Accelerated long-term forgetting in patients with temporal lobe epilepsy: A study pre and post-surgery

Thesis submitted for the degree of

Doctorate in Clinical Psychology

Clinical Psychology Unit

Department of Psychology

University of Sheffield

Stephen Evans

BSc (Hons) Dunelm

MSc Dunelm

2012

Declaration

This thesis is submitted for the degree of Doctorate in Clinical Psychology at the University of Sheffield. It has not been submitted for any other qualification or to any other academic institution.

Structure and word count

Both the literature review and empirical report have been prepared in accordance with guidelines for authors submitting articles to the British Journal of Clinical Psychology (BJCP). Writing style, figure and table formatting conform to the guidance set out by the Publication Manual of the American Psychological Society (sixth edition).

Literature Review

Excluding references	7997
Including references	9725

Research Report

Excluding references	11947
Including references	12958

Total word count

Excluding references and appendices	19944
Including references and appendices	29421

Main abstract

ALF is a relatively newly described phenomenon in neuropsychology and refers to a deficit in retaining recently learned information over delays of 24 hours or more, despite normal memory acquisition and retention over short delays of up to 30 minutes. The underlying causes of this phenomenon are currently unknown, however one of the proposed theories suggests that memories must go through a period of "slow" consolidation, that is, after a period of initial learning and consolidation, memories remain vulnerable to disruption until a "slow" consolidation process has occurred. Medial temporal lobe and neocortical structures are indicated in this process, including the hippocampus. This thesis examined the possibility that seizure activity disrupts the "slow" consolidation process, thereby resulting in ALF.

Literature Review

A literature review explores the relationship between aspects of seizure activity thought to impair memory more broadly in TLE, and considers these in light of papers reporting ALF. Methodological issues are common in the ALF literature, with papers adopting heterogeneous testing procedures of varying quality. The main findings from the review suggest that that the relationship between seizure activity and ALF is mixed. It is recommended that future studies adopt more robust testing methodology and develop AB experimental designs to assess salient factors that may mediate ALF.

Research Report

An empirical study adopted a longitudinal pre/post surgery design to examine the hypothesis that ALF is related to ongoing seizure activity. The results suggest that epilepsy surgery can improve ALF in medically-refractory patients with TLE, and this appears to bring their rate of forgetting in line with demographically matched healthy controls.

ACKNOWLEDGEMENTS

I would like to start by thanking all of the participants who agreed to take part in the study, without whom I would not have been able to submit this piece of work. Many thanks to my research supervisor, Dr Claire Isaac, for sharing her knowledge and expertise, and keeping me calm when I felt like I was running out of time! Your advice and support has been superlative throughout and I don't think I could have found a more supportive supervisor to guide me through this challenging process - thank you. I would also like to thank Dr Hazel Reynders, Debra Ford, and Dr Emily Mayberry for helping me recruit additional participants for the study. Many thanks also to Dr Gemma Elliott, for liaising with me about this project intermittently for two years, and always answering my seemingly countless queries.

Additional thanks goes to my parents whose support[and dedication to my education has inspired me to work hard and has given me a platform to develop and grow, and ultimately produce this doctoral thesis. It has been a long hard road but it was worth the time and effort.

A special thanks to my beautiful fiancéé, your love, kindness and support have lifted me and helped me achieve this incredible milestone.

Table of Contents

Literature Review
Does seizure activity mediate accelerated long-term forgetting in temporal lobe epilepsy? A review of the literature

Introduction 2
Aims of present study 6
Method 7
Identification of studies 7
Exclusion criteria 7
Study Quality 9
Results 12
ALF findings and reported seizure correlates 15
Positive associations 16
Negative associations 17
Summary 18
Onset and duration of condition 19
Single case 19
Group studies 20
Summary 20
Seizure control through AEDs 21
Case studies 21
Group studies 22
Summary 24
Sub-clinical Seizures 24
Summary 25
Discussion 28
Future Directions 29
Footnotes 31
References 32
Can epilepsy surgery ameliorate accelerated long-term forgetting in temporal lobe epilepsy? A longitudinal group study
Introduction 44
Main Aims 51
Hypotheses 51
Method 52
Design 52
Setting 52
Participants 53

TLE Participants 53
Controls 53
Measures 57
Primary matching measures 57
Additional measures 57
Seizure diary 57
Perceived memory questionnaire 57
Assessment of mood 58
ALF materials 58
Visual Scenes test overview 58
Visual Scenes Recall 58
Visual Scene Recognition 59
Stories test overview 60
Story Recall 61
Story Recognition 61
Procedure 61
Visual Scenes Test 62
Statistical Analysis 64
Corrected measures 64
Group analysis 64
Individual analyses 65
Sample size calculations 65
Results 66
Data checking 93
Group Analysis 93
Visual Scenes 93
Item Free Recall 93
Spatial Free Recall 93
Descriptive Free Recall 93
Visual Scenes Recognition 93
Visual Recognition 93
Story Recall 93
Long Delay Story Recall 93
Repeated Story Recall 93
Story Recognition 93
Long Delay Story Recognition 93
Repeated Story Recognition 93

The Effect of Seizures on Forgetting 93
Correlations 93
Individual Analysis 93
Forgetting rates 93
Psychosocial measures & perceived memory 93
Discussion 93
Clinical implications 93
Future directions 93
Conclusions 93
References 93
Appendices 99

Literature Review

Does seizure activity mediate accelerated long-term forgetting in temporal lobe epilepsy? A review of the literature

Purpose. Accelerated long-term forgetting (ALF) is a newly identified phenomenon seen in some individuals with temporal lobe epilepsy (TLE) and is characterised by abnormal forgetting over hours or weeks, despite normative initial acquisition and short-term retention. The relationship between seizure activity and ALF has not been fully explored in the literature, despite theoretical arguments suggesting that seizure activity may disrupt the "stable environment" needed for long-term consolidation.

Methods. Systematic review principles were applied to search the relevant databases for published studies in ALF. Studies were included if they examined ALF in TLE, were English language papers, and assessed forgetting rate over delays up to 24 hours or more. A Quality Rating Scale adapted from Elliott (2012) was used to rate the selected papers on methodological criteria pertinent to ALF research.

Results. Twenty-four papers were reviewed for the study, comprising 10 single case and 14 group studies. Methodological quality varied amongst the studies.

Five areas related to seizure activity were explored: the effects of seizures during the delay period, onset and duration of condition, seizure control through anti-epileptic drugs (AEDs), subclinical seizures, and seizure control through epilepsy surgery.

Conclusions. Evidence for the role of seizure activity in ALF appears mixed, with methodological issues, lack of adequate reporting, and a lack of AB experimental designs highlighting the need for additional research in this field.

Key words: Epilepsy, Accelerated Long-term Forgetting, Seizures, Epilepsy Surgery, Anti-epilepsy Drugs, Sub-clinical Seizures

Introduction

Epilepsy is defined as "a chronic brain disorder of various aetiologies, characterised by recurrent seizures due to excessive discharge of cerebral neurons" (Gastaut, 1973). It is the third most prevalent chronic neurological disorder, affecting approximately 1% of the population (Hauser & Hesdorffer 1990). The salient identifying symptom of epilepsy syndromes is seizures and excessive discharge of neurons (Martin, 2006). Seizures are described as single sudden events caused by these neural discharges which produce a change in sensation, consciousness, or cognition, and can lead to observable convulsions (Lee, 2004). The International League Against Epilepsy (ILAE) distinguishes between symptomatic focal epilepsies (seizures occurring in a specific part of the brain with a particular aetiology) and idiopathic generalized epilepsies, which are syndromes without an underlying structural brain lesion or other neurologic signs or symptoms, and are presumed to be genetic and age dependent (Engel, 2001). Physical symptoms can vary from case to case, depending on the type of epilepsy and where it presents in the brain.

Memory problems are commonly observed in people with epilepsy (Lezak, 2004) and although their performance on standardised intelligence tests can be normal, they are more likely to exhibit impaired cognitive performance compared to age- and education-matched controls (Motamendi & Meador, 2003). Vingerhoets (2006) reviewed cross-sectional and prospective studies over the last 70 years, examining data from both adult and child studies. Their findings suggest that 10-25% of individuals evidence clinically significant intellectual or cognitive decline over the life span.

Temporal lobe epilepsy (TLE) is the most common form of adult-onset focal epilepsy and one in which memory-related brain structures are directly involved in seizure activity (Bortz, 2003). It is therefore unsurprising that people with TLE evidence memory impairments, with researchers and clinicians traditionally observing deficits in

verbal and visual memory (Lezak, Howieson, & Loring, 2004). The material-specific memory model posits that left TLE is traditionally associated with verbal deficits (Mungas, Elton, Walton, & McCutchen, 1985) and right TLE with impairment of visual memory (Milner, 1965). In a recent review Butler and Zeman (2008) outline several explanations for these impairments drawn from decades of research into memory problems in epilepsy. These include: the impact of neuropathic processes in the brain, hippocampal atrophy or sclerosis, and lateralization of epileptogenic activity. Salient clinical factors include: age of onset of epilepsy, number of seizures over a patient's lifespan, seizure frequency, duration of the condition, psychosocial factors, and the cognitive effects of AED use. It is also important to consider the impact of surgery on individuals' memory, as some patients undergo surgical intervention due to chronic AED-refractory seizures. It is proposed that a complex interplay of the above factors over the life span mediate the progressive memory deficits observed in patients with TLE.

There exists a body of research evidencing memory impairments in TLE from a few seconds after initial acquisition up to around 30 minutes, however recent studies have reported on TLE patients who appear to evidence impairments over longer delays than can be identified on standard tests of memory (typically 30 minutes). In these cases retention of newly learned information remains intact over short delays, but forgetting rates accelerate over longer time periods (typically over days and weeks). It is proposed that this phenomenon constitutes a distinct type of forgetting known as accelerated long-term forgetting (ALF). ALF was first described in the literature in a number of case studies (DeRenzi & Lucchelli, 1993; Lucchelli & Spinnler, 1998) with the latter describing the case of GB, a 65-year-old man with a two year history of memory difficulties following a mild head trauma. Electroencephalographic (EEG) scans indicated that GB evidenced focal epileptic activity in the left temporal lobe with

secondary diffusion to the right frontal region. Neuropsychological testing revealed that GB performed normally on standard memory tests but evidenced ALF when retested on verbal and visual tests at intervals over 24 hours.

The case of GB and other early studies into ALF appeared to show promising evidence of a novel memory deficit. However subsequent findings have been mixed, with some work supportive of the early findings (Helmsteader, Hauf, & Elger, 1998; Mayes et al., 2003) and some unsupportive (Bell, 2006; Bell, Fine, Dow, Seidenberge, & Hermann, 2005). Despite this lack of consistency, ALF does appear to be primarily related to TLE, with a recent study by Muhlert et al. (2011) reporting ALF in verbally and visually learned material over a three-week delay in patients with TLE but not patients with idiopathic generalised epilepsy (IGE). It is fair to say then, that there is a small but growing body of research evidencing ALF in patients with TLE, but questions remain about the prevalence of ALF and its underlying neuropathological processes.

The specific mechanisms involved in the rapid loss of memories over the long delay remain unknown and for us to understand these we must visit the theoretical memory literature. Underpinning many of the arguments around memory is the function of the hippocampus, which is known to be vital for learning and retention. Previous research has shown that bilateral damage to the hippocampus can lead to severe anterograde amnesia, which is defined as the inability to remember events that occur following the onset of the condition/trauma (Lezak, 2004). This can be contrasted with retrograde amnesia, which is the loss of memories acquired prior to onset (Hunkin, Parkin, & Longmore, 1994). It has been documented that individuals with damage to the hippocampus evidence a temporally graded retrograde amnesia which seems to spare memories from the distant past (Squire, 1992). These findings relate to the classic work of Ribot (1881) who observed that memory appears to degrade sequentially, with recent memories lost first, followed by older, more established, memories.

A theoretical account of amnesia in light of Ribot's observations was developed by Squire and Alvarez (1995) who proposed the Standard Model. This model posits that the neocortex is the permanent repository of memory and that memory formation must include an interaction between the neocortex and the medial temporal lobe (MTL) memory system, including the hippocampus. It is thought that information is initially established quickly as short-lived changes in the reciprocal connections between neocortex and medial temporal lobe. The medial temporal lobe then stores enough information to point to, and activate, relevant sites in the neocortex, but not the entire memory itself. Consolidation is the process of gradual reorganisation of memory storage and is thought to occur when the neocortical representations are reactivated by the medial temporal lobe, causing gradual and long-lasting change in cortical areas (Squire & Alvarez, 1995).

ALF is of potential theoretical importance as it informs theories of memory function, specifically the role of the hippocampus and neocortex in the retention of newly learned information. Mayes et al. (2003) present three hypotheses to explain the possible causes of ALF in TLE. The first considers that ALF is caused by structural damage to the medial temporal cortex, including the hippocampus, and that this damage alone causes ALF, either through disruption of the slow consolidation process or by preventing the multiple rehearsals needed to consolidate the material. The second proposes that seizure activity following memory acquisition disrupts the transfer of long-term memories or their establishment in the neocortex, possibly through overt seizures or sub-clinical discharges during sleep. The third posits that damage to the neocortex prevents memory representations from becoming established over time.

In consideration of these three theoretical positions, recent reviews have highlighted the relationship between structural pathology and ALF (see Bell & Giovagnoli, 2007, and Butler & Zeman, 2008). However, the relationship between

seizure activity and ALF has not been thoroughly evaluated in the literature, despite being alluded to in several papers (see Blake, Wroe, Breen, & McCarthy, 2000, and Jokeit, Daamen, Zang, Janszky, & Ebner, 2001). It is important that we explore the role of seizure activity in ALF as it has implications for our understanding of the neural basis of memory, specifically whether the slow consolidation process in the Standard Model is vulnerable to disruption due to seizure activity. Evidence for this will provide support for the seizure-disruption theory proposed by Mayes et al. (2003). These findings are equally as important clinically as they are theoretically, as they may have implications for the way clinicians conduct memory assessments with TLE patients, perhaps requiring rethinking and redevelopment of standardised memory tests to include assessments of ALF.

Aims of present study

The primary aim of this review was to evaluate the literature on ALF in TLE to establish whether seizure activity appears to mediate the rapid loss of memory over long delays. We aim to explore how features known to impact more broadly on memory loss in TLE outlined in Butler and Zeman (2008) relate to ALF in TLE. It is clearly important that the testing methods used to identify ALF are of high methodological quality, as many of the studies use small n exploratory samples or case studies and therefore the likelihood of type 1 errors is high. With that in mind, the conclusions drawn from the results are contingent on identifying whether any heterogeneity in the reviewed papers reflects specific methodological weaknesses or is the consequence of current or historical seizure activity.

Method

Identification of studies

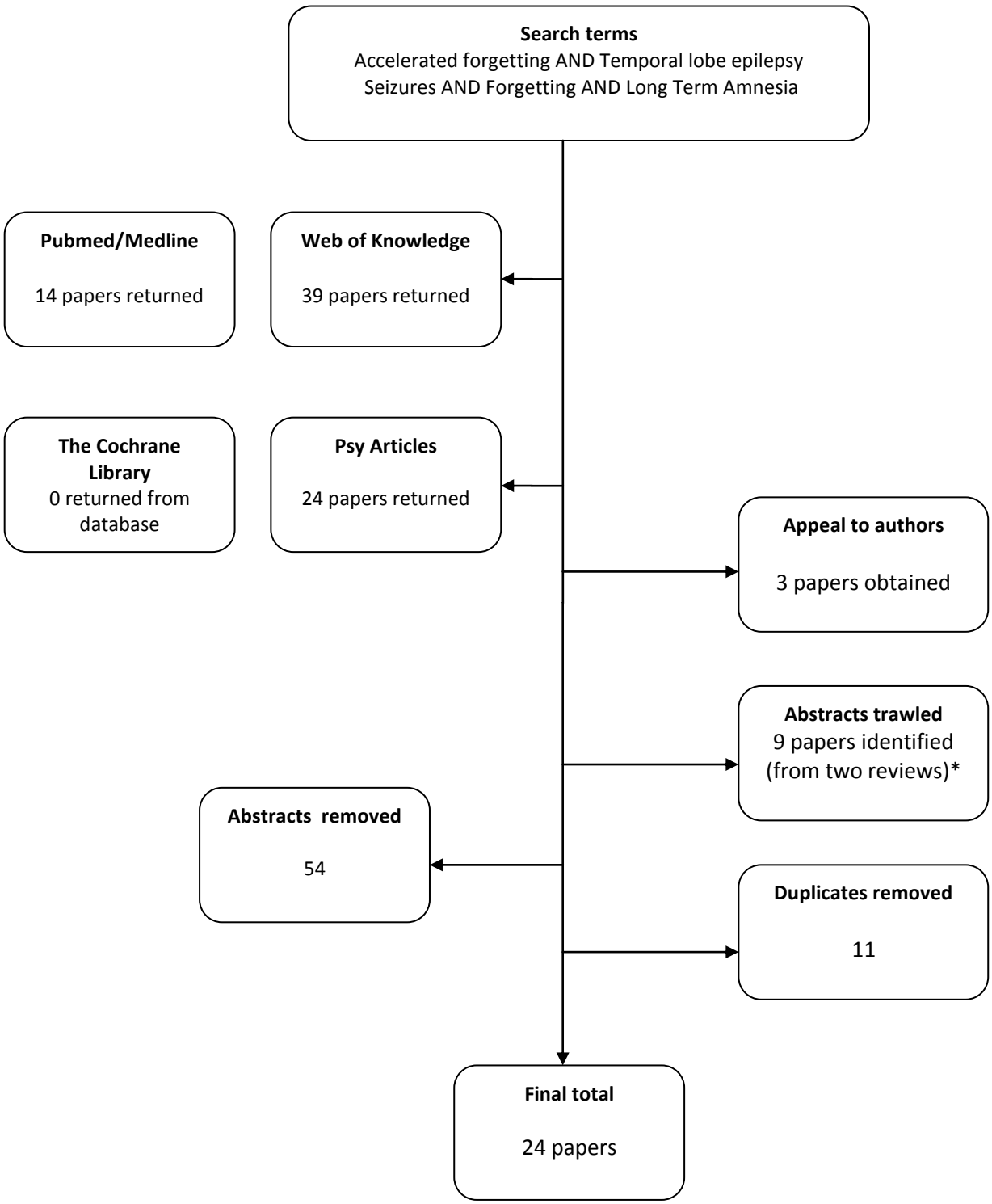
The databases of Medline, Web of Knowledge (WOK), Psy Articles, Psy Info and the Cochrane Library were searched using the search terms *Accelerated Forgetting, Temporal Lobe Epilepsy, Seizures, Forgetting* and *Long-term Amnesia*. Where necessary Boolean Operators "AND" and "OR" were used to refine the search terms. Figure 1 presents information on the search strategy process. Following the initial database search, additional references were extracted by trawling the reference lists of key articles and an additional paper-specific search was performed using the "basic search" and "advanced search" function on the Ovid databases of Psych Info and Psych Articles. One article (DeRenzi & Lucchelli, 1993) was not available through any of the online databases listed above. A physical copy of the paper was located in the periodicals section of the University of Sheffield Library.

Exclusion criteria

Articles were excluded if they were not available in English language format or did not look explicitly at forgetting over delays of 24 hours or more. This was the case for one article (Manning et al., 2006) which was only available in French (English abstract). Only articles looking at TLE were reviewed, although papers were accepted if other types of epilepsy were examined as well as TLE (e.g. Muhlert et al., 2011 looked at TLE and IGE).

Figure 1.

Search strategy flow chart



* Reviews used were Bell and Giovagnoli (2007) & Butler and Zeman (2008)
Databases were searched on 08.2011 and again on 03.2012

Study Quality

One of the difficulties in assessing the ALF literature is the methodological confounds in comparing forgetting rates between patients and healthy controls (Isaac & Mayes, 1999a). The ALF literature comprises heterogeneous testing methods and materials which lead to confusion in interpretation and reduced reliability of test results. A recent review by Elliott (2012) identified six methodological markers of reliable testing procedures in forgetting research which are listed below.

Inclusion of control participants matched for age and IQ - this is deemed important as memory and IQ have been found to be positively correlated, as have age and forgetting (Mayes, 1986); *tests of both recall and recognition included* - studies have previously found mixed results in recall and recognition in ALF studies (Butler & Zeman, 2008) therefore it is important that both are examined in ALF research (Elliott, 2012); *ceiling and floor effects avoided* - preventing ceiling and floor effects is important because amnesic participants often perform at floor level and controls at ceiling level (Isaac & Mayes, 1999a), therefore if present, floor and ceiling effects will result in an underestimation of forgetting rates. Elliott (2012) proposes that test materials are piloted to prevent this from occurring; *rehearsal effects avoided* – to avoid the participants rehearsing information between tasks, Elliott recommends the use of stimuli that are difficult to rehearse such as a large number of discrete designs for the visual task. Furthermore, to prevent the effects of repeated recall different stimuli should be tested at different time points; i*nclusion of short filled delay at initial test* – to prevent the participants using short-term memory (STM) between the completion of the learning trial and the immediate delay testing, a distractor task should be used (as proposed by Isaac & Mayes, 1999a, 1999b). This is important as reliance on STM may mask consolidation deficits over short delays. Note, from here on in STM will be defined as memory that decays after only a few seconds, with long-term memory (LTM)

comprising anything that exceeds this rapid initial decay of material, as proposed by Baddeley (2002); *matching procedure used* - to prevent a higher initial rate of learning in the control group and avoid subsequent scaling effects, Elliott propose that a matching procedure is used during the initial learning trial. This may comprise extended exposure to the material for the TLE group, repeated presentation of the materials, or learning to criterion.

Quality rating scale

For the purpose of this study a quality rating scale (QRS) was developed using the six methodological markers identified in Elliott (2012). The markers were separated into nine units (recall & recognition comprised two units, one point awarded for the inclusion of each) and were assigned a dichotomous score (0 or 1). The scores represent the presence (1) or absence (0) of that methodological marker. Expert consultation revealed that the markers carried equal weighting in assessing the quality of the testing procedure. Qualitative labels were assigned to the reviewed articles with 0-3 considered "low quality", 4-6 "average quality", and 7-9 "high quality". Overall three studies fell into the "high quality" range, 14 studies fell into the "average quality" range and seven fell into the "low quality" range (see table 1). Inter-rater agreement of the ratings was established using Cohen's Kappa equation:

$$\kappa = \frac{\Pr(a) - \Pr(e)}{1 - \Pr(e)}$$

Table 2 illustrates the Kappa scores across all nine items on 80% of the reviewed papers[1]. Analysis of the scores revealed almost perfect agreement across the nine methodological markers (κ = .787-1, n = 19).

Table 1.

Quality Rating Scale (QRS) Rankings

Study Type	QRS score		
	Low Quality	Average Quality	High Quality
Group Study	3	8	2
Single Case	4	5	1
Case Series	0	1	0
Total	7	14	3

Note, $n = 24$

Table 2.

Cohen's Kappa ratings across nine methodological markers of ALF quality ratings

	Methodological makers								
	VER/VIS	AGE	IQ	REC	CFA	RA	ID15	MP	ILE
Rater 1	12	18	12	9	9	9	2	10	13
Rater 2	12	18	12	9	7	9	2	10	15
κ	1	1	1	1	.787	1	1	1	.732

VER/VIS - verbal and visual materials used, CFA - ceiling and floor effects avoided, RA - rehearsal avoided, ID15 - immediate delay after 15 seconds, MP - matching procedure, ILE - initial learning equated

Results

A total of 10 single case papers and 14 group studies were included in the review. Single cases included: Cronel-Ohayon et al. (2006); DeRenzi and Lucchelli (1993); Gallasi et al. (2011); Holdstock, Mayes, Isaac, Gong, and Roberts (2002); Jansari, Davis, McGibbon, Firminger, and Kapur (2010); Kapur et al. (1997); Kapur et al. (1996); Lucchelli and Spinnler (1998); Mayes et al. (2003); and O'Connor, Sieggreen, Ahern, Schomer, and Mesulam (1997). Group studies included: Bell (2006); Bell et al. (2005); Blake et al. (2000); Butler et al. (2009); Davidson, Dorris, O'Regan, and Zuberi (2007); Giovagnoli and Avanzini (1999); Helmsteader et al. (1998); Jokeit et al. (2001); Mameniskiene, Jatuzis, Kaubrys, and Budrys (2006); Manes, Graham, Zeman, De Lujan Calcagno, and Hodges (2005); Martin et al. (1991); Muhlert et al. (2011); Tramoni et al., (2011); and Wilkinson et al., (2012).

Twenty three of the 24 papers were adult studies with the exception of Cronel-Ohayon et al. (2007) who report a long-term follow-up of a boy between the ages of 9 and 18. Twenty two of the papers report on participants with TLE and heterogeneous aetiologies including: head injuries (e.g. Holdstock et al., 2002; Mayes et al., 2003), encephalitis (O'Connor et al., 1997), and onset from unknown causes (Kapur et al., 1997; Lucchelli & Spinnler, 1998). Three papers report data on individuals with transient epileptic amnesia, a form of TLE in which seizure activity results in transient amnesia (Butler et al., 2009; Butler et al., 2007; Manes et al., 2005).

Table 3.

ALF in TLE single case studies

Study	n	Type of epilepsy	Testing delay	Type of materials used	Methodological quality*	Quality rating score (QRS)	Outcome
Cronel-Ohayon et al., 2007	1	TLE (left) cps Olfactory	60 min, 7 days, 29 days	Verbal, visual	A, CF, RA**, MP, ID 15**, ILE	4	ALF after 1 wk
DeRenzi & Lucchelli, 1993	1	Head injury	Imm, 4 hr, 13 day, 33 day	Verbal, visual	-	-	ALF after 13 days
Gallasi et al., 2011	1	TLE	Imm, 1 wk	Verbal, visual	A, IQ	3	ALF < post surgery (not visual)
Holdstock et al., 2002**	2	TLE following head injury	-	Verbal	A, IQ, RA, ID15, MP, ILE	6	-
Jansari et al., 2010****	1	TLE (right)	Imm, 30 min, 1 day, 1 wk, 2 wks, 4 wks	Verbal	A, IQ, RR, RA, ILE	5	ALF after 1 d (a) & recall ALF after 1 d (b)
Kapur et al., 1996	2	TLE head injury "Grand Mal"	Imm, 30 min, 6 wks	Verbal, visual (recall & recog)	A, IQ, RR, ILE	5	ALF after 6 wks
Kapur et al., 1997	1	TLE (left) absences	Imm, 30 min, six wks	Verbal, visual (recall & recog)	A, IQ, RR, ILE	5	ALF after 6 wks
Lucchelli & Spinnler, 1998	1	TLE (left) complex partial	Imm, 10 (vis) 60 min, 24 hr, 7 d, 41 d	Verbal, visual	A, ILE	3	ALF after 7 days (ver) norm (vis)
Mayes et al., 2003	1	TLE following head injury	Imm, 30 min, 3 wks	Verbal, visual	A, IQ, RR, RA, ID15, MP, ILE	8	ALF after 3 wks
O'Connor et al., 1997	1	TLE	2 hr, d 2-4, 1 wk	Verbal	A, MP, ILE	3	ALF after 1 day (< with seiz cont)

Methodological quality based on quality criteria set out in Elliott, 2012: A - age matched controls, IQ - IQ matched controls, RR - recall and recognition, CFA - ceiling and floor effects avoided, RA - rehearsal avoided, ID15 - immediate delay after 15 seconds, MP - matching procedure, ILE - initial learning equated

Table 4.

ALF in TLE group studies

Study	n	Type of epilepsy	Testing delay	Type of materials used	Methodological quality*	Quality rating score (QRS)	Outcome
Bell et al., 2005	Exp n=42 control n=49	TLE (left & right)	Imm, 30 min, 24 hrs	Verbal, visual	A, IQ, RR, CFA, RA	6	No ALF at 24 hrs
Bell, 2006	Exp n=25 control n=25	TLE (6 right, 11 left, 2 bilateral)	Imm, 30 min, 2 wk delay	Visual, verbal	A, RR, CFA, RA	4	No ALF at 2 wk delay in TLE group
Blake et al., 2000	Exp n =21 control n=16	TLE (left & right)	Imm, 30 min, 8 wks	Verbal	A, IQ, RR, RA, MP, ILE	6	ALF in left TLE group Seiz<mem
Butler et al., 2009	Exp n=22 Control n=20	TEA	Imm, 30 min, 3 wks	Verbal	A, CF, MP, IL	4	ALF after 3 wks?
Davidson et al., 2007	Exp n=21 control n=21	IGE	Imm, 30 min, 1 wk	Verbal, visual	A, IQ, CF, MP	5	Initial learning worse in IGE
Giovagnoli & Avanzini, 1999	Exp n=131 control n=36	TLE (left & right)	Imm, 30 min	Verbal, visual	-	-	Left TLE impaired verbal tests
Helmsteader et al., 1998	Exp n=55 control n=21	TLE (28 left, 27 right)	Imm, 30 min, 1 wk	Verbal, visual & self-report	A, IQ, CF, RA	5	ALF present after 1 wk
Jokeit et al., 2001	Exp n=10	Refractory TLE	Imm, 30 min, 24 hrs	Visual (word position test)	MP, ILE	2	Seiz within 24h<mem
Mameniskiene et al., 2006	Exp n=70 control n=59	TLE	Imm, 4 wks	Visual, verbal	A, CF	3	Frequent seizures > poor recall
Manes et al., 2005	Exp n=7 control n=7	TEA	Imm, 30 min 6 wks	Verbal, visual	A, IQ, RR, ILE	5	ALF in verbal material
Martin et al., 1991	Exp n=21 control n=21	Unilateral TL dysfunction	30 min, 24 hr	Selective reminding test	CFA, RA, MP, ILE	4	ALF present after 24 hrs
Muhlert et al., 2011	Exp n=28 control n=15	TLE (14) & IGE (14)	40 sec, 30 min, 3 wk	Visual, verbal	A, IQ, RR, CFA, RA, ID 15, MP, ILE	9	ALF in TLE group. Seiz not sig
Tramoni et al., 2011	Exp n=5 control n=5	TLE	Imm, 1 hr, 6 wk delay	Verbal, visual	A, RR	3	Story recall impaired
Wilkinson et al., 2012	Exp n=22 control n=7	TLE (15 RHS, 12 LHS)	Imm, 1 hr, 6 wks	Verbal, visual	A, IQ, CFA, MP,RA ILE	6	ALF present

Methodological quality based on quality criteria set out in Elliott, 2012A - age matched controls, IQ - IQ matched controls, RR - recall and recognition, CFA - ceiling and floor effects avoided, RA - rehearsal avoided, ID15 - immediate delay after 15 seconds, MP - matching procedure, ILE - initial learning equated

The review is structured into five sections exploring the relationship between seizure activity and ALF: the effects of seizures during the delay period, onset and duration of condition, seizure control through AED, sub-clinical seizures, and seizure control through epilepsy surgery. The QRS will be used to rate the methodological strength of the papers in light of any ostensible associations between seizure activity and ALF.

