

Available online at www.sciencedirect.com**SciVerse ScienceDirect**Journal homepage: www.elsevier.com/locate/cortex**Research report****Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy**

Heather Wilkinson^a, Juliet S. Holdstock^b, Gus Baker^c, Andrea Herbert^d, Fiona Clague^{e,f}
and John J. Downes^{b,*}

^a Department of Psychology, University of Chester, UK^b School of Psychology, University of Liverpool, UK^c University Department of Neurosciences, Walton Centre for Neurology and Neurosurgery, Liverpool, UK^d Department of Clinical and Community Psychology, Devon Partnership NHS Trust, Exeter, UK^e Clinical Psychology Department, Astley Ainslie Hospital, Edinburgh, UK^f Department of Clinical and Health Psychology, School of Health in Social Science, The University of Edinburgh, UK

ARTICLE INFO

Article history:

Received 18 December 2009

Revised 24 February 2010

Accepted 15 December 2010

Action editor Sergio Della Sala

Published online 11 February 2011

Keywords:

Memory

Recall

Consolidation

Seizures

Hippocampus

ABSTRACT

Introduction: We investigated whether pre-surgical patients with temporal lobe epilepsy (TLE) forget verbal and non-verbal material faster than healthy controls over retention intervals of an hour and 6 weeks, and whether any observed memory loss was associated with structural changes to the hippocampus and/or seizure frequency.

Methods: A mixed factorial design compared the performance of 27 patients with TLE and 22 healthy control participants, matched for IQ, age and gender, on tests of story recall and complex figure recall at three delays: immediate, 1 h and 6 weeks. Performance of the patient and control groups was matched at the immediate delay, which enabled comparisons of forgetting rate over the longer delays.

Results: We found that TLE can affect the acquisition and retention of new memories over a relatively short delay of 1 h. This deficit was associated with structural hippocampal abnormality, with a material-specific effect that was particularly evident for the verbal task. We also found evidence of accelerated long-term forgetting in both patient groups, for the verbal and non-verbal tasks. It was demonstrated most strongly on the verbal task by the patients with right lateralized hippocampal sclerosis whose verbal recall was normal at the 1-h delay. Accelerated long-term forgetting was not associated with hippocampal pathology, but was associated with the frequency of epileptic seizures.

Discussion: The findings from the verbal task in particular provide evidence consistent with an extended period of memory consolidation that can be disrupted by both left and right TLE. The material-specific effects at the 1-h delay only, suggest that the initial consolidation of verbal and non-verbal, information depends on the integrity of the left and right hippocampus, respectively.

© 2011 Elsevier Srl. All rights reserved.

* Corresponding author. School of Psychology, University of Liverpool, Liverpool L69 7ZA, UK.

E-mail address: down@liverpool.ac.uk (J.J. Downes).

0010-9452/\$ – see front matter © 2011 Elsevier Srl. All rights reserved.

doi:10.1016/j.cortex.2011.01.002

1. Introduction

Patients with temporal lobe epilepsy (TLE) often report experiencing problems with memory in everyday life and yet in many cases can perform normally on standardized neuropsychological tests of memory used in clinical assessment (Blake et al., 2000). The standardized tests used for clinical purposes are, however, limited in the durations over which memory is tested, the longest retention delay being 30 min. It has been argued that acquisition and initial consolidation of long-term memories can sometimes be spared in patients with TLE, enabling them to perform normally on standardized memory tests, but that an extended period of consolidation, that occurs over days, weeks, months or even years, and is required for long-term maintenance of the memories, is disrupted by this disorder (Blake et al., 2000). Indeed, a number of single cases have been reported of individuals with TLE whose memory is unimpaired after the kind of short delays used in clinical testing, but who show more rapid forgetting of information than healthy individuals over longer delays of several weeks (Kapur et al., 1997; O'Connor et al., 1997; Mayes et al., 2003). This pattern has been termed long-term amnesia. None of these cases, however, have had typical mesial TLE: one had treatment for testicular cancer and very frequent complex partial seizures (O'Connor et al., 1997), another had seizures secondary to a traumatic head injury that resulted in considerable bilateral damage to the frontal and temporal lobes [but excluded the hippocampus (HC)] (Mayes et al., 2003), and the third had a late seizure onset which occurred at 56 years of age (Kapur et al., 1997). The results from these case studies may not therefore generalize to more typical cases of TLE, but may reflect idiosyncratic seizure type and location. The possibility that long-term forgetting may be a more general characteristic of TLE has been investigated by a small number of group studies, with mixed results (see Bell and Giovagnoli, 2007; Butler and Zeman, 2008a, 2008b for reviews).

Studies using the Selective Reminding Test (Buschke, 1973; Buschke and Fuld, 1974) have found that patients with TLE were impaired relative to controls on tests of learning and at memory after delays of both 30 min, and a longer delay of 24 h and 13 days, respectively (Giovagnoli et al., 1995; Bell et al., 2005). Similarly, recall of the story from the logical memory subtest of the Wechsler Adult Intelligence Scale III (Wechsler, 1997) was impaired after both short and long delays in patients with TLE (Bell, 2006). None of these studies found an interaction between group (patients vs controls) and memory test delay and therefore found no evidence for accelerated long-term forgetting in the patient group. However, the lack of an interaction is difficult to interpret in these studies because the memory performance of the patients and controls was not equated at the short delay (see Huppert and Piercy, 1978; Isaac and Mayes, 1999). So, although these studies show clear memory deficits in these patients at both short and long delays, they provide no strong evidence concerning the relative rates of forgetting over long delays of the patients and healthy controls. Similarly, two further studies have reported deficits in verbal and non-verbal memory in TLE over both short and long delays, but neither study examined whether there was an interaction between participant group and

memory test delay (Helmstaedter et al., 1998; Mameniskienu et al., 2006). Thus, although these latter two studies show that the patients' memories were very impaired at the longest delays, again, they provide no information about the relative rates of forgetting of the patients and healthy controls.

There are two studies in the literature that have matched the memory performance of the patients and controls on the initial memory test and found accelerated forgetting in the patient group over delays of 24 h to 8 weeks (Martin et al., 1991; Blake et al., 2000). Martin et al. (1991) used the Selective Reminding Test to compare free recall of verbal material (unrelated word lists) by 21 patients with TLE and 21 tension headache control subjects at delays of 30 min and 24 h. They found a significant group by delay interaction, with the TLE and tension headache control groups performing at an equal level during the final learning and the 30 min delayed memory trials, but the TLE patients performing significantly worse than the controls at the 24-h delay. There was no significant interaction with laterality of epileptic focus.

One limitation of the study of Martin et al. (1991) was that the TLE group consisted of both pre- and post-surgical patients and so it is difficult to infer whether the accelerated forgetting is a function of temporal lobe resection or of TLE per se. In the subsequent study conducted by Blake et al. (2000), only pre-surgical patients were included. Forgetting was assessed over delays of up to 8 weeks in 21 consecutive partial seizure patients, which included 14 pre-surgical TLE patients with either a right or left epileptic focus. The patients' performance on standardized tests of memory (WMS-R) and object naming (Graded Naming Test) did not differ significantly from the healthy controls, but, despite this, almost half of the patients reported that their everyday memory was moderately or severely impaired. To explore accelerated forgetting, the patients were repeatedly presented with a short story until their recall reached 90% correct or for a maximum of ten trials. The number of learning trials required to reach criterion did not differ significantly between the patient and control groups indicating intact learning in the patient group. Nevertheless the patients with a left hemispheric epileptic focus recalled significantly less of the story than healthy controls and the patients with a right hemispheric focus after an 8-week delay. The recall of the three groups did not differ after a 30-min delay. Similar findings were reported for recognition, which was significantly poorer for the left hemisphere group than healthy controls, although the difference between the left and right hemisphere groups did not quite reach statistical significance.

In summary, Blake et al. (2000) showed normal learning and short-term retention (30 min) in TLE, but accelerated loss of this normally learnt information over an 8-week period. Furthermore, it was found that the long-term forgetting of the verbal material used in this study was associated with a left rather than right seizure focus, consistent with reports of lateralization of verbal memory to the left temporal lobe (e.g., Milner, 1971).

Our study investigated why TLE can result in accelerated loss of memories over short and extended time periods. We were interested in whether the same or different variables were associated with forgetting over relatively short and long retention intervals. To do this, following the methodology of Blake

et al. (2000), we matched the performance of pre-operative patients with TLE that had resulted in left or right lateralized hippocampal sclerosis and healthy controls on immediate verbal and non-verbal, visuospatial, recall and then investigated forgetting over delays of 1 h and 6 weeks. In particular, we investigated whether forgetting over these delays was associated with measures of hippocampal sclerosis (hippocampal volume, T2 relaxation time) or seizure frequency or both.

We were interested in the possible contribution of the HC to long-term forgetting because it is believed to have a central role in current models of memory consolidation (e.g., Alvarez and Squire, 1994). It could therefore be predicted that the integrity of this structure may be important for long-term retention. Indeed, hippocampal size, as determined by magnetic resonance imaging (MRI), in healthy individuals has been found to predict verbal recall over a long retention interval of approximately 11 weeks (Walhovd et al., 2004). In that study, hippocampal volume was more important for recall after long than short delays of up to 30 min. An investigation of transient epileptic amnesia (TEA) however, found significant or close to significant correlations between verbal and non-verbal recall and hippocampal volume after a 30-min delay but not after a long, 3-week delay (Butler et al., 2009). Considering TLE, there is strong evidence that the HC is involved in memory retention over 30 min delays used in clinical assessment (e.g., Baxendale, 1995; Baxendale et al., 1998), but it has not been investigated to date whether hippocampal atrophy is associated with long-term accelerated forgetting in TLE. This therefore remains to be determined and was a main focus of our study.

