Does accelerated long term forgetting occur in patients recently diagnosed with localisation related epilepsy?

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master of Philosophy by Marion Ashe

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Abstract: Does accelerated long term forgetting occur in patients recently diagnosed with localisation related epilepsy?

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Purpose: Memory difficulties are a problem for many people with epilepsy, caused by a variety of factors. Research has identified 'accelerated long term forgetting' as a possible cause for discrepancy between subjective and objective memory performance in patients with epilepsy, with research focusing on refractory epilepsy. The aim of this study was to examine the objective and subjective memory performance of patients recently diagnosed with epilepsy, including long term forgetting rates.

Methods: Newly diagnosed patients with localisation related epilepsy (n=14), and healthy controls (n=13) matched to age, gender and education level were assessed for intellectual functioning, general memory, subjective memory, and anxiety and depression. Furthermore, they were asked to learn a story and a set of visual scenes to a pre-set criterion level, with recall and recognition of both tested after 30 minutes and after three weeks.

Results: Patients and controls did not differ in their performance as measured by general memory score on Wechsler Memory Scale (WMS) (p=0.281). However, patients demonstrated significantly impaired retention on the learnt story over 30 minutes (p=0.024) and significantly impaired recall over three weeks (p=0.021), when compared to controls. In the visual scenes test, patients demonstrated impaired initial learning (p=0.018), but once learnt, retained the same amount of information as controls over a 30 min period (p=0.652). However, patients had significantly poorer recall (p=0.002) and increased forgetting rates (p=0.003) after three weeks, which correlated with lifetime number of generalised seizures (p=0.040). Seizures during the three week delay had no relationship to three week forgetting scores. Subjective memory scores did not differ between patients and controls, and were correlated with anxiety but not long term forgetting.

Conclusion: Compared to controls, recently diagnosed patients demonstrated impaired delayed recall of a story, and accelerated long term forgetting of a visual scenes task. Caution is needed interpreting these results because of the small numbers, and difficulty accounting for contributing factors to cognitive impairment (such as AED use and pathology). However these are the first results of long term forgetting investigations in recently diagnosed patients, and bring into question the need for memory testing over extended delays.

Contents

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Author's Declaration

This thesis is the result of my own work, and the material presented within it has not been previously presented, nor is currently being presented, for any other degree or qualification.

The study was designed by myself, under the guidance of my supervisor Professor Gus A Baker. All of the recruitment and assessment of participants was carried out by myself. Advice on the sample size calculation was given by Dr Stephen Lane, medical statistician at the University of Liverpool. The rest of the statistical analysis was decided on and carried out by myself, and I was responsible for the interpretation and writing up of the data.

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Abbreviations used in the text

AED – Anti-Epileptic Drug
ADM – Auditory Delayed Memory
AIM – Auditory Immediate Memory
ALF – Accelerated Long-term Forgetting
CBZ – Carbamazepine
CI – Confidence Intervals
CPS – Complex Partial Seizures
CSM – Common Sense Model (of illness representation)
CT – Computed Tomography
ECG – Electrocardiogram
EEG – Electroencephalogram
FSIQ – Full Scale Intelligence Quotient
GABA – Gamma-Aminobutyric Acid
GBP – Gabapentin
GCS – Glasgow Coma Scale
GM – General Memory
GTCS – Generalised Tonic Clonic Seizures
HADS – Hospital Anxiety and Depression Scale
HS – Hippocampal Sclerosis
IEDs – Interictal Epileptiform Discharges
IGE – Idiopathic Generalised Epilepsy
ILAE – International League Against Epilepsy
IQ – Intelligence Quotient
IQR – Interquartile Range
LEV – Levetiracetam
LMS – Logical Memory Story
LTG – Lamotrigine
LTP – Long Term Potentiation
MMPI – Minnesota Multiphasic Personality Inventory
MMSE – Mini Mental State Exam
MQ – Memory Questionnaire
MRI – Magnetic Resonance Imaging
PB – Phenobarbital
PGS – Primary Generalised Seizures
PHT – Phenytoin
PIQ – Performance Intelligence Quotient
SD – Standard Deviation
SGS – Secondary Generalised Seizures
SPSS – Statistical Package for Social Sciences
TEA – Transient Epileptic Amnesia
TLE – Temporal Lobe Epilepsy
TPM – Topiramate
VDM – Visual Delayed Memory
VIQ – Verbal Intelligence Quotient
VIM – Visual Immediate Memory
VNS – Vagus Nerve Stimulation
VPA – Sodium Valproate
WASI – Weschler Abbreviated Scale of Intelligence
WMS – Weschler Memory Scale

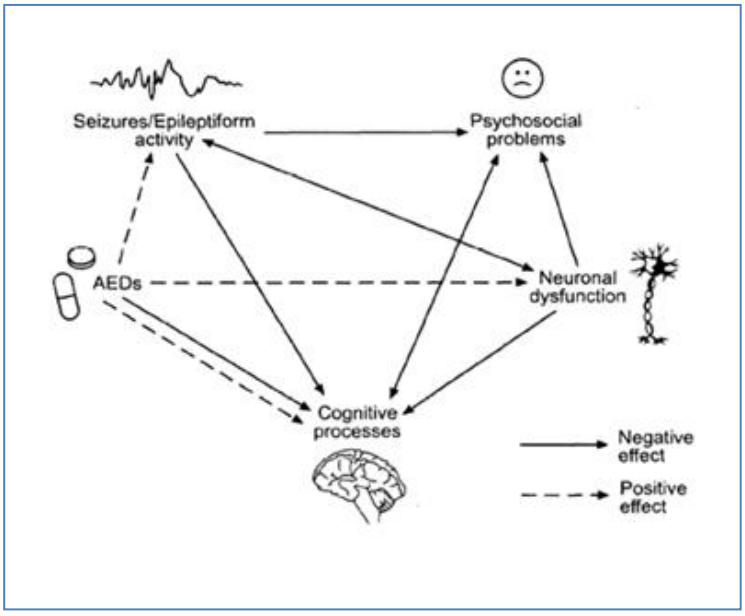
Chapter 1 Introduction

This chapter will briefly introduce the main issues to be discussed in this thesis and provide a short summary of the structure.

Affecting around 50 million people around the world, epilepsy is one of the most common neurological problems. Epilepsy describes a diverse family of disorders, characterised by at least one seizure and an enduring alteration in the brain increasing the likelihood of further seizures (Fisher *et al.*, 2005). However, there are many other ways that epilepsy can impact on a patient's life, which has been recognised by the ILAE (International League Against Epilepsy) in their move towards a new definition of epilepsy, encompassing the neurobiological, cognitive, psychological and social consequences of epilepsy (Fisher *et al.*, 2005). A general overview of epilepsy and its diagnosis and management will be given in Chapter 2.

The focus of this thesis will be the effects of epilepsy on cognitive functioning, with particular attention to memory functioning. Memory is our mental ability to retain and retrieve information, and is what allows us to change our behaviour according to past experience. It is a vital part of being able to function in the world, allowing us to form an idea of ourselves and also to form relationships with others. Memory difficulties can affect relationships, education and employment as well as our psychological well being and quality of life, so it is an area worthy of investigation. Chapter 3 will give an overview of types of memory and some of the theories behind memory processes.

Figure 1.1: Relationship of epilepsy factors and cognition (Aldenkamp, 2006)



Epilepsy has an effect on memory, but there are many potential inter-related causes which are difficult to disentangle (see figure 1.1). Chapter 4 will discuss objective memory problems in temporal lobe epilepsy, and their relationship to various factors including pathology, seizures, anti-epileptic drugs (AEDs) and mood factors.

Epilepsy seems to affect both objective and subjective memory, but it has been found that complaints often do not correlate with performance on neuropsychological tests. Subjective memory complaints in people with epilepsy and their relationship to neuropsychological assessment performance will be discussed in Chapter 5.

Chapter 6 will then discuss further one possible explanation for this discrepancy – Accelerated Long-term Forgetting (ALF). This is the idea of an impairment – possibly a consolidation problem – causing people to forget information significantly more over an extended period of time, when their memory over short intervals (as measured in neuropsychological tests) is intact. Studies that have

examined memory performance over extended delays will be reviewed, along with potential theories behind ALF.

ALF has been demonstrated in people who have had epilepsy for a number of years, but it has not been investigated in newly diagnosed patients. Cognitive functioning more generally in newly diagnosed patients with epilepsy has been examined in a number of studies, and these will be reviewed and discussed in Chapter 7. A number of problems have been identified but, similar to most neuropsychological studies in epilepsy patients, there are many confounding factors and potential methodological flaws that can affect the interpretation of the results, which will be discussed in this chapter.

The aim of this thesis is to examine memory functioning, both subjective and objective, in patients recently diagnosed with localisation related epilepsy. Memory functioning will be examined over an extended period, to investigate long term forgetting rates, as it is felt that this will provide an interesting insight into mechanisms of memory problems in epilepsy patients and also assess the clinical need for extended delay memory testing. The aims and hypotheses of the study will be outlined in more detail in Chapter 8, and the research methods employed to achieve those aims outlined in Chapter 9. A series of analyses of the results of the study will be undertaken, to assess the findings regarding each hypothesis, which will be reported in Chapter 10. Chapter 11 will discuss these results, and how they help to contribute to our understanding of memory functioning in recently diagnosed epilepsy, as well as examining the limitations of the research and considering clinical implications and potential future research directions.

Chapter 2 Epilepsy

2.1 Definition

Epilepsy is a family of chronic neurological disorders characterised by recurrent, unprovoked seizures. A seizure can be defined as 'a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain' (Fisher *et al.*, 2005).

The word 'epilepsy' comes from a Greek word meaning 'to be seized by forces from without' (Browne & Holmes, 2004). It was initially recognised by Hippocrates as an organic process of the brain. However, many ancient writers considered seizures to be caused by supernatural forces, a view that still persists in some developing countries (for example, in Kenya there is a poor understanding of the condition, and five people were recently burned alive for being labelled witches as they were accused of casting a spell on a boy who had an epileptic seizure (Joseph, 2009)).

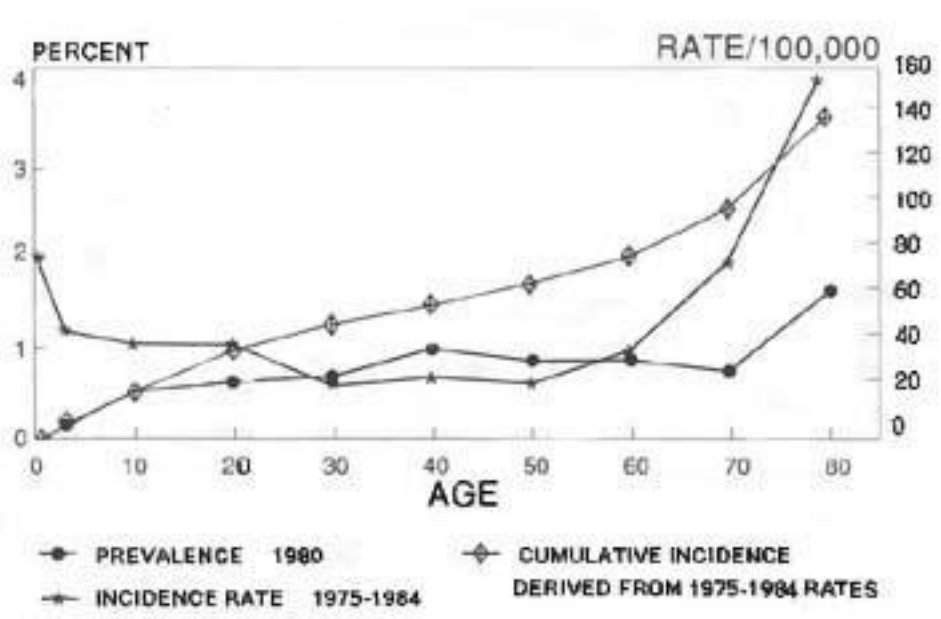
John Hughlings Jackson, a pioneer of epileptology, made unparalleled contributions to furthering the understanding of epilepsy in the late 19th century, defining epilepsy as 'occasional, sudden, excessive, rapid and local discharges of the grey matter' (Sengoku, 2002). By studying individual clinical cases he endeavoured to find the mode of onset and pattern of seizures, leading to the concept of focal epilepsies.

We now understand epilepsy as a complex symptom which can be caused by a variety of pathological processes in the brain. Clinicians might define it as 'the recurrent paroxysmal transient disturbance of brain function due to disturbance of electrical activity in the brain, where the disturbance is unrelated to infection or

acute cerebral insult' which can manifest through clinical seizures (GPnotebook). On the other hand, a person with epilepsy may look at the disorder in a very different way, defining it according to their experiences of attacks and the impact the disorder has on their life, their self-image, and their psychosocial wellbeing (Browne & Holmes, 2004). Epilepsy can be for some people (but not all) a very disruptive problem, affecting all areas of a person's life, and limiting their independence and quality of life.

Epilepsy is a common neurological disorder, with around 50 million people worldwide living with epilepsy (WHO, 2009). In the UK, active epilepsy has a lifetime prevalence of around 400 per 100,000 people (Sander, 2003). However, we all have around a 10% lifetime risk of having a seizure, and around 3% risk of developing epilepsy (Pohlmann-Eden *et al.*, 2006). The onset of epilepsy is most common in young children and older adults (see figure 2.1).

Figure 2.1: Prevalence, cumulative incidence and incidence rates of epilepsy (Hauser & Annegers, 1993)



2.2 Classification

Two systems of classification can be used for epilepsy: classification of the seizures themselves and classifications of the epilepsy type or syndrome. Classification of seizures allows them to be viewed as single independent events based on clinical and electroencephalographic information. The International League Against Epilepsy (ILAE) has standardised what was once a minefield of terminology (see table 2.1) (Bancaud *et al.*, 1981). Seizures are initially classified into one of two broad groups, partial seizures (seizures that can be localised to a particular area of the brain) and generalised seizures (seizures that are bilaterally symmetrical and cannot be localised to a particular area or hemisphere of the brain), and further classified according to other features such as impairment of consciousness and type of clinical manifestation (Browne & Holmes, 2008).

Partial seizures beginning in one area of the brain can be simple (no impairment of consciousness) or complex (with impairment of consciousness or altered awareness, often complicated by automatisms like lip-licking or fiddling) and can progress to become secondary generalised. This is when a simple or complex partial seizure progresses to a generalised tonic-clonic seizure (rhythmic jerky contraction and relaxation of muscles alongside autonomic features such as increased heart rate, blood pressure and flushing, followed by relaxation, drowsiness or confusional state). Generalised seizures can be absence (sudden short-lasting impaired responsiveness), myoclonic (sudden brief muscle contractions), tonic (sudden increased tone), atonic (sudden loss of muscle tone) or tonic-clonic (Browne & Holmes, 2008).

Table 2.1: International Classification of Epileptic Seizures (Bancaud et al., 1981)- reproduced with permission

I. Partial seizures	A. Simple partial seizures	1. With motor signs	a) Focal motor without march b) Focal motor with march (Jacksonian) c) Versive d) Postural e) Phonatory
		2. With somatosensory or special-sensory symptoms	a) Somatosensory b) Visual c) Auditory d) Olfactory e) Gustatory f) Vertiginous
		3. With autonomic symptoms or signs	
		4. With psychic symptoms	a) Dysphasia b) Dysmnesic c) Cognitive d) Affective e) Illusions f) Structured hallucinations
	B. Complex partial seizures	1. Simple partial seizures at onset, followed by impairment of consciousness	a) With simple partial features b) With automatisms
		2. With impairment of consciousness at onset	a) With impairment of consciousness only b) With automatisms
	C. Partial seizures evolving to secondarily generalized seizures	1. Simple partial seizures evolving to generalized seizures	
		2. Complex partial seizures evolving to generalized seizures	
		3. Simple partial seizures evolving to complex partial seizures evolving to generalized seizures	

II. Generalized seizures	A. Absence seizures	1. Typical absence seizures	a) Impairment of consciousness only b) With mild clonic components c) With atonic components d) With tonic components e) With automatisms f) With autonomic components
		2. Atypical absence seizures	
	B. Myoclonic seizures C. Clonic seizures D. Tonic seizures E. Tonic-clonic seizures F. Atonic seizures		
III. Unclassified epileptic seizures			

With regard to classifying type of epilepsy, it can be categorised as 'localisation related', when the seizures can be localised to one area of the brain (ie partial seizures) or 'generalised', when there are primary generalised seizures (ILAE, 1989). Epilepsy can also be classified by the cause as far as it is known (idiopathic, cryptogenic or symptomatic) and type of epilepsy, or epilepsy syndrome. If a cause, such as a brain tumour or arterio-venous malformation, is found then epilepsy is said to be 'symptomatic', whereas epilepsy is 'cryptogenic' if there is likely to be a cause but it cannot be identified. 'Idiopathic' epilepsy is thought to be caused by genetic factors, and is associated with no structural brain abnormality (ILAE, 1989). For example, 'symptomatic localisation-related epilepsy' would involve seizures arising from a known localised structural abnormality, with or without spread to the rest of the brain.

This allows common patterns of seizure types to be categorised further according to other factors like aetiology, age of onset, classic EEG findings etc, as epileptic syndromes such as childhood absence epilepsy, juvenile myoclonic epilepsy and Lennox-Gastaut syndrome. Whilst many patients will not fit into the classification of an epilepsy syndrome, if they do it can be a useful tool for assessing management and prognosis, as effective medication and the progression of the disorder can to an extent be predicted by the syndrome.

2.3 How do seizures happen?

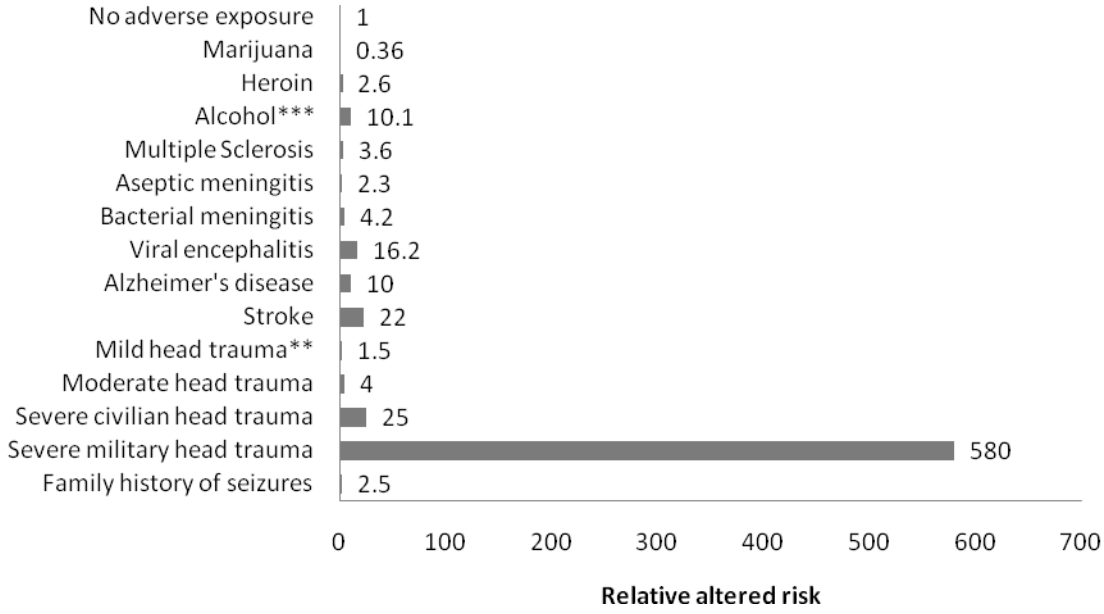
There are numerous causes of epilepsy, but the primary disorder is due to abnormal neuronal discharges. Focal seizures are caused by abnormal neuron discharge and seizure activity in specific areas of the brain. The basic mechanism of neuronal excitability is the action potential, transmitted down the axon of a neuron to stimulate neurotransmitter release at the synapse (Browne & Holmes, 2008). Seizures occur due to a combination of high-frequency bursts of action potentials, associated with a spike on EEG (electroencephalogram), and hypersynchronisation of a population of neurons, and recruitment of adjacent neurons, to create abnormally linked discharges from a large number of cells together. The abnormal neuronal activity which leads to this 'electrical storm' can come about due to either abnormal neuronal membranes or an imbalance in inhibitory and excitatory influences (Browne & Holmes, 2008). Anti-epileptic drugs tend to work by affecting one of these processes, either modulating ion channels in the membrane, or affecting the activity of inhibitory or excitatory neurotransmitters (Browne & Holmes, 2008).

2.4 What causes epilepsy?

The potential to have an epileptic seizure is present throughout the population. In as many as 60% of people with epilepsy no identifiable aetiology is found

(Sander & Hart, 1990). However, epilepsy can be due to an underlying brain disorder and these causes can be split into a number of areas. Congenital malformations, or damage to a baby's brain during pregnancy, at delivery or shortly after can cause epilepsy by scar formation. Head injuries, central nervous system infections, cerebrovascular disease and tumours are all potential causes of epilepsy (see figure 2.2 for relative risks of various predisposing factors).

Figure 2.2: Factors associated with an increased risk of epilepsy relative to people without those adverse exposures. Produced using data from (Hauser & Annegers, 1993)



** Not statistically significant. ***One pint of 80% proof alcohol, 2.5 bottles of wine/day.

Certain drugs, toxins, or metabolic disturbances can also provoke seizures, or lower the seizure threshold, although this is not the same as causing epilepsy. One of the most common causes of provoked seizures is alcohol use or withdrawal, but withdrawal or use of other toxins can also cause seizures, including heavy metals or organophosphates (Allen *et al.*, 2006). Some drugs such as antipsychotics or antidepressants can also lower a person's seizure threshold, making it more likely they will have a seizure if there is a precipitating factor. Metabolic disturbances that can cause seizures include

hypoglycaemia, hyponatraemia, hypomagnesaemia, hypocalcaemia, renal failure and liver failure (Allen *et al.*, 2006).

2.5 Diagnosis

Making a correct diagnosis of epilepsy is very important, as an erroneous diagnosis could result in not only needless distress but also unnecessary medication with serious side effects, potential loss of a driving licence and possible loss of a job (Browne & Holmes, 2008). It is also important to try and find a cause for the epilepsy, otherwise disease processes underlying seizures that are potentially treatable could be overlooked. A diagnosis of epilepsy type, and, where possible, syndrome, can also be helpful in directing treatment.

A diagnosis of epilepsy is largely clinical, based on a thorough history of seizures given by an eye-witness. There are some important differential diagnoses that should be ruled out depending on the presentation, including syncope, migraine, non-epileptic attacks and cardiac arrhythmias (Browne & Holmes, 2008). Investigations can be undertaken to rule out other causes of seizures, such as biochemical tests for electrolyte or glucose abnormalities, and a 12 lead ECG (electrocardiogram) looking for arrhythmias. An EEG, which provides a graphical representation of electrical activity in the cortex, can be useful in identifying some syndromes (such as idiopathic generalised epilepsy) but an interictal EEG is unlikely to capture all seizure activity so is often inconclusive. If further clarification is needed for diagnosis or seizure type, EEG recording can be taken during sleep, over longer periods, alongside video recording, or in conditions likely to initiate seizures (such as sleep deprivation) (Browne & Holmes, 2008). Imaging such as MRI (Magnetic Resonance Imaging) or CT (Computed Tomography) can also be used to look for any possible underlying cause of seizures by identifying structural abnormalities (Browne & Holmes, 2008).

2.6 Management

The management of epilepsy is based not only around eliminating or reducing seizures as far as possible, but also ameliorating or minimising the psychological and social problems the disease and its stigma can cause (Browne & Holmes, 2008). This includes issues such as loss of driving licence, self esteem issues, and common comorbidities like anxiety and depression.

Treatment of seizures themselves is usually pharmacological. The medications used will be guided by the seizure type and considerations regarding side effects, with monotherapy (single-drug therapy) whenever possible. Monotherapy with an appropriate drug is able to achieve seizure control in 60-90% of patients, without the added risks they are exposed to from multiple drugs (Browne & Holmes, 2008). However, if monotherapy is ineffective at the maximum dose, additional therapy can be added, following the principle of adding drugs with different mechanisms of action, or 'rational polytherapy' (Lee & Dworetzky, 2010). Antiepileptic drugs of choice for different seizure types are shown in table 2.2. They have various mechanisms of action, including inactivating sodium channels, attaching to GABA receptors to inhibit depolarisation, reducing calcium currents into cells and antagonising the excitatory neurotransmitter glutamate. These all have the effect of preventing excessive excitability, which can prevent seizures but also may have other unwanted effects, such as drowsiness.

Anticonvulsants also have other negative effects including, depending on the drug: allergic rashes, weight gain, irritability and importantly teratogenicity, among others. Certain anti-epileptic medications can be very detrimental to a foetus when taken during pregnancy, causing physical malformations or cognitive and behavioural difficulties (Morrow *et al.*, 2006; Bromley *et al.*, 2009). This means that the choice of medication in women prior to and of child-bearing age is a particularly important and difficult decision, requiring thorough discussion of potential risks and benefits with the patient (Winterbottom *et al.*, 2009).

The recent SANAD trial was a large multicentre randomised controlled trial assessing a number of the standard and newer anti-epileptic medications. The arm studying patients with generalised seizures found sodium valproate to be the most effective drug, it being more efficacious than lamotrigine and better tolerated and more efficacious than topiramate, although the potential difficulties using valproate in women of childbearing age were noted (Marson *et al.*, 2007b). The arm studying patients with partial epilepsies showed lamotrigine to be the drug of choice, as it was as effective as carbamazepine and better tolerated, as well as being better tolerated than topiramate, gabapentin and oxcarbazepine (Marson *et al.*, 2007a).

Table 2.2: Antiepileptic drugs of choice, using information from (BNF, 2010)

Seizure type		1st line medication	2nd line medication
Partial seizures with or without secondary generalisation		Carbamazepine Lamotrigine Oxcarbazepine Sodium Valproate	Clobazam Gabapentin Levetiracetam Pregabalin Tiagabine Topiramate Zonisamide
Generalised seizures	**Generalised tonic clonic**	Carbamazepine Lamotrigine Sodium Valproate	Clobazam Levetiracetam Oxcarbazepine Topiramate
	Absence	Ethosuximide Sodium Valproate	Clonazepam Lamotrigine
	Myoclonic	Sodium Valproate	Clonazepam Lamotrigine Levetiracetam Topiramate
	Atypical absence, atonic and tonic	Sodium Valproate Lamotrigine Clonazepam	Clobazam Ethosuximide Levetiracetam Topiramate

If epilepsy is not adequately controlled by medication, there are potentially other options, depending on the epilepsy type. Surgery can be considered in patients with

medically intractable partial epilepsy who have a localised seizure focus on MRI or EEG, if their seizures are significantly affecting their quality of life. Removing the area of cortex where seizures are initiating, so long as it can be well identified (through EEG, clinical history, neurological examination, neuropsychological assessment and both anatomical and functional neuroimaging) and safely resected, offers a potential opportunity for seizure freedom (Browne & Holmes, 2008). However, it is not always successful and can also leave patients with significant deficits, for example memory problems when surgery is undertaken for temporal lobe epilepsy.

Vagus nerve stimulation (VNS) and ketogenic diets are potential treatment options in certain types of epilepsy (Browne & Holmes, 2008). VNS involves implantation of a programmable stimulator subcutaneously in the chest, which stimulates the vagus nerve when activated. Reports of outcomes are mixed but mildly positive (Fisher & Handforth, 1999; DeGiorgio *et al.*, 2000; Ben-Menachem, 2002), but it is often used as a final resort when nothing else has worked. A ketogenic diet, involving eating a high proportion of fats to a small amount of carbohydrate and proteins, leads to the brain shifting to ketones as a major energy source rather than glucose, causing increased cerebral energy reserves and GABA shunt activation (Browne & Holmes, 2008). This can bring about seizure control in certain types of epilepsy without the side effects of medication or surgery (Cross & Neal, 2008). New treatment options are also being investigated for their effectiveness in epilepsy, including deep brain stimulation, which is successful in movement disorder treatment (Schulze-Bonhage, 2009).

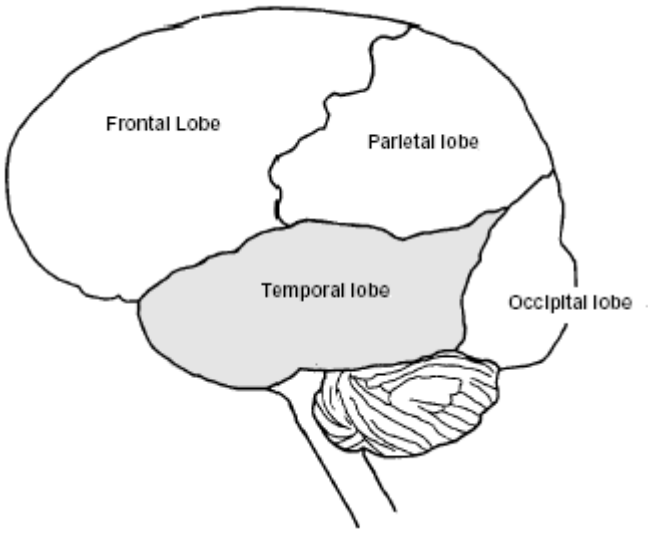
2.7 Temporal lobe epilepsy

This project will focus on temporal lobe epilepsy (TLE) as this is the population in which the majority of research on long term forgetting has been done (Martin *et al.*, 1991; Giovagnoli *et al.*, 1995; Bell *et al.*, 2005; Bell, 2006; Mameniskiene *et al.*, 2006; Wilkinson *et al.*, under review), and it will therefore be considered in a little more

detail. TLE was first recognised by John Hughlings Jackson in 1881 as a 'dreamy state' arising from the temporal lobe, and is now recognised as recurrent unprovoked seizures arising from the medial or lateral temporal lobe. It is probably the most common form of focal epilepsy, but the true prevalence of TLE is unknown (Ko & Sahai-Srivastava, 2009).

The temporal lobe is separated from the frontal and parietal lobes by the Sylvian, or lateral fissure (see figure 2.3). Portions of the temporal lobe are involved in episodic and semantic memories, emotions, and smell, which can help explain why some temporal lobe seizures can include memory phenomena like déjà vu and jamais vu, olfactory hallucinations and sensations of panic (Zeman, 2005). In the superior part of the temporal lobe, around the lateral fissure, is the auditory cortex. This can explain why in some temporal lobe seizures patients can experience auditory hallucinations, dysphasia or speech arrest (Zeman, 2005).

Figure 2.3: Lobes of the cerebrum (EpilepsyFoundation, 2010)



As for the causes of TLE, there is a link between the development of temporal lobe epilepsy and complex febrile seizures (febrile seizures lasting over 15 minutes, with focal features or recur within 24 hours). However, it is debatable whether it is the

febrile seizures that lead to epilepsy or rather they are just the first sign of the condition (see discussion in Chapter 4). The pathological change occurring most commonly in TLE is hippocampal sclerosis (HS), present in as many as 70% of patients treated surgically (Najm *et al.*, 2006). Similar to with febrile seizures, there is some debate as to whether the HS causes the epilepsy or is a result of it (Cendes, 2005). Other potential causative factors include: infections (herpes encephalitis, bacterial meningitis), trauma resulting in cortical scarring (eg forceps delivery), hamartomas, malignancies, vascular malformations, or rarely familial causes, but most commonly the epilepsy is cryptogenic (Ko & Sahai-Srivastava, 2009).

TLE can occur in any age group. Clinically, it can present with a variety of features dependent on the function of the area affected. Around 80% of patients will have some form of simple partial seizure, or aura, first – this can be somatosensory, sensory, autonomic or psychic (Ko & Sahai-Srivastava, 2009). Somatosensory or sensory auras would be things like gustatory or olfactory hallucinations, auditory hallucinations, disorders of perception like distortion of shape or size. Autonomic phenomena include changes in heart rate, sweating, and nausea, or an epigastric rising sensation. Psychic phenomena include feelings of déjà vu, jamais vu, derealisation, detachment, feeling familiarity or unfamiliarity, or even feelings of impending doom. These auras are simple partial seizures, and they may or may not progress to a complex partial seizure or on to a secondary generalised tonic-clonic seizure (Ko & Sahai-Srivastava, 2009).

Complex partial seizures involve impairment of consciousness, so the patient may stare motionlessly, be unresponsive, and demonstrate certain typical automatisms such as lip-smacking, chewing or making repetitive hand movements. Following a complex partial seizure, there will be a period of post-ictal confusion, often longer than the seizure itself. This post-ictal phase can help to distinguish complex partial seizures from absence seizures (Browne & Holmes, 2008). A complex partial seizure may also progress to a secondary generalised tonic-clonic seizure. In this case, it is likely that the generalised seizure may be all that is reported if a very careful history is not taken.

The initial management of TLE is similar to other epilepsies, and begins with antiepileptic medication (if the seizures warrant treatment). Carbamazepine or lamotrigine are generally used first line, and many of the newer anti-epileptic drugs are also licensed for use as second line agents.

If seizures are refractory, as is more likely if there is HS (Semah *et al.*, 1998), TLE can be responsive to surgical resection of the epileptogenic region. Extensive pre-operative testing is required, by MRI, video EEG and telemetry, neuropsychological testing and, where required, a Wada test to assess the functionality of the tissue to be removed (Browne & Holmes, 2008).

Apart from the direct effects of seizures, there are other ways that epilepsy impacts on a patient's life, for example via stigmatisation, poorer quality of life, driving and job issues, and cognitive complaints. One of the most commonly reported cognitive problems in epilepsy, particularly TLE, is with memory. In the next chapter, I will consider memory as a concept and discuss types and theories of memory.

Chapter 3 Memory

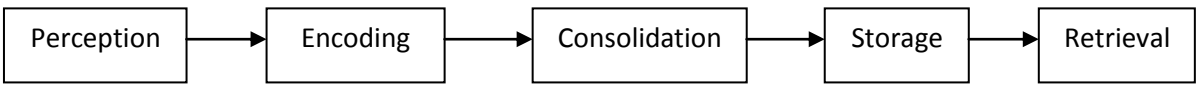
In this chapter memory will be considered as a concept, with a discussion of different types of memory as well as a brief overview of some of the theories of memory formation.

Memory is one of the highly interdependent features of cognition, alongside features including consciousness, orientation, attention, executive function, language, praxis, calculation and perception (Zeman, 2009). It is the capacity that allows our behaviour to change in relation to what has happened in the past using neural plasticity, and it has a relationship to learning (Zeman, 2009).

Learning is the process by which new information is acquired, whereas memory is the persistence of learning in a state that can be revealed at a later time (Squire, 1987). Thus, memory is the outcome of learning, and memories are only created when learning happens (Gazzaniga *et al.*, 2009). As memory cannot exist without learning and learning relies on memory, they are often thought of and tested together.

Learning and memory can be divided into stages, as a series of processes that come together to form a memory (see figure 3.1). In order to successfully utilise learning, each stage of the process must be intact.

Figure 3.1: The stages of remembering (from information given by Zeman (Zeman, 2009))



3.1 Models of Memory

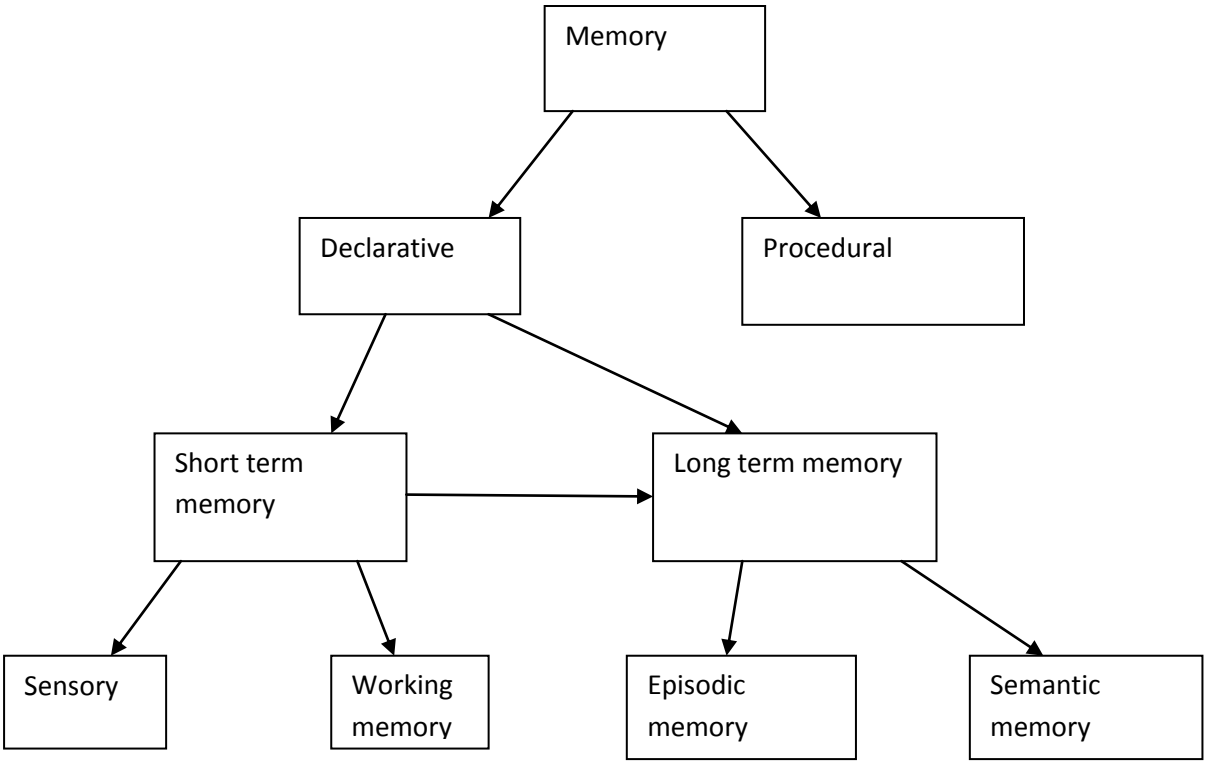
Memory can be classified in various ways, according to different aspects of the material remembered and the processes involved. Memory is by its nature something that persists over time, so memories can be classified according to how long they are remembered for.

There are two broad categories of memory: declarative and procedural (see figure 3.2). Declarative (or explicit) memory is memory for facts or knowledge that we have conscious access to, whereas procedural (or motor) memory is unconscious memory for learned tasks or skills, or 'knowing how' memory (Cohen & Squire, 1980; Longstaff, 2005). Within declarative memory, there is a temporal component, so declarative memory can be split up according to how long something is remembered for, into sensory memory, short-term memory and long-term memory. It can also be split according to the information remembered into episodic memory, or memory for specific events associated with a particular time and place, and semantic memory, memory of facts unrelated to specific events (Tulving, 1972). The focus of this introduction will be declarative memory, as this is the main focus within the current study. Whilst it is beyond the scope of this study, readers are directed to (Gazzaniga *et al.*, 2009) for a more detailed outline of further types of memory. Firstly, temporal classifications of memory and how they interact will be considered.

Sensory memory is over milliseconds or seconds, and does not require specific paying of attention. The auditory 'echo' that persists for a few seconds can be retrieved, even if attention is not paid, and is known as the sensory memory trace or sensory register. For audition, it is echoic memory whereas for vision it would be iconic memory (Gazzaniga *et al.*, 2009). These sensory traces are thought to decay very quickly, and are considered not accessible to conscious awareness, but can hold more information than can be converted into short term memory and reported

on (Sperling, 1960; Gazzaniga *et al.*, 2009). Iconic memory is visual information present for only a few hundred milliseconds which then rapidly decays, whereas the echoic trace for auditory information is thought to last up to 10 seconds (Sams *et al.*, 1993; Gazzaniga *et al.*, 2009).

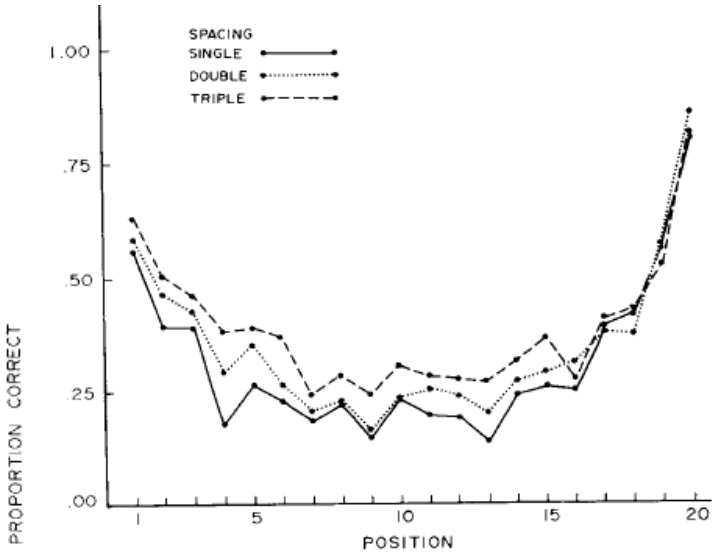
Figure 3.2: Tree of memory



Short term memory is, in contrast to sensory memory, freely available to our conscious awareness, however it has a much more limited capacity. It is only a temporary store, viable for seconds to minutes, and material requires repeated rehearsal to keep it there. Material in short term memory is thought to be lost by decay of information (hence the need for repeated rehearsal) or by disruption from other input, or a combination of both (Gazzaniga *et al.*, 2009). Primacy and recency effects are demonstrated in normal subjects when testing short term memory, for example by repeating back a list of unrelated words (Glanzer & Cunitz, 1966). Primacy is greater recall of material at the start of the list, because these have been rehearsed most and been transferred to long term memory, whereas recency is greater recall of material at the end of the list, because this has had less time to decay so is still in short term memory. This is known as the serial position effect (see

figure 3.3) (Glanzer & Cunitz, 1966). Primacy is affected by the speed of presentation, and is eliminated if the material is presented too quickly, whereas recency is eliminated by distraction tasks after the presentation (Gazzaniga *et al.*, 2009).

Figure 3.3: Serial Position Effect (Glanzer & Cunitz, 1966)- reproduced with permission



N.B. Spacing refers to the length of time between presentation of the words in the word list

There are several models of short term memory. The Atkinson and Shiffrin modal model (Atkinson & Shiffrin, 1968) suggests sensory information first enters a sensory register, or sensory memory, and then attentional processes move certain items into the short term memory. Items then move into the long term memory by repeated rehearsal, and at each stage information can be lost by interference, decay or a combination of the two. By this hierarchical model, items are passed from sensory memory to short term memory, and only then to long term memory, but this view is disputed by other experimental evidence, particularly studies of patients with brain damage which have been useful in examining how memory functions. Case studies of patients with very limited short term memory but almost intact abilities to form long term memories suggest that short term memory cannot be the only gateway to long term memory (Shallice & Warrington, 1970; Markowitsch *et al.*, 1999). A possible alternative view is that short-term memory is

based on the same neural networks as long term memory, but they are not activated in quite the same way (Zola-Morgan & Squire, 1993; Ranganath & Blumenfeld, 2005).

Another proposed model is the levels of processing model (Craik & Lockhart, 1972). This model proposes that there are other factors influencing what information is passed to long term storage, including that the 'deeper' an item is processed, the better it is stored in long term memory. This suggests elaborate encoding and relating information to previously acquired knowledge provides better learning than storing information as simple visual or verbal codes.

The working memory model (Baddeley & Hitch, 1974) is a widely accepted model proposed to explain some of the shortcomings of short-term memory models. Working memory is seen as a limited capacity store for both retaining information in the short term, and also processing that information during complicated tasks. It can involve information straight from the sensory input and information retrieved from the long term memory put together to enable processing complex tasks, such as driving (Longstaff, 2005). A multi-component model of working memory has been proposed (Baddeley & Hitch, 1974) and since updated (Baddeley, 2000; Repovs & Baddeley, 2006) to explain the shortcomings of the unitary model proposed by Atkinson and Shiffrin in 1968, initially comprising of a central executive assisted by two storage systems: the phonological loop and the visuospatial sketchpad. This has since been updated and a fourth component introduced to the model: an episodic buffer (Baddeley, 2000; Repovs & Baddeley, 2006). This provides a model of working memory as a limited capacity store providing an interface between perception, long term memory and action.

The phonological loop subsection of this working memory model is a short lived store for information presented acoustically, and coding mechanism for that information by repeated rehearsal sub-vocally. Subjects with problems in short term phonological memory tend to have lesions in the left temporo-parietal area

(Warrington *et al.*, 1971; Vallar *et al.*, 1997), suggesting this may be the anatomical base for the phonological loop, an idea backed up by functional neuroimaging studies suggesting the phonological loop is based in the left pre-frontal and parietal regions (Cabeza & Nyberg, 2000).

The visuospatial sketchpad is an equivalent store and processing mechanism for visual information. It provides a capacity to hold and manipulate visuospatial information, and it is thought that it might be possible to separate the visuospatial sketchpad into visual and spatial memory components (Repovs & Baddeley, 2006). Lesions particularly in the right hemisphere can lead to deficits in visuospatial working memory (Hanley *et al.*, 1991), and in functional neuroimaging studies, bilateral parietal activation is generally associated with spatial working memory (Smith *et al.*, 1996; Cabeza & Nyberg, 2000).

The central executive mechanism acts as a control system, overseeing the two subsystems and managing and directing attentional processes (Repovs & Baddeley, 2006). This is the least researched component of the original working memory model, as well as the least understood (Repovs & Baddeley, 2006). Executive functioning has been linked to the frontal lobes in neuroimaging studies (Smith & Jonides, 1997).

The idea of an episodic buffer has been added to the working memory model to explain some of the unexplained issues from the previous model. For example, it accounts for the advantage in recall for semantically linked words, provides an explanation for the links between working and long term memory, and explains how the two slave-systems (phonological loop and visuo-spatial sketchpad) interact and information from them binds together (Repovs & Baddeley, 2006). It is proposed to integrate information from both the working memory systems and long term memory, and represents a separate storage system using a multi-modal code (Repovs & Baddeley, 2006).

