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Transient epileptic amnesia: regional brain atrophy and its relationship to memory deficits

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Transient epileptic amnesia (TEA) is a recently recognised form of epilepsy of which the principle manifestation is recurrent, transient episodes of isolated memory loss. In addition to the amnesic episodes, many patients describe significant interictal memory difficulties. Performance on standard neuropsychological tests is often normal. However, two unusual forms of memory deficit have recently been demonstrated in TEA: (i) accelerated long-term forgetting (ALF): the excessively rapid loss of newly acquired memories over a period of days or weeks and (ii) remote autobiographical memory loss: a loss of memories for salient, personally experienced events of the past few decades. The neuroanatomical bases of TEA and its associated memory deficits are unknown. In this study, we first assessed the relationship between subjective and objective memory performance in 41 patients with TEA. We then analysed MRI data from these patients and 20 matched healthy controls, using manual volumetry and voxel-based morphometry (VBM) to correlate regional brain volumes with clinical and neuropsychological data. Subjective memory estimates were unrelated to performance on standard neuropsychological tests but were partially predicted by mood, ALF and remote autobiographical memory. Manual volumetry identified subtle hippocampal volume loss in the patient group. Both manual volumetry and VBM revealed correlations between medial temporal lobe atrophy and standard anterograde memory scores, but no relation between atrophy and ALF or remote autobiographical memory. These results add weight to the hypothesis that TEA is a syndrome of mesial temporal lobe epilepsy. Furthermore, they suggest that although standard anterograde memory test performance is related to the degree of mesial temporal lobe damage, this is not true for ALF and autobiographical amnesia. It is possible that these unusual memory deficits have a more diffuse physiological basis rather than being a consequence of discrete structural damage.

Keywords: transient epileptic amnesia; memory; epilepsy; MRI; voxel-based morphometry

Abbreviations: ALF = accelerated long-term forgetting; EMQ = everyday memory questionnaire; MTL = medial temporal lobe; MAMI = Modified Autobiographical Memory Interview; TIV = total intracranial volume; TLE = temporal lobe epilepsy; TGA = transient global amnesia; TEA = transient epileptic amnesia; VBM = voxel-based morphometry

Introduction

Memory complaints are common amongst people with epilepsy (Corcoran and Thompson, 1992; Fisher *et al.*, 2000), particularly temporal lobe epilepsy (TLE) in which brain regions crucial for memory are directly involved by seizure activity. Memory deficits in epilepsy may have a number of causes including underlying brain pathology, seizure activity, anticonvulsant medication and psychosocial factors. However, patients' performance on neuropsychological tests frequently fails to correlate with their subjective perceptions of memory function (Thompson and Corcoran, 1992; Vermeulen *et al.*, 1993; Piazzini *et al.*, 2001).

Most studies of memory in epilepsy have concentrated on medically refractory TLE, in which there is often significant structural damage to medial temporal lobe (MTL) regions including the hippocampus. Using MRI, such focal atrophy may be quantified by calculating the volumes of manually traced regions of interest (Lencz *et al.*, 1992; Cendes *et al.*, 1993; Coste *et al.*, 2002; Bernasconi *et al.*, 2003; Goncalves Pereira *et al.*, 2005) or by automated techniques such as voxel-based morphometry (VBM) (Ashburner and Friston, 2000; Bernasconi *et al.*, 2004). These techniques allow exploration of the relations between cognitive performance, clinical variables and structural brain pathology. Some studies of TLE have demonstrated associations between, for example, hippocampal volume and memory performance (Kilpatrick *et al.*, 1997; Reminger *et al.*, 2004; Alessio *et al.*, 2006). However, the investigation of memory dysfunction in medically refractory TLE is complicated by its varied origins, associated cognitive deficits and by the severity of the clinical syndrome.

Transient epileptic amnesia (TEA) is a subtype of TLE with a particularly intimate relationship with memory. In TEA, the principle manifestation of seizures is recurrent episodes of isolated memory loss (Gallassi *et al.*, 1988; Kapur, 1990; Zeman *et al.*, 1998; Butler *et al.*, 2007). TEA is predominantly a condition of middle and old age, and is more common in males than females. The amnesic episodes, characterised by a mixed anterograde and retrograde amnesia with apparent preservation of other cognitive functions, are in some respects similar to those seen in the syndrome of transient global amnesia (TGA). In contrast to TGA, however, attacks of TEA are by definition recurrent, whereas most patients with TGA have only a single episode. Furthermore, whereas episodes of TGA typically last ∼4–12 h, the average duration of attacks of TEA is 30–60 min. The amnesic episodes in TEA, unlike TGA, often occur upon waking and may be associated with other features suggestive of epilepsy such as olfactory hallucinations or oro-gustatory automatisms. The attacks usually cease with anticonvulsant treatment.

However, patients with TEA often complain of persisting memory difficulties. In particular, they may describe: (i) the excessively rapid decay of newly acquired memories over a period of days to weeks, and (ii) a loss of memories for salient personal events, such as holidays or weddings, from the remote past. Performance on standard neuropsychological tests of memory, which typically test retention of new information over delays of up to 30 min, is usually normal. Nevertheless, patients show accelerated long-term forgetting (ALF) over extended intervals (Manes *et al.*, 2005; Butler *et al.*, 2007). Furthermore, remote memory testing has revealed some patients to have deficits for autobiographical events that occurred up to 40 years before the clinical onset of seizures (Manes *et al.*, 2001, 2005; Butler *et al.*, 2007). These unusual memory deficits are of both clinical and theoretical significance (Butler and Zeman, 2008). Their pathophysiological bases remain unknown.

We have previously reported the clinical and neuropsychological features of a large series of patients with TEA (Butler *et al.*, 2007). The group as a whole was mildly impaired on standard tests of anterograde memory. A subgroup of patients, indistinguishable from healthy controls on these standard tests, nonetheless showed ALF over an extended delay of 3 weeks and temporally extensive autobiographical memory loss. In the present study, our aim was to investigate the relationship of these memory deficits to each other and to potential causal factors. We describe further data and analyses from the group of patients reported in Butler *et al.* (2007). Specifically, we examine (i) whether subjective measures of memory reflect objective performance on neuropsychological tests, (ii) whether TEA is associated with focal volume loss in the brain and (iii) whether memory function in TEA correlates with seizure variables or with regional brain volume.