Seizures during the delay period

Seizure activity during the delay period has been identified as a possible explanation for ALF, as it is thought that seizures may disrupt MTL activity or neocortical storage sites during the slow consolidation process, preventing memories from becoming established (Butler & Zeman, 2008). Nine studies (three single case and six group studies) report seizures during the delay period: Bell (2006), Bell et al. (2005), Jansari et al. (2011), Jokeit et al. (2001), Lucchelli and Spinnler (1998), Mameniskiene et al. (2006), Muhlert et al. (2011), O'Connor et al. (1997), and Wilkinson et al. (2012) (see Appendix A for tabulated overview).

ALF findings and reported seizure correlates

Seven out of the nine studies report ALF during the delay period, with the exception of Bell (2006) and Bell et al. (2005), who report a similar decline in forgetting between the epilepsy group and the controls. One explanation for this is that 45 out of the 49 participants in Bell et al. were seizure free during the delay period. As this was a group task the relevance of this was not considered in the overall analysis, therefore their finding that seizures did not correlate with ALF may be unreliable as such a small number of participants reported seizures during the delay. In consideration of their methodological quality Bell et al. scored 6 on the QRS and Bell scored 5, both falling within the "average" range. These are reasonably good scores with methodological strengths in both studies including adequately matching the TLE

participants' age and IQ to the controls', avoiding rehearsal before the immediate delay and testing both verbal and visual materials. Methodological weaknesses in both studies included not equating initial learning, which was particularly problematic in Bell et al. where the participants appeared to be clinically impaired on the WMS-III at immediate recall compared to the controls and were performing at a significantly different level to the controls at the short delay. Additionally, Bell et al. included patients who had undergone surgery, which may have diluted any potential change in the post-surgery group.

Positive associations

Three studies report positive associations between seizures during the delay and ALF: Mameniskiene et al. (2006), O'Connor et al. (1997), and Wilkinson et al. (2012). Mameniskiene et al. provides the most comprehensive analysis of seizures during the delay in a study measuring verbal and non-verbal memory of 70 participants and 57 controls at delays of immediate, 30 minutes and four weeks. Participants experiencing seizures during the delay were stratified into two categories ("less than four" & "more than four") with the participants in the "more than four" seizure category scoring significantly worse on both verbal and visual tests compared to individuals in the "less than four" seizure category. One of the strengths of this paper was the unusually large sample for this area (n = 70), however the study fell into the methodologically "low quality" range, scoring 3 on the QRS. Methodological weaknesses included lack of an IQ-matched control group and unequated initial learning between participants and controls. Additionally, the authors did not measure the interaction between the 30-minute and four-week delay, therefore we cannot accurately infer the rate of forgetting between the TLE and control group. O'Connor et al. report that seizures during the 24-hour delay period appeared to be modulating the participant's forgetting scores; however this paper also scored 3 on the QRS, with methodological weaknesses including the lack

of an IQ-matched control group and not piloting the measures for ceiling and floor effects (which were evident during the testing).

Wilkinson et al. (2012) provide compelling evidence for the relationship between seizures during the delay and ALF, reporting on 27 TLE participants tested over immediate, 30 minute and six-week delays on verbal and visual free recall tasks. Participants in their study evidenced ALF after the six-week delay on both tasks, with correlation analysis indicating that ALF over the longer delay correlated with the frequency of seizures during that period. This result appears to agree with the findings in Mameniskiene et al. (2006), however the paper is methodologically more robust, scoring in the "high quality" range on the QRS (7). Methodological strengths included adequately piloting the materials, matching the control group on key variables, and developing appropriate matching procedures.

Negative associations

Four studies do not report a positive association between ALF and seizures during the delay period (Jansari et al., 2010; Jokeit et al., 2001; Lucchelli & Spinnler 1998; Muhlert et al., 2011). Lucchelli and Spinnler (1998) report on one TLE participant, GB, who experienced a complex partial seizure a few minutes after completing 10 trials of a paired association task. The authors conclude that as he was able to recall the associations three days later, his forgetting rate had not been detrimentally affected by the seizure. However, the authors do not report whether GB experienced any additional seizures after this point, therefore this conclusion may be premature, as additional seizures may have lead to ALF. Given that GB's seizures were reportedly experienced during sleep, it may be that additional (perhaps sub-clinical) night-time seizures disrupted a longer-term consolidation process (this is considered in a later section). Methodologically this paper scored 3 on the QRS, falling into the "low quality" range; weaknesses included not matching the materials between GB and the

controls, only measuring recall, and not including IQ-matched controls. Equally. Muhlert et al. (2011) do not report an association with seizures during a three-week delay and ALF. In contrast to Lucchelli and Spinnler their study met the criteria for "high quality" on the QRS scale (9). Methodological strengths included matching participants on age and IQ, equating initial learning, and employing a matching procedure. It is therefore unlikely that the forgetting scores are an artefact of the testing methods. Jansari et al. (2010) and Jokeit et al. (2001) provide somewhat mixed evidence, with Jansari et al. reporting no association between seizures and ALF on a verbal story test after 24 hours, but reporting an improvement in story recognition following AED intervention. Jokeit et al. report mixed associations between ALF at 24 hours and seizures during the delay, with participants with right sided TLE reporting no association but left sided TLE participants showing the opposite. It cannot be said that either study conclusively demonstrates that seizure activity during the delay does not influence ALF.

Summary

From the available data it is difficult to establish a firm conclusion about the relationship between reported ALF and seizures during the delay period. However, there does appear to be some limited evidence that seizures play a role, with the caveat that there is only one study of high enough methodological quality to support confidently this position (Wilkinson et al., 2012). Studies that do not provide evidence for seizure correlates during the delay tend to describe small numbers of reported seizures (e.g. Lucchelli & Spinnler, 1998; Muhlert et al., 2011). There is therefore a risk that false negatives are being reported in the literature. The picture is further obscured as many papers inadequately report seizure activity during the testing period. One of the difficulties is identifying the relative contribution of seizures during the delay period and the cumulative effects of seizures over the lifespan on ALF. Given that some

studies do not report seizures during the delay period but still evidence ALF, we can conclude that additional factors need to be considered. One possible factor is the link between ALF and onset and duration of epilepsy.

Onset and duration of condition

Duration of the condition has been associated with cognitive decline over protracted time periods such as 30 years (Helmstaedter, 2002), as well as shorter durations of 18-20 years (Seidenberg, Pulsipher, & Hermann, 2007). However some participants have not evidenced cognitive decline despite long durations (Griffith et al., 2007). The reason for this dissociation is unclear, however Seidenberg et al. (2007) highlight the fact that the patients in the Griffith et al. (2007) study were older and had an average onset of 37 years, suggesting that long-standing refractory epilepsy that is diagnosed in childhood may be a contributing factor in cognitive decline. If this association is accurately inferred then it is possible that papers in the ALF literature may show a similar pattern.

Ten single case studies and nine group studies report data on onset and duration of condition in the ALF literature. The single case studies were: Cronel-Ohayon et al. (2007), DeRenzi and Lucchelli (1993), Gallasi et al. (2011), Holdstock et al. (2002), Jansari et al. (2010), Kapur et al. (1997), Kapur et al. (1996), Lucchelli and Spinnler (1998), Mayes et al. (2003), and O'Connor et al., (1997) - see appendix A.3 for tabulated overview. The nine group studies were: Bell et al. (2005), Blake et al. (2000), Butler et al. (2009), Helmstaedter et al. (1998), Mamineksiene et al. (2006), Martin et al. (1991), Muhlert et al. (2011), Tramoni et al. (2011), and Wilkinson et al. (2012).

Single case

Age of onset varies amongst the papers with three papers (Jansari et al., 2010; Kapur et al., 1997; Lucchelli & Spinnler, 1998) evidencing an onset age of 50 or above, four studies reporting onset between the ages of 20 and 40 (DeRenzi & Lucchelli, 1993;

Gallasi et al., 2011; Kapur et al., 1996; O'Connor et al., 1997) and three studies reporting onset in the teenage years or younger (Cronel-Ohayon et al., 2007; Holdstock et al., 2002; Mayes et al., 2003). Review of the papers does not reveal any discernible pattern between age of onset and ALF in the single case literature. Three of the papers report a long duration of 20 years or more (Gallassi et al., 2011; Holdstock et al., 2002; Mayes et al., 2003) with the remaining seven reporting durations of 10 years or less. As with age of onset, there does not appear to be an obvious relationship between duration of epilepsy and ALF.

Group studies

All nine papers report age of onset with only one paper (Butler et al., 2009) reporting an onset over age 50. Three of the papers report an onset between the ages of 20 and 40 (Butler et al., 2009; Martin et al., 1991; Muhlert et al., 2011), with the remaining six papers reporting an onset under 20 years. This indicates that the group studies have a proportionately younger onset than the single case studies. As with the single case papers however, there is no discernible pattern between onset and duration and presentation of ALF.

Summary

It does not appear that age of onset or duration of condition is associated with ALF in the papers reported here. We might have expected studies with shorter durations to show ALF less frequently given the evidence in the wider literature suggesting that longer duration of epileptic condition is linked to cognitive decline (Vingerhoets., 2006). A potential confound is the lack of consideration of the impact that duration of epilepsy has on ALF with none of the studies exploring the association directly. Given the lack of direct consideration of the associations between age of onset and duration and the observed heterogeneity of the participants, it is important that we explore papers

which have used a more direct experimental approach to assess the impact of seizure activity on ALF.

Seizure control through AEDs

Research into the clinical effectiveness of AEDs in treating epilepsy has shown that although medical intervention demonstrates effectiveness in reducing seizures for around 60-70% of individuals (Wiebe et al., 2001), the improvement in seizure activity can be offset by the adverse AEDs have on cognition (Hermann, Meador, Gaillard, & Cramer, 2010). One of the challenges when applying this to ALF research is how far we are able to separate the confounding effects of the medication with the reported benefits of seizure reduction. A way to explore this is to assess participants before they have controlled their seizures pharmacologically and then retest them in the post-AED period (AB design). The following section will consider how successful AED intervention is at (a) eliminating seizure activity, and (b) improving ALF.

Case studies

Jansari et al. (2010) is the only paper using an AB pre- and post-AED intervention, reporting on a patient RY, a 62-year-old man who complained that his memories seemed to fade over a period of around four-to-six weeks. He had an unremarkable medical history but reported that he had experienced déjà vu symptoms since childhood which had worsened in the year prior to treatment (ostensibly in conjunction with his memory difficulties). At the time of testing he was experiencing four or five "episodes" per month. Initial neuropsychological testing revealed memory performance broadly in the high ranges, although his memory of a recently learned story over a week (and beyond) was significantly impaired compared to controls. Successful treatment with AEDs controlled his seizures, and when retested post-surgery, RY evidenced worse initial encoding of verbal information, but ALF improved for repeated recollected material. Methodologically Jansari et al. scored 5 on the QRS, within the

"average quality" range; methodological strengths included using an age- and IQ-matched control group, and testing both recall and recognition. However, the study was somewhat limited by exclusive use of verbal materials.

There is some additional support for these findings from Tramoni et al. (2011) who adopted a similar approach with six TLE patients who were prescribed mono-therapeutic treatment which successfully controlled their overt seizures. Post-AED, the participants in Tramoni et al. show no significant ALF on tests of verbal and visual memory compared to controls. However the Tramoni et al. paper is slightly less methodologically robust that Jansari et al. (2010), scoring 4 on the QRS and falling at the lower limit of the "average quality" range. Methodological weaknesses include the lack of an IQ-matched control group and the lack of data from the pre-intervention period, which means we are unable to conclude confidently that the participants' ALF improved post-intervention. Although Lucchelli and Spinnler (1998) do not report improvement in their patient (GB) following AED treatment (details of study reported earlier) it is methodologically weak, scoring 3 on the QRS and falling in the "low quality" range. Additionally GB appeared to be experiencing sub-clinical night time seizures which may have been causing his continuing ALF.

Group studies

Eleven of the ALF group studies report that their TLE participants were undergoing a course of poly- or mono-therapy: Bell (2006); Bell et al. (2005); Blake et al. (2000); Butler et al. (2009); Davidson et al. (2007); Giovagnoli and Avanzini (1999); Jokeit et al. (2001); Mameniskiene et al. (2006); Manes et al. (2005); Muhlert et al. (2011); and Wilkinson et al. (2012) (see appendix A for tabulated overview). Four group studies report successful control of seizures through AED use: Butler et al., Manes et al., Bell, and Bell et al., although the latter two papers only report control of seizures for part of their samples. AED intervention was not successful in controlling

overt seizures in the remaining seven studies so they will be not be considered further. Bell et al. will also be excluded from this appraisal as intra-group information about AED use is not provided. The remaining three group studies (Bell, 2006; Butler et al., 2009; Manes et al., 2011) evidenced seizure control through AED intervention (defined as no seizures for at least six months prior to the testing). Bell reported 66% of their sample of 25 achieved seizure control, however five of these individuals previously had epilepsy surgery. Due to the pooling of seizure and seizure-free participants, it is difficult to establish whether the lack of apparent ALF in this study is attributable to seizure control through AED, or successful seizure control due to epilepsy surgery. An additional drawback was this paper's testing methodology, with the paper scoring 4 on the QRS, falling at the lower end of the "average quality" range. Weaknesses in methodology included the lack of an IQ-matched control group and no matching procedure.

Both Butler et al. (2009) and Manes et al. (2005) report ALF despite successful AED intervention, with participants in Manes et al. impaired on tests of recall of verbal information after six weeks, and participants in Butler et al. significantly impaired compared to controls after a three-week delay on verbal and visual recall tasks. However, we must be cautious in attributing too much weight to these findings as neither study provides robust methodological experimentation. For instance, although participants in Manes et al. evidenced ALF, they were also impaired on standard memory tests and their learning was not equated with the control group. Methodologically this study scored 4 on the QRS, falling at the lower end of the "average quality" range. Butler et al. also scored 4 on the QRS. The main drawback of both studies is that memory assessments were not carried out before the AED interventions, therefore we are unable to compare the post-AED assessment data.

Summary

Evidence for the ameliorative effect of seizure reduction on ALF through AED intervention is rare in the ALF literature, particularly in group studies, with none of the reviewed papers offering substantive evidence of ALF improvement. One of the difficulties appears to be the refractory nature of the TLE cases in the ALF literature with most papers including participants with uncontrolled seizures of varying etiologies despite AED use. The only single case (Jansari et al., 2010) which directly developed an AB-style design found that AED may offer a seemingly paradoxical effect on memory, in that the effects of the medication may slow or disrupt initial acquisition but improve long-term retention by reducing the impact the seizures have on longer-term consolidation with repeated exposure to the materials.

Sub-clinical Seizures

Sub-clinical Seizures (SCS) are seizures without subjective or apparent objective somatic or neurological presentation (Babb, Wilson, & Isokawa-Akesson, 1987). They are most frequently observed during long-term EEG monitoring pre-epilepsy surgery, although only few studies have looked into their clinical characteristics (see Sperling & O'Connor, 1990, and Zangaladze, Nei, Liporace, & Sperling, 2008). Previous studies have found that they can impact cognitive performance (Bridgeman, Malamut, Sperling, Saykin, & O'Connor, 1989). SCS are highlighted as potential explanatory mechanisms for ALF, with a recent review concluding that ALF may be "partly attributed to subclinical-clinical epileptiform activity and structural damage" (Butler & Zeman, 2008). The process underpinning this effect is currently unknown although one hypothesis proposes that disruption of the "slow" consolidation process that occurs during sleep is responsible.

To date Jansari et al. (2010) is the only paper to test this hypothesis by using a sleep-deprived EEG on participant RY Initial neurological testing did not reveal

imaging data suggestive of epilepsy, however EEG monitoring showed right-temporal spike activity with increased epileptoform discharges appearing while RY was asleep. As described earlier, RY's memory profile showed variable improvement following pharmacological intervention, despite being seizure free during the delay period. The authors were unable to test RY again using EEG monitoring, therefore we are unable to conclude confidently that he was not experiencing subclinical seizures during the overt seizure-free period, which may have impacted ALF. As stated in the previous section Jansari et al. scores in the "average quality" range on the QRS, indicating that the testing methodology is reasonable. Additional supportive evidence is warranted, however.

Tramoni et al. (2011) offers this to some extent although methodologically this paper also falls in the "average quality" range. An interesting finding in this paper is that the authors report sub-clinical epileptic activity in all five of their participants despite them being seizure free the year leading up to the study. The participants appeared to evidence ALF between the one-hour delay period and six-week delay on a story recognition test compared to controls but not in learning new facts or single-item memory tasks. The reason for this variability is unclear and one of the difficulties with this paper is establishing the relative memory gains made by the participants following the elimination of their overt seizures through AED intervention the previous year. As mentioned in the above section, a way to answer this would have been to administer the memory assessments before commencing AEDs and compare this to subsequent performance.

Summary

The mixed outcomes and methodological quality in studies researching ALF and SCSs point to the need for further avenues of investigation to explain the variability of the findings. There is a paucity of available data in this area within the field of epilepsy

research (Zangaladze et al., 2008) and to our knowledge no published work is available specifically looking at the impact of sub-clinical seizures in ALF. The Tramoni et al. (2011) case highlights the potential importance of subclinical seizures, as it suggests that overt seizure control alone might not exclude the possibility that epileptogenic activity during sleep disrupts the slow consolidation process.

Seizure control through epilepsy surgery

Despite many new AEDs being released into the market in recent years, epilepsy surgery has shown to be the most effective method of reducing seizures is resecting the part of the temporal lobe responsible for the epileptic activity (Schmidt & Loscher, 2003). Surgical resection has been found to be effective in reducing drug-resistant partial seizures in 64-70% of patients with TLE (Engel, 2003). If seizures play an important role in the forgetting observed in ALF, controlling seizures through surgery might be expected to improve forgetting rates by reversing the disruptive effects the seizures have on the "slow" consolidation process.

Three studies in the ALF literature report post-surgery data, two group studies (Bell et al., 2005; Martin et al., 1991) and two single case studies (Cronel-Ohayon et al., 2007; Gallassi et al., 2011). To date only one of the studies (Gallassi et al., 2011) examined a patient before and after surgery. The patient, MT had partial epilepsy with secondary generalization from 38 years old and was successfully treated pharmacologically until he was 57, at which time his seizures became more frequent and within a year he was having one seizure per day. A left temporal polectomy was performed leading to a seizure-free profile after 15 months. ALF was assessed using a battery of standardized neuropsychological tests. The authors report that 15 months after surgery MT's ALF had improved and was not significantly different to the control group.

This paper scored 3 on the QRS, falling in the methodologically “low quality" range; weaknesses included the lack of an IQ-matched control group, an inadequately articulated matching procedure, and uncertainty as to whether initial learning was adequately equated at the 30-minute delay. It is possible therefore that the control group were performing at a different level to the participant, reflecting a scaling effect pre-surgery.

Bell et al. (2005) include 21 participants in their study, six of whom had undergone a left anterior temporal lobectomy and 15 were non-surgical participants. The drawback of conflating the sample in this way is that intra-group differences were not explored, therefore this study will be omitted from this discussion. Martin et al. (1991) report on 21 participants with unilateral TLE and 21 tension headache controls. The TLE participants had previously undergone a unilateral anterior temporal lobectomy or a temporal lobectomy, and were tested using a selective reminding test at immediate learning, 30 minute and 24-hour free recall. Participants in the TLE post-surgery group evidenced ALF at the 24-hour delay when compared to the control group. Methodologically this paper scored 4 on the QRS, falling in the "average quality" range. Methodological weaknesses included the lack of an age- or IQ-matched control group and the use of only verbal recall materials. As with Tramoni et al. (2011) one of the main drawbacks of this study is the lack of pre-surgery data.

One of the single case papers, Cronel-Ohayon et al. (2007), reported on a young boy JE who experienced left-sided TLE with olfactory auras. Following a year of unsuccessful polypharmacy, a left temporal lobectomy with amygdalo-hippocampal resection was performed resulting in JE being seizure free. Long-term memory assessments for verbal and visual material were conducted when he was 18, finding ALF at seven days and again at 29 days when compared to his dyzygotic twin brother. One of the drawbacks of this paper was the use of JE's twin brother who was of higher

intellectual functioning than JE.. This renders comparisons of forgetting less valid as IQ and memory have been found to correlate positively (Mayes, 1986). Methodologically this paper fell in the "high quality" range, scoring 7 on the QRS scale. Methodological strengths included having a well articulated matching procedure, equating initial learning, and using both verbal and visual testing materials. The main drawback of this study is the lack of a pre-surgery neuropsychology assessment which means it is not possible to establish if J.E.'s ALF scores improved following surgery.

Summary

There are only four reported studies in the ALF literature where participants' forgetting rates were assessed following epilepsy surgery. In each case overt seizure activity ceased following surgery but support for improved forgetting rates remains limited. Methodological problems obfuscate the picture further, as the reported cases are not methodologically robust enough to draw any firm conclusions about the effectiveness of epilepsy surgery in reducing ALF. The lack of pre/post surgery AB group designs is problematic as we are currently unable confidently to observe and compare any post-surgery (seizure free) gains to the pre-surgery (active seizure) period.

Discussion

This review used systematic principles to evaluate the literature on ALF in TLE, looking at six areas putatively linked to ALF in the wider TLE literature. The papers were of mixed methodological quality, with only three representing the highest rating on the QRS. We can conclude therefore that testing quality is average in this field. This is partly due to the lack of available testing materials to fulfil the Elliott (2012) criteria and also due to the marked difficulty in finding control groups matched for age and IQ.

The detail of the reporting was sub-optimal in several papers, with some studies only describing limited information on salient seizure activity (e.g. frequency, onset, and duration). This applied to both high quality papers and low quality papers. In most

cases the authors do not consider the relationship between current and historical seizure activity and ALF. It is important that researchers consider salient clinical correlates and pathological factors in their analyses, and report sufficient detail so that inferences can be made about this relationship.

Due to the variable reporting quality and small number of papers evidencing methodological robustness we should be cautious in drawing any firm conclusions about associations between seizure activity and ALF. However, there does appear to be some evidence that seizures mediate ALF, with Wilkinson et al. (2012) providing evidence of a relationship between frequency of seizures and ALF over a six-week delay. Similarly there appears to be limited support for the effects of AEDs in ameliorating ALF if seizure control is established (e.g. Jansari et al., 2010; Tramoni et al., 2011). It should be noted that the papers in this area are not as methodologically robust as would be desirable for us to draw any firm conclusions. Also, the direct role of SCS in ALF remains unclear, as findings from two of these papers (Jansari et al., 2011; Tramoni et al., 2010) suggest that SCS activity can persist even when overt seizure control is established through AED intervention, with one possibility being that this low-level seizure activity disrupts the "slow" consolidation process.

Given that AEDs appear unreliable in establishing complete seizure control, the clearest way to understand the role of seizure activity is to develop an AB pre/post surgery design. This will enable direct comparison of the seizure free period by comparing it to the (period of uncontrolled seizures. Few ALF papers have explored this to date, and the studies that have are methodologically limited (e.g. Gallassi et al., 2011). Therefore this appears to be a reasonable future avenue to pursue.

Future Directions

The evidence gathered in this review indicates that additional exploration of ALF is warranted, particularly given the paucity of high quality papers in this field.

Future studies might look to use the QRS as a quality control checklist to develop robust ALF testing methods. It is important that researchers report sufficiently a detailed history of their sample's epilepsy and seizure activity which should include: age of onset of epilepsy, number of lifetime seizures, duration of condition, seizure types over the life span, historical medication use, and pertinent imaging data. Proximal reporting should comprise information on current seizure activity, seizure frequency, seizure type, current AED use, and any imaging or EEG data. It is important that researchers develop ways to examine the relationship between sub-clinical seizures and ALF. Direct AB comparison designs are rare in this field, therefore additional research of high methodological standard is needed, preferably using a longitudinal pre- and post-surgery or pre- and post- AED design.

Footnotes

[1]Eighty percent of ALF papers were reviewed by two raters (GE and SE). The remaining six studies were additional studies added to the review after GE's involvement in the rating process had ceased.

References

Babb, T. L., Wilson, C. L., Isokawa-Akesson M. (1987). Firing patterns of human limbic neurons during stereoencephalography (SEEG) and clinical temporal lobe seizures. *Electroencephalographr Clin Neurophysiol, 66,* 467-482.

Baddeley, A. D. (2002). *Human Memory: Theory and Practice*. (Revised ed.) London: Lawrence Erlbaum Associates.

Bell, B. D. (2006). 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. doi:10.1080/ 13803390500434367

Bell, B. D., Fine, J., Dow, C., Seidenberg, M., & Hermann, B. P. (2005). Temporal lobe epilepsy and the selective reminding test: The conventional 30-minute delay suffices. *Psychological Assessment, 17*(1), 103-109. doi:10.1037/ 1040-3590.17.1.103

Bell, B. D., & Giovagnoli, A. R. (2007). Recent innovative studies of memory in temporal lobe epilepsy. *Neuropsychol Rev.* 17:455-476.

Blake, R. V., Wroe, S. J., Breen, E. K., & McCarthy R. A. (2000). Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. *Brain, 123*(3), 472-483. doi:10.1093/brain/123.3.472

Bortz, J. (2003). Neuropsychiatric and memory issues in epilepsy. Mayo Clin Proc, 78, 781-787. Retrieved from http://connection.ebscohost.com/c/articles/ 10544724/neuropsychiatric-memory-issues-epilepsy

Bridgeman, P. A., Malamut, B. L., Sperling M. R., Saykin, A. J., & O'Connor, M. J. (1989). Memory during subclinical hippocampal seizures. *Neurology, 39,* 853-856.

Butler, C. R., Graham, K. S., Hodges, J. R., Kapur, N., Wardlaw, J. M., & Zeman, A. Z. (2007). The syndrome of transient epileptic amnesia. *Annals of Neurology, 61*(6), 587-598. doi:10.1002/ana.21111

Butler, C. R., Bhaduri, A., Acosta-Cabronero, J., Nestor, P. J., Kapur, N., Graham, K. S., Hodges, J. R., & Zeman, A. Z. (2009). Transient epileptic amnesia: regional brain atrophy and its relationship to memory deficits. *Brain, 132*, 357-368.

Butler, C. R., & Zeman, A. Z. (2008). 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. doi:10.1093/brain/awn127

Butler, C. R., Bhaduri, A., Acosta-Cabronero, J., Nestor, P. J., Kapur, N., Graham, K. S., ... (2009). Transient epileptic amnesia: Regional brain atrophy and its relationship to memory deficits. *Brain*. 132(2):357-368

Cronel-Ohayon, S., Zesiger, P., Davidoff, V., Boni, A., Roulet, E., & Deonna, T. (2006). Deficit in memory consolidation (abnormal forgetting rate) in childhood temporal lobe epilepsy. Pre and post operative long-term observation. *Neuropediatrics*. 37(6):317-324.

Davidson, M., Dorris, L., O'Regan, M., & Zuberi, S. M. (2007). Memory consolidation and accelerated forgetting in children with idiopathic generalized epilepsy. *Epilepsy and Behavior*. 11(3):394-40

De Renzi, E., & Lucchelli, F. (1993/1996). Dense retrograde amnesia, intact learning capability and abnormal forgetting rate: A consolidation deficit? *Cortex/ Neurocase, 29/2*(1), 449-466/13a-xx. doi:10.1093/neucas/2.1.13-a

Elliott, G. (2012). Methodological issues associated with assessing forgetting rates: Do recent studies of accelerated long-term forgetting in epilepsy consider key

factors – A review. (Unpublished doctoral thesis). The University of Sheffield, Sheffield.

Engel, Jr., J. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE task force on classification and terminology. *Epilepsia, 42(6),* 796-803.

Engel, Jr., J. (2003). Reply to "Of cabbages and Kings: some considerations on classifications, diagnostic schemes, semiology and concepts". *Epilepsia, 44,* 4-6.

Gallassi, R., Sambati, L., Poda, R., Maserati, M. S., Oppi, Federico, Giulioni, M., & Tinuper, P. (2011). Accelerated long-term forgetting in temporal lobe epilepsy: Evidence of improvement after temporal pole lobectomy. *Epilepsy & Behaviour, 22*(4), 793-795. doi:10.1016/j.yebeh.2011.09.003

Gastaut, H. (1973). Dictionary of Epilepsy. In Martin, G.M. (Eds. 2), *Human Neuropsychology* (pp.398-399). Essex: Pearson.

Giovagnoli, A. R,. Casazza, M., & Avanzini, G. (1995). Visual learning on a selective reminding procedure and delayed recall in patients with temporal lobe epilepsy. *Epilepsia.* 36:704-711.

Giovagnoli, A. R,. Avanzini, G. (1999). Learning and memory impairment in patients with temporal lobe epilepsy: Relation to the presence, type and location of brain lesion. *Epilepsia, 40(7),* 904-911.

Griffith, H. R., Martin, R. C., Bambara, J. K., Faught, E., Vogtle, L.K., & Marson, D. C. (2007). Cognitive functioning over 3 years in community dwelling older adults with chronic partial epilepsy. *Epilepsy Research, 74,* 91–96.

Hauser, W. A., & Hesdorffer, D. C. (1990). *Epilepsy: Frequency causes and consequences*. New York: Demos.

Helmstaedter, C., Hauff, M., & Elger, C. E. (1998). 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 (Neuropsychology, Development and Cognition: Section A), 20*(3), 365-375. doi:10.1076/jcen.20.3.365.824

Helmstaedter, C. (2002). Effects of chronic epilepsy on declarative memory systems. *Prog Brain Res, 135,* 439-53. doi:10.1016/S0079-6123(02)35041-6 http://dx.doi.org/10.1016/S0079-6123(02)35041-6

Hermann, B., Meador, K. J., Gaillard, W. D., Cramer, J A. (2010). Cognition across the lifespan: Antiepileptic drugs, epilepsy, or both? *Epilepsy & Behaviour, 17,* 1-5.

Holdstock, J. S., Mayes, A. R., Isaac, C. L., Gong, Q., & Roberts, N. (2002). Differential involvement of the hippocampus and temporal lobe cortices in rapid and slow learning of new semantic information. *Neuropsychologia, 40*(7), 748-768. doi:10.1016/S0028-3932(01)00192-0

Hunkin, N. M., Parkin, A. J., & Longmore, B. E. (1994). Aetiological variation in the amnesic syndrome: Comparisons using the list discrimination task. *Neuropsychologia, 32*(7), 819-825. doi:10.1016/0028-3932(94)90020-5

Isaac, C. L., Mayes, A. R. (1999a). Rate of forgetting in amnesia: I. Recall and recognition of prose. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 25*(4), 942-962. doi:10.1037/0278-7393.25.4.942

Isaac, C. L., Mayes, A. R. (1999b). Rate of forgetting in amnesia: II. Recall and recognition of word lists at different levels of organization. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 25*(4), 963-977. doi:10.1037/0278-7393.25.4.963

Jansari, A. S., Davis, K., McGibbon, T., Firminger, S., & Kapur, N. (2011). When "long-term memory" no longer means "forever": Analysis of accelerated long-term forgetting in a patient with temporal lobe epilepsy. *Neuropsychologia,* (2010), *48*(6), 1707-xxxx. doi:10.1016/j. neuropsychologia.2010.02.018

Jokeit, H., Ebner, A., Holthausen, H., & Markowitsch, H. J. (1996). Reorganization of memory functions after human temporal lobe damage. *Neuroreport.* 7:1627-1630.