3.2 Long term memory and consolidation

Long term memory is information maintained over a significant period of time. This period of time is debatable but generally thought to be of the order of minutes to hours rather than seconds. Alternatively, material in long term memory can be considered as the material that can be recollected following distraction (Squire, 1986). It can be split according to the types of information stored into episodic memory (personal recollection of events in our lives) and semantic memory (knowledge of facts and concepts that are learnt, rather than experienced) (Tulving, 1972).

Memory is not fixed from the point of learning but over time continues to stabilise (Squire, 1986). The idea of consolidation has been around for over a century, since it was first proposed by Muller and Pilzecker ((Müller & Pilzecker, 1900) cited in (McGaugh, 2000)). Finding that newly learned information was disrupted by learning other information shortly after, they proposed that the processes that underlie the formation of new memories are fragile and consolidate over time. This hypothesis was supported by Duncan's research in 1949 that showed rats given an electric shock to the head shortly after learning a maze had much poorer memory for the maze than those who had no electric shock. Rats having shocks at longer delays had progressively better memory for the maze, with rats with a shock 1 hour or more after learning had equal memory to controls. This demonstrated that there may be a period after learning where the material learnt is susceptible to disruption, for example by electro-convulsive shock, but the material becomes more stable over time (Duncan, 1949).

Declarative memory relies on the hippocampus and medial temporal lobe structures for the encoding and short term retrieval of memories (Squire, 1992), but

over time retrieval is thought to become independent of the hippocampus (Kapur & Brooks, 1999). However, when and which memories become independent of the hippocampus is an issue of debate, as will be discussed.

The standard model of consolidation suggests that the hippocampus has a time-limited role, being vital for early storage and retrieval followed by a gradual reorganisation process whereby information is transferred to neocortical networks (Sutherland & McNaughton, 2000). A short-term consolidation process, lasting seconds to minutes, binds information into a memory trace, followed by a long-term consolidation process to stabilise it (Nadel & Moscovitch, 1997). The exact mechanism by which this happens is unclear, but Squire suggests that an important concept is that 'information in the medial temporal lobe directs consolidation by gradually changing the organisation of cortical representations, for example, strengthening connections between the cortical sites that participate in representing a memory' (Squire & Alvarez, 1995). Hippocampal synapses can change quickly, so the hippocampus acts as a short term temporary memory store, while neocortical synapses change slowly. If the hippocampal system repeatedly reactivates representations in the neocortex, strong interconnections between cortical sites form, able to support the memory independent of the hippocampus (Squire & Alvarez, 1995). According to this model, with a purely hippocampal lesion there would be temporally-limited retrograde amnesia, whereas more extensive damage to the temporal neocortex would result in more extensive retrograde amnesia (Squire & Alvarez, 1995). For example, a patient with hippocampal damage might have amnesia for a period of time before the damage, while the memories were still being consolidated, but have intact memory for events longer ago which had already been fully established in the neocortex independent of the hippocampus.

The Multiple Memory Trace theory (MMT) is another suggestion, which involves the hippocampus having a lifetime role in the retrieval of episodic autobiographic memories (Nadel & Moscovitch, 1997; Nadel *et al.*, 2000). This is that the hippocampus is always involved in retrieval and storage of episodic memories but semantic information is established in neocortex so can survive hippocampal

damage (Nadel *et al.*, 2000). As memory is created, a code in the hippocampus binds information stored in other brain regions to create a memory of a specific episode or scene, so interaction between the hippocampus and the other brain regions involved is required indefinitely. However, semantic memories are thought to be dependent on the hippocampus while they are consolidated and can later become independent (Nadel *et al.*, 2000), demonstrating a crucial distinction between episodic and semantic memories.

The cellular mechanism by which consolidation occurs is thought to be LTP (long term potentiation) (Squire & Alvarez, 1995). This is a form of synaptic plasticity, which involves the persistent enhancement of signal transmission between two neurons by their repeated synchronous stimulation (Cooke & Bliss, 2006). This follows the principles of Hebb's Law, that 'if a synapse is active when a post-synaptic neuron is active, the synapse will be strengthened' (Hebb, 1949; Gazzaniga *et al.*, 2009). Long term potentiation is thought to be a good model for memory because of its longevity, both processes require protein synthesis, and potentiation is input specific, so a single pathway can be potentiated without impacting other connections to that neuron, increasing the information coding capacity of the brain. Also, association means that a weak stimulus can combine with a strong stimulus, or other weak stimuli, to become potentiated, providing a mechanism for associating events or entities in our learning (Cooke & Bliss, 2006).

Consolidation does not merely provide a strengthening of memory traces, but also the opportunity for the integration of new memories with existing knowledge networks, so that they are accessible for delayed retrieval (Diekelmann *et al.*, 2009). It also appears to provide an opportunity for experience and emotion to modulate the strength of our memories, for example by the interaction of stress hormones like adrenaline and cortisol released in states of arousal (Gold & Van Buskirk, 1975; Sandi & Rose, 1994; Conrad *et al.*, 1997; McGaugh, 2000).

Sleep is thought to be important in the process of consolidation, and it has been clearly demonstrated that sleep after learning improves declarative memory performance, even when the confounding effects of circadian rhythms and fatigue at recall testing were removed (Gais *et al.*, 2006; Drosopoulos *et al.*, 2007), by stabilising memory traces and providing increased resistance to interference during consolidation (Ellenbogen *et al.*, 2006). However, there are also suggestions that sleep's role in consolidation might be more active, for instance by restructuring brain activity (Orban *et al.*, 2006) and through hormonal changes during sleep (Born & Wagner, 2009).

Another aspect of long term declarative memory is recognition memory, the ability to recognise something that has previously been encountered. This is a matching process, comparing the content of the environment with the content of a memory. Recognition is commonly split into two domains: recollection – remembering details about an experience, and familiarity – awareness that something has been encountered before but with no further knowledge about it (Eichenbaum *et al.*, 2007). Localising these separate processes to areas of the brain has been attempted, and it is thought that they rely on separate but interlinked structures. In functional neuroimaging studies (Yonelinas *et al.*, 2005; Diana *et al.*, 2007) it has been found that regions in the pre-frontal, parietal and medial temporal cortices interact to provide recognition memory. The hippocampus seems to be crucial for recollection but familiarity is more associated with the peri-rhinal cortex (Montaldi *et al.*, 2006; Diana *et al.*, 2007; Eichenbaum *et al.*, 2007). Within the structures that support recognition there are some very specific areas that fulfil a very specific role, for example the 'fusiform face area' in the fusiform gyrus of the inferior temporal lobe which is associated with face recognition, and damage to this area leads to prosopagnosia (failure to recognise faces)(Kanwisher, 2000).

3.3 Assessing memory problems

When people have problems with their memories, it can present in a number of ways, depending on where in the process is affected and to what severity. Amnesia is the general term for the disruption of memory, from the Greek 'amnesia' meaning forgetfulness. It can be typically described as retrograde or anterograde, depending on the clinical symptoms. Retrograde amnesia is the loss of memories prior to the event causing memory loss, whereas anterograde amnesia is the loss of ability to form new long term memories after the event (Gazzaniga *et al.*, 2009) Affected individuals tend to suffer from one or the other or a mixed picture of symptoms (Russell & Nathan, 1946). Memory problems are a common complaint brought to health professionals, and there can be a wide range of causes from genetic disorders, to metabolic or neurological dysfunction, to psychological distress.

The first step in assessing a person presenting with memory difficulties should always be a good clinical interview with personal (including developmental, educational, occupational and social history) along with a comprehensive medical history (Groth-Marnat, 2000). Assessment of memory includes questionnaires to assess subjective memory and neuropsychological assessment measures to assess objective memory performance (Brooks, 1999). These two types of memory assessment do not necessarily assess the same functions, as results have often been found to be weakly correlated, as will be discussed in Chapter 5. Goldstein and Polkey suggest that self-report questionnaires are more closely associated with behavioural measures of memory (Goldstein & Polkey, 1992).

In the sphere of neuropsychological testing, there are a number of single tests and batteries for testing memory. The majority of tests available assess the learning and retention of new information (Cull & Goldstein, 1997). The Weschler Memory Scale (WMS) is one of the most commonly used instruments in adults and adolescents in the UK and USA (Weschler, 1997a). It is composed of ten subtests measuring different aspects of memory, providing scores for auditory immediate memory, visual immediate memory, auditory delayed, visual delayed, auditory recognition delayed, working memory and general memory (Weschler, 1997a). There are other measures to test aspects of memory, for example word list learning tests like the

Rey Auditory Verbal Learning Test (Schmidt, 1996) (assessing verbal immediate memory, learning, verbal delayed recall and verbal recognition) and visual memory measures like the Complex Figure test (Osterrieth, 1944) (assessing immediate and delayed visual recall)(Groth-Marnat, 2000).

When assessing learning and memory, there can be many confounding effects. Age, intelligence and education all need to be considered in the interpretation of any memory scores. Most memory assessments, such as the WMS, have age-related norms so that age as a confounding factor is taken into account (Weschler, 1997a). The WMS-III is also co-normed with the Weschler Adult Intelligence Scale (WAIS) (Weschler, 1997b), so IQ-memory discrepancies can be interpreted as reliable or abnormal. Number of years in education can also influence the level of performance on learning and memory tasks, although it is not clear whether or not this is a factor separate to IQ (Rosselli & Ardila, 1991; Boone *et al.*, 1993). Other things that need to be taken into consideration when considering interpretation of memory test results include anxiety, depression, current situation, stress and lack of sleep. For more detailed descriptions of memory tests, see Chapter 9.

Memory can be a major problem for people with epilepsy. In the next chapter the relationships of memory problems with various causative factors in epilepsy will be studied in more depth.

Chapter 4 Objective memory problems in epilepsy and the factors involved

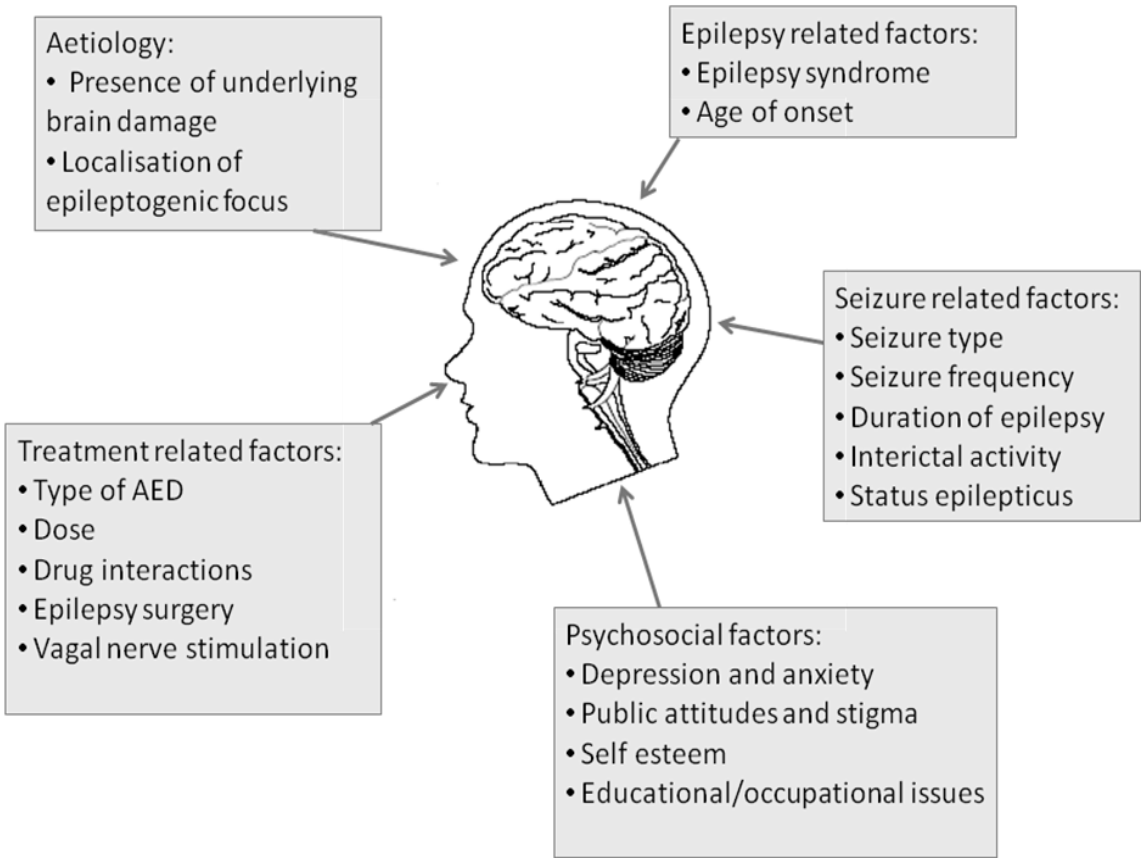
4.1 Background

Success in epilepsy treatment is generally considered to be good seizure control, for example in a large community-based study 41% of patients reported that seizure control was the most important aspect of their anti-epileptic medication (Fisher *et al.*, 2000). The importance of seizure freedom is borne out by findings that in well-controlled (unlike refractory) epilepsy patients' neuropsychological status and social functioning is similar to the general population (Aldenkamp, A. P. *et al.*, 2003), and seizure frequency has been found to correlate with health related quality of life scores (Baker *et al.*, 1997). However, there are also many other aspects of having epilepsy that affect patients' lives, and it is increasingly seen that optimal management of epilepsy goes beyond controlling seizures (Sander, 2005).

As well as lifestyle limitations including driving restrictions and employment difficulties, and social issues such as stigma and dependence on others, the cognitive effects of epilepsy are a major problem. Interictal memory problems in people with epilepsy have been observed for over 100 years (Gowers, 1881; Thompson, 1991). Interictal psychological functioning is crucial because this is the usual clinical state of the patient. Memory and cognitive problems have a significant impact on quality of life therefore they are an important issue (Giovagnoli & Avanzini, 2000). The effects of epilepsy on cognitive functioning have been much studied from a number of different approaches, from general intellectual abilities or global measures of cognitive function to specific tests of discrete neuropsychological functions such as memory assessment.

There are a number of factors involved in influencing cognitive outcome, with a variety of levels of evidence supporting them, including pathological abnormalities underlying the seizure disorder, seizure variables such as type and frequency, anti-epileptic drug use and mood disturbance (see figure 4.1). Complex interactions between them make it difficult to determine their individual contributions to cognitive dysfunction. It is important to understand the causative factors behind cognitive problems in epilepsy, which involves both identifying risk factors and examining the progression of cognitive difficulties within patients. With a better understanding of the causes and progression of cognitive problems in epilepsy comes a better understanding of how to minimise or mitigate those impairments. For the purposes of this project, the relationships found in temporal lobe epilepsy will be particularly considered because that will be the population studied.

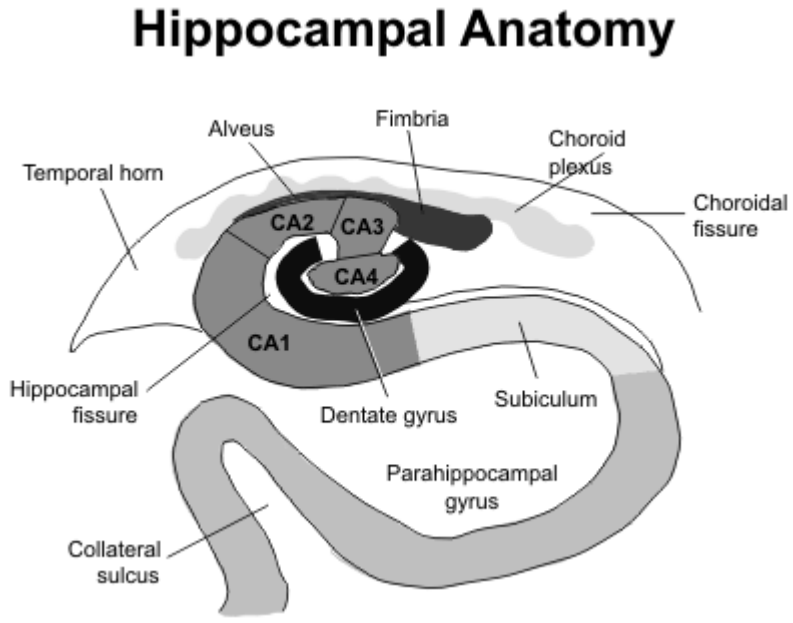
Figure 4.1: Factors affecting cognitive functioning in people with epilepsy



4.2 Pathology of TLE

Pathological abnormalities in TLE vary, from none in cryptogenic epilepsies to HS, gliomas, hamartomas, and vascular malformations in surgically treated patients (Wolf *et al.*, 1993). HS is the commonest pathological finding in TLE, found in around 70% of cases of intractable TLE (Najm *et al.*, 2006) and a key component of mesial TLE (Hermann *et al.*, 1997). Histologically, classic HS is characterised by destruction of the pyramidal neurons of Ammon's horn, especially in the subfield 'CA1', and also in 'CA3' and 'CA4', with relative sparing in subfield 'CA2' (see figure 4.2). However, dual-pathology cases with other neocortical temporal lobe pathology as well as HS might show a more diffuse pattern of neuronal loss (Najm *et al.*, 2006). Hippocampal abnormalities are typically unilateral, on the side of seizure onset, although can also be bilateral. Patients with right sided TLE may be more likely to have bilateral hippocampal atrophy (García-Fiñana *et al.*, 2006). Around half of those with histological HS will also have dentate gyrus cell abnormalities, and the neuronal damage also often involves the parahippocampal gyrus, uncus and amygdala (Gloor, 1991).

Figure 4.2: Hippocampal anatomy (Hesselink)



4.3 Do these pathological abnormalities correlate with cognitive functioning or memory?

There are a number of pathological abnormalities that have been investigated in TLE and considered in relation to the neuropsychological functioning of the patient. These are the presence of specific lesions, the presence or extent of HS, or hippocampal volume as a continuous variable.

4.3.1 *Findings from pre-surgical patients*

Many studies assessing neuropsychological performance in relation to pathological abnormalities have been conducted on pre-surgical patients, so that the pathological abnormalities can be assessed on the resected tissue. This has the benefit of allowing for accurate identification of pathology, but at the same time limits the population studied to those with medically refractory epilepsy. Comparisons have been made using neuronal cell loss, cell densities in different parts of the hippocampus and also the number and architecture of granule cells of the dentate gyrus, as well as the presence of HS.

It is generally proposed that the left hippocampus is more important for verbal memory and the right for non-verbal memory. Studies have shown that there is significant correlation between left HS or neuronal cell loss in the hippocampus and presurgical verbal memory impairment in patients with left temporal lobe foci (Sass, Spencer et al. 1990; Sass, Sass et al. 1992; Miller, Munoz et al. 1993; Rausch and Babb 1993; Saling, Berkovic et al. 1993; Pauli, Hildebrandt et al. 2006). This correlation is sometimes task specific, for instance it has been found that left HS is associated with impaired learning and recall of word pairs but not of a logical memory story (a story read to a patient thus recalled by them) (Rausch & Babb, 1993; Saling *et al.*, 1993), although this is not always the case (Miller *et al.*, 1993). It

has been suggested that the recall of prose may be more associated with the lateral component of the left temporal lobe, as there was a relationship found between prose recall and lateral temporal lobe resection but not mesial temporal lobe resection (Ojemann & Dodrill, 1985). In this context, HS or neuron loss is most commonly associated with impaired delayed recall (Miller *et al.*, 1993; Rausch & Babb, 1993; Saling *et al.*, 1993) or percent retention measures, while generally not associated with general cognitive ability, language competency (Sass *et al.*, 1992), attention, recognition memory or immediate memory (Miller *et al.*, 1993).

Findings of a relationship between HS and non-verbal memory are less consistent. Impaired delayed recall of a complex figure has been associated with HS, although this was found across left and right HS groups so is not demonstrative of a material specific deficit (Miller *et al.*, 1993). It has been proposed that this lack of a clear relationship between right-sided pathology and visual memory may be due to the way people verbalise even non-verbal information for storage and recall.

Studies have also tried to further clarify more precisely whereabouts neuron loss correlates with memory impairment. Rausch found that damage to neurons in either the anterior or posterior part of the left hippocampus was not sufficient to severely impair memory performance, extensive damage is required (Rausch, 1987). However, correlation has been found between percent retention of logical memory story and neuron loss in region 'CA3' and the hilar region of the hippocampus in left TLE patients (Sass *et al.*, 1992). The internal limb of the dentate gyrus has also been found to be particularly well correlated with measures of memory (Pauli *et al.*, 2006), as well as the degree of granule cell loss and abnormality of granule cell architecture in the dentate gyrus (Blümcke *et al.*, 2009).

Comparing patients with different types of left temporal lobe pathologies (HS, mesial tumour, lateral tumour), Helmstaedter and colleagues proposed that, due to surgical outcome data, patients with hippocampal pathologies were more likely to be impaired in delayed recall of a word list, while patients with lateral temporal

lobe lesions were expected to be worse at immediate recall and working memory. The 'hippocampal effect' was found in patients with HS who were more impaired in delayed recall of a word list (than patients with lateral tumours and also mesial tumours), but no 'lateral effect' (worse immediate and working memory with lateral lesions) (Helmstaedter *et al.*, 1997).

4.3.2 *Findings from MRI investigations*

A unilaterally small hippocampus and increased T2-weighted signal seen on MRI have been shown to be effective at identifying HS (Jackson *et al.*, 1990; Lencz *et al.*, 1992) and side of seizure onset (Jack Jr *et al.*, 1990; García-Fiñana *et al.*, 2006). This would suggest that, as well as by assessing patients' pathological abnormalities at surgery, quantitative MRI can also be used to assess temporal lobe or hippocampal damage in patients who don't need surgery. It also indicates that assessing the relationship between MRI abnormalities and neuropsychological status can give an idea of the relationship between pathological abnormalities and neuropsychological status.

MRI volumetrics have identified atrophy in TLE patients in the hippocampus (Jack Jr *et al.*, 1992; Quigg *et al.*, 1997; Woermann *et al.*, 1998; Tasch *et al.*, 1999; Daley *et al.*, 2006; García-Fiñana *et al.*, 2006; Oyegbile *et al.*, 2006), mesial temporal structures such as amygdala (Kälviäinen *et al.*, 1997; Martin *et al.*, 1999), fornix (Kuzniecky *et al.*, 1999; Martin *et al.*, 1999), and entorhinal cortex (Bernasconi *et al.*, 1999) as well as basal ganglia and thalamus (DeCarli *et al.*, 1998; Tuchscherer *et al.*, 2010). Extrahippocampal temporal regions (Moran *et al.*, 2001) and extratemporal regions such as cerebellum (Ney *et al.*, 1994; Specht *et al.*, 1997; Bohnen *et al.*, 1998; Sandok *et al.*, 2000) have also been found to be abnormal in TLE. MRI volumetrics have also been used in TLE patients to assess the whole brain, finding a relatively diffuse pattern of cerebral volume loss (in frontal, parietal and temporal but not occipital lobes (Hermann *et al.*, 2003)) or reduced total brain volume (Oyegbile *et al.*, 2006),

with white matter reduced more than grey matter (Hermann *et al.*, 2003; Oyegbile *et al.*, 2006).

The relationships of hippocampal and temporal lobe volumes to memory have been investigated. The volume of the left (dominant) hippocampus has been shown to be correlated with delayed recall or retention of verbal information, including a logical memory story (Lencz *et al.*, 1992) and also verbal paired associates, with a weaker and less consistent correlation with immediate recall (Griffith *et al.*, 2003). This is consistent with the post-surgical findings discussed demonstrating that hippocampal pathology correlated better with delayed than immediate recall (Miller *et al.*, 1993; Rausch & Babb, 1993; Saling *et al.*, 1993). Volume of the left temporal lobe has also been shown to correlate with verbal recall of a word list (Lencz *et al.*, 1992). This is in conflict with the aforementioned pre-surgical findings, that patients with hippocampal pathology are more impaired at word list recall, whereas logical memory story recall might be more related to the lateral temporal lobe (Rausch & Babb, 1993; Saling *et al.*, 1993). No reliable relationships have been found between right hippocampal volume and visual memory measures, a finding consistent with previous studies (Griffith *et al.*, 2003).

For people with epilepsy, abnormalities outside the temporal lobes also exist. Therefore it is unsurprising that cognitive abnormalities often extend beyond the field of memory. Neuropsychological impairment in patients has been found to correlate with total brain volume (Oyegbile *et al.*, 2006). The reduction in white matter raises the idea of reduced cortical connectivity in TLE and this is a model for the diffuse cognitive dysfunction which is seen (Hermann *et al.*, 2003). The cause of the widespread volume abnormalities is unclear, but it could be due to the effects of seizures or their treatment on brain growth and cognitive development, the progressive adverse effects of longstanding epilepsy on brain structure and function, or discrete cerebral insults antedating or related to the onset of the focal epilepsy. Animal studies might suggest that white matter is particularly vulnerable to seizure activity, particularly in immature rat brains (Dwyer & Wasterlain, 1982).

In summary, findings from both MRI studies and pre-surgical patients show a number of abnormalities in TLE that correlate with various cognitive measures, largely in the temporal lobe and hippocampus as well as more diffuse volume abnormalities. Left hippocampal volume or HS correlates with retention or delayed recall of verbal information. More diffuse white matter changes, total brain volume reduction and diffusely reduced cortical thickness correlate with more extensive cognitive and executive dysfunction. It would seem clear that pathological changes in epilepsy have a significant detrimental effect on neuropsychological functioning.

4.4 Relationship of duration of epilepsy with neuropsychological functioning

When considering the factors involved in cognitive problems in epilepsy, it is important to consider how the problems might progress over time, to identify cognitive trajectories in epilepsy and to try and further disentangle the relationships of causative factors. Alongside this goes investigation into cognitive impairments in newly diagnosed patients, which will be considered in a later chapter.

Cognitive decline in patients with chronic epilepsy may be due to progression of a disease underpinning epilepsy, progression of epilepsy (via kindling or further epileptogenesis), injuries associated with epilepsy (head injuries, status epilepticus) and physiological or pathological aging (Helmstaedter, 2002). Duration of epilepsy is a factor in cognitive impairment encompassing these independent issues. It can be an easier variable to measure than many of these individually, and by finding out if duration of epilepsy has a relationship with neuropsychological functioning, it is possible to identify whether epilepsy has a course of progressive cognitive decline over and above that found in healthy control subjects.

Investigations into the effect of duration of epilepsy can be either cross-sectional, where duration is examined as a co-variant in cognition, or prospective longitudinal studies where cognitive change over time is examined. Cross sectional studies are more common as they are easier to undertake, but they are only able to provide an indirect evaluation of cognitive change over time and disentangling other factors from the analysis is problematic. For example, longer duration of epilepsy is heavily confounded by aging, which is independently associated with cognitive decline. In contrast, prospective longitudinal studies allow researchers to compare a patient's performance with themselves over time, and with a control group practice effects can be taken into account to allow assessment of the patients' cognitive trajectory compared to a healthy population. However, these tend to cover a period of up to 10 years rather than assess the lifetime cognitive trajectory and the pattern of change is not clear – whether it is linear or there are 'critical periods'. Also, it is uncertain whether any changes are permanent in nature or merely transitory (Hermann, BP *et al.*, 2006).

Prospective longitudinal studies assessing patients' cognitive trajectories have yielded mixed results. Some have found worsening performance with time in patients with localisation-related epilepsy on delayed recall of verbal paired associates and a complex figure, compared to healthy controls (Andersson-Roswall *et al.*, 2004). Others have identified a lack of practice effects in patients, whereby performance does not decline but is significantly worse when compared to a score predicted by healthy control results (Hermann, BP *et al.*, 2006). Holmes and colleagues described no significant deterioration in patients over a 10-year period, but there were no controls so practice effects were not accounted for (Holmes *et al.*, 1998). Hermann and colleagues also identified adverse cognitive outcomes in a subset of 20-25% of patients. Those with baseline volumetric abnormalities on MRI, low baseline full-scale IQ (demonstrating increased cognitive vulnerability with lower intellectual capacity) and to a lesser extent longer duration of epilepsy and higher age were most vulnerable to these adverse cognitive outcomes (Hermann, BP *et al.*, 2006).

Other studies have not found relative progressive cognitive decline in patients with epilepsy. For example, Helmstaedter and colleagues demonstrated with age regression that, although TLE patients perform cognitively worse than controls and decline over time, this decline is at a similar rate to that in a normal population but starting from a lower point (Helmstaedter & Elger, 1999; Helmstaedter & Elger, 2009). Rather than the steep increase in learning and memory performance seen in controls in adolescence until their early twenties, patients demonstrated little increase in performance and began to decline earlier. These findings suggest that cognitive impairment is a developmental problem, rather than a degenerative process of accelerated deterioration related to ongoing disease. However, Jokeit points out that the measure of intelligence used in these studies is one to assess premorbid functioning, so not really representative of intellectual functioning (Jokeit *et al.*, 2000).

Another interesting finding concerns cerebral reserve – the idea that subjects with higher education, greater occupational attainment, or increased participation in mindful activities may benefit from increased plasticity or neuro-protection that may serve to delay or attenuate disease effects (Stern, 2002). Some studies have suggested that duration of epilepsy is linked to neuropsychological impairment, but it is a relationship mediated by years of education (a common measure of cerebral reserve) (Oyegbile *et al.*, 2004; Pai & Tsai, 2005), proposing that a patient with less education might have a more rapidly progressive cognitive decline .

If there is a progressive cognitive decline in epilepsy patients steeper than that found in a normal population, it leads to the question of whether or not seizures may be related to cognitive performance.

4.5 Relationship of seizures and discharges to cognitive impairment

In an animal model, even brief seizures have been shown to worsen emotional and spatial memory (Majak & Pitkänen, 2004). However, the evidence that these effects are also present in humans is less clear, perhaps due to the difficulties disentangling confounding factors.

In a study assessing partial epilepsy patients' memory during video-EEG telemetry, where information was presented at the start of telemetry and recalled 48 hours later, there was no significant correlation between number or timing of seizures and memory performance – although most seizures were not generalised (Bergin *et al.*, 1995). This suggests that isolated seizures do not cause increased forgetting of recently learned material. The effects of seizures over a longer period, either with cross-sectional or longitudinal studies, have also been investigated.

Some of these studies have demonstrated no impact of total lifetime number of seizures (Kramer *et al.*, 2006) or EEG abnormalities (Scott *et al.*, 1967) on cognition in epilepsy. Others have demonstrated strong correlations between total spike activity in depth electrodes and intelligence and other neuropsychological measures (Rausch *et al.*, 1978) in a group of patients with refractory temporal lobe epilepsy. However, Rausch and colleagues warned against interpreting this as a cause and effect relationship, suggesting that whilst it could show that an active epileptic site is disruptive of function, it could also be the case that interictal spike discharges could be a manifestation of underlying pathology.

Reviews within this area of the literature have demonstrated mixed results. Dodrill considered longitudinal cognitive investigations in patients with epilepsy, finding support overall for a 'mild' connection between seizures and cognitive change (Dodrill, 2004). This was supported by findings including significant relationships between increased number of seizures and decreased scores on tests of various

abilities (Rodin, 1968; Dodrill & Wilensky, 1990; Dodrill, 2002), changes in intellectual functioning corresponding to changes in seizure frequency (Seidenberg *et al.*, 1981), declines in diffuse areas of cognitive functioning but most consistently memory, and controls performing better over time than patients. However, several studies reviewed found it difficult to connect seizure frequency with loss of abilities. In a further, more select review, Vingerhoets considers some of the studies reviewed by Dodrill (those longitudinal studies with data on seizure types and frequency) and one additional study (Vingerhoets, 2006). From these, the conclusion is drawn that overall patients with chronic pharmacoresistant epilepsy show a mild decline in cognitive function, particularly memory, compared to matched controls over a time period, but this is not generally well associated with seizure-related factors.

Cognitive decline related to seizure activity has also been considered in specific groups of patients. For example, Mantoan et al studied memory in relation to interictal epileptiform discharges and neuronal loss (detected by proton MR spectroscopy) in a group of patients with TLE and HS (Mantoan *et al.*, 2009). Interictal epileptiform discharges (IEDs) were found to correlate with impaired immediate and delayed verbal recall in left HS, and bilateral IEDs correlated with poor verbal learning in right HS. Interictal discharges and neuronal metabolism were shown to be related to verbal memory function in the mesial temporal lobes.

4.6 Is neuronal loss accelerated by seizures?

It can be demonstrated reasonably consistently that pathological abnormalities have an effect on at least certain types of memory in patients with TLE. So, if seizures do cause cognitive problems with the progression of epilepsy, is the mechanism acceleration of neuronal loss? In a study of MRI total brain abnormalities in TLE, the impact of clinical seizure variables, eg duration of epilepsy, on cognition is mediated by its relation with grey matter and CSF volume abnormalities. This

suggests that clinical seizure variables may affect cognition via their impact on brain volume (Oyegbile *et al.*, 2006).

A kindling model of TLE in rats would suggest that repeated seizures might cause selective loss of neurons in the hippocampus (Cavazos & Sutula, 1990; Cavazos *et al.*, 1994). However, using the pilocarpine model of initiating seizures no progressive neuronal loss was demonstrated in rats having recurrent seizures (Zhao *et al.*, 1994), so even in rats without all the confounding factors it is difficult to know if seizures cause neuron loss. One way to examine this is to consider the relationships of seizure variables (such as frequency, type and duration of epilepsy) to pathology, using cross-sectional or prospective longitudinal studies.

HS is one pathology in TLE that has been much investigated, and whether HS is the cause or effect of epilepsy is a longstanding and highly debated question. It has been shown in some cases to develop following status epilepticus (Nohria *et al.*, 1994; Wieshmann *et al.*, 1997), head injury (Bigler *et al.*, 1997), and demonstrated following prolonged febrile convulsions (Jackson *et al.*, 1998; Shinnar, 1998; Sloviter, 1999; Schulz & Ebner, 2001). However, although there is a relationship between HS and prolonged febrile seizures, it is debated whether the febrile seizures cause the HS or the febrile seizures occur because the hippocampus was already damaged (Cendes, 2005). Complex febrile seizures may also have an impact on global brain development, as findings suggest patients who have experienced complex febrile seizures have lower total cerebral volumes than those who have not (Theodore *et al.*, 2003). It has been suggested that the risk of neuronal damage from febrile convulsions is dependent on genetic susceptibility combined with environmental interaction (Sutula & Pitkanen, 2001).

Cross sectional studies have found factors predicting or correlating with MRI hippocampal volumes (or atrophy) including: duration of epilepsy, neurodevelopmental insult (early recurrent seizures, initial precipitating injury), history of febrile seizures, early (<5 years) onset (Salmenperä *et al.*, 1998;

Salmenperä *et al.*, 2001) and total lifetime number of generalised tonic-clonic seizures (Kalviainen *et al.*, 1998; Tasch *et al.*, 1999; Fuerst *et al.*, 2001; Seidenberg *et al.*, 2005) but not consistently frequency of partial seizures. In contrast, mean hippocampal and amygdaloid volumes in people with a seizure onset less than 1 year previously did not differ from controls (Salmenperä *et al.*, 2001). These findings would suggest a combination of progressive and neurodevelopmental effects on brain volume.

Longitudinal studies in epilepsy patients assessing progression of cerebral damage have found mixed results. Liu et al felt that brain volume reduction in epilepsy was the cumulative effect of initial precipitating injury and age-related atrophy, rather than seizure frequency and duration of epilepsy, as these were found to have no significant effect on cerebral volume reduction (Liu *et al.*, 2005). Patients with TLE had reduced hippocampal volumes at baseline compared to other epilepsies and controls, but similar volume reduction over 3.5 years. Contrary to this, other longitudinal studies over a similar time period (3.4 years, 3.5 years) have found that in TLE (mild or intractable) there was a strong correlation between frequency of partial seizures (Fuerst *et al.*, 2003) or generalised seizures (Briellmann *et al.*, 2002) and hippocampal volume loss ipsilateral to seizure onset (Briellmann *et al.*, 2002; Fuerst *et al.*, 2003). Patients becoming seizure free in one of these studies showed no hippocampal volume loss, but due to numbers this should be interpreted with caution (Fuerst *et al.*, 2003).

Overall, results are very mixed and inconclusive, but there are suggestions that pathological abnormalities in TLE are, at least in some cases, correlated with duration of epilepsy or number of seizures and thus a progressive disorder.

4.7 Does the age of onset of epilepsy affect cognitive prognosis?

Age of onset is a variable often interlinked with duration of epilepsy, as a patient with an earlier age of onset will likely have a longer duration of epilepsy throughout their lifetime. However, these two variables have different effects on neuropsychological functioning, as an earlier age of onset will mean seizures affecting a less developed brain which can cause different outcomes. Early age at onset of epilepsy is not a risk for cognitive impairment per se, for example a benign myoclonic epilepsy will start early in life but have little cognitive impact, but in a specific population such as TLE patients an early age of onset is often associated with a worse prognosis (van Rijckevorsel, 2006).

Unlike in adults, where there is a reasonably stable cognitive substrate that is the target of adverse epilepsy factors, in children there is a dynamic pattern of cognitive and brain development (Hermann *et al.*, 2008). There is some evidence suggesting that recurrent seizures in a developing brain are associated with adverse effects on both brain structure and function (Hermann, B *et al.*, 2002). The immature brain is more prone to seizures than the mature brain, which is borne out by animal studies (Michelson & Lothman, 1991), alongside the clinical observation that the incidence of seizures is highest during the first decade of life and many childhood seizure disorders remit (Holmes, 1997). This is thought to be due to variation in the balance of excitation and inhibition (Holmes, 1997). It seems from animal models that seizures in a developing brain cause less neuronal damage and cell loss than in an adult brain (Lado *et al.*, 2000; Marsh *et al.*, 2006). However, early seizures can cause changes in the function of neurotransmitter systems and intrinsic neuronal properties, and thus have an adverse effect on brain development and function in the long term, which could lead to cognitive or behavioural problems (Wasterlain *et al.*, 1999; Marsh *et al.*, 2006).

Onset of epilepsy early in life has been postulated to account for more generalised intellectual impairment in addition to memory problems in TLE due to the possible

interference in neurodevelopment, whereas later onset may be associated with more specific impairments related to the site of the discharges or pathophysiology. For example, in those with no pathological lesions or only HS, verbal memory has been shown to be reduced in patients with both early (before age 15) and late onset whereas IQ was significantly more impaired in those with early onset epilepsy (Kaaden & Helmstaedter, 2009). In those with more pathology than just HS, IQ was equally poor in early and late onset groups, and worse than verbal memory function. This suggests verbal memory loss is perhaps a good indicator of mesial temporal lobe function, whereas IQ, verbal and figural learning performance reflect more extra-temporal or 'whole-brain' functions. Age of onset seems to have more of an impact on these 'whole-brain' functions, suggesting disruption during development interferes with global functioning as well as localised functions (Kaaden & Helmstaedter, 2009).

Similarly, in a cross sectional study childhood onset (up to 14) TLE was associated with worse verbal, performance, and full-scale IQ and verbal and non-verbal memory measures than late onset and controls (Hermann, B *et al.*, 2002). These findings of worse performance across a range of functions with early onset epilepsy are corroborated by findings in patients with generalised epilepsy (O'Leary *et al.*, 1981; O'Leary *et al.*, 1983). Childhood onset TLE has also been associated with widespread reduced cerebral volume in all lobes, i.e. extratemporal volume loss. So, early onset TLE is associated with generalised adverse neurodevelopmental impact, in terms of both structural changes and cognitive impairments.

Considering duration of epilepsy and progression of impairment, patients with early onset have been found to be at risk of declining performance relative to chronicity of epilepsy when compared to those with later onset (Hermann, BP *et al.*, 2002). This generalised cognitive vulnerability, or increased risk of further cognitive decline, may be due to a lack of cerebral reserve (see earlier section on 'duration of epilepsy'). The concept of cerebral reserve is thought to help understand the risk of age-related decline when people have suffered an early brain insult.

In contrast to the concept that childhood onset epilepsy might cause cognitive impairment due to poor cerebral reserve, there are also suggestions that an early age of onset of epilepsy may mean that cortical reorganisation can occur due to cerebral plasticity, when there is a non-diffuse neuropathology like HS. This would mean protection of particular functions such as memory in the presence of HS (Seidenberg *et al.*, 1997). Furthermore, the study suggested that in an early onset epilepsy (before 5 years) with a single focal lesion, cerebral reorganisation of function may occur, allowing for preservation of memory even following surgery. However, these conclusions were based on a number of assumptions and extrapolations, and only relevant to a small population.

Helmstaedter and colleagues' findings discussed earlier suggesting that cognitive impairment in epilepsy is not due to a progressive process but rather impaired neurodevelopment followed by normal aging processes from a lower level are also important in this discussion (Helmstaedter & Elger, 1999; Helmstaedter & Elger, 2009). This is the theory that 'normal senescence brings patients to mnesic disability at a younger age' p439 (Helmstaedter, 2002), with early age of onset representing a developmental hindrance factor (Kaaden & Helmstaedter, 2009).

To further investigate the effects of neurological insults on the developing brain, Dikmen et al compared the neuropsychological performance of patients with early onset seizures (before five years), early onset brain damage without seizures, late onset (age 17-50) seizures and late onset brain damage without seizures (Dikmen *et al.*, 1975). Those with early onset seizures performed significantly worse across most measures than all of the other groups, while those with early onset brain damage did not differ in performance from those with later insults. This emphasises the importance of early onset of cerebral damage on neuropsychological performance across pathologies.

Early onset of epilepsy impacts on cognitive functioning not only due to its effect on the structure and function of neurons, but also through education and social processes. Children with epilepsy generally have poorer academic performance than would be expected at school (Williams, 2003; Bishop & Slevin, 2004). This may be partly due to neurodevelopmental effects of seizures and AEDs, but also depends on personality of the child, social variables, family adjustment and school environment (Seidenberg & Berent, 1992; Williams, 2003; Bishop & Slevin, 2004). For example, stigma may cause lower expectations in parents and teachers, which could affect the child's effort, self-belief and academic performance (Williams, 2003).

In summary, it seems that an early age of onset of TLE is associated with poor performance in neuropsychological tasks. This is characterised by a more generalised pattern of impairment than later onset seizures, probably due to interference with neurodevelopment by either an insult causing the epilepsy, epileptogenesis, or the seizures themselves, alongside the impact of family, school and social environment on educational performance.

4.8 Anti-epileptic medication – the effects on cognition and memory

Anti-epileptic drugs (AEDs) exert their effect by producing changes in the excitation levels in the central nervous system, and as these changes are global it is unsurprising that it is thought that some, if not all, AEDs have an effect on cognition and behaviour (Ortinski & Meador, 2004). The cognitive effects of antiepileptic medication first became a focus of interest in the 1970s (Ideström *et al.*, 1972; Dodrill & Troupin, 1977), probably stimulated by the growing number of treatment options available at that time (Aldenkamp, Albert P. *et al.*, 2003). However, it is suggested that the adverse cognitive and behavioural effects of AEDs are more subtle than once thought and have been over-estimated (Kwan & Brodie, 2001), as patients established on target doses with no active seizure disorder have been shown to not cognitively deteriorate over a 5-year period (Dodrill & Wilensky, 1992).

Significant problems arise in designing a methodologically sound study that can identify cognitive impairment caused by AEDs whilst avoiding confounding factors, so while there has been much research, few studies are useful for drawing reliable conclusions (Vermeulen & Aldenkamp, 1995; Cochrane *et al.*, 1998). Randomised clinical trials with monotherapy in patients with newly diagnosed epilepsy are the best procedure for assessing the cognitive effects of AEDs (Aldenkamp, 2001), as randomisation removes selection bias when allocating treatments so is the least biased method (Cochrane *et al.*, 1998). Studies using add-on or polytherapy designs make the identification of the responsible treatment factors more complex as drug therapy is usually not standardised. Combinations of AEDs may interact with or potentiate one another, which would affect the conclusions that can be drawn. Also, as polytherapy is used in refractory patients ongoing seizure effects are likely to confound the results (Vermeulen & Aldenkamp, 1995). However, as many patients require polytherapy for seizure control, the results can be clinically relevant, reflecting issues faced in real life. Studies using healthy controls are often limited by brief exposure periods and a different cerebral substrate that the drugs are acting on, but can provide some useful indications for future research.

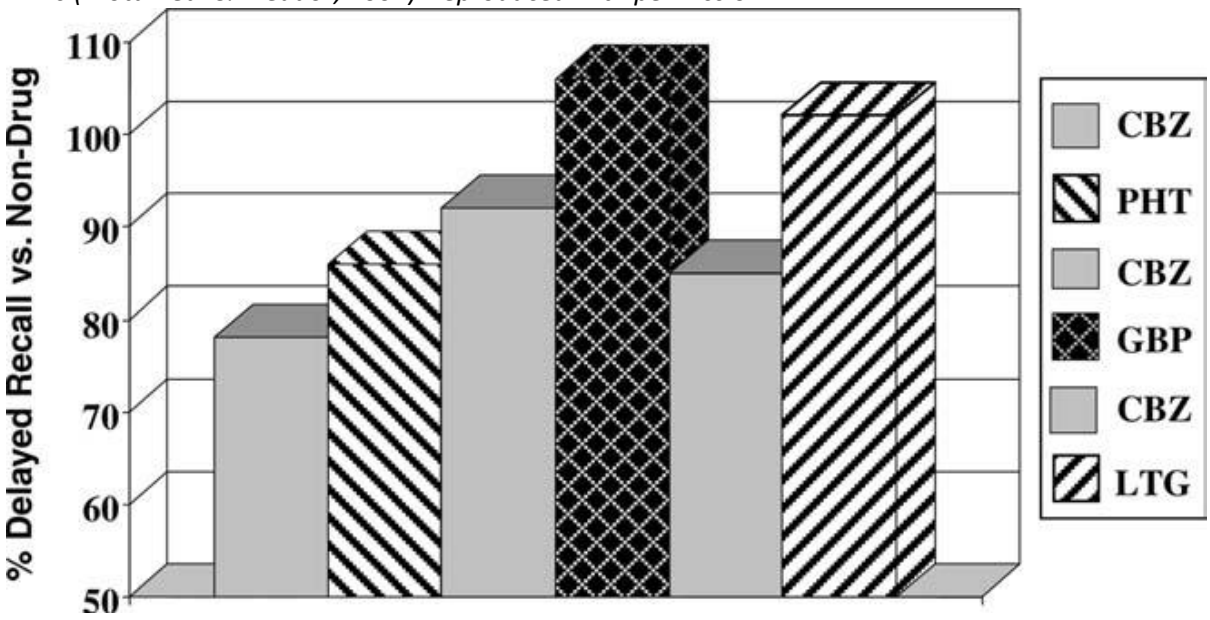
Another problem with studies into the cognitive effects of AEDs is individual variance – medications that work well for some may not work at all for others, or those that cause no side effects at a large dose in one patient may cause toxicity in another at a lower dose. These unconventional patients may appear as outliers and affect the mean so by grouping all patients together, an effect may become non-significant (Devinsky, 1995).