Methods

Subjects

The participants in this study have been previously described in Butler *et al.* (2007). Patients with TEA were recruited to the The Impairment of Memory in Epilepsy (TIME) Project via the British Neurological Surveillance Unit between August 2003 and April 2005. The following diagnostic criteria were used (Zeman *et al.*, 1998):

(1) a history of recurrent witnessed episodes of transient amnesia
(2) cognitive functions other than memory judged to be intact during typical episodes by a reliable witness
(3) evidence for a diagnosis of epilepsy based on one or more of the following:

 (a) epileptiform abnormalities on electroencephalography
 (b) the concurrent onset of other clinical features of epilepsy (e.g. lip-smacking, olfactory hallucinations)
 (c) a clear-cut response to anticonvulsant therapy

Seven patients from the original cohort of 50 were unable to travel to Edinburgh or Cambridge for scanning. These seven were clinically and neuropsychologically indistinguishable from the rest of the group. Two patients had additional pathology revealed by MRI—one a temporal ridge meningioma and the other focal bilateral temporal lobe degeneration—and were excluded from further analysis. Therefore, 41 patients were included in the present study. All underwent detailed clinical evaluation, neuropsychological assessment and MRI brain scanning (see below). All patients were on anticonvulsant monotherapy: 19 on carbamazepine (mean daily dose = 505 mg), eight on sodium valproate (mean daily dose = 1050 mg), 10 on lamotrigine (mean daily dose = 117 mg), three on phenytoin (mean daily dose = 250 mg) and two on levetiracetam (mean daily dose = 1500 mg). All had been seizure-free for at least 6 months at the time of testing. A subset of 22 scanned patients (subgroup 1), in whom standard anterograde

memory test performance was normal, underwent further testing of memory retention over an extended delay of 3 weeks (see below).

Twenty age- and education-matched, healthy control subjects, described in Butler *et al*. (2007), underwent MRI scanning, standard neuropsychological testing and assessment of forgetting over a 3-week interval. Seventeen of these control subjects were volunteers, usually a spouse or close friend, nominated by patients from subgroup 1. A further three control subjects were obtained from the volunteer panel of the Medical Research Council Cognition and Brain Sciences Unit at the University of Cambridge. Controls were neurologically normal and did not have specific complaints of memory or other cognitive impairment.

The study was approved by the Multicentre Research Ethics Committee, United Kingdom (MREC 03/10/77). All patients gave written, informed consent.

Subjective memory assessment

Self-completion questionnaires were used to assess subjects' own perception of their everyday memory and memory for remote, personally experienced events. In the everyday memory questionnaire (EMQ) (Thompson and Corcoran, 1992), respondents are asked to estimate the frequency of 18 everyday memory failures, such as misplacing objects around the house, forgetting people's names or having to repeatedly check whether a certain task has been completed. Ratings range from zero (not at all) to five (more than once a day), giving a maximum possible score of 90. In the very long-term memory questionnaire (VTLMQ—see Supplementary material) subjects are asked to rate how often they have forgotten 13 types of personally salient fact or event such as weddings, holidays, major projects or funerals. Frequency is scored from zero (never) to four (many times), giving a maximum possible score of 52.

Neuropsychological assessment

General neuropsychology

Standard tests were used to assess general intelligence (Wechsler Abbreviated Scale of Intelligence; Wechsler, 1999), anterograde memory [immediate and 30 min delayed recall of the Logical Memory story (from Wechsler Memory Scale-III; Wechsler, 1997)], copy and 30-min delayed recall of the Rey-Osterreith complex figure (Osterreith and Rey, 1944), the Recognition Memory Test for words and faces (Warrington, 1984), language (Graded Naming Test; McKenna and Warrington, 1980) and executive function [letter and category fluency, Wisconsin Card Sorting Test (WCST) (Kongs *et al*., 2000)]. A summary measure of anterograde memory (zmem) was calculated for each patient by averaging the *z*-scores for delayed Logical Memory recall, delayed Rey figure recall, word recognition and face recognition memory. The Hospital Anxiety and Depression Scale (HADS) questionnaire was administered as a measure of current symptoms of anxiety and depression (Zigmond and Snaith, 1983).

Remote autobiographical memory

A semi-structured interview, the Modified Autobiographical Memory Interview (MAMI), was used to assess memories for personal facts and personally experienced events from each decade of the subject's life (Butler *et al*., 2007). For two topics (e.g. 'holiday') from each decade, subjects were asked to answer five questions designed to probe semantic, or factual, memory (e.g. 'How long did you stay?') and produce one detailed episodic memory (e.g. 'Can you recall any incident, even if minor, that occurred during your holiday in Seton Sands?'). Episodic

memories were scored out of five according to their degree of specificity and experiential detail, based on the scheme described by Graham and Hodges (1997). A witness was present in all cases to corroborate the subject's account. Average scores across all decades were calculated for the semantic (MAMI-s) and the episodic (MAMI-e) components.

Long-term forgetting

This was tested in a subgroup of 22 patients (subgroup 1) and 20 control subjects. A list of 15 words (from the Rey Auditory Verbal Learning Task; Schmidt, 1996) was orally presented over a minimum of five and a maximum of 15 trials until the subject attained 90% accuracy at free recall. Recall of the words was then tested at delays of 30 min, 1 and 3 weeks. A similar procedure was used for recall of a short prose passage from the Rivermead Behavioural Memory Test (RBMT; Wilson *et al*., 1991) and for reproduction of seven visually presented designs (from the Graham-Kendall Memory for Designs test; Graham and Kendall, 1968). Long-term forgetting was defined as the percentage change in recall score between the 30 min and the 3 week delay, a more negative score indicating greater forgetting. A composite long-term forgetting measure (zALF) was calculated for each patient by averaging the long-term forgetting *z*-scores across the three material types: word list, prose passage and designs.

Magnetic resonance imaging

Magnetic resonance imaging was performed on a 1.5 T GE Signa LX scanner (GE Medical Systems, Milwaukee, USA) at the SFC Brain Imaging Research Centre for Scotland, Western General Hospital, Edinburgh (23 patients and 8 control subjects) or on a scanner of the same model at the MRIS Unit, Addenbrooke's Hospital, Cambridge (18 patients and 12 control subjects). Structural images were acquired in the coronal plane, perpendicular to an axis connecting the anterior and posterior commissures (AC-PC axis), using a coronal T_1-weighted three dimensional spoiled gradient-echo sequence (echo time = 3.36 ms, repetition time = 8.20 ms, flip angle = 15°, slice thickness = 1.7 mm, slice gap = 0 mm, field of view = 22 cm, matrix = 256 × 192).