Jokeit, H., Daamen, M., Zang, H., Janszky, J., & Ebner, A. (2001). Seizures accelerate forgetting in left-sided temporal lobe epilepsy. *Neurology, 57*(1), 125-126. doi:10.1212/WNL.57.1.125

Kapur, N., Miller, J., Colbourn, C., Abbott, P., Kennedy, P., & Docherty, T. (1997). Very long-term amnesia in association with temporal lobe epilepsy: Evidence for multiple-stage consolidation processes. *Brain and Cognition, 35*(1), 58-70. doi:10.1006/brcg.1997.0927

Kapur, N., Scholey, K., Moore, E., Barker, S., Brice, J., & Thompson, S. (1996). Long-term retention deficits in two cases of disproportionate retrograde amnesia. *Journal of Cognitive Neuroscience, 8*(5), 416-434. doi:10.1162/jocn.1996.8.5.416

Lee, G.P. (2004). Differential diagnosis in epilepsy. In Martin, G.M. (2nd ed.), *Human Neuropsychology* (pp.398-399). Essex: Pearson.

Lezak, M.D., Howieson, D.B., Loring, D.W., (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Lucchelli, F., & Spinnler, H. (1998). Ephemeral new traces and evaporated remote engrams: A form of neocortical temporal lobe amnesia? A preliminary case report. *Neurocase, 4*(6), 447-459. doi:10.1080/13554799808410638* (*3)

MacDonald, S. W. S., Stigsdotter-Neely, A., Derwinger, A., & Backman, L. (2006). Rate of acquisition, adult age, and basic cognitive abilities predict forgetting: New views on a classic problem. *Journal of Experimental Psychology: General, 135*(3), 368-390. doi:10.1037/0096-3445.135.3.368

Mameniskiene, R., Jatuzis, S., Kaubrys., G, & Budrys, V. (2006). The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. *Epilepsy & Behaviour, 8*(1), 278-288. doi:10.1016/j.yebeh. 2005.11.003

Manes, F., Graham, K. S., Zeman, A., De Lujan Calcagno, M., & Hodges, J. R. (2005). Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. *Journal of Neurology, Neurosurgery & Psychiatry, 76*(10), 1387-1391. doi:10.1136/jnnp.2004.036582

Manning, L., Voltzenlogel, V., Chassagnon, S., Hirsch, E., Kehrli, P., & Maitrol, D. (2006/2005). Selective memory impairment for public events associated with accelerated forgetting in a patient with left temporal lobe epilepsy. *Rev Neurol (Paris)/Epilepsy Research, 162*(2)/*64*(1-2), 222-228/45-xx. doi:10.1016/j.eplepsyres.2005.02.003

Martin, G. N. (2006). *Human Neuropsychology* (2nd ed.). Pearson Education Limited: Essex.

Martin, R. C., Loring, D. W., Meador, K. J., Lee, G. P., Thrash, N., & Arena, J. G. (1991). Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. *Neuropsychology, 5*(1), 3-12. doi:10.1037/0894-4105.5.1.3

Mayes, A. R. (1986). Learning and memory disorders and their assessment. *Neuropsychologia, 24*(1), 25-39. doi:10.1016/0028-3932(86)90041-2

Mayes, A. R., Isaac, C. L., Holdstock, J. S., Cariga, P., Gummer, A., & Roberts, N. (2003). Long-term amnesia: A review and detailed illustrative case study. *Cortex, 39*(4-5), 567-603. doi:10.1016/S0010-9452(08)70855-4

Milner, B. (1965). Visually guided maze learning in man: effects of bilateral hippocampal, bilateral frontal and unilateral cerebral lesions. *Neuropsychologia, 3,* 317-338.

Motamendi, G., & Meador, K. (2003). Epilepsy and Cognition. (2003). *Epilepsy & Behaviour, S25-S238. doi:10.1016/j.yebeh.2003.07.004*

Muhlert, N., Grunewald, R. A., Hunkin, N. M., Reuber, M., Howell, S., Reynders, H., & Isaac, C. (2011). Accelerated long-term forgetting in temporal lobe and idiopathic generalised epilepsies. *Neuropsychologia, 49*(9), 2417-2426. doi:10.1016/j.neuropsychologia.2011.04.018

Mungas, D., Ehlers, C., Walton, M., & McCutchen, C. B. (1985). Verbal learning differences in epileptic patients with left and right temporal lobe foci. *Epilepsia, 26,* 340-345.

O'Connor, M., Sieggreen, M. A., Ahern, G., Schomer, D., & Mesulam, M. (1997). Accelerated forgetting in association with temporal lobe epilepsy and paraneoplastic encephalitis. *Brain Cogn.* 35:71-84.

Osterrieth, P. A. (1944). The test of copying a complex figure: A contribution to the study of perception and memory. *Archives de Psychologie, 30,* 286–356.

Ribot, T. (1881). *Les maladies de la mémoire*. Paris: Baillière. Retrieved from http://www.bookrags.com/research/ribot-thodule-1839-1916-lmem-01/

Schmidt, W., & Loscher (2003). How effective is surgery to cure seizures in drug-resistant temporal lobe epilepsy? *Epilepsy Research, 56,* 85-91. doi: 10.10.1016/j.eplepsyres.2003.10.004

Seidenberg, M., Pulsipher, D. T., & Hermann, B. (2007). Cognitive progression in epilepsy. *Neuropsychology Review, 17,* 445-454. DOI 10.1007/s11065-007-9042-x

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective [Review]. *Current Opinion in Neurobiology, 5*(2), 169-177. doi:10.1016/0959-4388(95)80023-9

Squire, L. R. (1992). Memory and the hippocampus: A synthesis from findings with rats, monkeys, and humans. *Psychological Review, 99*(2), 195-231. doi:10.1037/0033-295X.99.2.195

Tramoni, E., Felician, O., Barbeau, E. J., Guedj, E., Guye, M., Bartolomei, F., & Ceccaldi, M. (2011). Long-term consolidation of declarative memory: Insight from temporal lobe epilepsy. *Brain, 134*(3), 816-831. doi:10.1093/brain/ awr002

Vingerhoets, G. (2006). Cognitive effects of seizures. *Seizure, 15,* 221-226. doi: doi:10.1016/j.seizure.2006.02.012

Wiebe, S., Blume, W. T., Girvin, J. P., Eliasziw, M. (2001). A Randomised controlled trail of surgery for temporal-lobe epilepsy. *N. Engl. J. M,345,* 311-318.

Wilkinson, H., Holdstock, J. S., Baker, G., Herbert, A., Clague, F., & Downes, J. J. (2012). Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. *Cortex, 48*(3), 317-332. doi:10.1016/j.cortex.2011.01.002

Zangaladze, A., Nei, M., Liporace, J.D., & Sperling, M.R. (2008). Characteristics and clinical significance of subclinical seizures. *Epilepsia, 49(12),* 1528-1167. Doi:10.1111/j.1528-1167.2008.01672.x

Appendix A (Literature review Tables)

Appendix A.1

Table of seizures during the delay and accelerated long term forgetting

Investigator (year)	Number of seizures reported during the delay	Number of days seizures experienced	Number of participants reporting seizures	Seizures correlated with memory	QRS score	ALF Present
O'Connor et al., 1997	Multiple	7	1 (100%)	+	3	✓
Lucchelli & Spinnler., 1998	1	1	1 (100%)	-	3	✓
Jansari et al.,2010	1	1	1 (100%)	-	5	✓***
Jokeit et al., 2001	NR	20/55 days*	NR	+left - right	2	✓
Bell et al., 2005	1	1	4/49 (8%)	3- 1+****	6	✘
Bell et al., 2006	1-3 (M)*****	NR	10/25 (40%)	-	4	✘
Mameniskiene et al., 2006	25.7%<4 p/m, 50% > 4 p/m	5.3 p/m (M)	53/70 (76%)	+	3	✓
Muhlert et al., 2011	TLE 3.14 (M) IGE 20 (M)**	NR	12/28 (42%)	-	9	✓
Wilkinson et al., 2012	NR	NR	NR	+	6	✓

*Treatment paradigm tested ALF after 24 hours on multiple occasions

**TLE participants experienced 8 simple partial and 14 complex partial seizures; IGE group experienced 1 GTC and 99 absence seizures

***Participant experienced one seizure during experiment one and was seizure free during experiment 2

**** One of the participants who experienced seizures during the delay period showed an isolated memory deficit at 24 hour delay period

*****1 participant experienced 2 seizures, the remaining 9 experienced between 1 and 5.

Appendix A.2

Single-case table of Onset, duration and frequency and Accelerated forgetting in temporal lobe epilepsy

Investigator (year)	Onset	Duration	Frequency	Type	QRS score	Seizures during delay	ALF present
Single case studies							
DeRenzi & Lucchelli., 1993	24	3	No seizures	Head injury	-	✗	✓
Kapur et al., 1996	32	4	No seizures	TLE head injury "Grand Mal"	5	✗	✓
Kapur et al., 1997	57	5	NR	TLE (left) absences	5	✓	✓
O'Connor et al., 1997	37	10	20-30 p/d	TLE	3	✓	✗
Lucchelli & Spindler., 1998	63	2	2/3 pm (during sleep)	TLE (left) complex partial	3	✓	✓
Holdstock et al., 2002**	17	28	20-30 cps p/m	TLE following head injury	6	NR	✓
Mayes et al., 2003	17	28	20-30 cps p/m	TLE following head injury	8	NR	✓
Cronel-Ohayon et al., 2007	9	3	None following surgery (age 12)	TLE (left) cps Olfactory	4	✗	✓
Jansari et al., 2010****	62	9	4/5 "episodes" twice p/m (a) seizure free (b)	TLE (right)	5	✓	✗*
Gallasi et al., 2011	38	20	2 p/y (when controlled) - daily at 57	TLE	3	✗	✗*

Appendix A.3

Group table of Onset, duration and frequency and Accelerated forgetting in temporal lobe epilepsy

Investigator (year)	Onset	Duration	Frequency	Type	QRS score	Seizures during delay	ALF present
Group studies							
Martin et al., 1991	20.5 (L) 12.9 (R)	NR	NR	TLE	4	NR	✓
Helmstaedter et al., (1998)	13	NR	NR	TLE	5	✗	✓
Blake et al., (2000)	12.95	20.1 (SD 12.7)	6 sp, 13 cp, <1 sg	TLE	6		✓
Bell et al., (2005)	13.1 (R) 20.1 (L)	NR	NR	TLE	6	✓	✗
Mamineksiene et al., (2005)	19.0 (11.7)	14.2 (10.4)	6.6 (5.6)	TLE	3	✓	✓
Butler et al., (2009)	60.3 (8.0)	6.45 (5.9)	12.0 (10.9)	TEA	4	✗	✓
Muhlert et al., (2011)	22.1 (14.1)	24.3 (16.9)	3.8	TLE	9	✓	✓
Tramoni et al., (2011)	Between 8 and 20 yrs	0	0	TLE	4	✓	✓
Wilkinson et al., (2012)	11.47 (L) 17.29 (R)	23.33.(L) 21.38 (R)	21.40 (L) 41.09 (R)	TLE	6	✓	✓

* ALF for visual material evident

Appendix A.4

Table of AED use in accelerated long-term forgetting literature

Investigator (year)	N	Single AED	Poly-pharmacy	Type	Seizure control	QRS score	ALF present
Bell et al., (2005)	42	NR	NR	NR	14% of sample	6	✘
Bell et al., (2006)	25	23	NR	NR	66% of sample	4	✘
Blake et al., (2000)	21	M = 2.00	M = 2.00	NR	no	6	✓
Butler et al., (2009)	41	41	0	VAL, LMT, PHY, LEV	yes	4	✓
Davidson et al., (2007)	21	14	2	LMT, VAL	no	5	✓
Giovagnoli & Avanzini, (1999)	131	NR	NR	CRB, PB, VGB	no		✓
Jansari et al., (2010)	RY	yes	no	LMT	yes	5	✓
Jokeit et al., 2001)		NR	NR	NR	no	2	✓
Lucchelli & Spinnler (1998)					yes		
Manes et al., (2005)	6	5	1	CRB, VAL, LMT	yes	5	✓
Mameniskiene et al., (2012)	70	36	34	NR	no	3	✓
Muhlert et al., (2011)	14	6	8	LEV, CRB, PRG, PHY, LMT	no	9	✓
Tramoni et al., (2011)	5	5	0	LAM, LEV, VAL, CRB	yes†	3	✘†
Wilkinson et al., 2012	27	2	25	NR	no	6	✓

† EEG showed activation of spiking during slow wave sleep †† Improvement in recognition following seizure reduction NR = not reported

Research report

Can epilepsy surgery ameliorate accelerated long-term forgetting in temporal lobe epilepsy? A longitudinal group study

Objectives. To investigate whether seizure control following epilepsy surgery improves accelerated long-term forgetting (ALF) in patients with temporal lobe epilepsy (TLE).

Design. A quantitative longitudinal pre/post surgery design was used to explore the impact of surgery on ALF.

Methods. A parallel set of verbal and visual ALF testing materials were administered with seven TLE patients and twenty five controls. Performance was measured on tests of recall and recognition at three delay periods (immediate, 30 minutes and one week) pre- and post-surgery.

Results. The results suggested that ALF improved in the patients with TLE post-surgery for both visually and verbally learned material.

Conclusions. The findings offer the first group level data supporting the theory that uncontrolled seizures result in ALF in TLE. Controlling seizures with epilepsy surgery may be a route to improved long-term memory retention.

Key words: *Accelerated Long-term Forgetting, Temporal Lobe Epilepsy, Seizures, Epilepsy Surgery, Memory*

Introduction

Epilepsy is the most common serious neurological problem in the United Kingdom, with approximately 456,000 individuals experiencing the condition. It is more common in children and in individuals over 65, but reportedly occurs across all ages, races and socio economic groups (The National Epilepsy Society, 2010). Epilepsy is not considered a specific disease or pathological process but rather a behavioural disturbance arising from a hyperexcitable and hypersynchronous discharge of nerve

cells (seizures) of various etiologies (Lezak, Howeison, & Loring, 2004). Causal factors include tumours, infection, birth trauma, traumatic brain injuries, and scarring of neural tissue, as well as progression from unknown origins.

The International League Against Epilepsy (ILAE) traditionally classifies two broad types of epileptic seizures: focal (or partial) seizures are localised to a particular part of the brain (such as the temporal lobes); generalised seizures involve large regions of the brain, covering both cerebral hemispheres (ILAE, 1989). Cognitive difficulties are well documented in individuals with epilepsy and may be attributed to many factors including: seizure etiology, frequency, duration of condition, duration of seizure activity, cerebral tumours, lesions pre-dating onset, age of seizure onset, structural damage due to seizures, psychosocial factors, ictal and interictal physiological, seizure-related dysfunction and antiepileptic drug effects (Vingerhoets, 2006).

Memory difficulties are common amongst individuals with epilepsy (see Thompson & Corcoran 1992) particularly in TLE, where memory-related brain structures are directly involved in seizure activity (Bell & Giovagnoli, 2007). Memory loss in TLE has been found to be associated with the degree of medial temporal lobe pathology, with typical deficits including impaired verbal and visual memory (Lezak et al., 2004). Difficulties have also been found in recalling and recognising newly-learned information (Isaac & Mayes, 1999a). There is also some evidence that laterality of seizure focus differentially affects memory functions, whereby individuals with left-sided TLE evidencing impaired verbal memory (Hermann, Seidenberg, Schoenfeld, & Davies 1987) and individuals with right-sided TLE evidencing deficits in visual memory (Lezak et al., 2004).

In contrast to some of the traditional memory difficulties seen in TLE, where information is usually lost over the first few seconds or minutes after learning, recent research has shown that some individuals show a distinct pattern of forgetting, whereby

normal learning and retention is established over brief delays, but forgetting accelerates at a greater rate than controls over delays of weeks or months (Bell & Giovagnoli, 2007). This relatively newly described phenomenon is termed accelerated long-term forgetting (ALF) by most researchers, and although it has also been called long term amnesia (Kapur et al., 1996). The former term will be used throughout this paper for consistency.

ALF was initially reported in a number of single case studies (see De Renzi & Lucchelli, 1993; Kapur et al., 1996), however more latterly it has been investigated with larger samples, with two recent reviews (Bell & Giovagnoli, 2007; Butler & Zeman, 2006) describing evidence of ALF in group studies (Manes et al., 2005; Mameniskiene, Jatuzis, Kaubrys, & Budrys, 2006; Butler et al., 2007) and in case studies (Cronel-Ohayon et al., 2006). There is some disparity, however, between reported findings, and papers evidencing ALF in TLE have not always been replicated (Bell, Fine, Dow, Seidenberg, & Hermann, 2005), or have been only partially replicated (Mameniskiene et al., 2006). The inconsistent findings in relation to ALF continue to present a challenge to our understanding of the phenomenon, as we do not have a clear picture of what causes this distinctive pattern of forgetting. Several avenues of research offer insight into the variable findings in the ALF literature focussing on: clinical/subclinical seizure activity (Blake, Wroe, Breen, & McCarthy 2000; Jokeit, Daamen, Zang, Janszky, & Ebner 2001); structural neuropathology (Wilkinson et al., 2012); medication effects (Jokeit et al., 2001); underlying psychosocial factors (Giovagnoli & Avanzini. 1999; Blake et al., 2000; Butler et al., 2007) and poor research methodology (Bell et al., 2005; Bell, 2006).

To understand the possible explanatory mechanisms for ALF we must consider the classic work of Theodule Ribot, who made the seminal observation that older memories appear to be less prone to disruption than more recently formed ones in

individuals with anterograde amnesia (Ribot, 1881). This led him to conclude that memories are temporally graded, with older memories less susceptible to disruption following a traumatic event than those that were more recently established. Linked to Ribot's findings, the process of consolidation is essential to our understanding of how these theoretical processes translate to the clinical presentations of ALF. Consolidation is a neurobiological process hypothesised to aid in the transfer of short- to long-term memory storage and was proposed by Hebb (1949). Squire and Alvarez (1995) draw a distinction in the role of consolidation in learning new material, distinguishing between the roles of "fast" and "slow" consolidation. The former is thought to involve medial temporal lobe (MTL) structures, including the hippocampus, and accounts for memory retention over shorter intervals. The latter is thought to involve the gradual transfer of memories out of the MTL into neocortex over longer periods of time (usually a week and beyond). One of the postulated explanations for ALF is that during this period memories that have been subjected to the "fast" consolidation process are vulnerable to disruption as it is thought that stability in the neocortical environment is required for successful "slow" consolidation.

Mayes et al. (2003) postulate three explanations for ALF in TLE; the first two posit that pathology causes damage to either medial temporal lobe structures or the neocortex, preventing the slow consolidation process due to damage in either of these systems. Previous research has examined the role of structural pathology in ALF (see Wilkinson et al., 2012; Muhlert et al., 2011) with both papers highlighting the possibility that ALF is related to temporal damage outside medial temporal lobe (MTL) structures and view MTL damage as a possible marker for this. The third position suggests that epileptogenic seizure activity disrupts the neocortical environment, thus preventing memories from transferring from the hippocampus to the neocortex (Kapur et al., 1997; Squire & Alvarez, 1995).

One of the challenges in investigating seizure activity is the limited ability to observe it objectively. Two approaches are generally adopted. The first involves electroencephalographic (EEG) measurement, which is the most effective way to measure seizure activity directly, and involves recording the brain's electrical activity by placing electrodes directly on the scalp or using an electrode cap. However, this is often only available in a clinical environment as the equipment cannot be transported home without the use of an ambulatory EEG. The alternate method is to use self-report diaries, which despite lacking the objective precision of EEG monitoring, allows us to track the frequency and type of seizures in a patient's day-to-day life. However, self-reporting of seizures is limited to an individual's knowledge of seizure type and this method can only be used to document overt seizure activity.

Despite the techniques we have available to measure seizure activity, there continues to be a dearth of studies exploring the role of uncontrolled seizures in ALF. The few studies that have explored this report mixed findings and suffer methodological weaknesses. For example, Mameniskiene et al. (2006) recruited 70 patients with TLE who underwent a neuropsychological assessment of verbal and non-verbal memory. Testing of long-term memory after four weeks revealed that the TLE patients showed ALF compared to controls, and the number of complex partial seizures experienced were significantly associated with forgetting. However, the results are somewhat limited as the authors did not explore the interaction between the immediate delay and the extended delay and therefore the patients may have been evidencing a classic amnesic pattern of memory loss, as opposed to ALF, which requires normative memory acquisition over short delays. An earlier study by Jokeit et al. (2001) examined ten TLE patients using a word-position associative learning test whilst being monitored using EEG. Participants were presented with 12 words randomly positioned on a computer screen in four possible positions (left, right, down or up) and were asked to remember

the positions. The process was repeated three times with each presentation followed by cued recall to establish initial learning. The participants were then retested at 30 minute and 24-hour delays, with ALF calculated by subtracting the 24-hour delay scores from the 30 minute scores. The authors found no general effect of seizures on retention performance, however patients with left-sided TLE showed ALF on the memory task if a seizure was experienced during the 24-hour delay. The main drawbacks of this study were the lack of a control group and the fact that it only tested spatial recognition.

Two recent studies have considered the relationship between seizures and ALF, Muhlert et al. (2011) reported no correlation between seizures and ALF in a sample of seven TLE participants on verbal and visual memory tasks tested at three delays: immediate, 30 minute and one week. However, the number of seizures experienced by the group over the week was very small, therefore the reliability of the correlates in this study can be called into question. Wilkinson et al. (2012) provided more substantive evidence of the role of seizures in ALF, with 27 TLE patients completing tests of verbal and visual recall at three delays: immediate, one hour and six weeks. Participants' seizure frequency over the six week delay was found to be positively associated with ALF.

One of the drawbacks of the studies reported so far is that none adopted an AB experimental design to compare forgetting rates during a period of seizures (A) and then again when seizures are controlled (B). Few studies examining ALF have used this method, however the ones that have use two approaches. The first is to test for ALF pre- and again post-AED intervention, with the goal of comparing the seizure-free (post-AED) period with the pre-intervention period. This has achieved some success, with Tramoni et al. (2011) and Jansari et al. (2012) reporting improvements post-seizure remission. Of interest, Jansari et al. found that overt seizure elimination appeared to attenuate ALF of verbally presented story tests if the materials were repeatedly exposed

in the recognition trial. However they did not find the same outcome in a story recall test. The reasons for this are unclear although it may be due to the fact that their participant was experiencing sub-clinical seizures. This finding is of interest though as it might suggest that improving seizures allows patients with TLE to retain more information if rehearsal is adopted.

One of the drawbacks of AED intervention is that they do not work for every patient with TLE. Some individuals opt to have the epileptogenic tissue resected. This has been found to control drug-resistant seizures in approximately 70% of patients with TLE (Schmidt & Loscher, 2003). In theory, the role that seizures play in ALF could be established by conducting an ALF assessment pre- and post-epilepsy surgery to compare ALF scores in the seizure-free post-surgery period to the epileptogenic pre-surgery period. Few studies have been able to achieve this due to the lengthy recovery time needed after surgery, difficulties finding a control group matched for age and IQ, and the problems associated with re-testing ALF with currently available materials (Elliott, 2012). Muhlert, 2010 (unpublished doctoral thesis) conducted a study with a single post-surgery participant whom he tested prior to surgery and one year after an amygdalohippocampectomy. The results indicated that pre-surgery the participant performed normally on recall and recognition tasks after 30 minutes, but ALF was detected on visual recognition tasks after 24 hours and one week. Muhlert., drew two conclusions from his paper: firstly, the measures may not have been sensitive enough to detect the impairment in this individual and secondly, parallel versions of visual/recall aspects of the tests should be developed for use pre- and post-surgery with a larger sample to prevent practice effects.

To our knowledge there is only one published pre/post surgery study in the ALF literature, a single case study by Gallassi et al. (2011) who looked at ALF pre- and post-left temporal polectomy in a patient MT. MT was a 58 year old man who experienced

daily seizures and left-frontotemporal pulsating headaches before receiving surgery. He had experienced subjective memory deficits just under a year prior to the surgery, which he reported had been worsening over time. Neuropsychological examination revealed ALF at the one-week delay pre-surgery, which was calculated by averaging forgetting scores (30 minute minus one week) across three tests of verbal and visual memory. The authors retested MT 15 months after surgery and found that ALF had improved on measures of verbal memory but not visual memory. Despite these positive findings, the study was methodologically limited due to the authors using a control group which was not IQ-matched and only using tests of recall and not recognition. They also retested the participant with identical materials pre- and post-surgery which may have confounded the results due to repeated exposure to the testing materials.

Main Aims

The current study aimed to develop the first pre/post surgery group study in ALF, looking to replicate the findings of Gallassi et al. (2011) using a parallel set of verbal and visual ALF testing materials from Elliott (2010). The aim was to explore whether seizure reduction, if established through epilepsy surgery, would ameliorate ALF in the TLE group. We looked to investigate one of the possible causes of ALF outlined by Mayes et al. (2003), namely that seizure activity disrupts the stable environment required for the process of "slow" consolidation, therefore preventing the retention of newly acquired memories over long-delays. Our second aim was to investigate whether repeated recall of the materials ameliorated ALF at either the pre- or post-surgery testing intervals, testing the findings of Jansari et al. (2010).

Hypotheses

1. Pre-surgery participants with TLE will evidence ALF compared to demographically matched controls, which will be evidenced by significant differences between the groups on forgetting scores over the one-week delay.

2. The rate of forgetting post-surgery will improve compared to pre-surgery, evidenced by statistically insignificant group forgetting scores between the TLE and control group over the one-week delay.
3. Repeatedly recalling the verbal story materials at the 30-minute delay will not attenuate ALF in the TLE group pre-surgery, but will attenuate ALF in the TLE group post-surgery.

Method

Design

This study comprised a longitudinal quasi-experimental pre/post-surgery design, using a repeated battery of measures to assess ALF pre- and up to one year post-epilepsy surgery. The project formed the second phase of a larger project looking into ALF in TLE. Some data from the pre-surgery time period were available from a previous study (see figure 1). The ALF materials comprised two parallel sets of visual and verbal testing materials (set A & set B) developed by Elliott (2010). One set presented and tested pre-surgery and the other presented and tested post-surgery. Each set comprised recall and recognition paradigms which were used to test retention of visual scenes and verbal story tests. The presentation of the sets of stimuli was counterbalanced between the participants and controls such that half the participants would receive set A first, and half the participants set B. Targets were distributed evenly throughout the presentations for the visual scenes test.

Setting

This study was conducted in clinics at the Royal Hallamshire Hospital (RHH) in conjunction with the Clinical Psychology Unit at the University of Sheffield. The project was ethically approved by the South Yorkshire Research Ethics Committee (see appendix A). Participants gave informed consent before participating in the project.

Participants

TLE Participants

TLE participants were recruited from the Royal Hallamshire Hospital (RHH). Participants who matched the inclusion criteria were identified by a consultant clinical neuropsychologist. The inclusion criteria required that individuals: a) had a formal diagnosis of TLE, b) Were due to undergo epilepsy surgery, c) spoke English as their first language, d) were aged between 18 and 75, e) were assessed as having a Full Scale IQ above 80 on the Wechsler Adult Intelligence Scale - third edition (WAIS-III; Wechsler, 1997b), and d) were not diagnosed with co-morbid neurological conditions or severe psychiatric illness. A total of twelve participants (six male, six female) were recruited, with seven of these comprising pre-surgery participants previously recruited in Elliott (2010) (see tables 1 & 2 for demographic data). TLE participants permitted us to access additional information about seizure activity through their medical records. This information included age onset of epilepsy, seizure frequency, MRI scan data and current medication use.

Seven of the 12 TLE participants had epilepsy surgery during the study (see table 1) with surgery comprising a left (n =3) or right (n = 4) amygdalo-hippocampectomy, depending on the lateralisation of the patients epileptic activity (established through EEG and MRI data).

Controls

Control participants were recruited via email or poster, either from Sheffield Teaching Hospitals or the University of Sheffield email systems. Potential candidates were provided information sheets and were recruited to the study following completion of the reply slip (see appendix B for information sheet and reply slip). A total of 60 participants were recruited (24 male, 38 female) with 29 of these comprising pre-existing participants from the Elliott (2010) study (see figure 1 for participant pathway).

Background measures collected from the controls at the initial testing appointment included reading derived IQ scores, handedness, psychosocial measures and medical screening questions pertaining to exclusion criteria.