Finally, the wide variety of neuropsychological tests used across different studies also makes it difficult to undertake reasonable meta-analysis and draw any reliable conclusions from previous research.

A meta-analysis of reports of the cognitive side effects of the commonly used 'older' AEDs (Phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ) and sodium valproate (VPA)) found that all of the medications, even those considered cognitively safe, demonstrated some cognitive side effects compared to no treatment (Vermeulen & Aldenkamp, 1995). The 'milder' drugs CBZ, VPA and PHT were associated with a mild, general psychomotor slowing. PB had significantly worse effects, with only minor differences between the others when a usual therapeutic dose was considered. Polytherapy was also shown to be more cognitively detrimental than monotherapy with any drugs; even if the two drugs used individually have mild effects, when given together interactions make them more harmful.

A further study has compared the cognitive effects of CBZ and VPA using both healthy volunteers and also a group of newly diagnosed untreated epilepsy patients as control groups (Shehata *et al.*, 2009). Both treated and untreated patients performed worse than healthy controls in a number of cognitive tests (including verbal reasoning, memory for objects, memory for beads, and non-verbal short term memory) and behavioural functions (including depression, aggression and neurosis). Treated patients had worse scores in memory for digits forward and backward and verbal short term memory, but not to a significant level. Within the treatment groups, dose of AED was significantly associated with neurosis and aggression but no cognitive measures, and duration of treatment associated with object, bead and non-verbal short term memory as well as depression, psychosis and aggression. In comparison of the different drug groups, VPA was associated with significantly higher levels of aggression and neurosis. No other differences between drug groups were found.

Figure 4.3: Delayed recall performance of a story in healthy volunteer studies on various AEDs (Motamedi & Meador, 2004)- reproduced with permission



CBZ = carbamazepine; PHT= phenytoin; GBP = gabapentin; LTG = lamotrigine

Assessing memory performance specifically is limited in most studies, and it is difficult to assess independently because of the effects of slowed mental processing and attention on memory tasks. In healthy volunteer studies, Meador et al demonstrated a 15% reduction in delayed recall of a paragraph in those taking PHT and CBZ compared to non-drug controls (see figure 4.3) (Motamedi & Meador, 2004). Examining memory processes in more detail in refractory TLE patients treated with CBZ, PHT and PB, it was found that serum AED level was significantly related to verbal and non-verbal retention but not encoding (Jokeit *et al.*, 2005). This suggests that high levels of CBZ, PHT, and PB have a particular effect on memory, but not attention or mental speed, as encoding was unaffected. Interestingly Jokeit et al also found high carbamazepine serum levels to be associated with reduced activation of the medial temporal lobes (using fMRI) in memory retrieval.

Research has also been undertaken into the cognitive and behavioural effects of the newer AEDs. The effects of lamotrigine (LTG) and levetiracetam (LEV) will

particularly be focused on here, as these are the two most commonly prescribed in the population that will be studied in this project.

In healthy volunteer studies comparing the cognitive effects of LTG with CBZ (Meador *et al.*, 2001) and TPM (Meador *et al.*, 2005), participants on LTG performed significantly better than those on CBZ and TPM on variables spanning objective cognitive and subjective behavioural measures. Also, compared to the non-drug group participants on LTG were impaired on significantly fewer measures than those taking both CBZ and TPM. The most susceptible domains to impairment by AEDs are sustained attention, processing speed, tasks requiring attention like recall of a paragraph and, with some drugs (CBZ and TPM) verbal fluency. On a specific memory measure in these studies, delayed recall of a paragraph, compared to the non-drug average participants taking LTG and gabapentin (GBP) performed no worse but those taking CBZ, PHT and TPM recalled 10-20% less than non-drug groups (Hermann *et al.*, 2010).

In patient studies, the cognitive profile of LTG has been assessed as monotherapy in newly diagnosed patients, and more frequently as add-on therapy (Smith *et al.*, 1993; Marciani *et al.*, 1998; Gillham *et al.*, 2000). Comparing LTG with CBZ in newly diagnosed patients, it was suggested that LTG had a comparatively favourable effect on long term cognitive function (Gillham *et al.*, 2000). LTG compared to placebo as an add-on in a double blind crossover trial in a group of partial seizure patients found LTG to have no adverse cognitive effects compared to placebo and increases on a subjective measure of happiness (Smith *et al.*, 1993). LTG has also been shown to reduce spontaneous epileptiform discharges on EEG (Binnie *et al.*, 1986; Marciani *et al.*, 1996), which may help to explain its favourable cognitive profile.

LEV has relatively little cognitive data available, a small sample study suggested it had no cognitive effects but this only included ten patients (Neyens *et al.*, 1995). A randomised, crossover, double blinded trial of healthy volunteers comparing its

cognitive profile to CBZ found those taking LEV to perform better than those on CBZ on 44% of variables, and compared to the non-drug average LEV impaired participants on significantly fewer measures (Meador *et al.*, 2007). LEV has also been shown to improve attention and verbal fluency (Piazzini *et al.*, 2006) and have a sustained positive impact on attention and both long and short term memory (Zhou *et al.*, 2008) as an add-on therapy in patients with partial seizures, independent of seizure reduction. The mechanism for this is unclear, although LEV is derived from piracetam, a drug that has also been shown to improve learning, memory and attention (Genton & Van Vleymen, 2000). As little evidence is yet available on the cognitive safety of LEV these results should be interpreted with caution, although the possible positive cognitive effects are somewhat supported by improvements shown in Mini-Mental State Exam (MMSE) scores (a very crude test) after 12 months of LEV therapy (Wu *et al.*, 2009) and improvements in subjective cognitive functioning assessments (Cramer *et al.*, 2000).

There is some evidence that 'older' AEDs in particular may have a negative effect on cognition, especially when used as part of a polytherapy regime or in high doses. Studies have suggested that PB is the AED with the most detrimental effect on cognition (Vermeulen & Aldenkamp, 1995). On the other hand, there is no convincing evidence that LTG or LEV impair neuropsychological functioning, and indeed there are some studies suggesting LEV may exert beneficial effects on cognition.

4.9 Mood

Depression is a common comorbid mood disorder associated with epilepsy, with a significantly higher prevalence than that in a matched population of healthy controls or even patients with other chronic diseases (Perini *et al.*, 1996; Marsh & Rao, 2002; Kanner, 2003; Baker, 2006). Prevalence varies depending on assessment and definition of depression, but has been quoted as being between 20 and 60% in patients with recurrent seizures and between 10 and 20% in those with controlled

epilepsy, demonstrating the importance of seizure control for mood (Hecimovic *et al.*, 2003; Kanner, 2003). Depressive symptoms can manifest as major depressive disorder, atypical depression, dysthymia or a dysthymic-like disorder with intermittent symptoms (Miller *et al.*, 2008). Anxiety is also more common in patients with epilepsy than in the general population (Marsh & Rao, 2002; Beyenburg *et al.*, 2005; Mensah *et al.*, 2007). Depressed mood and anxiety are important factors for quality of life in epilepsy, having been shown, in some studies, to have more of an impact than seizure control in patients with epilepsy (Boylan *et al.*, 2004; Johnson *et al.*, 2004).

The cause of higher rates of depression in patients with epilepsy is thought to be multifactorial – including the psychological impact of epilepsy and its associated challenges, the endocrine or metabolic effects of seizures, and a possible common underlying pathology (ie the relationship between the two conditions is bidirectional (Hesdorffer *et al.*, 2000; Kanner, 2008)) (Miller *et al.*, 2008). It has also been proposed that particular epileptic foci might lead to higher rates of depression and anxiety (Hixson & Kirsch, 2009). TLE seems associated with higher rates of depression than epilepsy generally (Perini *et al.*, 1996; Quiske *et al.*, 2000), particularly left TLE (Harden & Goldstein, 2002). Higher rates of anxiety have also been found in left TLE patients than right TLE patients and controls (Andelman *et al.*, 2001). There are also links between some AEDs (notably LEV) and behavioural disturbance and mood disorders, particularly in patients with a past history of psychiatric disturbance (Hixson & Kirsch, 2009).

Depression itself has been demonstrated to be reliably associated with objective memory impairment (Burt *et al.*, 1995). Suggested reasons for this include mood congruency effects (that learning of negative information is best and learning of positive information impaired), that reduced motivation or energy means patients have impoverished output, or that there is impaired ability to use effortful memory strategies because of poor attention or motivation. So, a higher rate of depression in patients with epilepsy might be thought to correlate with memory impairments.

Examining this possibility, Elixhauser et al found a weak but significant correlation between memory performance scores and 3 subsections of mood scoring (tension / anxiety, confusion / bewilderment and anger / hostility) in patients with any type of epilepsy (Elixhauser *et al.*, 1999). However, mood correlated better with perceived cognitive function scores on a quality of life measure, which is a relationship that will be discussed further in the next chapter.

In examining the relationship between mood and objective memory in TLE, Helmstaedter et al found depressed mood to correlate with some objective memory performance measures, particularly in patients with left TLE with lateral temporal lobe lesions, i.e. those with more depression performed worse. There was no significant correlation between lateralisation and localisation of the lesion with mood, despite correlation between laterality and localisation of lesion with memory performance measures (Helmstaedter *et al.*, 2004). The finding that site and side of lesion affects the association between mood and memory in TLE patients, supports findings that the association between mood and memory is stronger in left TLE (Paradiso *et al.*, 2001).

Depression and anxiety are not the only psychological disturbances found in patients with epilepsy – for example TLE patients have been found to be affected across nearly all emotional-behavioural domains including somatisation, depression, anxiety, obsessive compulsive traits, hostility and psychoticism (Hermann *et al.*, 2000a). Higher levels of depression and anxiety have been associated with various factors including increasing duration of epilepsy (Hermann *et al.*, 2000b), patient perceived seizure severity (Smith *et al.*, 1991), number of complex partial seizures (Grabowska-Grzyb *et al.*, 2006), increased frequency of seizures (Jacoby *et al.*, 1996) and mesial temporal sclerosis (Quiske *et al.*, 2000). However, using the Minnesota Multiphasic Personality Inventory (MMPI) (Butcher *et al.*, 1989) as a measure of psychopathology, poor neuropsychological functioning has been shown not to be related to psychopathology in TLE (Moehle *et al.*, 1984).

Whatever the relationship between objective memory performance and mood disorders, depression is also known to affect subjective reporting of memory due to a catastrophising bias (Baker *et al.*, 2009). This, along with other factors involved in subjective memory reporting in epilepsy, will be discussed in the next chapter.

4.10 Summary

The relationships of various factors to memory performance in TLE have been considered, and the only thing that is clear is that this is a multifactorial problem from which it is not simple to extricate answers.

Pathological lesions seem to be associated with worse memory performance, particularly problems in delayed verbal memory when the lesion is on the left. Clinical seizure variables like type and frequency of seizures and duration of epilepsy have a less perceptible relationship with memory functions, although an early age of onset seems to be particularly associated with a risk of impairment of generalised cognitive functions. Other factors like AED use and mood disorders may have some independent effect on cognition but likely any neuropsychological problems are due to the interaction of many of these factors.

Chapter 5 Subjective memory problems in epilepsy

5.1 Background

Investigating the relationships between different factors and objective cognitive problems found in neuropsychological testing of patients with epilepsy allows us to consider the causes of identified memory deficits. However, whether or not objective problems correlate with subjective complaints is another question entirely. Therefore, in this chapter subjective reports of memory problems in epilepsy patients will be considered along with their relationship to objective problems.

There are a number of cognitive problems that people with epilepsy recognise (see table 5.1), and cognitive problems which are also reported by relatives and caregivers (see figure 5.1).

Table 5.1: Common reports of cognitive impairments in people with epilepsy (Baker et al., 2009)

Forgetting the way around familiar places
Impaired ability to do mental arithmetic
Forgetting names of familiar people
Difficulty retaining a telephone number
Difficulty paying attention to a speech or news broadcast
Difficulty understanding something you have heard or read
Difficulty learning something new
Slowness of thought
Difficulty following instructions
Impaired eye-hand co-ordination
Sleepiness / tiredness
Lethargy / sluggishness
Forgetting anniversaries, appointments and dates
Epilepsy and Cognitive Function Survey, International Bureau for Epilepsy (2004)

Specifically, people with epilepsy generally perceive their memory performance to be worse than controls (Vermeulen *et al.*, 1993). In a survey of 760 patients, 54% of

patients (compared to 23% of controls) described their memory as a moderate to severe nuisance in daily functioning (Thompson & Corcoran, 1992). These were not only individuals with intractable epilepsy but included those with controlled seizures, suggesting that memory complaints are not confined to patients with refractory epilepsy. Within this questionnaire, the frequency of a list of memory problems was described, showing that the most commonly reported problem among patients with epilepsy was the 'tip of the tongue' phenomenon, reported as occurring at least daily in 43% of patients (see table 5.2).

Figure 5.1: Common problems for children and teenagers with epilepsy reported by their caregivers (Baker et al., 2008)

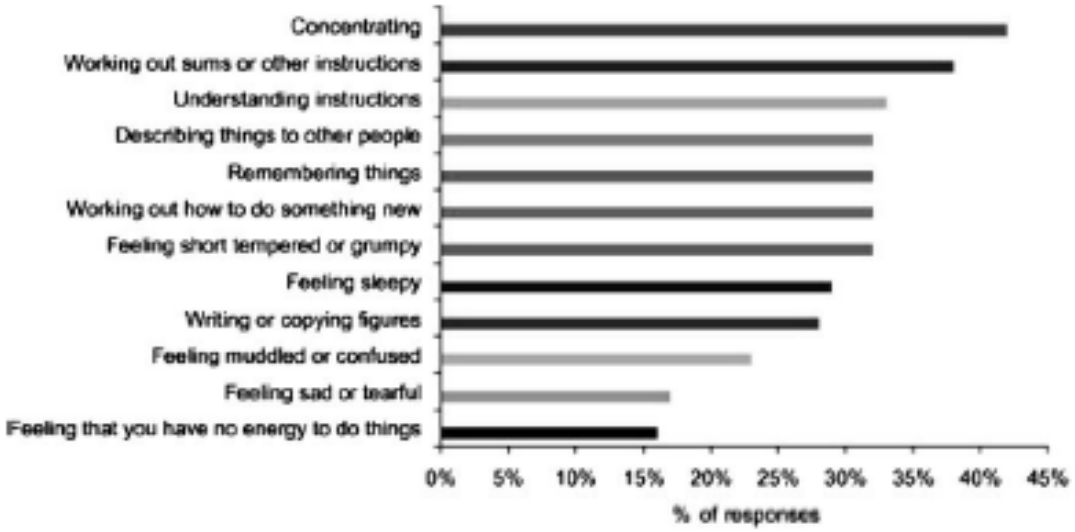


Table 5.2: The top 5 memory problems in each group (% reporting problem at least daily)(Thompson & Corcoran, 1992)

Epilepsy	Non-epilepsy
1. Tip of the tongue (43%) 2. Going back to check (39%) 3. Forgetting where you've put things (33%) 4. Forgetting names (31%) 5. Forgetting you were told something (30%)	Going back to check (20.5%) Forgetting where you've put things (18.5%) Forgetting names (14%) Tip of the tongue (14%) Rambling on (11%)

5.2 Epilepsy specific factors affecting subjective memory

There are a number of epilepsy related factors that might be thought to affect subjective memory, including epilepsy duration, age of onset, frequency of seizures, seizure type and medication. However, subjective memory does not seem to be dependent on many of these factors including type of seizures (Giovagnoli *et al.*, 1997; Piazzini *et al.*, 2001; Salas-Puig *et al.*, 2009), lateralisation of epilepsy (Hendriks *et al.*, 2002), frequency of seizures (Giovagnoli *et al.*, 1997; Au *et al.*, 2006; Salas-Puig *et al.*, 2009) or age of onset (Giovagnoli *et al.*, 1997; Au *et al.*, 2006). One study finds duration of epilepsy to correlate weakly but significantly with complaints (Hendriks *et al.*, 2002), while this is contradicted elsewhere (Giovagnoli *et al.*, 1997; Piazzini *et al.*, 2001; Au *et al.*, 2006). However, frequency of seizures has been shown to correlate strongly with anxiety and depression levels, which link to memory complaints (Piazzini *et al.*, 2001).

Around 50% of a large international study of over 5000 patients with epilepsy reported problems with memory as a side effect of medication (Baker *et al.*, 1997). This included 47% of those on CBZ monotherapy reporting memory difficulties, 48% on PHT, 37% on VPA and 30% on PB. However, Baker and colleagues note that other factors than AED use might also explain these concerns but it is not possible for them to disentangle these. A large community-based cross-sectional study in the Netherlands of patients with epilepsy taking medication (around 80% on monotherapy) has also found over 60% had cognitive complaints that they related to use of AEDs, predominantly memory problems and concentration difficulties (Carpay *et al.*, 2005). Results regarding the relative impact of medication on memory complaints is mixed – some have found no medication effect (no difference between complaints in relation to number of medications or dosing) (Hendriks *et al.*, 2002; Au *et al.*, 2006), whereas elsewhere polytherapy has been shown to be associated with poorer subjective memory (Giovagnoli *et al.*, 1997; Salas-Puig *et al.*, 2009).

5.3 Relationship of complaints to performance

Perception of cognitive functioning is shown to be an important factor in quality of life, but weak or insignificant correlations have been demonstrated between subjective and objective cognitive functioning (Vermeulen *et al.*, 1993; Giovagnoli *et al.*, 1997; Elixhauser *et al.*, 1999; Piazzini *et al.*, 2001; Baños *et al.*, 2004; Au *et al.*, 2006; Maarika *et al.*, 2009), and the reasons behind this are much discussed. Many epilepsy patients referred with memory complaints perform at average or higher than average levels on neuropsychological testing (Thompson & Corcoran, 1992). These discrepancies have been demonstrated in various populations as well as in patients with epilepsy, including populations as varied as the elderly, stroke patients, and menopausal women (Kahn *et al.*, 1975; Lincoln & Tinson, 1989; Weber & Mapstone, 2009), so it cannot solely be a problem related to epilepsy factors. Complaints that cannot be explained cause problems for both patients and clinicians (Vermeulen *et al.*, 1993), so it is important to understand other factors that could be causing this discrepancy so that they can be addressed.

The relationship between patients' perceptions of their memory and their performance is far from simple. If subjective memory does not correlate with objective performance, there are a number of possible explanations:

i) that there is an impairment but it is not identified by neuropsychological tests, ie a methodological problem,
ii) that the perception of memory problems reflects another problem such as a another cognitive deficit, or
iii) that there is a problem with meta-memory, self-monitoring of one's memory performance which could be affected by mood disorders or epilepsy itself.

i) Methodological problems

In a review of the topic of correlation between subjective and objective memory measures in people with epilepsy, Hall and colleagues found a number of methodological issues present in most of the studies that makes it difficult to compare results across studies and draw firm conclusions as to the nature of the relationship, which will be discussed below (Hall *et al.*, 2009). However, although inconsistent results are found, it seems that overall there is a lack of correlation, based on studies comparing subjective and objective memory in corresponding domains (Baños *et al.*, 2004) and those finding a correlation in controls but not in patients with epilepsy (Piazzini *et al.*, 2001). So, discrepant objective and subjective scores cannot be wholly attributed to methodological flaws (Hall *et al.*, 2009), but there are a number which will be discussed in more detail.

Sampling methods may affect the results of studies comparing objective and subjective memory problems (Hall *et al.*, 2009). The majority of studies reviewed by Hall and colleagues had recruited patients from hospital or specialist tertiary clinics, or included pre-surgical patients. These are likely to be the most difficult to control cases of epilepsy, mostly refractory to medication, so the results from these studies may be difficult to generalise to a wider population of people with epilepsy, as around 70% are well controlled by medication. Also, some studies recruited participants as those referred to neuropsychology as having memory complaints, reducing the generalisability of results. On the other hand, these refractory patients are the population of patients who are most likely to have complaints about memory so they are the most relevant for finding out what factors are involved.

It is thought that some memory tests or even some tasks within memory tests are more relevant to everyday memory failures than others (Vermeulen *et al.*, 1993), for example story or word list tasks may test functions used more regularly than a visual memory test (Sunderland *et al.*, 1983). The nature of everyday memory failures has been suggested not to be adequately assessed by conventional cognitive tests (Piazzini *et al.*, 2001). As the tests used are generally designed to screen for brain damage or help identify localisation and lateralisation of a lesion, their ecological validity in real-life situations can be questioned. It has been commented

that the Weschler Memory Scale (WMS) fails to assess the same memory skills that are required in 'everyday' situations (Hall *et al.*, 2009). The Rivermead Behavioural Memory Test (RBMT) is thought to be a more ecologically valid test but studies using this measure still show only slight correlation with memory complaints (Elixhauser *et al.*, 1999). A 'Memory in Reality' test has also been used to try and improve ecological validity but this also had few correlations with memory complaints (Helmstaedter *et al.*, 1998), and only in participants without memory impairment.

The delay included in standard memory tests to measure long term memory function is generally 30 minutes, which may not be long enough to detect consolidation problems. Accelerated long term forgetting (ALF) is the idea that affected patients have normal memory over a short period but a problem with slow consolidation that means they forget things more quickly over days to weeks than other people. This would not be identified by standard memory tests and is thus another possible explanation for the discrepancy between subjective and objective assessment that will be discussed in detail in the next chapter.

Another problem is with interpreting memory complaints, in that a person might feel they have a good memory for some things (eg faces) but poor memory for others (eg directions) and by using a single combined score on a unitary scale these variations will be hidden. It has been suggested that some complaints do correlate with aspects of performance, but using a single complaint index can hide this correlation (Vermeulen *et al.*, 1993). Some studies have split subjective questionnaires into subscales such as: absentmindedness, memory for semantic structures, retrieval, rote memory and childhood memory (Vermeulen *et al.*, 1993; Hendriks *et al.*, 2002). Epilepsy patients have been found to have particular complaints in retrieval, memory for semantic structures and absentmindedness, suggesting their biggest problems compared to controls reflect absentminded behaviour and memory for complex meaningful information (Hendriks *et al.*, 2002). However, while studies employing a single overall measure to assess subjective memory complaints often find no correlation with performance (Blake *et al.*, 2000;

Andelman *et al.*, 2004), studies using more detailed subjective assessment covering separate memory domains and also other relevant cognitive functions have also identified no correlation with objective memory performance (Baños *et al.*, 2004).

The level of cognitive demands in daily life have also been proposed as a potential modifying factor for memory complaints, as it would seem to follow that more demands in daily life would lead to a higher rate of memory failures (Gleissner *et al.*, 1998). However, it was found that those with more objective impairment generally had lower cognitive demands (probably due to their memory deficits) and experienced a perception of greater impairment, so the idea of cognitive demands as a variable interfering with subjective-objective correlations is unlikely.

As responding to a questionnaire asking about memory failures is in itself a memory task, subjects with better memories might remember a larger proportion of their memory failures whereas those with significant memory problems might forget them (Vermeulen *et al.*, 1993). This was evident in a study using both retrospective and prospective rating of memory, where the prospective ratings showed that both patients and controls had underestimated the frequency of memory failures in the retrospective questionnaire (Thompson & Corcoran, 1992). Those who had most underestimated their memory failures were those who reported fewer failures on retrospective questioning, suggesting that those with more memory failures might be the least likely to report them. In some studies the opinions of relatives and friends of the patients' memory problems are also assessed, to investigate whether they are better correlated with objective performance. However, these findings have been inconsistent, one study finding patients to be more accurate with relatives underestimating memory problems (Helmstaedter & Elger, 2000) and one finding relatives to be more accurate (McGlone, 1994).

In controls, correlations have been found between memory complaints and performance where there is none in patients (Piazzini *et al.*, 2001), which would

suggest that the lack of correlation in patients is not merely due to methodological flaws in study design. It is clear that there are a number of potential methodological flaws but if there are still correlations between controls' complaints and performance then it would follow that there are other epilepsy or disease related factors influencing the relationship as well.

ii) Other cognitive problems causing memory complaints

Complaints of poor memory may also be due to other problems, for example patients may interpret cognitive problems such as visuo-spatial difficulties, attention and concentration problems or language difficulties as a memory problem (Hall *et al.*, 2009). Batteries incorporating testing of various domains allow for this possibility to be excluded. It has been observed that mild language difficulties are present in patients with TLE complaining of memory difficulties (Mayeux *et al.*, 1980), and Helmstaedter and colleagues found language functions (including verbal fluency, vocabulary and confrontation naming) to predict nearly 30% of variation in memory complaints, verbal fluency being the strongest predictive factor in subjective memory scores (Helmstaedter & Elger, 2000). This suggests that language performance is important for subjective reporting of memory difficulties, and may explain some of the discrepancy, but there must be other factors involved as well. There have been studies demonstrating that attention and concentration deficits, in contrast, demonstrate little or no correlation with memory complaints (Vermeulen *et al.*, 1993; Piazzini *et al.*, 2001; Baños *et al.*, 2004).

iii) Interference with self-monitoring of memory

It may be that epilepsy itself interferes with self-perception of memory (McGlone & Wands, 1991), or that other factors like mood and psychological factors could interfere with memory perception. As well as the well-documented relationship between mood and objective memory discussed in the previous chapter, mood can also have a significant impact on subjective memory reporting. In many of the studies examining the relationship between complaints and performance, it is noted that patients with epilepsy have significantly higher levels of anxiety and

depression than the controls (Giovagnoli *et al.*, 1997; Piazzini *et al.*, 2001; Andelman *et al.*, 2004), and a number of studies have examined the relationship of anxiety and depression to memory complaints.

When the correlation between mood and subjective memory is compared to that between objective and subjective memory, mood (or anxiety and depression) is found to correlate better than any objective memory measures with complaints (Giovagnoli *et al.*, 1997; Elixhauser *et al.*, 1999; Piazzini *et al.*, 2001; Au *et al.*, 2006; Maarika *et al.*, 2009). When regression is used to calculate the influence of various factors on subjective complaints, psychosocial or emotional factors account for up to 58% of variance, and a greater proportion of variance than any objective neuropsychological measures (Piazzini *et al.*, 2001; Baños *et al.*, 2004; Au *et al.*, 2006; Butler *et al.*, 2009). This impact of mood on the relationship between cognitive complaints and performance has also been demonstrated in other chronic conditions, such as multiple sclerosis (Maor *et al.*, 2001) and following head injuries (Lannoo *et al.*, 1998). There is evidence for a stronger relationship between memory complaints and depression and anxiety, than there is between memory complaints and objective memory performance, but there are other factors that are also important, and the relationship is still neither simple nor clear.

Neuroticism has also been suggested to influence memory complaints – it has been shown to explain around 20% of variance in memory complaints (Vermeulen *et al.*, 1993) and correlate significantly but not overwhelmingly with cognitive complaints (Hendriks *et al.*, 2002). Neuroticism may predispose some individuals to attach significance to commonplace forgetting – misinterpreting it as deteriorating memory function, as it has been suggested that there is an inverse relationship between neuroticism generally and subjective cognitive complaining, not just in people with epilepsy (Cañizares *et al.*, 2000).

Chronic disease rather than epilepsy-specific factors might account for some of the variance, due to limitation of activities and social and economic stresses leading to

negative self-evaluation, which could lead patients to overestimate memory problems (Vermeulen *et al.*, 1993). The ways in which people represent and respond to their experiences with chronic illness can be quite different depending on their knowledge, their coping mechanisms and their health outcomes, and the Common Sense Model (CSM) of illness representation can be used to investigate people's adjustment to chronic conditions (Leventhal *et al.*, 1998). If we can better understand the ways people view and respond to epilepsy it might allow for better understanding of the formation of beliefs about memory difficulties.

The CSM suggests that people derive their personal representation of their illness from both internal and external information (ie their own perception of personal experiences and also information from significant others), and it may be conscious or unconscious, have more than one level or aspect, and change over time with adapting circumstances and experience (Leventhal *et al.*, 1998). Coping strategies are employed and their effectiveness evaluated by feeding back through experience to affect the illness representation. It has been shown that certain coping strategies, particularly avoidance and emotionally-focussed strategies, are associated with perceiving a disease as highly symptomatic with serious consequences (Hagger & Orbell, 2003). So, theoretically, difficulty coping with epilepsy and the use of these mechanisms could mean patients perceiving their disease as highly symptomatic and overstating memory difficulties. There may also be an element of attentional bias, whereby once a person knows they have a condition they are particularly alert to anything associated with that condition (Hall *et al.*, 2009).

It seems that mood and other psychosocial factors might have quite an important impact on subjective memory reporting, and seem to explain some of the discrepancy between objective performance scores and subjective complaints. However, these issues do not explain all of the variance so the discrepancy is likely to be due to a number of factors interacting with one another. If these discrepancies between performance and complaints are true discrepancies as it appears, it is important that objective functioning, subjective functioning and mood are all assessed separately, as the constructs are related but independent, and all are

different aspects of a patient's functioning and important for their quality of life and the impact of disease (Elixhauser *et al.*, 1999).

One of the possible reasons for a failure of neuropsychological assessment to identify actual memory deficits is accelerated long term forgetting, which will be discussed further in the next chapter.

Chapter 6 Accelerated long term forgetting

6.1 Background

As discussed in the previous chapter, objective measures of memory performance often do not correlate with subjective memory complaints in patients with epilepsy, and as unexplained complaints are a worry for both patients and clinicians, it is important to try to explain these discrepancies. As discussed, it is likely that there are a number of contributing factors that influence reporting of memory problems, such as mood and psychological wellbeing, but it has also been proposed that there is actual memory impairment that is not identified by standard neuropsychological tests. One possible reason for this is that the standard length of delay tested is too short, and there may be a problem, termed 'accelerated long term forgetting' (ALF) with retention or consolidation of memories over days to weeks while memory over a delay of 30 minutes is unimpaired.

Accelerated long term forgetting shows a different pattern from the typical amnesic syndrome, when patients would characteristically demonstrate impaired recall and recognition of information presented within seconds, so long as rehearsal is avoided by distraction. This initial impairment does not increase after the first few minutes (Isaac & Mayes, 1999). In contrast, patients studied with ALF demonstrate unimpaired memory at initial testing and after a 30 minute delay, with forgetting accelerating after this time.

A number of case reports first emerged of epilepsy patients with this interesting pattern of memory impairment, in those with various aetiologies of epilepsy including closed head injuries and paraneoplastic limbic encephalitis, tending to be quite severe individual cases (Kapur *et al.*, 1996; Kapur *et al.*, 1997; O'Connor *et al.*, 1997; Mayes *et al.*, 2003). A number of group studies have since been undertaken

Table 6.1: Summary of studies assessing long term forgetting in patients with epilepsy

Reference	Participants	Measures for long term memory assessment	Time delay	Findings
(Butler *et al.*, 2009)	General: 41 pts with TEA identified by TIME project 20 healthy controls matched by age and education ALF: Long term forgetting tested in subgroup of 22 patients and 20 controls	**Verbal (story and word list) and non-verbal recall** average z score across -15 words from Rey Auditory Verbal Learning Task, -Rivermead Behavioural Memory Test, -7 designs from Graham-Kendall Memory for Designs test	30 minutes, 1 week, 3 weeks	Combined z-score showed ALF in patients Long term forgetting had no relation to volume of medial temporal structures or standard measures of anterograde memory
(Butler *et al.*, 2007)	General: 50 patients with TEA (TIME study) overall ALF: subset of 24 TEA patients (with normal performance on standard memory tests and no cognitive deficit) and 24 pair-wise matched (age and education) controls	**Verbal (word list) and non-verbal recall** 15 words from Rey Auditory verbal learning task 7 visual designs from Graham Kendall memory for designs test	30 minutes, 1 week, 3 weeks	**Verbal**: Patients' recall worse at 30 mins and declined significantly more by 1 week than controls. Little further change by 3 weeks **Non-verbal**: No difference between patients and controls at 30 minutes, patients significantly worse at 1 and 3 wks
(Davidson *et al.*, 2007)	21 children with IGE aged 8-16 21 healthy controls matched for age and IQ	**Verbal (story) recall and recognition and non-verbal recall** Childrens' Memory Scale – stories and dot locations subtests	30 minutes, 7 days	**Verbal:** Patients poorer at initial learning, but no significant group difference at 30 minutes, patient group significantly worse at 1 week at recall (no difference at recognition) **Non-verbal:** No significant differences, but trend to patients being worse at initial trials needed and recall at 1 week
(Bell, 2006)	25 patients with cryptogenic TLE 25 healthy controls 'loosely' matched for age, education, sex and handedness	**Verbal (story) recall and recognition** Logical memory story subtest - WMS-III	30 minutes, 2 weeks	Patients performed generally worse than controls at all measures but no evidence of accelerated forgetting

(Mameniskiene *et al.*, 2006)	70 patients with TLE 59 healthy controls age matched (patients had less education)	**Verbal (story and word list) and non-verbal recall** Rey Auditory Verbal Learning Test (RAVLT) (Lithuanian equivalent) Immediate and delayed recall of short verbal logical story (VLS) Rey-Osterrleith complex figure test	30 minutes, 4 weeks	Patients scored significantly worse on all short and long term measures with higher percentage forgotten over 4 weeks Those who had seizures between visits performed worse at second visit despite similar immediate and delayed results.
(Bell *et al.*, 2005)	42 patients with TLE and lateralised seizure onset 49 healthy controls matched to age, education and gender (but with higher IQ than patients)	**Verbal (word list) and non-verbal recall** 12 word list - Selective reminding test procedure 12 geometric figures – Selective reminding test procedure	30 minutes, 24 hours	**Verbal:** Both R and L TLE patients significantly worse than controls, but no difference between groups in rate of loss between tests **Non-verbal:** R and L TLE patients significantly worse than controls, but no difference between groups in rate of loss between tests
(Manes *et al.*, 2005)	7 patients with TEA 7 healthy controls matched to age and estimated premorbid IQ (NART)	**Verbal (story) and non-verbal recall and recognition** Logical memory story recall and recognition Visual reproduction of designs: recall and recognition	30 minutes, 6 weeks	**Verbal:** No significant difference between groups at 30 minutes, with significant drop in both groups by 6 weeks but significantly worse in patients **Non-verbal:** No evidence of accelerated forgetting
(Blake *et al.*, 2000)	23 patients with partial epilepsies 19 healthy controls matched to age, education and IQ	**Verbal (story) recall and recognition** 1 of 2 stories from Adult Memory and Information Processing Battery	30 minutes, 8 weeks	No difference between groups in initial learning or recall at 30 minutes, patients significantly poorer on recall and recognition of story at 8 weeks
(Giovagnoli *et al.*, 1995)	28 patients with cryptogenic TLE 25 healthy controls 'loosely' matched to age, socioeconomic level and profession	**Non-verbal recall** 10 abstract designs - Selective Reminding test procedure	1 hour, 1, 3, 6, 13 days	No significant difference between groups at delayed recall scores

(Martin *et al.*, 1991)	21 TLE patients post unilateral anterior temporal lobectomy (n=6) or candidates for surgery (n=15) 21 healthy controls matched to education but *not* age or IQ	**Verbal (word list) recall and recognition** 12 word list - Selective Reminding Test procedure	30 minutes, 24 hours	No difference between groups initially or at 30 minutes, patient group had significantly poorer recall over 24 hours. No difference in recognition
(Wilkinson *et al.*, under review)	27 pre-surgical TLE patients with hippocampal abnormality (n=15 left-sided abnormality, n=12 right-sided abnormality) 22 healthy controls matched to age, gender and IQ (NART)	**Verbal (story) and non-verbal recall** Adjusted version of logical memory story from WMS-III Rey-Osterreith complex figure test	1 hr, 6 wks	**Verbal:** At 1 hour, L sided patients significantly poorer recall, after 6 weeks both patient groups significantly poorer than controls **Non-verbal:** At 1 hour R sided patients significantly poorer recall, at 6 weeks both patient groups significantly poorer than controls

over a range of intervals, some providing more evidence than others for ALF. These are summarised in Table 6.1 and a brief description of each will be given to give an idea of the level of information currently available.

6.2 Papers with evidence of ALF

Martin et al (Martin *et al.*, 1991) tested 21 patients with temporal lobe epilepsy, either pre (n=15) or post (n=6) surgery, compared to 21 controls with tension headaches. A Selective Reminding Test of 12 unrelated words was used to assess verbal recall and recognition at 30 minute and 24 hour delays, whereby a word list was learnt over 12 trials until two consecutive trials were correct, with only the words forgotten being prompted each time. This method of selective reminding is aimed to avoid the idea of 'over-learning' (Bell 2005) when all of the material is repeatedly presented. There was found to be no difference between the patients and controls in performance on the final trial or in recall at 30 minutes. A group by time interaction was found after 24 hours, showing significantly poorer free recall performance among patients at 24 hours. There were no group differences found in recognition performance over time. The controls had significantly higher mean IQ than patients, which could have skewed the results in their favour, so results were analysed with IQ as a co-variate which showed that there was still a significant group by time interaction not explained by IQ. However, the small group size needs to be taken into account when interpreting results as it could mean the study is underpowered.

A cohort of 23 patients with partial epilepsies and 19 education and IQ matched healthy controls were studied with no significant differences on standard memory neuropsychological assessment (Blake *et al.*, 2000). Participants were asked to learn one of two stories from the Adult Memory and Information Processing Battery over a maximum of ten trials until 90-100% correct (Coughlan & Hollows, 1985). They were tested on recall at 30 minutes and recall and recognition at eight weeks. There were no differences between patient and control groups at number of trials needed,

performance in first three trials, or recall at 30 minutes. Both groups showed significantly poorer recall at eight weeks, with patient group significantly worse than controls at both recall ($p=0.014$) and recognition ($p=0.047$). Within these results, left hemisphere patients were also significantly poorer than both controls and right hemisphere patients on eight week recall, with no significant difference between right hemisphere patients and controls. So accelerated forgetting of verbal information was demonstrated in patients with left hemisphere localisation related epilepsy.

Accelerated forgetting has been investigated alongside autobiographical amnesia in the syndrome of transient epileptic amnesia. A group of seven right handed patients with TEA in remission were studied, alongside seven healthy right handed controls matched for age and estimated premorbid IQ (Manes *et al.*, 2005). Accelerated forgetting was assessed with both an orally presented logical story and reproduction of four designs, with recall tested immediately, at 30 minutes and at six weeks and recognition tested at 30 minutes and six weeks for both tests. The results for logical memory showed no difference between groups immediately or at 30 minutes in recall or recognition. Both groups showed significant change over six weeks in recall, with the TEA group performing highly significantly worse ($p<0.001$) confirming accelerated forgetting of verbal information. Although the majority of the patients reached floor level by six weeks, because the control group were well spread with none at floor or ceiling it can be considered as a valid result demonstrating accelerated forgetting. Recognition scores showed no deterioration over six weeks in the control group but significant forgetting in the patient group. The results for visual reproduction show no data for recall at six weeks because all patients reached floor level, but a significant difference between groups' recall at 30 minutes. Recognition was near perfect in both groups, with some deterioration over six weeks in patients but no significant difference between the groups. Thus, the visual reproduction part of the assessment did not provide very useful results as recall was too near floor and recognition too near ceiling levels, despite the positive results in the verbal component.

The largest study so far into accelerated forgetting (Mameniskiene *et al.*, 2006) looked further into the relationship between long term forgetting and seizure frequency. A cohort of 70 patients with TLE was recruited alongside 59 controls matched to age and gender (although controls had longer mean time in education, more students and less unemployment). Long term forgetting was assessed with a word list (equivalent to the Rey Auditory Verbal Learning task) learned over five attempts, verbal logical story and Rey-Osterreith complex figure. Recall was tested at 30 minutes and after four weeks. Patients were worse than controls on all recall measures (immediately, after 30 minutes and after four weeks) apart from complex figure copying, with significantly increased forgetting rates over the four week delay. Comparing the effect of seizures, those experiencing seizures during the four week delay showed significantly increased rates of forgetting of the verbal logical story compared to patients who had no seizures. Those with seizures involving impaired consciousness showed increased forgetting rates across all measures compared to those with no impairment of consciousness. Also patients with four or more seizures showed an increased rate of forgetting of the logical story compared to those with less than four seizures. Abnormal interictal EEG was also associated with increased forgetting on all measures. These results not only seem to confirm increased rates of forgetting in patients with TLE but also go further in discussion of a mechanism. However, caution should be advised when labelling this increased forgetting as the previously described accelerated long term forgetting, because the patients not only showed forgetting of a larger proportion of the information but also impairment at the initial recall and first delayed recall of information. This shows that they did not have intact initial memory, so the faster rate of forgetting could merely be demonstrative of a more general memory impairment rather than specifically accelerated forgetting. Due to the large numbers and controlling for age and gender, as well as the consideration of seizures, this study is one of the most robust.

Whether the phenomenon of accelerated forgetting might also be present in children with idiopathic generalised epilepsy has also been studied (Davidson *et al.*, 2007), by testing 21 children with IGE aged 8-16 and 21 control subjects matched to age and IQ. Assessment involved use of the Stories and Dot locations subtests of the

Children's Memory Scale (Cohen, 1997) to assess verbal and visuospatial memory, learning to 90% and 83% accuracy respectively over up to ten trials, with delayed recall and recognition tested after 30 minutes and one week. There were no significant differences found at 30 minutes but the patient group scored significantly worse than controls after one week in story recall, although there was no group difference on recognition. On visual recall, there was a trend towards a difference after one week, and no difference after 30 minutes, but no significant difference and no difference on recognition. These results are suggestive of accelerated forgetting, especially of verbal material, on recall after a one week delay in children with IGE, suggesting that it is not only patients with temporal lobe epilepsy that suffer from this problem. This also has implications for children's learning and intellectual development.

Butler et al studied patients with transient epileptic amnesia and some of the neuropsychological features associated with the condition, including accelerated forgetting (Butler *et al*., 2007). A group of 24 patients were studied with TEA who performed normally on standard anterograde memory tests, 12 of whom had subjective complaints of accelerated forgetting, and 24 controls matched to age and education. A word list from Rey Auditory Verbal Learning Task was presented over five to 15 trials until 90% accuracy was reached at free recall (Schmidt, 1996). Recall was subsequently tested at delays of 30 minutes, one week and three weeks. The same process was undertaken with seven designs from the Graham-Kendall memory for designs test (Graham & Kendall, 1968). On the verbal test, there was no difference in number of trials taken to reach the criterion, but a small but significant difference in 30 minute recall, worse in patients. After one week patients experienced significantly accelerated forgetting with little further change up to three weeks. On the designs tests, there was no difference in number of trials or recall at 30 minutes, but patients' performances declined significantly faster over three weeks. Notably, when the patient group was split, those with a subjective complaint demonstrated significant accelerated forgetting of both words and designs, while those with no complaint were no different to controls, despite there being no difference between the patient groups on any other neuropsychological measure.

Butler et al again looked at accelerated forgetting as one of the types of memory problem found in patients with transient epileptic amnesia, with a subset of patients who were also involved in the 2007 study (Butler *et al.*, 2009). Accelerated forgetting was tested in a group of 22 patients with TEA and 20 control subjects. A 15 word list (from Rey Auditory Verbal Learning Task), seven designs from Graham-Kendall memory for designs test and a short prose passage (from Rivermead Behavioural Memory Test) were presented over five to 15 trials until recall was 90%. Recall was then tested on all three measures, at 30 minutes, one week and three weeks. Long term forgetting was calculated as a composite measure across the three tests. There was found to be significant accelerated forgetting using the composite measure in the patient group compared to controls. This did not correlate with hippocampal volumes, seizure variables or any anterograde standard memory measures. Accelerated forgetting has been demonstrated to occur in at least a proportion of patients with TEA.

Pre-operative temporal lobe epilepsy patients with hippocampal atrophy have been studied to assess accelerated forgetting over a six week period, matching participants' performance on initial recall to assess rate of forgetting more accurately (Wilkinson *et al.*, under review). A group of 27 patients and 22 healthy controls matched for age, gender and IQ were investigated. Participants were read a short verbal story up to five times until 75% was remembered at free recall. They were also shown and asked to copy a Rey-Osterreith complex figure, with no learning criterion. Recall for both items was tested at one hour and six weeks. There was significant group by delay interaction for both tasks, with patients demonstrating significantly faster forgetting of both verbal and non-verbal material over the six week delay. Patients with left hippocampal atrophy had significantly faster forgetting of the verbal test over one hour, and both groups of patients had faster forgetting over the six week time delay. In visual testing, patients with right hippocampal atrophy performed worse at one hour, but not significantly so. Both patient groups showed faster forgetting than controls over the six week delay. These results demonstrated a material specific effect of lateralisation of

hippocampal sclerosis over a short delay, but increased forgetting over the longer period was not associated with pathology. Participants were otherwise well matched to controls to avoid condounders, suggesting this is an interesting finding.