Manual volumetric analysis

Volumetric analysis was performed using Analyze 7.0 software (Mayo Clinic, Rochester, MN, USA), which allows simultaneous viewing in coronal, sagittal and horizontal orientations. The data were resampled onto a 0.86 mm voxel grid and alignment to the AC-PC axis was checked manually. The hippocampus and amygdala were segmented manually using the protocol described by Pruessner *et al*. (2000). Further segmentation of the hippocampus into head, body and tail sections was performed according to the landmarks used by Malykhin *et al*. (2007) (see Fig. 1). Volumes were corrected for total intracranial volume (TIV), estimated using the method described by Eritaia *et al*. (2000). The correction was performed using the formula: adjusted volume of structure x = (volume of structure x/TIV) × mean TIV of all participants. A single investigator (AB), blinded to the participants' details, performed the segmentation of all images. In order to assess intrarater reliability, 20 hemispheres were segmented twice, at an interval of 1 month. The intraclass reliability coefficients were 0.92 for hippocampal and 0.87 for amygdalar volumes.

Statistical analysis

Neuropsychological and volumetric data of the patient and control groups were compared using independent sample *t*-tests or the
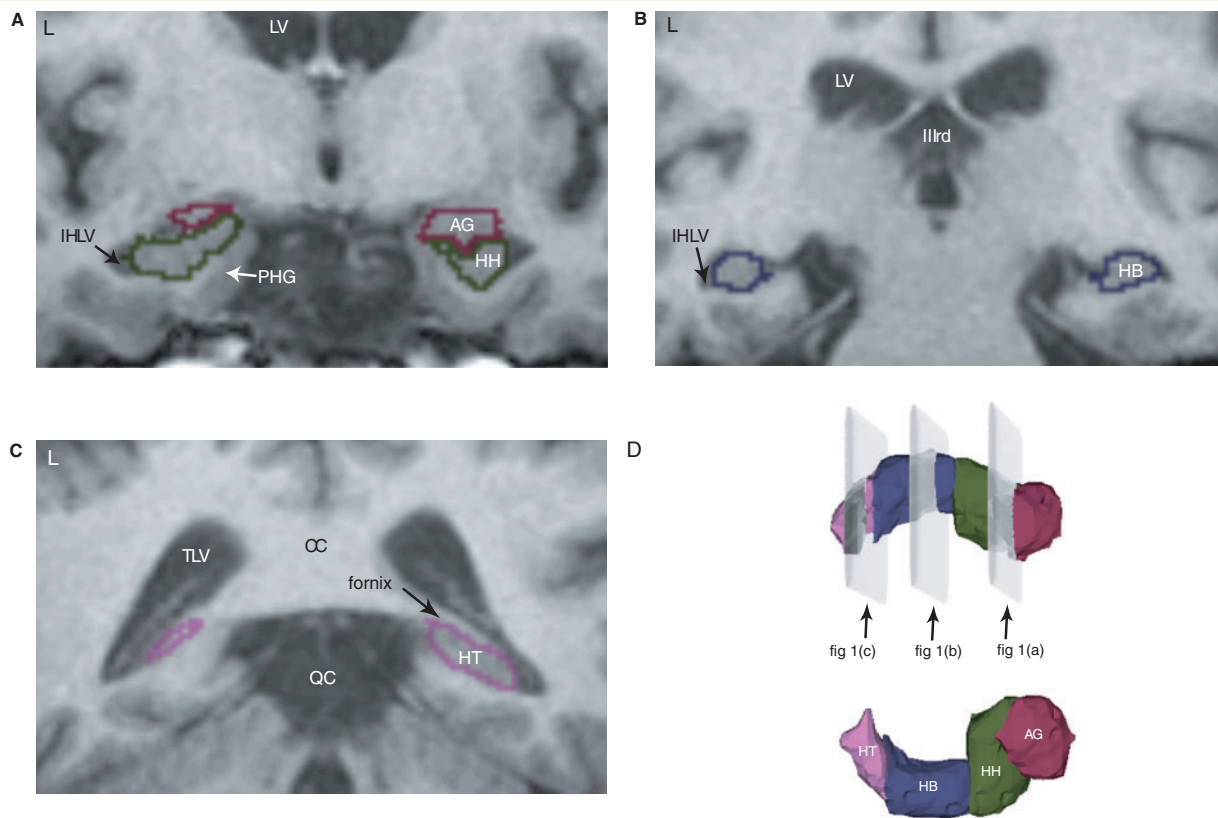
Fig. 1 Coronal MRI scans (in native space) from a single subject showing the (**A**) amygdala and hippocampal head, (**B**) hippocampal body and (**C**) hippocampal tail. A three dimensional rendering of the volumes of interest (**D**) indicates the planes of the coronal slices. AG = amygdala, CC = corpus callosum; HH = hippocampal head; HB = hippocampal body; HT = hippocampal tail; L = left; LV = lateral ventricle; IHLV = inferior horn of the lateral ventricle; PHG = parahippocampal gyrus; TLV = trigone of the lateral ventricle; QC = quadrigeminal cistern; IIIrd = third ventricle.

Mann–Whitney U-test where appropriate. Multiple regression analyses with forward variable selection were performed to investigate predictors of subjective memory scores. Pearson's correlations were used to examine the relations between manual volumetric measurements, clinical variables and cognitive performance. The significance level for all analyses was set at $P < 0.05$.

Voxel-based morphometry

VBM is a technique for voxel-wise analysis of local differences in brain tissue content (Ashburner and Friston, 2000) which has been used to study several types of brain disorder including temporal lobe epilepsy (Keller *et al.*, 2002a; Bonilha *et al.*, 2004, 2007a). The technique uses a spatial pre-processing stage followed by statistical analysis.

Pre-processing

The images were pre-processed using an automated pipeline described by Acosta-Cabronero *et al.* (2008). Briefly, skull-stripping was performed using the hybrid watershed algorithm or HWA (Ségonne *et al.*, 2004) in FreeSurfer v.3.04 (http://surfer.nmr.mgh.harvard.edu). Stripped volumes were then bias-corrected using the non-parametric non-uniform intensity normalisation or N3 v.1.10 (Sled *et al.*, 1998). Finally, a fine brain extraction that excludes venous sinuses and cerebrospinal fluid was performed using the brain extraction tool v.2.1 or BET2 (Smith, 2002) in FSL v.3.3 (http://www.fmrib.ox.ac.uk/fsl). All volumes were

then spatially normalised and segmented using the unified segmentation model provided in SPM5 (Wellcome Department of Cognitive Neurology, London; http://www.fil.ion.ucl.ac.uk/spm), running on Matlab version 6.5.1 (MathWorks, Natick, MA, USA). The segments were modulated to compensate for volumetric differences introduced into the warped images. Modulation has the effect of preserving the total amount of grey matter represented by multiplying by the relative volumes. Finally, grey-matter segments were smoothed using an 8-mm FWHM isotropic Gaussian kernel. Spatial smoothing is required prior to statistical analysis in order to cope not only with systematic miswarping to template but also with inter-subject variations in anatomy, to improve the signal-to-noise ratio and to render the data more normally distributed.