More recent studies have shown that other scan protocol parameters may offer greater potential in identifying pathology within the HC and related structures. One such parameter is T2 relaxation time, which is believed to provide an index of structural integrity. Bernasconi et al. (2000) have shown that T2 relaxation times are more sensitive than T1 volumetry analysis in detecting hippocampal sclerosis. A number of studies have also looked at the relationship between T2 relaxation times and memory measures. For example, Lillywhite et al. (2007), reported negative correlations between left hippocampal T2 relaxation time and verbal memory in newly diagnosed patients with left TLE, whereas Baxendale et al. (1998) reported a relationship between right-sided hippocampal T2 relaxation time and non-verbal memory performance in a group of TLE patients. In the present study, we selected TLE patients who had left or right lateralized structural hippocampal abnormality, which enabled us to determine whether structural hippocampal integrity, as measured using both T1 volumetry and T2 relaxometry, was associated with verbal and non-verbal recall over both a shorter 1-h delay, and a long, 6-week delay.

Hippocampal atrophy is not the only factor that may lead to accelerated memory loss in TLE. In the group study reported by Blake et al. (2000), accelerated long-term forgetting was found despite very few of the patients having structural changes to the temporal lobe as indicated by MRI. Blake et al. attributed the long-term verbal memory deficits associated with left TLE in that study to the effect of seizure activity during the 8-week retention interval. This is consistent with the finding that higher seizure frequency and particularly the occurrence of seizures with loss of consciousness were

associated with poorer verbal memory in TLE patients after a 4-week delay (Mameniskiene et al., 2006). Furthermore, accelerated forgetting has been reported to be associated with other disorders involving seizure activity such as TEA (Butler et al., 2007; Butler and Zeman, 2008a, 2008b; Butler et al., 2009; Manes et al., 2008), and idiopathic generalized epilepsy (Davidson et al., 2007), although in TEA, accelerated long-term forgetting appears to be independent of the frequency of overt seizures (Butler et al., 2009). In our study, seizure frequency was recorded during the 6 week retention interval to determine whether there was an association between seizure frequency and memory performance in our patient groups.

In summary, we matched the performance of pre-operative patients with TLE that had resulted in left or right lateralized hippocampal sclerosis and healthy controls on immediate verbal and non-verbal, visuospatial, recall and then investigated forgetting over delays of 1 h and 6 weeks. In addition, we investigated whether forgetting over the 1 h and 6 week delays in our patients correlated with lateralized neuroanatomical measures, including hippocampal volume, and with clinical measures, which included seizure frequency to determine whether any accelerated forgetting over these time intervals was associated with structural brain changes, seizure activity, or both.

2. Methods

2.1. Participants

Twenty seven patients with TLE were recruited from The Walton Centre for Neurology and Neurosurgery (WCNN), Liverpool, who met the following criteria: (a) they were being considered for epilepsy surgery; (b) they had been scanned using the MRI volumetric protocol developed at the Magnetic Resonance and Image Analysis Research Centre (MARIARC), University of Liverpool; (c) they met the criteria described below for having either left or right hippocampal volume abnormality; (d) there was no evidence of current or recent psychiatric illness (depression, anxiety) measured using The Hospital Anxiety and Depression Scale (HADS; Snaith and Zigmond, 1986); (e) there was no history of head injury or neurological illness other than epilepsy, no signs of drug abuse, or Non-Epileptic Attack Disorder (NEAD).

The focus of this study was the investigation of the relationship between lateralized hippocampal sclerosis and memory performance in TLE. It was therefore not appropriate to select patients on the basis of lateralization of seizure activity as determined by electroencephalography (EEG), as this may not correspond to lateralization of hippocampal sclerosis. Rather, the patients were selected purely on the basis of lateralization of hippocampal sclerosis as determined by the neuroimaging procedures described below. The patients were classified as having either left or right hippocampal volume abnormality according to whether their scan results revealed: (a) abnormal hippocampal volume in one hemisphere; and/or (b) abnormal relative hippocampal volumes i.e., an abnormal asymmetry score (see below). These criteria were based on comparisons with Cezayirli's (2000) healthy control data set and the actual cut-offs used were:

- (1) Abnormal HC volumes: right <1.99 ml left <1.94 ml.
 (2) Abnormal relative HC volume: right asymmetry score <-.06, left asymmetry score >.22.

Fifteen of the patients had left hippocampal volume abnormality (LHS group) and 12 patients had right hippocampal volume abnormality (RHS group). All patients apart from two were on polytherapy regimes, and it is worth noting that for most, their seizures were relatively uncontrolled, which is one of the reasons they were being considered for surgical intervention.

Twenty-two healthy control participants who had no previous history of epilepsy, neurological or psychiatric illness were recruited from the areas of Liverpool, the Wirral and West Lancashire. The control group was closely matched to the two patient groups for age, gender and estimated IQ (see Table 1). Using the National Adult Reading Test (NART; Nelson and Willison (1982)), error scores were used to derive estimates of full-scale, verbal, and performance IQ (FSIQ, VIQ, and PIQ respectively) for all participants from tables provided in the manual. One-way analysis of variances (ANOVAs) failed to detect any reliable group differences on the three scores [FSIQ, $F(2,48) = 2.31, p = .11$; VIQ, $F(2,48) = 2.28, p = .11$; PIQ, $F(2,48) = 2.16, p = .13$]. Due to limited testing time, measures of performance on standardized tests of language, executive functions and memory are not available for the participants of this study.

As shown in Table 1, the RHS and LHS patients were well matched on clinical variables. Between group *t*-tests revealed no reliable differences between the groups for the following variables: age at which seizures started, $t(25) = 1.39, p > .05$; number of seizure-related episodes, $t(24) = 1.78, p > .05$; duration of epilepsy, $t(25) < 1$; and HADS anxiety and depression scores for the two test sessions [HADS anxiety: session 1, $t(24) < 1$, session 2 $t(24) < 1$; HADS depression: session 1, $t(24) < 1$, session 2 $t(24) = 1.16, p > .05$].

The study was approved by the South Sefton Research Ethics Committee. All participants gave informed consent prior to taking part in the research.

2.2. MRI protocol

2.2.1. Acquisition

The patients were scanned using the 1.5 T SIGNA whole body MR system at MARIARC (University of Liverpool). None of the control participants were scanned. The procedure described by Mackay et al. (2000) was followed. A sagittal spin echo localiser (TE = 16 msec, TR = 500 msec) was used to prescribe the scans. Images were acquired using a spoiled gradient echo (SPGR) pulse sequence (TE = 9 sec, TR = 34 sec, flip angle = 30°). 124 coronal T1 weighted images were acquired. The Field of View (FOV) of the images was 20 cm and each image refers to a contiguous section of tissue of 1.6 mm thickness. Acquisition time was 13 min and 56 sec for a 1NEX scan.

For T2 mapping, images were acquired at four different echo times using an FSE sequence (TR = 4000 msec, TE = 25, 50, 75, 100 msec, FOV = 20 cm). This sequence collected two echos (TE = 25 and 50 msec) from two slices in one 6 min 24 sec scan, and was repeated (TE = 75 and 100 msec) so that images were obtained for all four TEs. Two slices were prescribed from the sagittal localiser on a slice showing the long axis of the HC so that anterior and central slices could be positioned perpendicular to the structure to reduce partial voluming effects from surrounding tissue and cerebrospinal fluid (CSF).

2.2.2. Post-acquisition reformatting

The MR images were reformatted using ANALYZE software (MAYO Foundation, Minnesota, USA) running on a SPARC 10 workstation (SUN Microsystems, CA, USA). The $256 \times 256 \times 124$ acquired voxels of side .78 mm \times .78 mm \times 1.6 mm were linearly interpolated to $256 \times 256 \times 254$ cubic voxels of side .78 mm. The HC and amygdala are optimally visualised, and their volumes best measured, on image sections oriented perpendicular to the long axis of the HC (Bartzokis et al., 1993). These sections were obtained by reformatting oblique sections through the cubic voxel data within the ANALYZE software (see Mackay et al., 2000 for details).

2.2.3. Structure identification

Point counting procedures were used to estimate the volumes of the HC, amygdala, and temporal lobe (see Mackay et al.,

Table 1 – Clinical characteristics and neuropsychological data for left (LHS) and right hippocampal sclerosis (RHS) patient groups and healthy control participants. Mean and SD of each group are provided.

	LHS (n = 15)	RHS (n = 12)	Control (n = 22)
Age	34.80 (10.13)	38.67 (8.07)	41.14 (12.24)
NART FS IQ	106.00 (10.95)	103.92 (9.01)	111.14 (10.10)
NART VIQ	104.47 (10.10)	102.83 (8.43)	109.32 (9.20)
NART PIQ	105.73 (9.73)	104.25 (8.13)	110.36 (9.04)
Years education	12.36a (2.13)	13.08 (2.81)	13.41 (2.15)
Age seizure onset	11.47 (9.34)	17.29 (12.07)	n/a
No. seizure-related episodes	21.40 (20.59)	41.09b (35.58)	n/a
Duration	23.33 (11.74)	21.38 (12.13)	n/a
Session 1 HADS anxiety	7.80 (3.78)	7.36b (3.14)	6.27 (3.53)
Session 1 HADS depression	4.87 (3.44)	5.55b (3.45)	2.91 (2.54)
Session 2 HADS anxiety	6.80 (3.71)	7.27b (3.44)	6.14 (3.54)
Session 2 HADS depression	3.27 (2.40)	4.64b (3.64)	2.14 (2.83)
No. days between test sessions	43.67 (6.06)	44.00 (4.07)	42.45 (6.83)

Notes: a = Mean based on 14 patients, b = Mean based on 11 patients; n/a not applicable

2000). The structure identification procedures used are described below.

2.2.3.1. **HC.** The anterior boundary of the HC is the posterior boundary of the amygdala, which was taken to be the anterior limit of the alveus. The posterior boundary is reached when the lateral ventricles divide into the frontal and temporal horns.

2.2.3.2. **AMYGDALA.** At its anterior boundary the amygdala merges with the white matter of the temporal pole, therefore its anterior limit was the last slice on which the boundary of the amygdala is distinguishable.

2.2.3.3. **TEMPORAL LOBE.** The posterior boundary was the slice marking the anterior limit of the division of the lateral ventricles into their frontal and temporal horns.

