Memory Dysfunction and Pathology in Children with Temporal Lobe Epilepsy

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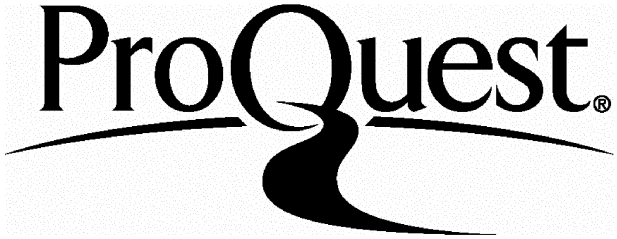

Abstract

Temporal lobe epilepsy is known to affect cognitive functions in both adults and children, with memory being particularly seriously affected. Traditionally, clinical and neurophysiological data have provided information regarding seizure lateralization and this has been related to memory deficits. This technique, which has demonstrated the material-specificity of temporal lobe function, is unable to control for the high degree of bilateral temporal lobe pathology that is often seen in patients with temporal lobe epilepsy.

Modern imaging technology has enabled the non-invasive investigation of the brain and the quantification of temporal lobe pathology. In this thesis, three quantitative magnetic resonance techniques were used to evaluate the degree of temporal lobe damage in children with temporal lobe epilepsy. These were hippocampal volumetry, T2 relaxometry and proton magnetic resonance spectroscopy. The first two techniques both measure pathology in the hippocampus, but in different ways. Specifically, volumetry assesses how much tissue has been lost, whilst T2 assesses the integrity of the remaining tissue. Spectroscopy, by contrast, investigates the biochemistry of the medial temporal lobe, providing information that is not available from standard magnetic resonance imaging.

This information about medial temporal lobe pathology was related to memory performance. Measures of left temporal, and particularly left hippocampal, pathology were found to be associated with scores on a number of verbal memory tests. However, measures of right temporal pathology were not

associated with any test of memory, even those thought to be dependent on the right temporal lobe.

The response of the epileptic brain to surgery was investigated using the magnetic resonance techniques and neuropsychological measures. The results suggested that outcome differed depending on the type of surgical procedure. In particular, the contralateral hippocampus appeared to show a volume increase following a temporal lobectomy, but an increase in T2 relaxation time following a temporal lesionectomy. Spectroscopic data showed a trend towards more normal biochemistry in both groups. Immediate memory function was found to improve in patients who had a lesionectomy, but worsen following temporal lobectomy. The relationship between these findings is discussed.

This thesis demonstrates the use of quantitative magnetic resonance techniques in the investigation of temporal lobe epilepsy of the relationship between temporal lobe epilepsy and memory dysfunction.

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Abbreviations

3D	-	Three-dimensional
AM	-	Amygdaloid body
AMIPB	-	Adult Memory and Information Processing Battery
ANOVA	-	Analysis of variance
BPVS	-	British Picture Vocabulary Scale
C1	-	First cranial vertebra
C'	-	Immediate Composite score
C	-	Delayed Composite score
C%	-	Percentage of the Composite score retained
CA	-	Cornu ammonis
CAVLT-2	-	Childrens Auditory-Verbal Learning Test (2nd edition)
CDLT	-	Coughlan Design Learning Test
Cho	-	Choline-containing compounds
CHQ	-	Child Health Questionnaire
cm	-	Centimetre
cm^3	-	Cubic centimetre
CPS	-	Complex partial seizure
Cr	-	Creatine and phosphocreatine
CSF	-	Cerebrospinal fluid
CT	-	X-ray computed tomography
D'	-	Immediate visual reproduction score
D	-	Delayed visual reproduction score
D%	-	Percentage of the visual reproduction score retained
DLI	-	Design Learning Intrusions
DLT	-	Design Learning Total
DNET	-	Dysembryoplastic neuroepithelial tumour
EEG	-	Electroencephalography
FSIQ	-	Full Scale Intelligence Quotient
GD	-	Glial density
GFAP	-	Glial fibrillary acidic protein
HF	-	Hippocampal formation
HFV	-	Hippocampal formation volume

Hz	-	Hertz
Tukey's h-s-d	-	Tukey's honestly-significant-difference test
ICV	-	Intracranial volume
IQ	-	Intelligence Quotient
LM - D	-	Delayed Logical Memory score
LM - I	-	Immediate Logical Memory score
LM %	-	Percentage of the Logical Memory score retained
m	-	Month
mm	-	Millimetre
mm^3	-	Cubic millimetre
MNI	-	Montreal Neurological Institute
MP-RAGE	-	Magnetization-prepared rapid acquisition gradient echo
MQ	-	Memory Quotient
MR	-	Magnetic resonance
MRI	-	Magnetic resonance imaging
MRS	-	Magnetic resonance spectroscopy
ms	-	Millisecond
MTS	-	Medial temporal sclerosis
NAA	-	N-acetylaspartate
ND	-	Neuronal density
PET	-	Positron emission tomography
PHA-L	-	*Phaseolus vulgaris* leucoagglutinin
PHG	-	Parahippocampal gyrus
PIQ	-	Performance Intelligence Quotient
RC	-	Repeatability coefficient
SD	-	Standard deviation
SPECT	-	Single photon emission computerised tomography
SPS	-	Simple partial seizure
T	-	Tesla
TE	-	Echo time
TI	-	Inversion time
TLE	-	Temporal lobe epilepsy
TR	-	Recovery time
TROG	-	Test for reception of grammar
VIQ	-	Verbal Intelligence Quotient
VPA Del	-	Delayed recall score for the verbal paired-associate learning test

VPA Easy	-	Total number of easy pairs correctly recalled in the learning trial of the verbal paired-associate learning test
VPA Hard	-	Total number of hard pairs correctly recalled in the learning trial of the verbal paired-associate learning test
VPAL	-	Verbal paired-associate learning test
VPA Score	-	Weighted learning score for the verbal paired-associate learning test
vSRT	-	Verbal selective reminding test
WAIS	-	Wechsler adult intelligence scale
WCST	-	Wisconsin card sorting test
WISC	-	Wechsler intelligence scale for children
WMS	-	Wechsler memory scale
WOND	-	Wechsler objective numerical dimensions
WORD	-	Wechsler objective reading dimensions
WRMT	-	Warrington recognition memory test
y	-	Year

Chapter 1. Introduction

"If our brains were simple enough to understand, we wouldn't be able to understand them."

Anonymous graffiti

Memory has been considered and discussed for many centuries, at least as far back as Plato, who described memory as a wax tablet on which perceptions or ideas might be imprinted and retained (Parkin, 1987). The analogies used to describe memory have changed over the years; in medieval times it was regarded as a complex hydraulic system, in the seventeenth century as clockwork, in the nineteenth century as electricity. Today we still use analogies - the brain as a computer being the most common. Despite this very long-standing interest in memory as a concept, its scientific investigation has only a century of work behind it. In this time ideas have moved from the simple analogy to today's complex multicomponent view of the memory system.