Statistical analysis

The pre-processed grey matter images were analysed using SPM5. First, a group analysis was performed to compare regional differences in grey matter volume between patients and control subjects. Four covariates of no interest were entered into the statistical model: study centre, sex, age and TIV [calculated in SPM5 using a previously described method (Pengas *et al.*, 2008)]. Second, multiple-regression analyses were performed to identify brain regions where, in the patient population, grey matter volume covaried linearly with a series of clinical and neuropsychological variables. The dependent variables investigated were: duration of epilepsy; lifetime number of seizures; performance on standard

tests of anterograde memory in which the group as a whole was impaired relative to controls (delayed recall of the Logical Memory story and Rey complex figure; recognition memory for words and faces; and zmem); autobiographical memory (MAMI-s and MAMI-e) and, for the subgroup of patients in which long-term forgetting tests were administered, accelerated long-term forgetting (zALF). Again, study centre, sex, age and TIV were entered into the design matrix as covariates of no interest. A grey-matter mask, created by binarising the probabilistic grey-matter map, and a relative threshold mask of 0.8, were applied. Resultant t-statistic maps were thresholded (i) at $P < 0.001$ uncorrected for multiple comparisons in the temporal lobes, the presumed site of pathology in TEA which we hypothesised to be related to memory function, or (ii) at $P < 0.05$ with false discovery rate (FDR) correction where there was no prior hypothesis.

Results

Participants

The demographic, clinical and objective neuropsychological data have been reported previously (Butler *et al*., 2007) and are summarised in Table 1. The mean patient age was 67.7 years (standard deviation, SD = 8.9). There were 28 male and 13 female patients. The average IQ was well matched across groups [patient mean = 119.2 (SD = 12.7), control mean = 121.2 (SD = 14.9), $P = 0.598$]. The patient group as a whole was impaired on standard memory tests relative to control subjects (zmem = −1.0; $P < 0.001$), and on the semantic and episodic components of the MAMI

(MAMI-s: patient mean = 8.9 (SD = 0.7), control mean = 9.5 (SD = 0.4), $P < 0.001$; MAMI-e: patient mean = 7.5 (SD = 1.4), control mean = 9.1 (SD = 0.7), $P < 0.001$). Subgroup 1 was unimpaired on all standard neuropsychological measures, but showed autobiographical memory impairment [MAMI-s: patient mean = 9.0 (SD = 0.6), $P < 0.001$; MAMI-e: patient mean = 7.7 (SD = 1.1), $P < 0.001$] and ALF [zALF = −1.5 (SD = 1.3); $P < 0.001$].

A past history of anxiety or depression was not more common among patients (22%) than controls (20%). Patients scored slightly higher on the HADS [patients: mean = 10.9 (SD = 6.4); controls: mean = 7.5 (SD = 3.1); $P = 0.008$], with higher ratings on the depression section [patients: mean = 5.3 (SD = 3.8); controls: mean = 2.7 (SD = 1.7); $P = 0.001$] but not on the anxiety section [patients: mean = 5.6 (SD = 3.7); controls: mean = 4.7 (SD = 2.5); $P = 0.276$] of the questionnaire. In the patient group, HADS score did not correlate with performance on standard anterograde memory tests (zmem) ($r = −0.19$, $P = 0.906$), autobiographical memory (MAMI-e) ($r = −0.08$, $P = 0.642$) or very-long term memory (zALF) ($r = −0.126$, $P = 0.577$).

Subjective memory scores

Patients rated their memories significantly worse than controls on both the EMQ [patients: mean = 29.7 (SD = 16.2); controls: mean = 13.8 (SD = 9.7); $P < 0.001$] and the VTLMQ [patients: mean = 10.0 (SD = 7.1); controls: mean = 2.4 (SD = 2.9); $P < 0.001$].

Multiple linear regression analysis was used to investigate which demographic and neuropsychological factors were predictive of

Table 1 Demographic, clinical and neuropsychological characteristics of TEA patient group and control subjects

	All patients ($n = 41$) Mean (SD)	Subgroup 1 ($n = 22$) Mean (SD)	Controls ($n = 20$) Mean (SD)
Age (years)	67.7 (8.9)	66.4 (8.8)	67.5 (8.6)
Sex distribution	28M/13F	12M/10F	8M/12F
Education (years)	12.5 (3.0)	13.2 (3.0)	13.0 (3.3)
Age at onset of seizures (years)	61.1 (9.2)	60.3 (8.0)	NA
Total number of seizures	18.5 (17.7)	20.5 (19.3)	NA
Seizure frequency (per year)	13.2 (11.7)	12.0 (10.9)	NA
Duration of epilepsy (months)	81.3 (69.4)	77.4 (71.9)	NA
Full scale IQ	119.2 (12.7)	124.7 (10.7)	121.2 (14.9)
Logical memory delayed recall (25)	11.9 (5.1)*	14.7 (2.8)	14.6 (3.7)
Rey figure delayed recall (36)	15.6 (6.4)*	16.7 (5.6)	19.9 (6.3)
RMT (words) (50)	46.3 (3.6)*	47.7 (2.0)	48.4 (1.7)
RMT (faces) (50)	41.2 (5.2)**	43.4 (3.8)	45.4 (2.8)
zmem	−1.0 (1.1)**	−0.4 (0.6)	0.0 (0.7)
Rey figure copy (36)	34.6 (3.0)	35.5 (1.3)	35.4 (1.2)
Graded faces (60)	40.3 (9.6)	42.6 (8.1)	44.6 (7.4)
Graded naming (30)	21.7 (5.0)	23.4 (3.0)	23.9 (3.8)
Letter fluency	41.8 (14.1)	48.2 (11.8)	45.0 (10.3)
Category fluency	19.9 (5.9)	22.5 (5.2)	22.7 (4.6)
WCST categories	2.9 (1.3)	3.23 (1.3)	3.8 (1.3)
HADS (42)	10.9 (6.4)*	10.4 (6.1)	7.5 (3.1)
MAMI-s (10)	8.9 (0.7)**	9.0 (0.6)**	9.5 (0.4)
MAMI-e (10)	7.5 (1.4)**	7.7 (1.1)**	9.1 (0.7)
zALF	NA	−1.5 (1.3)**	0.0 (1.0)

*Significantly different from control group ($P < 0.05$). **Significantly different from control group ($P < 0.001$).
IQ = intelligence quotient; NA = not applicable; RMT = Recognition Memory Test; WCST = Wisconsin Card Sorting Test.

subjective memory scores. Separate analyses were conducted using EMQ and VTLMQ scores as dependent variables. The independent variables entered into the regression models were: age, sex, zmem, zALF, MAMI-e (highly correlated with MAMI-s and potentially more closely associated with subjective memory complaints), letter fluency (as a measure of executive function) and total HADS score. Only variables that met the forward selection criterion ($P < 0.05$) were retained. The resulting models are shown in Table 2.