6.3 Papers not showing evidence of ALF

Giovagnoli and colleagues (Giovagnoli *et al.*, 1995) assessed 28 patients with temporal lobe epilepsy with no detected lesion on CT or MRI and 25 healthy controls from clinical staff partly matched to age, profession and socioeconomic group. A selective reminding test was administered consisting of ten abstract designs, repeated over 18 trials until two consecutive correct trials with recall tested at one hour and one, three, six, and 13 days. On initial testing right TLE patients were significantly worse than both controls and left TLE patients on all measures, with no difference between left TLE patients and controls. All subjects got significantly worse over the trials from day one onwards, but there was no group by time interaction, and no evidence of accelerated forgetting. Compared to the left TLE group and controls, the right TLE group had significantly less schooling, were slightly older, and performed less well at Raven Coloured Progressive Matrices which estimates abstract reasoning. These discrepancies may bias the results and explain why right TLE patients performed worse.

Bell et al (Bell *et al.*, 2005) tried to collect data to assess the possible benefits from an extra long term memory assessment, assessing patients on both an individual and group level. They studied 42 patients with temporal lobe epilepsy (20 with right TLE, 22 with left TLE) and 49 controls matched to age, education and gender (although controls had significantly higher IQ). Assessment was auditory (12 item word list) and visual (12 geometric figures) using the selective reminding procedure up to a maximum of 6 trials, with free recall measured after sixth trial, at 30 minutes and after 24 hours. Participants were judged to have memory impairment with a score of more than one standard deviation below the control mean. Verbal results showed left TLE patients to be significantly worse than controls on immediate, 30

minute and 24 hour recall, with no difference in the rate of information lost at either delay. There was also no difference in the percentage of patients and controls with isolated memory impairment at 24 hours. Similar results were found in the visual assessment. This study has demonstrated no evidence of accelerated forgetting, suggesting that if it is a real phenomenon found in TLE as previous studies suggest, it is not found consistently in all TLE patients.

Bell also investigated forgetting over a longer delay of two weeks in 25 patients with TLE (6 post-surgical) and 25 controls matched to age, gender and years of education (but with a significantly higher IQ) (Bell, 2006). Participants were tested with the logical memory subtest of the WMS-III (Weschler, 1997a), two stories presented orally to them, and free recall was tested immediately, after 30 minutes and after two weeks. If there was no recall a standard cue was used. Yes/no recognition questions were also asked at 30 minutes and two weeks. Again, the patients were analysed as a group and individually, and memory impairment was judged to be a score greater than one standard deviation below the control mean. The TLE patient group was found to perform worse than controls on immediate, 30 minute and two week delayed recall, but there was no evidence of disproportionate forgetting. Patients were also significantly poorer at both 30 minute and two week recognition but with no disproportionate rate of forgetting. Individually, more of the patients had impaired retention at the 30 minute delay, but not at the two week delay, and fewer showed isolated impaired retention at two week delay. Bell again failed to find evidence of accelerated forgetting in temporal lobe epilepsy patients. 56% of the patients had also been included in the previous study, and been shown not to exhibit accelerated forgetting over 24 hours. Also, there was no mention of whether or not the participants had subjective memory complaints, which have been shown to correlate with accelerated forgetting (Butler *et al.*, 2007).

6.4 Problems with designs

One of the problems with both of Bell's studies is that the patients and controls had significantly different initial recall rates. This can cause a problem for a number of

reasons, including scaling, as the higher performing group, the controls, had a larger amount of information after initial recall that they could forget. Long term consolidation therefore could be affected by a participant's rate of learning, attention and encoding ability. If more information is encoded into memory, this could lead to a greater amount of information available for forgetting. If the controls forget the same amount as patients, it will appear that forgetting rates are equal but in fact the controls will have forgotten a smaller proportion of the initial information. This can lead to an underestimation of the worse performing group's forgetting, as they had much less to forget. Because of this possibility, it may be more effective to ensure that patient and control groups are matched on their levels of initial recall.

Many of the other studies got around this problem by having a specific learning criterion both groups must reach (eg (Wilkinson *et al.*, under review)), although in some cases (Giovagnoli *et al.*, 1995; Bell *et al.*, 2005) this did not work as the patient group failed to reach criterion in the specified number of trials. Mameniskiene and colleagues bypassed the problem of groups not matching at initial recall by investigating the percentage of information initially remembered that was forgotten rather than merely the amount of information forgotten (Mameniskiene *et al.*, 2006).

Another problem with the patient group having a poorer memory than controls at the initial testing or short delay is that it is difficult to discover the mechanism for any problems or increased forgetting rates over the longer delay. If the groups are shown to be different in their memory for items at the initial testing session and the short delay, this shows a general memory impairment. If the memory at a short delay is abnormal then the amount of information retained over a longer period will be affected, as impaired encoding and initial retrieval of the information could cause problems over a longer delay, as well as consolidation problems. This means that poorer recall over a long delay could be interpreted as 'ALF' when it is merely a manifestation of a more global memory impairment.

Some of the studies (Martin *et al.*, 1991; Bell, 2006) mentioned above included post-operative temporal lobe epilepsy patients. These patients, having had at least a significant portion of one of their hippocampi removed, will likely have some memory problems that may be different from those with intact hippocampi and thus could confound the results.

It has been demonstrated that there are two recall mechanisms present in free recall (Glanzer & Cunitz, 1966). The primacy effect is achieved through rote learning fixing items in the long term memory and the recency effect is due to short term memory. If immediate recall is tested of, for example, a word list, without any distraction between presentation of the list and recall, then some of the immediate recall will be due to short term memory. This creates a problem when comparing immediate and 30 minute recall, as any decay cannot be differentiated between loss from long term memory or failure to convert short term to long term memory. Because of this, it may be seen to be more useful to perform a short distraction task in between presentation and initial recall to ensure that any recall is due to long term memory and not due to short term memory and the recency effect.

6.5 Testing procedures and populations

The types of test used to assess different domains of very long term memory vary between the studies examined, so the tests used for each domain will be considered and the results obtained from them, as well as what this could mean.

Verbal recall and recognition were tested by two main groups of tests: stories and word lists. Stories were used in 7 studies (Blake *et al.*, 2000; Manes *et al.*, 2005; Bell, 2006; Mameniskiene *et al.*, 2006; Davidson *et al.*, 2007; Butler *et al.*, 2009; Wilkinson *et al.*, under review), with three testing recognition as well as recall. The story used most commonly was one of the logical memory stories in WMS-III, or a modified version of it. Also used were the story subtest of the Children's Memory Scale, stories from the Adult Memory and Information Processing Battery and a prose passage from the Rivermead Behavioural Memory Test. Only one of the studies

testing verbal recall of a story (Bell, 2006) failed to demonstrate accelerated forgetting in patients, using the WMS logical memory story. In those testing recognition memory of stories, one found accelerated forgetting over a period of 8 weeks (Blake *et al.*, 2000) while two found no difference between groups over one and two week intervals (Bell, 2006; Davidson *et al.*, 2007).

A word list was used to assess verbal recall in five studies (Martin *et al.*, 1991; Bell *et al.*, 2005; Mameniskiene *et al.*, 2006; Butler *et al.*, 2007; Butler *et al.*, 2009) as well as verbal recognition in one (Martin *et al.*, 1991). 15 words from the Rey Auditory Verbal Learning Task or an equivalent were used in three of these, and 12 words from the Selective Reminding Test in the other two studies. Again, accelerated forgetting was demonstrated in patients for verbal recall in all studies bar one (Bell *et al.*, 2005), but was not found in verbal recognition (although this was only examined in one study). Stories and word lists both seem to show similar evidence of verbal long term forgetting.

Non-verbal recall and recognition were tested in eight studies (Giovagnoli *et al.*, 1995; Bell *et al.*, 2005; Manes *et al.*, 2005; Mameniskiene *et al.*, 2006; Butler *et al.*, 2007; Davidson *et al.*, 2007; Butler *et al.*, 2009; Wilkinson *et al.*, under review) using a variety of tests. The Rey-Osterreith Complex Figure test was used in two, Graham Kendall Memory for Designs test in two, visual selective reminding test in two and also dot locations subtest from Children's Memory Scale and visual reproduction of designs subtest of WMS-III. Four found significant accelerated forgetting in patients (Mameniskiene *et al.*, 2006; Butler *et al.*, 2007; Butler *et al.*, 2009; Wilkinson *et al.*, under review)– mostly using Rey-Osterreith complex figure, one found a trend towards accelerated forgetting (Davidson *et al.*, 2007) and three found no evidence.

Thus, accelerated forgetting has been demonstrated in both verbal and non-verbal recall, with more evidence in verbal recall, across both story and word list testing. So it would seem to follow that testing for ALF would need to look at both verbal and non-verbal recall, as there is no strong evidence for one being more affected

than the other. Which is more affected is likely to be predicted by the laterality of the epilepsy as well, for example verbal memory would be more affected by epileptic foci in the left temporal lobe, as demonstrated by Blake et al (Blake *et al.*, 2000).

The length of time delay used in the studies varies from 24 hours to eight weeks. In general, verbal accelerated forgetting seems to be more apparent earlier, from 24 hours (Martin *et al.*, 1991), apart from in Bell's studies where it is not present at all. Non-verbal accelerated forgetting seems to be slightly more delayed, eg in Butler's study with one and three week test points, a trend for ALF is shown in non-verbal recall after one week and significant levels after three weeks, whereas significant ALF is shown in verbal recall after one week (Butler *et al.*, 2007). Davidson et al, testing after one week, also only showed a trend towards ALF in non-verbal recall compared to significant ALF in verbal recall (Davidson *et al.*, 2007). There are no studies testing over less than three weeks that demonstrate significant non-verbal ALF. Considering this, if non-verbal ALF is to be tested I would propose that the time delay would need to be at least three weeks from initial testing to a final delayed recall test.

Looking at the populations of patients studied, it is clear that there is evidence for accelerated long term forgetting in TEA in particular. Patients with TLE or partial epilepsies more generally have also been examined with slightly more mixed results, four studies showing accelerated forgetting over delays from 24 hours to eight weeks and three studies (two of which study largely the same population) finding no evidence for ALF. There is also a suggestion that the phenomenon might occur in children with idiopathic generalised epilepsy. Mameniskiene's study has also compared results within TLE patients between seizure types, finding those with simple partial seizures to have significantly less accelerated forgetting than those with complex partial and secondary generalised seizures during the study period (Mameniskiene *et al.*, 2006)

6.6 Proposed mechanisms of accelerated forgetting

The mechanism that underlies accelerated forgetting is not fully understood, and it is not yet clear how it fits in with previously held theories. As previously discussed, the process of remembering can be split into a number of stages: perception, encoding, consolidation, storage and retrieval. Squire and Alvarez described two processes of long term consolidation – a fast and a slow process, with the fast process based in the medial temporal lobe structures including the hippocampus, where synapses can change quickly and slow consolidation occurring as the medial temporal lobe repeated co-activates the neocortex, where synapses change slowly, until connections form within it (Squire & Alvarez, 1995).

It has been proposed that accelerated forgetting is due to a problem with long term (slow) consolidation of memories, and that findings of accelerated forgetting demonstrate that memories have an extended period of vulnerability. This is most likely an extended period of consolidation, compatible with Squire's proposal, and mesial temporal lobe insult disrupts some crucial aspects of the consolidation process (Blake *et al.*, 2000). It is also suggested that the findings are consistent with the idea that there are two consolidation systems, fast and slow, as the patients showed normal memory at shorter delays, indicating an intact fast consolidation system, with only a deficit on longer delays (Blake *et al.*, 2000).

It is claimed that the subjects' initial normal performance in the same study shows that their results cannot be explained by a deficit in retrieval or encoding. However, this is disputed by Davidson et al, who found accelerated forgetting of word recall but intact recognition, and claim that the normal word recognition scores suggest that ALF must be a problem with retrieval rather than poor retention (Davidson *et al.*, 2007). They propose that it is not a consolidation defect unless consolidation is redefined in broader terms as 'the process of stabilization of the memory trace and its maturation into a form suitable for later retrieval'. The idea that ALF is a retrieval problem is not backed up by other studies assessing recognition, as even those who found normal recognition deny that this demonstrates a retrieval

problem, claiming words can be stored poorly in degraded form (Martin *et al.*, 1991).

Whatever type of memory deficit accelerated forgetting is, the pathophysiology of the process is still unclear. As discussed in Chapter 4, there are a number of possible factors that interact to cause memory difficulties in patients with epilepsy. Seizure activity is widely proposed as a possible mechanism of disrupting consolidation, partially due to reports of patients having fewer memory problems once their seizures are controlled on anti-convulsants (eg(O'Connor *et al.*, 1997)). Mameniskiene et al's results supported this view, demonstrating an increase in accelerated forgetting in patients who had seizures during the study, particularly complex partial or generalised seizures. They also demonstrated a correlation between subclinical epileptiform activity and increased forgetting (Mameniskiene *et al.*, 2006). Wilkinson et al also found a significant correlation between seizure activity and 6 week forgetting rate (Wilkinson *et al.*, under review). Jokeit et al studied forgetting during video-telemetry and found that memory performance for new material was related to the occurrence of seizures in the left temporal lobe (Jokeit *et al.*, 2001).

However, other studies have failed to find the same correlations. Overt seizure frequency has been found to not be related to long term memory performance (Blake *et al.*, 2000; Butler *et al.*, 2009), and significant accelerated forgetting has been found while none of the patients involved had a seizure during the study period (Manes *et al.*, 2005; Butler *et al.*, 2007). It is proposed that these patients with no overt seizures could still have subclinical epileptiform activity, disrupting the activation of neocortical cell assemblies, and thus interrupting slow consolidation (Blake *et al.*, 2000). Butler suggests that, in TEA, because of the relationship between TEA attacks and waking from sleep, there could be subclinical epileptiform activity occurring during sleep which may disrupt sleep-dependent memory consolidation (Butler *et al.*, 2007).

Another possible proposed mechanism is a structural abnormality, which may be causing both the epilepsy and the accelerated forgetting. It is thought that ALF may be a mild form of the amnesic syndrome caused by subtle damage to the medial temporal lobes (Butler & Zeman, 2008), as many of the initial case studies that emerged demonstrating ALF reported structural lesions in the medial temporal lobe. However, no correlation was found between hippocampal atrophy and ALF, although this could be due to insensitive techniques (Butler *et al.*, 2009). Wilkinson, studying patients with hippocampal abnormalities, found that performance at one hour was associated with hippocampal pathology but not performance at 6 weeks, again suggesting that there is more than one mechanism of memory problem in epilepsy (Wilkinson *et al.*, under review). Indeed, the general absence of hippocampal damage is particularly noted to explain why fast consolidation is intact in certain studies (Blake *et al.*, 2000). An alternative structural cause of ALF has also been proposed – a high rate of ischaemic risk factors was noted among patients with TEA (Manes *et al.*, 2005), and three had non-specific vascular changes on MRI. It is purported that it may be worth investigating a link between mild cerebrovascular disease and accelerated forgetting.

Anti-convulsant medications tend to have some cognitive side effects, and have been suggested as a possible mechanism for accelerated forgetting. Jokeit et al found high serum levels of anticonvulsants to be associated with poor recall over a 30 minute delay (Jokeit *et al.*, 2005). However, particularly relating to TEA, most of the patients had memory complaints before they were started on treatment, and some report improvement in their memory since initiation of treatment (Butler & Zeman, 2008). Also, in cases of TEA, the doses of anticonvulsant used are generally very low and thus unlikely to cause the types of side effects Jokeit studied. So at least in cases of TEA, AEDs are unlikely, although not impossible, to be the cause of accelerated forgetting.

Psychological problems can cause memory issues. However, four of the studies demonstrating accelerated forgetting also assessed mood with the Hospital Anxiety

and Depression Scale and found it not to correlate with forgetting rate (Blake *et al.*, 2000; Butler *et al.*, 2007; Butler *et al.*, 2009; Wilkinson *et al.*, under review).

6.7 Summary

In summary, ALF has been demonstrated inconsistently in a variety of populations including TEA, TLE and other partial epilepsies and children with IGE. There are a number of methodological pitfalls to studying long term forgetting, such as how to ensure results over a delay interval that can be comparable, and which domains to test over what time period. The mechanisms causing ALF are as confused as those involved in any memory impairment in epilepsy, but there is a suggestion that seizures or interictal discharges may have an important role by disrupting long term consolidation, alongside possibly pathological changes and AEDs.

ALF has been demonstrated in a variety of groups of patients, but always in those with refractory epilepsy, and even some post-surgical patients. A group it has not been examined in is those recently diagnosed with epilepsy, where some cognitive deficits are demonstrable, as will be discussed in the following chapter.

Chapter 7 Cognitive problems in newly diagnosed epilepsy

7.1 Background

Cognitive research undertaken in newly diagnosed or recent onset epilepsy minimises the confounding variables of duration of epilepsy, lifetime number of seizures and AEDs and allows for clarification of the relationship of various factors to patients' problems. When considered alongside other research, it can also give an idea of cognitive progression through epilepsy. To assess the current level of evidence regarding cognition in recently diagnosed epilepsy, a systematic review of the literature has been undertaken. Studies looking at patients with a diagnosis of epilepsy for less than 12 months, comparing patients to controls (or normative data) and using objective neuropsychological assessment were included. Studies examining childhood-onset epilepsy were excluded as different cognitive problems may be caused by the effects of seizures and underlying lesions on neurodevelopment, as discussed in Chapter 4. Studies reviewed are summarised in Table 7.1.

The results demonstrated by these studies were mixed, with some offering clear evidence of cognitive impairments in newly diagnosed patients, some demonstrating no difference between patients and controls, and some providing an unclear picture of possible or varied impairment. There are a number of problems with studying cognitive performance in a population of 'newly diagnosed' patients with epilepsy, which can lead to difficulty drawing conclusions from the data, which will be considered in this review.

Table 7.1: Summary of studies examining cognition in newly diagnosed epilepsy

Study	Patients	Controls	Domains assessed	Results	Methodological issues (see key below)
(Kalviainen *et al.*, 1992)	74 newly diagnosed untreated patients with single (46) or several (28) unprovoked seizures	39 healthy subjects	General intellectual functioning Verbal ability Verbal learning and memory Attention and flexibility of mental processing Simple psychomotor speed	No differences single vs several seizures. Pts worse than controls on memory (imm and delayed recall and delayed recognition of word list) and attention. 30% of patients' scores indicate subtle memory and attention dysfunction (>1SD).	b, e
(Helmstaedter *et al.*, 1993)	16 newly diagnosed untreated patients with complex partial (CPS) or primary generalised seizures (PGS)	19 healthy subjects	Attention Visuoperceptual speed Verbal fluency Memory	CPS patients sig worse than controls on sustained attention, verbal learning ability, visual retention. PGS in between CPS and controls. Patients with structural lesion on imaging poorer than controls and pts without lesion.	a, c, e, f, g
(Pulliainen & Jokelainen, 1994)	43 newly diagnosed untreated patients	21 healthy subjects	General Intellectual functioning Motor speed and coordination Visual motor speed Attention and concentration Memory and learning Mood state	Patients worse than controls on some motor speed measures and symbol digit task, otherwise no diff. Patients more depression and helplessness than controls	a, b, c, d, e
(Äikiä *et al.*, 1995)	56 newly diagnosed untreated patients with cryptogenic partial epilepsy	48 healthy subjects	General intellectual functioning Verbal memory – story and list learning	No difference between controls and pts at story recall. Pts worse on delayed recall of word list (no difference learning, immediate recall or recognition). More pts impaired (>1SD) at delayed recall and % retention of word lists (52% pts v 15% controls)	c, e

(Kalviainen *et al.*, 1995)	100 newly diagnosed untreated patients with 2 unprovoked seizures or 1 seizure and distinct EEG	59 patients with single seizure, no relapse over next year and no AED	General intellectual functioning Verbal fluency Verbal memory – story and list learning Attention and flexibility	No differences between groups	b, d, e, h
(Gigli *et al.*, 1996)	8 newly referred, previously untreated, patients with clinical and/or EEG evidence of cryptogenic TLE	9 healthy subjects	Attention Psychomotor speed Verbal and visual memory	No significant differences between pts vs controls, or Left vs Right TLE patients.	a, c, e, f, g
(Prevey *et al.*, 1998)	201 newly diagnosed untreated or undertreated patients with secondary generalised seizures (SGS) (119), or complex partial seizures (CPS) (82)	45 healthy subjects	General intellectual functioning Verbal and visual memory Motor speed and integration Concentration and mental flexibility Emotional/personality factors	Control subjects better than pts on 17 of 18 measures, but not all significant. Patients sig worse on memory and motor speed / integration. SGS worse than CPS measures taxing concentration and flexibility	c, d, e, g Previously diagnosed but undertreated patients included
(Aikia *et al.*, 1999)	89 newly diagnosed untreated patients with partial epilepsy	48 healthy subjects	General intellectual functioning Verbal immediate and delayed memory - story and word list	Pts worse at immediate and delayed recall of word list than controls	c, d, e
(Ogunrin *et al.*, 2000)	60 newly diagnosed, previously untreated patients with epilepsy from Nigeria	60 healthy subjects	Short term memory Psychomotor speed Sustained attention	Pts sig worse on all measures except response bias on vigilance test	d, b, e

(Pulliainen *et al.*, 2000a)	52 newly diagnosed untreated patients with partial (26), or generalised (26) epilepsy	26 healthy subjects	General intellectual functioning Motor function and co-ordination Concentration, attention and mental flexibility Memory	Patients sig worse on motor speed and co-ordination and sustained attention, as well as delayed figural memory. No differences between patient groups. Within patients, those impaired have less education and are older, with a trend towards more seizures and more symptomatic aetiology	a, e
***et al.*, 2001)**	39 newly diagnosed untreated patients with left TLE, 16 patients with chronic (>10 yrs) left TLE (both groups remote symptomatic or cryptogenic)	46 healthy subjects	Verbal intellectual functioning Verbal memory - story and list learning	No differences on story recall. Both patient groups worse than controls at immediate and delayed recall and % retention of word list. Chronic pts most affected. Individual – 56% new pts impaired (>1SD) on delayed recall (vs 17% controls), moderate impairment associated with SGS not aetiology	c, d, e, g
(Aikia *et al.*, 2006)	105 newly diagnosed untreated patients, having had at least 2 partial seizures (+/- GTCS) in last 12 months	19 Patients with single seizure not requiring AED	General intellectual functioning Memory Attention, concentration and mental flexibility Verbal fluency Psychomotor speed	No sig differences between groups in scores	d, e, g, h
(Wesnes *et al.*, 2009)	570 newly diagnosed untreated patients across 21 countries	Data from Cognitive Drug Research (CDR) system normative database	Psychomotor speed, Vigilance Memory Attention and concentration Mental flexibility	Pts with epilepsy impaired compared to normative database on power of attention and visual recognition tasks. Impairments more marked with increasing age.	a, b, c, d, e, g

(Taylor *et al.*, 2010)	155 newly diagnosed untreated patients with epilepsy	87 healthy subjects	Psychomotor speed Memory Information processing Mental flexibility Mood	In raw scores, patients worse than controls on 10/16 measures. Adjusted for age, sex and education: pts worse on psychomotor speed, verbal and visual memory. Between seizure types: generalised worse on motor speed No influence of seizure history Mood not correlated with scores	a, g

Drawbacks in design: (if not mentioned in report, classed as negative)

a) Controls not well matched to patients (ie not matched to age and education)
b) Seizure type not taken into account, either during selection or analysis
c) Seizure frequency or total number of seizures not taken into account
d) Presence of pathology not taken into account
e) Mood not taken into account
f) Small sample size
g) Inadequate exclusion criteria for participants (need at least: alcohol/drug misuse, learning difficulties, progressive neurological disease, major psychiatric disease)
h) Control group not neurologically normal

7.2 Drawbacks of the research

Potential confounding factors

There are a number of potential confounding factors present in many studies on this topic, which can temper the interpretation of results and make their findings less clear than they may seem. These include clinical, demographic or seizure related patient factors that could impact on cognitive functioning, and also factors concerned with the matching of controls.

i) Matched controls

The control groups in these studies are very important, because it is their performance that is used as a standard with which to compare the patient groups and state whether or not they are impaired. Therefore, it is important that controls are as well matched to patients as possible, as regards variables that could affect cognitive functioning other than seizures or epilepsy. All of the studies have patients and controls matched for age, which can clearly affect cognitive functioning. Another demographic variable that is generally quoted is gender, and the majority of the studies have matched the gender of patients to controls although there are two that have not (Pulliainen & Jokelainen, 1994; Gigli *et al.*, 1996).

Years of education, or level of education, is often used as a variable to try to predict intellectual ability, as years of education has been shown to correlate with IQ (eg r=0.70 (Matarazzo, 1972)) and is identifiable without testing so easier to use when recruiting matched controls. A number of the studies have controls matched to education level, however there are some where the controls have significantly higher levels of education (Helmstaedter *et al.*, 1993; Pulliainen & Jokelainen, 1994; Pulliainen *et al.*, 2000a; Taylor *et al.*, 2010) and some where level of education is not mentioned (Gigli *et al.*, 1996; Aikia *et al.*, 2006). Where there are unequal levels of education between the groups this could explain any cognitive differences, rather than any epileptic activity, so a difference might be found between patients with

epilepsy and healthy controls where there would be no true difference if the groups were well matched (ie a type I error).

In some instances IQ, or verbal IQ, is used as a measure to match patients and controls while assessing other cognitive functions for comparative impairment. This allows for close matching so that individual functions can be examined in more detail, however if epilepsy is thought to impair general intellectual functioning a reduced IQ would be expected compared to controls otherwise matched.

Another issue with controls is whether or not they are neurologically normal. They will tend to be recruited using the same exclusion criteria as patients (see below) but in some studies controls are patients who have had a single seizure (Kalviainen *et al.*, 1995; Aikia *et al.*, 2006). If the effects of frequency or number of seizures is the focus of investigation, or the effects of AEDs, this is understandable, but patients having had a single seizure may have an underlying epileptogenic process so cannot be considered neurologically normal. If it is an underlying epileptogenic process that causes impairment then they could be affected by that and a finding of no difference with patients having had two or more seizures may be a type II error and misleading.

ii) Patient factors

There are a number of variables within patient groups that could affect cognitive functioning and not be noted or controlled for in these studies, which could therefore affect results giving either type I or type II errors.

The exclusion criteria for patients (and controls) involved in these studies is important, as other problems such as severe psychiatric disturbance, alcohol or drug abuse or ongoing neurological disease could also affect cognitive functioning and the results of neuropsychological assessments. Not all the reports clearly state

the exclusion criteria used for each study, but those excluded include individuals with major psychiatric issues, mental retardation or learning difficulties, alcohol or drug abuse, progressive neurological disease, any previous neurological disease that could affect cognition, other major medical illnesses, or acute symptomatic seizures. When the exclusion criteria are strict, this suggests that other likely causes of cognitive impairment apart from epilepsy or seizures have been minimised, but when there are inadequate exclusion criteria there could be other factors interfering with cognitive functioning.

There are other seizure-related clinical variables that could affect cognitive functioning between patients, such as seizure type, previous seizure activity and pathology. The type of epilepsy, whether it is primary generalised or localisation-related, could have an impact on cognitive functioning. If studies have a mixed cohort of patients, or unspecified epilepsy types, there could be a pattern of impairment in one group but not the other which would be misleading if all the patients are analysed together. Some of the studies have only studied localisation related epilepsy (Äikiä *et al.*, 1995; Gigli *et al.*, 1996; Prevey *et al.*, 1998; Aikia *et al.*, 1999; Aikia *et al.*, 2001; Aikia *et al.*, 2006) and some have assessed cohorts of partial and generalised patients separately (Helmstaedter *et al.*, 1993; Pulliainen *et al.*, 2000a; Taylor *et al.*, 2010). However, some have assessed patients having any type of seizure together (Kalviainen *et al.*, 1992; Pulliainen & Jokelainen, 1994; Kalviainen *et al.*, 1995; Ogunrin *et al.*, 2000; Wesnes *et al.*, 2009) which could reduce the specificity of the results, and the likelihood of finding a true significant impairment.

When epilepsy is localisation related, there are other factors which come into play. Whether or not there is a lesion, or any pathological abnormalities on imaging can have a significant impact on cognition, as discussed in Chapter 4. In some studies the presence of abnormalities on imaging is used as an exclusion criterion (Kalviainen *et al.*, 1992; Äikiä *et al.*, 1995; Gigli *et al.*, 1996; Taylor *et al.*, 2010) to try and avoid this as a confounding factor, or pathology is taken into account during analysis (Helmstaedter *et al.*, 1993; Pulliainen *et al.*, 2000a), but others include patients with both cryptogenic and symptomatic epilepsy in one group (Pulliainen

& Jokelainen, 1994; Kalviainen *et al.*, 1995; Prevey *et al.*, 1998; Aikia *et al.*, 1999; Aikia *et al.*, 2001; Aikia *et al.*, 2006), while others do not comment on any imaging findings (Ogunrin *et al.*, 2000; Wesnes *et al.*, 2009). Where these studies are trying to investigate the effect of seizures and epilepsy on cognition rather than any particular structural lesions, any pathological abnormalities become confounding factors that can affect the way the results are interpreted. On the other hand, if the aim of the study was to identify cognitive problems associated with epileptogenic pathology it would be important to ensure the location and type of lesion was consistent between patients.

Where localisation related epilepsy is examined, the probable location and laterality of seizure focus could affect the type of cognitive problem, for example a left temporal lobe focus could be associated with verbal memory deficits. In the majority of studies, even when only partial seizure patients are studied, this is not mentioned or controlled for with any extra analysis. There are three studies assessing a more specific population of TLE patients (Helmstaedter *et al.*, 1993; Gigli *et al.*, 1996; Aikia *et al.*, 2001). The problem with only assessing a more specific population is that, while the results may be more accurate for that population, they are less generalisable to a population of patients with epilepsy in general.

When deciding whether factors are confounding variables, it is important to keep in mind the specific aims of each study. If the aim is to identify whether or not there are any signs of cognitive impairment after minimal amounts of seizure activity, then it is incredibly difficult to identify suitable participants. Those having partial seizures particularly may have years of simple or complex partial seizures without realising what they are and present for medical attention following a generalised seizure, and even if patients have only generalised seizures they could have multiple seizures before one is witnessed or it is clear that they are seizures. Once a patient presents, a diagnosis of epilepsy would not generally be made until at least two seizures have occurred, so a 'newly diagnosed' patient will have had at least two seizures, likely more, as well as interictal epileptiform discharges. The total number of seizures, or previous seizure activity, is used in some studies during

analysis to see if it has an effect on any cognitive impairment found (Kalviainen *et al.*, 1992; Pulliainen *et al.*, 2000a; Taylor *et al.*, 2010), but generally is not used in analysis and ignored as a potential confounder.

As has been discussed, mood and psychosocial factors are also important factors in both subjective and objective cognitive functioning. Only three of the studies reviewed here use a measure to assess the participants' mood status (Pulliainen & Jokelainen, 1994; Prevey *et al.*, 1998), and only one of these analyses the relationship between mood and cognition (Taylor *et al.*, 2010). This is another potential methodological flaw, as if there was mood disturbance causing cognitive problems (and feelings of depression have been shown to be more common in newly diagnosed epilepsy patients than controls (Pulliainen *et al.*, 2000b)) and mood was not assessed, the cognitive problems could be attributed to epilepsy.

AED use is another potential confounding factor in cognitive studies in epilepsy patients, but in these studies all of the participants have been assessed before the start of AED treatment, so that is one major factor avoided and ruled out by the study designs.

Limitations in study design

The gold-standard study design for minimising bias is a randomised controlled trial, but that would not be appropriate to address the questions asked in these studies, as an observational study is needed. Ideally, a prospective study carrying out neuropsychological assessment with people before their first seizure and following any seizures would allow for investigation of the cognitive effects of seizures and the early stages of epileptogenesis. However, as this would require seeing a huge number of healthy people to catch enough having seizures to draw conclusions it is an unrealistic aim, and retrospective studies of patients recruited from presentation are far more manageable. Longitudinal studies are able to give information about the progression of cognitive functioning from diagnosis, which

would seem to be more useful than a snapshot from a cross-sectional study. A number of the reports reviewed are part of a longitudinal study, for instance assessing the effects of various AEDs, but only the baseline scores have been considered for the purposes of this review.

One of the major issues in any clinical research is the number of participants involved, and the statistical power that provides for reporting findings. It is likely that if cognitive impairment is present from diagnosis in some patients with epilepsy, it will only be in a subset of patients (Kalviainen *et al.*, 1992) and will vary person to person. This means that in small studies differences may appear non-significant if only a few patients are impaired, or likewise be exaggerated if a sample contains many such patients, so the results need to be considered in the context of the study.

The selection of participants for research can often be a situation for introducing bias, as it is important that the sample included in the study is representative of the population that the results will be generalised to. However when newly diagnosed patients are concerned, the vast majority will be diagnosed at clinics by a neurologist, regardless of the type or severity of their condition (in contrast to chronic patients when neurologists may only see those who have uncontrolled seizures), so selection bias in patients is not a major issue. The selection and recruitment of controls is not generally discussed in any detail, but merely quoted as 'volunteers'. There is a possibility that people who are likely to volunteer for a cognitive functioning study might either be those who are particularly worried about their cognitive functioning or those who are confident in their functioning and are eager to test themselves, so may not be a representative sample of the population. It is unclear how this can be minimised whilst acting ethically and not coercing people into participating.

Lastly, one of the major problems with reviewing this research is that different cognitive processes were examined across the studies, including memory and learning, attention and concentration, motor speed and co-ordination,

visuoperceptual speed, verbal fluency, reaction times, intellectual functioning and mental flexibility. These cognitive functions are diverse and not necessarily interrelated, so it is difficult to compare and draw conclusions when research has tested different processes. Even within these general functions there is much diversity, for example within memory there are many different types of memory, thought to rely on different areas of the brain. Therefore it is difficult to directly compare results relating to different processes, and this was further compounded by the variety of testing methods used for each process.

7.3 Papers identifying impairments in newly diagnosed patients

A number of studies have demonstrated cognitive impairments in patients newly diagnosed with epilepsy, which will be considered first. The drawbacks of these studies are noted in table 7.1, but the findings will be discussed below. These studies assessed a range of populations of seizure patients, some more specific than others. Patients diagnosed with any or an unspecified type of epilepsy were assessed in three of the studies, only patients with partial onset epilepsy were assessed in three of the studies, patients with partial epilepsy were compared to those with primary generalised epilepsy in three of the studies and in one study patients had had any sort of unprovoked seizure, with or without a diagnosis of epilepsy.

A sub-set of those patients having had any unprovoked seizure were found to have cognitive impairment compared to controls when memory and attention were assessed in patients with a single or several unprovoked seizures before starting anti-epileptic drug (AED) therapy, and compared to healthy controls (Kalviainen *et al.*, 1992). Subtle memory or attention dysfunction was found in the scores of a sub-set of patients (around 30%). Patients in general performed worse than controls at immediate and delayed recall of a word list, delayed recognition of a word list, and some of the attentional measures. Poor memory performance was correlated with poor attention, suggesting that the attention impairment demonstrated could lead

to memory problems. Within the patients, there were no differences in any of the neuropsychological measures tested between those having a single or several seizures.

Some studies have assessed patients newly diagnosed with any type of epilepsy. Pullainen et al found newly diagnosed patients with epilepsy performed worse than controls on some motor speed tasks and a visual motor speed task, quite a limited range of impairment considering the extensive testing (Pulliainen & Jokelainen, 1994). A Nigerian population of newly diagnosed untreated epilepsy patients were found to have slower reaction times than controls, poorer attention, and perform worse at both verbal and visual memory than controls.(Ogunrin *et al.*, 2000). Any correlation between attention and memory was not discussed, but attention deficits could affect memory performance, as demonstrated previously (Kalviainen *et al.*, 1992), and the type of memory tested was immediate memory which might be worst affected by attention problems. This generalised pattern of impairment is the most diffuse and extensive demonstrated yet, perhaps reflecting the wide range of patients studied. Newly diagnosed patients have also been found to be impaired on attention and visual recognition tasks, with impairments becoming more marked with increasing age in a large international study (Wesnes *et al.*, 2009). The problem with this trial was that no controls were assessed, so patients' results could only be compared to a normative database. This means that only their performance on certain tasks can be judged, so impairments could easily be missed. These studies on any type of epilepsy patient show a mixed range of impairments, perhaps due to the mixed cohort.

Some studies have focused on slightly more specific groups of patients, such as those with partial onset epilepsy. Newly diagnosed cryptogenic partial epilepsy patients have been found to be significantly poorer at delayed recall of a word list (Äikiä *et al.*, 1995), with no differences on recall of a story, or immediate recall of a word list. This seems to show a specific impairment in delayed recall of unrelated verbal material. Newly diagnosed partial epilepsy patients generally have also been shown to be impaired at both immediate and delayed recall of a word list, but not a

story(Aikia *et al.*, 1999). Interestingly, patients who would later become refractory to treatment performed worse overall than those who would be controlled by treatment, suggesting that memory impairment at diagnosis is a potential predictor of seizure outcome. As these studies were done on a relatively specific population, it could be that they have been able to identify in more detail a specific deficit. This finding is also backed up by another study showing newly diagnosed or untreated partial epilepsy patients perform worse than controls at a motor speed task and immediate and delayed verbal memory (for a word list), with patients having secondary generalised seizures performing worse than those without on some of the most taxing measures of concentration and flexibility (Prevey *et al.*, 1998). This demonstrates impairment in verbal memory in patients generally with additional impairments in executive functions in those with generalised seizures, suggesting generalised seizures may have an impact on interictal executive function. These studies focusing on partial-onset seizure patients all seem to suggest a similar deficit in verbal memory of a word list, particularly delayed recall.

Other studies have compared groups with different types of seizure onset. Patients with complex partial seizures have been found to perform significantly worse than controls on measures of sustained attention, verbal learning ability and visual retention, while patients with primary generalised seizures performed in between the controls and those with complex partial seizures (Helmstaedter *et al.*, 1993). Again, a correlation between attention and memory was not mentioned but impaired attention could have impacted on memory scores. In this study, patients with a structural lesion on imaging were found to perform worse across nearly all domains than patients without a lesion. Newly diagnosed patients with no structural lesions have been found to perform significantly worse (following adjustment for age and education) than controls at finger tapping, motor speed, figure recognition, immediate and delayed recall of a word list and immediate recall of a story (Taylor *et al.*, 2010). Analysis to identify differences between epilepsy types found that those with primary generalised epilepsy performed worse than those with partial epilepsy at motor speed. In another study, when those with newly diagnosed partial and generalised seizures were investigated, patients did not differ in cognitive or motor measures according to seizure onset, but performed

generally worse than controls in visual motor tasks, mental flexibility and delayed visual memory (Pulliainen *et al.*, 2000a). Risk factors for impairment within the patient groups were also investigated, finding that abnormal imaging findings, higher age, lower level of education and higher total number of seizures correlates with worse concentration and memory performance.

In summary of the studies with positive findings, a wide range of cognitive deficits have been demonstrated in patients newly diagnosed with a variety of epilepsy types. Studies assessing patients newly diagnosed with any epilepsy type have results varying from impairments solely in motor speed to global cognitive impairment. These disparate results may reflect the differences in testing procedures, or the wide variety of patient populations studied, but it is fair to say that some form of cognitive impairment has been demonstrated in each case. With such a wide population to assess, it is unsurprising that there is such variance between results.

Research assessing more distinct populations was able to identify more specific impairments. Studies assessing partial seizure patients identified impairments particularly in delayed, but also immediate verbal memory. None of these studies commented on the localisation of the epilepsy but the most common type of partial epilepsy is temporal lobe epilepsy, which has a clear association with memory deficits. When comparing patients with partial to generalised onset seizures, no significant differences were found, apart from one finding of slower motor speed in generalised seizure patients. When comparing those with complex partial seizures and those with secondary generalisation it was shown that the latter had more problems with concentration and mental flexibility. One consistent finding has been that patients with a structural lesion or abnormal imaging have worse cognitive performance (although the domains affected likely depend upon the location of the lesion).

7.4 Papers failing to identify impairments in newly diagnosed patients

There are some studies which have failed to identify any cognitive impairment in newly diagnosed patients. When patients having had 2 unprovoked seizures or 1 seizure and an abnormal EEG were assessed, there were found to be no significant difference in intellectual functioning, verbal fluency, verbal immediate and delayed memory for a word list and a story, or attention and flexibility when compared to controls who had a single seizure with no relapse over the next year (Kalviainen *et al.*, 1995). Newly diagnosed partial epilepsy patients were also found to be not different in intellectual functioning, verbal memory of a word list and story, visual memory, attention, mental speed, verbal fluency or reaction times from a control group having had a single seizure (Aikia *et al.*, 2006). However, in both of these studies the controls had also had a seizure, so as discussed previously they are not neurologically normal so the results need to be interpreted with caution.

Gigli et al also found no significant difference between confirmed cryptogenic TLE patients and healthy controls, assessing verbal memory, attention, reaction time and recognition of words and dots (Gigli *et al.*, 1996). The baseline results showed no significant difference between patients and controls on any measure, or between right and left TLE patients. However, due to the small sample size it is difficult to draw firm conclusions from this. Also, the volunteer controls were matched to the patients by age but no other measures, so many other factors could have influenced their performance on the tests.

7.5 Discussion

Despite the difficulties with confounding factors and study design, there are some conclusions that can be drawn from the reports presented. The weight of the evidence, as it stands, supports the idea that at least a proportion of patients with epilepsy have some form of cognitive impairment from diagnosis. The evidence is

neither overwhelming nor universal and often mixed as to the nature of the deficit, but there are a few clear points which are reinforced between studies. Firstly, partial epilepsies in particular seem to be likely to be associated with a verbal memory deficit, most commonly in delayed recall of a word list. This could suggest a problem with encoding from short to long term memory, with retrieval, or with consolidation. Secondly, patients who experience generalised seizures might be more likely to have difficulties with executive functions such as concentration, mental processing and motor speed. Thirdly, the presence of a structural lesion seems to be associated with greater cognitive impairment, although in studies examining only those without structural lesions (eg (Taylor *et al.*, 2010)) deficits were still evident.

As cognitive problems have been identified from diagnosis in adult patients before the start of anti-epileptic treatment, there are implications for the understanding of cognitive problems in epilepsy. As mentioned previously, a number of factors are considered important regarding the development of cognitive impairments in epilepsy, including anti-epileptic medications, underlying aetiology, repeated seizure activity and psychosocial issues. The findings of problems before the use of anti-epileptic medications means that these cannot be entirely blamed for cognitive problems, even if they have some effect later. Smith et al has also found attention and motor speed deficits in unmedicated patients with epilepsy (Smith *et al.*, 1986). The findings regarding structural lesions demonstrate the impact that aetiology and pathology can have on cognitive function, although as impairments were also found without these it is clear that this cannot be the only factor. When seizure activity is considered, the finding of no impairments in patients compared to controls when controls had had a seizure may suggest that the seizure activity may be an important factor in cognitive impairment. Also, the findings of cognitive problems in adult-onset epilepsy show that problems are not purely related to the interruption of neurodevelopment when epilepsy begins in childhood.

As impairments seem to be present in patients without structural abnormalities, this suggests that underlying epileptogenesis could also have a role in cognitive

dysfunction (Hermann, B *et al.*, 2006). Epileptogenesis can be defined as 'the alteration of a normal neuronal network into a hyperexcitable network in which recurrent, spontaneous seizures occur' (Badawy *et al.*, 2009a). This can involve multiple mechanisms, including abnormality of neuronal structure and organisation, ion channel dysfunction and disturbances in network function. Alterations such as axonal sprouting, network reorganisation, or changes in neurotransmitters can lead to the predisposition to have recurrent seizures (Badawy *et al.*, 2009a; Badawy *et al.*, 2009b), and these changes could also potentially contribute to cognitive dysfunction.

Another factor not really addressed so far is the possible impact of psychological wellbeing on cognitive functioning. As discussed, whilst some of the studies used some form of mood assessment as part of their protocol (Pulliainen & Jokelainen, 1994; Prevey *et al.*, 1998; Taylor *et al.*, 2010) the majority did not relate them to neuropsychological performance. Patients have been found, between the studies, to have more depression, helplessness, tension and confusion and less vigour than controls. Both mood and a perceived loss of control has been demonstrated to correlate with subjective cognitive complaints after a first seizure (Velissaris *et al.*, 2009), although not with attention or processing speed. Mood is generally thought to correlate better with subjective than objective cognitive complaints (as discussed in Chapter 5), demonstrated here by a lack of correlation between mood scores and results on neuropsychological tests in the studies reviewed. A study analysing the results from a group of patients and controls assessed in one of the reviewed reports (Pulliainen *et al.*, 2000a) has also looked at the relationship between depressive or other negative mood states and cognitive functioning in newly diagnosed patients (Pulliainen *et al.*, 2000b). It was found that just one motor speed measure was correlated with depression and negative mood, so despite a higher rate of depression, bewilderment and lack of vigour than controls newly diagnosed patients cognitive problems cannot be explained by psychological factors.

The results from these studies are interesting for the understanding of cognitive impairments in epilepsy, but the evidence is neither universal nor overwhelming,

and there are a number of confounding factors and methodological flaws that are difficult to limit. More research is needed in this field, preferably with consistent use of testing procedures for comparisons. Future research could focus on specific groups of patients, as this is more likely to bring focussed clear results, when compared to well matched healthy controls.

Chapter 8 Study aims and objectives

8.1 Aims

The aim of this research is to investigate memory functioning in newly diagnosed patients with localisation related epilepsy, particularly looking at long term forgetting:

- To identify if there is any evidence of accelerated forgetting in newly diagnosed patients with localisation related epilepsy
- To identify differences between rates of forgetting in recall and recognition
- To identify differences in rates of forgetting between verbal and visual memory
- To identify any correlation between subjective memory complaints, objective memory performance (both initial and over a long delay) and mood
- To examine the relationship between seizure related variables and neuropsychological performance

By identifying these differences in forgetting rates we hope to be able to gain further insight into the mechanisms of previously unidentified memory problems in epilepsy. This study will be unique as we will be assessing newly diagnosed patients, so we will be able to give an idea as to whether ALF might be present from early in the course of epilepsy, or whether it develops over time, which again will help to identify the mechanisms involved.