Table 1

TLE and control group demographics: means, standard deviations and t-test

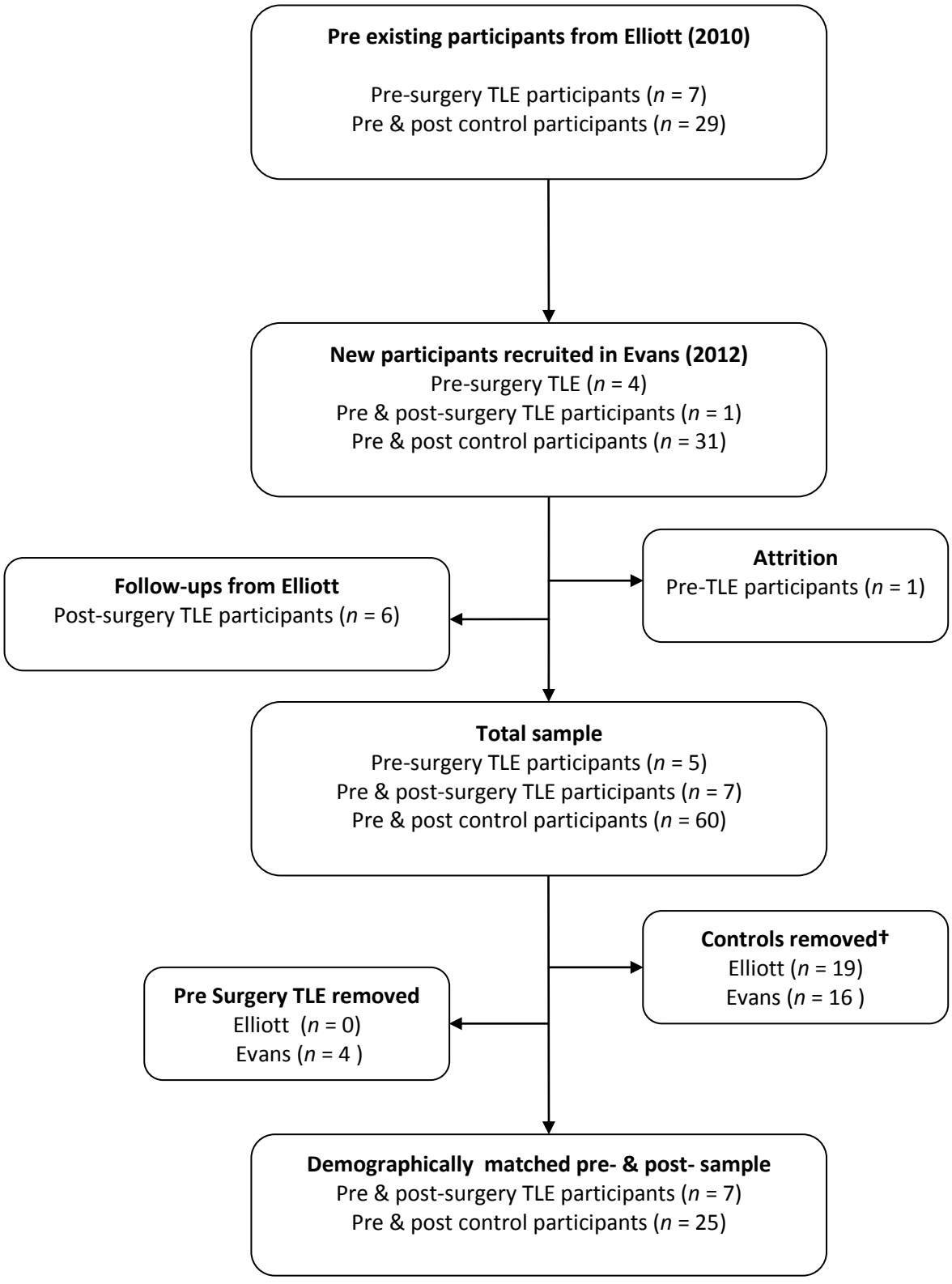
	Group			
	PTLE	Controls	SSCON	PPTLE
N	12	60	25	7
Gender (M/F)	6M, 6F	23M, 37F	12M, 13F	3M, 4F
Age	39.42	38.40	37.10	39.71
IQ	93.83*	105.63*	99.40	94.00
Anxiety (HADS)	8.75	5.80	6.44	10.00
Depression (HADS)	5.08	2.34	3.12	5.14

Table 1: *significantly different to the control group ($p<0.05$)
PTLE = pre-surgery TLE participants
SSCON = subsample of the control group matched for age and IQ
PPTLE = TLE pre/post surgery participants (TLE patients who had epilepsy surgery during the study)

Table 1 indicates that controls and participants with TLE were matched on key variables known to affect forgetting including age, IQ and levels of anxiety/depression. One way analysis of variance (ANOVA) reported significant differences between the groups on reading derived full scale IQ (FSIQ) and years in education. To account for the difference between the groups, a subgroup of 25 control participants (SSCON) was extracted that was well matched with the TLE participants.

Figure 1.

Recruitment pathway for Elliott (2010) and Evans (2012)



† controls removed to ensure demographics matched for age and IQ

Table 2.
Characteristics of TLE Participants

ID	Sex	Age (years)	Education (years)	FSIQ	Age of onset	Duration (years)	Seizure frequency	Seizure types	MRI	Seizure onset EEG	No. of AEDs†
TLE 1	M	41	11	110	2	39	4-6 monthly	CPS, GTCS, Aura	Left MTS	Left	2
TLE 2	F	41	13	82	9 months	40	10-15 monthly	SPS, CPS, GTCS	Left MTS	Left	3
TLE 3	F	57	10	99	47	10	6–7 daily	Auras, GTCS	Left amygdala abnormality, left CD	Left frontal semiology	1
TLE 4	M	54	10	87	7 months	53	7 monthly	NC	<Right HC volume	Right	3
TLE 5	F	21	17	92	17	4+	5-7 monthly	Auras, SPS, CPS, GTCS	Right MTS	Right	2
TLE 6	F	42	16	108	24	18	Every 10-28 days	SPS, CPS	Right HCS	Right	2
TLE 7	M	20	11	85	19	2	1 monthly	CPS	Right MTS	Right	1
TLE 8	F	42	13	113	36	6	4-6 monthly	CPS	Right MTS	Right	2
TLE 9	M	29	14	102	28	1	1 weekly	Absence	Left MTS	Left	1
TLE 10	M	51	11	83	5	40	4-6 monthly	SGN	Unknown	Right	2
TLE 11	M	57	16	108	31	20	1 monthly	NC	Left MTS	Left	3
TLE 12	F	42	12	114	40	2	1 daily	NC	Left HCS	Left	2

MTS = mesial temporal sclerosis; HC = hippocampus; HSC = hippocampal sclerosis; CD = cortical dysplasia; SPS = simple partial seizure; CPS = complex partial seizure; GTCS = generalised tonic clonic seizure; AEDs = antiepileptic drugs †participants in the PPTLE group were on the same number of AEDs at the post-surgery testing interval.

Measures

Primary matching measures

The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001), is a reading task used to measure premorbid functioning comprising 50 words reads aloud from a stimulus card. This measure was used to measure the control group's pre-morbid full scale intelligence quotient (FSIQ). These were then compared to the TLE group's current FSIQ, measured using the Wechsler Adult Intelligence Scale (Wechsler, 1997), for demographical matching purposes. There is evidence of strong correlation between reading ability and intellectual functioning in healthy populations therefore estimated pre-morbid scores were deemed suitable estimates of IQ for the controls.

The Wechsler Adult Intelligence Scale, third edition (WAIS-III; Wechsler, 1997b), is a standardised of intelligence used in neuropsychology settings. Participants in the TLE group completed a WAIS-III up to one year prior to the ALF testing as part of their routine pre-surgery neuropsychological assessment to provide evidence of their current intellectual functioning. The WAIS-III evidences high reliability of average IQ scores (.94-.98) and high content, concurrent and predictive validity (.79-.98).

Additional measures

Seizure diary

Participants in the pre-surgery TLE group were asked to complete a seizure diary over the one-week delay to explore the relationship between frequency of seizures during the delay and ALF. Participants recorded the type of seizure they experienced and the date and time it occurred (see appendix B).

Perceived memory questionnaire

To explore the relationship between perceived memory and ALF, participants were asked to complete a perceived memory questionnaire. Both controls and TLE

groups were asked to fill in whether they felt they had a memory problem (yes/no) and, if so, whether this occurred over the first few minutes, first few hours, first few days or over a number of weeks. Patients with TLE were asked to report when their TLE was diagnosed.

Assessment of mood

Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a clinical tool that comprises 14 forced choice questions measuring levels of anxiety and depression over the past week. Cronbach's alpha reveals that the HADS shows good validity for both the anxiety and depression sub-scales (M = .83).

ALF materials

Visual Scenes test overview

The visual scenes test comprised 618 colour photographs (309 in set A, 309 in set B) displayed singly to the participants using Microsoft PowerPoint presentation software on a Dell net book computer. The visual scenes tests comprised a number of photographs displayed sequentially on the computer screen. Three sub-types of recall test were used: item free recall, spatial free recall, and descriptive free recall; a recognition sub-test was also used. Verbal memory was assessed using free recall and recognition of short stories. To ensure memory for the visual scenes was adequately matched between patients with TLE and the controls, a multiple presentation procedure was used. This involved repeating administration of the visual scenes test immediately after the first presentation for the TLE group.

Visual Scenes Recall

Visual recall was assessed using nine recall scenes which comprised photographs featuring prominent, easily identifiable environments. Each scene included six foreground items, some of which were not natural to the picture to prevent participants guessing items based on the theme of the scene. Three of the nine scenes

were tested at each delay (Immediate, 30 minute & 1 week). Recall performance was assessed using three measures: *item recall* tested how many individual items the participant was able to recall from the scene, with a maximum score of six per scene (eighteen per delay). This included items that were natural to the scene or items added artificially; *visual recall* required the participants to identify the correct location of each remembered item using a recall grid which was split into four numbered quadrants. This also had a maximum score of six per scene (eighteen per delay); *descriptive recall* required the participants to describe what any recalled items looked like or what they/it was doing (if applicable). The maximum score for descriptive recall was twelve points per scene, two per correct item (maximum 36 points per delay).

At presentation each recall scene was preceded with the name of the scene appearing in large black text on the centre of the computer screen. This provided the name of a scene which was followed by the corresponding picture (see figure 2). As the picture of the scene appeared, the top left quadrant was highlighted in yellow for one second, followed by the top right, then bottom left, then bottom right. After all four quadrants had been highlighted the picture of the scene remained on the screen for three additional seconds to allow participants to view the scene without any highlighted quadrants. The series of individual pictures and blank screens would recommence for a further eight pictures. The process repeated nine times in total, covering nine scenes.

Visual Scene Recognition

For presentation of the visual scenes stimuli for recognition a scene (photograph) appeared for one second on the computer screen followed by a blank screen (which also appeared for one second). Three matched recognition sets, containing 50 targets and 50 foils were presented at the three different time points (immediate, 30 minute & one-week delay).

Figure 2.

Detail of the experimental procedure

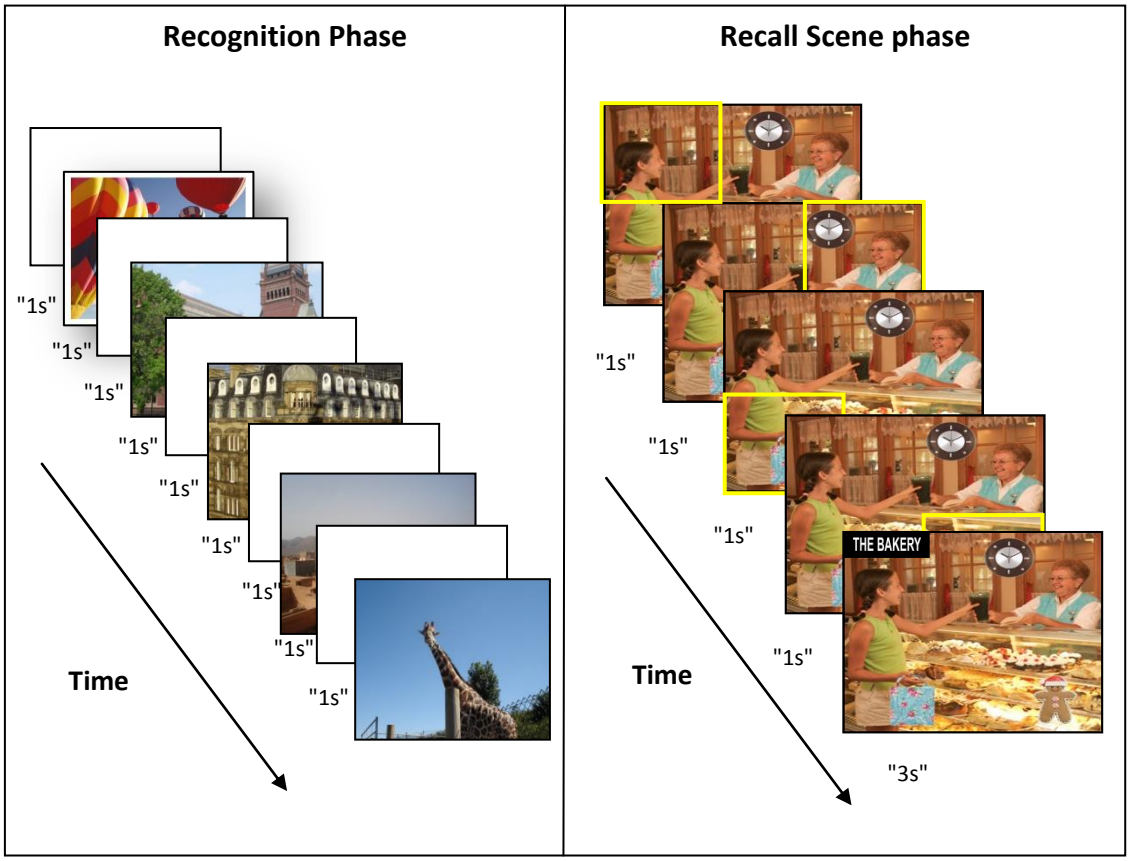


Figure 2. Schematic of the criterial recall and recognitions tests. Note, full recognition phase comprises nine photographs and nine blank screens, figure provides illustrative sequence with five blanks and five photographs. Each full presentation comprises nine sequences of recognition phases, each followed by a recall scene (different pictures and scenes are used for each phase).

Stories test overview

The story test comprised three stories each containing twenty information units matched for difficulty and length. The stories were previously recorded by a researcher in the department (GE) onto a Windows Media Audio File (WMF) and were played to the participants through a net book computer. The order of presentation of the stories was counterbalanced to minimise the possibility of order effects and a multiple presentation procedure was adopted as with the visual scenes test to ensure that initial learning was matched. This meant that TLE participants were played each story twice whereas controls were played each story just once. To prevent the participants from rehearsing the target story and to examine the effects of repeated rehearsal on ALF, only

the first story was recalled at all three delays. The remaining two stories were played at either the immediate and 30 minute delay or the immediate and one week delay (depending on the counterbalancing schedule).

Story Recall

Participants were asked to recall as much as the story as possible and scored a point if they remembered the actual words for each unit or a paraphrased the exact meaning of the words.

Story Recognition

The story recognition task comprised a twelve-question forced choice assessment procedure, with four possible answers to each of the twelve questions (e.g. what was the name of the boy, Wesley Mannningham, Wesley Massingham, Warren Massingham, Warren Manningham). The twelve questions were asked after each recall trial at each delay and the answer was positioned randomly for each question to prevent the participant from correctly guessing the same position each time. The questions were presented in chronological order so that earlier answers did not cue later responses.

Procedure

Participants were offered appointments at the RHH or at the University of Sheffield Clinical Psychology Unit. Home visits were also offered to reduce inconvenience caused by the testing procedure, which took place over four sessions, the initial session lasting around 1.5 hours and the one week follow up lasting around 20 minutes. The process was then repeated approximately six months after the initial testing sessions for the controls or at least six month post-surgery for the TLE group. This was to allow a sufficient post-surgical recovery for the TLE group. The first session comprised the initial presentation of the stimuli followed by testing the participants' recall and recognition at immediate and 30-minute delays. The HADS, WTAR and perceived memory questionnaire were completed and participants in the

TLE group were asked to fill in a seizure diary for the next week. The second testing session was used to assess the participants' memory after a one week delay.

Visual Scenes Test

The Administration of the visual scenes task was preceded by a practice trail, comprising one recall and eight recognition scenes, which followed the same testing procedure as the subsequent experimental trial. Participants were shown the following instructions before the practice presentation and again before the full initial presentation:

"You are about to see lots of pictures; your recognition for which will be tested. Each picture will appear for one second. During this time, you should name an object in the picture. So, if the picture has a car in it, just say "car." Some pictures appear five times in a row. One section will be outlined at a time - please name something in each of the outlined parts. These scenes have names. Read these aloud and remember them. You will later be asked to recall the parts of these pictures in detail."

Following the initial presentation the participants completed a 45 second distraction task which comprised a number appearing in large font on the screen which they were required identify as odd or even. The participants were then taken through either the visual scenes recall or recognition data collection procedure, the order of which was dependent on the counterbalancing procedure assigned to each participant number (see appendix B for counterbalancing ordering). Recall data was collected by asking participants to remember as much as they could about one of the nine visual scenes, for example:

"Can you tell me what was in the Car Boot Scene"

Participants were then asked to indicate where each previously recalled item was on a spatial recall grid (see appendix B for example grid). Following spatial recall the participants were asked to describe what any previously recalled items looked like. For

the visual scenes recognition test participants were shown another PowerPoint presentation which was preceded by the following instruction on screen:

"You will now see a series of pictures. You need to decide whether or not you have seen the picture before. Answer yes or no."

Answers were recorded as a hit (correct) or a false positive (incorrectly identifying an item as one that has been seen already on a recording sheet (see appendix B for exemplar form).

Stories Task

Free recall assessed the participants' ability to recount as much of the stories as possible without additional cueing or prompting. Participants were given the following instructions:

"I am going to play you three stories, one at a time. I want you to listen to each story and remember what happens in it. Try to remember the main points. After each story ends you will be asked to tell me as much as you can remember about the story. Pay special attention to the first story as I will be most interested in your memory for this one and will ask you about it again later today and next week."

Following the initial presentation participants were asked to think about the story for twenty seconds following each presentation (or after the second presentation for the TLE group) to match the immediate delay period across the participants. Note, although the participants were told to pay particular attention to the first story, the target stories were actually those tested at the 30 minute and one week delay.

Following each immediate recall task, participants were asked to complete the recognition task which required that they provide a verbal answer to twelve multiple choice questions read by the researcher about the story they has just heard. Participants were asked to wait until all of the potential answers were given before answering to ensure similitude between the presentation procedures.

Statistical Analysis

Data were analysed using IBM SPSS 20.0 for Windows (licence purchased from University of Sheffield). Descriptive statistics were produced and data were checked for normality, skewedness, floor and ceiling effects and outliers. Data were transformed using logarithm transforms in SPSS if data were not normally distributed. Bonferroni adjustment was used where multiple comparisons were made to reduce the likelihood of type-1 errors occurring.

Corrected measures

Descriptive free recall was calculated using %*d*, (s) a corrected measure which takes into consideration the number of items recalled when calculating descriptive information, which was developed by Muhlert et al. (2011). Visual scene recognition scores were analysed using signal detection theory (Macmillan and Creelman, 1991) which uses the number of hits (correctly identified items) and false positives (falsely identified items) to calculate an index of accuracy based on (d') scores (see appendix C for additional information for both corrected measures).

Group analysis

Independent samples t-tests were used to compare immediate memory performance between the control and TLE group to ensure initial learning was equated. This was performed at both pre- and post-surgery intervals to ensure consistency at both time points. An omnibus multiple analysis of variance (MANOVA) was used with the pre-surgery data to find any significant differences between the immediate and 30 minute and one-week delays. Split-plot analyses of variance were then used to look for significant group differences in forgetting rates between the TLE and control group for each of the individual experimental measures.

To investigate within group ALF pre- and post-surgery, paired sample t-tests of change scores were used. Change scores were obtained by subtracting the scores at the

one-week delay from the scores at the 30-minute delay, with a lower score representing fewer items lost over that delay. For the Long Delay Story Recall/Recognition tests the scores were calculated by subtracting the immediate scores from the one-week scores.

Pearson's bivariate correlations were used to measure the strength of the association between clinical measures deemed pertinent to forgetting. Due to multiple correlations being made a more stringent alpha level of .01 was applied to correlational statistics.

Individual analyses

Individual analysis was carried out by calculating the percentage of TLE and control participants who evidenced impaired retention over the 30 minute and one-week delay (calculation from Bell et al., 2005). Participants were considered impaired if they evidenced forgetting greater than 1.96 standard deviations from the mean of the control group (equivalent to a .05 alpha level).

Sample size calculations

The target sample size for a repeated measures split-plot ANOVA was 28 based on the sample required to detect a large effect size between the TLE group and the controls at an alpha level of .05 and 80% power (Cohen, 1992).

Results

Data checking

Tests of normality revealed non-normally distributed data for all of the ANOVA analyses as tested by the Shapiro-Wilk test. Data found violating this testing assumption was transformed using the SPSS data transform function. The specific transform function applied was dependent on the skew of the data. Due to the small sample sizes outliers (calculated as "difference" scores that are more than 1.5 box-lengths from the edge of their box) were not removed from the data set and on inspection no outliers were considered extreme (more than 3 box-lengths away from the edge of their box). Where necessary the Greenhouse Geisser correction was applied to identify and correct sphericity in the data.

Group Analyses

To ensure initial learning was adequately matched between the TLE and control participants, independent sample t-tests were used to compare performance on the eight test variables at the immediate delay. This was performed at both pre- and post-surgery assessments to ensure initial matching was achieved. Table 3 reports no significant differences between the groups on six of the eight variables pre-surgery, with the exception of visual recognition and repeated story recognition. Independent samples t-tests were run at the 30-minute delay on data from these tests and found no significant difference between the TLE and control group $t(30) = -.85$, $p > .05$ and $t(30) = -1.79$, $p > .05$ respectively, therefore pre-surgery materials appeared to be adequately matched at the short delay for these tests. On these grounds we decided to proceed with the analysis of this test. When the t-tests were re-run post-surgery they revealed significant mean differences between the groups on all four story tests. Additional analysis of these results have been included as the effects on rate of forgetting following epilepsy surgery was still considered to be valuable even if initial learning was not matched.

Table 3

Immediate recall and recognition scores for visual and verbal test scores at pre surgery and post surgery

	Pre TLE		Pre CON		Pos TLE		Pos CON	
Variable	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Visual scenes								
Item recall	13.86	4.30	15.40	2.45	11.43	6.50	15.28	2.49
Visual recall (z')	6.37	1.04	6.23	1.68	5.56	2.23	6.59	0.77
Descriptive recall (s)	71.66	18.60	78.34	10.47	69.21	18.53	80.50	10.55
Visual Recog (d')	2.91*	0.96	4.02*	0.53	3.44	0.96	3.44	0.92
Verbal stories								
Story Recall	11.57	5.16	11.28	4.47	7.86*	4.77	12.04*	3.10
Story Recog	9.57	1.13	9.84	1.60	8.14*	2.19	10.20*	2.08
Repeated story recall	10.71	3.03	12.36	3.33	8.14*	3.62	13.04*	3.42
Repeated story recog	8.14*	2.12	9.92*	1.73	7.85*	2.27	9.64*	1.97

Data from six experimental tests were initially entered into a multivariate repeated measures analysis of variance MANOVA with factors delay (immediate, 30 minute & one week) and group (TLE & Control). The MANOVA run with the pre-surgery data found a significant delay-by-group interaction, Pillai's trace = 0.286, $F(2,29) = 5.797$, $p < .05$, $\eta^2_p = .286$, indicating that forgetting differed significantly between the groups at the pre-surgery testing interval. When the MANOVA was rerun post-surgery the delay-by-group interaction did not reach statistical significance, Pillai's trace = 0.069, $F(2,29) = 1.082$, $p > .05$, $\eta^2_p = .069$. We felt it was important to explore the results from the individual sub-tests post-surgery given the variation observed post-surgery by Gallassi et al. (2011) and the exploratory nature of this research. The MANOVA was also run pre-surgery with the addition of the five patients with TLE

who did not have epilepsy surgery during the study (PTLE group). The MANOVA found a significant delay-by-group interaction, Pillai's trace = 0.253, F (2,34) = 5.747 , $p < 0.05$, $\eta^2_p = .253$, indicating that forgetting differed significantly between the PTLE group and the controls.

Visual Scenes tests

Item free recall

The ANOVA run with the pre-surgery data found a main effect of group approaching significance $F(1,30) = 4.077$, $p = .052$, $\eta^2_p = .120$, a significant main effect of delay $F(2,60) = 43.288$, $p < .001$ $\eta^2_p = .591$, but no significant delay-by-group interaction $F(2,60) = 0.831$, $p > .05$, $\eta^2_p = .027$. This indicates that both groups forgot more information over time but that this was at a comparable level over the three delays. When the ANOVA was rerun with post-surgery data it revealed a significant main effect of group $F(1,30) = 7.193$, $p < .05$ $\eta^2_p = .193$, a significant main effect of delay $F(1.483,44.498) = 16.681$, $p < .001$, $\eta^2_p = .357$, and as at pre-surgery, no significant delay-by-group interaction $F(1.483,44.498) = 0.144$, $p > .05$, $\eta^2_p = .005$ (see figure 2).

Figure 2

Pre- and post-surgery comparison of mean item free recall scores on the visual scenes test

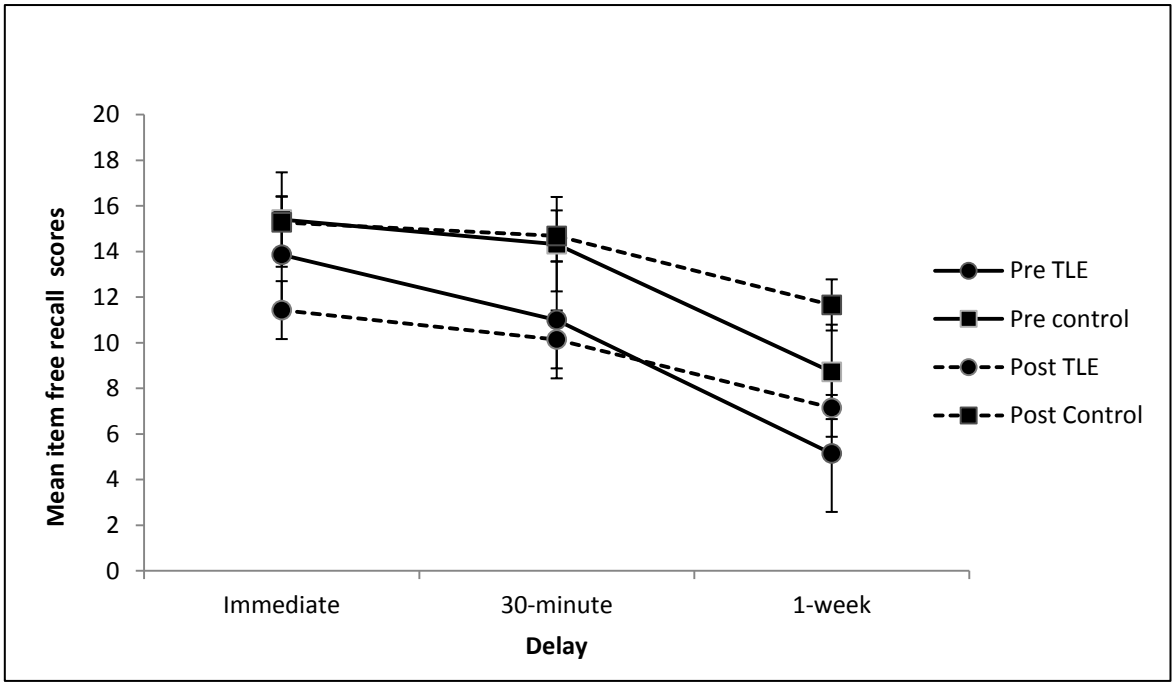
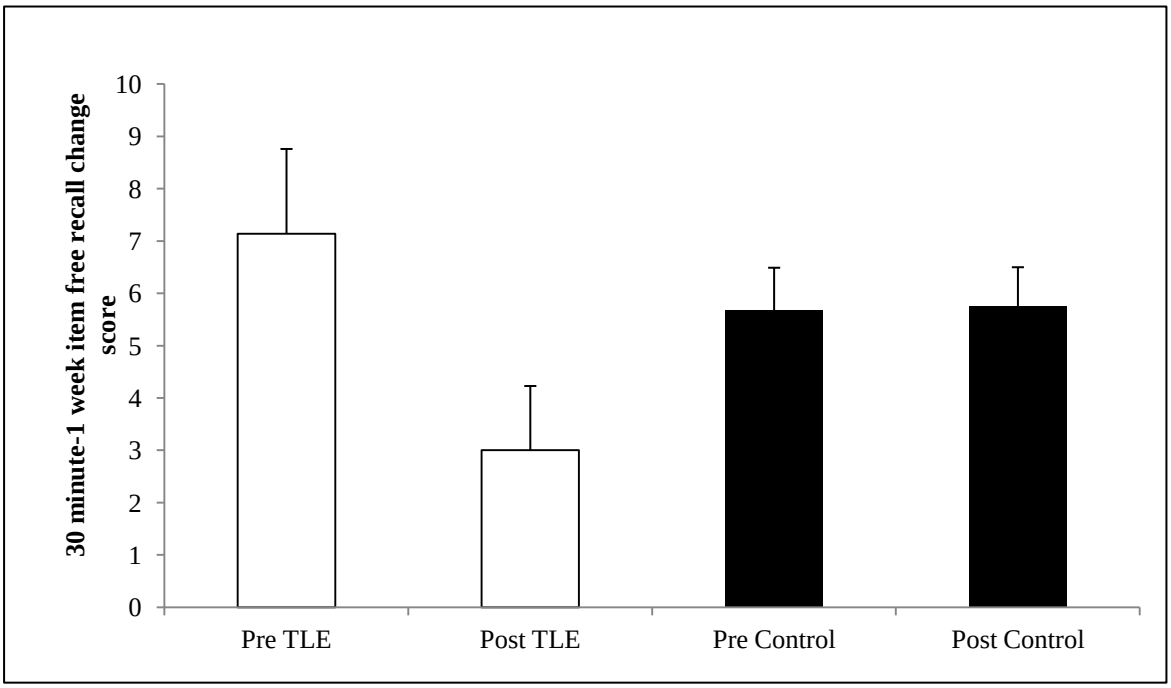


Figure 3

Pre- and post-surgery comparison of 30 minute to one week item free recall change scores on the visual scenes test



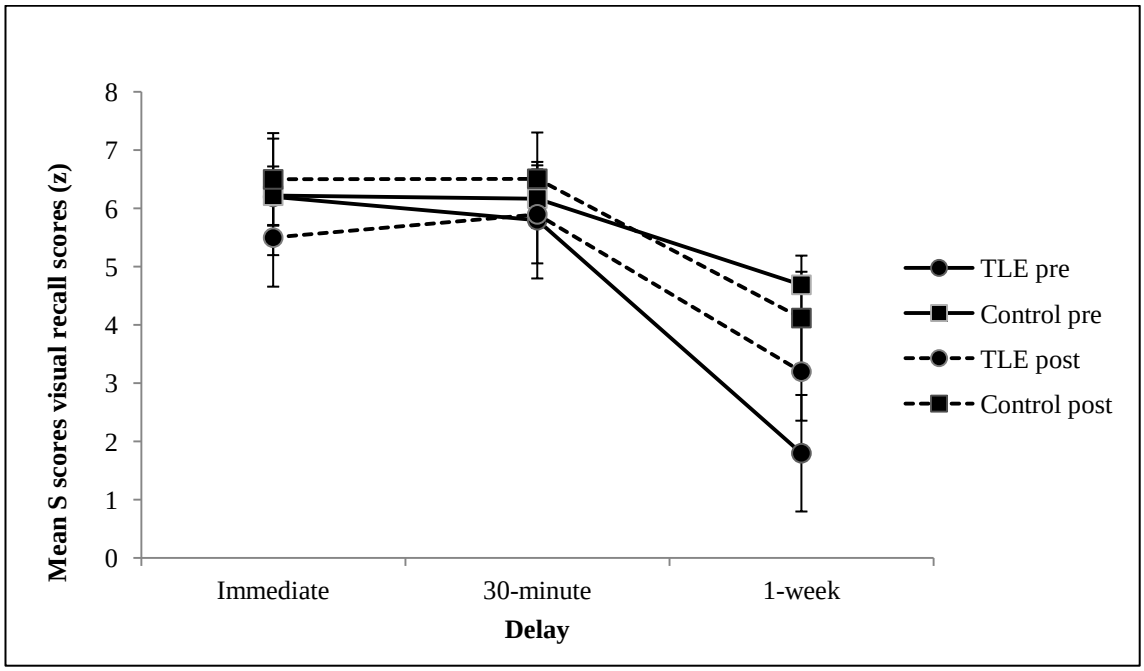
Visual free recall

Split-plot ANOVAs were used to compare visual recall between the groups (TLE & Control) at the three delays (immediate, 30 minute & one week) pre- and post-surgery. The ANOVA at the pre-surgery testing interval found a significant main effect of group $F(1,30) = 4.384$, $p < .05$ $\eta^2_p = .127$, a significant main effect of delay $F(1.353,40.599) = 30.235$, $p < .001$ $\eta^2_p = .502$, and a significant delay-by-group interaction $F(1.353,40.599) = 6.890$, $p < .05$ $\eta^2_p = .187$. Analysis of paired contrasts revealed no significant interaction between the immediate and 30-minute delay $F(1, 30) = 0.521$, $p > .05$, $\eta^2_p = .029$. However, a significant interaction was found over the 30 minute and one-week delay $F(1, 30) = 11.265$, $p < .05$, $\eta^2_p = .273$. This indicates that forgetting was accelerated in the TLE group over the longer delay. When the ANOVA was rerun at the post-surgery testing interval it found a significant main effect of delay

$F(1.631, 48.938) = 54.447$, $p < .001$ $\eta^2_p = .594$, but no main effect of group $F(1, 30) = 2.770$, $p > .05$, $\eta^2_p = .085$, and no significant delay-by-group interaction $F(1.631, 48.938) = 0.268$, $p > .05$ $\eta^2_p = .009$. This indicates that the TLE group were not evidencing ALF post-surgery (See figure 4).