In recent years, new neuroimaging techniques have vastly increased our ability to investigate and understand functions of the brain, and in particular to examine specific regions and relate their integrity to cognitive functions such as memory. The advent of non-invasive, non-ionizing imaging techniques has resulted in an explosion of research studies, both in normal humans and in those suffering from a wide variety of neurological disorders. Traditional neuropsychological techniques, which related cognitive deficits to circumscribed brain lesions, have been adapted to the new methods, so that whereas previously

brain lesions were only definitively identified at autopsy, they can now be visualised, quantified, and their progression followed in time from the outset.

This chapter introduces the topics which are explored in this thesis - cognitive impairments (particularly impairments of memory), epilepsy and the pathology associated with it, and magnetic resonance imaging and its use in quantifying such pathology. These three subjects are discussed with reference to the way in which they are interrelated. Firstly though, some of the recent history of the investigation of memory function is explored.

1.1 The Investigation of Memory

It is widely accepted that memory is not a unitary function but is a system composed of several subcomponents (Squire & Knowlton, 1996). The study of both animals with experimental brain lesions and human amnesic patients has shown that cognitive (fact-and-event) memory can be dissociated from non-cognitive (behavioural) memory (Figure 1.1). The two types of memory are different not only in the kinds of memoranda retained, but also in the way in which the information is stored. Cognitive memory, such as the memory for personal events, can store information after just a single trial and this information can readily be applied in new situations (Squire & Knowlton, 1996). Non-cognitive memory, by contrast, is normally unconscious, acquired across many trials and is not generally accessible outside the learning situation. This type of memory includes skill and habit learning, and priming.

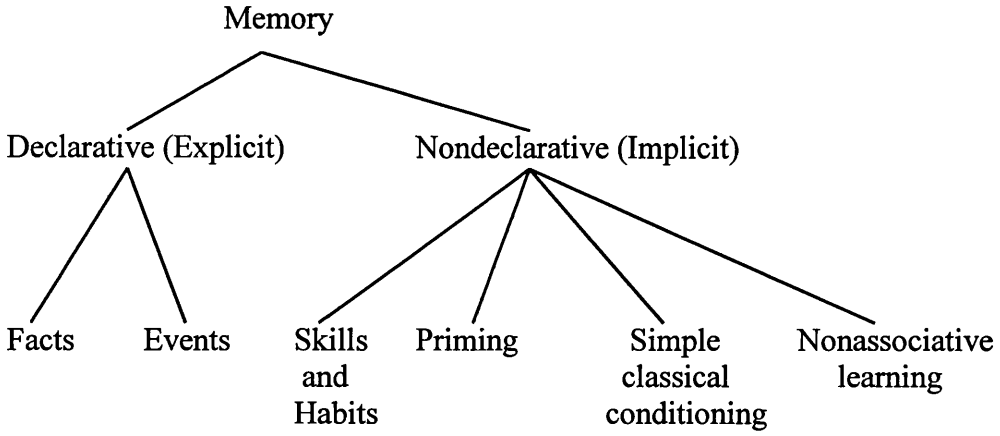

Figure 1.1 The classification of long-term memory (from Squire & Knowlton, 1996)

On the basis of data obtained from amnesic patients, cognitive memory can in turn be divided into different components. In general, these patients do not have difficulty remembering information that has just been given to them, provided that they are allowed to rehearse it subvocally. An example of this kind of information would be a telephone number, which can be remembered for as long as it is recited. Distraction, however, results in the loss of this information. This implies a distinction between short- and long-term memory (Baddeley & Warrington, 1970), with short-term being a period measured in seconds. Presumably, the memory system that supports short-term memory is physically separate from that which supports longer-term memories.

However, the system subserving long-term cognitive memories may not be required indefinitely. The phenomenon of retrograde amnesia, in which the patient forgets memories which were learnt before the onset of amnesia, is frequently temporally graded (Squire & Knowlton, 1996), in that more recent memories are lost more readily than those which are more distant. This implies that the memory trace is 'transferred' to another system. This idea has recently

been challenged, however (Nadel & Moscovitch, 1997). In the model proposed by Nadel and Moscovitch, each subsequent activation of a memory trace occurs in a different experiential context, and as such is laid down as a new trace (the trace is 're - membered'). A remote memory, therefore, will have multiple traces and will be easier to recall since there will be a greater number of access routes to it, although a memory recovered in such a fashion by an amnesic might not have the full complexity of an autobiographical episode. Recent memories, by the same token, would be more susceptible to even minimal damage (Nadel & Moscovitch, 1997). This implies that the extent of retrograde amnesia and its temporal gradient are entirely dependent on the size of the lesion to the memory system.

But where is this memory system? The study of patients with lesions to various regions of the brain has revealed the importance of the medial temporal lobes in normal cognitive memory function (Squire & Zola-Morgan, 1991). The main regions of the medial temporal lobe memory system are the hippocampus, the amygdala, the entorhinal and perirhinal cortices, and the parahippocampal cortex. Damage to any or all of these structures results in a significant memory impairment, and this was dramatically demonstrated when Scoville and Milner (1957) described a profound anterograde amnesia following bilateral medial temporal lobe resection in the patient HM. He has been shown to have lost (bilaterally) the medial temporal pole, most of the amygdala, most or all of the entorhinal cortex and at least half of the hippocampus (Corkin et al., 1997). His long term memory deficit is such that although his IQ and immediate memory abilities are normal, he does not know where he lives, nor what he ate for breakfast, and he cannot remember or recognize memoranda for a wide variety

of stimuli, even after short delays (Corkin, 1984). He does, though, seem to have gained some memory for facts since his surgery (so called semantic memory), such as the fact that a man called Kennedy was assassinated and that Skylab was "a docking place in space".

More limited pathology restricted to a small area of the medial temporal lobe bilaterally (such as a subfield of the hippocampus) has a reportedly lesser, though still grave, effect (Zola-Morgan et al., 1986; Squire & Knowlton, 1996). This indicates that the adjacent cortical regions also make important contributions to memory function. This received recent support from a study of three patients who became amnesic during early childhood (Vargha-Khadem et al., 1997). The only pathology common to all three patients is bilaterally damaged hippocampi. Their episodic memory is very impaired, but all three have acquired levels of semantic knowledge and literacy skills commensurate with their VIQs. One patient in particular has learnt who Martin Luther King was and what 'encumber' means, yet has been amnesic since at least the age of four. The authors suggest that the preserved semantic memory of these patients, when considered together with results from work with experimentally lesioned monkeys, indicates a role for the cortex underlying the hippocampus in context-free semantic memories. Context-rich episodic memories, however, require the integrity of the hippocampi.