8.2 Hypotheses

With the aim above in mind, the following hypotheses have been developed:

1. Accelerated forgetting of a) verbal recall, b) verbal recognition, c) visual recall and d) visual recognition will be present in at least a subset of patients with newly diagnosed localisation related epilepsy compared to controls
2. Initial forgetting rates will be correlated with standard memory test scores, but long-term forgetting rates will not
3. Patients newly diagnosed with localisation related epilepsy will have higher rates of subjective memory complaints than controls
4. Long term forgetting rates will be a better predictor of subjective memory complaints than standard neuropsychological tests
5. Patients newly diagnosed with localisation related epilepsy will have higher rates of anxiety and depression than controls
6. Measures of depression and anxiety will be a better predictor of subjective memory complaints than standard neuropsychological tests
7. Seizure / epilepsy related factors
    - Patients with secondary generalised seizures will have worse neuropsychological performance and higher rates of long term forgetting than those having complex or simple partial seizures and controls
    - Patients with a greater total number of seizures will have worse neuropsychological performance and higher rates of long term forgetting than those having fewer seizures
    - Patients with an abnormality found on MRI will have worse neuropsychological performance and higher rates of long term forgetting than those with no abnormality
    - Patients having a seizure during the delay between initial assessment and follow up will have worse rates of forgetting than those not having a seizure during the delay

Chapter 9 Methods

9.1 Design

In order to fulfil these aims, a quantitative cohort study will be conducted, studying two populations: patients with recently diagnosed localisation related epilepsy and matched healthy controls. The control group was needed as the assessments used are not standardised, and it was necessary to show that poor performance was due to true impairment rather than test difficulty. The control group were matched to patients by age, gender and years of education on an individual basis, as close as was feasible, as these are variables that might otherwise affect their performance on the memory test and cause a type 1 error.

9.2 Participants

Participants were patients recently diagnosed (in the last 6 months) with localisation related epilepsy from clinics at the Walton Centre, Liverpool and controls. The initial intention was to investigate only patients recently diagnosed with temporal lobe epilepsy, but as there have been significant time constraints on this study and there were not enough patients being diagnosed with temporal lobe epilepsy, it was decided that the inclusion criteria would be widened to patients diagnosed with any localisation related epilepsy to try and gather a more useful sample size. Diagnosis was based on the clinical judgement of a consultant neurologist specialising in epilepsy. Clinical information alongside results from EEGs and imaging were gathered where possible, so that this information could be used in the analysis of results.

Participants were aged 16 to 80, as the neuropsychological tests in this research include normative data encompassing this age range. They had English as a first language, and full scale IQ of greater than 70 (as measured by WASI – see below), so that learning disability or language issues did not confound the neuropsychological evaluation. Exclusion criteria were:

- A history of drug or alcohol abuse (more than 50 units of alcohol per week regularly at any point in the last five years, or drug abuse)
- Any major psychiatric disorders (psychiatric diagnoses requiring medication)
- A history of moderate or severe brain injury – this might be defined as Glasgow Coma Scale (GCS) of 12 or less (Marion, 1999), but for the purposes of this study classification was based on the reports of patients and families, who do not know GCS. Other measures of severity include length of coma or duration of post-traumatic amnesia (Sherer *et al.*, 2008). In this study, a head injury associated with either a period of unconsciousness longer than 15 minutes or post traumatic amnesia for six hours or more was classed as moderate or severe (DWP, 2010).
- Progressive or degenerative neurological condition
- Previous neurosurgery

These exclusion criteria were necessary to, as far as possible, avoid confounding factors that could affect participants' cognitive functioning other than seizure or epilepsy variables.

For the patient subgroup, information was also accessed on seizure type, total number of seizures, time since first seizure, seizure frequency and current medication, alongside any information about abnormalities on imaging or EEG reports where possible. Control participants had the same inclusion and exclusion criteria as patients, apart from the diagnosis of epilepsy.

9.3 Sample size

The primary outcome measure for this study was the proportion of forgetting of the verbal logical memory story between 30 minute recall and three week recall. A sample size calculation was undertaken based on results found by Wilkinson et al, as a similar outcome measure was used in this study, a proportional forgetting rate of a logical memory story in patients with temporal lobe epilepsy (Wilkinson *et al.*, under review). To achieve power of 80%, and significance level of 0.05, a sample size of 21 in each group would be needed to recognise a difference of 0.15 with standard deviation of 0.19 (this sample size calculation was done by Dr Stephen Lane, Statistician at University of Liverpool). This is a smaller difference than that found in Wilkinson's study (0.27), but this study was investigating newly diagnosed patients so the difference might be expected to be smaller. A difference of 0.15 might be thought to be a minimum clinically significant difference. Therefore, the aim was to recruit a sample size of 21 in each participant group, 42 participants in total.

The sample size of the study was limited by the number of people diagnosed with localisation related epilepsy during the study period, and as a result it was recognised that the study might be underpowered. However, smaller group sizes are more acceptable in neuropsychological studies due to the nature of testing very specific populations, and many of the studies into this field so far have had small group sizes (Blake et al. (2000) n = 23, in Martin et al. (1991) n = 21 and in Bell (2006), n = 25).

9.4 Ethical Approval

Ethical approval was obtained from the North West Research Ethics Committee in January 2010 (ref: 09/H1001/98). Amendments to the Participant Information Sheet and Consent Form were made following the researcher's practical experience to

provide more accurate information about the assessments, which were approved as minor amendments by the Ethics Committee in April 2010. Research governance approval was obtained from the Walton Centre NHS Foundation Trust R&D Committee. All participants gave written informed consent for their participation in the research.

9.5 Recruitment

At the start of the study clinic letters were reviewed from all fast track and new patient epilepsy clinics at the Walton Centre in the previous six months to identify any potentially suitable patients who had been diagnosed with localisation related epilepsy within this time. These patients were then invited to join the study by a written invitation letter (see appendix 1), alongside an information sheet explaining the purpose, process and possible risks and benefits of the study (see appendix 2), and also seen on their next visit to clinic if it was during the recruitment period to follow up the invitation.

The author also went through the notes and referral letters for patients who would be attending all epilepsy clinics at the Walton Centre each week (including both new patient and follow-up consultant clinics and nurse-led clinics) to try and identify any potentially suitable patient participants, either recently diagnosed or with first or second seizures who might be diagnosed at clinic. If any were identified the author sat in on the clinic to see whether they were actually suitable and, if so, speak to them about the research and invite them to join the study. The author also sat in on all fast track clinics in case a patient was suitable. This approach allowed the author to meet many of the patient participants at their initial diagnosis and assess them soon after. However, one of the drawbacks in recruiting patients at diagnosis is that it is very difficult to know from referrals whether or not patients will be diagnosed until they are seen in an epilepsy clinic and a detailed history taken, so it was a time-intensive approach that required seeing many patients in order to recruit a few. On the other hand, the opportunity to sit in on

clinics regularly allowed the author to gain a better understanding of epilepsy generally and the wide range of difficulties and problems the disease, its course and its treatment causes.

Once recruited, patient participants were asked if they knew anybody without epilepsy of a similar age and same gender as them who might be willing to participate as a control, and if so to give them an information sheet explaining the study so that they could contact the researcher if they wish to participate. Asking friends and relatives is a method for recruiting matched controls that has been used in a number of studies investigating accelerated forgetting (Blake *et al.*, 2000; Bell *et al.*, 2005; Bell, 2006; Butler *et al.*, 2007; Butler *et al.*, 2009). However, largely due to the time commitments involved in participating in the study, a number of the patients were unable to find people willing to act as controls, so an advert was posted on the intranet at the Walton Centre for staff members to volunteer as control participants to match to the remaining patients. For each patient, the author aimed to recruit a control of the same gender and level of education, and within five years of the same age, either through patients or the advert.

9.6 Data Collection

9.6.1 General

Once the participant had been given all the information and agreed to be involved in the research, two assessments – a long (around three hour) first assessment and a brief (15 minute) follow-up three weeks later – were arranged with the participant at times that were mutually convenient to the participant and the author. Verbal consent was taken when arranging these assessments and written consent for participation in the research was obtained at the start of the first assessment, so that there was time between arranging and carrying out the assessment for the participant to consider their decision and think of any questions they might have. The author personally conducted all of the assessments, to ensure consistency of assessment and avoid observer bias. Participants were offered the option of having

the assessments either in a room in the Clinical Trials Unit at the Walton Centre or as home visits. Having all the assessments in the Clinical Trials Unit would ensure consistency, and no distractions. On the other hand, a number of people found it difficult to get to the Walton Centre and were happier to participate if the assessments could be done as home visits. Where this was the case, lone worker policy was followed to ensure the safety of the author and it was ensured that there was a quiet space in the home with a table and chairs and distractions were minimised.

9.6.2 First Assessment

Table 9.1: Battery of tests administered at the initial assessment

Test		References	Cognitive function tested
Weschler Abbreviated Scale of Intelligence (WASI)		(Weschler, 1999)	General intellectual functioning
Weschler Memory Scale, 3rd Edition (WMS-III)		(Weschler, 1997a)	General memory functioning
Hospital Anxiety and Depression Scale (HADS)		(Zigmond & Snaith, 1983)	Emotional well-being : anxiety and depression
Memory Questionnaire		(Thompson & Corcoran, 1992)	Subjective view of memory functioning
Experimental tests	**Logical Memory Story A from WMS-III**		Long term verbal learning and memory
	Visual Scenes Test		Long term visual learning and memory

The first assessment took between two and a half and three and a quarter hours in all participants, varying depending on the speed at which tests were completed and how many breaks in between tests participants wanted. Breaks, tea, coffee or water were offered between tests within the assessment to ensure that the participant's performance was not affected by fatigue or boredom. After written consent had been obtained, each assessment began with a clinical history (including seizure history in patients), to get an idea of the participant's current health status and

discover any factors (such as alcohol, medication, or previous neurological history) that could impact on neuropsychological performance and confound the findings.

Following the history taking, the tests administered at the initial assessment are listed above (table 9.1) with a brief description of each following:

a) Weschler Abbreviated Scale of Intelligence (WASI) (Weschler, 1999)

The WASI is an abbreviated version of the Weschler Adult Intelligence Scale- 3rd Edition (WAIS-III) (Weschler, 1997b), which is thoroughly validated, with normative data and scoring procedures provided in the accompanying manual. It consists of four of the subtests of the WAIS-III which can be used to produce three index scores of intellectual functioning: verbal (VIQ), performance (PIQ) and full-scale (FSIQ).

Two subtests are combined for the verbal score: vocabulary and similarities (see table 9.2). The vocabulary subtest comprises asking the participant to define a series of words, for which they score zero, one or two depending on how well they are able to define each word. The similarities subtest comprises asking the participant to explain how two words are alike, and again scoring zero, one or two depending on how well they are able to verbalise the similarity.

Table 9.2: Sample items for verbal subtests of WASI

Subtest	Sample item
Vocabulary	Tell me what PERFORM means
Similarities	In what way are NEAR and DISTANT alike?

Two subtests are combined to give the performance score: block design and matrix reasoning. For the block design subtest, the participant is given a number of blocks which have some sides all red, some sides all white and some sides half red and half white. The time it takes them to copy various designs of increasing difficulty using the blocks is measured (see figure 9.1). The matrix

reasoning subtest comprises the participant being shown a series of incomplete patterns, with a set of five potential options to complete each pattern (see figure 9.2). The scores from the four subtests are scaled according to age, then combined to give the verbal, performance and full scale (FSIQ = all four subtests) scores.

Figure 9.1: Example design from WASI: block design subtest

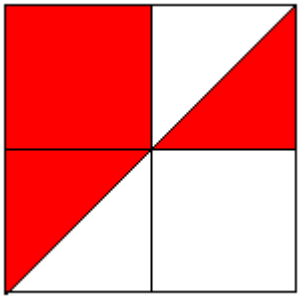
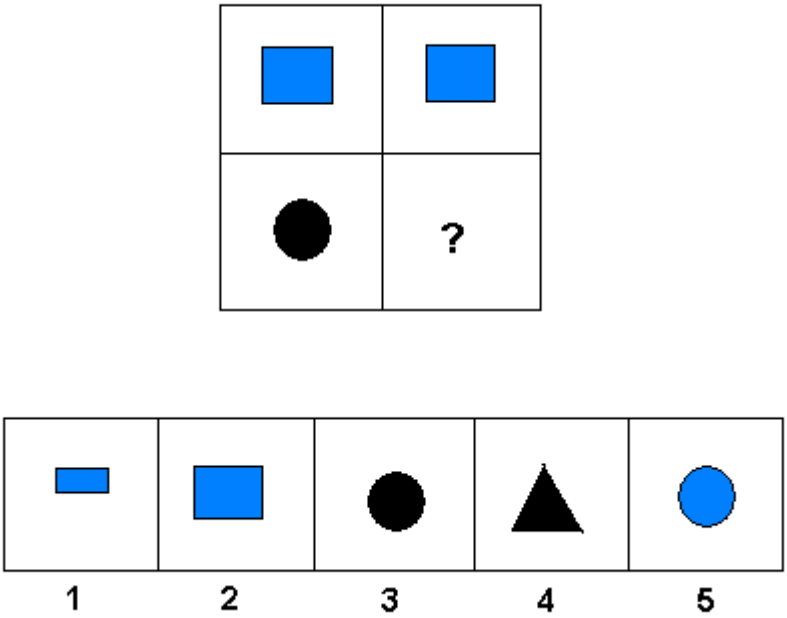


Figure 9.2: Example item from WASI: Matrix Reasoning subtest



It was felt that a rating of intellectual functioning was needed as part of the assessment, both to assess differences between patients and controls and to identify any correlation between domains of intellectual functioning, memory, and long term forgetting. The WASI provides a shortened but thorough method

of assessing verbal and performance skills which has been extensively normed and validated, so factors such as age are taken into account.

b) Weschler Memory Scale – 3rd Edition (WMS-III) (Weschler, 1997a)

Table 9.3: WMS-III primary indices and the subtests used

Primary Index	Subtests included	Description of function tested
Auditory Immediate	Logical Memory I Verbal Paired Associates I	Ability to recall information immediately after oral presentation
Visual Immediate	Faces I Family Pictures I	Ability to recall information immediately after visual presentation
Immediate memory	Logical Memory I Faces I Verbal Paired Associates I Family Pictures I	Ability to recall both visual and auditory information immediately after presentation
Auditory delayed	Logical Memory II Verbal Paired Associated II	Ability to recall information presented orally after a 25-35 minute delay
Visual delayed	Faces II Family Pictures II	Ability to recall information presented visually after a 25-35 minute delay
Auditory recognition delayed	Logical Memory II recognition VPA II recognition	Ability to recognise orally presented information after a 25-35 minutes delay
General memory	Logical Memory II Faces II Verbal Paired Associates II Family Pictures II Auditory Recognition Delayed total score	Ability to recall and recognise orally and visually presented information after a delay
Working memory	Letter-Number Sequencing Spatial Span	Ability to remember and manipulate both orally and visually presented information in short term memory storage

The WMS-III provides a general assessment of memory functioning in adolescents and adults that has been heavily researched and validated, and co-normed with the WAIS-III. There are 11 subtests, of which six are primary and five optional, which are combined to give eight primary index scores (see table 9.3). Many of these subtests are administered in two conditions – to assess initial recall and delayed recall 25-35 minutes later.

- Logical Memory – Two stories are orally presented to the participant (the second one is presented twice) and after each presentation the participant is asked to recall as much as they can of the story, as close to the same words as they can remember. They are asked to recall both stories again after a 25-35 minute delay filled with other subtests, and then asked some yes/no recognition questions about the content of each story.
- Faces – a series of 24 photographs of faces are shown to the participant, and then another series of 48 photographs of faces (the same 24 plus 24 new faces). For each face in the second series the participant is asked to say whether or not they have seen the face in the first series. After a 25-35 minute delay they are shown another series of 48 faces (the original 24 plus 24 different new faces) and again asked to say for each face whether or not it was in the first series.
- Verbal Paired Associates – a list of eight pairs of unrelated words (such as badger – paper) are orally presented to the participant, and then they are given the first word of each pair and asked for the corresponding word. There are four trials of the list of word pairs, with them being presented in a different order (but the same pairs) each time. After a 25-35 minute delay participants are again given the first word of each pair and asked for the corresponding word. Recognition of word pairs is also tested when participants are asked to report whether or not a word pair has been presented before when a list of 24 word pairs is read by the examiner.
- Family Pictures - four pictures are presented each involving a number of family members carrying out activities. After presentation, participants

are asked who was in each scene, whereabouts they were and what they were doing. After a delay of 25-35 minutes participants are asked the same questions again, with no further presentation of the scenes.

- Letter-Number Sequencing – A string of mixed letters and numbers is read by the examiner, and the participant has to reorganise the string into numbers first, in ascending order, and then letters in alphabetical order. For example, 5-B-4-L would become 4-5-B-L. The length of the string is gradually increased.
- Spatial Span – a three dimensional block board is used. First the examiner points to a series of blocks and the participant has to touch the same blocks in the same order, with increasing numbers of blocks, then the examiner points to a string of blocks and the participant has to touch the blocks in reverse order.

The WMS-III is extensively normed so that raw scores are adjusted for age before conversion to index scores, allowing a wide range of ages of participants to be assessed and their performances compared to what would be expected at their age.

An assessment of general memory performance was needed for this study, partly to try and examine the discrepancy between subjective and objective memory functioning and whether it is due to failings in the objective assessment, and also to investigate any relationship between memory performance assessed traditionally with a 30 minute delay and long term forgetting.

The WMS-III was chosen for this study as it is currently the most widely used general memory assessment in patients with epilepsy referred to neuropsychology services for memory assessment. The strength of the predictive value of the WMS scores for long term forgetting rates will demonstrate the efficiency of this measure as an assessment to identify memory problems in patients with epilepsy. For example, if there is little correlation

between WMS scores and long term forgetting, and accelerated forgetting was present in the patient group, it might be important to introduce additional memory assessment as part of any neuropsychological battery used in assessing patients with epilepsy.

However, there are a number of drawbacks to using the WMS-III for detailed memory assessment. When considering the effectiveness of the WMS for lateralising temporal lobe epilepsy or lesions, a number of the subtests contain a mixture of verbal and non-verbal elements, rather than reflecting primarily the functions of one hemisphere or the other (Jones-Gotman *et al.*, 2010). Also, although the subtests attempt to assess different domains of memory, the verbal and nonverbal tasks are dissimilar and thus cannot provide a direct comparison of the hemispheres.

c) **Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983)**

The Hospital Anxiety and Depression Scale is a well-established and reliable instrument for the screening of individuals with clinically significant anxiety and depression. It is a self-report questionnaire with seven items for each subscale (see table 9.4), which gives a score for anxiety and for depression which can be categorised into normal, mild, moderate or severe.

Table 9.4: Example question and responses from each subscale of the HADS

Scale	Question	Responses	Score
Anxiety	I feel tense or 'wound up':	• Most of the time • A lot of the time • Time to time • All the time	3 2 1 0
Depression	I still enjoy the things I used to enjoy:	• Definitely as much • Not quite as much • Only a little • Hardly at all	0 1 2 3

A scale measuring anxiety and depression was needed as part of the assessment because it was felt to be important to investigate the emotional well-being of the participants so that it could be taken into account when looking at both the objective memory performance and the relationship between objective and subjective memory. The HADS was felt to be the most appropriate measure because it is a widely used and well validated measure and it is brief so avoiding lengthy interviews for the participant, when they already face a tiring assessment.

d) Memory Questionnaire (Thompson & Corcoran, 1992)

The Memory Questionnaire is a self-report instrument to assess an individual's view of their memory. Respondents are asked to rate the frequency of occurrence of 18 various everyday memory failings (see table 9.5 for an example), with a minimum total score of 18 and maximum of 108. There is also a general rating of how much of a nuisance the participant finds their memory to be, from 'no nuisance at all' (zero points) to 'a serious nuisance' (three points).

Table 9.5: Sample item from Memory Questionnaire

Sample question	Responses	Score
How frequently do you...	Not at all	1
...Forget where you have put something, or lose things around the house?	About once in the last 3 months	2
	About once a month	3
	About once a week	4
	About once a day	5
	More than once a day	6

An instrument was required as part of this study to assess the participants' views of their own memory, so that the relationships between subjective memory, objective general memory performance and long term forgetting could

be examined. This questionnaire was devised for a research study investigating subjective cognitive functioning in patients with epilepsy (Thompson & Corcoran, 1992), and has been used in other studies examining long term forgetting rates (Butler *et al.*, 2009), so it is designed for an appropriate population. Also, it comprises both a rating of frequency of individual problems and an overall nuisance rating, so there are a number of outcomes that can be analysed separately (such as the overall nuisance ratings, total scores for frequency of failings, which items are rated as more troublesome in which populations, and how frequently certain items are reported as a problem).

e) Experimental- Logical Memory Story (see appendix 4)

One of the logical memory stories from the WMS-III was administered again after the WMS assessment, but the administration was slightly adjusted. Performance at initial recall was assessed immediately, and the presentation and immediate assessment repeated until a learning criterion of 85% had been exceeded (28 or more out of 32, using a combination of the recall unit score and thematic unit score), up to a maximum of five trials. This allowed for matching of the groups at initial recall performance, so that the results from the delayed assessments could be compared with each other. A criterion of 85% was chosen as a suitable level because a 100% criterion could cause ceiling effects. The number of trials taken to reach the learning criterion was also noted, as this could be used as a measure of initial learning efficiency.

Delayed recall and recognition were assessed 25-35 minutes after the last learning trial had been completed, in the same way that they would be assessed in the WMS-III.

A logical memory story has been chosen to assess verbal long term forgetting as the aim is to sample memory in a way that is closer to the demands of everyday

life, so a text using meaningful prose can be thought to mimic what might be needed in everyday life rather than other verbal tests such as a word list or unrelated word pairs. It could be suggested that a story would be easier to rehearse than other potential verbal assessments and thus confound the results, but it was felt that as the participants were being asked to do so many different assessments at the initial visit it would be unlikely they would specifically rehearse this story and it was more important to use an ecologically valid test.

f) Experimental- Visual Scenes Test (see appendix 5)

Non-verbal delayed recall and recognition was also tested at both visits. The visual scenes test has been devised by Dr Nils Muhlert. It has been designed to test forgetting over long intervals, and is based on the 'family pictures' subtest of the WMS-III (Weschler, 1997a), along with elements from the spatial memory test (Baxendale *et al.*, 1998) and the complex pictures test (Mandler & Johnson, 1976). Item recall, spatial recall and descriptive recall are assessed. The objects in the scenes were chosen so as not to be too closely semantically related to the scene (i.e. not too easy to guess).

There are four scenes, each with items in each quadrant. First participants were told "You are going to be shown four pictures. In the corners of each of the pictures will be some objects. When I point to one of the corners I would like you to look at the objects in that corner. Later, I will ask you to remember what was in the pictures, so have a good look at each of the objects. Try to remember as many of the objects as possible."

Participants were then shown each picture in turn, with the examiner pointing to each corner of each picture for two seconds each. After the presentation of all of the scenes, the participant was asked to 'take away three from one hundred, and carry on taking away three' out loud for 20 seconds. This distraction period allows the investigator to ensure that the recall performance for the scenes is

relying on long term rather than short term memory by excluding 'recency' effects. Participants were then asked to recall items from the first scene, eg 'can you tell me what was in the beach picture?' Spatial recall was then assessed by asking participants to point to the corner where the objects were that they recalled. Descriptive recall was assessed by asking the participant to identify two descriptors for each object they recall. Similar to the logical memory story, it was important to match participants' performance on this initial recall. Therefore, if participants did not reach a learning criterion of 75%, the entire exercise was repeated until they did, up to a maximum of five trials.

As well as recall, recognition was also tested after a delay of 25-35 minutes. This was done with a series of four option forced choice questions, with the correct answer in a pseudorandomised position in the answers, with the question and four possible answers presented verbally. Two scenes were used for testing recall and two for recognition, as it was thought that the recognition memory questions may cue recall of the scenes.

This test was chosen to assess long term non-verbal memory because it has been designed for this purpose. The nature of encoding and storing simple geometric forms is likely to be different from complex visual scenes, and a test of visual memory using complex pictures is felt to be more representative of the complex visual world we ordinarily encounter (Mandler & Johnson, 1976). It was felt that using a complex visual scenes test to assess long term visual memory would therefore be more ecologically valid than one using geometric designs or random shapes.

9.6.3 Follow-up assessment

At the initial assessment, the date and time for the follow-up assessment were confirmed, as close to three weeks (21 days) later as is possible. This assessment was

carried out in the same location as the initial assessment (whenever possible), i.e. either the Clinical Trials Unit or a home assessment, so that the participant had the same stimuli around them and the situation allowed them optimal recall conditions. At the initial assessment the participant was not told what was involved at the second assessment, merely that it would last around fifteen minutes and be a follow-up to see how they are doing. This was to try and avoid rehearsal of any learnt material during the delay period which could affect the reliability of the results. As they had been through so many different assessments, even if the participants did try to rehearse the material, the chances of them rehearsing the right subtests were small.

At the follow-up visit, first the participant was asked if they had any questions about the previous session, as well as how they had been during the three week delay and if there had been any changes in medication. Patient participants were also asked if they had any seizures, and if so how many and to describe them so that they could be classified.

Participants were also assessed on their delayed recall and recognition of both the logical memory story that was presented until a criterion was reached, and the visual scenes test. This involved the same procedure as for testing delayed recall and recognition after 25-35 minutes. The participant was first asked to remember as much of the story as they could, without any further presentation, and asked the recognition questions which are part of the WMS-III. For the visual scenes test, recall of the beach and stage scenes was assessed, and recognition questions with four multiple choice answers were asked for the park and street scenes, as at 25-35 minutes. These delayed recall and recognition scores for verbal and visual information after a three week delay provided the basis for the long term forgetting scores.

Participants were thanked for their participation, and offered feedback on their results from the standardised tests from the initial assessment, and permission was

requested from the patient participants for their results to be given to their neurologists. This will provide a baseline comparison if they require any further neuropsychological assessment in the future. Participants were also asked if they would like to be sent a summary of the general findings of the study once analysis was complete.

9.7 Data entry and statistical analysis

The assessments for patients and controls were all carried out by the author, to ensure consistency of presentation and collection of data. The assessments were scored according to criteria set out in the test manuals, and checked before being entered into an SPSS (Statistical Package for Social Sciences) version 17.0 database. Confidentiality was maintained by providing each participant with a unique identifying number, which was used in databases and record sheets, with no identifying information stored alongside the data collected. The author conducted all the statistical analysis, using SPSS version 17.0, using statistical textbooks for reference and guidance (Kirkwood & Strerne, 2003; Kremelberg, 2010).

9.7.1 Demographic and Clinical Characteristics

Demographic characteristics recorded and included in analysis were age, gender, handedness, and both years of education and level of education (highest level of education undertaken – school, college or university). The locations of the two assessments were also considered and the length of time between assessments. Differences between the characteristics of the two groups (patients and controls) were analysed. First, the spread of the data was considered for continuous variables (age, years of education, length of time between assessments) to see whether they met the assumption of normality. Distribution was assessed by visually inspecting histograms and considering the values for skewness in each test variable. None of these measures differed from the normal distribution so parametric tests were suitable to analyse them. The means and standard deviations were used as a measure of central tendency and spread, and independent t tests used to assess

differences between the means. For categorical variables Fisher's exact tests were used to assess difference in proportions between the groups, as the expected numbers in the cells were too small for Chi Square analysis.

Clinical variables were described within the patient group. The distribution of data was considered and measures of central tendency were used to describe the data based on the spread. 'Time since diagnosis' and 'time since first seizure' were both negatively skewed variables, so medians and inter-quartile ranges were used to describe them. 'Time since diagnosis' was skewed because the majority of patients were recruited as they were diagnosed in clinic but those recruited via letter or in first follow-up had been diagnosed up to six months before assessment. 'Time since first seizure' was similarly negatively skewed as, while the majority had not had seizures for very long, there were a couple of patients who had had infrequent seizures for a number of years. When the distribution was normal, the mean and standard deviation was used as a measure of central tendency, and for categorical variables proportions were calculated.

9.7.2 Baseline neuropsychological assessment

Descriptive statistics were used to compare the performances of the patient and control groups in the intellectual functioning and memory assessments at the first visit. Again the spread of the data was considered and all scores from the WMS and the WASI fitted the normal distribution. Independent t tests were used to compare the means of the assessment results between groups. Intellectual functioning scores were correlated with years of education in each participant group separately. This was done using Pearson's R correlation coefficients as the scores fitted assumptions of normality. Intellectual functioning scores were also compared with WMS indices memory scores to assess the relationship between intellectual functioning and memory, using Pearson's R correlation coefficients.

9.7.3 Long term forgetting analyses

9.7.3.1 Hypothesis 1 analyses – differences in forgetting rates in patients and controls

As will be described in section 10.2.1a), the results of the long term forgetting tests were first considered according to age. Then, the distribution of the data was considered using histograms and the value for skewness, and any variables which did not fit assumptions of normality were described with non-parametric measures. In these variables, central tendency was described by median and inter-quartile range, and differences between groups examined with Mann Whitney U tests. In those variables which fitted assumptions of normality, means and standard deviations were used to describe central tendency and independent sample t tests used to compare differences between the group means. Where one group's data was skewed and the other normally distributed, non-parametric tests were used.

For the analysis of forgetting over time in the two groups, undertaking a mixed factorial ANOVA with between subjects factor of group (patients vs controls) and within subjects factor of delay (immediate, 30 minutes, 3 weeks) was considered. However, the primary outcome variable was the rate of forgetting over the delay between 30 minutes and 3 weeks, so it was considered more appropriate to compare this rate using independent sample t tests between the two groups. Also, the sample size number was small, thus reducing the power of ANOVA analysis to detect a difference between the groups.

Also, for each long term forgetting variable (three week verbal recall, three week visual recall, three week verbal recognition and three week visual recognition), the control group mean and standard deviation were used as an estimate of the population mean and standard deviation, and individual impairment was described as one standard deviation below the mean. The proportions impaired in each group were calculated, as well as the odds ratio of impairment with 'newly diagnosed epilepsy' as the exposure factor. The difference between proportions impaired in the two groups was assessed using Fisher's exact test, as the numbers were too small for Chi Squared to be valid.

9.7.3.2 Hypothesis 2 analyses- correlations between WMS subtest scores and long term forgetting rates

As the data from all of the long term forgetting measures, and that from the WMS subtests, was shown to fit assumptions of normality, it was possible to undertake correlation analyses using Pearson's R correlation coefficients to identify relationships between measures from the WMS and measures from the long term forgetting subtests, with verbal and visual subtests examined separately, in both patients and controls and in all participants together. Correlations within scores of the experimental tests were also examined, using Pearson's R correlation coefficients to identify relationships between the scores on various parts of the subtests.

9.7.3.3 Hypothesis 3 analyses – subjective memory complaints in patients and controls

Descriptive statistics were used to compare subjective memory complaints in patients and controls. As the overall MQ score data was normally distributed, an independent sample t test was used to compare the mean scores in the two groups. The nuisance rating could be categorical, or an ordinal variable, depending on how it was labelled. The proportions describing memory complaints as 'no nuisance' or a 'mild nuisance' were compared to those describing memory as a 'moderate nuisance' or 'severe nuisance', using Fisher's exact test. The categories had to be combined to create a 2x2 table so that the statistical test could be carried out. The most commonly reported problems were also described, or problems reported at least daily in each group. The proportions of participants rating each problem as happening 'once a day' or 'more than once a day' were calculated and the five most common noted. A Pearson's R correlation coefficient was calculated in each group for the relationship between memory complaint score and age, and a Spearman rank correlation coefficient (because the nuisance rating data was ordinal) was similarly calculated for the relationship between nuisance rating and age in each group. A Spearman rank correlation coefficient was also used to describe the

correlation between the two memory complaint scores (the total score and the nuisance score) as the nuisance scores are ordinal data.

9.7.3.4 Hypothesis 4 analyses – comparisons of subjective and objective memory performance

Pearson's R Correlation coefficients were calculated in each group for the relationships between various neuropsychological measures (intellectual functioning, WMS scores and long term forgetting scores) and memory complaint total scores, to compare subjective and objective memory performance. Spearman's rank correlation coefficients were also calculated in each group for the relationships between the same neuropsychological measures and memory nuisance rating.

9.7.3.5 Hypothesis 5 analyses – anxiety and depression levels in patients and controls

Distributions of the data were examined, and while anxiety scores were found to have a normal distribution, depression scores were negatively skewed. So, using descriptive statistics to compare results between the patient and control groups, an independent t test was used to compare mean anxiety scores and Mann Whitney U test to compare depression scores, with median and inter-quartile range as measures of central tendency and spread. The proportions of patients and controls in each category of anxiety and depression were compared using Fisher's exact tests.

9.7.3.6 Hypothesis 6 analyses – relationship between psychological wellbeing and subjective memory function

In each participant group, Pearson's R correlation coefficients were calculated for the relationships between anxiety and depression scores and memory complaint total score. Spearman rank correlation coefficients were calculated for the relationships between anxiety and depression scores and memory nuisance rating scores, and also between anxiety category and memory complaint total and nuisance scores. No correlations between subjective memory and depression

category were examined as there was only one participant from each group not in the 'normal' category for depression. The correlation coefficients calculated in this section could be compared to those calculated for hypothesis 4 to assess good predictors of subjective memory functioning.

It was hoped that it might be possible to undertake multiple regression analysis to identify the important factors determining subjective memory rating, but there were not enough participants to make this valid.

9.7.3.7 Hypothesis 7 analyses – relationships between long term forgetting and clinical variables

To compare long term forgetting in those with different seizure types, the performance of participants who had had generalised seizures were compared with those who had not. Comparisons were made across psychological wellbeing scores and neuropsychological functioning scores, including full-scale IQ, WMS general memory and results from the long term forgetting tests. Distribution of measures was considered and where the distribution fitted assumptions of normality, means and standard deviations were compared using independent sample t tests. Where the distribution was skewed medians and inter-quartile ranges were used as measures of central tendency and spread and differences between groups examined with Mann Whitney U tests. Proportions were compared using Fisher's exact tests.

Analysis was also undertaken to find a relationship of long term forgetting with number of seizures. For this, Pearson's R correlation coefficients were calculated for the relationships between both total lifetime generalised seizure number and duration of seizures and a range of neuropsychological variables, including those measuring long term forgetting.

It was not possible to undertake analysis of results based on pathology, as there were not enough patients with abnormalities on imaging to make any analysis valid.

The mean long term forgetting scores (in verbal recall, verbal recognition, visual recall and visual recognition) of patients having had a seizure during the interval were compared with those not having a seizure using independent sample t tests.

It was intended that multiple regression analysis would be undertaken on verbal long term forgetting and visual long term forgetting results separately, but there were not enough participants.

9.7.3.8 Individual level analyses

As discussed in section 9.7.3.1, participants were classified as 'impaired' on long term forgetting scores if they had results more than one standard deviation below the control mean. This was used to define groups so that comparisons could be made in the differences in scores between those impaired and those not impaired. This was described separately in those impaired in three week verbal recall and those impaired in three week visual recall. A range of demographic, clinical and neuropsychological variables were compared between those impaired and not impaired, using independent sample t tests to compare means if the distribution was normal and non-parametric tests (Mann Whitney U) to compare performance in variables with a skewed distribution. Proportions were compared using Fisher's exact tests.

During the statistical analysis, multiple comparisons and correlations were undertaken. It is noted that this increases the chance of type I errors, particularly using a significance level of 5%. A Bonferroni correction could have been used to reduce this risk of type I errors. However, a Bonferroni correction is conservative

and, particularly in studies such as this with a small sample size, increases the risk of type II errors and makes it difficult to detect 'small' or 'medium' effects (Nakagawa, 2004). Due to the large number of comparisons and correlations the use of a Bonferroni correction would have the result of no significant findings. As the aim was to look for patterns and potential trends that can be further explored in future research, it was decided that this correction would not be applied, but the results need to be interpreted with caution because of this.

Chapter 10 Results

10.1 Baseline characteristics

A total of 27 participants were assessed, between 16 and 77 years of age, including 14 patients and 13 controls. The primary outcome measure for the study was three week forgetting of the story. As age cannot be taken into account due to the lack of standardised norms for scoring this test, and age might be expected to be related to forgetting, the three week forgetting data for all participants was first investigated according to age group. Both patient and control participants were categorised together according to decades, and mean three week verbal forgetting scores were considered for each decade (see Table 10.1 and Figure 10.1).

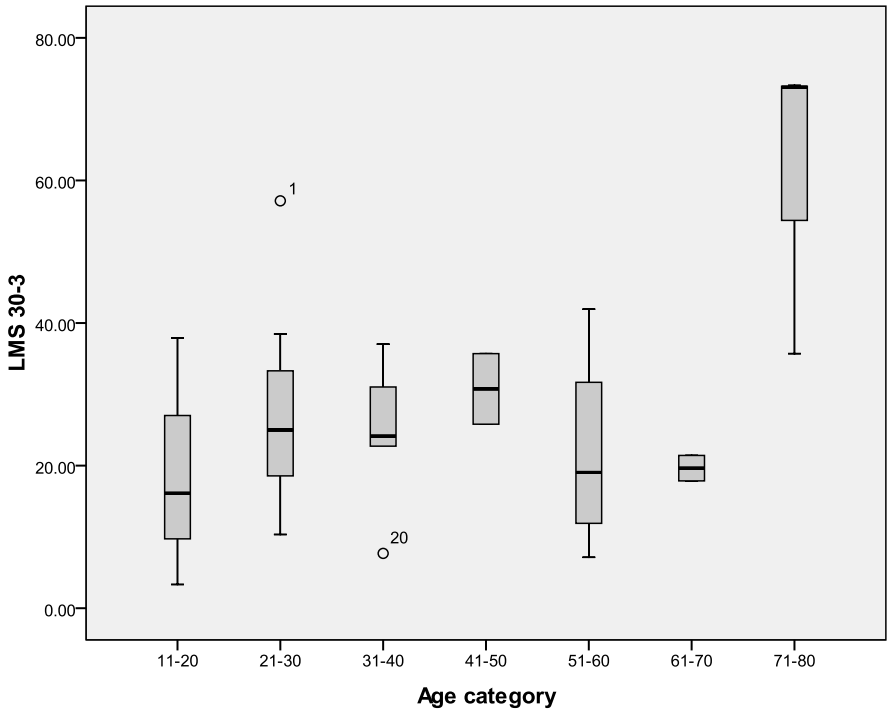
Table 10.1: Mean 3 week verbal forgetting according to age

Age	n	LMS 30-3 mean (SD)	
0-20	3	19.13 (17.49)	Between groups
21-30	8	27.65 (14.72)	one way ANOVA:
31-40	5	24.53 (11.02)	F=2.98 (p=0.030*)
41-50	2	30.76 (7.00)	
51-60	4	21.80 (14.69)	
61-70	2	19.65 (2.52)	
71-80	3	60.71 (21.65)	

*p<0.05, LMS 30-3 is % of story forgotten between 30 minutes and 3 weeks

This demonstrates a clear deterioration in forgetting after the age of 70, and it was subsequently felt that including those over 70 might confound results and affect the reliability of any findings of differences between patients and controls. As there were only three participants over 70 it was not possible to examine them separately and consider their pattern of forgetting. Thus, for the analysis of the results including long term (three week) forgetting, the scores of those over 70 have been excluded to avoid this potential confounding effect.

Figure 10.1: Distribution of 3 week verbal forgetting scores according to age



After the participants over 70 have been excluded so as to avoid the confounding effect of the three week forgetting results, 13 patients and 11 controls remain.

Baseline demographic variables, clinical characteristics and baseline standard neuropsychological assessment results have also been examined in the cohort of 27 participants prior to exclusion of the over 70s, so as to ensure there are no clear differences between the original sample and the final study group used for analysis. Details of these results can be found in appendix 6.

10.1.1 Demographics (see table 10.2)

Differences between patient and control groups in age, gender, handedness and education (both years and level of education) were analysed. No significant differences were found in any demographic variable.

Table 10.2: Participants' demographic information

		All	Patients	Controls	Difference (95% CI)	Significance (*p* value)
Number of participants		24	13	11		
Age/years Mean (SD)		36.21 (15.74)	37.62 (16.17)	34.55 (15.83)	3.07 (-16.68, 10.54)	0.644
Gender	**M**	13 (54.2%)	6 (46.2%)	7 (63.6%)		0.444
	F	11 (45.8%)	7 (53.8%)	4 (36.4%)		
Handedness	**R**	21 (87.5%)	11 (84.6%)	10 (90.9%)		1.000
	L	3 (12.5%)	2 (15.4%)	1 (9.1%)		
Education /years Mean (SD)		13.58 (2.83)	13.00 (2.48)	14.27 (3.17)	-1.27 (-1.12, 3.66)	0.281
Education /level	**school**	9 (37.5%)	5 (38.5%)	4 (36.4%)	School vs higher education	1.000
	college	6 (25.0%)	5 (38.5%)	1 (9.1%)		
	university	9 37.5%)	3 (23.1%)	6 (54.5%)		

10.1.2 Procedure (see table 10.3)

The procedure of assessment, i.e. where assessment took place and the time delay between the two assessments, could have an impact on results, so differences in these measures between groups have been considered. Differences in proportions of

patients and controls having their initial assessments at home or in the Clinical Trials Unit (CTU) were examined and found to be not significant (p=0.679). One patient had their follow up assessment in a different location to their initial assessment, this was because the date of her follow-up fell on a bank holiday and the CTU was not available, and it was felt to be more important to ensure consistency of time delay than of location. However, this change did not affect the difference in proportion of home and CTU visits between patients and controls, which remained not significant. Not every participant was able to have their follow-up assessment exactly 21 days after their initial assessment, so the mean interval between assessments has also been examined, finding no significant difference in interval between patients and controls (p=0.654).

Table 10.3: Procedural details of assessments in patients and controls

Procedure		All (n=24)	Patients (n=13)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
Location of initial assessment	**CTU**	8 (33.3%)	5 (38.5%)	3 (27.3%)		0.679
	Home	16 (66.7%)	8 (61.5%)	8 (72.7%)		
Location of follow up assessment	**CTU**	7 (29.2%)	4 (30.8%)	3 (27.3%)		1.000
	Home	17 (70.8%)	9 (69.2%)	8 (72.7%)		
Interval between/days Mean (SD)		21.00 (0.89)	20.92 (0.64)	21.09 (1.14)	-0.17 (-0.93, 0.60)	0.654

CTU = Clinical Trials Unit

10.1.3 Clinical Variables

The clinical seizure variables of patients have been examined (see table 10.4). Over half of the patients assessed (53.8%) had had both partial and generalised seizures, while two (15.4%) had had simple and complex partial seizures only and four (30.8%) had had generalised seizures only at diagnosis, with a mean total lifetime

number of two generalised seizures. The median time from diagnosis to the first assessment was four weeks, although the median time since the patients' first seizure was 18 months. This highlights the difficulty of trying to assess patients early in the course of epilepsy, as they will likely have a period of waiting between first seizure and diagnosis to see how things go.

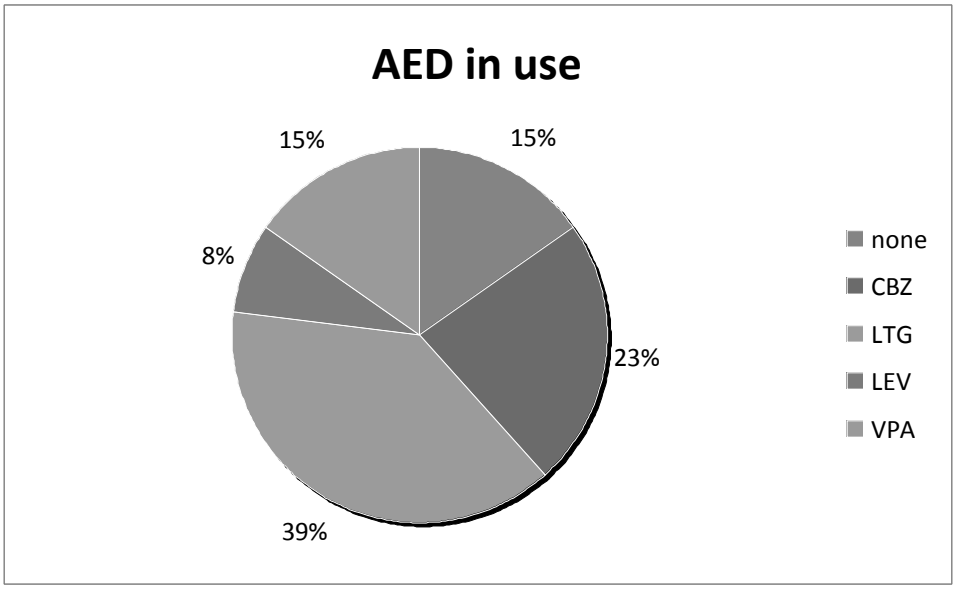
Table 10.4: Clinical variables in patients

Patients		**N=13**
Seizure type	**Partial only**	2 (15.4%)
	Partial and generalised	7 (53.8%)
	Secondary generalised only	4 (30.8%)
Total number of generalised seizures Mean (SD)		2.23 (1.30)
Time since diagnosis / weeks Median (IQR)		4.00 (1.75, 12.75)
Time since first seizure / months Median (IQR)		18.00 (5.25, 66.00)
Number of medications Median (IQR)		1 (1, 1)
Age of onset Mean (SD)		34.23 (16.75)

The mean age of onset of seizures was 34.23 years, although the distribution of age of onset in patients was bi-modal with a peak in the 20s and a smaller peak in the 60s as might be expected considering the distribution of age of onset of epilepsy in the general population.

Medication is expected to be a confounding factor in this study, and all but two of the patients were on one AED. Unfortunately, although lamotrigine was the most commonly taken medication (39%), patients were taking a range of AEDs (see figure 10.2) so it will be difficult to allow for AED use in the analysis of experimental results.