Absolute volumes were measured in millilitres (mls). Total intracranial volumes (icv's) were not available, so the volumes reported below are unadjusted. Although initial studies in the field (e.g., Barr et al., 1990) reported correlations between unadjusted neuroanatomical variables and memory performance, the use of measures adjusted for head size and a variety of other relevant factors (e.g., age and sex) has become the norm. However, the use of adjusted measures is not without problems. Arndt et al. (1991) showed that the commonly used methods of head-size correction resulted in less reliable measures than the raw volumes. This conclusion was confirmed by Mathalon et al. (1993), although they also suggested that any change in reliability associated with the use of corrected measures resulted from two influences: an increase in error variance and a reduction in true score variance. These authors found that the correlations between brain structural volumes and age generally improved with the adjusted measures. However, in most cases, where the latter correlations were significant, so too were the correlations using the unadjusted measures. Furthermore, improvements in correlations were only found when the correlation between icv and the structure of interest was itself significant. In this respect, it is worth noting that the robust correlation between hippocampal volume and icv typically found in healthy samples, has been reported as non-significant in the case of TLE (see e.g., Briellmann et al., 1998). Thus, the use of non-corrected neuroanatomical measures is not without precedent, and at worst, is likely to provide a conservative test of the relationship between brain structure volumes and memory.

A measure of asymmetry was also derived for the hippocampal volumes. This was computed by subtracting the left from right hippocampal volumes and expressing this difference as a proportion of their mean volume, i.e., $(R - L)/[(R + L)/2]$. More positive values therefore indicate a relatively larger left hippocampal volume, whereas more negative values indicate a relatively larger right HC.

3. Materials

3.1. Verbal recall test

The verbal recall test used a short story, which had been piloted on volunteer undergraduates in the School of Psychology at The University of Liverpool. The story itself was one that had

originally been derived from Isaac and Mayes (1999), but had been increased in length to improve test sensitivity and difficulty, whilst also attempting to avoid floor and ceiling levels on initial learning. The story consisted of a section of prose that was divided into 73 consecutive idea units for the purposes of scoring. Each idea unit comprised an element of information such as a person's name or action from the story.

3.2. Non-verbal recall test

A standard copy of the Rey-Osterrieth Complex Figure Recall Test (ROCFT; Osterrieth, 1944), printed on an A4 sheet, was administered to the participants.

4. Procedure

Testing was conducted in either the participant's home or in the School of Psychology at the University of Liverpool. For TLE patients, the time of the last seizure was recorded at the start of each session, and none of the patients were post-ictal at the time of testing (i.e., had not had a seizure within the preceding 24 h).

In session 1, participants were first read the short prose passage, comprising the verbal recall test, and were instructed to try to remember as much of it as possible for a later memory test. Immediately following presentation of the story participants were asked to recount the passage in as much detail as possible. Recall was scored by assigning one point for each correctly recalled unit of information and half a point for each unit that was partially recalled. All participants were required to recall up to a learning criterion of 75% of the story units (55 points). If the overall score fell below the 55 points required to reach 75% criterion, the passage was read again and the process was repeated until the performance criterion was achieved or a maximum of five presentations had been given.

Immediately after completion of the story recall task, participants were instructed to copy the Rey Complex Figure and were instructed that they would later be asked to draw it from memory. When participants had completed this task, both the copy and the original figure were removed from view and after a 30 sec unfilled delay, participants were asked to draw it from memory in as much detail as possible. A learning to criterion procedure was not used for this test because, as will be seen in the Results section, control and patient performance was good, and well matched at the 30 sec test, after a single exposure. At 1 h and 6 weeks later, participants were once again asked to recall the story in as much detail as they could remember and to draw the Rey Figure from memory.

In order to determine whether there was a relationship between seizure activity and memory performance after the 6-week delay, the patients were asked to record the date, time and type of any seizures they experienced in epileptic symptom diaries of the sort used in the WCNN, Liverpool, during the intervening time between the 1-h and 6-week test session. The patients were asked to rate their seizures using an A–D scale: A = Strange taste in the mouth, B = Become vague, mumble, search around floor, C = A + B followed by collapse and convulsion, D = Absence or muscle jerks or seizures involving the whole body (tonic clonic). They were

also asked to number how many times the seizure occurred, e.g., they reported ‘3A’ in the diary for three seizures with a strange taste etc. They also recorded the time that the seizure occurred and whether it occurred when they were asleep or awake and any triggers that they may have experienced before the seizure, e.g., ‘missed medication’.

5. Results

5.1. Dependent variables

Recall performance for both the verbal and non-verbal tasks was recorded initially as raw scores and then transformed to percent correct within the SPSS 16 software. This applied also to the verbal task acquisition variable, trial 1 recall, whereas the second acquisition variable, trials to criterion, was recorded in its raw form. Additional, proportional measures of forgetting were derived from this data using the following formulae: immediate recall (imm) to 1-h recall (1 h) forgetting = $(\text{imm} - 1\text{h}) / (\text{imm})$; 1-h recall to 6 weeks recall (6 w) forgetting = $(1\text{h} - 6\text{w}) / (1\text{h})$. These proportional measures, because they correct, to some extent, for potentially differing absolute performance levels, provide a more robust measure of forgetting, particularly for the 1 h–6 w interval.

For the correlational analyses, the above memory measures were used together with two additional sets of variables, one neuroanatomical and one clinical. The set of neuroanatomical variables comprised the following: Left and right hippocampal, amygdala and temporal lobe volumes (mls), and left and right anterior (hippocampal) T2 relaxation times. In addition, total (left + right) hippocampal volume, and the derived measure of hippocampal asymmetry were included. The set of clinical variables included: age of seizure onset; duration of epilepsy; days elapsed between test sessions; number of seizure-related episodes between the two test sessions; and the four scores from the HADS (anxiety and depression at each test session).

6. Data analysis

The analyses are reported in three sections, broadly following the template provided by Blake et al. (2000). In the first, the combined TLE group is compared with controls, whereas for the second, the combined group is divided into their respective (RHS and LHS) subgroups. Analysis of the combined TLE group and controls was conducted partly to establish the comparability of the broad pattern of results with that reported by Blake et al. (2000), in addition to providing a guide for the subsequent subgroup analyses. As such, only main effect and interaction terms are reported. For both the combined and subgroup analyses, a mixed factorial ANOVA with one between-subjects factor (group, with either two or three levels), and one within-subjects factor (delay, with three levels) was performed on the raw recall data. Principally, this allowed us to determine whether recall performance across the three delays was matched in the groups being compared. A significant interaction would indicate otherwise, in other words, differential forgetting across the sampled time periods.

For the subgroup analyses, this was followed by simple main effects analyses following the procedures laid out in Kirk (1988). Where the interaction using the RHS/LHS subgroups was unreliable, but that using the combined TLE group was significant, the same follow-up analyses were used for the former. In this case, it was assumed that smaller group sizes led to a reduction in power, and the significant interaction detected in the combined TLE group analysis provided a priori justification for further analyses. In situations where a factor comprised three levels, the simple main effect, if significant, was partitioned into single degree of freedom (single df) contrasts. Where delay was the factor of interest, the ‘repeated’ contrasts available in SPSS were used: thus, performance at the first level (imm) was compared with performance at the second level (1 h), which in turn was compared with performance at the third level (6 w), allowing us to determine whether performance dropped significantly for each pair of consecutive delays. Where group was the factor of interest, user-defined contrasts were used, allowing pairwise comparisons between each of the three groups (this type of analysis was also used for the two verbal acquisition variables: trial 1 recall, and trials to criterion). In addition, the two derived measures of forgetting were analysed using one-way ANOVAs with the same user-defined contrasts.

In the third analysis section, the relationships between memory scores and both MRI volumetric measures and clinical variables were examined using Pearson’s *r*. Where appropriate, the relationships between learning (i.e., trials to criterion), memory over short delays, and memory over long delays were examined in for the combined TLE group and the RHS and LHS subgroups separately. For the correlational analyses, the criterion for significance was set at $p < .01$ to take into account, to some extent, multiple comparisons, whereas the conventional .05 level was used in all other cases.

6.1. Combined TLE group results

Mixed factorial ANOVAs revealed that for both the verbal and non-verbal tasks there were significant main effects of group [verbal: $F(1,47) = 24.39$, $p < .01$; non-verbal: $F(1,47) = 9.99$, $p < .01$] and delay [verbal: $F(2,94) = 475.09$, $p < .01$; non-verbal: $F(2,94) = 228.08$, $p < .01$] and significant group by delay interactions [verbal: $F(2,94) = 17.14$, $p < .01$; non-verbal task: $F(2,94) = 3.524$, $p < .05$]. For both tasks the effect of group was due to the poorer performance, averaged over the three delays, of the patients relative to controls, whereas the main effect of delay was due to a decrease in recall performance with increasing delay. As can be seen in Tables 2 and 3, the significant group by delay interactions are the result of faster forgetting of both types of material in the patients than the controls. The nature of this accelerated forgetting was explored in more detail in the RHS/LHS subgroup analysis below.

6.2. RHS/LHS subgroup results

6.2.1. Verbal task

6.2.1.1. ACQUISITION VARIABLES. As can be seen in Table 2 the performance of both groups of patients was poorer than the controls on the two acquisition measures. One-way between

Table 2 – Story Recall performance for the TLE group as a whole, the subgroup of patients with left lateralized hippocampal sclerosis (LHS), the subgroup with right lateralized hippocampal sclerosis (RHS) and healthy controls. Shown are means and SDs (in parentheses) for recall on the first learning trial, trials to criterion, criterion recall, and recall at 1 h and 6 weeks, together with the imm–1 h and 1 h–6 week measures of forgetting (see text for an explanation of these measures).

Group	Learning trial 1	Trials to criterion	Criterion recall	1-h delay	6-week delay	Imm–1 h	1 h–6 w
All TLE patients (<i>n</i> = 27)	37.74 (19.66)	3.37 (1.18)	82.33 (3.97)	66.89 (12.45)	20.41 (13.03)	.19 (.15)	.69 (.19)
LHS (<i>n</i> = 15)	40.80 (19.67)	3.33 (1.29)	82.53 (4.68)	63.11 (12.57)	19.20 (14.02)	.23 (.15)	.69 (.22)
RHS (<i>n</i> = 12)	33.92 (19.82)	3.42 (1.08)	82.08 (3.03)	71.62 (10.99)	21.92 (12.11)	.13 (.13)	.71 (.16)
Controls (<i>n</i> = 22)	66.39 (22.09)	1.95 (.95)	83.97 (4.73)	71.49 (9.03)	41.18 (9.01)	.15 (.09)	.42 (.14)

subject ANOVAs revealed a significant effect of group on trial 1 recall and the number of trials to reach criterion, [$F(2,48) = 11.81, p < .01$] and [$F(2,48) = 10.14, p < .01$], respectively. Further contrast analyses revealed that, in both cases, the TLE subgroups were matched, but both were significantly different from the control group (Trial 1: RHS–LHS $p = .40$, RHS–control $p < .01$, LHS–control $p < .01$; Trials to criterion: RHS–LHS $p = .84$, RHS–controls $p < .01$, LHS–controls $p < .01$).