Unilateral damage has a less catastrophic effect. Studies of patients with unilateral temporal lobectomy have shown that this surgery does not result in amnesia, but instead produces material-specific memory deficits which are dependent on the side of operation (Milner, 1975). For example, left unilateral removal selectively impairs the learning and retention of verbally coded

information (by whatever modality) (Milner, 1968a) whilst right-sided removal disrupts learning and retention of nonverbal memoranda (Corkin, 1965; Milner, 1968b). This latter finding does not occur as consistently as the former (Rausch, 1991; Loring et al., 1991).

These material-specific deficits have been shown to be greater with more extensive and posterior resections. Most experimental support for this has come from studies at the Montreal Neurological Institute (MNI), reported notably in Philip Corsi's doctoral thesis (Corsi, 1972) and in a number of other papers (e.g. Smith & Milner, 1981; Jones-Gotman, 1986; see Jones-Gotman, 1987 for a review). Corsi used four memory tasks; two designed to test verbal memory and two to test non-verbal memory. The verbal tasks involved the recall of consonant trigrams using a Brown-Peterson distractor technique, and the Hebb recurring digit task, a test of incidental learning (Hebb, 1961). The non-verbal tasks were an experimental analogue of Hebb's recurring digits using block tapping, and a test in which the patient was required to remember the position of a circle on a horizontal line, with and without distraction (Posner & Konick, 1966). Not only did Corsi find that patients with left temporal lobe resection did more poorly on the verbal memory tests than those whose right temporal lobe was removed, he also found that the degree of impairment was dependent on the extent of hippocampal removal. The converse was true for the non-verbal memory tasks, with patients who had undergone right temporal lobectomy showing deficits proportional to the extent of hippocampal removal. This implies two things: one, that the tasks used are critically dependent on the hippocampus, and two, that the degree of post-operative memory impairment is dependent on the extent of resection.

The paradigm, however, is not immune to criticism. Corsi had larger sample sizes on the side of the expected material-specific memory deficit, so that more right than left temporal lobectomy patients were tested on the non-verbal memory tasks. This gives greater statistical power to data on the side of the expected deficit. In addition, a large minority of cases (44%) were tested during the initial three weeks following surgery, with no reassurance that they were equally distributed between groups. Since the magnitude of memory deficit is much greater at three weeks than at one year post-resection (Milner, 1975), it is perfectly plausible that the increased deficit for patients with extensive resections is due to an over-representation of such patients in the 'early-tested' group. Furthermore, even if there were an equal distribution, reliable inferences could not be made due to the combination of relatively acute and stable lesions. In addition to these concerns, Corsi included a few cases of adult head injury. The onset of temporal lobe epilepsy following head injury is common in childhood, but much less frequent in adults. This means that there could be widespread brain damage in these adult cases, affecting many cognitive abilities in addition to memory (Loring et al., 1991).

In addition, attempts to replicate Corsi's work in similar populations have not been particularly successful, either using his memory tests (Rausch & Ary, 1990) or ones not used by Corsi but which had previously shown clinical sensitivity (Loring et al., 1991). Rausch and Ary (1990) administered the recurring digits and block-tapping task to patients following left or right temporal lobectomy. They found that patients with left resections performed normally on both measures, but patients with right temporal lobe resections performed slightly below normal on the verbal (but not the non-verbal) memory

task. The patients did show selective memory deficits, since patients with left temporal lobe resections were markedly impaired on the recall of a prose passage and the learning of novel word-pairs, whilst patients with right-sided removals were not. They concluded that these differences between the two studies were due to greater epileptogenic involvement of lateral neocortex beyond the resection line in Corsi's patients, since patients at MNI who had large resections had presurgical evidence of a more posterior seizure onset.

In addition, the conclusion that post-operative memory impairment is dependent on the extent of resection has not survived closer analysis. More recent work (Chelune, 1995) has instead suggested that post-operative memory impairment is related to the pre-operative level of function. Those patients with relatively preserved memory abilities prior to temporal lobectomy are those who suffer the greatest drop in memory function following surgery. A retrospective analysis of the data from 383 temporal lobectomy patients seen at MNI between 1960 and 1981 also indicated that extent of resection did not explain the performance of these patients on tests of memory function (Leonard, 1991).

In summary, it is widely accepted that left temporal lobectomy results in a verbal memory impairment, whilst non-verbal memory is impaired following right-sided removal, when compared to normal controls. However, this latter finding does not occur consistently, and concern has been voiced as to its continued orthodoxy (Baxendale et al., 1997). In addition, the finding of increased impairment with greater hippocampal resection, though generally robust in the hands of the group at MNI, does not appear to have been replicated outside that centre. This is probably due to differences in the patient populations, such as exclusion on the basis of low IQ, the proportion of patients with tumours

as opposed to hippocampal pathology, and the age at onset of the patients' epilepsy.

1.2 The Structure of the Hippocampal System

As has been discussed above, the integrity of the hippocampal system is of great importance for normal cognitive memory functions. In order to understand the way in which damage to this region can result in memory impairments, it is helpful to have an understanding of its structure.

The hippocampus (the word is from the Greek for seahorse, which it is said to resemble) is a cylindrical structure which forms a semicircle around the thalamus. It is located in the medial temporal lobe, medial to the temporal horn and beneath the anterior cistern (Figure 1.2), and can be divided into three main segments. From posterior to anterior these are the tail, the body, and the head, and these three regions are different in terms of their orientation as well as their shape.

When a frontal section (i.e. perpendicular to the antero-posterior axis) is examined under the microscope, it can be seen that the hippocampus is formed of two cortical laminae that are embedded into each other. These are the cornu ammonis (from the Latin for ram's horn) and the dentate gyrus. The cornu ammonis, along with the dentate gyrus, is a simple cortex (known as allocortex) (Duvernoy, 1988). The cornu ammonis is connected to the rest of the cortex (known as isocortex) by the subiculum, which is therefore a transition zone.