Figure 4

Pre- and post-surgery comparison of mean visual recall memory scores (z) for the TLE and control groups of the visual scenes test

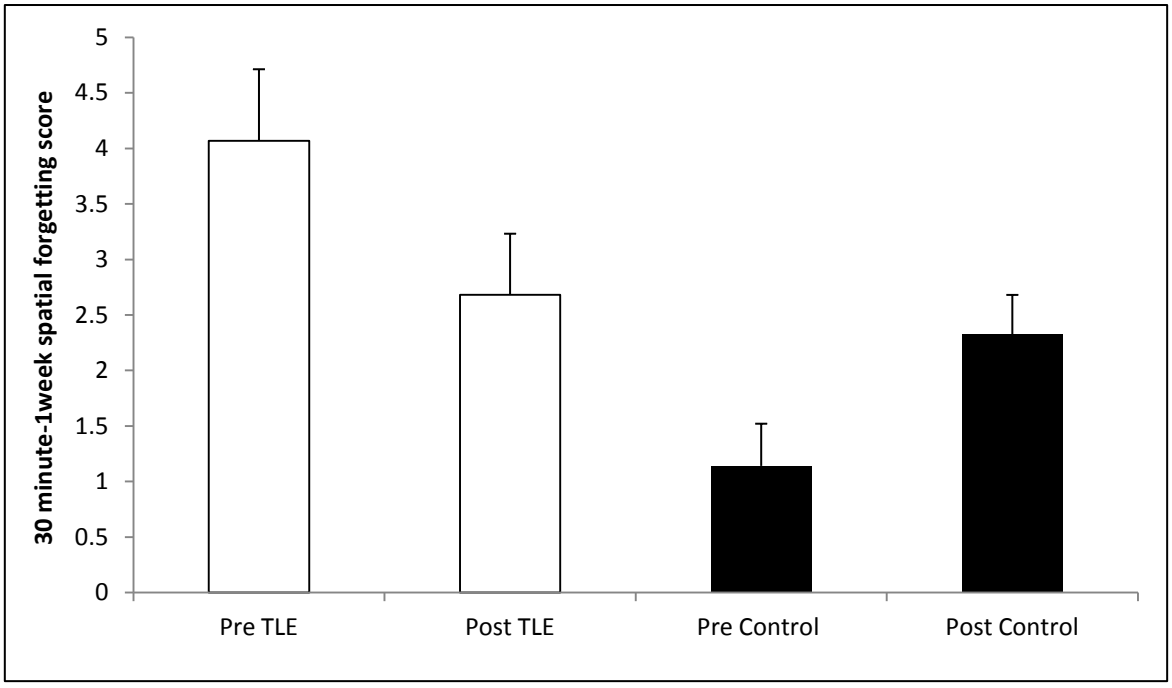


Paired sample t-tests were used to identify any statistically significant differences in change scores for visually recalled (spatially discriminated) material between the pre- and post-surgery assessments. Participants in the TLE group correctly retained numerically more spatial information between the 30 minute and one-week delay post-surgery ($M = 2.68$, $SD = 1.45$) compared to pre-surgery ($M = 4.07$, $SD = 1.71$). This constitutes a small but not statistically significant improvement in spatial recall (*s*) 95% CI [-.44, 3.21], $t(6) = 1.854$, $p > .113$, $d = 0.7$. Participants in the control group did not correctly identify more spatial information between 30 minutes and one

week post-surgery (M = 2.046 , SD = 1.370) compared to pre-surgery (M = 1.149, SD = 1.899) 95% CI [-1.913, 0.138] $t(24) = -1.793$, $P > .05$, $d = -.366$ (see figure 5).

Figure 5

Pre- and post-surgery comparison of 30 minute to one week mean visual recall (z) change scores on the visual scenes test



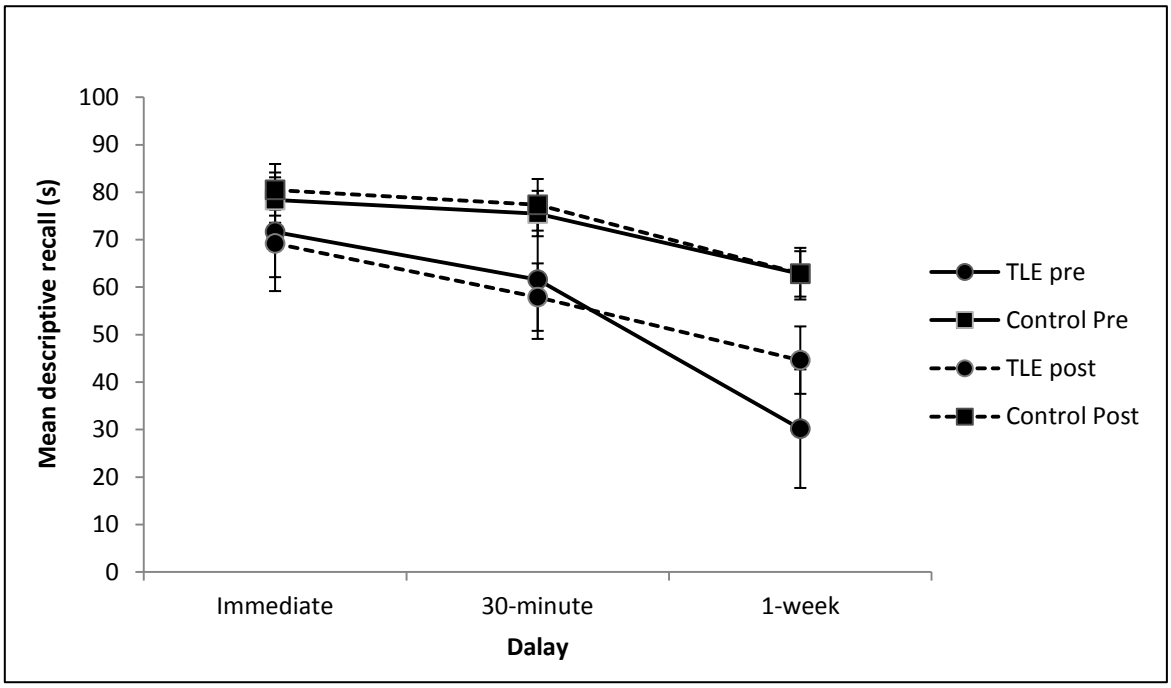
Descriptive free recall

Split plot repeated measures ANOVAs were used to compare the groups at the three delays (immediate, 30minute & one week) pre and post-surgery. The ANOVA comparing the groups at pre-surgery found a significant main effect of group $F(1,30) = 12.783$, $p < .01$, $\eta^2_p = .299$, a significant main effect of delay $F(1.528, 45.826) = 23.448$, $p < .001$, $\eta^2_p = .439$, and a significant delay-by-group interaction $F(1.528, 45.826) = 4.688$, $p < .05$, $\eta^2_p = .135$. Analysis of the contrasts between the pairs of delays found no significant interaction between the immediate and 30-minute delay $F(1,30) = 1.540$, $p > .05$, $\eta^2_p = .49$. However an interaction approaching significance was found between the 30 minute and one-week delay $F(1,30) = 3.479$, $p = .072$, $\eta^2_p = .104$, and a significant interaction was found between the immediate and one-week

delay $F(1,30) = 7.102$, $p < .05$, $\eta^2_p = .191$. This indicates that the TLE participants were evidencing ALF between the immediate and one-week delay pre-surgery. When the ANOVA was rerun post-surgery it revealed a significant main effect of delay $F(1.60, 48.912) = 16.746$, $p < .001$, $\eta^2_p = .358$, a significant main effect of group $F(1, 30) = 7.469$, $p < .05$, $\eta^2_p = .199$, but no significant delay-by-group interaction $F(1.60, 48.912) = .702$, $p = .05$ $\eta^2_p = .023$. This shows that TLE group were not evidencing ALF post-surgery (see figure 6).

Figure 6

Pre- and post-surgery comparison of mean descriptive free recall (s) scores for the TLE and control group on the visual scenes test

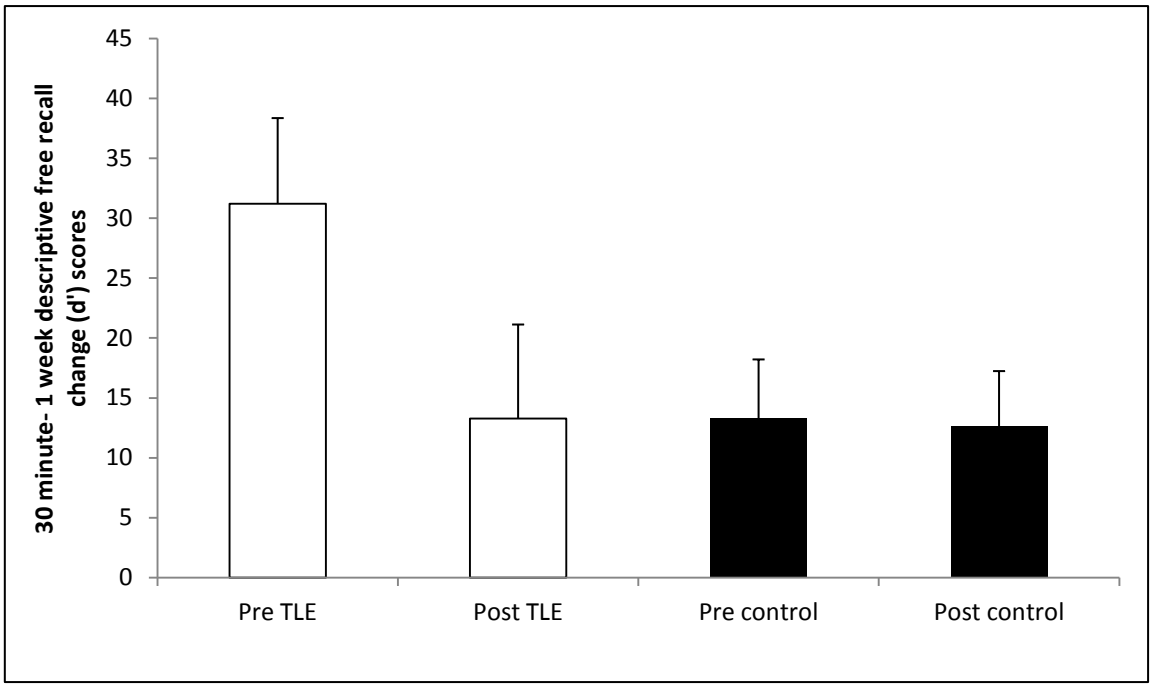


Paired sample t-tests were used to identify any statistically significant differences in change scores for descriptive recall between the pre- and post-surgery assessments. Participants in the TLE group recalled more descriptive information between the 30 minute and one-week delay post-surgery (M=31.19, SD = 18.91) compared to pre-surgery (M= 13.27, SD = 20.76). This constitutes a non-significant

improvement in descriptive recall (*d*) in the post-surgery group of 11.08, 95% CI [-9.00, 44.75], $t(6) = 1.635$, $p > .05$, $d = 0.62$. Participants in the control group did not correctly identify more descriptive information post-surgery compared to pre, $t(24) = 0.96$, $p > .05$, $d = 0.36$ (see figure 7).

Figure 7

Pre- and post-surgery comparison of 30 minute and one week descriptive free recall (s) change scores on the visual scenes test



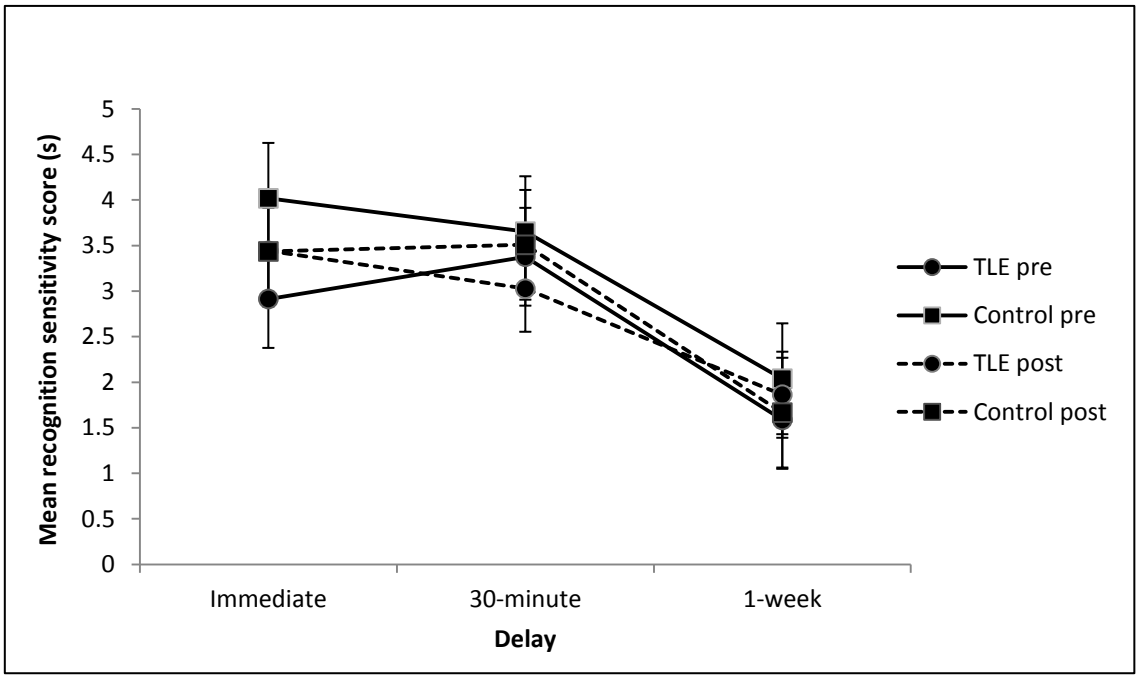
Visual recognition

Using d' scores two split-plot ANOVAs were run over the three delays pre- and post-surgery. The pre-surgery ANOVA revealed a significant main effect of group $F(1,30) = 6.144$, $p < .05$ $\eta^2_p = .170$, a significant main effect of delay $F(2,60) = 60.332$, $p < .001$ $\eta^2_p = .668$, and a delay-by-group interaction approaching significance $F(2, 60) = 2.668$, $p = .54$ $\eta^2_p = .093$. When the ANOVA was rerun post-surgery it found a significant main effect of delay $F(1.629, 46.754) = 23.805$, $p < .001$ $\eta^2_p = .442$. However it revealed no significant main effect of group $F(1, 30) = 0.122$, $p > .05$, $\eta^2_p =$

.004, and no significant delay-by-group interaction $F(1.629, 46.754) = 0.821$, $p > .05$ $\eta^2_p = .28$. This indicates that the TLE group were not experiencing ALF post-surgery (see figure 8).

Figure 8

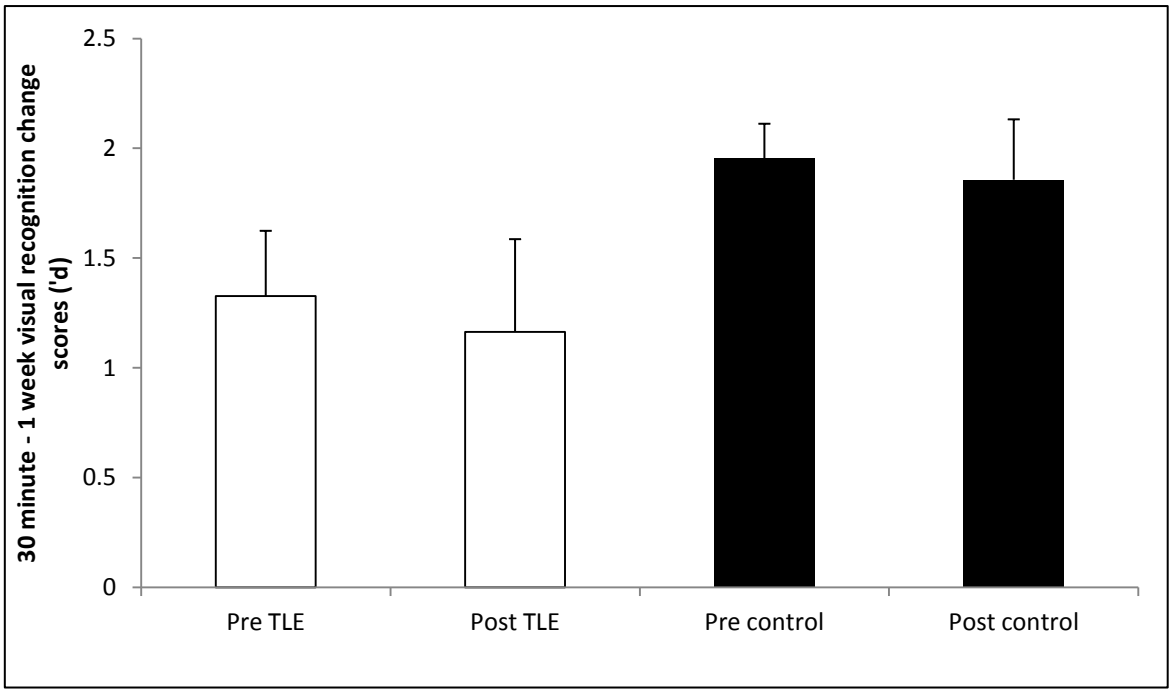
Pre- and post-surgery comparison of mean visual recognition (d') scores on the visual scenes test



Paired sample t-tests were used to identify any statistically significant differences in change scores for visual recognition between the pre- and post-surgery assessments. Participants in the TLE group correctly retained more items from the visual recall task between the 30 minute and one week post-surgery ($M = 1.16$, $SD = 1.12$) compared to pre-surgery ($M = 2.12$, $SD = 1.19$). This indicates that participants were more accurate at identifying items post surgery, with an increase in d' of .95 which was approaching statistical significance, 95% CI [-.50, 1.97], $t(6) = 2.325$, $p < 0.59$, $d = 0.87$. Participants in the control group did not correctly recognise more visual information post-surgery compared to pre, $t(24) = .296$, $p > .05$, $d = 0.059$ (see figure 9).

Figure 9

Pre- and post-surgery comparison of 30 minute to one week visual recognition change scores ('d) on the visual scenes test



Stories tests

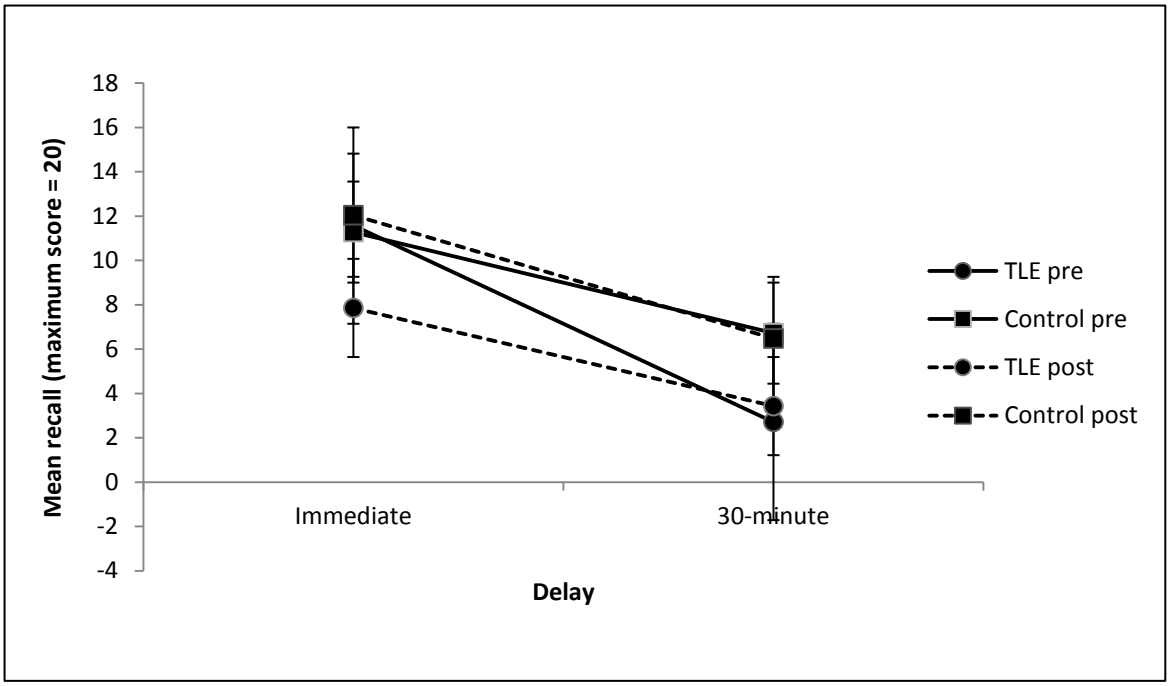
Story recall

A split plot repeated measures ANOVA comparing story recall over the one-week delay at the pre-surgery assessment found no significant main effect of group $F(1,30) = 1.401$, $p > .05$, $\eta^2_p = .45$, a significant main effect of delay $F(1,30) = 91.433$, $p < .001$, $\eta^2_p = .753$, and a significant delay-by-group interaction $F(1,30) = 9.379$, $p < .05$, $\eta^2_p = .238$, indicating that the TLE group were experiencing ALF over one week. When the analysis was rerun with the post-surgery data it revealed a significant main effect of group $F(1,30) = 6.576$, $p < .05$, $\eta^2_p = .180$, a significant main effect of delay $F(1,30) = 62.506$, $p < .001$, $\eta^2_p = .676$, but no significant delay-by-group interaction

$F(1,30) = 0.802$, $p > .05$, $\eta^2_p = .026$. This indicates that the TLE group were no longer experiencing ALF post-surgery (see figure 10).

Figure 10

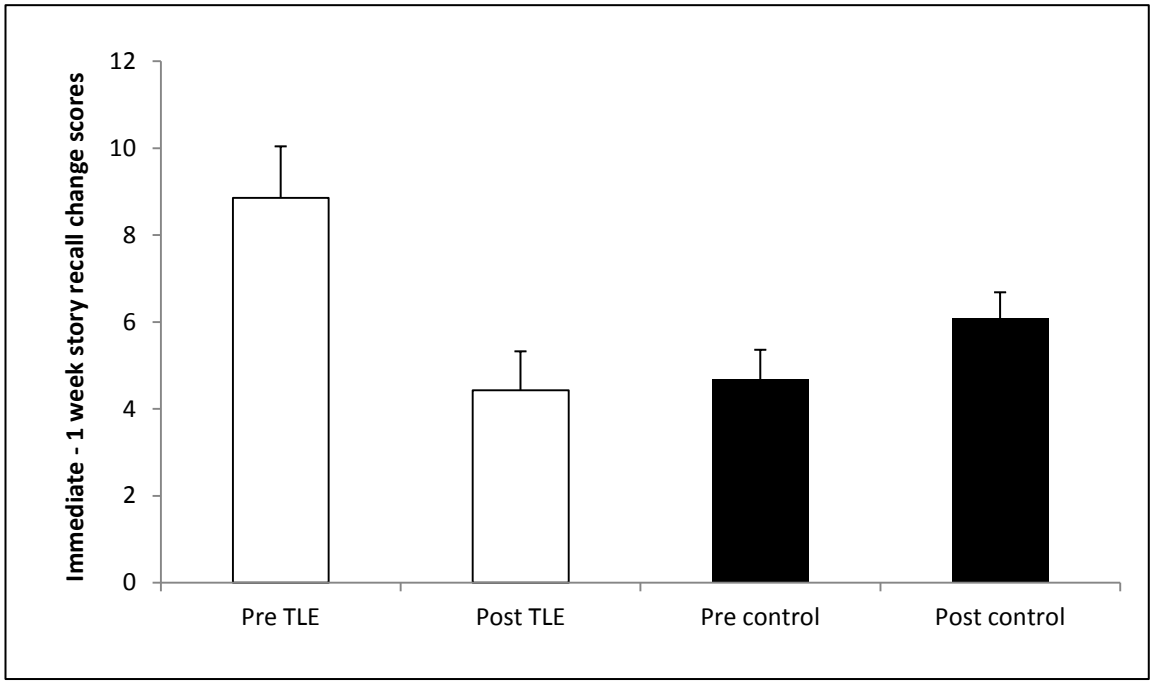
Pre- and post-surgery comparison of mean 30 minute to one week recall scores on the verbal story test



Paired sample t-tests were used to identify any statistically significant differences in change scores for verbal story recall between the pre- and post-surgery assessments. Participants in the TLE group correctly recalled more story items over the one-week delay following surgery, as evidenced by a lower post-surgery change score ($M = 4.43$, $SD = 2.37$) compared to pre-surgery ($M = 8.86$, $SD = 3.13$). This constitutes a statistically significant increase of 4.43 items, 95% CI [2.17, 6.68], $t(6) = 4.80$, $p < .003$, $d = 1.82$. The control group did not recall significantly more items post-surgery compared to the pre-surgery, recalling a non-statistically significant 1.4 fewer items post surgery, 95% CI [-3.003, 0.203], $t(24) = -1.802$, $p > .05$, $d = -0.360$ (see figure 11).

Figure 11

Pre- and post-surgery comparison of immediate to one week recall change scores on the verbal stories test

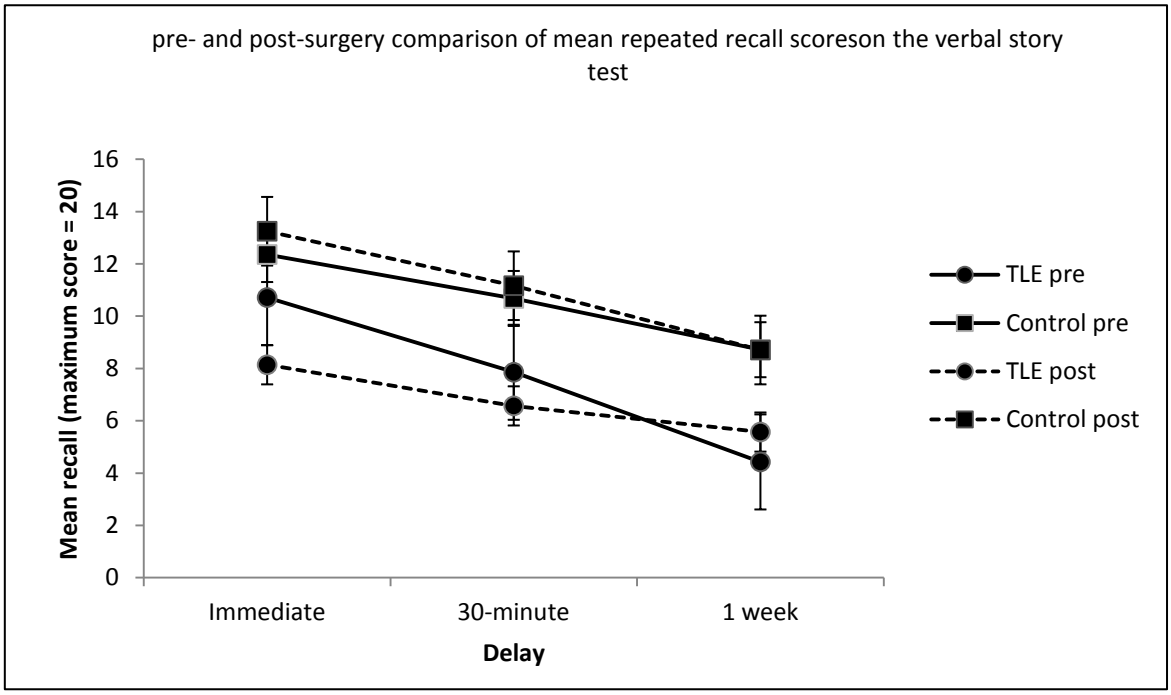


Repeated story recall

Split plot ANOVAs comparing story recall over the three delays were used to explore the effect of repeated recall at the 30-minute delay. The ANOVA run with pre-surgery data found a significant main effect of group $F(1,30) = 6.488$, $p < .05$, $\eta^2_p = .178$, a significant main effect of delay $F(1.757, 52.717) = 38.692$, $p < .001$, $\eta^2_p = .563$, and a delay-by-group interaction approaching significance $F(1.757, 52.717) = 2.753$, $p = .079$, $\eta^2_p = .084$. When the ANOVA was run at the post-surgery testing interval it found a significant main effect of group $F(1,30) = 8.755$, $p < .05$, $\eta^2_p = .226$, a significant main effect of delay $F(2, 60) = 67.990$, $p < .001$, $\eta^2_p = .440$, and no significant delay-by-group interaction $F(2, 60) = 1.93$, $p > .05$, $\eta^2_p = .062$.

