed non-significant differences in self-perception of retrieval quality between groups. Our results are in accordance with those of Denkova et al. (2006), suggesting that the left-lateralized pattern supports AM per se, rather than being the influence of verbal stimuli or the lack of richly detailed recollections. Furthermore, we did not include a pre-scanning interview, in order to avoid refreshment of the memory trace prior to the fMRI experiment (Denkova et al. 2006; Gilboa 2004). The study paradigm was otherwise easy to perform and resulted in robust activation of the AM functional network. In addition, the correlation between the AMI scores for AM and the enhanced right-lateralized fMRI activity elicited by BMTLE patients further strengthens our findings. Finally, although we tested patients after ATLR, it has been shown that episodic memory impairment in patients awaiting surgery with temporal lobe damage or dysfunction caused by recurrent seizures is similar to that of the patients who have already undergone resective surgery (St-Laurent et al., 2011; Viskontas et al. 2000; see Vilà-Balló et al. 2017 for a similar example outside the AM domain). Therefore, we propose the current fMRI paradigm as a potential clinical tool to evaluate AM, as the

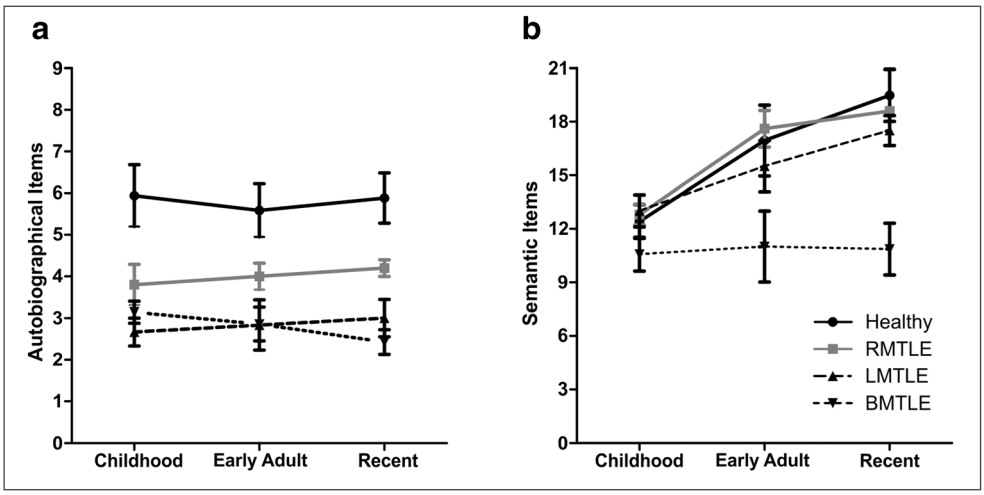

Fig. 4 Mean scores for the autobiographical and semantic items of the AMI. Mean scores (with standard error of the mean) for each group (Healthy, RMTLE, LMTLE, BMTLE) and time period (childhood, early adulthood, recent) for the autobiographical (**a**) and semantic (**b**) items of the AMI. LMTLE and BMTLE patients scored significantly lower than healthy subjects for autobiographical items, while only BMTLE patients showed significant impairment in the semantic scores

development of new strategies to evaluate recruitment of different functional regions or the functionality of remnant tissue in a damaged structure, may be a helpful complementary tool especially in therapeutic options assessment. Nevertheless, it is important to consider that one limitation of our study is the small sample size of each patient group. While further studies are required to replicate the results observed, we should emphasise that the small sample size was in part motivated by: i) the uncommon presence of bilateral HS; and ii) a very strict patient selection criteria which reduced heterogeneity between patients, but which should thereby also ensure consistent findings. On the other hand, even though previous publications support that the impairment on AM in patients awaiting ATLR is similar to that of patients who have already undergone surgery, the present findings should be verified in larger prospective studies comparing performance in TLE patients, before and after surgery or in a replication study to this one that uses a presurgical unilateral group as a control. A larger sample would also allow the investigation of differences between age at onset or epilepsy duration which may be of interest in order to determine the possible influence of these factors and could also provide additional information**.** Finally, the inclusion of a non-temporal epilepsy group would also be a control group of interest in future studies.

Conclusions

The compromised MTL engagement during AMT retrieval, with evidence of a reduced fMRI activity pattern, and lower episodic AM scores shown by the patient groups support the idea that hippocampal integrity is critical for AM retrieval as long as the memory to be retrieved exists. However, the enhanced fMRI activity shown in right temporal, extra-temporal and spared MTL regions by LMTLE and BMTLE patients suggests the presence of brain reorganization and plasticity after MTL damage. The present findings provide a more detailed evaluation of AM in TLE patients and may play a compelling role in the study of the severity and progression of the disease and also in presurgical planning for patients with epilepsy, in whom the indicators of the recruitment of different functional regions or the functionality of remnant tissue in a damaged structure is paramount. In addition, these results may also be useful in patient therapeutic management in relation to the development of rehabilitation strategies.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests relevant to the manuscript.

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