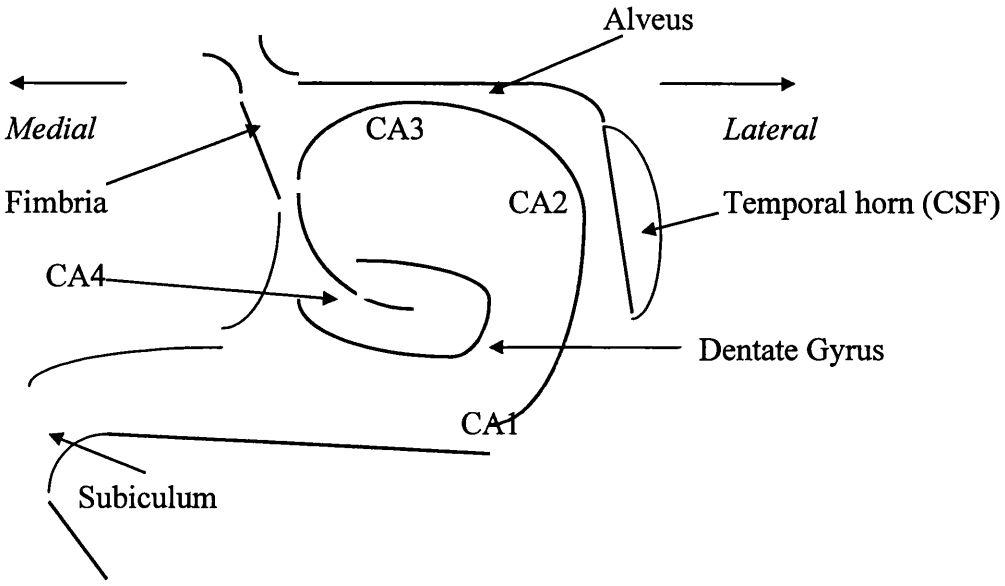

Figure 1.2 A stylized structure of the hippocampus showing the subfields of the cornu ammonis (CA1 - 4), the dentate gyrus, the alveus and fimbria, the temporal horn and the subiculum.

Frontal sections of the hippocampus also reveal a heterogeneous structure to the cornu ammonis that can be divided into four subfields. These were named by Lorento de No in 1934 (Duvernoy, 1988) and are known as CA1, CA2, CA3 and CA4. CA1 is linked to the subiculum, and with CA3 makes up most of the hippocampus proper. CA1 is selectively vulnerable to hypoxia and is sometimes known as the 'vulnerable sector' (Duvernoy, 1988). CA2 is smaller, and in some species is so indistinct as to be ignored (Brown & Zador, 1990) - however, it is clear in both humans and simians (Amaral, Insausti & Cowan, 1984). CA3 is found at the curve of the cornu ammonis where it enters the concavity of the dentate gyrus. CA2 and CA3 are similar in appearance, but there are fine unmyelinated fibres running through CA3, which are mossy fibres from the dentate gyrus (Duvernoy, 1988). CA4 is in close contact with the dentate gyrus and is frequently known as the hilar region, or the hilus. The side of the cornu ammonis abutting the ventricular cavity is covered by a thin lamina of white

matter called the alveus. This joins the fimbria which extends backwards into the fornix.

The dentate gyrus is concave and encloses the hilus. It is narrow and composed mainly of small neurons called granule cells, and, like the cornu ammonis and the subiculum, constitutes a functional unit (Duvernoy, 1988). Together, these three constitute the hippocampus proper.

Inputs to the hippocampus are numerous and arise mainly from the entorhinal cortex, which receives information from a wide variety of sources through the perirhinal and parahippocampal cortices. In the macaque monkey, the perirhinal and parahippocampal cortices provide as much as two-thirds of the cortical input to the entorhinal cortex (Insausti, Amaral & Cowan, 1987). These structures in turn receive input from widespread areas of neocortex, with the major perirhinal afferents being from visual areas, insular cortex and orbitofrontal areas (Suzuki & Amaral, 1994b). In contrast, the parahippocampal cortex receives input from polymodal association cortices, as well as a variety of frontal sites and the posterior parietal lobe (Suzuki & Amaral, 1994b). This indicates the position of these cortical regions as recipients of convergent sensory information (Jones & Powell, 1970). In addition, the projections from these regions to the entorhinal cortex are topographically organised, such that perirhinal cortex projects to the rostral two-thirds of entorhinal cortex, whilst the parahippocampal cortex projects to the caudal two-thirds (Suzuki & Amaral, 1994a).

The entorhinal cortex is also arranged topographically, such that lateral entorhinal cortex projects to caudal regions of the hippocampus, whilst more medial entorhinal cortex projects rostrally (Witter, Van Hoesen & Amaral,

1989). These inputs travel to the hippocampus via the perforant pathway, with two possible endings. The fibres either terminate in CA1, CA2 and CA3, or in the granule cell layer of the dentate gyrus. This latter target is the more densely innervated by the perforant path fibres, which have an excitatory action on the hippocampus. The dentate gyrus then sends projections to the pyramidal cells of CA4 and especially CA3 via the mossy fibres. These in turn send outputs via the alveus and the fimbria to the fornix, but also project on to CA1 via the Schaffer collaterals. Axons from CA1 also traverse the alveus and the fimbria, but there is a supplementary link to the subiculum which provides the major input to the fornix (Duvernoy, 1988).

Because of the functional link between these structures, the entorhinal cortex, dentate gyrus, cornu ammonis and subiculum are frequently known collectively as the hippocampal formation (although see Section 1.6.1 for an alternative definition). The major efferent pathway of this unit is via the fimbria to the fornix at the posterior end of the hippocampus, and from there to the anterior thalamus, either directly or via the mamillary bodies. There are also projections to cortical association areas via the entorhinal cortex (Duvernoy, 1988). The reciprocal connections between the entorhinal cortex and the perirhinal and parahippocampal cortices are strong and indicate a feedback system within these structures (Suzuki & Amaral, 1994a). In addition, the two hippocampi are joined by the hippocampal commissure. However, in primates these fibres are few and do not extend through much of the hippocampus (Amaral et al., 1984).

In the early 1970s, Anderson et al. (1971) suggested a lamellar hypothesis of hippocampal organisation. This states that . . .

'the four pathways successively activated when a stimulus is delivered to the entorhinal area, i.e. the perforant path, the mossy fibres, the Schaffer collaterals, and finally the alvear fibres of CA1, are all oriented in the same direction, namely nearly transversely to the longitudinal axis.'

This implies that the hippocampus is organised in parallel lamellae, and that these small strips could function independently, albeit with some lateral inhibition or excitation from neighbouring lamellae. However, this hypothesis has been shown to be incomplete, in that there are far more longitudinal fibres connecting the lamellae than previously thought (Amaral & Witter, 1989). Studies using the anterograde tracer *Phaseolus vulgaris* leucoagglutinin (PHA-L) have shown that the projections in the longitudinal axis of the hippocampus are at least as extensive as those in the transverse. Indeed, some of these projections appear to be specifically organised to integrate distant regions of the hippocampus (Amaral & Witter, 1989). This means that when trying to understand the structure and function of the hippocampus it is highly important to realise its three-dimensional nature. This also applies to the interpretation of data from *in vitro* hippocampal slice experiments.

1.3 Epilepsy

1.3.1 Adult Epilepsy

Epileptic seizures are not uncommon - as many as one person in twenty will experience at least one seizure during their lifetime (Kolb & Whishaw, 1996) - but the occurrence of multiple seizures is more rare. Epilepsy is a condition in which there are recurrent abnormal electrical discharges within the brain, often associated with motor movements and disturbance of consciousness.