6.2.1.2. RETENTION VARIABLES. The initial mixed factorial ANOVA revealed significant main effects of group [$F(2,46) = 13.60, p < .01$] and delay [$F(2,92) = 518.60, p < .01$], and a significant group by delay interaction [$F(4,92) = 9.66, p < .01$].

The interaction, which is shown in Fig. 1, was explored using the procedures described earlier. Simple main effects analyses of delay showed that forgetting was significant for each of the three groups ($p < .01$ in each case). Furthermore, there was a significant reduction in recall from immediate to 1 h, and from 1 h to 6 w for each of the three groups ($p < .01$ for all contrasts).

Group simple main effects revealed a non-significant effect at immediate testing [$F(2,48) < 1$], confirming that the learning to criterion methodology had been successful in matching the performance of the three groups. In contrast, significant effects of group were found at 1 h [$F(2,48) = 3.23, p < .05$] and at 6 w [$F(2,48) = 20.02, p < .01$]. Subsequent contrast analyses revealed that for the 1-h delay, the effect of group was due to the poor performance of the LHS patients relative to the other two groups (the performance of the RHS group was actually numerically greater than the controls at 1 h; see Fig. 1 and Table 2). The differences in 1-h recall between the LHS and RHS patients and the LHS patients and controls were both significant [$t(46) = 2.06, p < .05$ and $t(46) = -2.34, p = .02$ respectively] but this was not the case for the RHS–control contrast [$t(46) < 1$]. At 6 w story recall performances of both TLE subgroups were reliably different from the controls

[LHS–controls, $t(46) = -5.72, p < .01$; RHS–controls, $t(46) = -4.67, p < .01$], whereas the difference between patient groups was unreliable, $t(46) < 1$.

The forgetting measures were analysed using one-way ANOVAs with the afore-mentioned user-defined contrast analyses. These analyses confirmed that the LHS patients showed more accelerated forgetting over the imm–1-h interval (see Fig. 2). The imm–1-h measure differed significantly between the three participant groups [$F(2,48) = 3.26, p < .05$]. The contrast analyses revealed that the LHS group showed significantly greater forgetting from immediate to 1-h testing than both the RHS and control groups [$t(46) = -2.29, p = .03$ and $t(46) = -2.14, p = .04$ respectively], and that the difference between the RHS and control groups was unreliable [$t(46) < 1$; as with the raw recall data, the RHS group actually performed best on this measure, in that they showed the least forgetting]. There was also a significant group difference for the 1 h–6 w forgetting measure, $F(2,48) = 15.82, p < .01$, but in this case both patient groups showed equivalent and significantly faster forgetting than the controls [RHS–LHS, $t(46) < 1$; RHS–control, $t(46) < 4.65, p < .01$; LHS–control, $t(46) = 4.69, p < .01$].

6.2.2. Non-verbal task

6.2.2.1. COPY PERFORMANCE. The three groups were matched on copy performance for the Rey Figure [$F(2,48) = 1.84, p = .17$] and performed effectively at ceiling on this task (see Table 3). Furthermore, none of the single df contrasts revealed significant pairwise differences between the three groups ($p > .05$ for each contrast). We therefore found no evidence of visuo-perceptive/constructive problems in our patient groups.

6.2.2.2. RETENTION VARIABLES. As with the verbal memory data, a mixed factorial 3×3 ANOVA with one between subject factor of group (left hippocampal abnormality, right hippocampal abnormality, controls) and delay (30 sec, 1 h, 6 weeks),

Table 3 – Rey Complex Figure recall performance for the TLE group as a whole, the subgroup of patients with left lateralized hippocampal sclerosis (LHS), the subgroup with right lateralized hippocampal sclerosis (RHS) and healthy controls. Shown are the means and SDs (in parentheses) for copy performance, recall at 30 sec, 1 h and 6 weeks, together with the imm–1 h and 1 h–6 week measures of forgetting (see text for an explanation of these measures).

Group	Copy	30 sec	1 h	6 weeks	Imm–1 h	1 h–6 w
All TLE patients (<i>n</i> = 27)	96.91 (4.64)	64.31 (10.53)	49.72 (13.80)	19.07 (10.81)	.23 (.19)	.61 (.21)
LHS (<i>n</i> = 15)	98.33 (3.12)	64.58 (11.44)	51.50 (14.57)	19.88 (10.46)	.21 (.20)	.57 (.21)
RHS (<i>n</i> = 12)	95.14 (5.69)	63.98 (9.76)	47.50 (13.05)	18.07 (11.61)	.25 (.19)	.67 (.21)
Controls (<i>n</i> = 22)	94.45 (7.82)	68.65 (15.16)	61.20 (18.21)	33.45 (12.55)	.11 (.17)	.42 (.24)

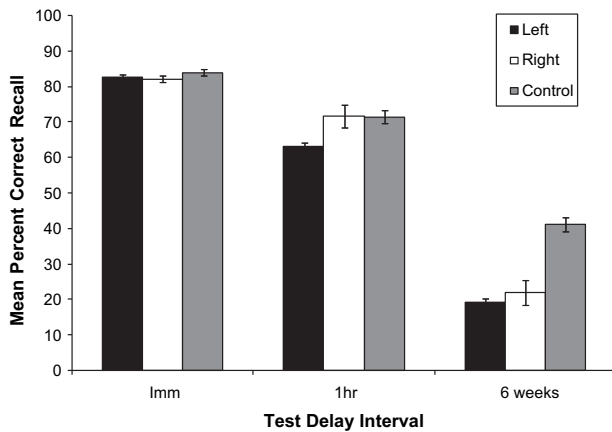


Fig. 1 – Story recall performance (mean percent correct and S.E's) for patients with left and right hippocampal sclerosis and controls at immediate test, and 1 h and 6 week delays.

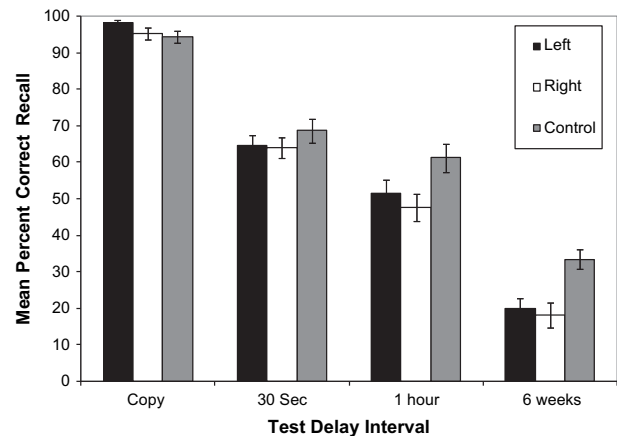


Fig. 3 – Rey Figure recall Performance (Means and S.E's) for patients with left and right hippocampal sclerosis and controls at immediate test, and 1 h and 6 week delays.

revealed significant main effects of group, $[F(2,46) = 5.04, p < .01]$, and delay, $[F(2,92) = 229.02, p < .01]$. Unlike the analysis of the verbal recall data, for visual recall the group by delay interaction did not reach statistical significance, $[F(4,92) = 1.84, p > .05]$. However, given the evidence of differential forgetting of patients and controls in the combined TLE group analysis, we proceeded with the contrast analyses.

As with the verbal task, recall performance on the non-verbal task across the three delays dropped significantly for each group ($p < .01$ in each case, see Fig. 3). Furthermore, the reductions in performance from immediate to 1 h, and from 1 h to 6 w were significant for each of the three groups ($p < .01$ for all contrasts). Comparing performance of the three groups at each of the three delays revealed a non-significant effect at immediate testing $[F(2,48) < 1]$. In contrast, significant effects of group were found at 1 h $[F(2,48) = 3.32, p = .04]$ and at 6 w $[F(2,48) = 9.19, p < .01]$. Contrast analyses revealed that the difference in 1-h recall between the RHS patients and the controls was significant $[t(46) = 2.38, p = .02]$ whereas the RHS–LHS and LHS–control contrasts were both non-significant $[t(46) < 1, t(46) = 1.81, p > .05]$. At 6 w Rey

figure recall performances of both patient groups were reliably different from the controls [LHS–controls, $t(46) = -3.46, p < .01$; RHS–controls, $t(46) = -3.66, p < .01$], whereas the difference between patient groups was unreliable $[t(46) < 1]$.

The forgetting measures were analysed using one-way ANOVAs with the afore-mentioned user-defined contrast analyses. These analyses confirmed that the RHS patients showed more accelerated forgetting over the imm–1-h interval (see Fig. 4). There was a marginally non-significant effect of group for the imm–1-h measure $[F(2,48) = 2.77, p < .07]$. The contrast analyses revealed that the RHS group showed significantly greater forgetting from immediate to 1-h testing than the control group $[t(46) = 2.20, p = .03]$, whereas immediate to 1-h forgetting for the LHS group was not reliably different from either the control or RHS groups $[t(46) < 1$ and $t(46) = 1.61, p > .05$ respectively]. For the 1 h–6 w forgetting measure, a significant group effect emerged $[F(2,48) = 4.89, p = .01]$. In this case, the RHS group showed faster forgetting than the controls $[t(46) = 3.01, p < .01]$ but not the LHS group $[t(46) < 1]$,

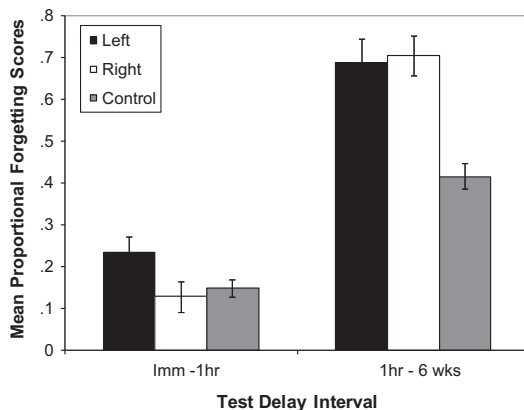


Fig. 2 – Story recall mean proportional forgetting scores (and S.E's) for patients with left and right hippocampal sclerosis and controls between immediate and 1 h delays and 1 h and 6 week delays.