Figure 12

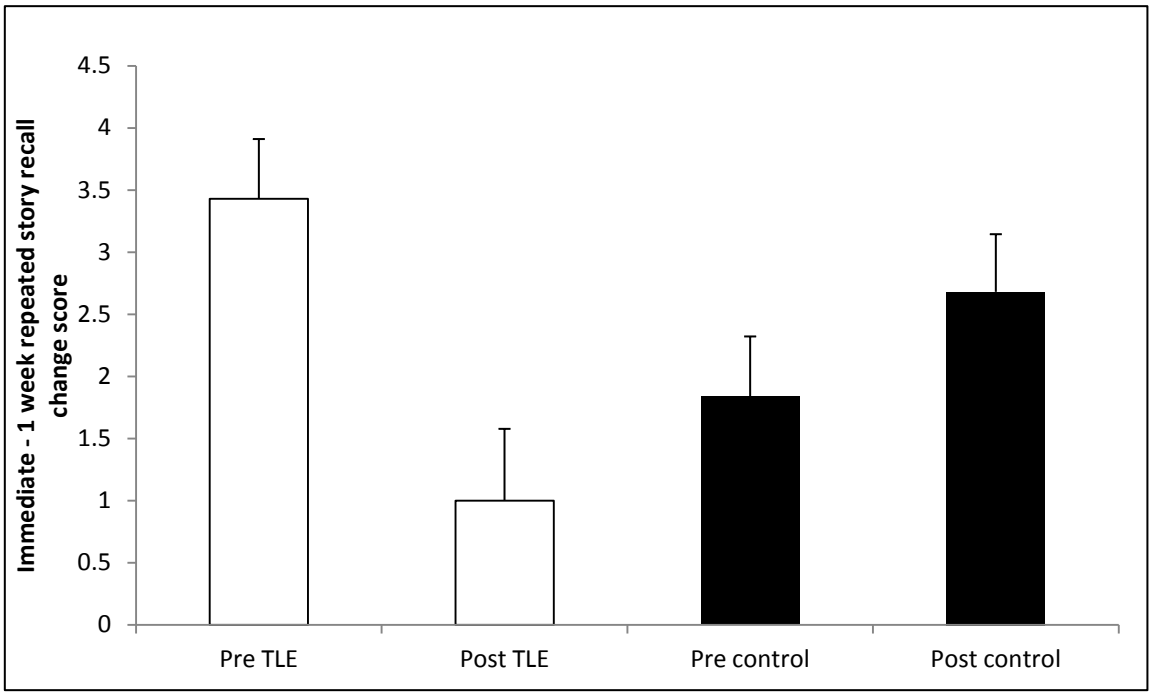
Pre- and post-surgery comparison of mean repeated recall scores on the verbal story test



Paired sample t-tests were used to identify any statistically significant differences in change scores for repeated story recall between the pre- and post-surgery assessments. Participants in the TLE group correctly recalled more story items over the one-week delay post-surgery when the information was repeated recalled, as evidenced by a lower change score (M = 1.00, SD = 1.53) compared to pre-surgery (M = 3.43 , SD = 1.27). This constitutes a statistically significant increase of 2.43 items, 95% CI [1.03, 3.83], $t(6) = 4.25$, $p < .005$, $d = 1.61$. The control group did not recall more story items post-surgery (M = 2.541, SD = 2.484) compared to pre-surgery (M = 1.833, SD = 2.220), this constitutes a non significant decrease of -0.708 items remembered over the two assessments, 95% CI [-2.381, 0.964], $t(24) = -.876$, $p < .005$, $d = -0.179$ (see figure 13).

Figure 13

Pre- and post-surgery comparison of repeated rehearsal change scores on the verbal story test



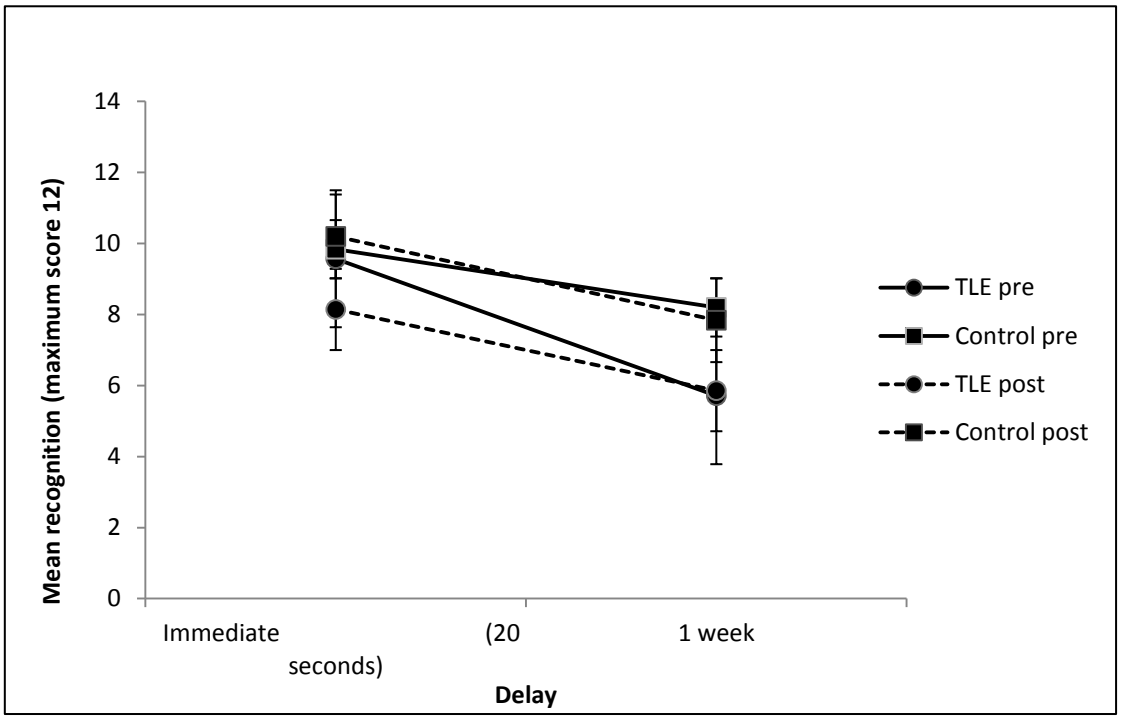
Story recognition

Split plot ANOVAS were used to identify any statistically significant group differences over the 30 minute and one-week delay at the pre and post-surgery assessment for story recognition. The ANOVA run on the pre-surgery data found main effect of group approaching significance $F(1, 30) = 3.473$, $p = .072$, $\eta^2_p = .104$, a significant main effect of delay $F(1, 30) = 50.273$, $p < .001$, $\eta^2_p = .626$, and a significant delay-by-group interaction $F(1, 30) = 8.178$, $p < .05$, $\eta^2_p = .214$. This indicates that the TLE participants experienced ALF over the long delay pre-surgery. When the ANOVA was rerun with data from the post-surgery assessment it found a significant main effect of group $F(1, 30) = 5.180$, $p < .05$, $\eta^2_p = .147$, a significant main effect of delay $F(1, 30) = 28.285$, $p < .001$, $\eta^2_p = .485$. However, the delay-by-group

interaction was no longer significant $F(1, 30) = 0.993$, $p > .05$, $\eta^2_p = .000$. This indicates that the TLE group were not experiencing ALF post-surgery (see figure 14).

Figure 14

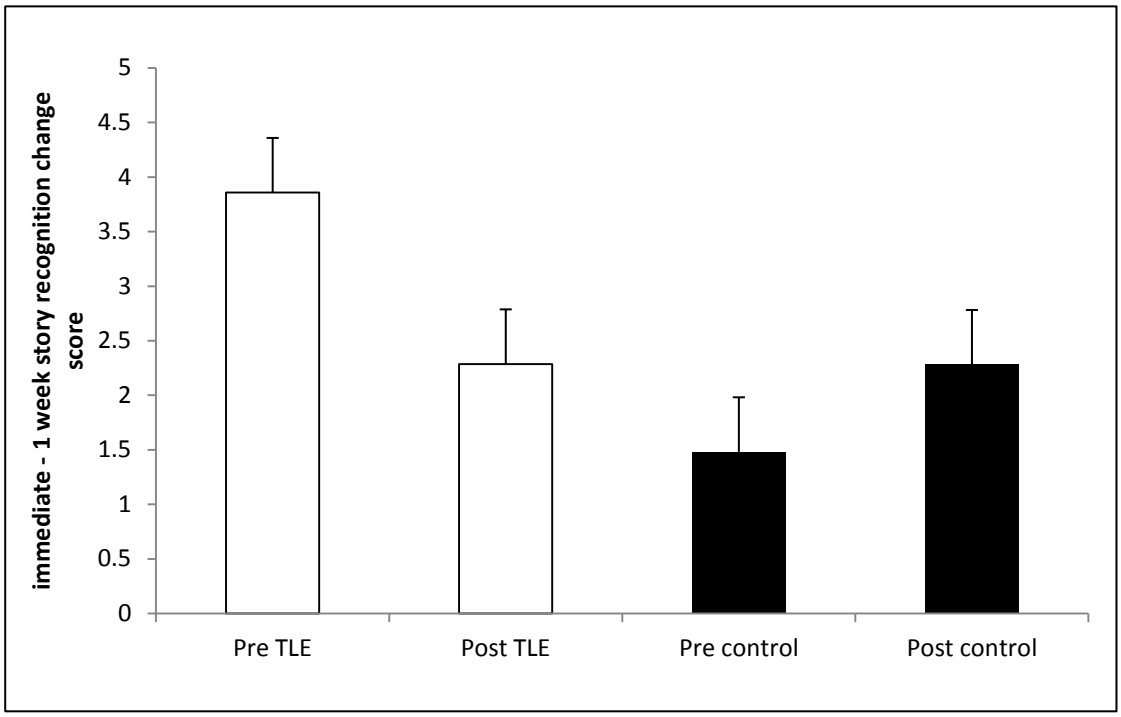
Pre- and post-surgery comparison of mean 30 minute to one week recognition scores on the verbal story test



Paired sample t-tests were used to identify any statistically significant differences in change scores for story recognition between the pre- and post-surgery assessments. Participants in the TLE group correctly identified slightly more items following epilepsy surgery ($M = 2.286$, $SD = 1.976$) compared to pre-surgery ($M = 3.857$, $SD = 2.340$). This constitutes a non-statistically significant increase of 1.571 items 95% CI [-1.091, 4.234], $t(6) = 1.444$, $p > .05$, $d = 0.546$. Participants in the control group recognised slightly less items post-surgery ($M = 2.288$, $SD = 2.189$) compared to pre-surgery ($M = 1.480$, $SD = 1.686$), a non-statistically significant decrease of -0.800 items 95% CI [-1.825, 0.225], $t(24) = -1.611$, $p > .05$, $d = -0.322$ (see figure 15).

Figure 15

Pre- and post-surgery comparison of immediate to one week recognition change scores for the verbal story test



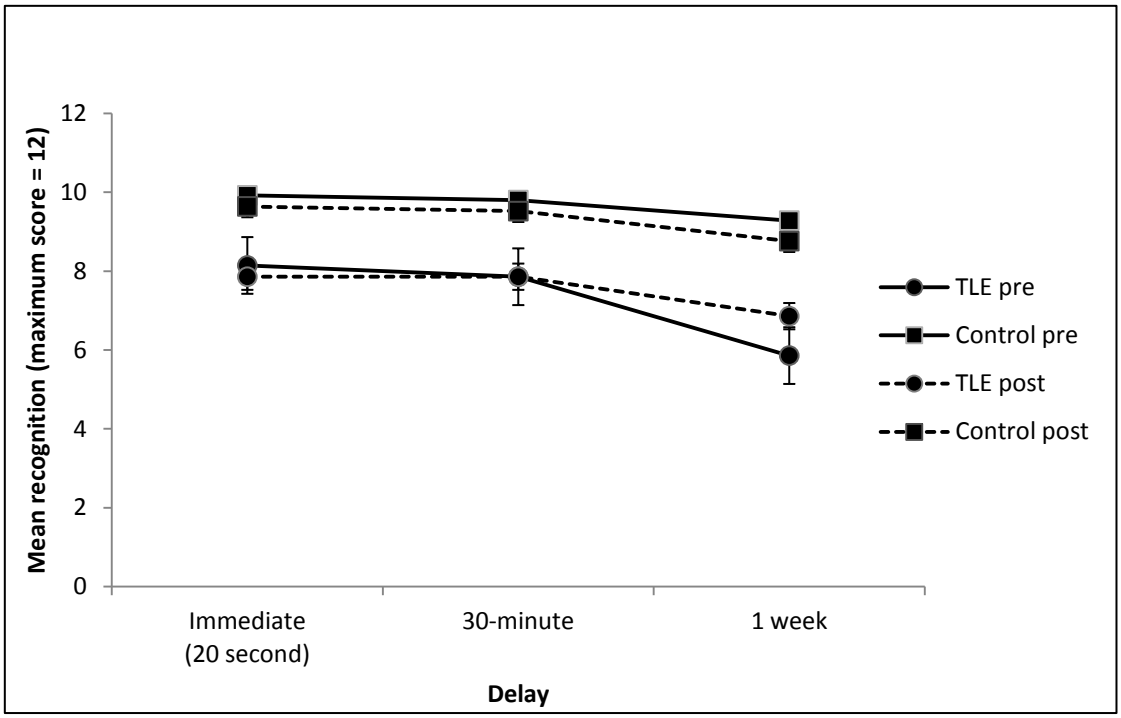
Repeated story recognition

Split plot ANOVAs were used to compare repeated story recognition performance of the TLE and control group across the three delays at the pre- and post-surgery assessments The ANOVA using the pre-surgery data found a significant main effect of group $F(1, 30) = 10.557$, $p < .05$, $\eta^2_p = .260$, a significant main effect of delay $F(1.409, 42.274) = 16.768$, $p < .001$, $\eta^2_p = .359$, and a significant delay-by-group interaction $F(1.409, 42.274) = 5.480$, $p < .05$, $\eta^2_p = .154$. Planned contrasts performed between the pairs of delays (20 seconds to 30 minutes & 30 minutes to one week) found no significant delay-by-group interaction over the short delay $F(1, 30) = .204$, $p < .05$, $\eta^2_p = .007$, but a significant interaction between the 30 minute and one-week delay $F(1, 30) = 7.449$, $p < .05$, $\eta^2_p = .199$. This indicates that the TLE participants experienced ALF of verbal material over the long delay despite repeated recall of the

material at 30 minutes. When the ANOVA was rerun with the post-surgery data it found a significant main effect of group $F(1, 30) = 4.532$, $p < .05$, $\eta^2_p = .131$, and a significant main effect of delay $F(11.396,41.868) = 6.497$, $p < .05$, $\eta^2_p = .178$. However, the delay-by-group interaction was not significant post-surgery $F(11.396,41.868) = 0.084$, $p > .05$, $\eta^2_p = .003$.

Figure 16

Pre- and post-surgery comparison of mean repeated story recognition scores on the verbal story test

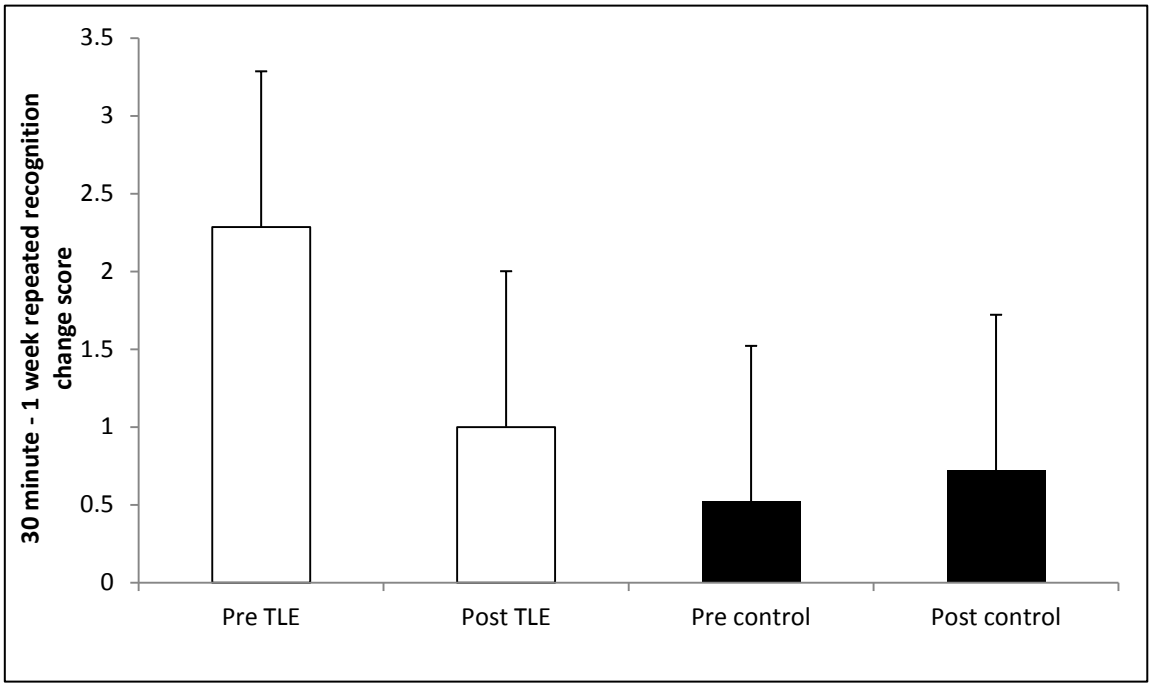


Paired sample t-tests were used to identify any statistically significant differences in change scores for repeated story recognition between the pre- and post-surgery assessments. TLE participants correctly identified more items post-surgery ($M = 1.000$, $SD = 1.528$) compared to pre-surgery ($M = 2.285$, $SD = 1.704$). This constitutes a statistically significant increase of 1.286 items 95% CI [0.406, 2.165], $t(6) = 3.576$, $p < .05$, $d = 1.352$. Participants in the control group recognised marginally less items post-surgery ($M = 0.720$, $SD = 1.400$) compared to pre-surgery ($M = 0.520$, $SD = 1.262$), a

non-statistically significant decrease of -0.200 items 95% CI [-0.905,0 .505], $t(24) = -0.586$, $p > .05$, $d = -1.171$ (see figure 17).

Figure 17

Pre- and post-surgery comparison of repeated recognition change scores for the verbal stories test



The Effect of Seizures on Forgetting

Seizure frequency could not be correlated with ALF pre-surgery due to the homogeneity of reported seizure activity. Six out of the seven patients with TLE experienced seizures during the delay therefore meaningful analysis was not possible. The five additional TLE pre-surgery patients were combined to see if this would allow additional analysis. However, four out of the five participants experienced a seizure during the delay, therefore it was still not possible to run an analysis. All seven patients with TLE were seizure free post-surgery.

Correlations

Pearson's bivariate correlations were used to investigate the relationship between change scores on the main five experimental tests (item-recall, spatial-recall, descriptive-recall, story-recall and story-recognition) with ten variables considered

relevant to forgetting in TLE: full Scale IQ, perceived long-term memory, age of onset of epilepsy, duration of epilepsy, frequency of seizures, AED use, and HADS derived anxiety and depression scores. None of the variables significantly correlated with each other at a .01 or .05 alpha level.

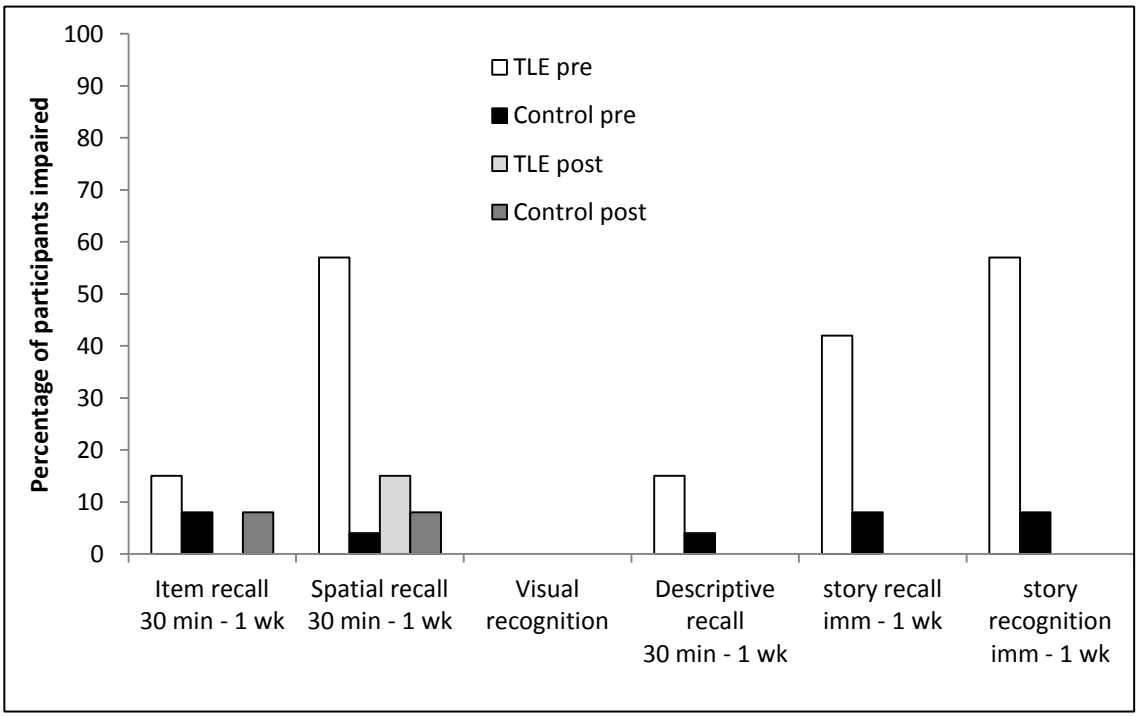
Individual Analysis

Forgetting rates

Figure 18 indicates that a greater number of TLE participants evidenced ALF at the pre-surgery testing interval than the control group. Following epilepsy surgery both TLE participants and controls evidenced a similar degree of impairment across the tests, indicating that ALF improved in the TLE participants post-surgery.

Figure 18

Pre- and post-surgery comparison of percentage of participants impaired over the one-week delay



Psychosocial measures & perceived memory

Perceived memory was not found to be significantly correlated with ALF over the 30 minute or one-week delay on any of the subtests. The same results were found when the correlations were repeated post-surgery. A paired sample t-test was used to detect any statistically significant within group differences in the TLE group HADS score pre- and post-surgery. TLE participants scored lower on the HADS anxiety subscale post surgery (M = 5.858, SD = 5.727) compared to pre-surgery (M = 10.00, SD = 4.726). This constitutes a statistically significant decrease of 4.143 points, 95% CI [-0.176, 8.462], $t(6) = 2.347$, $p < .05$, $d = 0.87$.

Discussion

This paper explored the relationship between seizures and ALF by establishing whether seizure elimination through resective epilepsy surgery improved ALF in patients with AED- refractory TLE. ALF assessments were conducted pre-surgery and again between six months and one year post-surgery (controls were assessed over an equivalent period of time). Participants were matched on key demographic characteristics with a group of healthy controls. A repeated exposure matching procedure was successful in equating initial learning in six out of the eight sub-tests pre-surgery. Results from the remaining sub-tests (visual recognition and repeated story recognition) were interpreted cautiously. Patients with TLE exhibited ALF compared to controls pre-surgery, showing significantly greater forgetting over a one-week delay on spatial recall, descriptive free recall and tests of story recall and recognition. Visual recognition was borderline impaired (approaching significance pre-surgery).They showed normal retention on visual scene item free recall and verbal recognition. They exhibited ALF on the repeated recall story recall test but not on the repeated recognition test.

Omnibus analysis indicated that the TLE group did not show ALF over the one-week delay post-surgery. Rather, post-surgery patients with TLE exhibited normative retention over the one-week delay on tests of descriptive free-recall, visual scene recognition and tests of story recall and recognition. They significantly improved compared to their pre-surgery performance on visual item free recall and story recall. They also showed significant improvement on repeatedly recalled and recognised verbal story tests.

As predicted by the first assumption, pre-surgery patients with TLE showed significantly worse retention over one week than the control group. Performance over 30 minutes was consistent with previous findings, where patients with TLE have been shown to match controls over short delays on verbal and visual material when initial learning is equated (Martin et al., 1991; Blake et al., 2000 & Muhlert et al., 2011). When tested between 30 minutes and one week, the TLE group exhibited ALF on six of the eight sub-tests, with the exception of item free recall and visual recognition. Additional analysis did not reveal a clear explanation for why they performed better on these sub-tests. Possibilities include poor test-sensitivity or it may be a particularly easy sub-test. This is unlikely however, as the TLE group significantly improved on this sub-test post-surgery. If the test had been too easy we might have expected the control group to have performed at ceiling pre-surgery.

The pre-surgery findings are in line with those reported in Muhlert et al. (2011) who conducted similar analyses with 14 patients with TLE, testing long-term forgetting over three weeks. Comparing individual analyses between the present study and Muhlert et al. reveals a similar percentage of patients with TLE evidencing ALF, with approximately half of the participants in each study showing impaired retention pre-surgery on spatial free recall, descriptive free recall, story recall and story recognition. One difference between our findings and Muhlert et al. is the lack of impairment found

in our item recall sub-test. This may be due to one of the explanations outlined above or the fact that the long-term delay period was longer in the Muhlert et al. study. However, this does not explain why our participants evidence similar impairments across the other sub-tests.

Equating initial learning post-surgery was achieved on four out of the eight sub-tests in the TLE group, but all four story tests were significantly different to the controls at initial assessment. In contrast to pre-surgery, their performance on the visual recognition test at the immediate delay was not significantly different to the controls post-surgery. It is not apparent why these changes occurred, although it may be due to the resection of the hippocampus. Previous research has identified that memory problems can affect some people who have had epilepsy surgery (Sherman et al., 2011). However, it should be noted that some people also appear to improve following surgery, most likely due to improved seizure control. As with the pre-surgery visual recognition test, we should proceed cautiously when interpreting the results from the post-surgery story sub-tests, as they may constitute a scaling effect.

Post-surgery patients with TLE evidenced unimpaired retention over the one-week delay on all eight sub-tests, supporting hypothesis two, that eliminating seizure activity would improve ALF post-surgery. This represented a change from significant ALF pre-surgery, to no significant ALF post-surgery in tests of spatial recall, descriptive recall, story recall, repeated story recall, story recognition and repeated story recognition. The TLE patients were borderline impaired on spatial recognition pre-surgery and were unimpaired post-surgery. Change scores comparing pre- and post-surgery within-group forgetting revealed improvement on all six sub-tests, with significant improvements on item free recall, visual recognition and story recall. Individual analyses also revealed that none of the post-surgery TLE patients

experienced ALF, and their forgetting was not significantly different to the control group.

The findings partly support those made in Gallassi et al. (2011) who found that their participant (MT) improved on tests of visual and verbal recall following a temporal polectomy. However, both pre- and post-surgery MT evidenced accelerated forgetting over the short delay. This is methodologically problematic as it might be suggestive of traditional anterograde amnesia as opposed to ALF. The patients with TLE in this study did not evidence anterograde amnesia for the verbal tests as they were equated for initial learning post-surgery and forgetting over the short delay was not significantly different to the controls. However, we found that verbal recall was not equated post-surgery therefore we must be cautious in attributing the ALF improvement in the verbal stories test. We did however, find significant improvement in visual forgetting, which supports Gallassi et al.

In consideration of other findings in the literature linking seizure activity to ALF, Mameniskiene et al. (2006) found that frequency of seizures during the study period was related to poorer recall over a four week delay, and that higher seizure frequency was associated with ALF. However, the authors did not measure the interaction between the short- and long-delays it is difficult to draw firm conclusions from this paper, as it was not clear whether the participants were experiencing accelerated forgetting over the short-delay. A more recent study by Wilkinson et al. (2012) did measure the interaction over the short delay, as well as the long delay, and found that seizure activity during a six-week delay was associated with ALF. The current study cannot make similar inferences about seizure frequency, however the marked improvement in ALF post-surgery and contemporaneous remission of seizure activity is supportive of the hypothesis that seizure activity relates to ALF.

As mentioned in the paragraph above, this study makes a case for seizure activity causing the pre-surgery ALF. However, we were not able to statistically associate seizure frequency with forgetting pre-surgery, even when pooling the five additional pre-surgery patients with TLE. Although this challenges our second assumption and excludes a direct causal link being made between seizure activity and forgetting, an explanation can be provided in that only one participant reported being seizure-free during the one-week delay pre-surgery. The opposite then occurred post-surgery, with all seven patients with TLE seizure free during the one-week delay. It is not possible to say unequivocally that the elimination of seizures post-surgery relates to the marked improvement found in the patients with TLE; however it is the most likely interpretation of these findings.

A potential confound to the hypothesis that seizures cause ALF is that a reduction in AED use post-surgery improved ALF due to the elimination of the memory difficulties associated with AED use. However this was not the case in this study as the patients with TLE were continuing AED intervention during the post-surgery period.

In consideration of how this work fits with other published findings we will focus on the results reported in Bell (2006) and Muhlert et al. (2011). These papers report different findings and draw different conclusions from their respective data. Bell report no significant differences between the percentage of their TLE and control participants who experienced ALF over a two week delay. As stated earlier, Muhlert et al. found that around 50 percent of their sample experienced ALF over a three-week delay. Two explanations are outlined in Muhlert et al. for these differences, the first posits that the participants in Bell evidenced accelerated forgetting over the short delay, therefore the results might reflect a scaling effect. The second proposes that the insignificant findings relate to the use of a pooled sample of individuals, some of whom were post-surgical patients. Given the findings from this study, the heterogeneity in

ALF presentation in Bell likely relates to the number of participants who were seizure free due to epilepsy surgery. This point is not picked up on in either of the studies described above but it fits with our general findings.

Previous research has shown that repeated testing of recall and recognition can improve ALF over delays of 24 hours if seizure control is established (Jansari et al., 2011). Our findings confirm that pre-surgery repeated testing on the verbal story test at 30 minutes attenuated ALF over one week in the TLE group for recognition but not recall. The control participants' retention was not associated with repeated recall at 30 minutes. Post surgery, the TLE group evidenced improved story recall and recognition over one week with repeated testing at the 30-minute delay. Our findings are different to those of Jansari et al. who found recall and recognition impaired pre- and only recognition improved post-AED intervention (with the control of overt seizures). The reasons for this are not clear, however it may relate to the fact that JR was experiencing sub-clinical seizures even during the post-AED period which were differentially affecting recall and recognition, thus leaving the "slow" consolidation process susceptible to disruption. However this is somewhat speculative and is not corroborated by others findings so it may require further investigation.

We found that self-reported anxiety and depression were not correlated with retention over the one-week delay when comparing the six sub-test change scores pre- and post-surgery. We also found that participant's perceived memory did not correlate with retention over the 30 minute or the one-week delay. This was the case pre- and post-surgery. This supports the findings of Blake et al. (2000) and Muhlert et al. (2011), both of whom did not find a significant relationship between retention and perceived memory over long-delays. However, Muhlert et al. found a relationship between perceived memory and retention over the 30-minute delay. It is not clear why this discrepancy occurred, but the position outlined by Muhlert et al., seems plausible, that

these findings may be an artefact of small sample numbers. We did however, find a significant improvement in anxiety scores in the TLE group post-surgery.