The causes of these abnormal discharges are not fully understood, but they fall into three general categories. Firstly, seizures may occur in a normal brain with a transient change in brain chemistry such as hypoglycaemia. Secondly, the brain may appear structurally normal but nonetheless have a permanent tendency to seizures owing to some unknown biochemical or genetic abnormality. Finally, a definite structural abnormality can be the precipitating factor (Jackson, 1993).

It is this last category which has proved most informative for the investigation of memory function. Given the importance of the medial temporal lobes for memory function, any patient with seizures originating from these areas would be likely to suffer from memory problems. Patients with temporal lobe epilepsy (TLE) make up about a quarter of all epilepsies (Hauser et al., 1991; Hauser, 1992).

The pathology in TLE can vary considerably, but is most often associated with damage to the medial temporal lobe. Although this pathology primarily affects the hippocampus, the amygdala and surrounding regions are also frequently involved (Wieser et al., 1993). The histopathologic damage is characterized by a loss of pyramidal cells from the CA1 and (to a much lesser extent) CA3 regions, and also by a loss of interneurons from the hilus (CA4) (Gloor, 1991). When damage to these areas results in the loss of more than 50% of the neurons, the pathology is described as medial temporal sclerosis (MTS) (Babb & Brown, 1987). This neuronal loss is commonly associated with gliosis, which is predominantly an increase in astrocytes (Meldrum & Corsellis, 1984), and axonal sprouting by the surviving neurons (Sutula et al., 1989). The mechanisms by which MTS is caused are uncertain (see Section 1.2), but one

possibility is that MTS is a reaction to injury that results in neurons undergoing apoptosis (McNamara, 1992) and as a consequence there is lesion-induced axonal sprouting (McKinney et al., 1997). However, it has been shown (in rats) that MTS is not a progressive disease, and that although rats with experimentally-induced hippocampal epilepsy do have neuronal damage in CA1, this is no worse in animals who have had many more seizures (Bertram et al., 1990).

1.3.2 Childhood Epilepsy

Epilepsy is the most common brain disease of childhood, with a prevalence of between 3 and 6 per 1000 and an incidence of between 43 to 152 per 100,000 (Forsgren, 1996). About 20 to 25% of childhood epilepsies will involve partial seizures (such as temporal lobe epilepsy), which can either be complex (CPS) in which consciousness is either altered or lost, or simple (SPS) in which this does not happen. Both types of partial seizure generally involve psychic phenomena such as déjà vu coupled with motor phenomena such as lip smacking, chewing or swallowing (Brett & Neville, 1997; Aicardi, 1992). Automatisms such as repetitive fumbling with buttons or carrying out tasks such as sweeping or cleaning may also be seen.

The causes of TLE are not always clear, although complex febrile convulsions in infancy are an important contributory factor (Ounsted et al., 1966; Ounsted et al., 1987). There seems to be a strong genetic factor related to TLE following complex febrile convulsions (Brett & Neville, 1997). This is shown by the increased incidence of seizures in siblings of TLE patients who had a complex febrile convulsion (an incidence of 30%), compared with siblings

of TLE patients with brain insults such as birth injury or meningitis (9-10%) or no obvious aetiology (2%). The genetic factor appears to be an inherited tendency towards febrile convulsions. This factor also plays a part in the prognosis of TLE patients. Other factors such as an IQ below 90 or an onset of seizures before the age of about two-and-a-half are associated with a poor prognosis, but if a history of febrile convulsions in a first-degree relative is also present, this is not the case (Lindsay et al., 1979).

Treatment for TLE is generally anti-epileptic drug therapy, either in combination or as monotherapy. However, when Kotagal and colleagues (Kotogal et al., 1987) studied a group of childhood TLE patients for five years, it was found that the seizures of only 18% of patients were fully controlled, and none were seizure-free off drugs. This suggests that childhood TLE is frequently intractable to medication. As a result, it is now accepted that surgery for relief from seizures should be considered at an earlier age, certainly before adolescence (Brett & Neville, 1997).

1.4 Temporal Lobectomy in Childhood

1.4.1 Surgical Intervention

It has been recognized for more than 20 years that, in marked contrast to the bleak outlook for those children who do not have surgery, temporal lobectomy carried out on children with medically refractory epilepsy can provide an effective treatment. Davidson and Falconer (1975) published a study of outcome following temporal lobectomy in children under the age of 16. Their

study involved a group of 40 patients with drug-resistant epilepsy, who were followed for between one and 24 years after surgery. More than half of the patients had a diagnosis of MTS, and of these, 58% became seizure-free post-operatively. In addition, 80% of those with a hamartoma or small astrocytoma (a further quarter of the series) were seizure-free at follow-up. Falconer (1972) commented on the excellent outcome in paediatric temporal lobectomy and concluded that it was more successful than in adult patients. It has been shown, however, that those patients who do not have surgery and whose epilepsy continues into late adolescence, and beyond, have a significantly poorer outlook (Lindsay et al., 1984). Lindsay and colleagues (1984) found that a number of patients in their series deteriorated significantly between the ages of five and fifteen. They recommended that in cases such as these surgery should not be delayed; indeed, temporal lobectomy should not be considered only as a last resort but as a sensible alternative to drug therapy in cases where there is obvious drug resistance. In support of this, the authors report

'When operation was performed in this series, and in other children we have studied, we saw a quite remarkable reversal of social, intellectual and characterological (*sic)* handicap.'

They concluded that all children still suffering from TLE at school-leaving age should be reviewed as candidates for surgery. As with adult epilepsy surgery, however, there has yet to be a controlled, randomized trial comparing surgical treatment with optimal medical and psychosocial intervention.

There is still little information, however, about surgical outcome in patients below the age of 12 (Davidson & Falconer, 1975; Whittle et al., 1981). However, Duchowny and colleagues (Duchowny et al., 1992), in a series of sixteen such children, found that surgery in the first decade of life could be highly beneficial, provided the patients were carefully selected. They did not

concur with the suggestion that surgery in childhood is ultimately more successful than in adults, and pointed to a study whose only conclusion was that psychosocial rehabilitation was better in children than adults (Jensen, 1976). However, another study of 50 patients below the age of 18, some of whom were operated on as young as seven (Meyer et al., 1986), demonstrated clear benefits gained by early surgical intervention in terms of social outcome. This study also showed a potential for improvement in some components of the Wechsler Intelligence Scale, provided the operation took place within a few years of the onset of seizures. However, it was not stated which components were improved.

Despite this encouraging trend, there are also clear disadvantages of temporal lobectomy. This is not only due to the possibility of physical side-effects such as hemiparesis or visual field deficits, but also the increased chance of cognitive or memory deterioration. The effects of right and left temporal lobectomy on memory in adults have been outlined in Section 1.1 (Milner, 1968a; Milner, 1968b; Novelly et al., 1984; but see Rausch, 1991), but this has only been in comparison to normal subjects. Temporal lobectomy can also result in a decrease in memory function from pre-operative levels (Chelune, 1995). Those patients most at risk for this memory decrement following surgery are the patients with the greatest pre-operative memory abilities. Patients who have significant memory impairments before surgery do not appear to suffer much further loss as a result of temporal lobe removal (Chelune, 1995).