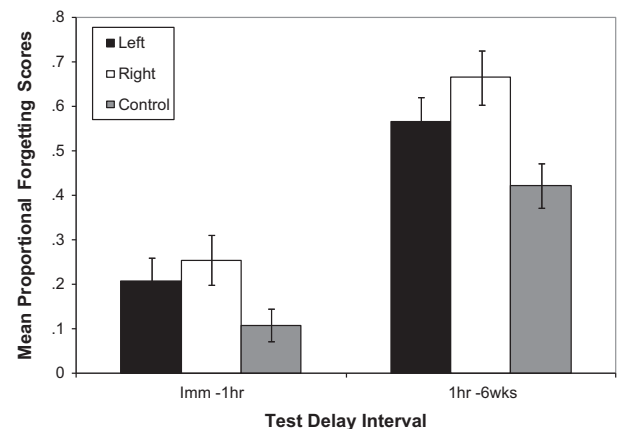


Fig. 4 – Rey Figure recall mean proportional forgetting scores (and S.E's) for patients with left and right hippocampal sclerosis and controls between immediate and 1 h delays and 1 h and 6 week delays.

and the LHS group showed faster forgetting than the controls but at a marginally non-significant level [$t(46) = 1.91, p = .06$].

7. Correlational analyses

Correlations were conducted between: (i) the set of neuro-anatomical measures and verbal and non-verbal memory measures; (ii) the set of clinical variables and verbal and non-verbal memory measures; and (iii) the memory measures themselves. For each set of correlations, we report those for the verbal followed by those for the non-verbal memory measures for the combined TLE group first. Where appropriate we also include analyses for the RHS/LHS subgroups. This was not attempted with the neuroanatomical measures because these were used as criterion variables in the subgroup allocation. Any correlations, therefore, are likely to be attenuated because of the artificially reduced ranges of values, and therefore obfuscate the trends existing in the complete patient sample. As noted above, given the number of correlations being performed at each of these stages, p was set to .01, rather than the conventional .05.

7.1. Memory-neuroanatomical correlations

7.1.1. Verbal memory

The results of the correlations between MRI brain measures and verbal memory performance for the combined group are shown in Table 4. Significant correlations were found between left hippocampal volume and trials to criterion, 1-h recall, and the imm-1 h forgetting measure, whereas the correlations with recall at 6 w and the 1 h-6 w forgetting measure were unreliable. A similar pattern emerged for the sets of correlations involving hippocampal asymmetry and hippocampal T2 relaxation time. In both cases, the correlations with 1-h recall, and the imm-1 h forgetting measure were significant, whereas the remaining ones were unreliable. Thus, the principal significant correlations to emerge involved the 1 h memory measures and the left hippocampal measures. None of the correlations involving the remaining recall memory measures or involving right-sided and/or non-hippocampal neuroanatomical measures were found to be reliable.

7.1.2. Non-verbal memory

The results of the correlations between the neuroanatomical measures and non-verbal memory performance are shown in Table 5. As can be seen, only two of these were significant. In both cases, the relevant memory variable was the imm-1 h forgetting measure, and the two structures involved were both right-sided: right hippocampal volume and right amygdala volume. Thus, none of the correlations between the non-verbal memory variables and left-sided neuroanatomical measures were significant.

7.2. Memory-clinical correlations

7.2.1. Verbal memory

The results of the correlations between clinical measures and verbal memory performance in the combined TLE group are shown in Table 6. Marginally non-significant correlations

Table 4 – Pearson r correlations between story recall and MRI-derived neuroanatomical measures in the combined TLE group ($n = 27$). Exact probability values are shown in parentheses with significant correlations highlighted in bold.

	L. hipp. vol.	R. hipp. vol.	Total hipp. vol.	Hipp. asymmetry	L. amyg. vol.	R. amyg. vol.	L. temp. vol.	R. temp. vol.	L. ant. T2	R. ant. T2
Trials to criterion	-.501 (.008)	-.050 (.805)	-.358 (.067)	.369 (.058)	-.164 (.425)	-.084 (.683)	-.107 (.594)	-.025 (.900)	.385 (.052)	-.133 (.517)
Criterion recall	-.142 (.479)	-.181 (.367)	-.219 (.273)	-.012 (.951)	-.138 (.501)	-.189 (.354)	-.011 (.956)	-.278 (.161)	-.046 (.822)	.163 (.426)
1-h recall	.536 (.004)	-.368 (.059)	.088 (.662)	-.688 (< .001)	.073 (.724)	-.208 (.307)	.064 (.753)	-.319 (.104)	-.598 (< .001)	.214 (.293)
6-w recall	.302 (.126)	-.155 (.441)	.086 (.668)	-.308 (.118)	-.069 (.736)	-.082 (.691)	-.285 (.149)	-.255 (.200)	-.147 (.474)	.010 (.960)
Imm-1 h forgetting	-.588 (.001)	.329 (.093)	-.149 (.459)	.702 (< .001)	-.112 (.585)	.167 (.414)	-.065 (.748)	.249 (.210)	.603 (< .001)	-.181 (.375)
1 h-6 w forgetting	-.133 (.510)	.030 (.880)	-.064 (.750)	.083 (.682)	.043 (.833)	-.083 (.685)	.329 (.094)	.157 (.436)	-.081 (.694)	.044 (.830)

Table 5 – Pearson r correlations between Rey Figure recall and MRI-derived neuroanatomical measures in the combined TLE group ($n = 27$). Exact probability values are shown in parentheses with significant correlations highlighted in bold.

	L. hipp. vol.	R. hipp. vol.	Total hipp. vol.	Hipp. asymmetry	L. amyg. vol.	R. amyg. vol.	L. temp. vol.	R. temp. vol.	L. ant. T2	R. ant. T2
30 sec (imm) recall	.152 (.450)	-.129 (.520)	.007 (.971)	-.147 (.466)	-.261 (.197)	-.198 (.332)	-.132 (.511)	-.121 (.548)	-.214 (.293)	.002 (.991)
1-h recall	.177 (.376)	.338 (.085)	.352 (.072)	.122 (.544)	.123 (.548)	.307 (.128)	-.101 (.617)	-.067 (.740)	.096 (.640)	.118 (.567)
6-w recall	.054 (.789)	.108 (.590)	.111 (.581)	.067 (.740)	-.261 (.197)	-.112 (.587)	-.209 (.295)	-.005 (.980)	.151 (.461)	-.321 (.110)
Imm-1 h forgetting	-.102 (.614)	-.504 (.007)	-.419 (.029)	-.259 (.192)	-.353 (.077)	-.528 (.006)	.099 (.625)	-.033 (.870)	-.262 (.196)	-.132 (.519)
1 h-6 w forgetting	.210 (.292)	-.063 (.754)	.091 (.650)	-.252 (.206)	.359 (.072)	.124 (.547)	.211 (.291)	-.141 (.484)	-.284 (.160)	.346 (.083)

Table 6 – Pearson r correlations between story recall and the clinical variables in the combined TLE group ($n = 27$). Exact probability values are shown in parentheses with significant correlations highlighted in bold.

	No. seizure-related episodes	Age seizure onset	Duration	Days between test sessions	Session 1 HADS anxiety score	Session 1 HADS depression score	Session 2 HADS anxiety score	Session 2 HADS depression score
Trials to criterion	.088 (.669)	-.107 (.595)	.260 (.190)	.314 (.111)	-.227 (.265)	-.122 (.553)	-.019 (.927)	-.107 (.603)
Criterion recall	-.020 (.924)	.003 (.990)	.036 (.858)	-.248 (.213)	.177 (.386)	-.155 (.449)	.291 (.149)	-.110 (.593)
1-h recall	-.045 (.827)	.466 (.014)	-.356 (.068)	-.217 (.277)	-.038 (.856)	.209 (.306)	-.220 (.279)	-.040 (.846)
6-w recall	-.547 (.004)	.179 (.371)	.147 (.463)	-.232 (.245)	.330 (.099)	.306 (.129)	.292 (.147)	.291 (.149)
Imm-1 h forgetting	.046 (.823)	-.477 (.012)	.364 (.062)	.147 (.465)	.077 (.708)	-.253 (.213)	.292 (.148)	.007 (.972)
1 h–6 w forgetting	.591 (< .001)	-.076 (.706)	-.246 (.216)	.181 (.366)	-.377 (.057)	-.300 (.137)	-.421 (.032)	-.335 (.095)

were found between age at seizure onset and both 1-h recall ($p = .014$) and the imm-1 h forgetting measure ($p = .012$). No significant correlations were found between age at seizure onset and memory performance at the other delays. Given that 1-h recall and imm-1 h forgetting correlated significantly with left hippocampal volume and left anterior hippocampal T2 relaxation time, we also investigated whether age of seizure onset correlated with these MRI measures. Age of seizure onset was found to correlate significantly with left hippocampal volume ($r = .535$, $p = .004$), but not anterior hippocampal T2 relaxation time ($r = -.329$, $p = .1$). Significant correlations were also found between the number of seizure-related episodes and both 6-w recall, and 1 h–6 w forgetting.

The correlation between number of seizure-related episodes and 1 h–6 w forgetting was also significant when considering LHS patients ($r = .739$, $p = .002$), but failed to reach the adopted significance threshold ($r = .602$, $p = .05$) for RHS patients. As shown in Table 1, the mean number of seizure-related episodes in the RHS group was almost twice that seen in the LHS group, and the weaker effect is therefore most likely due to the smaller number of patients in that group.