Age, sex, zmem and letter fluency were not predictive of either subjective memory measure. EMQ score was predicted by total HADS score ($\beta = 0.53$, $P = 0.008$) and zALF ($\beta = -0.41$, $P = 0.03$). The model was able to explain 49% of the variance in EMQ score. VTLMQ score was predicted by total HADS score ($\beta = 0.54$, $P = 0.002$) and MAMI-e ($\beta = -0.35$, $P = 0.036$). The model was able to explain 51% of the variance in VTLMQ score.

Manual volumetrics

As shown in Table 3 and Fig. 2, significant differences were found between patients and controls in the volumes, corrected for TIV, of both the left [patients: mean $= 2776\,\text{mm}^3$ (SD $= 447$); controls: mean $= 3009\,\text{mm}^3$ (SD $= 274$); $P = 0.016$] and right [patients: mean $= 2934\,\text{mm}^3$ (SD $= 498$); controls: mean $= 3201\,\text{mm}^3$ (SD $= 268$); $P = 0.009$] hippocampus. When the longitudinal subdivisions of the hippocampus were compared, the hippocampal body volumes of patients and controls differed significantly in both the left [patients: mean $= 920\,\text{mm}^3$ (SD $= 190$); controls: mean $= 1032\,\text{mm}^3$ (SD $= 114$); $P = 0.006$] and right [patients: mean $= 968\,\text{mm}^3$ (SD $= 163$; controls: mean $= 1082\,\text{mm}^3$ (SD $= 138$); $P = 0.012$] hemispheres. The volumes of the hippocampal head and tail did not differ significantly between groups in either hemisphere.

There was no significant difference detected in the volume of the left [patients: mean $= 1281\,\text{mm}^3$ (SD $= 371$); controls: mean $= 1271\,\text{mm}^3$ (SD $= 217$); $P = 0.898$] or right [patients: mean $= 1275\,\text{mm}^3$ (SD $= 304$); controls: mean $= 1265\,\text{mm}^3$ (SD $= 232$); $P = 0.886$] amygdala.

Correlational analyses

In order to identify potential causal factors for the interictal memory impairment seen in TEA patients, correlational analyses were carried out between hippocampal volumes, seizure variables and memory test scores. The results are shown in Table 4. Hippocampal volumes did not correlate with any neuropsychological measure in the control group.

Seizure variables

In the patient group, there was no significant correlation between hippocampal volumes and duration of epilepsy or seizure frequency. A positive correlation was found between left hippocampal volume and the lifetime number of seizures ($r = 0.344$, $P = 0.028$).

Standard anterograde memory

The overall anterograde memory score (zmem) showed a significant positive correlation with right ($r = 0.352$, $P = 0.024$), and a

Table 2 Multiple regression analyses investigating predictors of subjective memory scores

Independent variable	Dependent variable	β	t	P
EMQ	HADS	0.53	3.03	0.008
	zALF	−0.41	−2.38	0.030
VTLMQ	HADS	0.54	3.46	0.002
	MAMI-e	−0.35	−2.24	0.036

Table 3 Manually traced volumes of hippocampus (head, body and tail) and amygdala in TEA patients and controls corrected for total intracranial volume

|	Mean (SD) volume mm³		P
	Patients	Controls	
L hippocampus			
Total	2776 (447)	3009 (274)	0.016
Head	1539 (350)	1636 (228)	0.275
Body	920 (190)	1032 (114)	0.006
Tail	319 (98)	342 (119)	0.432
R hippocampus			
Total	2934 (498)	3201 (268)	0.009
Head	1672 (383)	1789 (259)	0.232
Body	968 (163)	1082 (138)	0.012
Tail	327 (104)	329 (79)	0.911
L amygdala	1281 (371)	1271 (217)	0.898
R amygdala	1275 (304)	1265 (232)	0.886

trend towards correlation with left ($r = 0.299$, $P = 0.057$) hippocampal volumes. Delayed recall of the Rey figure correlated with right hippocampal volume ($r = 0.315$; $P = 0.045$). Recognition memory for faces correlated with right hippocampal volume ($r = 0.320$, $P = 0.041$) and tended towards correlation with left hippocampal volume ($r = 0.294$, $P = 0.062$). Neither recognition memory for words nor logical memory scores correlated significantly with hippocampal volumes.

Autobiographical memory

The average semantic (MAMI-s) and episodic (MAMI-e) autobiographical memory scores did not correlate with volumes of either hippocampus or with any seizure variable. There was no correlation between either measure of autobiographical memory and any standard measure of anterograde memory.

Accelerated long-term forgetting

In subgroup 1, the overall anterograde memory score (zmem) again correlated with right hippocampal volumes ($r = 0.457$, $P = 0.032$) but not left hippocampal volumes ($r = 0.367$, $P = 0.093$). The average score for forgetting over 3 weeks (zALF) was unrelated to hippocampal volumes. No significant relationships were found between long-term forgetting scores and seizure variables. Long-term forgetting did not correlate with any standard measure of anterograde memory or with autobiographical memory scores.
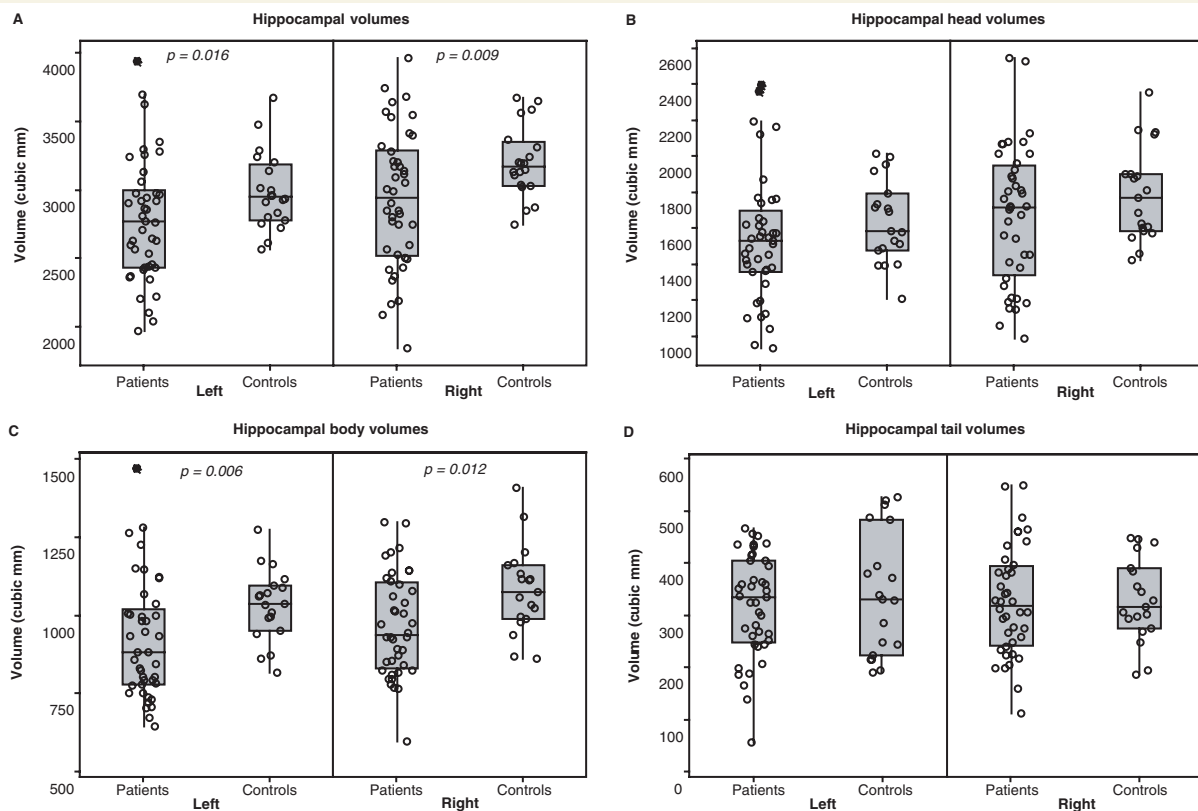
Fig. 2 Boxplots showing medians (horizontal lines), interquartile ranges (grey boxes) and ranges (vertical lines) of volumes (adjusted for TIV) of the (**A**) hippocampus, (**B**) hippocampal head, (**C**) hippocampal body and (**D**) hippocampal tail, in patients and controls. Outliers are shown as crossed symbols. Where significant, *P*-values are shown above the corresponding boxplot.