Figure 10.2: AED being taken by patients



As the patients were largely recruited at diagnosis, many had not had investigations by the time they were assessed. During analysis any outstanding investigation results were chased up, but five (35.7%) of the patients did not undergo EEG recording, so results from these patients were unavailable. This was down to the decision of the clinician managing the patients. They were patients with a clear history of localisation related epilepsy in whom it was felt an EEG would not affect management. Obtainable results from patient investigations are shown in table 10.5.

Table 10.5: Patient investigation results

		Patients (n=13)	Details
MRI / CT	**Normal**	11 (84.6%)	
	Abnormal	2 (15.4%)	1 showing right hippocampal sclerosis, 1 showing DNET in right temporal lobe
EEG	**Normal**	7 (53.8%)	
	Abnormal	1 (7.7%)	Clear epileptic activity with left sided temporal focus
	Not done	5 (38.5%)	
Laterality	**Left**	1 (7.7%)	According to EEG
	Right	2 (15.4%)	According to MRI abnormalities
	Unknown	10 (76.9%)	

DNET = Dysembryoplastic neuroepithelial tumour

Table 10.6: Localisation of epileptic focus in patients

	Patients (n=13)
TLE confirmed by investigations	3 (23.1%)
TLE diagnosed clinically based on history	8 (61.5%)
Secondary generalised seizures suggested clinically, origin unclear	2 (15.4%)

The investigation results can be considered alongside the clinicians' clinical opinions based on the patients' histories to give an idea of the localisation of epileptic foci in the patient group (see Table 10.6). All patients were considered by consultant epileptologists to have localisation related epilepsy, which in 11 (84.6%) could be localised to the temporal lobes (as documented in their notes). Although this was only confirmed by investigations in three patients, the others had histories suggestive of TLE, demonstrating that the majority of the patients had likely TLE. The remaining two patients had histories suggestive of secondary generalised seizures but of unclear origin, so they may have had TLE or may have had other localisation related epilepsies.

10.1.4 Background intellectual functioning – WASI

Table 10.7: Mean scores for VIQ, PIQ and FSIQ in patient and control groups

	Overall (n=24)	Patient (n=13)	Control (n=11)	Difference (95% CI)	Significance (*p* value)
VIQ	102.92	97.38	109.45	-12.07	0.060
Mean (SD)	(15.76)	(14.01)	(15.78)	(-24.68, 0.54)	
PIQ	111.58	104.38	120.09	-15.71	0.001**
Mean (SD)	(13.07)	(10.45)	(10.71)	(-24.68, -6.73)	
FSIQ	108.04	101.00	116.36	-15.36	0.005**
Mean (SD)	(13.99)	(11.44)	(12.35)	(-25.44, -5.29)	

*p<0.05, **p<0.01, ***p<0.001, VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ = Full scale IQ

Results from the WASI can be used to give a score for VIQ, PIQ and FSIQ. Patients performed significantly worse than controls in PIQ and FSIQ (p=0.001, p=0.005

respectively) (see table 10.7), despite similar levels of education. When the relationship between education and intellectual functioning is examined, in all participants years of education are significantly correlated with VIQ and FSIQ scores (p<0.05) (see table 10.8). However, when the groups are split, years of education only significantly correlates with VIQ and FSIQ in controls, with no correlations between years of education and any intellectual functioning measure in patients.

Table 10.8: Correlations between intellectual functioning scores and education

All participants (n=24)	**Years of education**
VIQ	0.446 (p=0.029)*
PIQ	0.259 (p=0.222)
FSIQ	0.427 (p=0.037)*
Patients (n=13)	
VIQ	0.144 (p=0.639)
PIQ	-0.276 (p=0.361)
FSIQ	-0.073 (p=0.812)
Controls (n=11)	
VIQ	0.612 (p=0.045)*
PIQ	0.551 (p=0.079)
FSIQ	0.760 (p=0.007)**

Values reported are Pearson's R correlation coefficients and p values,
*p<0.05, **p<0.01, ***p<0.001
VIQ = Verbal IQ, PIQ = Performance IQ, FSIQ= Full Scale IQ

10.1.5 Background memory scores – WMS

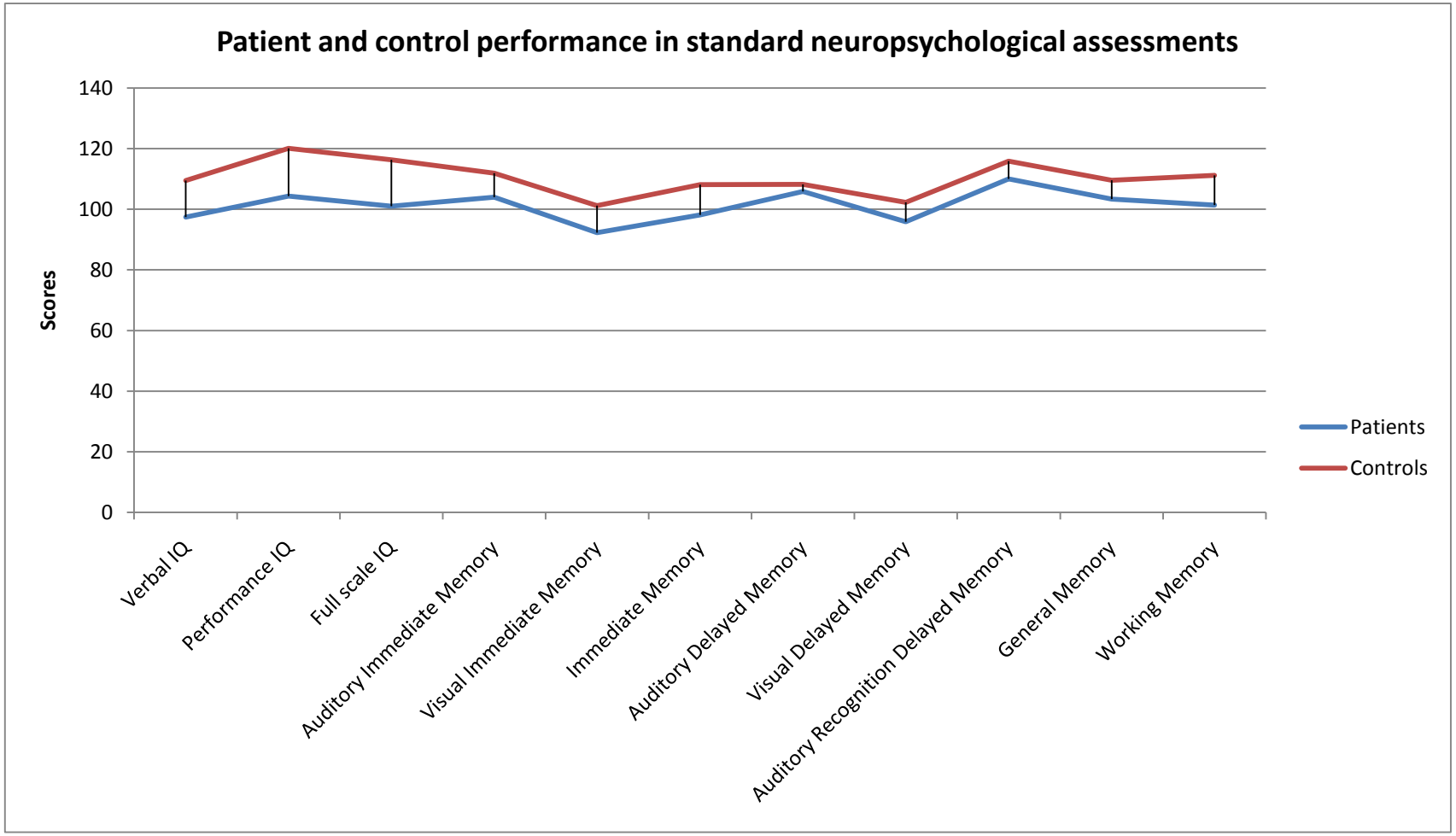
The WMS provides scores on eight separate indices, as shown in table 10.9. Between patients and controls, there were no significant differences.

Table 10.9: Mean scores (SD) in WMS indices

	All (n=24)	Patients (n=13)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
Auditory Immediate Memory (AIM)	107.63 (15.62)	104.00 (13.45)	111.91 (17.51)	-7.91 (-21.02, 5.20)	0.224
Visual Immediate Memory (VIM)	96.38 (13.18)	92.31 (11.54)	101.18 (13.88)	-8.87 (-19.63, 1.88)	0.101
Immediate Memory (IM)	102.71 (14.71)	98.15 (13.04)	108.09 (15.31)	-9.94 (-21.93, 2.06)	0.100
Auditory Delayed Memory (ADM)	106.50 (14.02)	105.08 (11.67)	108.18 (16.83)	-3.11 (-15.21, 9.00)	0.600
Visual Delayed Memory (VDM)	98.83 (13.68)	95.92 (12.14)	102.27 (15.15)	-6.35 (-17.90, 5.20)	0.266
Auditory Recognition Delayed Memory (ARDM)	112.71 (10.73)	110.00 (10.80)	115.91 (10.20)	-5.91 (-14.86, 3.04)	0.185
General Memory (GM)	106.17 (13.85)	103.31 (11.99)	109.55 (15.67)	-6.24 (-17.95, 5.48)	0.281
Working Memory (WM)	105.88 (17.14)	101.38 (17.27)	111.18 (16.13)	-9.80 (-24.04, 4.44)	0.168

Background neuropsychological variables and differences between patients and controls are shown in figure 10.3.

Figure 10.3: Results from standard neuropsychological assessments in patients and controls



10.2 Long term forgetting results

Consideration of the long term forgetting results of the study will be ordered according to the hypotheses outlined previously.

10.2.1 Hypothesis 1: Accelerated forgetting of a) verbal recall, b) verbal recognition, c) visual recall and d) visual recognition will be present in at least a subset of patients with newly diagnosed localisation related epilepsy compared to controls

10.2.1a) Verbal recall over 3 weeks

Various parameters of the long-term verbal subtest, the logical memory story (LMS) have been examined, considering differences between patients and controls (see table 10.11).

Number of trials is the number of presentations of the material given that it took for the participant to reach the criterion level required (85%) and thus provides a measure of initial learning efficiency. 'LMS 0' is a measure of the participants' recall performance on the trial (as a percentage of the total possible score) when they reached the criterion level, and is used for calculating the amount of information forgotten at delays. 'LMS 30' is a score for information recalled after a 30 minute delay (as a percentage of total possible score), and 'LMS 3' is a similar measure for information recalled after a three week delay.

'LMS 0-30' and 'LMS 30-3' are the forgetting scores. 'LMS 0-30' is the percentage of information which had initially been recalled when the participant reached criterion level which was not recalled after the 30 minute

delay, and thus suggests the amount of information forgotten between the initial learning and the 30 minute delay. It is calculated with this formula:

$$LMS\ 0-30 = \frac{\%\ recall\ at\ final\ trial - \%\ recall\ at\ 30\ minutes}{\%\ recall\ at\ final\ trial} \times 100$$

$$LMS\ 0-30 = \frac{LMS\ 0 - LMS\ 30}{LMS\ 0} \times 100$$

Similarly, 'LMS 30-3' is calculated as a percentage of information forgotten between 30 minutes and three weeks, using a similar formula:

$$LMS\ 30-3 = \frac{\%\ recall\ at\ 30\ minutes - \%\ recall\ at\ 3\ weeks}{\%\ recall\ at\ 30\ minutes} \times 100$$

$$LMS\ 30-3 = \frac{LMS\ 30 - LMS\ 3}{LMS\ 30} \times 100$$

Table 10.10: Key to verbal long term forgetting variables

Variable	What it measures
LMS 30	% recall of story at 30 minutes
LMS 0-30	% of story forgotten between final trial and 30 minutes
LMS 3	% recall of story at 3 weeks
LMS 30-3	% of story forgotten between 30 minutes and 3 weeks
LMSR 30	% recognition of story at 30 minutes
LMSR 3	% recognition of story at 3 weeks
LMSR 30-3	% difference in recognition between 30 minutes and 3 weeks

By calculating these forgetting scores as a percentage of initial and 30 minute recall scores, a rate of forgetting is calculated which does not rely on the initial or 30 minute recall performance being perfectly matched. For example, a participant could have poor recall at 30 minutes due to an encoding problem

(say 50%) but retain a high proportion of that information over three weeks (say 80%). If only the recall scores were analysed, this would show 40% recall at three weeks, but by calculating the forgetting rates between the two intervals it is possible to better understand the pattern of memory impairment in this participant.

The performance of patients and controls has been compared (see table 10.11). There is no significant difference in initial learning (as demonstrated by number of trials taken to reach criterion). Although recall performance at 30 minutes was not significantly different between patients and controls, patients had forgotten a significantly higher percentage of the initially remembered material (p=0.024) (see figure 10.4). After the three week delay, patients' recall performance was significantly worse than controls (p=0.021), although the difference in the percentage of information forgotten between the 30 minute recall and the three week recall was not significant (p=0.077).

Table 10.11: Performance of patients and controls in verbal recall

LMS	All (n=24)	Patients (n=13)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
Number of trials to criterion median (IQR)	1 (1, 2)	1 (1, 3)	1 (1, 2)		0.588
Performance at criterion mean (SD)	92.97 (4.04)	92.79 (3.47)	93.18 (4.80)	-0.39 (-3.90, 3.12)	0.819
LMS 30 mean (SD)	89.59 (6.62)	87.26 (7.04)	92.33 (5.11)	-5.07 (-10.27, 0.23)	0.060
LMS 0-30 mean (SD)	3.66 (5.72)	6.02 (5.96)	0.86 (4.10)	5.16 (0.75, 9.57)	0.024*
LMS 3 mean (SD)	67.71 (12.35)	62.50 (13.44)	73.87 (7.56)	-11.36 (-20.85, -1.88)	0.021*
LMS 30-3 mean (SD)	24.55 (12.58)	28.71 (13.08)	19.63 (10.46)	9.08 (-1.08, 19.24)	0.077

*$p<0.05$

LMS 30= % of story recalled at 30 minutes; LMS 0-30 = % of story forgotten between final trial and 30 minutes; LMS 3 = % of story recalled at 3 weeks; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks

Individual impairments

As well as looking at the overall group means for forgetting scores, impairment has been considered on an individual basis. Using the control mean and standard deviation as an estimate of the population mean and standard deviation, impairment has been defined as more than one standard deviation below the mean (table 10.12).

Table 10.12: Individual impairment of verbal retention over 3 weeks

LMS recall 30-3	Patient	Control	Difference
Impaired	6 (46.2%)	1 (9.1%)	p=0.078
Not impaired	7 (53.8%)	10 (90.9%)	

LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks

Figure 10.4: Recall of the story over time in patients and controls

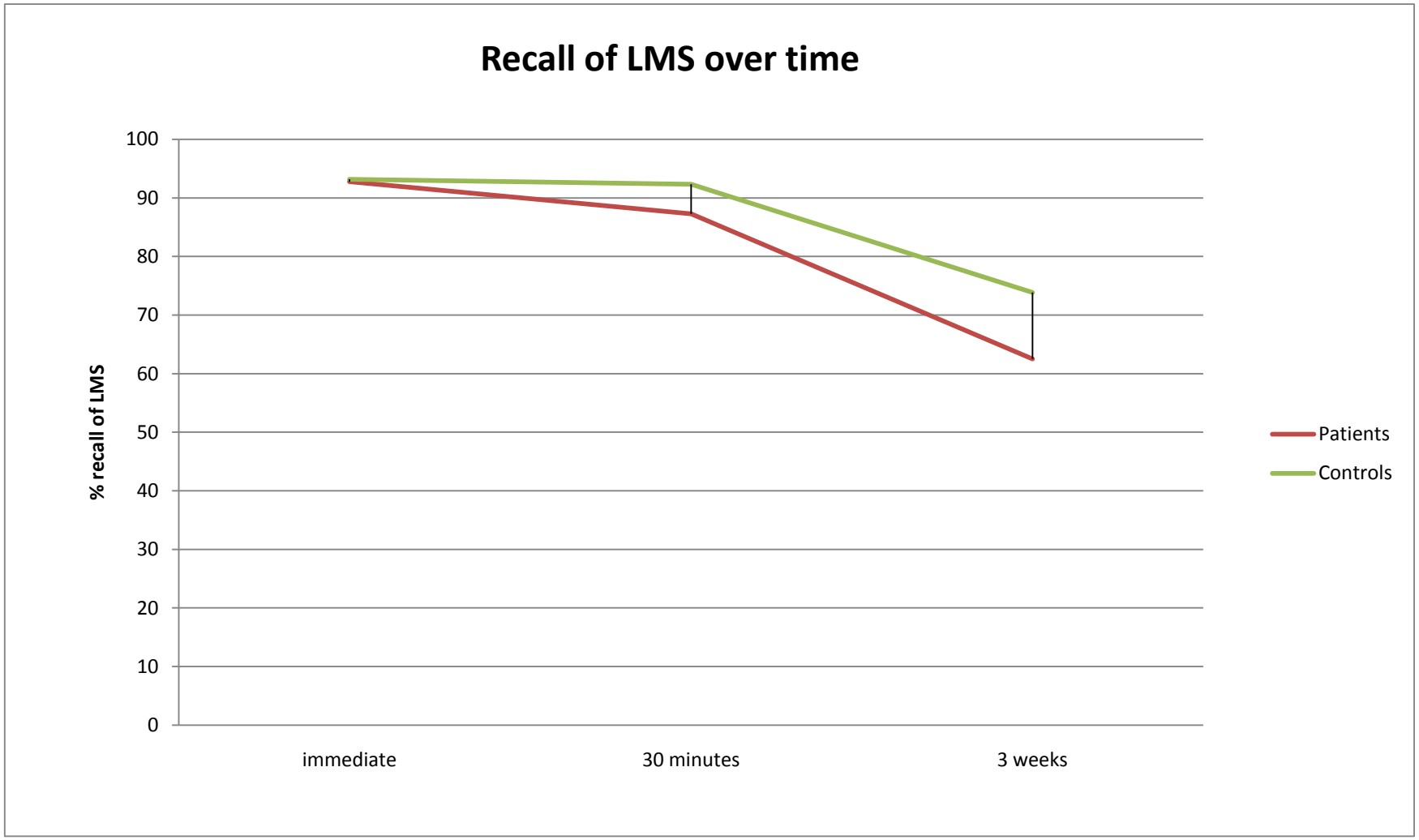
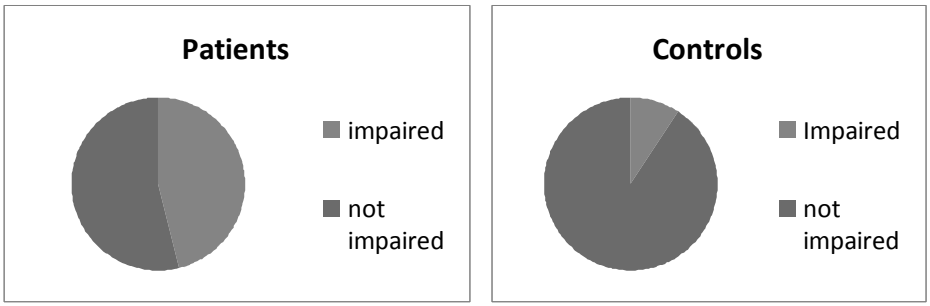


Figure 10.5: Graphical representation of numbers of controls and patients impaired at LMS 30-3



LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks

Looking at LMS 30-3, it seems to be clearly shown by the pie charts (figure 10.5) that more patients than controls are impaired, but using Fisher's exact test (as the expected numbers are too small for Chi Square to be valid) the difference is non-significant (p=0.078). An odds ratio for impairment of retention over the three week delay with an 'exposure' to epilepsy can be calculated as 8.57 (95% CI 0.84, 87.83) but again this is not significant as the confidence intervals include 1.

Table 10.13: Individual impairment of verbal retention over 30 minutes

LMS recall 0-30	Patient	Control	Difference
Impaired	7 (53.8%)	1 (9.1%)	p=0.033
Not impaired	6 (46.2%)	10 (90.9%)	

LMS 0-30 = % of story forgotten between final trial and 30 minutes

Considering LMS 0-30, Fisher's exact test demonstrates a significant difference in impairment between the patient and control groups at the 5% level (see table 10.13). An exposure to epilepsy gives an odds ratio for impairment of retention over 30 minutes of 11.67 (95% CI 1.14, 119.54), which is significant.

10.2.1b) Verbal recognition over three weeks

For the verbal recognition section a number of variables are indentified. 'LMSR 30' is the recognition score at 30 minutes, as a percentage, and 'LMSR 3' is the recognition score at three weeks, as a percentage. 'LMSR 30-3' is a forgetting score, noting the percentage of information recognised at 30 minutes no longer recognised after three weeks, calculating using the following formula:

$$LMSR\,30-3 = \frac{\%\,recognition\,at\,30\,mins - \%\,recognition\,at\,3\,weeks}{\%\,recognition\,at\,30\,mins} \times 100$$

$$LMSR\,30-3 = \frac{LMSR\,30 - LMSR\,3}{LMSR\,30} \times 100$$

Differences between the mean and median (depending on whether measures were skewed) have been analysed between patients and controls (see table 10.14). As for all long term forgetting scores, participants over the age of 70 have been excluded to avoid confounding.

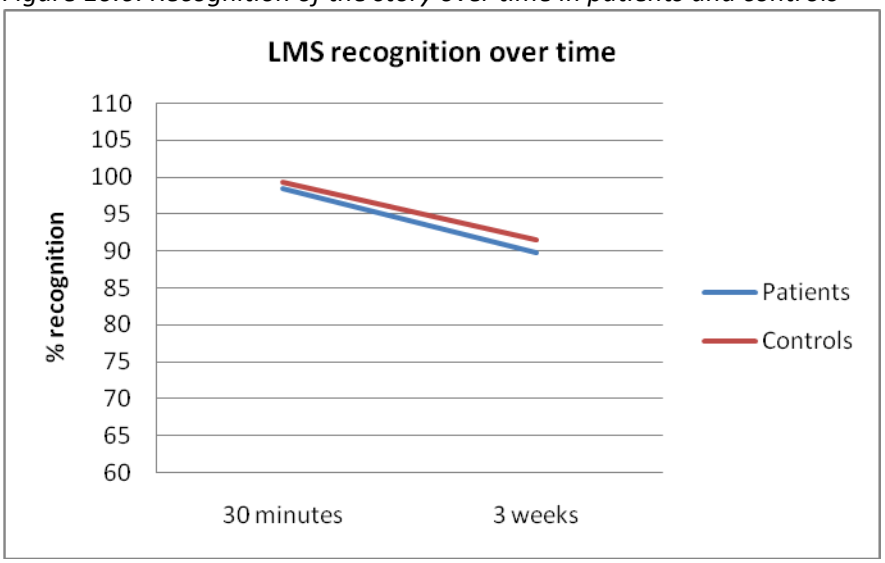
Table 10.14: Performance of patients and controls in verbal recognition

	All (n=24)	Patients (n=13)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
LMSR 30 median (IQR)	100 (100, 100)	100 (96.67, 100)	100 (100, 100)		0.370
LMSR 3 mean (SD)	90.56 (6.49)	89.74 (6.45)	91.52 (6.73)	-1.77 (-7.36, 3.82)	0.518
LMSR 30-3 mean (SD)	8.39 (6.58)	8.79 (6.89)	7.92 (6.54)	0.87 (-4.83, 6.57)	0.755

LMSR 30 = % recognition of story at 30 minutes, LMSR 3 = % recognition of story at 3 weeks, LMSR 30-3 = % difference in recognition between 30 minutes and 3 weeks

There is no significant difference between the groups in recognition at either time point, and also no significant difference in 'recognition forgetting' between 30 minutes and three weeks (see figure 10.6).

Figure 10.6: Recognition of the story over time in patients and controls



Individual impairment

As for LMS recall, individual impairment has also been investigated for LMs recognition using the control mean and standard deviation as an estimate of the population mean and standard deviation (see table 10.15). There is no difference in impairment between the groups as tested by Fisher's exact test (p=0.565), and the odds ratio for impairment of recognition following exposure to epilepsy is also not significant: 1.82 (95% CI 0.14, 23.25).

Table 10.15: Individual impairment of verbal recognition over 3 weeks

LMS recognition 30-3	Patient	Control	Difference
Impaired	2 (15.4%)	1 (9.1%)	p=0.565
Not impaired	11 (84.6%)	10 (90.9%)	

LMSR 30-3 = % difference in recognition of story between 30 minutes and 3 weeks

10.2.1c) Visual recall over 3 weeks

Participants over the age of 70 have again been excluded from the analysis of results from the visual scenes task (VST). Also, one patient under 70 failed to reach the criterion level of recall during the presentation trials, so their results have also been excluded from the analysis.

A number of variables are presented measuring different parameters, as for the LMS subtest, and the differences between patients and controls investigated (see table 10.17).

As with the LMS, number of trials is the number of presentations that it took for the participant to reach the criterion level required (75%), providing a measure of initial learning efficiency. 'VST 0' is a measure of the participants' recall performance on their final trial (as a percentage of the total possible score), and is used for calculating the amount of information forgotten at delays. 'VST 30' is a score for information recalled after a 30 minute delay (as a percentage of total possible score), and 'VST 3' is a similar measure for information recalled after a three week delay.

'VST 0-30' and 'VST 30-3' are the forgetting scores. 'VST 0-30' is the percentage of information which had initially been recalled when the participant reached criterion level which was not recalled after the 30 minute delay, and thus suggests the amount of information forgotten between the initial learning and the 30 minute delay. It is calculated with this formula:

$$VST\ 0-30 = \frac{\%\ recall\ at\ final\ trial - \%\ recall\ at\ 30\ minutes}{\%\ recall\ at\ final\ trial} \times 100$$

$$VST\ 0-30 = \frac{VST\ 0 - VST\ 30}{VST\ 0} \times 100$$

Similarly, 'VST 30-3' is calculated as a percentage of information forgotten between 30 minutes and three weeks, using a similar formula:

$$VST\ 30-3 = \frac{\%\ recall\ at\ 30\ minutes - \%\ recall\ at\ 3\ weeks}{\%\ recall\ at\ 30\ minutes} \times 100$$

$$VST\ 30-3 = \frac{VST\ 30 - VST\ 3}{VST\ 30} \times 100$$

Table 10.16: Key to visual long term forgetting variables

Variable	What it measures
VST 30	% recall of scenes at 30 minutes
VST 0-30	% of scenes forgotten between final trial and 30 minutes
VST 3	% recall of scenes at 3 weeks
VST 30-3	% of scenes forgotten between 30 minutes and 3 weeks
VSTR 30	% recognition of scenes at 30 minutes
VSTR 3	% recognition of scenes at 3 weeks
VSTR 30-3	% difference in recognition between 30 minutes and 3 weeks

Patients demonstrated worse learning efficiency than controls (p=0.018). There was no difference between patients' and controls' recall performance after 30 minutes, or the percentage of information retained over the 30 minute delay (table 10.17). However, patients had significantly poorer recall after three weeks (p=0.002), and a significantly higher rate of forgetting, over a three week period (p=0.003). This can be seen graphically in figure 10.7.

Table 10.17: Performance of patients and controls in visual recall

VST	All (n=24)	Patients (n=12)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
Number of trials Mean (SD)	2.43 (0.51)	2.67 (0.49)	2.18 (0.41)	0.49 (0.09, 0.88)	0.018*
Performance at criterion Mean (SD)	90.15 (6.95)	88.55 (5.86)	91.90 (7.87)	-3.36 (-9.34, 2.62)	0.256
VST 30 Mean (SD)	89.69 (5.97)	88.67 (3.83)	90.79 (7.73)	-2.11 (-7.64, 3.41)	0.426
VST 0-30 Mean (SD)	0.02 (4.91)	-0.44 (6.12)	0.52 (3.38)	-0.95 (-5.30, 3.39)	0.652
VST 3 Mean (SD)	63.53 (24.92)	49.48 (23.84)	78.86 (15.68)	-29.38 (-47.06, -11.70)	0.002**
VST 30-3 Mean (SD)	29.36 (26.49)	44.05 (26.74)	13.33 (14.69)	30.71 (11.97, 49.46)	0.003**

*$p<0.05$, **$p<0.01$

VST 30 = % recall of scenes at 30 minutes; VST 0-30 = % of scenes forgotten between final trial and 30 minutes; VST 3 = % recall of scenes at 3 weeks; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks

Individual impairment

Using the control mean and standard deviation as an estimation of population mean and standard deviation, participants were identified as impaired if they scored more than one standard deviation below the mean (see table 10.18, figure 10.8).

Table 10.18: Individual impairment of visual recall over 3 weeks

VST recall 30-3	Patient	Control	Difference
Impaired	7 (58.3%)	1 (9.1%)	p=0.027
Not impaired	5 (41.7%)	10 (90.9%)	

VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks

Figure 10.7: Recall of the visual scenes over time in patients and controls

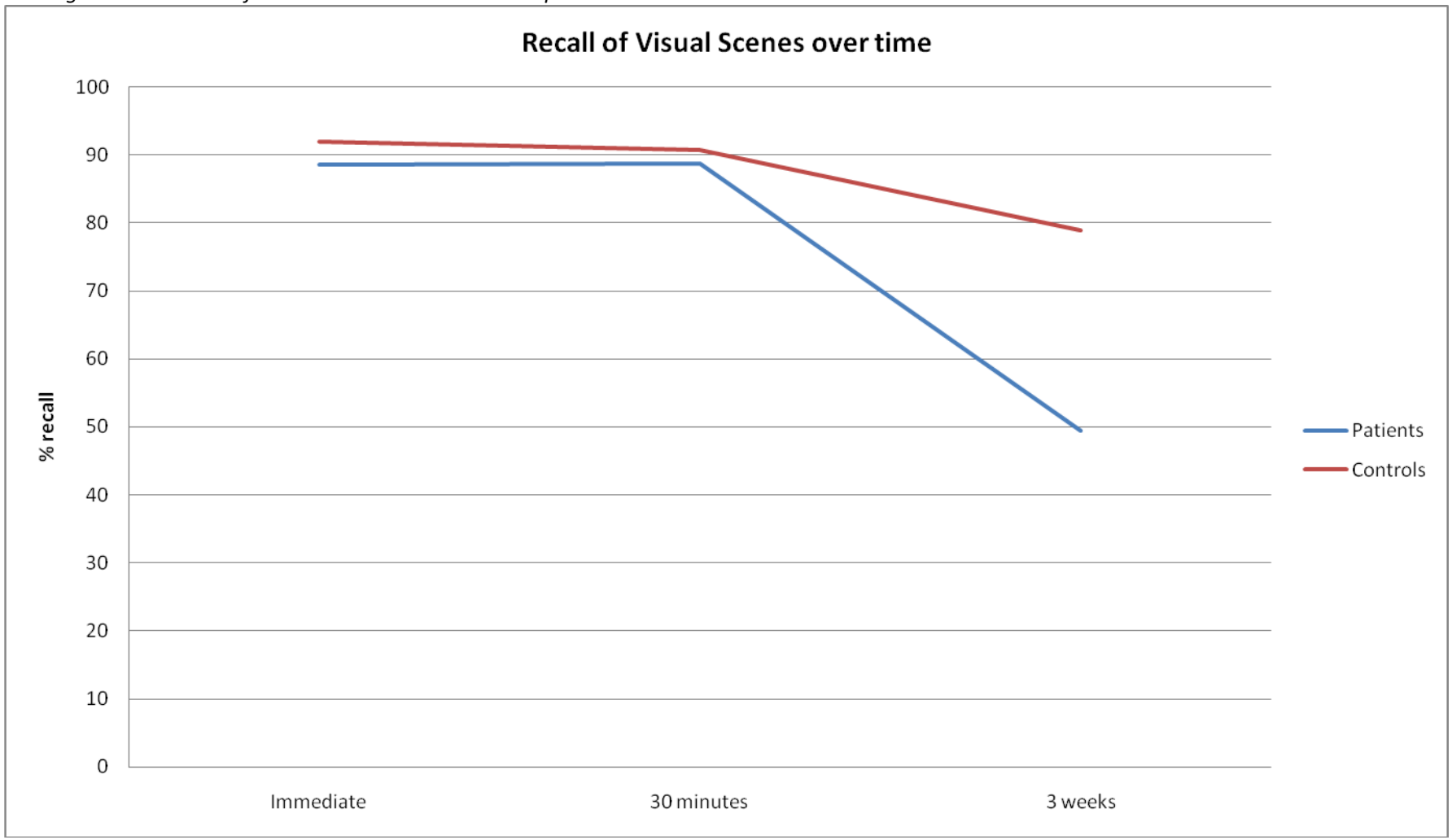
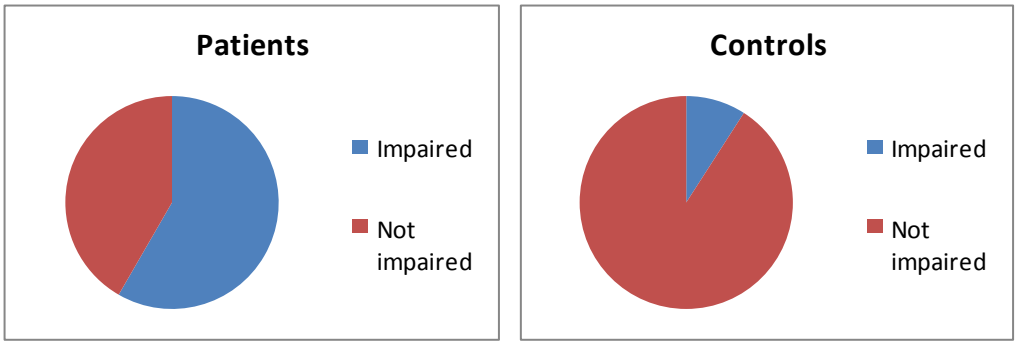


Figure 10.8: Graphical representation of numbers of controls and patients impaired at VST 30-3



Fisher's exact test demonstrates that there is a significant difference between patients and controls when it comes to the number impaired (p=0.027). The odds ratio for impairment of retention of visual information when exposed to epilepsy is 14.00 (95% CI 1.33, 147.43), which is significant as the confidence intervals do not include the value of 1.

Table 10.19: Individual impairment of visual recall over 30 minutes

VST recall 0-30	Patient	Control	Difference
Impaired	1 (8.3%)	1 (9.1%)	p=1.00
Not impaired	11 (91.7%)	10 (90.9%)	

VST 0-30 = % of scenes forgotten between final trial and 30 minutes

Considering forgetting scores over the 30 minute delay (table 10.19), there is no difference between groups as identified by Fisher's exact test (p=1.000). The odds ratio for impairment with epilepsy is 0.91 (95% CI 0.05, 16.54) which is not significant.

10.2.1d) Visual recognition over three weeks

As for the verbal recognition section, a number of variables are indentified and compared. 'VSTR 30' is the recognition score at 30 minutes, as a percentage, and 'VSTR 3' is the recognition score at three weeks, as a percentage. 'VSTR 30-3' is a forgetting score, noting the percentage of information recognised at 30 minutes no longer recognised after three weeks, calculating using the following formula:

$$VSTR\ 30-3 = \frac{\%\ recognition\ at\ 30\ mins - \%\ recognition\ at\ 3\ weeks}{\%\ recognition\ at\ 30\ mins} \times 100$$

$$VSTR\ 30-3 = \frac{VSTR\ 30 - VSTR\ 3}{VSTR\ 30} \times 100$$

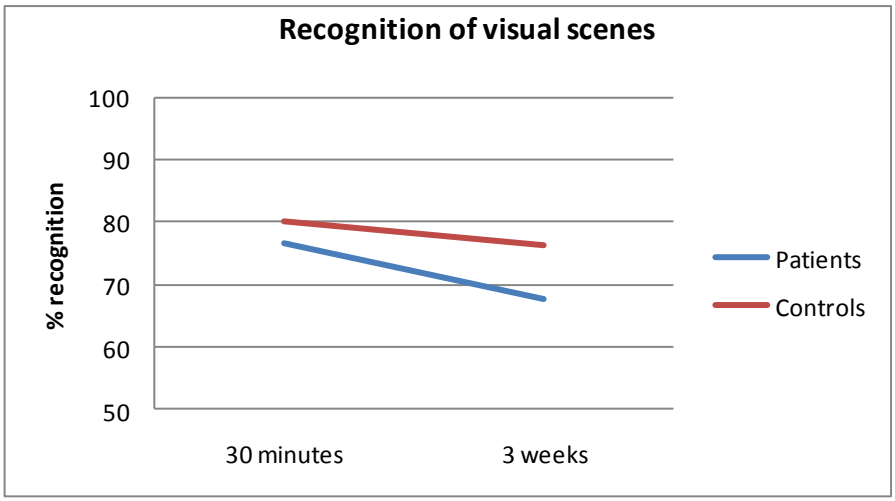
There is no significant difference in any of the recognition measures between patients and controls (see table 10.20 and figure 10.9).

Table 10.20: Performance of patients and controls in visual recognition

	All (n=23)	Patients (n=12)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
VSTR 30 Mean (SD)	78.26 (11.90)	76.56 (13.62)	80.11 (10.01)	-3.55 (-14.00, 6.90)	0.487
VSTR 3 Mean (SD)	71.74 (12.34)	67.71 (12.16)	76.14 (11.46)	-8.43 (-18.70, 1.85)	0.103
VSTR 30-3 Mean (SD)	-7.57 (16.14)	-9.86 (21.57)	-5.07 (6.94)	4.79 (-9.36, 18.94)	0.478

VSTR 30 = % recognition of scenes at 30 minutes; VSTR 3 = % recognition of scenes at 3 weeks; VSTR 30-3 = % difference in recognition between 30 minutes and 3 weeks

Figure 10.9: Recognition of the visual scenes over time in patients and controls



Individual impairment

When individual impairment is considered (table 10.21), there are more patients than controls impaired at 'recognition forgetting' over three weeks, but the difference is not significant using the Fisher's exact test (p=0.069). The odds ratio for impairment is 10.00 (95% CI 0.96, 104.49), which is also not significant.

Table 10.21: Individual impairment of visual recognition over 3 weeks

VST recognition 30-3	Patients	Controls	Difference
Impaired	6 (50.0%)	1 (9.1%)	p=0.069
Not impaired	6 (50.0%)	10 (90.9%)	

VST recognition 30-3 = % difference in recognition between 30 minutes and 3 weeks

10.2.2 Hypothesis 2: Initial forgetting rates will be correlated with WMS subtest scores, but long term forgetting rates will not

10.2.2a) Verbal

The relationship between scores on the LMS subtest and corresponding auditory memory scores from the WMS has been examined, so that the validity of the WMS for predicting long term forgetting can be estimated. Correlations have been examined using Pearson's correlation coefficients in all participants, and also in patient and control groups separately (table 10.22).

Table 10.22: LMS subtest correlations with auditory memory scores from WMS

	All (n=24)	Patients (n=13)	Controls (n=11)
LMS trials with Auditory immediate memory	-0.595 (0.002**)	-0.480 (0.097)	-0.843 (0.001**)
LMS 30 with Auditory Delayed Memory	0.503 (0.012*)	0.663 (0.014*)	0.381 (0.247)
LMS 0-30 with Auditory Delayed Memory	-0.203 (0.342)	-0.533 (0.061)	0.240 (0.477)
LMS 0-30 with % recall story	-0.284 (0.178)	-0.525 (0.066)	-0.234 (0.488)
LMS 0-30 with General Memory	-0.334 (0.111)	-0.609 (0.027*)	0.163 (0.641)
LMSR 30 with Auditory recognition delayed memory	0.115 (0.592)	0.000 (1.000)	0.192 (0.571)
LMS 3 with Auditory Delayed Memory	0.431 (0.036*)	0.794 (0.001**)	0.009 (0.979)
LMS 30-3 with Auditory Delayed Memory	-0.240 (0.258)	-0.601 (0.030*)	0.167 (0.624)
LMS 30-3 with % recall story	-0.052 (0.810)	-0.536 (0.059)	0.327 (0.326)
LMS 30-3 with General Memory	-0.199 (0.350)	-0.634 (0.020*)	0.446 (0.169)
LMSR 30-3 with Auditory Recognition Delayed Memory	-0.172 (0.422)	-0.150 (0.624)	-0.172 (0.613)

Values are Pearson's correlation coefficients with *p* values. *$p<0.05$, **$p<0.01$
LMS trials = number of trials of story to reach criterion; LMS 30 = % recall of story at 30 minutes; LMS 0-30 = % of story forgotten between final trial and 30 minutes; LMSR 30 = % recognition at 30 minutes; LMS 3= % recall of story at 3 weeks; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = difference in recognition between 30 minutes and 3 weeks

The number of trials taken to reach criterion level for the story correlates significantly with Auditory Immediate Memory (AIM) in all participants (p=0.002) showing that this is a good measure of initial learning efficiency. When all participants are analysed together, the only other significant correlations are between 30 minute (p=0.012) and three week (p=0.036) recall scores and the Auditory Delayed Memory (ADM) score from the WMS. The correlation with 30 minute recall is as would be expected considering it is a very similar test, whilst the correlation with three week recall suggests that the ADM score may be predictive of recall over longer delays.

Within the patient group, recall at 30 minutes (p=0.014) and three weeks (p=0.001) again correlate with ADM score. Forgetting rate over the 3 week delay also correlates with both ADM score (p=0.030) and General Memory (GM) score (p=0.020) suggesting that long term forgetting of a verbal story in this group of patients can be predicted by the WMS. GM score also correlates significantly with forgetting rate over the 30 minute delay (p=0.027).

Within the control group, there are no significant correlations apart from number of trials with AIM.

10.2.2b) Visual

Correlations between corresponding variables of the Visual Scenes Test and visual memory scores from the WMS have also been examined (table 10.23).

When all participants are considered together, there is significant correlation between number of trials taken to reach criterion and Visual Immediate Memory (VIM) scores in the WMS (p=0.016). However, when the groups are analysed separately this correlation is no longer apparent (p=0.114, p=0.248). There are no other significant correlations between the WMS visual memory

scores and the VST scores, despite similarities between the VST and the family pictures subtest of the WMS.

Table 10.23: VST subtest correlations with visual memory scores from WMS

	All (n=24)	Patients (n=12)	Controls (n=11)
VST trials with Visual Immediate Memory	-0.497 (0.016*)	-0.480 (0.114)	-0.380 (0.248)
VST 30 with Visual Delayed Memory	0.312 (0.148)	0.503 (0.096)	0.207 (0.542)
VST 0-30 with Visual Delayed Memory	0.371 (0.081)	0.292 (0.357)	0.549 (0.080)
VST 0-30 with % recall family pictures	0.029 (0.894)	0.484 (0.111)	-0.283 (0.399)
VST 0-30 with General Memory	0.170 (0.437)	0.102 (0.753)	0.273 (0.417)
VSTR 30 with Visual Delayed memory	-0.058 (0.794)	0.050 (0.876)	-0.253 (0.452)
VST 3 with Visual Delayed Memory	0.241 (0.269)	0.212 (0.509)	0.125 (0.714)
VST 30-3 with Visual Delayed Memory	-0.203 (0.353)	-0.170 (0.597)	-0.063 (0.853)
VST 30-3 with % recall family pictures	0.156 (0.476)	0.153 (0.635)	0.105 (0.760)
VST 30-3 with General Memory	-0.320 (0.137)	-0.361 (0.249)	-0.194 (0.567)
VSTR 30-3 with Visual Delayed Memory	-0.155 (0.479)	-0.216 (0.500)	-0.013 (0.970)

Values are Pearson's correlation coefficients with *p* values. *$p<0.05$

VST trials = number of trials to reach criterion; VST 30 = % recall of scenes at 30 minutes; VST 0-30 = % of scenes forgotten between final trial and 30 minutes; VSTR 30 = % recognition of scenes at 30 minutes; VST 3 = % recall of scenes at 3 weeks; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in recognition between 30 minutes and 3 weeks

10.2.2c) Correlations between subtests of the experimental tests

Within each experimental subtest, correlations between variables have been examined using Pearson's correlation coefficients, in all participants, patients and controls.

In all participants together, and in patients, number of trials significantly correlates (p=0.038) with LMS 0-30 (see table 10.24). This suggests that patients needing more trials to reach criterion will also forget a larger percentage of the information after 30 minutes. This would suggest that repeated presentation of the story does not independently improve recall, but rather needing more trials to reach criterion is associated with poorer verbal memory so poorer recall after 30 minutes. Number of trials does not correlate with longer term forgetting scores. Forgetting rates over the two intervals do not correlate, although when all participants are considered together recall scores at each delay correlate significantly (p=0.043).