7.2.2. Non-verbal memory

The results of the correlations between clinical measures and verbal memory performance in the combined TLE group are shown in Table 7. No significant correlations were found between age of seizure onset and visual memory measures. However, as with the analysis of the verbal memory data, significant correlations were found between the number of seizure-related incidents and both 6-week recall and 1 h–6 w forgetting.

For the RHS and LHS subgroups, the correlations between number of seizure-related episodes and 6-w recall and 1 h–6 w forgetting were unreliable (RHS $r = .568$, $p = .068$; LHS $r = .444$, $p = .097$). As noted above, the contrasting patterns of correlations found in the combined TLE and subgroup analyses are most likely due to the resulting small group sizes for the latter.

7.3. Correlations between memory measures

These correlations were conducted separately for the RHS and LHS subgroups given that different patterns of memory performance were found between groups in the ANOVA analyses reported above.

7.3.1. Verbal memory

For the LHS subgroup, significant correlations were found between trials to criterion and both 1-h recall and imm-1 h forgetting, but not with the 6-w memory measures. Recall at 6 weeks and 1 h–6 w forgetting correlated significantly with each other but not with any of the other memory measures. For patients with right lateralized hippocampal sclerosis, there were no significant correlations between trials to criterion or immediate recall and any of the other memory measures. Recall at 6 w and 1 h–6 w forgetting correlated significantly with each other but not with any of the other memory measures.

Table 7 – Pearson *r* correlations between Rey Figure recall and the clinical measures in the combined TLE group (*n* = 27). Exact probability values are shown in parentheses with significant correlations highlighted in bold.

	No. seizure-related episodes	Age seizure onset	Duration	Days between test sessions	Session 1 HADS anxiety score	Session 1 HADS depression score	Session 2 HADS anxiety score	Session 2 HADS depression score
30 sec (imm) recall	-.243 (.231)	.169 (.398)	-.127 (.529)	-.142 (.480)	-.021 (.921)	.194 (.342)	-.110 (.593)	-.241 (.236)
1-h recall	-.259 (.201)	-.184 (.359)	.223 (.264)	.116 (.563)	.288 (.154)	.211 (.301)	.206 (.313)	-.076 (.713)
6-w recall	-.636 (<.001)	-.093 (.645)	.172 (.392)	-.033 (.872)	.221 (.277)	.393 (.047)	.020 (.925)	.085 (.681)
Imm-1 h forgetting	.100 (.626)	.326 (.097)	-.300 (.128)	-.308 (.118)	-.250 (.218)	-.047 (.821)	-.222 (.276)	.012 (.953)
1 h-6 w forgetting	.541 (.004)	.066 (.745)	-.049 (.810)	.089 (.659)	.068 (.740)	-.264 (.192)	.075 (.715)	-.009 (.965)

7.3.2. Non-verbal memory

For the LHS subgroup, correlations between immediate recall and each of the other memory measures were unreliable. Recall at 6 w and 1 h-6 w forgetting correlated significantly with each other, but not with any of the other memory measures, although there was a trend for a correlation between imm-1 h and 1 h-6 w forgetting ($p = .019$).

Likewise, for the RHS subgroup, all correlations involving immediate recall were non-significant. Recall at 6 w and 1 h-6 w forgetting correlated significantly with each other, and there was a trend between 1 h and 6-w recall ($p = .012$), but none of the other correlations between memory measures reached or approached statistical significance.

8. Discussion

In our study we found that patients with TLE showed deficits in both the acquisition of new memories and recall of successfully acquired memories over delays of 1 h and 6 w. Our investigation of the specific patterns of memory loss shown by patients with left or right lateralized hippocampal pathology on tests of verbal and visuospatial memory suggested that the deficit in memory acquisition and accelerated memory loss over the 1-h delay may be mediated, at least in part, by a different mechanism to that underlying the accelerated loss of memory over the longer 6-w delay. In support of this, we found that verbal recall was lost at an accelerated rate in the patients with right lateralized hippocampal sclerosis despite their normal retention of verbal material over the 1-h delay, and that the long-term verbal retention of both groups of patients did not correlate significantly with measures of acquisition or short-term retention. Furthermore, we showed that retention over the relatively short 1-h delay, but not the 6-w delay, was associated with the presence of hippocampal pathology in either the left or right HC. Specifically, pathology in the left HC was associated with verbal memory deficits in acquisition and 1 h, but not 6-w retention, and pathology in the right HC was associated with visuospatial memory deficits at only the 1-h delay. We therefore suggest that the presence of hippocampal pathology in patients with TLE can result in deficits in acquiring new memories and retaining successfully acquired memories over relatively short delays, but does not underlie accelerated forgetting over longer delays of several weeks.

Rather, we found that accelerated forgetting over the longer 6-w delay was associated with the frequency of seizures during that period. This finding is consistent with other work that has suggested that long-term forgetting in TLE results from the disruption of consolidation processes by the occurrence of epileptic seizures (Mameniskiene et al., 2006). Each aspect of our findings is discussed in greater detail below.

8.1. Acquisition

Our patients with TLE required more trials to learn the verbal recall task to criterion level than healthy controls suggesting a deficit in the acquisition of new verbal memories. This is consistent with some previous studies (e.g., Giovagnoli et al., 1995; Bell et al., 2005; Bell, 2006; Davidson et al., 2007), but

inconsistent with the findings of Blake et al. (2000). The difference between our findings and those of Blake et al. most likely relates to the presence of hippocampal pathology in our patients. Whereas few of Blake et al.'s patients had structural changes within the medial temporal lobe, our patients were specifically selected according to the presence of lateralized structural changes (atrophy or abnormal T2 relaxation times) within the HC. Indeed, we found a significant relationship between left hippocampal volume and the number of trials required to reach criterion (patients with smaller left hippocampal volume required more learning trials) and a trend for a relationship between left anterior hippocampal T2 relaxation time and number of trials to reach criterion ($r = .386$, $p = .052$). Our findings therefore suggest that, although deficits in the acquisition of new memories may not occur in TLE patients when medial temporal lobe pathology is absent (e.g., Blake et al., 2000), such deficits are seen in patients whose epilepsy is accompanied by structural hippocampal abnormality, and that these deficits become more severe as the severity of hippocampal pathology increases.

8.2. Accelerated forgetting

A different pattern of retention was found for the verbal and non-verbal tasks. Considering the combined TLE group, there was evidence of accelerated forgetting of both verbal and non-verbal material (i.e., significant group by delay interactions). When considering the more detailed subgroup analyses, the LHS subgroup forgot verbal material at an accelerated rate (relative to controls) over both the 1-h and 6 w delays, whereas the patients with right lateralized hippocampal sclerosis showed normal retention at the 1-h delay but accelerated forgetting over the following 6 w. Although not quite as clear-cut, a similar pattern emerged on the non-verbal task, with the RHS, but not the LHS group, showing faster forgetting over 1 h and both groups showing faster forgetting over the 6-w delay (although, for the LHS group $p = .06$ for this effect). The pattern of performance shown by the RHS group on the verbal task and, to a lesser extent, the LHS subgroup on the non-verbal task, is therefore very similar to the pattern of long-term amnesia reported in TLE by Blake et al. (2000) and contrasts with the findings of Giovagnoli et al. (1995), Bell et al. (2005) and Bell (2006). In what follows, to avoid repeated qualification, we focus our attention to the more robust findings relating to the verbal task.

Could the pattern of memory performance shown by our patients be explained by reliance at immediate test on working rather than long-term memory? If it were the case that working memory, but not long-term memory, was matched in the patients and controls at the short delay, then we might expect to see rapid forgetting in the patients between immediate and 1 h tests, thus making it unlikely that accelerated forgetting would be observed over the 6-w delay. This is not the pattern observed for the verbal task in our study. Accelerated forgetting over the long 6-w interval was observed in both subgroups, and for the RHS patients, this was the case even though recall at the 1-h delay did not differ significantly from controls.

The presence of accelerated forgetting of verbal material over both the 1-h retention interval and the long 6-w retention interval in the LHS patients is somewhat surprising, as the only other studies that have reported accelerated forgetting in TLE over extended time periods (Martin et al., 1991; Blake et al., 2000) have reported normal recall at a short retention interval (30 min), i.e., the pattern shown by our RHS patients. One possibility is that our memory test was more sensitive than those used in these two previous studies and so revealed memory loss at the short, 1 h, as well as the extended delay. This explanation seems unlikely though, because although our LHS patients showed a deficit at the 1-h delay, this was not the case for the RHS patients who went on to show a deficit at the 6-w delay. These latter patients showed a pattern identical to that reported by Martin et al. (1991) and Blake et al. (2000). We think that it is more likely that, as for memory acquisition, the difference in findings between studies may relate to differences in the characteristics of the TLE patients included in the present study and previous work. We only included patients who had MRI evidence of structural changes to the HC that were lateralized to the right or left HC. This enabled us to examine whether there was a relationship between our memory measures and measures of hippocampal integrity. Indeed, we found that forgetting of verbal material over the 1-h retention interval in our study was related to the extent of structural changes in the left HC in our patients, and it is quite possible that the extent of hippocampal abnormality present in patients included in the previous studies differed from our study. For example, Blake et al. (2000) reported a very low incidence of hippocampal sclerosis in their left TLE patients who showed normal retention after a 30-min delay but accelerated forgetting over the subsequent 8 weeks. Thus, accelerated forgetting of verbal material over a relatively short 1-h interval in our study appeared to be associated with the presence of sclerotic changes in the left HC.

Consistent with this finding, forgetting over the initial 1-h delay in the non-verbal task was also associated with measures of hippocampal abnormality, in that case right hippocampal volume. It should be noted though that whilst the RHS patients forgot non-verbal information significantly faster than controls over the 1-h delay, the LHS patients forgot more than the controls, but were not reliably different from them or the RHS patients. The deficit in the patients with left lateralized hippocampal sclerosis may relate to the potential for visuospatial memories to be encoded both verbally and non-verbally. Indeed, although the Rey Figure is used extensively as a test of visuospatial memory, some argue that it does not provide a good indicator of right temporal lobe integrity and may be solved using verbal strategies (Kneebone et al., 2007). Such an explanation would predict poorer performance of patients than controls; in the case of the left lateralized patients because of disruption to a verbally re-encoded representation of the visual stimulus and in the case of right lateralized patients because of disruption of the original visual representation of the stimulus. The latter may be expected to produce poorer performance than the former, as was the case here.