Table 4 Correlation of clinical and neuropsychological variables with hippocampal volumes

	LHC (r)	RHC (r)
Age at onset	−0.037	−0.004
Duration of epilepsy	−0.170	−0.260
Seizure frequency	−0.025	0.005
Number of seizures	0.344*	0.286
zmem	0.299	0.352*
Rey figure delayed recall	0.180	0.315*
RMT (faces)	0.294	0.320*
LM delayed recall	0.073	0.158
RMT (words)	0.266	0.228
MAMI-s	0.082	0.131
MAMI-e	−0.165	0.084
zALF	−0.178	0.036

*$P < 0.05$.
LHC = left hippocampus; LM = logical memory; RHC = right hippocampus; r = Pearson's correlation coefficient, RMT = Recognition Memory Test.

Voxel-based morphometry

The results of the VBM analyses are shown in Table 5 and Fig. 3. Results are reported at an uncorrected threshold of $P < 0.001$ within the temporal lobes, and at $P < 0.05$ FDR corrected in other brain regions. However, even at the uncorrected threshold, extratemporal clusters were rare and, where present, small (<40 voxels).

Group analysis

No regions were identified in which patients had reduced grey matter volume. On the contrary, patients appeared to have increased grey matter in inferior temporal and parahippocampal regions bilaterally.

Epilepsy variables

No clusters were identified that correlated with duration of epilepsy, seizure frequency or total number of seizures.

Standard anterograde memory

In the patient group, the summary score of standard anterograde memory measures (zmem) correlated with a cluster of voxels in the left MTL. Recognition memory for faces correlated with bilateral medial temporal regions. Delayed recall of the Rey figure correlated with a cluster in the right hippocampus.

Autobiographical memory

In the patient group, neither episodic nor semantic MAMI scores correlated with any MTL voxels.

Table 5 Group and correlational VBM analyses

	BA	x	y	z	Cluster size	P(FDR)	t	z
Controls < patients								
L inferior temporal gyrus	37	−38	−42	−14	139	0.055	5.22	4.67
L inferior temporal gyrus	20	−42	−28	−20		0.055	4.86	4.41
L parahippocampal gyrus	37	−22	−40	−6	109	0.055	4.74	4.31
R fusiform gyrus	37	38	−40	−16	23	0.074	4.32	3.99
R inferior temporal gyrus	20	52	−12	−24	13	0.098	4.00	3.73
R inferior temporal gyrus	36	36	0	−36	44	0.103	3.96	3.69
R parahippocampal gyrus	30	26	−22	−26	17	0.119	3.87	3.62
zmem								
L parahippocampal gyrus	20	−30	−24	−18	59	0.968	4.19	3.75
RMT (faces)								
R parahippocampal gyrus	20	24	−16	−18	73	0.265	4.61	4.05
L parahippocampal gyrus	34	−18	4	−18	85	0.265	4.59	4.04
Rey figure delayed recall								
R hippocampus	20	34	−20	−16	51	0.383	4.23	3.78

Results are reported at $P < 0.001$ (uncorrected) for temporal lobe peaks and $P < 0.05$ (FDR corrected) for extratemporal peaks.
BA = Brodmann area; FDR = false discovery rate corrected; RMT = Recognition Memory Test.

Accelerated long-term forgetting

In subgroup 1, no brain regions were found that correlated with the summary score (zALF) or any of the individual tests of long-term forgetting.

Discussion

In this study, we explored the interictal memory deficits observed in patients with TEA, their interrelationships and their correlations with clinical and neuroimaging data. Patients' subjective impression of memory impairment, as assessed using questionnaires tapping everyday and long-term memory, were partially predicted by mood, and by measures of ALF and remote autobiographical memory, but not by standard measures of anterograde memory. TEA was associated with subtle MTL atrophy, which correlated with performance on standard tests of anterograde memory, but not with measures of ALF or of autobiographical amnesia.

Subjectively reported memory difficulties are common and pronounced in TEA, as demonstrated by patients' responses to the EMQ and VTLMQ. These responses failed to correlate with any standard measure of anterograde memory, but were independently related both to mood and performance on novel tests that examined forgetting over an extended delay and remote autobiographical memory. Performance on standard memory measures has been shown to correlate poorly with subjective complaints in other types of epilepsy (Thompson and Corcoran, 1992; Piazzini et al., 2001; Banos et al., 2004), although this finding is not universal (Helmstaedter et al., 1998). The relation between mood and subjective memory difficulties in epilepsy is widely recognized (Elixhauser et al., 1999; Piazzini et al., 2001). Our results suggest that, in TEA at least, ALF and autobiographical memory impairment may play an additional role. Nonetheless, considerable unexplained variance remains in our models, which may be attributable to several factors. The types of memory failure

reported by patients, particularly in day-to-day memory, may reflect problems with attention and concentration rather than memory per se. Furthermore, the high average IQ in this group may mean that patients are particularly aware of changes in their memory abilities, especially when sensitised by ictal memory failure.