Table 10.24: Correlations between scores of LMS

LMS	All	Patients	Controls
LMS trials with LMS 0-30	0.425 (0.038*)	0.624 (0.023*)	-0.330 (0.321)
LMS trials with LMS 30-3	0.187 (0.381)	0.181 (0.554)	-0.008 (0.981)
LMS 0-30 with LMS 30-3	0.187 (0.382)	-0.009 (0.978)	0.088 (0.796)
LMS 30 with LMS 3	0.417 (0.043*)	0.499 (0.083)	-0.324 (0.331)

Values are Pearson's correlation coefficients with *p* values. *p<0.05
LMS trials = number of trials of story to reach criterion; LMS 0-30 = % of story forgotten between final trial and 30 minutes; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMS 30 = % recall of story at 30 minutes; LMS 3 = % recall of story at 3 weeks

Table 10.25: Correlations between scores of VST

VST	All	Patients	Controls
VST trials with VST 0-30	-0.396 (0.062)	-0.640 (0.025*)	0.160 (0.639)
VST trials with VST 30-3	0.340 (0.112)	0.205 (0.523)	-0.246 (0.467)
VST 0-30 with VST 30-3	-0.032 (0.884)	0.059 (0.855)	-0.061 (0.859)
VST 30 with VST 3	0.309 (0.151)	-0.053 (0.869)	0.585 (0.059)

Values are Pearson's correlation coefficients with *p* values. *p<0.05
VST trials = number of trials of scenes to reach criterion; VST 0-30 = % of scenes forgotten between final trial and 30 minutes; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VST 30 = % recall of scenes at 30 minutes; VST 3 = % recall of scenes at 3 weeks

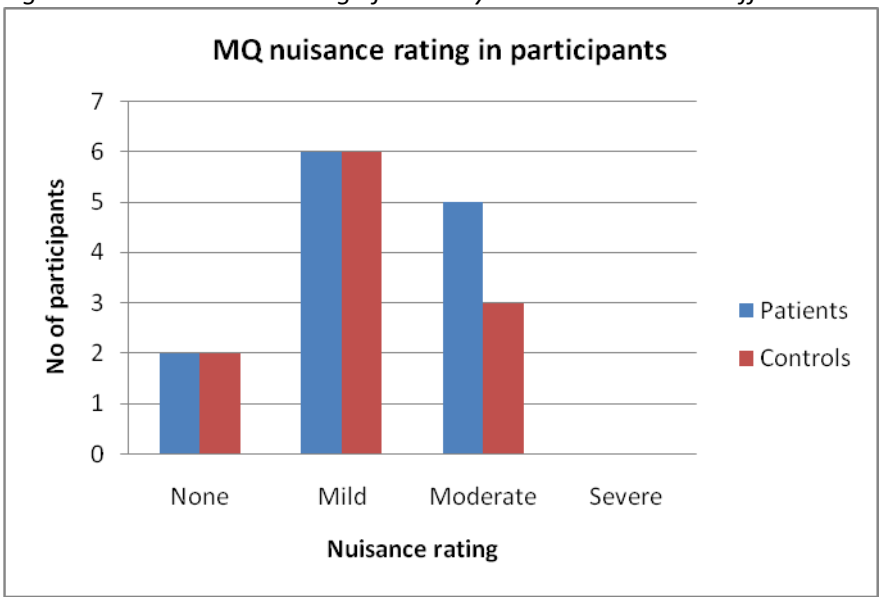
The only significant correlation between scores of the VST is between number of trials and VST 0-30 in patients (p=0.025) (see table 10.25). Unlike in the LMS subtest, this is a negative correlation, suggesting that patients having more presentations of the information will forget less of it over the 30 minute delay.

10.2.3 Hypothesis 3: Patients newly diagnosed with localisation related epilepsy will have higher rates of subjective memory complaints than controls

Subjective memory complaints, as recorded on the Memory Questionnaire (MQ), can be considered as two scores: a score for the total reported frequency of all the memory problems questioned (MQ score), and a score for the rating of how much of a nuisance any memory and concentration problems are for the participant. As numbers are too small to do a valid Chi Square test on the categories of nuisance rating, the categories of 'none' and 'mild' have been combined and 'moderate' and 'severe' combined to allow for a Fisher's exact test to be carried out.

The most frequently reported problems have also been examined to investigate if different problems are reported in patients and controls. As memory might be thought to worsen with age and the questionnaire scores are not adjusted in any way for age, the correlations between both scores and age in patients and controls were also examined, to see if this could be a potential cause of variance in memory complaints (see table 10.26).

Figure 10.10: Nuisance rating of memory and concentration difficulties



In the study participants under the age of 70, there was no significant difference between total MQ score in patients and controls, or between the proportions of participants rating their memory a 'moderate' or 'severe' nuisance (using Fisher's exact test) (see figure 10.10).

Table 10.26: Responses from MQ in patients and controls

MQ		Patients (n=13)	Controls (n=11)	Difference (95%CI)	Significance (*p* value)
Total score Mean (SD)		47.69 (12.29)	48.82 (16.32)	-1.13 (-13.25, 10.99)	0.849
Nuisance rating	No nuisance or mild nuisance	8 (61.5%)	8 (72.7%)		0.679
	Moderate or severe nuisance	5 (38.5%)	3 (27.3%)		
Problems reported at least daily		Losing things (38%) Forgetting names (31%) Going back to check (31%) 'Tip of the tongue' (31%) Forgetting what happened yesterday (23%)	Forgetting what you're saying (36%) Letting yourself ramble on (36%) Losing things (36%) 'Tip of the tongue' (36%) Forgetting names (18%)		
MQ score correlation with age		0.303 (*p*=0.314)	0.082 (*p*=0.810)		
Nuisance score correlation with age		0.176 (*p*=0.565)	-0.030 (*p*=0.929)		
Correlation between MQ score and MQ nuisance		0.535 (*p*=0.059)	0.508 (*p*=0.111)		

MQ = Memory Questionnaire

The most commonly reported complaints were similar in the two groups, with losing things, finding a word is 'on the tip of your tongue' and forgetting names in the top five problems reported at least daily in both groups. Patients seemed to report more going back to check and forgetting what happened yesterday. Controls on the other hand report that they might be more likely to forget what they are saying or ramble on. However, due to the small differences between frequencies and the small numbers involved it is

impossible to come to any real conclusions about group differences in nature of complaints.

Neither total MQ score nor nuisance score correlated significantly with age in either patients or controls. Interestingly, total MQ score does not correlate significantly with nuisance rating, which would seem to suggest that these two scores are measuring different aspects of subjective memory.

10.2.4 Hypothesis 4: Long term forgetting rates will be a better predictor of subjective memory complaints than standard neuropsychological tests

Table 10.27: Correlations between MQ scores and neuropsychological assessments

Correlations with MQ score	All (n=24)	Patients (n=13)	Controls (n=11)
VIQ	0.065 (0.763)	0.431 (0.142)	-0.249 (0.460)
PIQ	0.031 (0.886)	0.341 (0.255)	-0.286 (0.394)
FSIQ	0.056 (0.794)	0.480 (0.097)	-0.327 (0.326)
WMS – General Memory	-0.096 (0.655)	0.112 (0.717)	-0.261 (0.439)
Auditory Immediate Memory	-0.209 (0.327)	-0.017 (0.957)	-0.374 (0.257)
Visual Immediate Memory	-0.201 (0.346)	-0.190 (0.535)	-0.260 (0.440)
Immediate Memory	-0.241 (0.256)	-0.093 (0.763)	-0.411 (0.209)
Auditory Delayed Memory	-0.128 (0.552)	0.064 (0.837)	-0.257 (0.446)
Visual Delayed Memory	-0.122 (0.571)	-0.120 (0.696)	-0.146 (0.668)
Auditory Recognition Delayed Memory	0.103 (0.631)	0.421 (0.152)	-0.212 (0.531)
Working Memory	-0.071 (0.741)	0.198 (0.517)	-0.366 (0.269)
LMS 30-3 score	-0.061 (0.777)	-0.000 (0.998)	-0.109 (0.749)
LMSR 30-3 score	-0.071 (0.741)	0.032 (0.918)	-0.166 (0.627)
VST 30-3 score	0.095 (0.667)	-0.069 (0.832)	0.528 (0.095)
VSTR 30-3 score	0.040 (0.858)	0.140 (0.665)	-0.169 (0.620)

Values are Pearson's correlation coefficients with *p* values.
VIQ = Verbal IQ; PIQ = Performance IQ; FSIQ = Full Scale IQ; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = % difference in recognition of story between 30 minutes and 3 weeks; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in recognition of scenes between 30 minutes and 3 weeks

Table 10.28: Correlations between MQ nuisance ratings and neuropsychological assessments

Correlations with MQ nuisance	All N=24	Patients N=13	Controls N=11
VIQ	0.030 (0.888)	-0.111 (0.719)	0.410 (0.211)
PIQ	-0.020 (0.926)	0.123 (0.688)	0.005 (0.988)
FSIQ	0.024 (0.912)	0.010 (0.973)	0.347 (0.296)
WMS – General Memory	-0.206 (0.334)	-0.504 (0.079)	0.174 (0.609)
Auditory Immediate Memory	-0.206 (0.334)	-0.264 (0.383)	0.131 (0.700)
Visual Immediate Memory	-0.204 (0.339)	-0.525 (0.065)	0.192 (0.572)
Immediate Memory	-0.201 (0.346)	-0.403 (0.172)	0.212 (0.532)
Auditory Delayed Memory	-0.082 (0.703)	-0.314 (0.296)	0.283 (0.398)
Visual Delayed Memory	-0.320 (0.127)	-0.704 (0.007**)	-0.008 (0.982)
Auditory Recognition Delayed Memory	-0.066 (0.759)	-0.143 (0.641)	0.090 (0.793)
Working Memory	-0.076 (0.723)	0.231 (0.448)	-0.363 (0.273)
LMS 30-3	0.114 (0.503)	0.121 (0.693)	0.080 (0.814)
LMSR 30-3	0.384 (0.064)	0.248 (0.414)	0.543 (0.085)
VST 30-3	0.222 (0.308)	0.344 (0.274)	0.091 (0.790)
VSTR 30-3	0.125 (0.571)	0.231 (0.470)	-0.252 (0.455)

Values are Pearson's correlation coefficients with *p* values. *$p<0.05$, **$p<0.01$
VIQ = Verbal IQ; PIQ = Performance IQ; FSIQ = Full Scale IQ; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = % difference in recognition of story between 30 minutes and 3 weeks; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in recognition of scenes between 30 minutes and 3 weeks

To investigate this hypothesis, correlations were examined between MQ score and measures of intellectual functioning, WMS index scores, and long term forgetting scores from the experimental subtests (using Pearson correlation coefficients) (see table 10.27). Correlations were also examined between the same neuropsychological measures and the nuisance rating from the MQ, using Spearman rank as the nuisance rating scores are ordinal data (see table 10.28).

The only significant correlation was found between the Visual Delayed Memory score from the WMS and the MQ nuisance rating in patients ($p=0.007$). This suggests that long term forgetting scores are no better at predicting subjective memory than standard neuropsychological tests.

10.2.5 Hypothesis 5: Patients newly diagnosed with localisation related epilepsy will have higher rates of anxiety and depression than controls

The mean anxiety scores for each group have been compared using an independent sample t test, as well as consideration of the number of participants in each group falling into each category of anxiety. As the numbers are too small to do a valid chi squared test on categories of anxiety these were combined as 'normal to mild' and 'moderate to severe', to allow for a Fisher's exact test to be carried out. The data on depression rates was skewed, so the median and inter-quartile range have been used as a measure of central tendency, compared using Mann Whitney U test (see table 10.29).

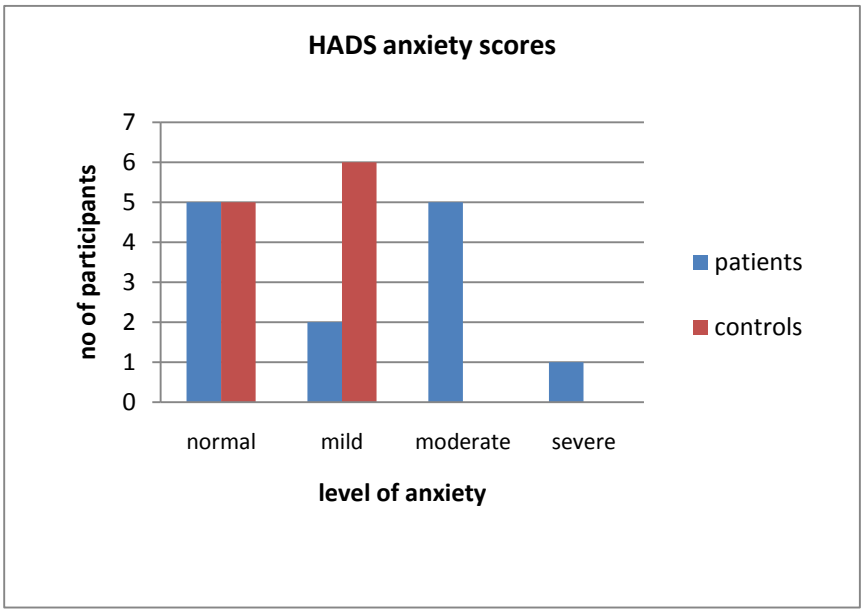
Table 10.29: Anxiety and depression scores in patients and controls

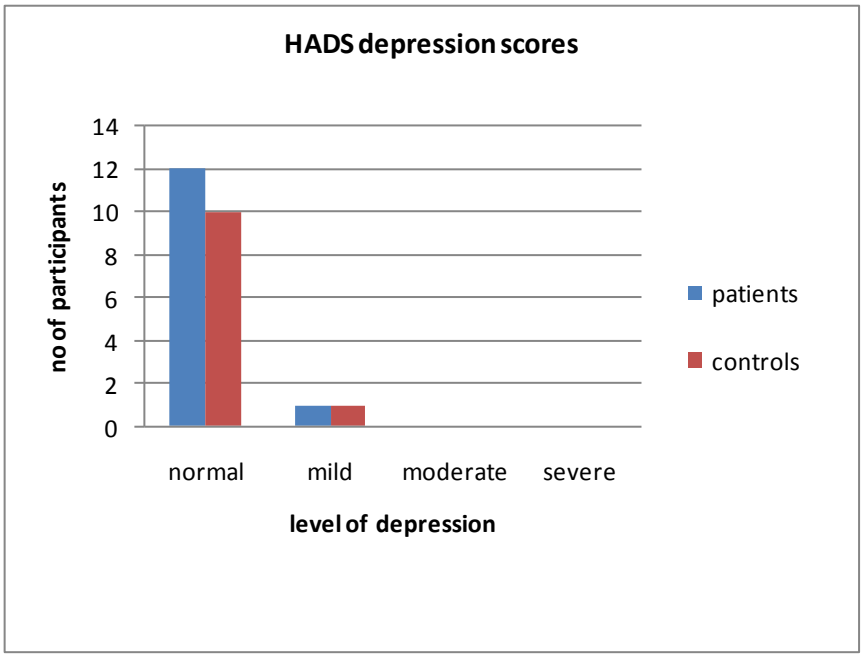
HADS		Patients (n=13)	Controls (n=11)	Difference (95% CI)	Significance (*p* value)
HADS anxiety score Mean (SD)		8.85 (4.06)	6.91 (2.43)	1.94 (-0.86, 4.74)	0.165
Anxiety	Normal-mild	7 (53.8%)	11 (100.0%)		0.016*
	Moderate-severe	6 (46.2%)	0 (0.0%)		
HADS depression score Median (IQR)		3.0 (1.0, 4.5)	2.0 (1.0, 6.0)		0.746
Depression	Normal	12	10		1.000
	Mild	1	1		
	Moderate	0	0		
	Severe	0	0		

Values are Pearson's correlation coefficients with *p* values. *p<0.05
HADS = Hospital Anxiety and Depression Scale

Results show that there is no significant difference in mean anxiety scores between patients and controls (p=0.165), however a significantly higher proportion of patients have scores in the moderate to severe range (p=0.016) (see figure 10.11). There are no differences between patients and controls in depression scores, or depression categories.

Figure 10.11: Anxiety and depression in patients and controls





10.2.6 Hypothesis 6: Measures of depression and anxiety will be a better predictor of subjective memory complaints than standard neuropsychological tests

To investigate this hypothesis, the correlations of MQ total score and MQ nuisance rating with anxiety and depression scores were calculated (table 10.30). Anxiety category was also correlated with both MQ total score and MQ nuisance rating, although correlations with depression category were not calculated as there was only one participant in each group not in the 'normal' category.

Table 10.30: Correlations between memory complaints and anxiety and depression

All participants (n=24)	MQ total score	MQ nuisance
Anxiety score	0.505[a] (0.012*)	0.366[b] (0.078)
Anxiety category	0.557[b] (0.005**)	0.354[b] (0.089)
Depression Score	0.345[a] (0.098)	0.449[b] (0.028*)
Patients (n=13)		
Anxiety score	0.716[a] (0.006**)	0.517[b] (0.071)
Anxiety category	0.742[b] (0.004**)	0.498[b] (0.083)
Depression Score	0.613[a] (0.026*)	0.833[b] (<0.001***)
Controls (n=11)		
Anxiety score	0.378[a] (0.251)	-0.043[b] (0.899)
Anxiety category	0.404[b] (0.218)	0.128[b] (0.708)
Depression Score	0.146[a] (0.669)	-0.039[b] (0.909)

Values are Pearson's correlation coefficients (a) and Spearman rho correlation coefficients (b) with *p* values. *p<0.05, **p<0.01, ***p<0.001
MQ = Memory Questionnaire

In all participants, anxiety scores were significantly correlated with total frequency of reported memory problems ($p=0.012$, $p=0.005$), while depression scores were significantly correlated with nuisance ratings ($p=0.028$).

Considering patients only, a similar pattern emerges, with anxiety scores correlated at the with total MQ scores ($p=0.006$, $p=0.004$), but not significantly with nuisance ratings ($p=0.071$, $p=0.083$). Depression scores are correlated at the with nuisance ratings ($p<0.001$), and also with total MQ score ($p=0.026$). When compared to the correlations between memory complaints and neuropsychological performance, these results demonstrate that, in patients, anxiety and depression scores are more predictive of memory complaints than neuropsychological performance.

In controls, there are no significant correlations between memory complaints and anxiety or depression scores.

Unfortunately, given the small numbers of participants involved, it is not appropriate to undertake multiple regression analysis to determine predictors of subjective memory complaints.

10.2.7.1 Hypothesis 7a: Patients with secondary generalised seizures will have worse neuropsychological performance and higher rates of long term forgetting than those having complex or simple partial seizures and controls

As there are only two patients who had not had generalised seizures, participants were split into two groups for this analysis: those having generalised seizures and those not (including both patients with partial seizures only and controls). The demographics of these groups have been compared to ensure that changing the groups has not created any significant differences (see table 10.31). There are no significant differences in age, gender or years of education between the two groups.

Table 10.31: Demographic comparison of the 'generalised seizure' and 'no generalised seizure' groups

		Generalised seizures (n=11)	No generalised seizures (n=13)	Difference (95% CI)	Significance (*p* values)
Age Mean (SD)		38.45 (16.05)	34.31 (15.87)	4.15 (-9.41, 17.70)	0.532
Gender	**Male**	6 (54.5%)	7 (53.8%)		1.000
	Female	5 (45.5%)	6 (46.2%)		
Years of education Mean (SD)		13.27 (2.61)	13.85 (3.08)	-0.57 (-3.02, 1.87)	0.631

Differences between the two groups in neuropsychological performance have been examined, including scores from questionnaires, standard assessments and experimental long–term forgetting scores (see table 10.32).

Table 10.32: Neuropsychological performance in those with and without generalised seizures

		Generalised seizures (n=11)	No generalised seizures (n=13)	Difference (95% CI)	Significance (*p* values)
HADS Anxiety Mean (SD)		8.55 (4.23)	7.46 (2.79)	1.08 (-2.06, 4.23)	0.477
HADS Depression Median (IQR)		3.0 (1.0, 5.0)	2.0 (1.0, 5.0)		1.000
MQ score Mean (SD)		48.00 (12.95)	48.38 (15.29)	-0.39 (-12.51, 11.74)	0.948
MQ nuisance	None – mild	6 (54.5%)	10 (76.9%)		0.397
	Moderate – severe	5 (45.5%)	3 (23.1%)		
FSIQ Mean (SD)		99.18 (11.51)	115.54 (11.48)	-16.36 (-26.12, -6.59)	0.002**
General Memory Mean (SD)		100.09 (9.83)	111.31 (14.99)	-11.22 (-22.18, -0.25)	0.045*
LMS trials Median (IQR)		2.0 (1.0, 3.0)	1.0 (1.0, 2.0)		0.213
LMS 0-30 Mean (SD)		7.12 (5.63)	0.72 (3.99)	6.40 (2.32, 10.49)	0.004**
LMS 0-30	impaired	7 (63.6%)	1 (7.7%)		0.008**
	Not impaired	4 (36.4%)	12 (92.3%)		
LMS 30-3 Mean (SD)		31.28 (11.52)	18.85 (10.76)	12.43 (2.98, 21.87)	0.012*
LMS 30-3	impaired	6 (54.5%)	1 (7.7%)		0.023*
	Not impaired	5 (45.5%)	12 (92.3%)		
LMSR 30-3 Mean (SD)		9.78 (6.87)	7.22 (6.36)	2.57 (-3.04, 8.17)	0.352
LMSR 30-3	impaired	2 (18.2%)	1 (7.7%)		0.576
	Not impaired	9 (81.8%)	12 (92.3%)		
VST trials Median (IQR)		3.00 (2.75, 3.00)	2.00 (2.00, 2.00)		0.002**
VST 0-30 Mean (SD)		-0.86 (6.63)	0.70 (3.19)	1.55 (-2.79, 5.89)	0.466

VST 0-30	impaired	1 (10.0%)	1 (7.7%)		1.000
	Not impaired	9 (90.0%)	12 (92.3%)		
VST 30-3 Mean (SD)		49.93 (24.97)	13.54 (13.97)	36.39 (19.37, 53.41)	<0.001***
VST 30-3	impaired	7 (70.0%)	1 (7.7%)		0.006**
	Not impaired	3 (30.0%)	12 (92.3%)		
VSTR 30-3 Median (IQR)		12.18 (-2.50, 22.14)	7.69 (0.00, 9.55)		0.641
VSTR 30-3	Impaired	5 (50.0%)	2 (15.4%)		0.169
	Not impaired	5 (50.0%)	11 (84.6%)		

*p<0.05, **p<0.01, ***p<0.001

HADS = Hospital Anxiety and Depression Scale; MQ = Memory Questionnaire; FSIQ = Full Scale IQ; LMS trials = number of trials of story to reach criterion; LMS 0-30 = % of story forgotten between final trial and 30 minutes; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = % difference in story recognition between 30 minutes and 3 weeks; VST trials = number of trials of scenes to reach criterion; VST 0-30 = % of scenes forgotten between final trial and 30 minutes; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in scene recognition between 30 minutes and 3 weeks

Those having had generalised seizures had no significant difference in anxiety, depression or memory complaint scores from those not having had generalised seizures. However, they had significantly worse FSIQ scores (p=0.002) and WMS general memory scores (p=0.045). In the LMS subtest, patients having had generalised seizures forgot significantly more of the material over both delay intervals (p=0.004, p=0.012 respectively), with no difference in initial learning or recognition. In the VST subtest, patients with generalised seizures performed significantly worse at initial learning efficiency (p=0.002) and forgetting over the three week delay (p<0.001) with no significant difference in forgetting over 30 minutes or recognition performance.

10.2.7.2 Hypothesis 7b: Patients with a greater total number of seizures will have worse neuropsychological performance and higher rates of long term forgetting than those having fewer seizures

To investigate this hypothesis, the correlation between a number of clinical seizure variables and scores from neuropsychological assessments has been examined (table 10.33). Total generalised seizure number is the number of generalised seizures the patient has had in their lifetime, seizure frequency is an estimation of the mean number of all seizures (partial and generalised) a patient would have in a year, and duration of seizures is the number of months since the patient's first seizure. Correlations between these variables and anxiety, depression, memory complaints, intellectual functioning, memory scores, and measures from the LMS and VST are examined, using Pearson correlation coefficients for continuous data and Spearman rank for ordinal data.

There are significant correlations of total number of generalised seizures with WMS general memory score ($p=0.006$) and with three week forgetting of visual scenes ($p=0.040$). The only other significant correlation is a negative relationship between 'recognition forgetting' of the LMS and duration of seizures, suggesting that patients with a longer duration of seizures have better verbal recognition over a three week interval, which is an unexpected finding.

Table 10.33: Correlations between seizure variables and neuropsychological assessment results

Patients (n=13)	Correlation with total generalised seizure number	Correlation with duration of seizures (months)
HADS anxiety	0.149 (0.626)	-0.053 (0.863)
HADS depression	0.206 (0.500)	-0.228 (0.455)
MQ score	0.265 (0.381)	-0.217 (0.477)
MQ nuisance	0.530 (0.062)	-0.337 (0.260)
FSIQ	-0.196 (0.521)	-0.239 (0.432)
General Memory	-0.716 (0.006**)	-0.133 (0.666)
LMS trials	0.552 (0.051)	0.139 (0.650)
LMS 0-30	0.395 (0.182)	0.117 (0.703)
LMS 30-3	0.430 (0.143)	0.166 (0.587)
LMSR 30-3	0.323 (0.282)	-0.615 (0.025*)
VST trials	0.506 (0.093)	-0.519 (0.084)
VST 0-30	-0.028 (0.930)	0.410 (0.185)
VST 30-3	0.599 (0.040*)	-0.148 (0.646)
VSTR 30-3	-0.038 (0.906)	0.444 (0.148)

Values are Pearson's correlation coefficients with *p* values. *p<0.05, **p<0.01
HADS = Hospital Anxiety and Depression Scale; MQ = Memory Questionnaire; FSIQ = Full Scale IQ; LMS trials = number of trials of story to reach criterion; LMS 0-30 = % of story forgotten between final trial and 30 minutes; LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = % difference in story recognition between 30 minutes and 3 weeks; VST trials = number of trials of scenes to reach criterion; VST 0-30 = % of scenes forgotten between final trial and 30 minutes; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in scene recognition between 30 minutes and 3 weeks

10.2.7.3 Hypothesis 7c: Patients with an abnormality found on MRI will have worse neuropsychological performance and higher rates of long term forgetting than those with normal imaging

Unfortunately, given the small numbers of patients and the fact that only three had abnormal imaging results (one of whom failed to reach VST criterion so there are only two in VST analysis), it is not possible to make a reasonable comparison between those with normal and abnormal imaging results, so this hypothesis cannot be investigated.

10.2.7.4 Hypothesis 7d: Patients having a seizure during the delay between initial assessment and follow up will have worse rates of forgetting than those not having a seizure during the delay

Patient participants have been split into those having any type of seizure during the delay between assessments (including both partial and generalised seizures) and those not. Their mean forgetting rates of LMS, LMSR, VST and VSTR over the three week delay are compared to each other using independent sample t tests, which demonstrate no significant difference between the two groups of patients in any measure (table 10.34). So, there is no difference in long term forgetting rates between those having seizures and those not, although the numbers involved are small.

Table 10.34: Long term forgetting in patients with and without seizures during 3 week delay

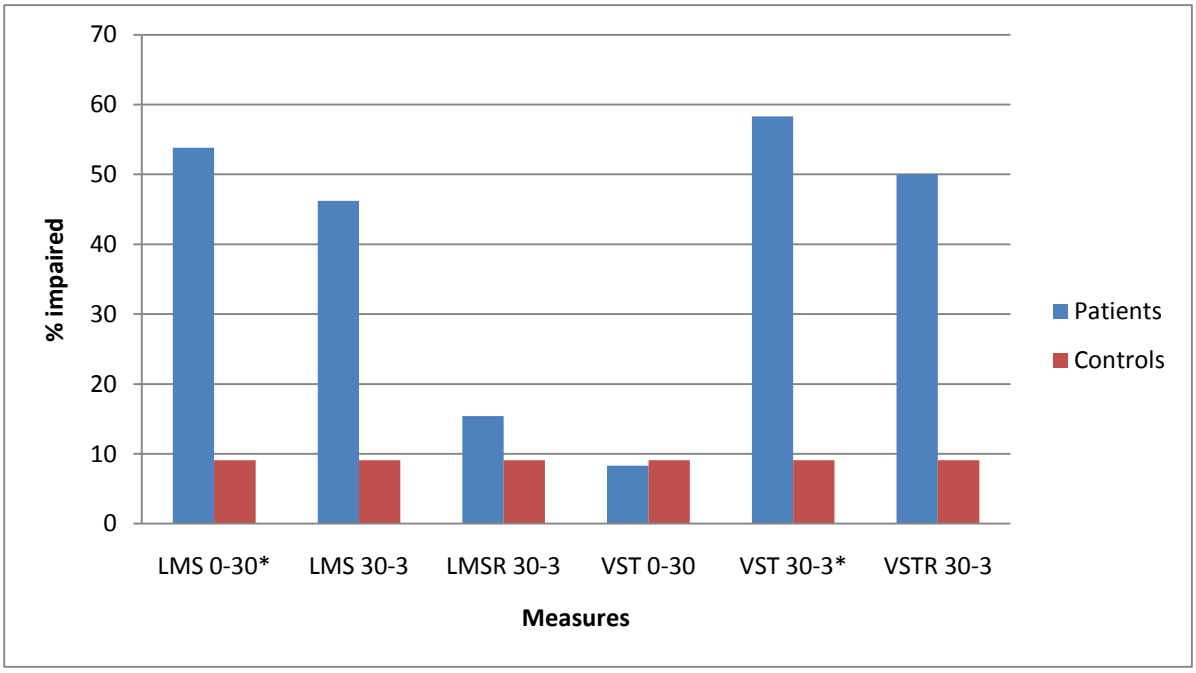
	Seizure during delay (n=5)	No seizure during delay (n=8)	Difference (95% CI)	Significance (*p* values)
LMS 30-3 Mean (SD)	23.84 (12.42)	31.75 (13.33)	-7.91 (-24.23, 8.41)	0.309
LMSR 30-3 Mean (SD)	9.43 (7.56)	8.39 (6.89)	1.04 (-7.92, 9.99)	0.804
VST 30-3 Mean (SD)	38.97 (32.18)	47.67 (24.16)	-8.70 (-44.77, 23.37)	0.603
VSTR 30-3 Mean (SD)	17.44 (16.22)	4.44 (21.40)	13.01 (-15.06, 41.07)	0.326

LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = % difference in story recognition between 30 minutes and 3 weeks; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in scene recognition between 30 minutes and 3 weeks

10.3 Individual level analysis

Figure 10.12 shows the percentage of patients and controls classed as 'impaired' (>1 SD below control mean) in each forgetting rate measure. This would seem to suggest that in four of the measures, LMS 0-30, LMS 30-3, VST 30-3 and VSTR 30-3, more patients are impaired than controls. However, as mentioned previously, only two of these differences in proportions are statistically significant (LMS 0-30 and VST 30-3).

Figure 10.12: Percentage of patients and controls with scores >1 SD below control mean ('impaired')



*p<0.05
LMS 30-3 = % of story forgotten between 30 minutes and 3 weeks; LMSR 30-3 = % difference in story recognition between 30 minutes and 3 weeks; VST 30-3 = % of scenes forgotten between 30 minutes and 3 weeks; VSTR 30-3 = % difference in scene recognition between 30 minutes and 3 weeks

As the two measures of long term recall forgetting (LMS 30-3 and VST 30-3) are the main outcome measures, the characteristics of participants who are impaired on these measures will be analysed, and compared to the characteristics of those not impaired.

10.3.1 Individual-level analysis of those impaired at three week verbal recall

Table 10.35: Characteristics of participants impaired at LMS 30-3

Variable		Impaired (n=7)	Not impaired (n=17)	Difference (95% CI)	Significance (*p* value)
Group	Patient	6 (85.7%)	7 (41.2%)	Fishers exact	0.078
	Control	1 (14.3%)	10 (58.8%)		
Age Median (IQR)		31.0 (24, 37.5)	35.0 (23, 54)		0.750
Education years Mean (SD)		13.86 (2.67)	13.47 (2.96)	-0.39 (-3.07, 2.30)	0.768
Anxiety score Mean (SD)		8.57 (4.72)	7.71 (2.97)	-0.87 (-5.30, 3.57)	0.665
Depression score Mean (SD)		2.43 (1.99)	3.41 (2.62)	0.98 (-1.31, 3.28)	0.384
MQ score Mean (SD)		47.57 (12.61)	48.47 (14.85)	0.90 (-12.39, 14.19)	0.890
MQ nuisance	None-mild	4 (57.1%)	12 (70.6%)	Fishers exact	0.647
	Mod-severe	3 (42.9%)	5 (29.4%)		
VIQ Mean (SD)		94.29 (17.08)	106.47 (14.20)	12.19 (-1.82, 26.19)	0.085
FSIQ Mean (SD)		98.29 (15.09)	112.06 (11.71)	13.77 (1.93, 25.62)	0.025*
WMS- General Memory Mean (SD)		98.57 (9.66)	109.29 (14.33)	10.72 (-1.59, 23.03)	0.085
WMS - Auditory Delayed Memory Mean (SD)		99.00 (6.51)	109.59 (15.23)	10.59 (-1.92, 23.09)	0.093
LMS 0-30	Impaired	4 (57.1%)	4 (23.5%)	Fishers exact	0.167
	Not	3 (42.9%)	13 (76.5%)		
LMSR 30-3	Impaired	1 (14.3%)	2 (11.8%)	Fishers exact	1.000
	Not	6 (85.7%)	15 (88.2%)		

*$p<0.05$

MQ = Memory Questionnaire; VIQ = Verbal IQ; FSIQ = Full Scale IQ; LMS 0-30 = % of story forgotten between final trial and 30 minutes; LMSR 30-3 = % difference in story recognition between 30 minutes and 3 weeks

Table 10.35 compares the characteristics of participants impaired at verbal recall over three weeks with those not impaired. The only significant difference is in FSIQ, where those not impaired had a significantly higher FSIQ than those impaired (p=0.025). There are no significant differences in group, age, education, anxiety, depression, subjective memory complaints, or scores on the WMS indices. There is also no significant difference between the proportions of participants impaired at verbal recall over the 30 minute interval, suggesting that impairment over the longer delay does not necessarily follow from impairment over the short delay.

Table 10.36: Characteristics of patients impaired at LMS 30-3

Within patients		Impaired (n=6)	Not impaired (n=7)	Difference (95% CI)	Significance (*p* value)
Seizure Type	Partial only	0 (0.0%)	2 (28.6%)	Partial only vs any gen	0.462
	Partial and gen	4 (60.0%)	3 (42.9%)		
	Gen only	2 (40.0%)	2 (28.6%)		
Duration of epilepsy Median (IQR)		12 (3, 66)	18 (8, 120)		0.471
Total gen seizure no Median (IQR)		2.5 (2.0, 3.5)	2.0 (0.0, 3.0)		0.194
Pathology	Yes	0 (0.0%)	3 (42.9%)		0.182
	No	5 (83.3%)	3 (42.9%)		
Age of onset Mean (SD)		26.17 (8.33)	41.14 (19.56)	14.98 (-3.65, 33.60)	0.101
Medication	None	0 (0.0%)	2 (28.6%)	None vs any med	0.462
	CBZ	1 (16.7%)	2 (28.6%)		
	LTG	4 (66.7%)	1 (14.3%)		
	LEV	1 (16.7%)	0 (0.0%)		
	VPA	0 (0.0%)	2 (28.6%)		
	Any med	6 (100.0%)	5 (71.4%)		

The clinical characteristics of patients impaired at three week verbal recall have also been compared with those not impaired in table 10.34. Where the distribution of data is skewed the median and inter-quartile range have been used as measures of central tendency spread. For comparing the proportions with different seizure types, the expected numbers were too small for Chi square to be valid so the 'partial and generalised' group were combined with the 'generalised only' group. This allowed for the proportions with partial seizures only and the proportions with any generalised seizures to be compared using Fisher's exact test. Similarly, the numbers taking different types of medication are not enough for a valid Chi square so the proportions on no medication have been compared to proportions on any medication with a Fisher's exact test. There are no significant differences between any of these measures in those impaired and those not impaired.

10.3.2 Individual-level analysis of those impaired at three week visual recall

Table 10.37: Characteristics of participants impaired at VST 30-3

Variable		Impaired (n=8)	Not impaired (n=15)	Difference (95% CI)	Significance (*p* value)
Group	Patient	7 (87.5%)	5 (33.3%)	Fishers exact	0.027*
	Control	1 (12.5%)	10 (66.7%)		
Age Mean (SD)		36.88 (18.45)	35.67 (15.36)	-1.21 (-16.19, 13.77)	0.868
Education years Median (IQR)		12.00 (10.25, 13.75)	15.00 (11.00, 17.00)	Mann Whitney	0.160
Anxiety score Mean (SD)		6.63 (3.34)	8.40 (3.46)	1.78 (-1.34, 4.89)	0.249
Depression score Mean (SD)		2.00 (1.77)	3.67 (2.69)	1.67 (-0.54, 3.87)	0.131
MQ score Mean (SD)		48.00 (18.06)	48.27 (12.54)	0.27 (-13.04, 13.57)	0.967
MQ nuisance	None-mild	6 (75.0%)	10 (66.7%)	Fishers exact	1.000
	Mod-severe	2 (25.0%)	5 (33.3%)		
PIQ Mean (SD)		103.5 (9.87)	116.06 (13.13)	12.57 (1.51, 26.19)	0.028*
FSIQ Mean (SD)		97.38 (13.41)	114.53 (10.54)	17.16 (6.62, 27.70)	0.003**
WMS – General Memory Mean (SD)		99.38 (11.43)	111.07 (13.10)	11.69 (0.25, 23.13)	0.046*
WMS - Visual Delayed Memory Mean (SD)		94.50 (11.23)	102.53 (13.72)	8.03 (-3.75, 19.81)	0.171
VST 0-30	Impaired	1 (12.5%)	1 (6.7%)	Fishers exact	1.000
	Not	7 (87.5%)	14 (93.3%)		
VSTR 30-3	Impaired	3 (37.5%)	4 (26.7%)	Fishers exact	0.657
	Not	5 (62.5%)	11 (73.3%)		

*p<0.05, **p<0.01

MQ = Memory Questionnaire; PIQ = Performance IQ; FSIQ = Full Scale IQ; VST 0-30 = % of scenes forgotten between final trial and 30 minutes; VSTR 30-3 = % difference in scene recognition between 30 minutes and 3 weeks

Table 10.37 shows the characteristics of participants impaired at three week visual recall compared to those not impaired. Those impaired include a significantly higher proportion of patients than those not impaired (p=0.027). Participants who are impaired have significantly lower PIQ and FSIQ scores (p=0.028 and p=0.003 respectively) and significantly lower GM scores (p=0.046). The majority of those impaired are not impaired at the 30 minute forgetting score, suggesting that those impaired demonstrate isolated impairment over the longer delay.

Table 10.38: Characteristics of patients impaired at VST 30-3

Within patients		Impaired (n=7)	Not impaired (n=5)	Difference (95% CI)	Significance (*p* value)
Seizure Type	**Partial only**	0 (0.0%)	2 (40.0%)	Partial vs Any gen	0.152
	Partial and gen	4 (57.1%)	2 (40.0%)		
	Gen only	3 (42.9%)	1 (20.0%)		
Duration of epilepsy Median (IQR)		18.0 (8, 60)	3.0 (2.5, 69)		0.219
Total gen seizure no Median (IQR)		2.0 (2.0, 3.0)	2.0 (0.0, 2.5)		0.137
Pathology	**Yes**	0 (0.0%)	2 (40.0%)		0.067
	No	7 (100.0%)	1 (20.0%)		
Age of onset Mean (SD)		36.29 (20.01)	32.40 (13.91)	3.89 (-27.6, 19.79)	0.722
Medication	**None**	1 (14.3%)	1 (20.0%)	None vs Any med	1.000
	CBZ	1 (14.3%)	1 (20.0%)		
	LTG	2 (28.6%)	3 (60.0%)		
	LEV	1 (14.3%)	0 (0.0%)		
	VPA	2 (28.6%)	0 (0.0%)		
	Any	6 (85.7%)	4 (80.0%)		

Patients impaired at visual recall over three weeks have also been analysed to compare the clinical characteristics of those impaired and not impaired (see table 10.38). As previously, the categories of seizure type and medication have been combined so that Fisher's exact tests can be carried out, as the numbers are too small for valid Chi square. No significant differences are found in any of the clinical measures compared between those impaired at visual recall and those not impaired.

Chapter 11. Discussion

11.1 Overview

This chapter will be a discussion of the results reported in Chapter 10. The patterns of forgetting in both verbal and visual memory will be considered in newly diagnosed patients with epilepsy, and how these can be interpreted. As the patterns seen in the verbal and visual subtests were quite different, they will be discussed separately and the results compared. Factors that could be involved in forgetting and their influence will be considered. Subjective memory scores and the factors influencing these will also be discussed. The limitations that affect the interpretation of findings are very important, and these will be examined henceforth. The importance of the research will also be considered along with its implications for both clinical practice and further research.

11.2 Long term forgetting – verbal

The pattern of verbal recall in patients compared to controls was reported in Chapter 10 and demonstrated in figure 10.5. It was hypothesised that a proportion of patients would demonstrate accelerated long term forgetting, i.e. normal recall over the short delay but increased forgetting compared to controls over the longer three week delay. The pattern demonstrated by the results of this study was a little different. At initial learning there was no difference between patients and controls, but after 30 minutes patients recalled less, suggesting impairment of delayed verbal recall over a short delay. This would follow on from results in previous studies, as reviewed in Chapter 7, which show newly diagnosed partial epilepsy patients have a particular impairment in delayed recall of verbal information (Äikiä *et al.*, 1995; Aikia *et al.*, 1999). Over the three week delay, there was no significant difference in the rate of forgetting but recall at the three week assessment was significantly

poorer in patients than controls. This seems to suggest a pattern of impairment in delayed recall of verbal information that is present after 30 minutes and persists over longer delays, rather than a pattern of ALF.

Of the patients classified as impaired at the 30 minute delay, nearly half (three out of seven) are no longer impaired after the three week delay. On the other hand, of those impaired at the three week delay a third (two out of six) were not impaired at the 30 minute delay. Although these numbers are very small this could possibly suggest that there is more than one pattern of impairment present in verbal recall in the patient group. A small number of patients could be showing ALF, whereas others have a pattern of poor retention over a short delay but good retention over the long delay. This second pattern could have come about because there was no distraction task administered after the presentation of the story to prevent the recency effect so initial recall could have been augmented by short term memory. If this was the case, and there was a problem encoding short term to long term memory, recall would be poor over the short delay but with no increased forgetting over a longer delay. Considering the multiple processes involved in memory, and the numerous ways that epilepsy can impact on memory, it would not be surprising if there was more than one pattern of impairment.

The results from the verbal recall subtest seem to correlate reasonably well with the WMS scores, initially with the number of trials, and also over both the short delay and long delay there are measures that correlate to WMS index scores. This would seem to suggest that the WMS and other similar tests with a 30 minute delay to assess long term memory could be valid for the prediction of very long term verbal memory over extended delays. However, the WMS scores between the groups were not significantly different while the LMS scores showed significant impairment in the patient group, so it may be that the very long term impairment is only partially predicted by WMS scores.

If the pattern in patients is one of persistent delayed verbal recall impairment across both delays, the next question would be what type of memory problem is that demonstrating. As the initial learning of information (as shown by the number of trials to reach criterion) was not impaired in patients, this would suggest that there is not a problem with the initial acquisition of information. Rather, there must be a problem either transferring information from short term to long term memory, maintaining it once it is in long term memory, or retrieving it from long term memory. The intact recognition that has been demonstrated might lead one to suggest that it could be a problem with retrieval of the information, as intact recognition suggests that it is still there to be accessed. However, in the literature on ALF a number of studies have identified no impairment in recognition and accelerated forgetting, and have identified this as a consolidation problem, as it is stated that words can be stored poorly in a degraded form (i.e. demonstrating a consolidation problem) but still be accessible to recognition processes (Martin *et al.*, 1991). Unfortunately the design of this study and the small numbers prohibit a more extensive evaluation of which processes are affected.

As there seems to be impairment in delayed verbal recall in patients, the causative factors behind this need to be examined. When those impaired over the three week delay were compared with those not impaired, the only significant difference was in full scale IQ. Patients generally had lower full scale IQs than controls, despite being matched to years of education. There was an interesting dissociation between years of education and intellectual functioning in patients, despite significant correlations in controls. This suggests that there might be other factors that have more of an impact on intellectual functioning than education in patients with epilepsy. However a further study would be required to identify what are likely to be epilepsy related factors interfering with this relationship in newly diagnosed patients.

Whatever is causing the lower levels of intellectual functioning in patients, they seem to be related to the long term forgetting measures. Therefore, one suggestion might be that the impaired long term verbal recall scores in patients are merely the

result of poorly matched patient and control groups, with different levels of intellectual functioning that are impacting on their memory scores as a part of general cognitive impairment. However, if poor intellectual functioning was having a general detrimental effect on memory, then all memory scores (i.e. including WMS indices) might be expected to be impaired. The fact that there are no significant differences between patients and controls on WMS scores would suggest that the impaired delayed verbal recall demonstrated in patients is not purely the result of general cognitive and memory impairment. It could be that poor intellectual functioning has a particularly selective effect on longer term recall performance, or there could be other factors at play which are affecting both intellectual functioning and delayed verbal recall. The tests employed measured the participants' memory performance, but not how that performance was achieved. For example, participants with a higher IQ could be using more effective memorising strategies during the delay interval. Unfortunately, there were not enough participants in the study to undertake multiple regression analysis, which might have allowed the results to be considered adjusted for IQ differences, to identify other significant factors involved.

Similarly, there were not enough participants to undertake thorough analysis of the influence of possible causative factors of the impairment, but they will be considered. As discussed in Chapter 4, there are many interacting factors that can combine to cause cognitive impairment in patients with epilepsy, including seizures and interictal discharges, pathology, AEDs and psychological factors.

The patients in this study were recruited at diagnosis, in order to try and discover whether there was any evidence of very long term memory impairment from early on in the course of the condition. However, even at diagnosis patients have often had a number of seizures, particularly partial seizures, which may have been going on for months or even years, so the potential effects of these seizures must be considered. Neither the total lifetime number of generalised seizures nor the duration that seizures had been occurring was associated with the three week verbal forgetting rate in patients. Also, whether or not patients had seizures during

the three week delay did not seem to affect their forgetting over the delay. Whilst these results do not rule out an impact of seizures on verbal recall over a three week delay, particularly considering the small numbers, it seems it is unlikely that seizures are the only mechanism of interference with long term memory. However, interictal discharges were not considered, and as the majority of patients did not have any EEG results, it is impossible to say how much of a factor these could have been.

In terms of pathology, unfortunately the numbers involved in the study were too small to undertake a meaningful analysis comparing those with pathological abnormalities on imaging to those without. This means that no comment can be made on the impact pathological lesions might have on delayed memory. However, there has been research suggesting that underlying pathology is associated with cognitive problems in newly diagnosed epilepsy (Helmstaedter *et al.*, 1993; Pulliainen *et al.*, 2000a).