The picture is less clear in children for a number of reasons. As well as the small number of such research studies (Fedio & Mirsky, 1969; Meyer et al., 1986; Adams et al., 1990; Szabó, Wyllie, Stanford et al., 1998), patients who have had temporal lobe surgery have not always been grouped separately from

those with extra-temporal resections, and children are frequently not differentiated from adolescents. The range of neuropsychological tests has also been limited, concerned mainly with IQ changes with little attention given to memory, despite the importance of the medial temporal lobe structures in subserving memory functions. Even when memory has been assessed, the test of choice has most often been the Wechsler Memory Scale (WMS) which has a number of limitations when used with patients, not least of which being its inability to clearly differentiate between verbal and non-verbal memory deficits. This inability may be due not to the insensitivity of the test, but to the unequal distribution of verbal and non-verbal subtests. However, a recent multicentre study in adults suggested that the non-verbal subtest of the WMS was not helpful in lateralizing non-verbal memory function (Barr et al., 1997). In addition, in the test's original form there were no measures of delayed recall, though all centres have now built in delayed recall scores (Milner, 1975; Parkin & Leng, 1993). It is also difficult to assess memory function in children owing to the paucity of suitable tests which are both developmentally sensitive and adequately standardized for different ages.

One exception to this is the study by Adams and colleagues (Adams et al., 1990) which examined 44 children treated by temporal lobectomy before their sixteenth birthdays. They measured verbal memory, using the Verbal Paired Associate Learning Test (VPAL) and the Story Recall test (also known as Logical Memory) of the WMS, both immediately and after a one hour delay. In addition, they used the Rey-Osterrieth figure to assess non-verbal memory. In both domains adequate normative data were either collected or already available. No difference was found between pre- and post-operative assessment

for IQ scores (in contrast to the improvement seen in adults [Milner, 1975]) or non-verbal memory, and verbal memory declined after surgery only in the left temporal lobectomy group. As a result they concluded that although there was clearly a risk of verbal memory deficit following left temporal lobectomy, this had to be set against the effects of continuing seizures on cognition and memory. However, their patient population was not made up entirely of TLE patients. There were nine (20%) who had some other form of pathology such as tuberous sclerosis or cortical dysplasia which may have resulted in damage outside the temporal lobe. Therefore their data need careful interpretation and should not be taken as being definitive.

Psychosocial outcome variables have only rarely been studied. In one such study, health-related quality of life was assessed using the Child Health Questionnaire (CHQ), which is a valid and reliable testing instrument (Gilliam et al., 1997). Whilst the parents of the children studied were generally satisfied with the outcome of surgery (85% satisfied), the children themselves reported significantly lower scale scores than age-matched controls in the domains of physical function, general behaviour, general health, self-esteem, emotional impact on parents, and time impact on parents. However, it is unknown whether this represents a change in the quality of life following surgery, because the questionnaire was not given pre-operatively.

1.4.2 Pathology of the Resected Temporal Lobe

As mentioned previously, the most frequently found lesion in pathological surveys of resections in all age groups is MTS, and this often presents as the only pathology (Bruton, 1988). Indeed, it accounts for up to 65% of all cases in

various series (Babb & Brown, 1987; Falconer, 1970) and in Bruton's review was the only pathology in 43% of cases. However, it has been suggested that in children it is more usual to see MTS in conjunction with some other lesion (Jay et al., 1993), the so-called 'dual pathology group' (Lévesque et al., 1991). Adams and colleagues (Adams et al., 1990), however, found MTS as a lesion secondary to other pathology in only three patients (7%) of their series of 44. The difference between these studies is likely to be patient selection, since patients with definitively identified MTS may be preferred for surgery - MTS will therefore be found more frequently in the post-surgical specimen. In addition, children have been shown to exhibit a higher proportion of neoplastic and malformative lesions than do adults (Jay et al., 1993).

As mentioned above, early febrile convulsions have a high association with TLE, and a history of these seizures is almost invariably associated with MTS in the resected specimen (Sagar & Oxbury, 1987). Of course, this does not imply that all febrile convulsions result in MTS. In a long-term follow-up study of 154 children admitted to hospital because of febrile convulsions, only nineteen developed epilepsy subsequently (Tsai & Hung, 1995). There must therefore be other factors involved in the aetiology of TLE following a febrile convulsion.

Also of interest are dysembryoplastic neuroepithelial tumours (DNET) which have only been described relatively recently (Daumas-Duport et al., 1988) although they may have been identified earlier by Cavanagh (1958), who referred to them as "certain small tumours of the temporal lobe". These are moderately common, highly treatable causes of refractory temporal lobe

epilepsy and tend to have a good prognosis with no evidence of recurrence (Jay et al., 1993).

1.5 Epilepsy and Research into Memory

The relationship between epilepsy and memory dysfunction has been of long-standing scientific interest. It is now well known that the areas of the brain which are most epileptogenic are those which are integral to normal memory function, i.e. the medial temporal lobe region including the hippocampus (Temple, 1997). Patients with TLE are particularly suitable subjects for memory research because their epilepsy is frequently well lateralized to one temporal lobe or the other, as determined by electroencephalographic (EEG) and neurological techniques. This often results in material-specific deficits in memory performance, such that left temporal lobe damage results in a verbal memory deficit, whilst damage to the right temporal lobe disrupts learning and retention of nonverbal memoranda (Delaney et al., 1980; Loring et al., 1988a). However, this latter result is not always found (Rausch, 1991; Loring et al., 1991; Barr et al., 1997).

Another reason for the suitability of patients with TLE for memory research is that a common treatment for intractable seizures (i.e. those which are persistent and not alleviated by anti-epileptic drugs) is unilateral temporal lobectomy. This also produces memory deficits as outlined above which are generally more clear-cut than those described pre-operatively, but it is not known clearly whether it is the surgery or pre-existing factors that underlie the

memory problems. It is known, however, that for a period following surgery of about six months (and longer if seizures continue), the operation exacerbates a pre-existing memory problem. In contrast, however, post-operative improvements in memory abilities have been noted (Milner, 1975; Rausch & Crandall, 1982).