One of the difficulties with previous research has been finding a control group matched for age and IQ, and often researchers have relied on less robust matching procedures (i.e. years in education or age - without IQ). This is problematic as these have not been shown to be reliable in adequately equating participants' demographics. A strength of this study was the use of a sub-sample of control participants drawn from a larger sample and matched on characteristics known to confound group comparisons of forgetting. An additional strength is our use of a parallel version of the ALF testing materials, comprising a set of verbal and visual recall and recognition tests. The post-surgery improvements are therefore unlikely to be related to repeated exposure to the materials.

One of the limitations of this study was the reduced initial encoding of information observed in participants both pre- and post-surgery but more predominantly post-surgery, with significantly lower registration of the materials occurring on the verbal sub-tests. Although our results suggest that ALF has improved post-surgery, it is possible that a scaling effect has occurred. However, due to the broad improvement observed across the different subtests, scaling effects are unlikely to account for the stark improvements observed.

This research demonstrates that a sub-sample of patients with TLE who are matched for age and IQ with a control group evidence significantly impaired retention when tested over a week. This is problematic as standard neuropsychological memory batteries only test at 30-minute delays. The likelihood of missing memory impairments in patients with TLE remains high until an improved understanding of the process of ALF is widely disseminated amongst clinicians. Given the findings that ALF might be improved following epilepsy surgery, it is important that potential benefits and

costs are known by clinicians and made available to patients, particularly given the inherent risks of epilepsy surgery, and the low quality of life that some individuals with medically refractory TLE experience. Our finding that repeated recall of the test materials attenuates ALF is of clinical importance, as it suggests that consolidation may be reinforced if appropriate rehearsal strategies are adopted. It appears that this affects recall and recognition differentially. Finally, we found that the TLE participants' HADS derived anxiety scores significantly improved post surgery suggests that seizure elimination and/or the subsequent memory gains may have positive psycho-social benefits.

Future work

Future work might look to repeat this study with a larger clinical sample to establish if the promising findings reported here have broad clinical support. One of the difficulties we experienced was finding variability in seizure presentations during the one-week delay pre-surgery. It was not possible therefore, to associate seizure frequency to retention *per-se*. A way to overcome the lack of heterogeneity in pre-surgery seizure activity observed during this study would be to record seizure activity over a longer period of time, as-per Wilkinson et al. (2012). This may generate a clearer picture of the association between seizure activity and retentive ability. If improved retention can be established with post-surgical seizure remission, we will have a strong argument for the direct role of current seizure activity on ALF. Complementing a larger study with a smaller case-series design may aid investigation of the heterogeneity reported in ALF. The use of robust ALF assessment tools, as well as neurological imaging data will help us establish how neuropathology interacts with seizure activity and subsequent forgetting. Finally, although the testing procedure adopted in this study was robust, one of the main drawbacks is the time it takes to administer. Developing a way to streamline the ALF assessment so that it is easier to administer in clinical

practice will ensure that neuropsychologists continue to develop accurate, reliable and applicable clinical tools to assess ALF.

Conclusions

In conclusion, this study demonstrates that seizures can disrupt the longer-term retention of newly learned memories in individuals with TLE over delays of one-week. It appears that this impairment can be improved following epilepsy surgery with seizure control. Our findings provide some supportive evidence to the theory of "slow" consolidation operating over a longer time frame than the processes involved in immediate acquisition of newly learned information. This appears to fit with the Standard Model of memory proposed by Squire and Alvarez (1995). We found evidence that the mechanism underpinning shorter term "quick" consolidation appears to be broadly intact in individuals with TLE. However, for approximately half of our sample, "slow" consolidation may have been impaired, evidenced by ALF over the one-week delay pre-surgery. The fact that this impairment improved post-operatively with seizure control lends credence to Mayes's theory that seizure activity in the temporal lobes is related to ALF.

References

Bell, B. D. (2006). 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. doi:10.1080/ 13803390500434367

Bell, B. D., Fine, J., Dow, C., Seidenberg, M., & Hermann, B. P. (2005). Temporal lobe epilepsy and the selective reminding test: The conventional 30-minute delay suffices. *Psychological Assessment, 17*(1), 103-109. doi:10.1037/ 1040-3590.17.1.103

Bell, B. D., & Giovagnoli, A. R. (2007). Recent innovative studies of memory in temporal lobe epilepsy. *Neuropsychol Rev.* 17:455-476.

Blake, R. V., Wroe, S. J., Breen, E. K., & McCarthy R. A. (2000). Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. *Brain, 123*(3), 472-483. doi:10.1093/brain/123.3.472

Butler, C. R., Graham, K. S., Hodges, J. R., Kapur, N., Wardlaw, J. M., & Zeman, A. Z. (2007). The syndrome of transient epileptic amnesia. *Annals of Neurology, 61*(6), 587-598. doi:10.1002/ana.21111

Butler, C. R., & Zeman, A. Z. (2008). 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. doi:10.1093/brain/awn127

Cohen, J. (1992). A Power Primer. *Psychological Bulletin, 112 (1),* 155-159. doi:10.1037/0033-2909.112.1.155

Commission on Classification and Terminology of the International League Against Epilepsy (1989). Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia, 30,* 389-399.

Cronel-Ohayon, S., Zesiger, P., Davidoff, V., Boni, A., Roulet, E., & Deonna, T. (2006). Deficit in memory consolidation (abnormal forgetting rate) in childhood temporal lobe epilepsy. Pre and post operative long-term observation. *Neuropediatrics*. 37(6):317-324.

De Renzi, E., & Lucchelli, F. (1993/1996). Dense retrograde amnesia, intact learning capability and abnormal forgetting rate: A consolidation deficit? *Cortex/ Neurocase, 29/2*(1), 449-466/13a-xx. doi:10.1093/neucas/2.1.13-a

Elliott, G. (2012). Methodological issues associated with assessing forgetting rates: Do recent studies of accelerated long-term forgetting in epilepsy consider key

factors? – A review. (Unpublished doctoral thesis). The University of Sheffield, Sheffield.

Engel, Jr., J. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: Report of the ILAE task force on classification and terminology. *Epilepsia, 42(6),* 796-803.

Gallassi, R., Sambati, L., Poda, R., Maserati, M. S., Oppi, Federico, Giulioni, M., & Tinuper, P. (2011). Accelerated long-term forgetting in temporal lobe epilepsy: Evidence of improvement after temporal pole lobectomy. *Epilepsy & Behaviour, 22*(4), 793-795. doi:10.1016/j.yebeh.2011.09.003

Giovagnoli, A. R,. Avanzini, G. (1999). Learning and memory impairment in patients with temporal lobe epilepsy: Relation to the presence, type and location of brain lesion. *Epilepsia, 40(7),* 904-911.

Hebb, D.O. (1949). *The organization of behavior.* New York: Wiley & Sons

Hermann, B.P., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Arch Neurol. 54*, 369-376.

Isaac, C. L., Mayes, A. R. (1999a). Rate of forgetting in amnesia: I. Recall and recognition of prose. *Journal of Experimental Psychology: Learning, Memory, and Cognition, 25*(4), 942-962. doi:10.1037/0278-7393.25.4.942

Jansari, A. S., Davis, K., McGibbon, T., Firminger, S., & Kapur, N. (2011). When "long-term memory" no longer means "forever": Analysis of accelerated long-term forgetting in a patient with temporal lobe epilepsy. *Neuropsychologia,* (2010), *48*(6), 1707-xxxx. doi:10.1016/j. neuropsychologia.2010.02.018

Jokeit, H., Daamen, M., Zang, H., Janszky, J., & Ebner, A. (2001). Seizures accelerate forgetting in left-sided temporal lobe epilepsy. *Neurology, 57*(1), 125-126. doi:10.1212/WNL.57.1.125

Kapur, N., Miller, J., Colbourn, C., Abbott, P., Kennedy, P., & Docherty, T. (1997). Very long-term amnesia in association with temporal lobe epilepsy: Evidence for multiple-stage consolidation processes. *Brain and Cognition*, *35*(1), 58-70. doi:10.1006/brcg.1997.0927

Kapur, N., Scholey, K., Moore, E., Barker, S., Brice, J., & Thompson, S. (1996). Long-term retention deficits in two cases of disproportionate retrograde amnesia. *Journal of Cognitive Neuroscience, 8*(5), 416-434. doi:10.1162/ jocn.1996.8.5.416

Lezak, M.D., Howieson, D.B., Loring, D.W., (2004). *Neuropsychological Assessment* (4th ed.). New York: Oxford University Press.

Macmillan, N.A., Creelman, C.D. (1991). *Detection Theory: A User's Guide*. New York: Cambridge University Press.

Mameniskiene, R., Jatuzis, S., Kaubrys., G, & Budrys, V. (2007). The decay of memory between delayed and long-term recall in patients with temporal lobe epilepsy. *Epilepsy & Behaviour*, *8*(1), 278-288. doi:10.1016/j.yebeh. 2005.11.003

Manes, F., Graham, K. S., Zeman, A., De Lujan Calcagno, M., & Hodges, J. R. (2005). Autobiographical amnesia and accelerated forgetting in transient epileptic amnesia. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(10), 1387-1391. doi:10.1136/jnnp.2004.036582

Martin, R. C., Loring, D. W., Meador, K. J., Lee, G. P., Thrash, N., & Arena, J. G. (1991). Impaired long-term retention despite normal verbal learning in patients with temporal lobe dysfunction. *Neuropsychology*, *5*(1), 3-12. doi:10.1037/0894-4105.5.1.3

Mayes, A. R., Isaac, C. L., Holdstock, J. S., Cariga, P., Gummer, A., & Roberts, N. (2003). Long-term amnesia: A review and detailed illustrative case study. *Cortex, 39*(4-5), 567-603. doi:10.1016/S0010-9452(08)70855-4

Muhlert, N. (2010). *Accelerated long term forgetting in temporal lobe epilepsy: A single case study post-surgery.* (Unpublished doctoral thesis). The University of Sheffield, Sheffield.

Muhlert, N., Grunewald, R. A., Hunkin, N. M., Reuber, M., Howell, S., Reynders, H., & Isaac, C. (2011). Accelerated long-term forgetting in temporal lobe and idiopathic generalised epilepsies. *Neuropsychologia, 49*(9), 2417-2426. doi:10.1016/j.neuropsychologia.2011.04.018

The National Society for Epilepsy. (2012). *What is epilepsy*. retrieved from http://www.epilepsysociety.org.uk/AboutEpilepsy/Whatisepilepsy

Ribot, T. (1881). *Les maladies de la mémoire*. Paris: Baillière. Retrieved from http://www.bookrags.com/research/ribot-thodule-1839-1916-lmem-01/

Schmidt, W., & Loscher (2003). How effective is surgery to cure seizures in drug-resistant temporal lobe epilepsy? *Epilepsy Research, 56,* 85-91. doi: 10.10.1016/j.eplepsyres.2003.10.004

Sherman, E. M. S., Wiebe, S., Fay-McClymont, Tellez-Zenteno, J., Metcalf, A., Hernandez-Ronquillo....Jette, N. (2011). Neuropsychological outcomes after epilepsy surgery: Systematic review and pooled estimates. *Epilepsia, 52(5),* 857-869. doi: 10.1111/j.1528-1167.2011.03022.x

Squire, L. R., & Alvarez, P. (1995). Retrograde amnesia and memory consolidation: A neurobiological perspective [Review]. *Current Opinion in Neurobiology*, *5*(2), 169-177. doi:10.1016/0959-4388(95)80023-9

Thompson, P.J., & Corcoran, R. (1992). Everyday memory failures in people with epilepsy. *Epilepsia. 33(Supple6),* S18 -20.

Vingerhoets, G. (2006). Cognitive effects of seizures. *Seizure, 15,* 221-226. doi: doi:10.1016/j.seizure.2006.02.012

Wilkinson, H., Holdstock, J. S., Baker, G., Herbert, A., Clague, F., & Downes, J. J. (2012). Long-term accelerated forgetting of verbal and non-verbal information in temporal lobe epilepsy. *Cortex, 48*(3), 317-332. doi:10.1016/j.cortex.2011.01.002

Wechsler, D. (1997a). *Wechsler Memory Scale – third edition.* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Adult Intelligence Scale – third edition.* San Antonio, TX: The Psychological Corporation.

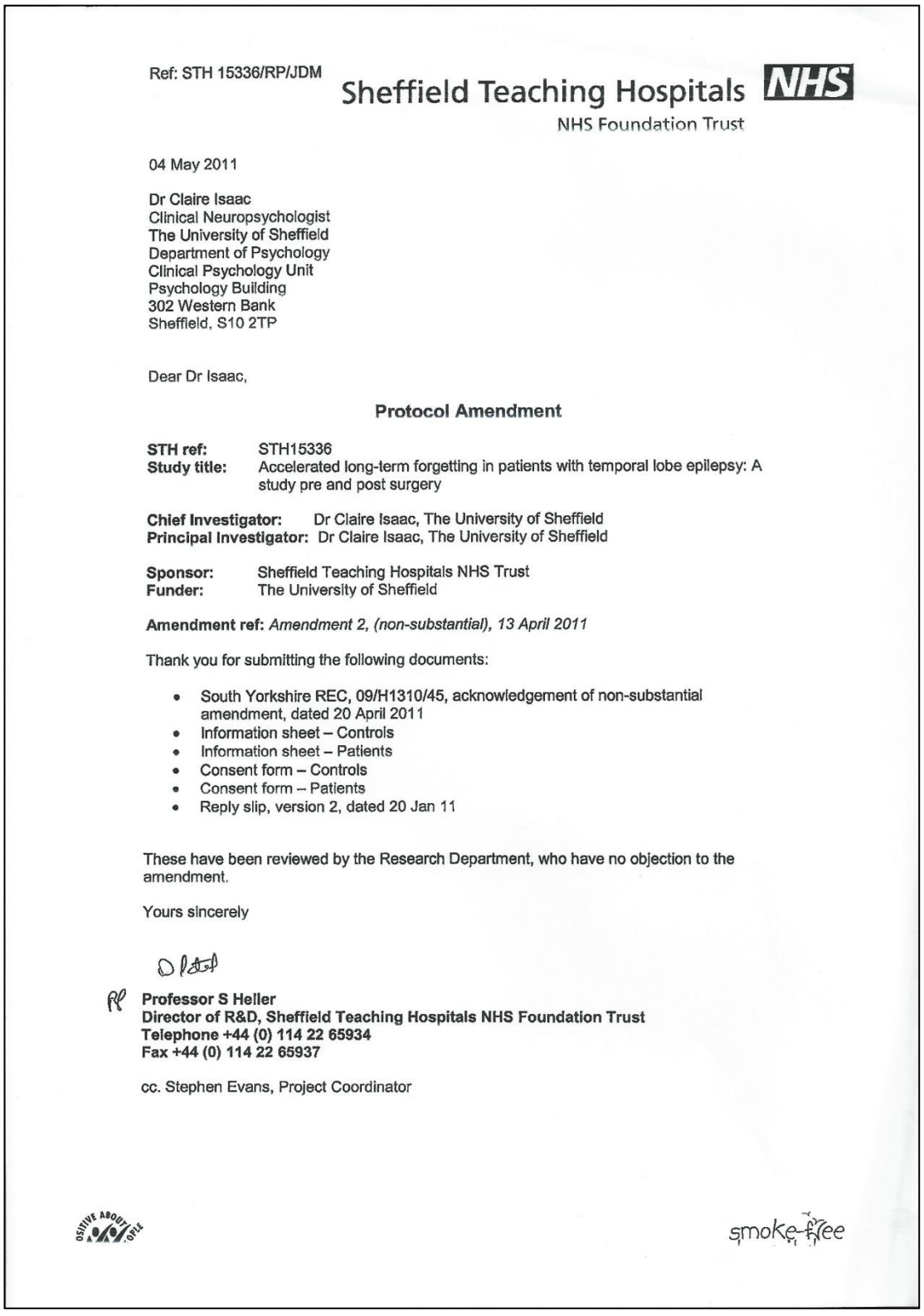
Wechsler, D. (2001). Wechsler Test of Adult Reading: Examiner's Manual. *San Antonio, Texas: The Psychological Corporation.*

Zigmond, A.S, & Snaith, R.P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatri Scand. 67,* 361–370.

APPENDIX A

Ethical Approval

Scan of major amendments Letter



Ref: STH 15336/RP/JDM

Sheffield Teaching Hospitals NHS
NHS Foundation Trust

04 May 2011

Dr Claire Isaac
Clinical Neuropsychologist
The University of Sheffield
Department of Psychology
Clinical Psychology Unit
Psychology Building
302 Western Bank
Sheffield, S10 2TP

Dear Dr Isaac,

Protocol Amendment

STH ref: STH15336
Study title: Accelerated long-term forgetting in patients with temporal lobe epilepsy: A study pre and post surgery

Chief Investigator: Dr Claire Isaac, The University of Sheffield
Principal Investigator: Dr Claire Isaac, The University of Sheffield

Sponsor: Sheffield Teaching Hospitals NHS Trust
Funder: The University of Sheffield

Amendment ref: *Amendment 2, (non-substantial), 13 April 2011*

Thank you for submitting the following documents:

- South Yorkshire REC, 09/H1310/45, acknowledgement of non-substantial amendment, dated 20 April 2011
- Information sheet – Controls
- Information sheet – Patients
- Consent form – Controls
- Consent form – Patients
- Reply slip, version 2, dated 20 Jan 11

These have been reviewed by the Research Department, who have no objection to the amendment.

Yours sincerely

Professor S Heller
Director of R&D, Sheffield Teaching Hospitals NHS Foundation Trust
Telephone +44 (0) 114 22 65934
Fax +44 (0) 114 22 65937

cc. Stephen Evans, Project Coordinator

APPENDIX B

Materials

1. ***Information Sheets***
    - *1.1 Reply Slip*
    - *1.2 Information Sheet (control)*
    - *1.3 Information Sheet (patient)*

2. ***Consent Forms***
    - *2.1 Consent Form (controls)*
    - *2.2 Consent Form (patients)*

3. ***Wechsler Test of Adult Reading (WTAR)***

4. ***Visual Scenes Tests***
    - *4.1 Recall Scenes (set A and set B)*
    - *4.2 Recall Response Form (set A exemplar)*
    - *4.3 Spatial Recall Response Grid*
    - *4.4 Exemplar Visual Recognition Scenes*
    - *4.5 Recognition Response Form (set A exemplar)*

5. ***Verbal Stories Tests***
    - *5.1 Stories Recall Response Form (set A exemplar)*
    - *5.2 Story Recognition Response Form (set A exemplar)*

6. ***Long-Term Memory Questionnaire***
7. ***Hospital Anxiety and Depression Scale (HADS)***
8. ***Seizure Diary***
9. ***Counterbalancing schedule***

B.1: Reply Slip

Version 2: 20.01.2011

The University Of Sheffield.

Department Of Psychology.
Clinical Psychology Unit.

Doctor of Clinical Psychology (DClin Psy) Programme
Clinical supervision training and NHS research training & consultancy.

Clinical Psychology Unit
Department of Psychology
University of Sheffield
Western Bank
Sheffield S10 2TN UK

Telephone: 0114 2226650
Fax: 0114 2226610
Email: c.harrison@sheffield.ac.uk

http://www.shef.ac.uk/

Reply Slip

Please tick the box next to the statements you agree with.

☐ I have read and understood the information sheet

☐ I would like to participate in this study

☐ I agree to the researcher (Stephen Evans) contacting me by telephone to discuss my participation further

Name:_____

Contact Number:_____

Please return this slip to Stephen Evans, The Clinical Psychology Unit, The University of Sheffield, Western Bank, Sheffield, S10 2TN. A stamped addressed envelope is included for this purpose.

Version 2: 20.01.2011

Reply Slip

Please tick the box next to the statements you agree with.

☐ I have read and understood the information sheet

☐ I would like to participate in this study

☐ I agree to the researcher (Stephen Evans) contacting me by telephone to discuss my participation further

Name:_____

Contact Number:_____

Please return this slip to Stephen Evans, The Clinical Psychology Unit, The University of Sheffield, Western Bank, Sheffield, S10 2TN. A stamped addressed envelope is included for this purpose.

B.2: Information Sheets

B1.1: *Information Sheet (control) Page 1*

The University Of Sheffield.

Department Of Psychology.
Clinical Psychology Unit.
Doctor of Clinical Psychology (DClin Psy) Programme
Clinical supervision training and NHS research training & consultancy.

Clinical Psychology Unit
Department of Psychology
University of Sheffield
Western Bank
Sheffield S10 2TN UK

Telephone: 0114 2226650
Fax: 0114 2226610
Email: c.harrison@sheffield.ac.uk

http://www.shef.ac.uk/

INFORMATION SHEET

What is the effect of surgery on long-term forgetting in temporal lobe epilepsy?

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

People with temporal lobe epilepsy often report problems with their memory and recent research has identified a particular difficulty with remembering information over long periods of time. This research will look into whether epilepsy surgery leads to an improvement in these difficulties, which we hope will provide further knowledge about the causes of memory problems in temporal lobe epilepsy. As part of this research we need healthy volunteers to act as a comparison group.

This study is being undertaken as part of an educational qualification.

Why have I been invited?

You have been invited to take part in this study as a healthy participant without epilepsy and with normal memory functioning. We will be comparing your performance on various memory tests with that of people with temporal lobe epilepsy who are a similar age and educational ability to you.

22

What will be involved if we agree to take part in the study?

If you chose to take part in this study we will ask you to attend for a total of 4 sessions. Each session would last for approximately 1 ½ hours. During the sessions you will be shown a number of pictures and hear stories which you will later be asked to remember. You will also be asked to fill out two questionnaires; one designed to assess your mood and the other to help us get an idea of how you view your memory. You will also be given a short reading test to assess your general intellectual ability.

Can I withdraw from the study at any time?

Yes. You are free to refuse to join the study and may withdraw at any time.

When and where will the interviews take place?

We could arrange to see you at the hospital or, if this is not convenient we would come to your home at a time which suits you. We would like to see you for 2 sessions (placed one week apart) as soon as possible and then again for 2 sessions (placed one week apart) in 6 months time.

What other information will be collected in the study?

With your agreement, we will ask you for information about your general medical health.

Will the information obtained in the study be confidential?

Anything you say will be treated in confidence, no names will be mentioned in any reports of the study and care will be taken so that individuals cannot be identified from details in reports of the results of the study.

Will anyone else be told about my participation in the study?

No.

What if I wish to complain about the way in which this study has been conducted?

If you have *any* cause to complain about *any* aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints

mechanisms are available to you and are not compromised in any way because you have taken part in a research study.

If you have any complaints or concerns please contact the project co-ordinator *(Stephen Evans)* or the project supervisor (*Dr Claire Isaac*) on 0114 222 6639. If this is not satisfactory, you can use the normal University complaints procedure and contact the following person: Dr David Fletcher, Registrar and Secretary's Office, University of Sheffield, Firth Court, Western Bank, Sheffield S10 2TN. Contact number: 0114 222 1100.

The normal hospital complaints procedure is also available to you. If you wish to use this service you should contact the following person: Andrew Cash, Chief Executive, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Glossop Road, S10 2JF. Contact number: 0114 271 3463

Independent Advice

Independent advice can be obtained from the Patients Advisory Liaison Service (PALS). A PALS officer can be contacted on 0114 2712450. Alternatively you can email pals@sth.nhs.uk or write to the PALS Manager, Sheffield, Teaching Hospitals NHS Foundation Trust, Patient Partnership Department, B Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.

Who has reviewed this study?

The South Yorkshire Research Ethics Committee has reviewed and approved this study.

Who should I contact if I would like further information about this study?

If you would like any further information about this study, please do not hesitate to contact the project-coordinator (*Stephen Evans*) by leaving a message with our research support officer (RCO) *(Christie Harrison)* on 0114 222 6650.

The End

24

B1.2: *Information sheet (patient)*

Page 1.

The University Of Sheffield.

Department Of Psychology.
Clinical Psychology Unit.

Doctor of Clinical Psychology (DClin Psy) Programme
Clinical supervision training and NHS research training & consultancy.

Clinical Psychology Unit
Department of Psychology
University of Sheffield
Western Bank
Sheffield S10 2TN UK

Telephone: 0114 2226650
Fax: 0114 2226610
Email: c.harrison@sheffield.ac.uk

http://www.shef.ac.uk/

INFORMATION SHEET

What is the effect of surgery on long-term forgetting in temporal lobe epilepsy?

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

People with temporal lobe epilepsy often report problems with their memory and recent research has identified a particular difficulty with remembering information over long periods of time. This research will look into whether epilepsy surgery leads to an improvement in these difficulties, which we hope will provide further knowledge about the causes of memory problems in temporal lobe epilepsy.

This study is being undertaken as part of an educational qualification.

Why have I been invited?

You have been invited to take part in this study as you have a diagnosis of temporal lobe epilepsy and are scheduled to undergo surgery.

What will be involved if we agree to take part in the study?

If you chose to take part in this study we will ask you to attend for a total of 4 sessions. Each session would last for approximately 1 ½ hours. During the sessions you will be shown a number of pictures and hear stories which you will later be asked to remember. You will also be asked to fill out two questionnaires; one designed to assess your mood and the other to help us get an idea of how you view your memory problems. Between testing sessions you would also be asked to keep a record of your seizures.

Can I withdraw from the study at any time?

Yes. You are free to refuse to join the study and may withdraw at any time. Please be assured that you will receive the same quality of care at the hospital whether you join the study or not.

When and where will the interviews take place?

We could see you when you are visiting the hospital or, if this is not convenient we would come to your home at a time which suits you. We would like to see you for 2 sessions (placed one week apart) before you underwent surgery and then again for 2 sessions (placed one week apart) 6 months after your surgery.

What other information will be collected in the study?

With your agreement, we will obtain information from your medical records about the course of your epilepsy, the nature and frequency of your seizures and your current medication.

Will there be effects on my treatment?

No, your participation in the study is not connected to your treatment in any way.

Will the information obtained in the study be confidential?

Anything you say will be treated in confidence, no names will be mentioned in any reports of the study and care will be taken so that individuals cannot be identified from details in reports of the results of the study.

Will anyone else be told about my participation in the study?

Yes. The team involved in your care at the hospital will be informed of your participation. We can also inform your GP if you wish.

What if I wish to complain about the way in which this study has been conducted?

If you have *any* cause to complain about *any* aspect of the way in which you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you and are not compromised in any way because you have taken part in a research study.

If you have any complaints or concerns please contact the project co-ordinator *(Stephen Evans)* or the project supervisor (*Dr Claire Isaac*) on 0114 222 6639. If this is not satisfactory, you can use the normal University complaints procedure and contact the following person: Dr David Fletcher, Registrar and Secretary's Office, University of Sheffield, Firth Court, Western Bank, Sheffield S10 2TN. Contact number: 0114 222 1100.

The normal hospital complaints procedure is also available to you. If you wish to use this service you should contact the following person: Andrew Cash, Chief Executive, Sheffield Teaching Hospitals NHS Foundation Trust, Royal Hallamshire Hospital, Glossop Road, S10 2JF. Contact number: 0114 271 3463

Independent Advice

Independent advice can be obtained from the Patients Advisory Liaison Service (PALS). A PALS officer can be contacted on 0114 2712450. Alternatively you can email pals@sth.nhs.uk or write to the PALS Manager, Sheffield, Teaching Hospitals NHS Foundation Trust, Patient Partnership Department, B Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF.

Who has reviewed this study?

The South Yorkshire Research Ethics Committee has reviewed and approved this study.

Who should I contact if I would like further information about this study?

If you would like any further information about this study, please do not hesitate to contact the project-coordinator (*Stephen Evans*) by leaving a message with our research support officer (RCO) *(Christie Harrison)* on 0114 222 6650.

The End

28

B2. Consent Forms

B2.1: *Consent Form (control)*

The University Of Sheffield.

Department Of Psychology.
Clinical Psychology Unit.

Doctor of Clinical Psychology (DClin Psy) Programme
Clinical supervision training and NHS research training & consultancy.

Clinical Psychology Unit
Department of Psychology
University of Sheffield
Western Bank
Sheffield S10 2TN UK

Telephone: 0114 2226650
Fax: 0114 2226610
Email: c.harrison@sheffield.ac.uk

http://www.shef.ac.uk/

Consent form for controls

Title of Project: Accelerated long-term forgetting in patients with temporal lobe epilepsy: A study pre and post-surgery

Name of Researcher: Stephen Evans

Participant Identification Number for this project:

Please initial box

5. I confirm that I have read and understood the information sheet dated *[20.01.2011]* (version 3.) for the above project and have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

6. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

7. I understand that my responses will be anonymised before analysis. I give permission for members of the research team to have access to my anonymised responses. ☐

8. I understand that data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐

5. I agree to take part in the above research project. ☐

Name of Patient _____ Date _____ Signature _____

Name of person taking consent (Lead Researcher) _____ Date _____ Signature _____

To be signed and dated in presence of the participant

Copies: 3

When completed, 1 for participant 1 for researcher site file;

30

B2.2: *Consent Form (patient)*

The University Of Sheffield.

Department of Psychology.
Clinical Psychology Unit.

Doctor of Clinical Psychology (DClin Psy) Programme
Clinical supervision training and NHS research training & consultancy.

Clinical Psychology Unit
Department of Psychology
University of Sheffield
Western Bank
Sheffield S10 2TN UK

Telephone: 0114 2226650
Fax: 0114 2226610
Email: c.harrison@sheffield.ac.uk

Consent Form for Patient

Title of Project: Accelerated long-term forgetting in patients with temporal lobe epilepsy: A study pre and post-surgery

Name of Researcher: Stephen Evans

Participant Identification Number for this project:

Please initial box

1. I confirm that I have read and understood the information sheet dated *[01.02.2011]* (version 3.) for the above project and have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that my responses will be anonymised before analysis. I give permission for members of the research team to have access to my anonymised responses. ☐
4. I understand that data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data. ☐
5. I agree to take part in the above research project. ☐

Name of Patient	Date	Signature

Name of person taking consent (Lead Researcher)	Date	Signature

To be signed and dated in presence of the participant

Copies: 3

When completed, 1 for patient; 1 for researcher site file; 1 (original) to be kept in medical note

29

B.3 Wechsler Test of Adult Reading (WTAR)

Front page

wtar UK

WECHSLER® TEST OF ADULT READING™

Record Form

Name: _____

Sex: ☐ F ☐ M Race/Ethnicity: _____ Education: _____

Examiner: _____

	Year	Month	Day
Date of Testing			
Date of Birth			
Age at Testing			

WTAR Scores

Predicted–Actual Comparison		Serial Assessment*	
Standard Score (Appendix A)		Time 2 Standard Score	
Demographics–Predicted Score (Appendix B)		Time 1 Standard Score	
Prediction Interval ☐ 90% ☐ 95%	–	Time 2 – Time 1 Difference	
Actual–Predicted Difference**		Statistical Significance (Table H.2) ☐ .05 ☐ .01	☐Yes ☐No
Cumulative Percentage*** (Table I.1)		Cumulative Percentage*** (Table H.4)	
>50%	☐	>50%	☐
25%–49%	☐	25%–49%	☐
10%–24%	☐	10%–24%	☐
5%–9%	☐	5%–9%	☐
2%–4%	☐	2%–4%	☐
1%	☐	1%	☐

* US Test–Retest Data is used for Serial Assessment

** If the difference ranges from -15 to -19, use cautiously with demographics to predict intellectual and memory functioning. If the predicted WTAR score is more than 20 points greater than the actual score, do not use WTAR score to predict intellectual or memory performance.