AEDs are often suggested, particularly by patients, as a causative factor in cognitive impairments (Baker *et al.*, 1997; Carpay *et al.*, 2005). Unfortunately it was not possible to assess patients before they started taking AEDs, as the assessment period was at least three weeks (not including arranging a convenient time) which would have substantially delayed starting treatment. So, patients were already taking a variety of medications, which must be considered at least a potential causative factor in memory impairment. Although nearly half the patients were on monotherapy (LTG) there were four different AEDs used in the study, and there were not enough participants to compare the results of individual AEDs on long term forgetting. However, it should be borne in mind that research into cognitive problems associated with AEDs has suggested cognitive problems to be dose-dependent, occurring at higher doses (Vermeulen & Aldenkamp, 1995)(see section 4.8 for further discussion), and the patients involved in the study were on low starting or maintenance doses. Also, cognitive problems particularly in the field of memory have previously been documented in newly diagnosed patients before starting medication, as discussed in Chapter 7.

Psychological factors such as anxiety and depression can be related to objective cognitive problems (Burt *et al.*, 1995) as well as cognitive complaints as will be discussed later, but there was no difference in anxiety or depression levels between those impaired at long term forgetting and those not impaired, which would suggest that they do not have a major role here.

Epileptogenesis, the process by which a normal brain is altered to become an environment in which spontaneous seizures occur, could be another causative factor in memory impairment in newly diagnosed patients. As discussed in Chapter 7, complex changes to the structure and function of neurons seem to occur in epileptogenesis (Badawy *et al.*, 2009a), and if these were occurring in neurons in the areas responsible for consolidation or retrieval of memories, then it is understandable why these functions might be impaired.

11.3 Long term forgetting – visual

The results of long term forgetting in the visual recall subtests seem to follow a different pattern from those of the verbal subtest, as shown in table 10.15 and figure 10.8. The hypothesis, as for verbal forgetting, proposed that at least a subset of patients would demonstrate accelerated long term forgetting in visual recall over the three week delay, i.e. that they would remember the information normally over the short 30 minute delay and forget a larger proportion than controls over the three week delay.

The results from this study demonstrated that patients had poorer initial learning performance than controls in the visual scenes test, taking on average more trials to reach the recall criterion of 75%. Over the 30 minute delay patients did not forget any more of the information than controls, and had a similar recall performance.

Over the three week delay, patients forgot a significantly higher proportion of the information than controls, and also considering participants individually a significantly higher proportion of patients than controls were impaired (58% vs 9%) at three week retention. Of those impaired after three weeks, only one (14%) had been impaired after 30 minutes.

If the initial learning impairment is taken out of consideration, this would appear to be a clear pattern of ALF in patients in visual recall performance. However, the initial learning impairment needs to be taken into account, and the possible reasons why this would happen, with normal recall after 30 minutes, need to be considered. The relationship between number of trials and 30 minute recall performance was considered, and in patients there was a significant negative correlation. This would demonstrate that there was a significant effect of over-learning – that the more times the material was presented to the patients the better they remembered it over the 30 minute delay. This effect was not found when number of trials was compared to three week forgetting, suggesting that the over-learning was only a temporary effect. Potentially, this could explain why 30 minute recall performance might be matched in patients and controls – theoretically if patients' visual memory is impaired they need more trials initially, then the over-learning effect will temporarily boost their 30 minute performance and when the effect wears off the three week memory will again be shown to be impaired. This would reduce the validity of the finding of intact recall at 30 minutes. However, greater number of trials was not associated with worse forgetting over the three week delay, which would seem to contradict this theory. It is interesting that an over-learning effect was seen in the visual test and not the verbal test, which could be because the visual test was more challenging, and reaching the recall criterion might involve processing the information at a deeper level rather than just repeating back a story, thus more effectively establishing it in long term memory.

Learning to criterion can be criticised as a method for assessing long term memory, in that it may artificially 'boost' memory performance with over-learning, as discussed above. It was used in this study to match the initial performance of

patients and controls so that the forgetting could be assessed without the problem of scaling, and is a method that has been used in a number of the previous studies on ALF (Butler, Butler, Davidson, Blake, Wilkinson). Other ALF studies have used a 'Selective Reminding Test' method (Bell 05, Giovag, Martin) but this was not appropriate for the material being tested in this study. It was therefore felt on designing the study that learning to criterion would be the least biased way to ensure matched initial recall, but its potential for affecting delayed memory performance should be borne in mind.

There is an alternative potential reason why recall was no different in patients and controls at 30 minutes in the visual task but not the verbal task. When the information was presented to the participants, in the visual test a distraction task (counting back from 100 in threes for 20 seconds) was used before immediate recall. This was to ensure all remembered information is from 'long term' memory, in contrast to the verbal task where this was not done so recency and short term memory would have more impact on recall scores. If immediate recall is based on information in long term memory, participants may take longer to reach the criterion but once reached the information is more likely to stay for 30 minutes, as it has already been encoded.

The pattern of impairment should help identify whereabouts in the memory process there is a problem. There was some initial learning impairment, as discussed, which would suggest an impairment encoding the information into long term memory. The visual test is felt to be more difficult than the verbal task (and a taxing test can expose more subtle impairments), and also included a distraction task, which could explain why this is different from the pattern seen in the verbal test. The lack of impairment over the 30 minute delay suggests that the material was well maintained over the short period once learnt, implying intact fast consolidation processes and retrieval. Based on this assumption, the significantly faster forgetting over the three week interval would demonstrate some interference with slow consolidation processes, however there is still a chance it could merely reflect the earlier encoding difficulties that were masked at the short delay by over-learning.

The recognition scores are difficult to interpret, as while there was no significant difference a larger proportion of patients than controls were impaired after the three week delay (50% vs 9%) which would match with the picture of a slow consolidation problem.

When considering correlation between the visual scenes test scores and the WMS indices to assess the reliability of the WMS for predicting very long term visual recall scores, it was found that the only correlation was between the number of trials taken to reach criterion level and the visual immediate memory score, when all participants were analysed together. Three week forgetting scores demonstrated no correlation with the WMS, and interestingly, neither did 30 minute forgetting scores. Some correlation would be expected, particularly at 30 minutes, due to the similarity of the 'family pictures' section of the WMS and the visual scenes test. This suggests that the WMS is not predictive of very long term visual memory.

Patients seem to have poorer memory for the visual scenes than controls, whether it is a slow consolidation problem causing ALF or merely a persistent encoding problem masked at 30 minutes. The possible causative factors for this need to be considered. As for the verbal results, there are a number to take into account. When those who are impaired at three week forgetting are compared to those not impaired, the significant differences are in group (more patients impaired), PIQ, FSIQ and WMS general memory score (those impaired have lower scores).

As discussed in the previous section relating to the verbal subtest, it is possible that the long term delayed recall impairments seen in patients are a reflection of general worse cognitive functioning in patients compared to, in hindsight, a poorly matched control group (despite controls being well matched on education), as evidenced by lower scores on PIQ, FSIQ and GM in those impaired. Patients and controls did not perform significantly differently on the WMS, but it is difficult to prove or disprove this idea without multiple regression analysis, which would need more participants.

Seizures do seem to have had some impact on visual delayed memory, as the total lifetime number of generalised seizures correlates significantly with the three week visual forgetting scores, with those having had more seizures forgetting more over the three weeks, as well as correlating significantly with WMS general memory score. This would suggest that the generalised seizures have somehow damaged or affected the efficiency of the processes of retaining long term visual memories. In contrast, seizures during the three week delay interval seemed to have no impact on forgetting rates (in this small sample) so it is possible the problem may be one affecting the underlying substrate and its effectiveness rather than interference with consolidation of individual memories. This could also be the effect of epileptogenesis, as discussed above.

Again, the effects of AEDs could not be analysed separately due to the small sample, so medication cannot be ruled out as a causative factor, despite the small doses used and the previous evidence of memory problems in patients newly diagnosed with epilepsy before starting medication. Similarly, there are not enough participants to analyse the effects of pathology in this study, and while it has previously been suggested not to be involved in ALF (Blake *et al.*, 2000; Wilkinson *et al.*, under review) it could potentially be involved in initial encoding problems. Psychological factors were also shown to have little impact on long term visual forgetting, with there being no difference in anxiety or depression in those impaired and not impaired.

As the laterality of seizure focus could not be identified in the majority of patients, it is impossible to compare visual and verbal impairment in left and right sided epilepsy patients to look for material specific laterality effects. Impaired long term recall in the two domains does not appear to be related, because of those impaired at visual three week forgetting, nearly half (3/7) were not impaired at verbal three week forgetting.

11.4 Subjective memory and psychological factors

Contrary to expectations, subjective memory scores were no worse in patients than controls. This is not in line with previous research on subjective rating of memory in people with epilepsy (Thompson, 1992; Vermeulen *et al.*, 1993), but on the other hand the majority of previous research has been undertaken with patients with long-standing epilepsy, rather than those who are newly diagnosed. It could be that memory complaints increase with time over the course of the condition, and have a progressive nature. Also, there is a chance of selection bias in the controls, as they were volunteers rather than being recruited systematically like patients. It may be that people who volunteered to act as controls did so partly because they had concerns about their memory and so wished to have it tested, which would mean their memory complaint scores would be abnormally high and not representative of the population.

There was little correlation between subjective and objective memory scores, as has been shown in previous literature (Vermeulen *et al.*, 1993; Giovagnoli *et al.*, 1997; Elixhauser *et al.*, 1999; Piazzini *et al.*, 2001; Baños *et al.*, 2004; Au *et al.*, 2006; Maarika *et al.*, 2009). Only one measure (visual delayed memory from WMS) showed significant correlation with the memory questionnaire nuisance rating, in patients only. It was hoped that the forgetting scores over the longer intervals would correlate better with memory complaints, if ALF had a role to play in the discrepancy, but this did not seem to be the case, as none of the three week forgetting measures correlated with any memory complaint score in either group. This demonstrates that discrepancy between subjective and objective functioning remains even when long term scores are taken into account.

In terms of psychological wellbeing, on the HADS, despite no significant difference in mean anxiety scores between patients and controls, significantly more patients had moderate or severe levels of anxiety than controls. This increased anxiety in patients just after diagnosis is understandable, considering the worrying time

patients are facing coming to terms with their condition and learning about it, and previous studies have found newly diagnosed patients to have higher levels of depression, tension, helplessness and confusion (Pulliainen & Jokelainen, 1994; Prevey *et al.*, 1998; Pulliainen *et al.*, 2000b; Taylor *et al.*, 2010). There was no difference between patients and controls in terms of depression scores however, which would have been expected from the literature (Pulliainen *et al.*, 2000b).

In patients both anxiety and depression scores, particularly anxiety, showed significant correlation with the memory complaint score. Depression score also correlated significantly with the nuisance rating score. It is interesting that anxiety correlated more strongly with the frequency of problems, indicating perhaps heightened self consciousness leading to picking up on little irritations, while depression correlated strongly with the degree of nuisance that those problems caused. The significant correlations between anxiety and depression levels and memory complaints are as expected from previous literature identifying this as a major factor in the discrepancy between subjective and objective memory functioning (Giovagnoli *et al.*, 1997; Elixhauser *et al.*, 1999; Piazzini *et al.*, 2001; Maarika *et al.*, 2009). However, it is interesting to note that there were no significant correlations between anxiety and depression scores and memory complaints in controls, and no reasonable explanation other than the small sample size can be considered to explain this.

It would be interesting to undertake multiple regression analysis to extrapolate the factors involved in predicting level of memory complaints. However, due to time constraints, recruiting numbers adequate to perform multiple regression was not possible.

11.5 Limitations of the research

There are a number of limitations identified, including the following:

1. The main and most frustrating limitation of the study is the small numbers of patients and controls involved. The sample size calculation undertaken prior to data collection suggested that a sample of 21 in each group would be needed to identify a difference of 15% between the patient and control groups in percentage of information forgotten over three weeks to a 5% significance level and power of 80%. However, only 14 patients and 13 controls were recruited, and following the exclusion of those over 70, analysis of long term forgetting was undertaken on 13 patients and 11 controls.

   This would suggest that the study is underpowered. Power analysis has been repeated post hoc, using the results and numbers found, using a statistical power calculator based on two sample tests using average values (DSS-Research). Considering the long term forgetting of the story, with mean values of 28.71 (13.08) in the patient group and 19.63 (10.46) in the control group, there is 47.2% power to detect a difference significant at the 5% level, so the study is underpowered to detect this difference in long term forgetting in the verbal subtest. In the visual subtest, with long term forgetting mean values of 44.05 (26.74) in the patient group and 13.33 (14.69) in the control group, there is 93.2% power to detect this difference significant at the 5% level. This shows that, considering the difference between groups at long term visual forgetting, the difference was larger than expected so there is still adequate power to detect this as a true difference.

   Before the study was undertaken, consultant neurologists running epilepsy clinics were asked about the feasibility of recruiting 21 patients with recently diagnosed TLE in the short time period available for data collection, and it was felt that this was a realistic aim. Potential patients were identified firstly by looking through patients who had attended epilepsy clinics in the previous six months to see if they were diagnosed with TLE or localisation related epilepsy, and they were contacted by invitation letter if it was felt they were suitable. There was a response rate of 64% to these letters, with

57% of those responding agreeing to participate in the study (four patients). However, half of these positive responders (two patients) later withdrew when they were unable to arrange a convenient time to be seen within the time constraints of the data collection period (one was in prison, one was unwilling to come to the Walton Centre and was having their house redecorated so didn't want a home visit). This meant that just 18% of the patients initially contacted by invitation letter were assessed for the study (two patients).

The author also recruited patients from epilepsy clinics. The author did as much as possible to ensure any suitable patients were identified and recruited, making sure all clinicians running clinics knew about the study, and the inclusion and exclusion criteria. Each week, the notes of the patients coming to all epilepsy clinics (new patient clinics, follow-up clinics and nurse-led clinics) were reviewed to identify any possible patients, and direct which clinics would be attended. The author sat in on at least two clinics a week, up to as many as five, and if a clinic with a potential patient was going to be missed a message was put into the notes to ask the clinician to tell the patient about the study, give them an information sheet and take their contact details if they were happy to give them so that the author could contact them after the clinic. A total of 17 suitable patients were seen by the researcher in clinics, of whom 76% initially agreed to participate in the study. One of these patients later was unable to arrange an assessment convenient for them, as they had to cancel arranged assessments four times at short notice, and was unable to rearrange within the data collection period. So 71% of suitable patients seen in clinic were assessed, showing that recruiting via meeting and explaining the study personally to patients was much more effective than inviting by letter, as would be expected.

The high rate of positive response from patients seen in clinics shows that when suitable patients were personally approached, they were generally happy to participate. This suggests that the numbers of patients recruited

could have been low because of a lack of suitable patients. The exclusion criteria of the study did rule out quite a number of potential patients who were diagnosed with localisation related epilepsy, particularly as a number of patients had a history of previous severe head injury, and also a number of otherwise identified patients reported alcohol or drug abuse or concurrent major psychiatric illness. These exclusion criteria were in place to avoid extra confounding factors that could otherwise explain cognitive difficulties apart from epilepsy-related factors, so were necessary for the reliability of drawing conclusions from the results. Also, the time period for recruitment was four and a half months, from mid-January to the end of May 2010, which was restricted by gaining ethical permission at one end and allowing time to finish data collection and analysis at the other end. This was initially felt to be long enough to recruit sufficient suitable patients, but the number of patients diagnosed with localisation-related epilepsy and meeting the inclusion criteria was lower than expected.

2. There was also a problem with recruiting enough matched healthy controls. Patients were asked at recruitment if they knew anyone of a similar age to them who might be willing to participate. This provided some of the controls, but 57% were unable to find somebody suitable who was willing to participate. The main problem with finding willing participants was the time commitment involved in participating in the study, which also discouraged the majority of those responding negatively to the invitation letter. The initial assessment took around three hours, and particularly potential controls who were working said they were unable to fit this in (despite offering evening or weekend assessments). As there was no reimbursement or incentive for participants, it is understandable that people were not willing to give up such a large chunk of time, but unfortunately it was necessary as full and comprehensive assessment of IQ and memory requires this length of time.

3. Apart from the small numbers of participants there were also a number of other limitations of the study, including difficulties with suitable participant groups. One of the difficulties with interpreting the long term forgetting results, as discussed in the previous sections, is identifying and controlling for the effect of participants' IQ on their long term forgetting scores. The significant differences in IQ between patients and controls make it difficult to assess memory results independently, as the differences in IQ not only reflect other cognitive processes, but can impact on memory scores via use of more effective memorisation strategies or recall strategies. Controls were recruited to be matched to patients at years of education, as IQ cannot be assessed prior to recruitment and it was felt that matching to education would be the most simple and effective way to try and find a control group similar to the patient group in terms of intellectual functioning. However, given the dissociation between years of education and IQ in patients, this was not the case. This dissociation cannot be fully examined as no pre-morbid measure of IQ was used as part of the battery, so it is not possible to identify whether it represents a deterioration in IQ with epileptogenesis or seizures or merely lower intellectual functioning in that cohort. When designing the study, it was felt that years of education would give the required results and only with hindsight it was felt that a pre-morbid measure would have been useful.

4. In terms of the patient group, it was initially hoped to recruit a group of patients all newly diagnosed with TLE. However, as there were problems with recruiting participants, this had to be expanded to patients newly diagnosed with any localisation related epilepsy. This made it slightly easier to identify suitable patients, not least because it is often difficult for clinicians to be confident about where an epileptic focus might be without imaging or electroencephalographic results, or even after these, but it is easier to say whether it is localisation related or generalised. However, a group of patients with an epileptogenic focus in the same area of the brain makes it easier to come to conclusions about the role of that area in long term forgetting. While TLE is the most common type of localisation related

epilepsy, the patients assessed could have had foci in other areas such as the frontal lobe, which might bring about a different memory profile. However, even within TLE patients there can be lesions in the lateral or mesial temporal lobe causing different profiles of impairment so focussing investigation on one type of epilepsy does not exclude variation within patients. Also, by assessing a wider population of patients the results are more generalisable to a population of newly diagnosed localisation related epilepsy patients.

5. Another problem with interpreting results in the patient group is the confounding factor of medication use. All bar two patients were taking one AED at the time of assessment, and they were taking a number of different medications, so it was not possible (particularly given the small numbers) to factor AED use into analysis. This was difficult to avoid because the extended delay aspect to testing meant, if patients were to be tested before initiation of medication, it would entail a three week delay before commencing AED therapy which was deemed unethical.

6. Another difficulty with trying to recruit and assess patients from diagnosis is that it is not the same as assessing at the start of epileptogenesis or even from their first seizure. Recruiting patients from diagnosis is the only way of identifying patients with epilepsy, but almost by definition patients have generally had at least two seizures at the time of diagnosis, and many have had more, particularly partial seizures, some for a number of months or years. If patients have had varying numbers of seizures, and a varying length of time with seizures (and therefore varying time with underlying epileptogenic changes in their brain substrate) this makes it difficult to draw conclusions about the effects of these variables on memory.

7. Little investigation data was available from the patients – it was possible to obtain imaging results (CT or MRI) in all patients, but there were no

measures such as volumetrics employed to examine the relationship of these with memory. Controls did not have any imaging so it was impossible to say whether or not they had any asymptomatic abnormalities, and also whether their brain volumes would correlate with memory and intellectual functioning. Fewer EEG results were available, as often EEGs were not requested in newly diagnosed localisation related epilepsy as it was felt that the result would not affect management or prognosis. Due to this, and the few abnormalities on imaging, it was generally difficult to determine laterality of seizure onset, which meant that it was impossible to consider differences in neuropsychological profile according to laterality of epilepsy.

8. The memory tests used to test long term forgetting are potentially restricting the usefulness of the findings. A logical memory story was used as a measure of verbal memory, because while word lists have identified more deficits, particularly in newly diagnosed patients with partial epilepsy (Äikiä *et al.*, 1995; Aikia *et al.*, 1999), it was felt that a story provides a more useful test of the kind of memory used in everyday life rather than a list of unrelated words with no semantic resonance. However, a story might be thought to be more easily rehearsed than other verbal measures, allowing for rehearsal strategies to have more of a confounding effect on results. A word list could have been used alongside the story, as has been done in previous studies (eg (Butler *et al.*, 2009)), but considering the length of the assessment it was felt that this would be too much to ask participants to undertake in one session. The visual scenes test was a test that has been developed by Dr Muhlert specifically for this type of research into long term forgetting. Although some of the information tested can be verbalised so it is not a pure test of visual memory, similarly it is felt that it tests memory similar to that used for everyday tasks and thus provides a useful relevant guide for a person's level of memory functioning on a day-to-day basis rather than merely in an isolated testing environment.

9. One problem with the interpretation of the tests and the comparison of results from them was a slight difference in procedure between the two subtests. As mentioned above, in the visual subtest a distraction task was used after presentation of the scenes to remove recency effects, but this was not done in the verbal subtest. This was an oversight on the author's behalf when initially designing the battery, and was only picked up after a number of participants had been tested. At that point it was felt that consistency of administration of the tests between subjects was more important than consistency of administration between subtests.

10. The testing of long term forgetting was undertaken at only one interval, three weeks after initial presentation of the material. Results were highly dependent on this assessment, and if participants had just had a busy day or were distracted on that one occasion their performance might be adversely affected. Also, assessing long term forgetting on one occasion means that the trajectory of forgetting over time cannot be fully assessed, and when the forgetting was accelerated.

11. Previous studies have suggested a link between ALF and TEA (Butler, Butler, Manes). As TEA originates in the temporal lobes, whether or not the patients with TLE had coexisting TEA could be relevant to the long-term forgetting results. However, no information was gathered specifically regarding possible episodes of amnesia. Detailed histories were taken in the clinic when patients were diagnosed (and often recruited), and classification of patients' seizures was based on their consultants' opinions. Seizure history was confirmed at the first assessment, but no further questions about episodes of amnesia were asked because the researcher does not have the experience to distinguish TEA from other differential causes. This means that no information is available to the researcher regarding the possibility of TEA co-existing with ALF in TLE.

12. From the perspective of investigating the subjective memory functioning of the patients, there were also a number of potential limitations. Within the testing battery there were no specific tests of language functions, or verbal fluency, which have been shown to be related to subjective memory complaints (Helmstaedter & Elger, 2000). There were also no attention or concentration measures used as part of the assessment battery, which might influence memory results.

13. Within the subjective memory questionnaire, there was no specific question about experience of accelerated forgetting. If this had been the case, it might have been possible to compare scores on that question with long term forgetting scores to see if that provided better correlation between subjective and objective measures.

14. There were also limitations caused by the statistical tests used. As mentioned in Chapter 9, a large number of comparisons and correlations were undertaken, which increases the chance of finding a false positive result, or type I error. In this situation, a Bonferroni correction can be used to reduce the chances of type I errors but this was not done in this study. It limits the ability of research, particularly with small sample sizes, to identify 'small' or 'medium' effect sizes, and increases the risk of type II errors. It has also been said that a Bonferroni correction discourages detailed analysis, as the more detailed analysis is undertaken the less the chance of significant findings (Moran, 2003). Moran suggests, instead, 'using the accepted $p<0.05$ cut-off and making reasonable interpretations based on experimental design, power analyses, differences between control and treatment groups, and basic logic' p405 (Moran, 2003). In this study, where there were a lot of interacting factors to be considered which require detailed analysis, and where the aim was to look for patterns and trends, it was felt that this was an approach more likely to yield findings of interest. However, the likelihood of type I errors needs to be borne in mind when interpreting these findings.

11.6 Strengths of research

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Despite the limitations, there were also a number of strengths of this study:

1. Patients were recruited and assessed as close to diagnosis as possible, so as to identify long term memory patterns from early on in the course of epilepsy.
2. The strict exclusion criteria employed reduced the impact of other potential influences on memory functioning.
3. A thorough battery including standardised assessment of IQ and memory was used alongside the long term forgetting tests.
4. A control group was also assessed with whom to compare the patients' results, who were well matched in terms of age, gender and education.
5. Long term forgetting was assessed in both verbal and visual domains, and also in both recall and recognition performance.
6. A measure of subjective memory was also employed to compare to the long term forgetting results.
7. A measure of psychological wellbeing was used, so that this could be taken into account in the analysis of both objective and subjective memory results.
8. All the assessments were carried out and scored by the author (and then checked) so that administration would be consistent.

11.7 Importance of this research, and clinical indications

This research provides the first indication of anterograde memory performance over extended delays in patients recently diagnosed with localisation related epilepsy. This has not been considered in previous studies in this area. Increased forgetting

was found in patients, in both verbal and visual domains over a three week delay from early on in the course of epilepsy, confirming previous research findings that patients are cognitively compromised from diagnosis (eg (Taylor *et al.*, 2010)).

Patients remembered nearly 10% less of the verbal information and over 30% less of the visual information than controls over three weeks. For the sample size calculation, a minimum clinically significant difference was felt to be a 15% difference in proportion of material forgotten over the time interval. This would suggest that the difference in forgetting of visual information over three weeks was not only statistically significant at the 1% level, but also clinically significant. This pattern of accelerated long term forgetting has not previously been identified in this population, and it is also particularly interesting that it is in this domain.

One of the key questions from the point of view of the clinical impications of the research is regarding whether or not standard memory tests are adequate for the assessment of memory in patients with epilepsy (particularly in this case in those newly diagnosed). The WMS was used as an example of a standard well-used memory battery, and scores in verbal long term forgetting seemed to be partially predicted by the WMS but those from the visual long term forgetting subtest were not. This gives a mixed picture, and whether extended testing delays are necessary in this population is still somewhat unclear.

Subjective and objective memory discrepancies in newly diagnosed patients were another focus of this research and it was found that they were not explained by long term forgetting, but were well correlated with psychological wellbeing.

Although in many ways this study has thrown up more questions than it can answer, this is to a large extent due to the small sample size, and it has provided an idea and outline design for a larger study that would be able to look into many of

these issues in more depth, with the advantage of a greater number of participants. With this in mind, the possibilities for future research directions are outlined below.

11.8 Future research directions

If this study can be adjusted for its methodological flaws and repeated on a larger sample of patients and controls, a lot more analysis would be possible and more interesting information extracted, particularly around the potential causative factors of extended long term memory impairment. It is frustrating for the author that recruiting more numbers was not possible in the timeframe, and the potential opportunities to discover some very interesting patterns and relations in this population are noted.

If possible, future investigations in this area could also look at long term forgetting rates in patients prior to medication. Because of the necessity of an extended delay within assessment due to the nature of the problem, this may be difficult, but so far no investigations into long term forgetting in epilepsy patients have been undertaken without medication, and it is important to exclude it as a causative factor, or at least try to extrapolate its influence through the use of statistical regression models.

More research is needed on accelerated forgetting generally, not only in newly diagnosed patients with epilepsy. One of the major problems with both reviewing the literature on ALF and designing the study was the lack of a standardised test for long term forgetting over an extended delay. This makes it difficult to compare the results of different studies using different measures over different lengths of time, and also means that there are no standardised population norms to identify levels of impairment, which is why a control group is needed. Testing of long term forgetting with a range of verbal and non-verbal tests might help identify the most effective type of test to be used for extended delays that provides the most useful

information whilst allowing for the least possible bias. Also, testing of long term forgetting in a healthy normal population considering a range of ages would allow for the creation of age-adjusted standardised norms with which to compare not just epilepsy patients but people with many varying conditions that could affect memory.

11.9 Summary

- The aim of this research was to investigate long term forgetting in patients newly diagnosed with localisation related epilepsy, in both verbal and visual domains. Overall, long term anterograde memory impairment was found in recently diagnosed patients.
- In the verbal domain, patients demonstrated impaired delayed recall over both the short and long delays.
- In the visual domain, patients demonstrated poorer initial recall than controls followed by ALF over the three week delay, to a clinically significant level, which was related to a greater number of lifetime generalised seizures.
- Verbal long term memory performance was partially predicted by WMS scores, but visual long term memory was not, which leaves the need for extended testing delays under question.
- There was no difference between patients and controls in subjective memory scores. Memory complaints were related to anxiety and depression, but not to any long term forgetting measures, suggesting that ALF is not the cause of reported discrepancies between subjective and objective memory.
- A number of limitations related to participants and study design, notably the small numbers involved in the study and discrepancies in IQ between the patient and control groups restrict the conclusions that can be drawn from the findings, particularly regarding specific mechanisms of impairment and causative factors.

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Appendix 1: Letter of Invitation

UNIVERSITY OF LIVERPOOL

Dear

My name is Professor Gus Baker, I am a clinical neuropsychologist based at the Walton Centre, Liverpool. As a patient with epilepsy treated at the Walton Centre, you have been identified as somebody who might be able to participate in a study I am undertaking. I would be most grateful if you could read through the information sheet attached to find out more about the study and decide whether or not you would like to be involved in it.

There is no pressure to take part, and your decision will not affect your care in any way. If you would like any more information, or once you come to a decision, feel free to contact me by phoning me or my researcher Marion Ashe on 0151 529 5417, emailing us at 'm.f.ashe@liv.ac.uk' or returning the slip below in the enclosed stamped addressed envelope. Even if you do not wish to participate I would appreciate a response, so that I can remove you from my contact lists and not bother you again.

If you decide you would like to be involved, thank you. We will contact you to arrange two sessions together. Also, as we are looking for healthy control participants, we will ask if you think you know of anybody, family or friends, of a similar age to you, whom you wouldn't mind telling about the study, giving an information sheet, and asking them to contact me to get involved too. If you would rather not, that is not a problem and you are still most welcome to participate.

Thank you for your time,
Yours sincerely

Professor G A Baker
Professor of Clinical Neuropsychology and Consultant Clinical Neuropsychologist

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I, ……, (*name)* am / am not *(delete as appropriate)* interested in participating in the study 'Accelerated forgetting in newly diagnosed temporal lobe epilepsy'.

If you would like to participate, please fill out your details below:
Address: _____
_____
_____
_____
Phone: _____
Email: _____

Appendix 2: Participant Information Sheet

Accelerated forgetting in newly diagnosed focal epilepsy.

This is an invitation to take part in a research study. Before you decide whether or not to take part, it is important to understand why the study is being done and what will be involved. Please take your time to read the information below carefully and discuss it with friends, family or your GP if you wish, before making a decision. You do not have to accept this invitation. If you would like any more information or something is not clear please contact us (see below for details).

Thank you for reading this.

Why is the study being done?

Memory problems are a major issue for many patients with epilepsy. Recent research has identified 'accelerated forgetting', a difficulty remembering things over long periods, as a possible cause. This research will investigate accelerated forgetting in newly diagnosed epilepsy, to try and understand how it happens.

This research is also being undertaken as part of an academic qualification.

Why me?

You may have been invited to take part because you have a diagnosis of focal epilepsy. We also need participants to act as healthy controls to compare their results with patients, so you may have been asked because you do not have epilepsy but know someone who does.

If you have ever had a serious head injury, brain surgery or a recent history of alcohol or drug abuse I am afraid you may not be able to take part, as these issues may interfere with your results. If this is the case, or you are unsure, please let us know.

What will I need to do if I take part?

If you are happy to take part, please contact us by ringing, emailing or writing (details below). We will go through this information with you and make sure you want to be involved. If you do, we will need access to your personal contact information.

We will arrange two sessions with you, 3 weeks apart, to carry out the assessments. Ideally, these sessions will be at the Walton Centre, but if necessary we can arrange home visits. At the first session we will give you questionnaires about mood and your view of your memory, assess your intellectual functioning, then go through a memory test including stories and pictures we will ask you to remember. This will take up to 3 hours, and the following session will last around 15 minutes. You will also be asked to keep a record of any seizures you have between sessions.

What will I get out of it?

On a personal level, we can't promise the study will help you. You will have a thorough memory assessment, and if any concerns are found you will be referred to the appropriate services. Also, you will be contributing to research that will increase understanding of memory problems in epilepsy, so that management can be improved.

What are the risks?

There will be no physical risks involved in this study. There is a chance that if memory difficulties are found, some people might be distressed. If this is the case we will provide support, both immediately and with referrals to appropriate services.

What if I don't want to take part?

If you don't want to take part, it will not affect your care in any way. Also you are welcome to withdraw at any point during the study if you change your mind, without needing to give a reason.

Will the information collected be confidential?

Yes. Personal contact details will be kept in a locked cabinet and only the researchers will have access to them. All results will be anonymised before analysis and care will be taken that nobody can be identified from the reports.

What if I want to complain?

If you are unhappy, or if there is a problem, please feel free to let us know by contacting Marion Ashe on 0151 529 5417 and we will try to help. If you remain unhappy or have a complaint which you feel you cannot come to us with then you should contact the Research Governance Officer on 0151 794 8290 (ethics@liv.ac.uk). When contacting the Research Governance Officer, please provide details of the name or description of the study (so that it can be identified), the researcher(s) involved, and the details of the complaint you wish to make.

If you wish, you can also use the hospital complaints procedure. To do so, contact Fran Seagreaves, Complaints & Legal Services Manager, The Walton Centre for Neurology & Neurosurgery NHS Trust, Lower Lane, Fazakerley, Liverpool, L9 7LJ. Contact number: 0151 5295530.

Will I hear the results?

Yes, we will contact all participants with a summary of the research findings (with no personal information) once the study is completed. Also if there are any individual problems identified by the study we will contact those involved to discuss their future care. We aim to publish the study findings in peer-reviewed journals.

Anything else?

All participants will be covered by a University insurance scheme.

If you would like any further information, or to discuss your participation in the study, please contact Marion Ashe on 0151 529 5417 (email m.f.ashe@liv.ac.uk) or Professor Gus Baker on 0151 529 5948 (email G.A.Baker@liverpool.ac.uk) or write to Neurological Science, Clinical Sciences Centre, Lower Lane, Liverpool, L9 7LJ.

CONSENT FORM –
Accelerated Forgetting in Newly Diagnosed Focal Epilepsy

Researcher: Marion Ashe

1. I confirm that I have read and have understood the information sheet dated 15/04/10 for the above study. I have had the opportunity to consider the information, ask questions and have had 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 rights being affected. ☐

3. I understand that, under the Data Protection Act, I can at any time ask for access to the information I provide and I can also request the destruction of that information if I wish. ☐

4. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from University of Liverpool, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research ☐

5. I agree to take part in the above study. ☐

Participant Name	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

The contact details of lead Researcher (Principal Investigator) are:
Professor GA Baker,
Division of Neurological Science,
Clinical Sciences Centre,
Lower Lane,
Liverpool, L9 7JL.
0151 529 5948
g.baker@liverpool.ac.uk

Appendix 4: Logical Memory Story

The logical memory story used for the assessment of long term forgetting was story A from the WMS-III which reads as follows:

'Anna Thompson of South London, employed as a cook in a school canteen, reported at the police station that she had been held up on the High Street the night before and robbed of fifty-six pounds. She had four small children, the rent was due, and they had not eaten for two days. The police, touched by the woman's story, made up a collection for her.'

This is split into 25 sub-units of recall, such as 'Anna', a point given for each correctly recalled. There are also seven additional thematic units, such as 'indication of a main character who is female' for which a point is given, so that those who remember the vague gist but not the exact story are still credited to a degree.

Appendix 5: Visual Scenes Test

Beach scene

Park scene

Stage scene

Street scene

Example recall sheet:

Table 1a. Beach recall score sheet

BEACH SCENE			
Objects	Full Point	Half Point	Spatial
Man AND golf club			Top Left (1)
Man			
First Descriptor			
Second Descriptor			
Boat			Top Right (2)
First Descriptor			
Second Descriptor			
Crocodile/ Alligator AND Bucket and Spade			Bottom Left (3)
Crocodile/ Alligator OR Bucket and Spade			
First Descriptor			
Second Descriptor			
Parasol/ Umbrella			Bottom Right (4)
First Descriptor			
Second Descriptor			
Total Items (Max=4)			
Total Spatial (Max=4)			
Total Descriptors (Max=8)			

Descriptors:

Man & Golf club:

He was ready to swing the golf club; the golf club was on the man's right hand side; he was playing left-handed; he was wearing a white hat/cap; he was wearing a short-sleeve/ checked shirt; wearing beige/ light brown clothes; he had black shoes; he had a black belt; he had one (white) glove; he was facing the R side of the picture.

Boat:

It was a rowing/ fishing boat; it was a blue boat; the boat was lying on its side; there were two oars inside; there were some (green) nets inside the boat; there was a plank/thwart across the boat.

Crocodile/alligator & bucket and spade:

The alligator had its mouth open; alligator was facing the middle / head to R / head towards sea; there was a blue spade; the spade was half buried / upright in sand; there was a green bucket; the bucket and spade were in front of the alligator.

Parasol:

It was green/turquoise/greeny-blue on the outside; it was white on the inside; it was spotted on the inside; it had a curled handle; it had a frilly/ruffled edge; the outside of the umbrella was facing the water OR the inside was facing the alligator/ beach OR handle to L.

Example recognition sheet:

Table 2b. **PARK Scene** recognition questions

	Question	Possible Responses			
Plane					
	What colour was the plane?	White	Black	Grey	Blue
	What was painted on the plane?	Some stars	A bird	Some numbers	A shark
Ice-cream Van					
	What was on the sign of the ice-cream van?	Two ice-creams	Three ice-creams	A child	A flag
	What was written inside the window of the ice-cream van?	D 2	D 1	C 2	C 1
Wheelbarrow					
	What colour was the wheelbarrow?	Red	Black	Green	Blue
	What was inside the wheelbarrow?	Two watermelons	Three large rocks	A pile of leaves	Two plants
Books & Cricket bat					
	Where was the cricket bat?	To the left of the books	To the right of the books	In front of the books	Behind the books
	What colour was the cricket bat?	Black and white	Green and black	Blue and yellow	Yellow and red
				Total (Max=8)	_____

Appendix 6: Baseline characteristics of all participants including those over 70

The demographic, clinical and baseline neuropsychological characteristics of the participant groups were analysed prior to the exclusion of participants over 70 to assess if this affected differences between groups. The results from all participants are presented below. There are no significant differences between groups in demographic variables, or procedural details.

Participants' Demographic Information

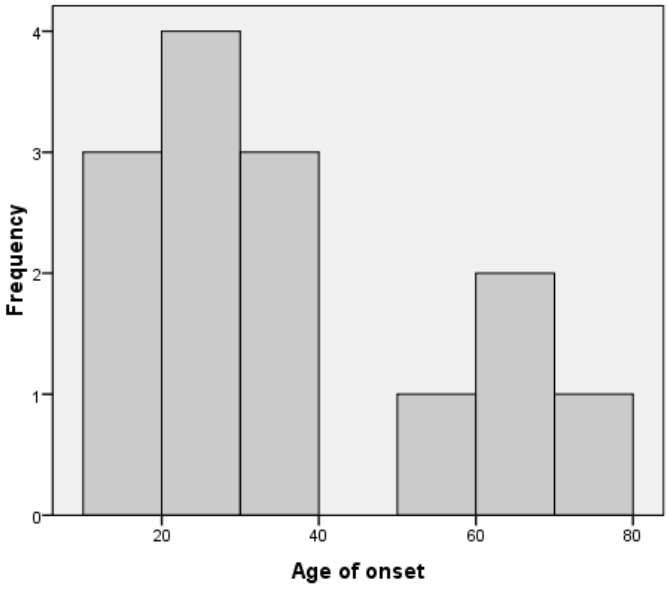
Demographics		All	Patients	Controls	Difference (95% CI)	Significance (*p*-value)
Number of participants		27	14	13		
Age/yrs Mean (SD)		40.37 (19.07)	40.07 (18.05)	40.69 (20.85)	-0.62 (-16.05, 14.81)	0.935
Gender	**Male**	13 (48.1%)	6 (42.9%)	7 (53.8%)		0.706
	Female	14 (51.9%)	8 (57.1%)	6 (46.2%)		
Handedness	**R**	24 (88.9%)	12 (85.7%)	12 (92.3%)		1.000
	L	3 (11.1%)	2 (14.3%)	1 (7.7%)		
Education /years Mean (SD)		13.56 (2.75)	13.21 (2.52)	13.92 (3.04)	-0.71 (-2.91, 1.50)	0.514
Education /level	**school**	10 (37.0%)	5 (35.7%)	5 (38.5%)	School vs higher education	1.000
	college	7 (25.9%)	5 (35.7%)	2 (15.4%)		
	university	10 (37.0%)	4 (28.6%)	6 (46.2%)		

Procedural details of assessments in patients and controls

Procedure		All (n=27)	Patients (n=14)	Controls (n=13)	Difference (95% CI)	p-value
Location of initial assessment	**CTU**	8 (29.6%)	5 (35.7%)	3 (23.1%)		0.678
	Home	19 (70.4%)	9 (64.3%)	10 (76.9%)		
Location of follow up assessment	**CTU**	7 (25.9%)	4 (28.6%)	3 (23.1%)		1.000
	Home	20 (74.1%)	10 (71.4%)	10 (76.9%)		
Interval between assessments/ days Mean (SD)		21.04 (0.85)	20.93 (0.62)	21.15 (1.07)	-0.23 (-0.91, 0.46)	0.504

Clinical variables in patients

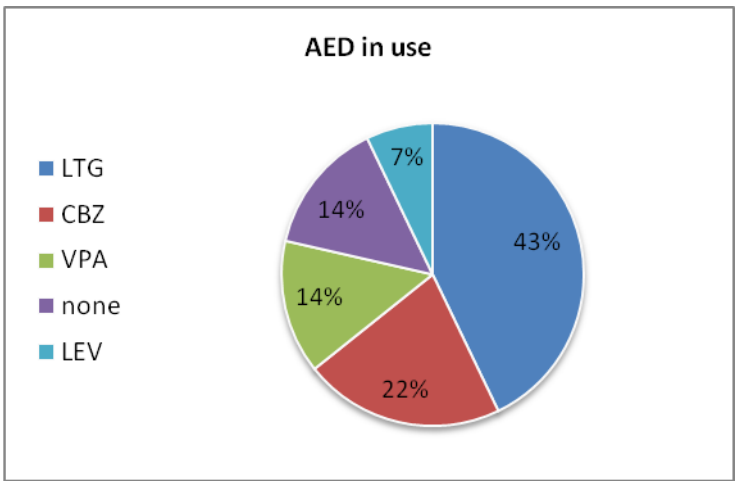
Patients		n=14
Seizure type	**Partial only**	3 (21.4%)
	Partial and generalised	7 (50.0%)
	Secondary generalised only	4 (28.6%)
Total number of generalised seizures Mean (SD)		2.07 (1.39)
Time since diagnosis / weeks Median (IQR)		4.00 (1.75, 12.75)
Time since first seizure / months Median (IQR)		18.00 (5.25, 66.00)
Number of medications Median (IQR)		1 (1, 1)
Age of onset Mean (SD)		36.93 (19.00)



Distribution of age of onset of epilepsy

Investigation results

Investigation results		Patients n=14
Imaging	**Normal**	11 (78.6%)
	Abnormal	3 (21.4%)
EEG	**Normal**	8 (57.1%)
	Abnormal	1 (7.1%)
	Not done	5 (35.7%)
Laterality of seizure onset	**Left**	1 (7.1%)
	Right	2 (14.3%)
	Unknown	11 (78.6%)



Background Intellectual Functioning - WASI

	Overall (n=27)	Patient (n=14)	Control (n=13)	Difference (95% CI)	*p*-value
VIQ	104.22	98.29	110.62	-12.330	0.034*
Mean (SD)	(15.34)	(13.88)	(14.70)	(-23.655, -1.004)	
PIQ	110.41	104.29	117.00	-12.714	0.009**
Mean (SD)	(13.12)	(10.04)	(13.14)	(-21.942, -3.487)	
FSIQ	108.07	101.50	115.15	-13.654	0.005**
Mean (SD)	(13.37)	(11.15)	(12.16)	(-22.890, -4.418)	

**$p<0.01$

Correlations between years of education and WASI scores

All participants (n=27)	**Years of education**
VIQ	0.389 (p=0.045)*
PIQ	0.227 (p=0.255)
FSIQ	0.387 (p=0.046)*
Patients (n=14)	
VIQ	0.210 (p=0.472)
PIQ	-0.273 (p=0.344)
FSIQ	-0.015 (p=0.959)
Controls (n=13)	
VIQ	0.508 (p=0.076)
PIQ	0.505 (p=0.079)
FSIQ	0.699 (p=0.008)**

Mean scores in WMS indices

	All (n=27)	Patients (n=14)	Controls (n=13)	Difference (95% CI)	*p*-value
Auditory Immediate Memory (AIM)	107.48 (14.87)	104.50 (13.06)	110.69 (16.51)	-6.19 (-17.95, 5.56)	0.288
Visual Immediate Memory (VIM)	96.74 (13.46)	91.50 (11.41)	102.38 (13.52)	-10.89 (-20.81, -0.96)	0.033*
Immediate Memory (IM)	102.85 (14.24)	98.00 (12.55)	108.08 (14.56)	-10.08 (-20.83, 0.67)	0.065
Auditory Delayed Memory (ADM)	106.48 (13.61)	104.86 (11.24)	108.23 (16.06)	-3.37 (-14.29, 7.55)	0.530
Visual Delayed Memory (VDM)	100.37 (14.32)	96.00 (11.67)	105.08 (15.82)	-9.08 (-20.04, 1.88)	0.100
Auditory Recognition Delayed Memory (ARDM)	112.59 (10.60)	111.07 (11.13)	114.23 (10.18)	-3.16 (-11.63, 5.31)	0.450
General Memory (GM)	106.85 (13.53)	103.57 (11.56)	110.38 (15.02)	-6.81 (-17.39, 3.76)	0.197
Working Memory (WM)	105.81 (16.33)	101.64 (16.62)	110.31 (15.38)	-8.67 (-21.39, 4.06)	0.173

Patients scored lower than controls on VIQ (p=0.034), PIQ (p=0.009) and FSIQ (p=0.005) and lower than controls in visual immediate memory (p=0.033) but there were no other significant differences in neuropsychological measures.