Memory research in children with TLE is rare, but at least one study has reported memory deficits similar to those demonstrated in adults (Jambaqué et al., 1993). This study investigated the cognitive performance of 60 epileptic children (mean age 10.9 years, mean age at onset of epilepsy 7.1 years) and 60 normal subjects with the Signoret Memory Battery. Of the 42 epileptic patients who had partial epilepsy, in only 18 was it localized to one of the temporal lobes (six right and twelve left). Memory testing consisted of the recall of a short passage of prose and of a complex geometric figure, as well as of a list of words and a list of abstract designs. There were also verbal and figural recognition tests, and paired-associate tasks for both words and figures. It was found that the mean score of patients with epilepsy was significantly lower than that of the controls on all the memory tasks, but there was also a difference between the right and left TLE patients. When all the visual tasks were grouped together to give one score, those with right-sided TLE did significantly worse than those whose seizures originated from the left. This was reversed for a 'verbal memory' score. However, no difference was found between the two groups for intelligence. This indicates hemispheric specialization for memory functions, which is comparable with that previously found in adults.

However, neither pre- nor post-surgical patients can be studied without limitations in experimental design. Studying patients after they have undergone

temporal lobe resection can produce bias in the results in several ways. Firstly, it is possible that patients are selected for radical resection on the basis of a more serious preoperative memory impairment. Secondly, those with relatively preserved preoperative memory ability may have more of their hippocampus spared through smaller resections. This is true for patients at some North American centres, but may be the reverse for some of the UK centres, where that group of patients receives a much smaller resection if their memory is already poor. Neither philosophy appears to affect surgical outcome, however, since it has been shown that there are no significant differences in outcome between patients with a small and those with a large resection (Leonard, 1991). The extent of both temporal neocortical and hippocampal resection, however, has been used to demonstrate the dissociations within different domains of memory function (Smith & Milner, 1981; Jones-Gotman, 1987; but see Leonard, 1991).

Secondly, the size of the neocortical removal varies with the extent of hippocampal resection, and any proportional deficit that is seen may be due to neocortical and not hippocampal excision. In addition, dysfunctional hippocampal tissue may have a deleterious effect on the performance of surrounding tissue in the temporal lobe, so that removal does not necessarily produce a significant loss of memory function. In fact it has been shown that altered neuronal activity in the hippocampus may disrupt certain forms of learning more than hippocampal ablation (Solomon et al., 1983). A further problem lies in the small sample sizes, which precludes the use of sophisticated multivariate analysis techniques, and in the large number of statistical tests performed, which increase the likelihood of a Type I error (a false positive).

Studying the relationship between memory impairment and hippocampal damage without the confound of surgical intervention, however, has also proved difficult. Theoretically, the correlation of presurgical memory impairments with histological analysis of sclerotic hippocampi should be a powerful technique (Sass et al., 1992a, 1992b; Oxbury & Oxbury, 1989). However, these studies have also produced somewhat contradictory findings. Sass and colleagues (Sass et al., 1992a) compared preoperative performance on a number of neuropsychological tests of memory with the volumetric neuronal cell densities (mean cell count per cubic millimetre (mm^3)) in various hippocampal subfields, as measured following temporal lobectomy. They found that statistically significant correlations existed only between the percentage retention score of the Logical Memory subtest (%LM) and hippocampal neuron loss in CA3 and the hilus for adult patients with left temporal lobe seizure foci. However, Oxbury & Oxbury (1989), who were also measuring neuronal densities, found that patients with MTS had a reduced performance on logical memory and VPAL regardless of the side of pathology. By contrast again, Saling and colleagues (Saling et al., 1993) found that only adult patients with histologically confirmed left MTS were impaired on the VPAL, but Miller and colleagues (Miller et al., 1993) showed that any left temporal damage, sclerotic or not, caused verbal memory impairment, but only in the delayed condition. This problem with replication is likely to be mainly a factor of patient selection, since some patients will have had unknown pathology, either in the ipsilateral temporal lobe, or elsewhere in the brain, or both (Marsh et al., 1997). In most of these papers, patients were identified as having unilateral temporal lobe epilepsy on the basis of neurological and EEG findings alone, which generally lateralizes

correctly but is not sensitive enough to discern bilateral pathology in cases with a unilateral seizure focus. These studies, moreover, have rarely quantified pathology in the temporal lobe outside the hippocampus of the resected specimen, and of course cannot examine the pathology of the non-resected side. Since it has been found that as many as 50% of TLE patients have bilateral temporal lobe pathology (Margerison & Corsellis, 1966) this could have a profound effect on correlative efforts such as those mentioned above.

Furthermore, the approach described above is reliant on the patients being studied going forward to have surgery, so that MTS can be definitively identified by neuropathological examination of the excised tissue. When adequate seizure control can be obtained through medication, or when localization of the focus is not precise enough to allow surgical intervention, such definitive identification may not be made. In such cases it is useful to be able to measure the pathology of the hippocampus and surrounding temporal lobe non-invasively, and furthermore, to establish the normality or otherwise of other brain tissue, including the contralateral temporal lobe. One non-invasive approach to investigating the brain of patients (and normals) is to use magnetic resonance imaging and spectroscopy techniques. These are introduced in the next section.

1.6 Magnetic Resonance Imaging and Spectroscopy

Magnetic resonance imaging (MRI) and spectroscopy (MRS) techniques have been used clinically since the mid-1980s to investigate brain structure and

biochemistry. MRI has provided an enormous increase in tissue contrast when compared to X-ray computed tomography (CT), and indeed, the level of detail and contrast between grey matter, white matter and abnormal tissue that is now obtainable with MRI was only previously available at post mortem. However, in patients with TLE, visual inspection of magnetic resonance (MR) images initially produced very variable findings, the apparent incidence of MTS ranging from 8% of cases to 70% (Brooks et al., 1990; Convers et al., 1990; Kuzniecky et al., 1987; Dowd et al., 1991). This is because the lesion can be subtle and may require an optimized scanning procedure for detection (Jackson et al., 1993; Ashtari et al., 1991), but also because of the subjective nature of visual interpretation alone. This has led to the development of quantitative MR techniques as an objective way of assessing hippocampal and temporal lobe pathology.

1.6.1 Hippocampal Volumetry

Because MTS causes a loss of cells in the hippocampus and surrounding areas, it is helpful for the diagnosis and lateralization of the epileptic focus that the volume of these regions be calculated. MRI can be used to quantify the volumes of a number of temporal regions, such as the hippocampal formation (which consists of the hippocampus proper, the subiculum, the dentate gyrus and the fimbria, but see Section 1.2 which describes the functional unit) (HF), the parahippocampal gyrus (PHG) and the amygdaloid body (AM) (Jack et al., 1989). It has been found that volumetric measures of the HF and AM are highly sensitive in providing lateralization of epileptic seizure foci (Cendes et al., 1993a); indeed, these have been reported to provide correct lateralization of the

seizure focus of all patients in one study which used the Wada test to confirm the focus (Loring et al., 1993). Surgical outcome at one-year follow-up is also good in cases where the hippocampus to be resected has been shown to be small using MR-based volumetry, although the relationship between outcome and the volume of the non-operated hippocampus is of borderline significance (Jack et al., 1992).