We have demonstrated volume reduction in the hippocampus of TEA patients using a manual delineation technique. Across the group, atrophy was detected in both left and right hippocampi. However, the overall degree of atrophy was subtle—about 8% of the total hippocampal volume. In this group of patients, it was not possible to distinguish electrophysiologically or radiologically between patients with a right or left-sided seizure focus. It may be, therefore, that averaging across the pathological and non-pathological hemispheres attenuated the observed volume differences. It cannot be assumed, however, that the pathology in TEA is as asymmetrical as that in other forms of TLE. Indeed, the semiology of TEA attacks, which is very similar to the classical amnesic syndrome, suggests that MTL dysfunction must be bilateral. It has been proposed that seizure activity in pure amnesic seizures might spread from one hippocampus to the other, without involving other brain regions, via the dorsal hippocampal commissure (Gloor et al., 1993). The syndrome of TGA, which is also characterised by transient anterograde and retrograde amnesia, but of which the aetiology remains uncertain, is associated with bilateral temporal lobe abnormalities on functional brain imaging (see Pantoni et al., 2000 for a review). Furthermore, high-signal lesions have been observed on diffusion-weighted MRI in one or both hippocampi (Sedlaczek et al., 2004, Winbeck et al., 2005; Bartsch et al., 2006). We are not aware of any study that has examined whether TGA is associated with volume loss using quantitative imaging techniques.

Using well-established anatomical landmarks to segment the hippocampus into head, body and tail regions, we found volume loss to be significant only in the hippocampal body. This contrasts with recent work employing similar methods in patients with
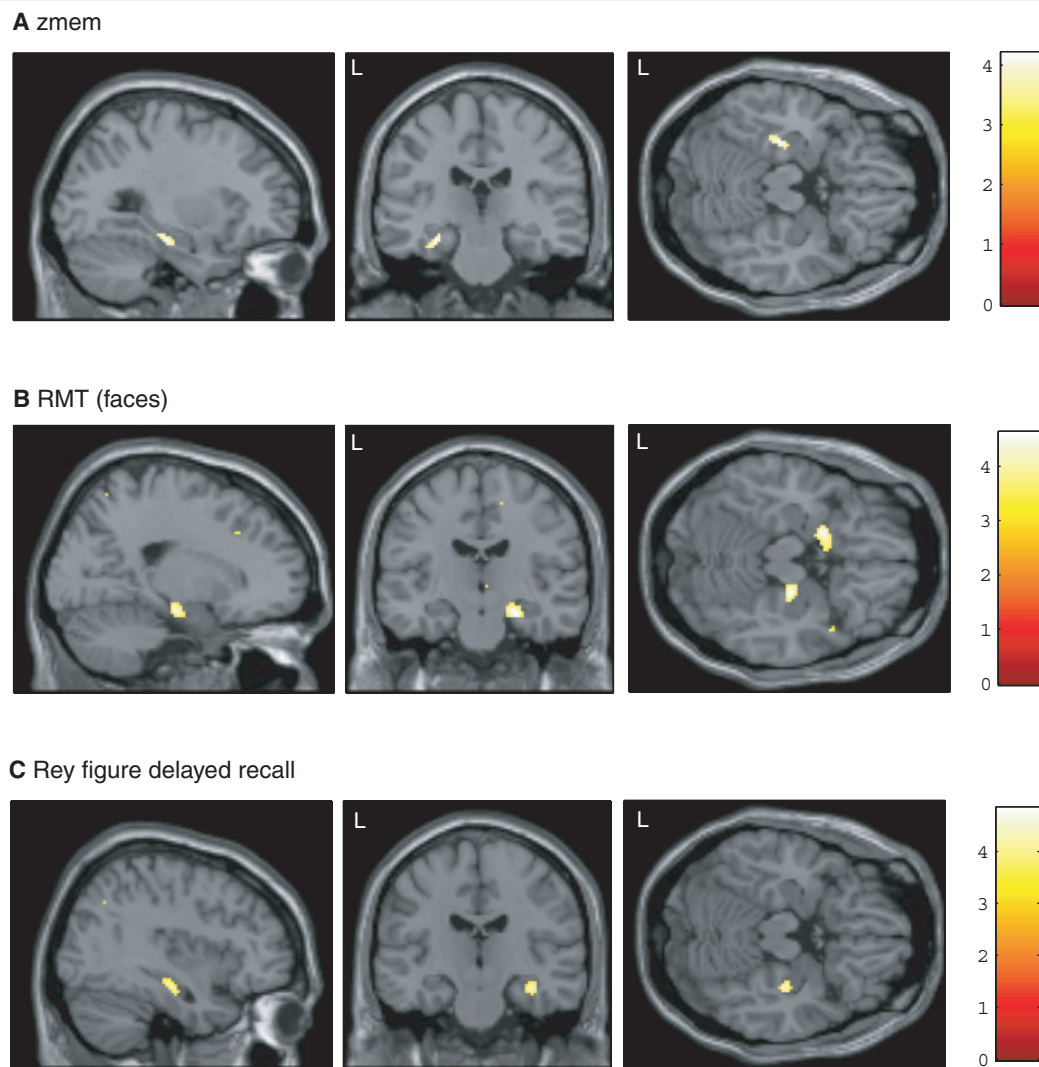
Fig. 3 Voxel-based morphometry results. The figure shows areas where, in the patient group, grey-matter volume was positively associated with (**A**) average anterograde memory score (zmem), (**B**) the faces subsection of the Recognition Memory Test (Warrington, 1984) and (**C**) delayed recall of the Rey complex figure (Osterreith and Rey, 1944). Results are displayed at an uncorrected significance threshold of $P < 0.001$, and overlaid on the SPM5 canonical single subject T1 volume. The values of the t-statistic are shown on the coloured bars. L = left.

medically intractable TLE, which found most atrophy in the hippocampal head (Bernasconi et al., 2003), although older findings include diffuse (Quigg et al., 1997; Van Paesschen et al., 1997) and focal hippocampal body (Bronen et al., 1995; Kuzniecky et al., 1996) atrophy.

No difference was detected in the size of the amygdala between TEA patients and control subjects. Although the anatomical boundaries of the amygdala are difficult to delineate on MR images (Pruessner et al., 2000), previous studies in medically refractory TLE have demonstrated amygdalar atrophy ipsilateral to the side of seizure onset (Cendes et al., 1993; Watson et al., 1997; Bernasconi et al., 2003). The atrophy is often, however, less marked than in the hippocampus.