*** Increased shading denotes increasing probability of a clinically significant difference.

WAIS–III^{UK} IQ Scores

☐ Demographics Predicted (Appendix C)		☐ WTAR Predicted (Appendix D)		☐ WTAR–Demographics Predicted (Appendix G)	
		VIQ	PIQ	FSIQ	
Actual WAIS–III^{UK} Score					
Predicted WAIS–III^{UK} Score					
Prediction Interval ☐ 90% ☐ 95%		—	—	—	
Actual-Predicted Difference					
Statistical Significance (Appendix I) ☐ .05 ☐ .01	☐Yes ☐No	☐Yes ☐No		☐Yes ☐No	
Cumulative Percentage* (Appendix I)					
>50%	☐	☐		☐	
25%-49%	☐	☐		☐	
10%-24%	☐	☐		☐	
5%-9%	☐	☐		☐	
2%-4%	☐	☐		☐	
1%	☐	☐		☐	

* Increased shading denotes increasing probability of a clinically significant difference. Demographics Predicted - Cumulative Percentages only available for US data use UK WTAR or WTAR Demographics Predicted (I3, I5)

PEARSON

Printed in England. ISBN 978 0 749115 96 8

E F
11 12

WTAR Word List - UK pronunciation guide

Say, **I will show you some words that I will ask you to pronounce.** Place the WTAR Word Card in front of the examinee. As you point to the card, say, **Beginning with the first word on the list, pronounce each word aloud. Start with this word** (point to item 1), **and go down this column, one after the other, without skipping any. When you finish this column, go to the next column** (point to the second column). **Pronounce each word even if you are unsure. Do you understand?** When you are sure that the examinee understands the task, say, **Ready? Begin.**

	Item	Pronunciation	Score (0, 1)		Item	Pronunciation	Score (0, 1)
1.	again	ah-GEHN ah-GAIN *or* uh-GEHN or uh-GAIN		26.	conscientious	con-shee-EN-shss	
2.	address	ah-DRESS *or* uh-DRESS		27.	homily	HOM-ih-lay *or* HOM-ih-lee	
3.	cough	kawf *or* kof		28.	malady	MAL-uh-day *or* MAL-uh-dee	
4.	preview	PREE-vyue		29.	subtle	SUH-tl	
5.	although	awl-THO		30.	fecund	FE-cund *or* FEE-cund	
6.	most	mohst		31.	palatable	PAL-ah-tuh-bul *or* PAL-uh-tuh-bul	
7.	excitement	eck-SITE-munt *or* ik-SITE-munt		32.	menagerie	meh-NA-juh-ree	
8.	know	noh *or* no		33.	obfuscate	OB-fuh-skate	
9.	plumb	plum		34.	liaison	lee-AY-zon *or* lee-AY-zn	
10	decorate	DEK-oh-rate *or* DEK-uh-rate		35.	exigency	eks-IH-jen-say *or* eks-IH-jen-see	
11.	fierce	fee-us *or* feerss		36.	xenophobia	zen-oh-FO-bee-uh	
12.	knead	need		37.	ogre	OH-gur	
13.	aisle	iyle		38.	scurrilous	SKUR-ih-lus *or* SKUR-uh-lus	
14.	vengeance	VEN-jnss		39.	ethereal	ih-THEE-ree-ul *or* ih-THEER-ee-ul	
15.	prestigious	pre-STIJ-us *or* pre-STEEJ-us		40.	paradigm	PAH-rah-dime	
16.	wreathe	reeTH *or* REEEth		41.	perspicuity	per-spuh-KYEW-uh-tee	
17.	gnat	nat		42.	plethora	PLETH-oh-rah *or* PLETH-eh-rah	
18.	amphitheatre	AM-fih-thee-uh-ter		43.	lugubrious	loo-GOOB-ree-uss *or* loo-GOO-bree-uss	
19.	lieu	loo *or* l(y)oo		44.	treatise	TREE-tiz *or* TREET-iz	
20.	grotesque	gro-TESK		45.	dilettante	DILL-ih-tan-tay *or* DILL-uh-tahnt	
21.	iridescent	ihr-ih-DESS-unt *or* ihr-uh-DESS-unt		46.	vertiginous	ver-TIDJ-in-iss	
22.	ballet	BA-lay *or* ba-LAY *or* bal-ay		47.	ubiquitous	you-BIC-wuh-tiss *or* you-BIC-wuh-tus	
23.	equestrian	eh-KWESS-tree-un *or* ih- KWESS-tree-un		48.	hyperbole	hy-PER-bul-lay *or* hy-PUR-bul-lay	
24.	porpoise	PAW-pss *or* POR-poyz (Scots)		49.	insouciant	in-SOO-see-yunt	
25.	aesthetic	ess-THET-ik *or* ees-THET-ik		50.	hegemony	heh-GEM-o-nee *or* heh-JEM-o-nee *or* HEH-geh-mon-ee	

WTAR Raw Score

WTAR Standard Score

B.4 Visual Scenes Tests

*B4.1: **Recall** - Set A*

NB: Actual size of scenes during initial presentation was 12” x 9” to fill PC Laptop Screen

A1: The Bakery Scene

A2: The Office Scene

A3: The River Scene

A4: The Bar Scene

A5: The Bathroom Scene

A6: The Stables Scene

A7: The Supermarket Scene

A8: The Winter Scene

A9: The Kitchen Scene

2.1: Recall *- Set B*

B1: The Park Scene

B2: The Flat Scene

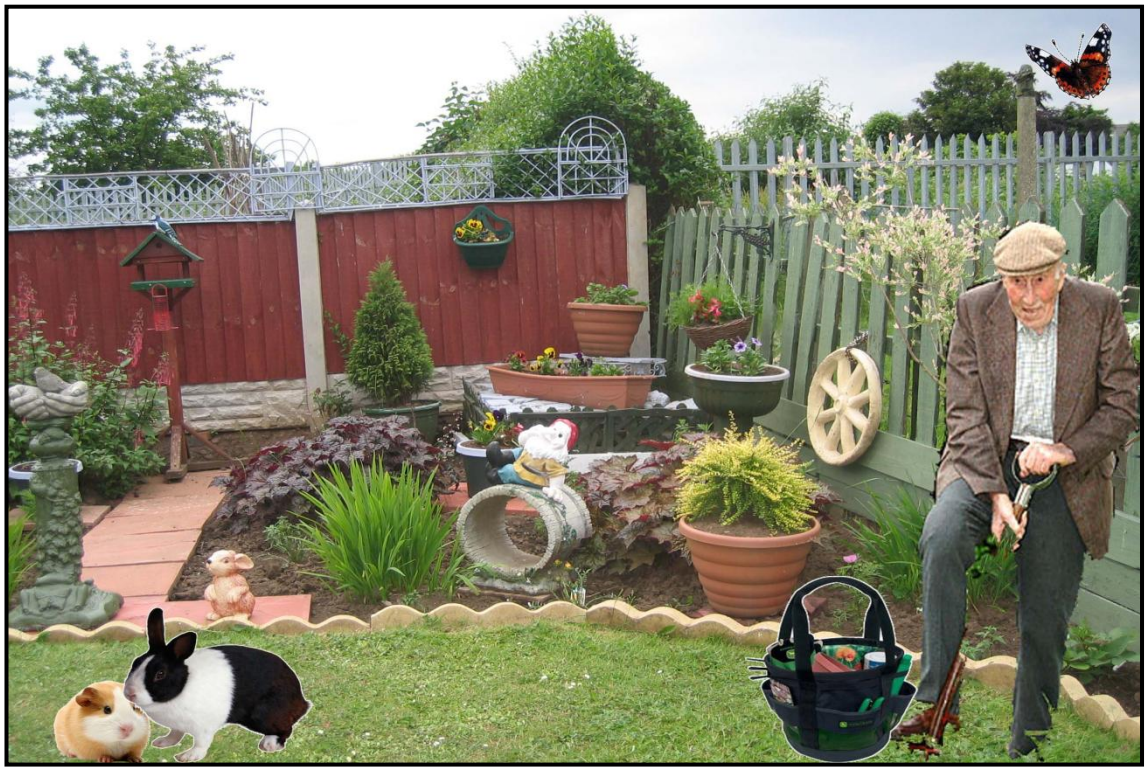
B3: The Classroom Scene

B4: The Car Boot Scene

B5: The Camping Scene

B6: The Playroom Scene

B7: The Garden Scene



B8: The Beach Scene

B9: The Library Scene

B4.2. *Recall Response Form:* A1 'The Bakery Scene'

ITEM RECALL: Can you tell me what was in The Bakery Scene?

- □ Baker / lady
- □ Girl
- □ Cabinet / cake display
- □ Drink
- □ Windows
- □ Clock
- □ Bag
- □ Gingerbread man

Other:_____ Score 0 – 6:_____

SPATIAL RECALL: Can you tell me where [insert item recalled] was? *(show participant the recall grid)*

- □ Baker / lady: 2
- □ Girl: 1 / 3
- □ Cabinet / display of cakes: 3 / 4
- □ Drink: 2
- □ Windows: 1 / 2
- □ Clock: 2
- □ Bag: 3
- □ Gingerbread man: 4

Other:_____ Score 0 – 6:_____

DESCRIPTIVE RECALL: Can you tell me what it / they looked like / what they were doing? *(Record descriptions of up to 2 attributes for up to 6 items previously recalled)*

☐ ☐ **Baker / lady** (e.g. serving the girl / passing the girl a drink*, old/,middle aged, wearing glasses, [blue] apron, [white] shirt, broach, gold earrings, short hair, ginger/blond hair, smiling)

☐ ☐ **Girl** (e.g. young, brown hair, [plaited] pigtails, [green] vest-top, [beige/cream] shorts, taking a drink from the lady*, smiling, carrying a bag*)

☐ ☐ **Cabinet / display of cakes** (3-4 shelves, many different types, pastries, gingerbread man*, buns on top shelf have cherries on, clear plastic/glass display)

☐ ☐ **Drink** (cola/coke, straw, in a glass, being passed between young girl and lady*)

☐ ☐ **Windows** (red tie-backs, brown wooden frames, 4 visible, wooden bars in a cross pattern, net curtains, white/cream net curtains, curtains hanging at top and bottom)

☐ ☐ **Clock** (round, dark brown outer frame, silver/chrome inner face, no numbers, [silver] roman numeral markers, time shows ten past ten, second hand at 12)

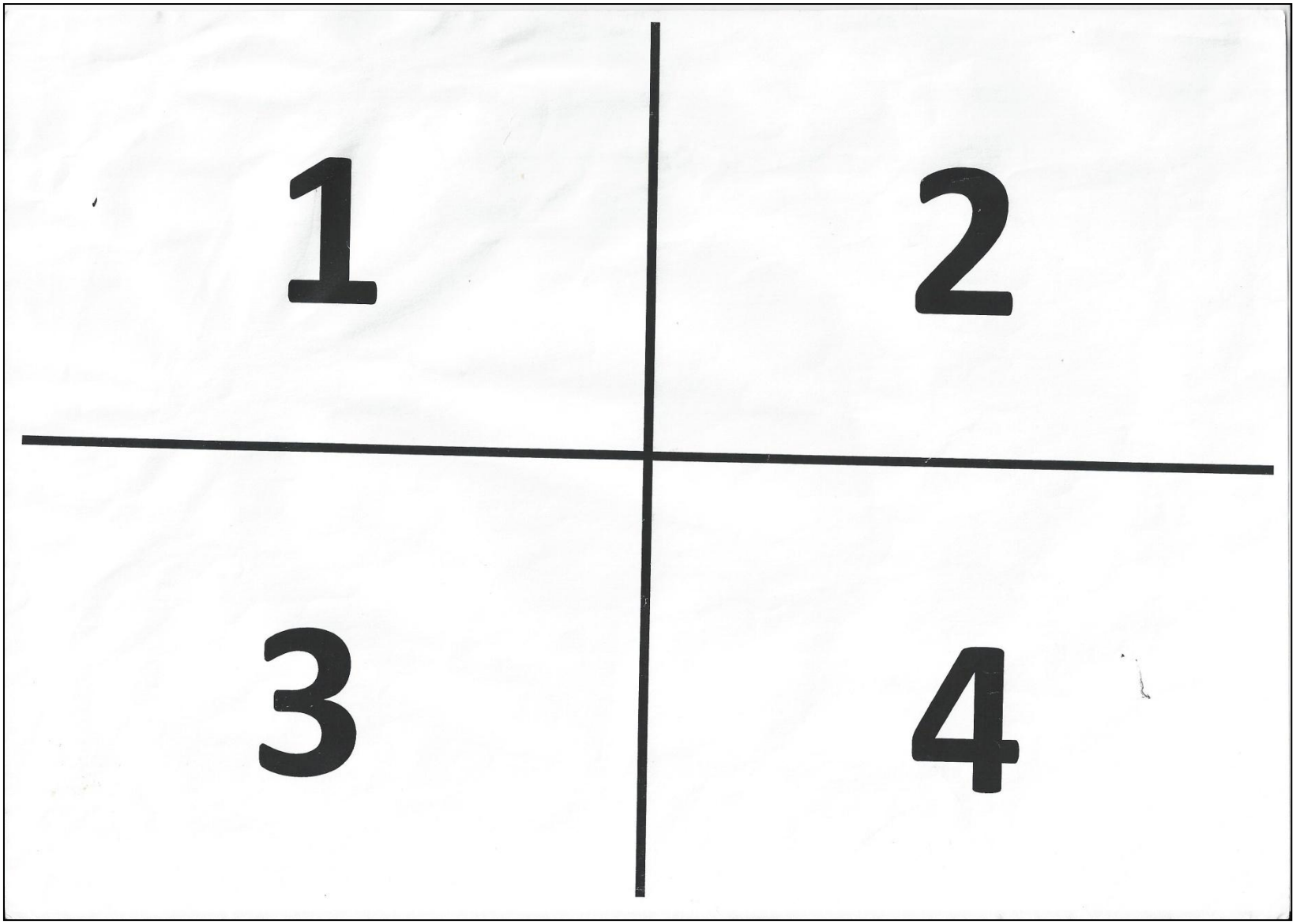
☐ ☐ **Bag** (carried by the girl*, carried in right hand, blue, pink flowers/ roses/green leaves, rectangle shape

☐ ☐ **Gingerbread man*** (in the cabinet / on the shelf, Santa Claus hat / red hat, white piping / icing, smiling, flower buttons)

** Only one point can be awarded for each description. The description may be scored for any of the items it relates to.*

Score 0 – 12:

B4.3. Spatial Recall Response Grid



4.4: Exemplar Visual Recognition Scenes

NB: Actual size of scenes during initial presentation & recognition testing was 12” x 9” to fill PC Laptop Screen

Set A: Example of Recognition Target

Set B: Example of Recognition Target

4.5: Exemplar Visual Recognition Response Form: Set A, Test 1

Participant No_____ **Delay:** ☐ Immediate ☐ 30 minute ☐ 1 week

Slide number	Response (Y / N)	Correct Response	Score
1	***Instructions***	***Instructions***	-
2		**Y**	
3		**N**	
4		**N**	
5		**Y**	
6		**Y**	
7		**Y**	
8		**N**	
9		**N**	
10		**N**	
11		**Y**	
12		**Y**	
13		**N**	
14		**N**	
15		**Y**	
16		**Y**	
17		**N**	
18		**Y**	
19		**N**	
20		**N**	
21		**Y**	
22		**Y**	
23		**N**	
24		**N**	
25		**Y**	
26		**Y**	
27		**Y**	
28		**N**	
29		**N**	
30		**N**	
31		**Y**	
32		**N**	
33		**Y**	
34		**Y**	
35		**N**	
36		**Y**	
37		**N**	
38		**N**	
39		**N**	
40		**Y**	
41		**Y**	
42		**Y**	
43		**N**	
44		**Y**	
45		**N**	
46		**Y**	
47		**Y**	
48		**Y**	
49		**N**	
50		**N**	
51		**N**	

Slide number	Response (Y / N)	Correct Response	Score
52		**Y**	
53		**Y**	
54		**N**	
55		**N**	
56		**N**	
57		**Y**	
58		**N**	
59		**Y**	
60		**N**	
61		**Y**	
62		**Y**	
63		**N**	
64		**N**	
65		**Y**	
66		**N**	
67		**N**	
68		**Y**	
69		**Y**	
70		**Y**	
71		**N**	
72		**Y**	
73		**N**	
74		**N**	
75		**Y**	
76		**N**	
77		**Y**	
78		**Y**	
79		**N**	
80		**Y**	
81		**N**	
82		**N**	
83		**Y**	
84		**Y**	
85		**N**	
86		**Y**	
87		**N**	
88		**N**	
89		**N**	
90		**Y**	
91		**Y**	
92		**Y**	
93		**N**	
94		**Y**	
95		**N**	
96		**N**	
97		**Y**	
98		**N**	
99		**Y**	
100		**Y**	
101		**N**	
Total Correct (max 100)			

5. Verbal Stories Tests

5.1: Exemplar Story Recall Response Form: Set A, Story 1

Story Recall
Set A
Response Sheet

Participant No____________

Story 1

Delay: □ Immediate □ 30 minute □ 1 week   Prompt given □

On the 12th /April, /Peter /Brooks /from Gloucester /became the first man /to travel around the coast /of Britain /in a wheel-chair. /The 27 year old /lost the use of his legs/ six years ago /in a car /accident. /The 4000 mile trip /took 14 weeks /and raised 50 000 pounds /for facilities /for the disabled /in Cheltenham. /

Total score (max 20):____________

Delay: □ Immediate □ 30 minute □ 1 week   Prompt given □

On the 12th /April, /Peter /Brooks /from Gloucester /became the first man /to travel around the coast /of Britain /in a wheel-chair. /The 27 year old /lost the use of his legs/ six years ago /in a car /accident. /The 4000 mile trip /took 14 weeks /and raised 50 000 pounds /for facilities /for the disabled /in Cheltenham. /

Total score (max 20):____________

Delay: □ Immediate □ 30 minute □ 1 week   Prompt given □

On the 12th /April, /Peter /Brooks /from Gloucester /became the first man /to travel around the coast /of Britain /in a wheel-chair. /The 27 year old /lost the use of his legs/ six years ago /in a car /accident. /The 4000 mile trip /took 14 weeks /and raised 50 000 pounds /for facilities /for the disabled /in Cheltenham. /

Total score (max 20):____________

5.2: Story Recognition Response Form: *Set A, Story 1*

Participant No_____ **Delay Key:** ☐ Immediate ◊ 30 minute ◯ 1 week

Story 1: *Tick the box next to the answer given (correct responses shown in bold)*

1. What was the man's name?
   - ☐ ◊ ○ **Peter Brooks**
   - ☐ ◊ ○ Peter Butcher
   - ☐ ◊ ○ Paul Brocks
   - ☐ ◊ ○ Paul Bailey
2. Where was he from?
   - ☐ ◊ ○ Cheltenham
   - ☐ ◊ ○ Worcester
   - ☐ ◊ ○ **Gloucester**
   - ☐ ◊ ○ Salisbury
3. Where did he travel?
   - ☐ ◊ ○ Around the coast of France
   - ☐ ◊ ○ Around the coast of Ireland
   - ☐ ◊ ○ **Around the coast of Britain**
   - ☐ ◊ ○ Across Britain
4. How did he travel?
   - ☐ ◊ ○ By bicycle
   - ☐ ◊ ○ **In a wheel-chair**
   - ☐ ◊ ○ On foot
   - ☐ ◊ ○ On crutches
5. When did he complete his journey?
   - ☐ ◊ ○ 21st August
   - ☐ ◊ ○ **12th April**
   - ☐ ◊ ○ 12th August
   - ☐ ◊ ○ 21st April
6. How old was he?
   - ☐ ◊ ○ 25
   - ☐ ◊ ○ 29
   - ☐ ◊ ○ **27**
   - ☐ ◊ ○ 23

7. What happened six years ago?

- ☐ ◊ ○ **He was involved in a car accident**
- ☐ ◊ ○ He was involved in a motor-cycle accident
- ☐ ◊ ○ He fell off a roof
- ☐ ◊ ○ He fell off a ladder

8. How many miles was the trip?

- ☐ ◊ ○ 2000
- ☐ ◊ ○ 5000
- ☐ ◊ ○ 3000
- ☐ ◊ ○ **4000**

9. How long did the trip take?

- ☐ ◊ ○ 4 weeks
- ☐ ◊ ○ **14 weeks**
- ☐ ◊ ○ 4 months
- ☐ ◊ ○ 40 days

10. How much money did he raise?

- ☐ ◊ ○ 100 000 pounds
- ☐ ◊ ○ 10 000 pounds
- ☐ ◊ ○ 5000 pounds
- ☐ ◊ ○ **50 000 pounds**

11. What was the money to be used for?

- ☐ ◊ ○ A spinal injuries unit
- ☐ ◊ ○ A children's hospital
- ☐ ◊ ○ **Facilities for the disabled**
- ☐ ◊ ○ The disabled Olympics

12. Where was the money to be used?

- ☐ ◊ ○ **Cheltenham**
- ☐ ◊ ○ Salisbury
- ☐ ◊ ○ Worcester
- ☐ ◊ ○ Gloucester

Score (max 12):_____

B.6: Long-Term Memory Questionnaire

The University Of Sheffield.

MEMORY QUESTIONNAIRE

In this questionnaire we would like you to think about the way your memory has been working.

PERSONAL DETAILS

SURNAME _____ FIRST NAME_____

ADDRESS _____ DATE OF BIRTH _____

_____

_____

TEL. NO. _____ FIRST LANGUAGE_____

GENDER Male Female (please circle)

If someone is helping you fill in this questionnaire, please tell us who this is:

_____

General Questions

When did your epilepsy start? _____

Do you have problems with your memory? Yes/No (circle one)

If Yes, please answer the following questions:

Do you forget things more quickly than you used to? Yes/No (circle one)

If yes, does this forgetting occur (please tick as appropriate):

in the first few minutes _____

in the first few hours _____

over a number of days _____

over a number of weeks_____

other (describe) _____

_____

37

B.7: Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Name: Date:

FOLD HERE

Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings he or she will be able to help you more.

This questionnaire is designed to help your clinician to know how you feel. Read each item below and **underline the reply** which comes closest to how you have been feeling in the past week. Ignore the numbers printed at the edge of the questionnaire.

Don't take too long over your replies, your immediate reaction to each item will probably be more accurate than a long, thought-out response.

A D

I feel tense or 'wound up'
- 3 Most of the time
- 2 A lot of the time
- 1 From time to time, occasionally
- 0 Not at all

I still enjoy the things I used to enjoy
- 0 Definitely as much
- 1 Not quite so much
- 2 Only a little
- 3 Hardly at all

I get a sort of frightened feeling as if something awful is about to happen
- 3 Very definitely and quite badly
- 2 Yes, but not too badly
- 1 A little, but it doesn't worry me
- 0 Not at all

I can laugh and see the funny side of things
- 0 As much as I always could
- 1 Not quite as much now
- 2 Definitely not so much now
- 3 Not at all

Worrying thoughts go through my mind
- 3 A great deal of the time
- 2 A lot of the time
- 1 Not too often
- 0 Very little

I feel cheerful
- 3 Never
- 2 Not often
- 1 Sometimes
- 0 Most of the time

I can sit at ease and feel relaxed
- 0 Definitely
- 1 Usually
- 2 Not often
- 3 Not at all

I feel as if I am slowed down
- 3 Nearly all the time
- 2 Very often
- 1 Sometimes
- 0 Not at all

I get a sort of frightened feeling like 'butterflies' in the stomach
- 0 Not at all
- 1 Occasionally
- 2 Quite often
- 3 Very often

I have lost interest in my appearance
- 3 Definitely
- 2 I don't take as much care as I should
- 1 I may not take quite as much care
- 0 I take just as much care as ever

I feel restless as if I have to be on the move
- 3 Very much indeed
- 2 Quite a lot
- 1 Not very much
- 0 Not at all

I look forward with enjoyment to things
- 0 As much as I ever did
- 1 Rather less than I used to
- 2 Definitely less than I used to
- 3 Hardly at all

I get sudden feelings of panic
- 3 Very often indeed
- 2 Quite often
- 1 Not very often
- 0 Not at all

I can enjoy a good book or radio or television programme
- 0 Often
- 1 Sometimes
- 2 Not often
- 3 Very seldom

Now check that you have answered all the questions.

A D

TOTAL

B.8: Seizure Diary

If you experience any seizures during the next week, please give details below. We would like you to record when the seizure occurred (day and time) and the type of seizure (if known).

Date	**Time**	**Type of seizure** (e.g. generalised, tonic-clonic, absences or auras, simple partial, complex partial).

B.9: Counterbalancing Schedule

Participant Number	Pre-surgery First Test for Controls							Post-surgery Second Test for Controls						
	Stimuli Set	*Immediate Recall Scenes*	*Immediate Recognition Set*	*30 min Recall Scenes*	*30 min Recognition Set*	*1 week Recall Scenes*	*1 week Recognition Set*	*Stimuli Set*	*Immediate Recall Scenes*	*Immediate Recognition Set*	*30 min Recall Scenes*	*30 min Recognition Set*	*1 week recall scenes*	*1 week recognition set*
1, 7, 13, 19, 25	**A** Recall first	1, 2, 3	1	4 ,5, 6	2	7, 8, 9	3	**B** Recog first	1, 2, 3	1	4 ,5, 6	2	7, 8, 9	3
2, 8, 14, 20, 26	**B** Recall first	1, 2, 3	1	4, 5, 6	2	7, 8, 9	3	**A** Recog first	1, 2, 3	1	4, 5, 6	2	7, 8, 9	3
3, 9, 15, 2, 27	**A** Recog first	4, 5, 6	2	7, 8, 9	3	1,2,3	1	**B** Recall first	4, 5, 6	2	7, 8, 9	3	1,2,3	1
4, 10, 16, 22, 28	**B** Recog first	4,5,6	2	7,8,9	3	1,2,3	1	**A** Recall first	4,5,6	2	7,8,9	3	1,2,3	1
5, 11, 17, 23, 29	**A** Recall first	7,8,9	3	1,2,3	1	4,5,6	2	**B** Recog first	7,8,9	3	1,2,3	1	4,5,6	2
6, 12, 18, 24, 30	**B** Recall first	7,8,9	3	1,2,3	1	4,5,6	2	**A** Recog first	7,8,9	3	1,2,3	1	4,5,6	2

APPENDIX C

Statistical Formulae

C1. Corrected Measure of Spatial Discrimination

C2. Corrected Measure of Descriptive Recall

C3. Signal Detection Theory

1. *Corrected Measure of Spatial Discrimination*

A corrected measure of spatial discrimination (see Hunkin et al., 1994) was used as the recall of spatial information varied depending on the number items recalled. For example, if only one item was recalled but the participant remembered its spatial location, this would lead to a 100% scores, clearly more than a participant who recalls six items but only recalls the correct spatial location for five of those items (who would score 80%).

Hunkin et al.'s discrimination score (*z*) is calculated as:

$$z = \frac{(r - x)}{sd}$$

where *z* = correct spatial responses; *x* = n.p.; n = number of items recalled; *p* = probability of recalling spatial information (by chance); *sd* = square root of (n.p.q); *q* = (1-p). The probability of recalling spatial information by chance was 0.25 (four potential grid locations).

2. Corrected Measure of Descriptive Recall

Muhlert (unpublished PhD thesis) devised a corrected measure of descriptive recall to account for the differences in the number of items recalled when calculating descriptive information. This descriptive score *%d* was calculated as (s used to avoid confusion with Cohen's d)

$$\%d = \left(\frac{d/2}{i}\right) \times 100$$

where: d = descriptive recall raw score (divided by 2 as it was scored up to two points for each item); i = item recall raw score. The score *%d* represents is the percentage of correctly recalled descriptive information about the remembered items.

3. Signal Detection Theory

signal detection theory was scored using to score visual scene recognition (see Macmillan & Creelman, 1991). The total number of hits and false positives were taken into account by calculating an index of accuracy (d') using the equation following formula:

$$d' = Z\left(\frac{yes}{signal}\right) - Z(\frac{yes}{non - signal})$$

Where: Z(Yes/Signal) = standard normal deviate corresponding to the percentage of hits; Z (Yes/Non-signal) = the percentage of false positives. Higher d' value reflects higher accuracy.

APPENDIX D

Correlation Matrices

D.2: *Pearson* ***r*** *correlation matrix of visual and verbal tests in the TLE group at the pre- and post-surgery testing intervals (n = 7). Probability values in parentheses and significant correlations are highlighted in bold.*

	Item free recall (pre)	Item free recall (post)	Visual free recall (Pre)	Visual free recall (post)	Desc free recall (pre)	Desc free recall (post)	Story recall (pre)	Story recall (post)	Story recognition (pre)	Story recognition (post)
Item free recall (pre)	-									
Item free recall (post)	**.855 (.014)***	-								
Visual free recall (pre)	**.768 (.044)***	.624 (.134)	-							
Visual free recall (post)	-.057 (.904)	.008 (.987)	.224 (.629)	-						
Desc free recall (pre)	**.798 (.032)***	.730 (.063)	.486 (.269)	.053 (.910)	-					
Desc free recall (post)	-.161 (.729)	-.281 (.542)	-.036 (.940)	-.256 (.580)	-.068 (.886)	-				
Story recall (pre)	.039 (.934)	-.033 (.945)	.252 (.586)	.093 (.843)	-.337 (.459)	-.722 (.067)	-			
Story recall (post)	.500 (.253)	.431 (.335)	.190 (.683)	.030 (.949)	.258 (.576)	**-.856 (.014)***	.638 (.123)	-		
Story recog (pre)	.566 (.186)	.414 (.355)	**.915 (.004)***	.445 (.317)	.257 (.577)	.116 (.805)	.179 (.701)	.013 (.987)	-	
Story recog (post)	.093 (.934)	-.129 (.783)	.085 (.855)	.617 (.140)	.181 (.697)	-.571 (.181)	.412 (.359)	.539 (.212)	.118 (.800)	-

note: Desc = descriptive* = < .05