Although the presence of accelerated forgetting over the 1-h delay in our study was inconsistent with the findings of Blake et al. (2000) and Martin et al. (1991), it should be noted

that, as discussed in the Introduction, reports of memory deficits at immediate testing and after a short delay of 30 min in patients with TLE are not uncommon (Giovagnoli et al., 1995; Bell et al., 2005; Bell, 2006; Helmstaedter et al., 1998; Mameniskiene et al., 2006). However, while our finding of impaired memory at the short 1-h retention interval in our patients with left lateralized hippocampal sclerosis is consistent with the impaired performance of patients from these studies at a 30-min retention interval, our findings differ from those of earlier studies in that accelerated forgetting was found in our patients over an extended 6-w period. This subsequent forgetting over the 6-w retention interval was uncorrelated with measures of retention over the shorter 1-h delay and therefore suggests that the left lateralized group was showing long-term forgetting over the 6-w delay over and above that expected from their 1-h delayed retention. Furthermore, for the patients with right lateralized hippocampal sclerosis, recall of the verbal material followed a pattern identical to that reported by Blake et al. (2000), i.e., unimpaired recall after the 1-h delay but accelerated forgetting over the subsequent 6 w.

Lateralization of accelerated forgetting of verbal material over the short 1-h delay is consistent with previous work that has associated verbal memory impairments with dysfunction of the left temporal lobe (e.g., Milner, 1971). We did not, however, find lateralization of accelerated forgetting of verbal material over the extended 6-w delay. We found accelerated forgetting of verbal material not only in the patients with left lateralized hippocampal sclerosis, but also in the patients with right lateralized hippocampal sclerosis despite normal performance after 1 h and the verbal nature of the task. There were also no significant correlations between measures of left (or right) hippocampal integrity and measures of recall/forgetting over the 6-w delay. These findings are therefore inconsistent with those of Blake et al. (2000) who reported greater accelerated forgetting of verbal material in their left than their right TLE group.

Forgetting over the longer 6-w retention interval in our study was found to correlate significantly with the number of seizures in the retention interval (although, given the smaller group sizes, results for the subgroup analyses were less clear-cut). This finding is consistent with reports that higher seizure frequency was associated with poorer verbal memory after a 4-w delay (Mameniskiene et al., 2006) and that the occurrence of a seizure during a 24-h retention interval impaired memory for the positions of words in left, but not right, TLE patients (Jokeit et al., 2001). Our data suggest that seizure activity still affects verbal recall at a longer 6-w delay. Our findings are also consistent with the report that a reduction in seizures led to increased memory test performance (O'Connor et al., 1997). Others, however, have not found a relationship between the frequency of overt seizures during the retention interval and performance of patients with TLE on memory tests after delays of 48 h and 8 w (Bergin et al., 1995; Blake et al., 2000). In addition, accelerated forgetting has been demonstrated in patients with TEA once seizures have been abolished by anti-epileptic medication (Butler et al., 2007; Manes et al., 2005), and accelerated forgetting of verbal and non-verbal material in this patient group was found not to correlate with either duration of epilepsy or seizure frequency

(Butler et al., 2009). It cannot, however, be ruled out that subclinical ictal activity may have contributed to accelerated forgetting in these cases. Indeed, due to the very low incidence of hippocampal sclerosis in their patients, Blake et al. (2000, p. 12) proposed that an active 'epileptic focus' is required to explain the phenomenon of long-term accelerated forgetting in TLE, consistent with our findings. They argued that a "stable environment" was required in the left temporal lobe for successful slow consolidation of verbal memories as memories remain vulnerable to disruption over an extended period of time. Both Blake et al. (2000) and Mameniskiene et al. (2006) proposed that exposure to a combination of frequent ictal and interictal discharges could disrupt memory consolidation.

An explanation of long-term accelerated forgetting in terms of disruption of consolidation by seizure activity could also potentially explain why accelerated forgetting of verbal material was found only in left TLE patients in the study of Blake et al. (2000), but in both patient groups in our study. In Blake et al.'s study, patients were categorized as having left or right TLE, that is, according to whether they had left or right lateralized seizures. In our study, patients were categorized according to the lateralization of hippocampal pathology, not the lateralization of seizure activity. It is therefore possible that seizure activity may be less clearly lateralized in our patient groups, than in the study of Blake et al. (2000). It should also be noted that patients with right lateralized structural volume reductions experienced around twice as many seizures during the 6-w delay as those with left lateralized structural volume reductions. Both these factors may have reduced any differences between the two patient groups in our study in the rate of forgetting of verbal material over the long retention interval.

Although our findings suggest that long-term forgetting in TLE is related to seizure activity during the long retention interval, we cannot rule out the possibility that forgetting over these long intervals is associated with structural damage to brain regions that were not investigated in this study. We investigated the relationship between the structural integrity of the HC and long-term retention and found that they were not related. We also found that there was no significant relationship between amygdala volume and whole temporal lobe volume, and long-term retention. Nevertheless, TLE can affect extensive cortical and subcortical structures (Mueller et al., 2006) and it remains to be determined by future work whether structural damage in regions beyond the temporal lobe contribute to long-term accelerated memory loss.

Another factor that may affect memory in patients with TLE, other than the presence of hippocampal sclerosis and seizure activity, is medication. Jokeit et al. (2005) found evidence for high anti-epileptic drug (AED) blood levels and poor retention over 30 min on auditory and visual memory tests. The exact effects of high AED blood levels and their relationship with retention over long delays have yet to be researched more closely. However, Cronel-Ohayon et al. (2006) and Butler et al. (2007) [the latter testing TEA patients] have found evidence that AEDs do not appear to have an effect on patients with TLE. One important factor may be the degree to which AEDs actually control seizures. O'Connor et al. (1997) report the case of JT, for whom there was evidence that his long-term (i.e., over days and longer) retention abilities were inversely related to seizure activity. Consistent with this, it

was found that during a controlled trial of paraldehyde his long-term retention improved as seizure activity decreased. In this respect, it should be remembered that all patients in the present study were being considered for epilepsy surgery partly because of relatively uncontrolled seizures. What our study does highlight are the possibly dissociable effects of structural hippocampal abnormality and seizure frequency on recall over short and extended delays. To examine the more complex relationships between these variables and medication would clearly require a much larger sample size than that used for the present study.

The results of our study show both similarities and differences to studies of forgetting over short and long delays in TEA. Similar findings to ours concerning the relationship between hippocampal volume measures and non-verbal memory over short and more extended delays have been recently reported for patients with TEA (Butler et al., 2009). Whereas, recall of the Rey Figure after a short (30 min) delay correlated with right hippocampal volume, there were no correlations between right hippocampal volume and forgetting of seven visually presented designs over a longer 3-w delay. There was also a close to significant correlation ($p = .057$) between left hippocampal volume and verbal forgetting over the short retention interval but not over the longer delay. Unlike our study, however, they found no significant correlations between seizure frequency and forgetting of verbal and non-verbal material over their long (3 w) retention interval (Butler et al., 2009). It remains to be determined whether these differences between studies relate to differences in the nature of the tests used to assess memory or to differences in the underlying cause of accelerated forgetting in the different patient groups.

8.3. Implications for theories of memory consolidation

The results of the present study are consistent with the view that memory consolidation is not a single process, but rather that there are 'fast' and 'slow' components of memory consolidation (Squire, 1994), and potentially distinct subsystems relating to different time frames within the consolidation process (McClelland et al., 1995; Kapur et al., 1997). The findings from our study suggest that different mechanisms may underlie accelerated forgetting in our TLE patients over a relatively short 1-h delay and a longer 6-w retention interval.

Accelerated forgetting over the 1-h delay was associated with hippocampal pathology, with greater pathology in the left HC associated with greater forgetting of verbal material over this time period and greater pathology in the right HC associated with greater forgetting of visuospatial material. In contrast, accelerated forgetting over the 6-w retention interval was not related to the presence of left or right hippocampal pathology. Instead, forgetting over this long delay was associated with the number of seizures in the intervening interval. Thus our data suggest that early 'fast' consolidation of verbal and visuospatial memories may depend on the integrity of the left and right HC, respectively, whereas later 'slow' consolidation of successfully acquired memories may depend on the maintenance of a stable environment in the medial temporal lobe and so can be disrupted by the occurrence of seizure activity (Blake et al., 2000).

8.4. Clinical implications

These findings have a number of implications for the management and treatment of TLE. They suggest, consistent with the claims of Blake et al. (2000), that only a subset of patients with TLE, who have sufficient hippocampal sclerosis, will demonstrate memory loss within the normal time period of clinical assessment (retention of intervals of 30 min). Thus, the presence of memory loss may often be missed in clinical practice. As we show, memory deficits, that are not present after a short delay, can emerge in patients with TLE over longer time periods such as an hour to a number of weeks. For example, we found that verbal recall was only impaired in patients with right hippocampal sclerosis at the long 6-w delay, and not the short 1-h delay. Therefore, our findings suggest that to obtain a complete picture of the memory impairments experienced by any individual patient, and the effectiveness of interventions on memory, assessment beyond the usual 30-min retention period used in clinical practice is required. In addition, our findings highlight the potential importance for long-term memory of reducing the frequency of epileptic seizures. They suggest that even patients with hippocampal sclerosis that affects memory over relatively short delays, could experience benefits in long-term memory from a reduction in seizure frequency.

9. Conclusions

The findings of our study show that TLE can affect the acquisition and retention of new memories over a relatively short delay of 1 h. This deficit appears to be related to the presence of hippocampal atrophy. In addition, our results suggest that TLE can also result in accelerated forgetting of memories that were successfully acquired over a longer time period of several weeks. Evidence of accelerated long-term forgetting was observed in both verbal and non-verbal tasks but the detailed pattern was more statistically robust for the verbal task. For that task, whilst accelerated forgetting was evident in both patient groups, it was demonstrated more strongly by the RHS patients whose verbal recall was normal at the 1-h delay, and for whom seizure activity was greater in the 6-w delay. This long-term forgetting does not appear to be associated with the presence of hippocampal pathology. Rather, as proposed by others, our data suggest that accelerated long-term forgetting in TLE may be associated with disruption of long-term consolidation processes by the occurrence of epileptic seizures.