Our VBM group analysis of patient versus control scans failed to confirm the manual finding of focal hippocampal atrophy. This is likely to be because the group differences are relatively subtle: the spatial normalization, tissue segmentation and smoothing components of image pre-processing in VBM inevitably lower the sensitivity of this method. A recent study of VBM in patients with Alzheimer's disease was able to detect an ∼20% reduction in hippocampal volume (as measured manually), at an uncorrected threshold of $P < 0.001$ (Acosta-Cabronero et al., 2008). The 8% reduction seen in TEA is probably below VBM resolution. Studies using VBM to investigate volume changes in TLE have usually focused on patients with medically intractable epilepsy, often including those with hippocampal sclerosis. Such studies (Keller et al., 2002a; Bernasconi et al., 2003; Bonilha et al., 2004, 2007b; Mueller et al., 2006) have revealed grey matter loss in an extensive network including the ipsilateral and contralateral hippocampus, parahippocampal cortices, cingulate cortex, thalamus, insula, frontal lobes and cerebellum [for a review see Keller and Roberts (2008)], largely confirming the findings of manual

volumetry. Atrophy is perhaps more restricted to the MTL in milder forms of TLE (Briellmann et al., 2007; Labate et al., 2008). Interestingly, the degree of atrophy does not correspond with the severity of the clinical syndrome (Briellmann et al., 2007).

We found positive correlations between the volume of MTL structures and performance on standard anterograde memory tests using both manual volumetrics and VBM. Right hippocampal volume was related specifically to performance on two tests of visuospatial memory—delayed recall of the Rey complex figure and face recognition memory. These results are consistent with the widely accepted notion that the hippocampus and surrounding cortices are crucially involved in the formation and at least initial retention of declarative memories, and that there is a degree of lateralization between verbal and non-verbal memory (Kelley et al., 1998). Correlations of MTL atrophy with cognitive performance have previously been demonstrated in patients with TLE using manual volumetrics (Lencz et al., 1992; Baxendale et al., 1998; Reminger et al., 2004). VBM studies, however, have implicated much more extensive brain atrophy in the memory deficits of TLE (Bonilha et al., 2007a; Focke et al., 2008). The findings of the present study indicate that TEA may involve more focal, if less marked, pathology.

We found no relationship between the volume of medial temporal structures and ALF or autobiographical memory impairment. The pathophysiological mechanisms underlying ALF are not yet known, but there are several possibilities. Firstly, it might be simply a mild form of the memory loss typically associated with MTL damage. TEA patients did show slightly increased forgetting over 30 min although this was not predictive of very long-term recall for individual subjects (Butler et al., 2007). The failure to find structural correlates of ALF in this study may then be due to the use of insufficiently sensitive techniques, or the existence of relevant atrophy beyond the hippocampus that was not detected by VBM. Secondly, ALF may be caused by intermittent neuronal dysfunction in the MTL. The close relationship between TEA attacks and waking from sleep raises the possibility that nocturnal, subclinical epileptic activity may disturb sleep-dependent memory consolidation processes (Stickgold, 2005). This possibility could be explored with prolonged EEG monitoring. Thirdly, ALF may be due to the effects of anticonvulsant medication. We consider this to be unlikely since patients (i) are generally on low doses of anticonvulsants and (ii) report that their memory improves on initiation of treatment. These explanations are not mutually exclusive and several factors may conjoin to produce ALF.

The cause of autobiographical memory loss in TEA is also unknown. Again, the failure to find structural correlates in this study may be due to the use of insufficiently sensitive neuropsychological or anatomical techniques. A further possibility is that seizure activity in the temporal lobes leads to functional disruption of memory networks (Manes et al., 2001). We consider it unlikely that purely psychogenic mechanisms play a major role. Current or previous diagnoses of anxiety or depression were not over represented amongst patients with TEA and, although patients scored slightly higher on the HADS than controls, this measure did not correlate with performance on standard tests of memory, with ALF or with autobiographical memory scores. The neural substrate of remote memory is currently debated. The so-called 'standard' theory holds that, following acquisition, all declarative memory traces gradually become independent of the hippocampus through a process of network reorganisation (Squire and Alvarez, 1995; Bayley et al., 2005). On the other hand, the 'multiple-trace theory' (Nadel and Moscovitch, 1997; Moscovitch and Nadel, 1998; Moscovitch et al., 2006) posits lifelong dependence of retrieval of episodic memories upon the hippocampus. Whilst temporally extensive impairment of episodic autobiographical memory has been shown to correlate with MTL volumes in several contexts including post-surgical TLE (Noulhiane et al., 2007) and Alzheimer's disease (Gilboa et al., 2005), such findings are not universal (Eustache et al., 2004; Bright et al., 2006). Further study of the syndrome of TEA, in which temporally extensive retrograde amnesia occurs in the context of late-onset MTL seizures, should help to inform this debate.

In the VBM group analysis, patients appeared to have increased grey matter volumes in the inferomedial temporal cortex—the inferior temporal gyrus, fusiform gyrus and parahippocampal gyrus—bilaterally. Similar findings have been reported in VBM studies of TLE patients (Woermann et al., 1999; Bernasconi et al., 2004; Bonilha et al., 2004), and are likely to be due to diminished grey–white matter demarcation in the temporal lobe of patients and subsequent tissue segmentation anomalies. In contrast, manual volumetric analysis of parahippocampal cortex in TLE has revealed grey matter volume reduction (Bernasconi et al., 2003). The findings in the present study require further exploration by manual delineation of the more lateral temporal cortices.

We identified no correlation between regional brain atrophy and the duration of epilepsy or frequency of seizures using manual volumetrics or VBM. The weak positive correlation seen between manually traced left hippocampal volume and the lifetime number of seizures was not supported by VBM and is likely to be spurious, driven by a small number of outlying results for which the estimated number of seizures is also probably less accurate. Similar investigations in medically refractory TLE have yielded mixed results, with some authors reporting positive (e.g. Kalviainen et al., 1998; Keller et al., 2002b; Seidenberg et al., 2005; Bonilha et al., 2006) and others negative (e.g. Spanaki et al., 2000; Jutila et al., 2001; Bernasconi et al., 2004) results. The negative findings in the present study should be interpreted with caution for a number of reasons including the inherent lack of sensitivity of cross-sectional analysis, the reliance upon retrospective patient reports, the relatively small sample size and the subtle degree of MTL atrophy.

In conclusion, we have demonstrated that patients with TEA have subtle volume loss in the hippocampus and show a mild deficit in performance on standard tests of anterograde memory. MTL volumes correlate with several measures of anterograde memory. However, the interictal memory deficits reported by the patients relate more closely to ALF and autobiographical amnesia. These novel forms of memory impairment are not clearly related to regional brain atrophy. Further studies using metabolic and functional imaging as well as electrophysiological measures may help to determine their pathophysiological origins and how they relate to current models of human memory.

Supplementary material

Supplementary material is available at *Brain* online.

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