Acknowledgements

We would like to thank our patient participants from the WCNN and the healthy control participants for taking part in this study. Some of these data contributed towards Fiona Clague's M.Sc. research which was partly supported by a research scholarship from Sanofi Synthelabo International Bureau of Epilepsy Scholarship.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

None of the authors has any conflicts of interest to disclose.

REFERENCES

- Alvarez P and Squire LR. Memory consolidation and the medial temporal lobe: A simple network model. *Proceedings of the National Academy of Sciences of the United States of America*, 91(15): 7041–7045, 1994.
- Arndt S, Cohen G, Alliger RJ, Swayze VW, and Andreasen NC. Problems with ratio and proportion measures of imaged cerebral structures. *Psychiatry Research: Neuroimaging*, 40(1): 79–90, 1991.
- Barr WB, Ashtari M, Schaul N, and Bogerts B. Relations between hippocampal volume and memory in patients with intractable seizures. *Journal of Clinical and Experimental Neuropsychology*, 12: 86, 1990.
- Bartzokis G, Mintz J, Marx P, Osborn D, Gutkind D, Chiang F, et al. Reliability of in vivo volume measures of hippocampus and other brain structures using MRI. *Magnetic Resonance Imaging*, 11(7): 993–1006, 1993.
- Baxendale SA. The hippocampus: Functional and structural correlations. *Seizure*, 4(2): 105–117, 1995.
- Baxendale SA, Van PW, Thompson PJ, Connelly A, Duncan JS, Harkness WF, et al. The relationship between quantitative MRI and neuropsychological functioning in temporal lobe epilepsy. *Epilepsia*, 39(2): 158–166, 1998.
- Bell BD, Fine J, Dow C, Seidenberg M, and Hermann BP. Temporal lobe epilepsy and the selective reminding test: The conventional 30-minute delay suffices. *Psychological Assessment*, 17(1): 103–109, 2005.
- Bell BD. WMS-III logical memory performance after a two-week delay in temporal lobe epilepsy and control groups. *Journal of Clinical and Experimental Neuropsychology*, 28(8): 1435–1443, 2006.
- Bell BD and Giovagnoli AR. Recent innovative studies of memory in temporal lobe epilepsy. *Neuropsychology Review*, 17(4): 455–476, 2007.
- Bergin PS, Thompson PJ, Fish DR, and Shorvon SD. The effect of seizures on memory for recently learned material. *Neurology*, 45(2): 236–240, 1995.
- Bernasconi A, Bernasconi N, Caramanos Z, Reutens DC, Andermann F, Dubeau F, et al. T2 relaxometry can lateralize mesial temporal lobe epilepsy in patients with normal MRI. *NeuroImage*, 12(6): 739–746, 2000.
- Blake RV, Wroe SJ, Breen EK, and McCarthy RA. Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. *Brain*, 123(3): 472–483, 2000.
- Briellmann RS, Jackson GD, Kalnins R, and Berkovic SF. Hemispheric volume deficits in patients with temporal lobe epilepsy with and without hippocampal sclerosis. *Epilepsia*, 39(11): 1174–1181, 1998.
- Buschke H. Stages of retrieval in verbal learning. *Journal of Verbal Behaviour*, 12: 543–550, 1973.
- Buschke H and Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*, 24(11): 1019–1025, 1974.
- Butler CR, Graham KS, Hodges JR, Kapur N, Wardlaw JM, and Zeman AZ. The syndrome of transient epileptic amnesia. *Annals of Neurology*, 61(6) 2007.
- Butler CR and Zeman AZ. Recent insights into the impairment of memory in epilepsy: Transient epileptic amnesia, accelerated long-term forgetting and remote memory impairment. *Brain*, 131(9): 2243–2263, 2008a.
- Butler CR and Zeman A. A case of transient epileptic amnesia with radiological localization. *Nature Clinical Practice Neurology*, 4(9): 516–521, 2008b.
- Butler CR, Bhaduri A, Acosta-Cabronero J, Nestor PJ, Kapur N, Graham KS, et al. Transient epileptic amnesia: Regional brain atrophy and its relationship to memory deficits. *Brain*, 132(2): 357–368, 2009.
- Cezayirli E. Age related changes in the hippocampal volume, T2 relaxation time and memory performance in healthy subjects aged from 20 to 80 years. Ph.D. University of Liverpool, 2005.
- Cronel-Ohayon S, Zesiger P, Davidoff V, Boni A, Roulet E, and Deonna T. Deficit in memory consolidation (abnormal forgetting rate) in childhood temporal lobe epilepsy. Pre and postoperative long-term observation. *Neuropediatrics*, 37(6): 317–324, 2006.
- Davidson M, Dorris L, O'Regan M, and Zuberi SM. Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. *Epilepsy and Behavior*, 11(3): 394–400, 2007.
- Giovagnoli AR, Casazza M, and Avanzini G. Visual learning on a selective reminding procedure and delayed recall in patients with temporal lobe epilepsy. *Epilepsia*, 36(7): 704–711, 1995.
- Helmstaedter C, Hauff M, and Elger CE. Ecological validity of list-learning tests and self-reported memory in healthy individuals and those with temporal lobe epilepsy. *Journal of Clinical and Experimental Neuropsychology*, 20(3): 365–375, 1998.
- Huppert FA and Piercy M. Dissociation between learning and remembering in organic amnesia. *Nature*, 275(5678): 317–318, 1978.
- Isaac CL and Mayes AR. Rate of forgetting in amnesia: I. Recall and recognition of prose. *Journal of Experimental Psychology: Learning, Memory, and Cognition*, 25(4): 942–962, 1999.
- Jokeit H, Daamen M, Zang H, Janszky J, and Ebner A. Seizures accelerate forgetting in patients with left-sided temporal lobe epilepsy. *Neurology*, 57(1): 125–126, 2001.
- Jokeit H, Kramer G, and Ebner A. Do antiepileptic drugs accelerate forgetting? *Epilepsy and Behavior*, 6(3): 430–432, 2005.
- Kapur N, Millar J, Colbourn C, Abbott P, Kennedy P, and Docherty T. Very long-term amnesia in association with temporal lobe epilepsy: Evidence for multiple-stage consolidation processes. *Brain and Cognition*, 35(1): 58–70, 1997.
- Kirk RE. *Experimental Design: Procedures for the Behavioral Sciences*. 2nd edn. Monterey, CA: Brooks/Cole, 1988.
- Kneebone AC, Lee GP, Wade LT, and Loring DW. Rey complex figure: Figural and spatial memory before and after temporal lobectomy for intractable epilepsy. *Journal of the International Neuropsychological Society*, 13(4): 664–671, 2007.
- Lillywhite LM, Saling MM, Briellmann RS, Weintrob DL, Pell GS, and Jackson GD. Differential contributions of the hippocampus and rhinal cortices to verbal memory in epilepsy. *Epilepsy and Behavior*, 10: 553–559, 2007.
- Mackay CE, Webb JA, Eldridge PR, Chadwick DW, Whitehouse GH, and Roberts N. Quantitative magnetic resonance imaging in consecutive patients evaluated for surgical treatment of temporal lobe epilepsy. *Magnetic Resonance Imaging*, 18(10): 1187–1199, 2000.
- Mameniskiene R, Jatuzis D, Kaubrys G, and Budrys V. The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. *Epilepsy and Behavior*, 8(1): 278–288, 2006.
- Manes F, Graham KS, Zeman A, de Lujan CM, and Hodges JR. Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. *Journal of Neurology, Neurosurgery and Psychiatry*, 76(10): 1387–1391, 2005.
- Manes F, Serrano C, Calcagno ML, Cardozo J, and Hodges J. Accelerated forgetting in subjects with memory complaints. A

- new form of mild cognitive impairment? *Journal of Neurology*, 255(7): 1067–1070, 2008.
- Martin RC, Loring DW, Meador KJ, and Lee GP. Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. *Neuropsychology*, 5(1): 3–12, 1991.
- Mathalon DH, Sullivan EV, Rawles JM, and Pfefferbaum A. Corrections for head-size in brain-imaging measurements. *Psychiatry Research: Neuroimaging*, 50(2): 121–139, 1993.
- Mayes AR, Isaac CL, Holdstock JS, Cariga P, Gummer A, and Roberts N. Long-term amnesia: A review and detailed illustrative case study. *Cortex*, 39(4–5): 567–603, 2003.
- McClelland JL, McNaughton BL, and O'Reilly RC. Why there are complementary learning systems in the hippocampus and neocortex: Insights from the successes and failures of connectionist models of learning and memory. *Psychological Review*, 102(3): 419–457, 1995.
- Milner B. Interhemispheric differences in the localization of psychological processes in man. *British Medical Bulletin*, 27(3): 272–277, 1971.
- Mueller SG, Laxer KD, Casdollar N, Buckley S, Paul C, and Weiner MW. Voxel-based optimized morphometry (VBM) of gray and white matter in temporal lobe epilepsy (TLE) with and without mesial temporal sclerosis. *Epilepsia*, 47(5): 900–907, 2006.
- Nelson HE and Willison J. *National Adult Reading Test*. Slough, England: NFER-Nelson, 1982.
- O'Connor M, Sieggreen MA, Ahern G, Schomer D, and Mesulam M. Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. *Brain and Cognition*, 35(1): 71–84, 1997.
- Osterrieth PA. Le test de copie d'une figure complexe: Contribution a l'etude de la perception et de la memoire. *Archives de Psychologie*, 30286–30356, 1944.
- Snaith RP and Zigmond AS. *The Hospital Anxiety and Depression Scale Manual*. Windsor, England: NFER-Nelson, 1986.
- Squire LR. Memory and forgetting: Long-term and gradual changes in memory storage. *International Review of Neurobiology*, 37243–37269, 1994.
- Walhovd KB, Fjell AM, Reinvang I, Lundervold A, Fischl B, Quinn BT, et al. Size does matter in the long run: Hippocampal and cortical volume predict recall across weeks. *Neurology*, 63(7): 1193–1197, 2004.
- Wechsler D. *Manual for the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III)*. San Antonio, TX: The Psychological Corporation, 1997.