A history of febrile convulsions has been shown to be associated with smaller hippocampal volumes ipsilateral to the seizure focus, though not the length of time that the patient has had seizures (Cendes et al., 1993a; Trenerry et al., 1993b). It has also been shown, by studying patients either with MTS, an extrahippocampal temporal lobe lesion or an extratemporal structural lesion, that significantly low HF volumes can differentiate between patients with MTS and those with other lesions (Watson et al., 1997). It appears that patients without pre-existing MTS can suffer epilepsy for many years without apparent damage to the hippocampus (Watson et al., 1997).

The ratio (side ipsilateral to focus/side contralateral to focus) of the hippocampal volumes has been reported to show a negative correlation with neuronal densities in all hippocampal subfields except CA2 (Lencz et al., 1992). This is consistent with earlier pathological data from cases of TLE showing that all subfields of the hippocampus, except for CA2, were affected by MTS (Babb & Brown, 1987). A subsequent study, however, which used a three-dimensional cell counting technique, found that a small HF volume was associated with pathology in all hippocampal subfields but not the dentate gyrus (Van Paesschen et al., 1997). However, this latter study did not use neuronal density as a measure of pathology, since this is subject to changes in the reference volume

due to the disease process, i.e. as a result of tissue shrinkage the neuronal density may actually be higher in pathological cases than it is in normal controls. Because of this, a ratio of glial density to neuronal density (GD/ND) was used, which has the advantage of being dimensionless. Van Paesschen and colleagues (1997) suggested that the total number of neurons in a hippocampal subregion might actually be a better correlate with MR-based HF volume, rather than the GD/ND ratio for one section. However, since the material in the study was obtained from partial surgical resections (i.e. the whole hippocampus was not removed), it was not possible to confirm this.

Studies of grey and white matter volumes both within and outside the temporal lobe have also been performed, and suggest that there is dysmorphic tissue outside the epileptogenic region. Unilateral left TLE patients have been shown to have bilateral reductions in temporal lobe grey matter volume, grey matter thickness and white matter surface area when compared with normal controls (Lee et al., 1995), even though hippocampal and parahippocampal volumes were not included in the analysis. In a more recent study, bilateral reductions were also found in frontoparietal grey matter volumes as well as temporal lobe white matter volumes in 14 adult men with intractable TLE (Marsh et al., 1997). The reduced white matter volumes may be a consequence of generalized seizures in this group causing a disruption of myelination (Breier et al., 1996a).

MR-derived HF volumes have also been used to link patients' impaired memory function with their damaged hippocampi. Poor performance on tests of verbal learning and memory has been shown to correlate highly with HF volume loss in post-herpes simplex encephalitis patients (Yoneda et al., 1994), while in

TLE patients left HF volume reduction has been associated with a poor WMS %LM score (Lencz et al., 1992). Somewhat surprisingly, given the findings of Sass and colleagues (Sass et al., 1992a; Sass et al., 1992b) who showed a link between reduced verbal memory and hippocampal cell loss (using the verbal Selective Reminding test (vSRT)), it has also been shown that performance on the vSRT correlates with left temporal lobe volume loss and *not* left HF volume loss (Lencz et al., 1992). Lencz and colleagues, who claimed that it demonstrated the relative strengths of the two methods, did not acknowledge this apparent contradiction between two papers from the same research centre. However, it has been shown in a 3-D cell counting study that hippocampal volume loss in TLE patients (as measured by MRI) is associated with pathology in hippocampal subregions CA1, CA2, CA3 and the hilus (Van Paesschen et al., 1997). Since the papers by Sass and colleagues (1992a, 1992b) indicated a correlation between HF neuronal densities and performance on the vSRT, this would imply that HF volume loss should also correlate with the vSRT.

In addition, hippocampal volume data are useful in predicting memory impairment following temporal lobectomy (Trenerry et al., 1993a). The degree of left hippocampal atrophy (based on the difference between the left and right HF volumes) correlated with the postoperative change on the WMS %LM score in this study. This implies that the more atrophied the left hippocampus, the greater the improvement in verbal memory after surgery, although this will not hold if there has been bilateral atrophy since it is a difference score which is being used. The analogous correlation was not seen for the volume of the right HF, where learning of designs, but not their recall, was affected. A subsequent study of 33 men and 42 women showed that this association was related to

gender (Trenerry et al., 1995). Although the verbal memory outcome of both men and women was predicted by the difference between right and left HF volumes, men showed a significant decline following left temporal surgery, whilst women showed a significant improvement.

Hippocampal volumes do not seem to be associated with scores on tests of higher cognitive function such as the Wisconsin Card Sorting Test (Trenerry & Jack, 1994), although there have been some instances of hippocampal volumes correlating with abilities such as confrontation naming (Shear et al., 1997).

Most studies that have used hippocampal volumetry as a quantitative tool have involved adult subjects. There have been a few developmental studies, however. One of these was of 99 normal children between the ages of 4 and 18 (Giedd et al., 1996). The volumes of the temporal lobe, amygdala and hippocampus were measured, and it was concluded that there were no significant volume differences between sexes, once a 9% correction for larger total cerebral volume in males had been accounted for. However, there were sex-specific maturational changes, such that the volume of the left amygdala increased significantly only in males, whilst the volume of the right hippocampus increased significantly only in females. The study supports a previously reported MRI study of young adults, indicating that females have proportionately larger HF volumes (Filipek et al., 1994). However, this does not seem to be supported by a different volumetric analysis of HF volumes in 30 children, this time between the ages of 7 and 11 (Caviness et al., 1996). This study suggested that the volumes of the hippocampi in girls are disproportionately large compared to boys, but failed to find any age-related change in volume.

Neither of these studies used optimal techniques for the measurement of HF volumes. The former used slices in the coronal axis with a thickness of two mm - both of these factors can result in increased partial volume effects and the unintended inclusion of cerebrospinal fluid (CSF) in the measured hippocampal volume. The coronal axis is not the best axis to use because it is not perpendicular to the long axis of the hippocampus. This increases the likelihood of both hippocampus and CSF being present in the same pixel, especially if the slice is thick, resulting in poor contrast and a more difficult and less accurate measurement. In addition, the hippocampus was measured until the anterior part of the mamillary bodies was seen, which may have left a large portion of the head of the hippocampus unmeasured. It is perfectly possible to measure the hippocampus past this point and obtain reliable volumes (Van Paesschen, 1997). The study of Caviness and colleagues (Caviness et al., 1996) used slice thicknesses of three mm, again in the coronal axis which has the problems outlined above. Finally, neither study used the optimal parameter to correct for head size, which is intracranial volume (ICV) (Free et al., 1995). In both the above studies, the HF volumes of girls were increased by 9% to bring them to the level of boys. However, this does not take account of the age-related increase in head size. Since people with larger heads tend to have larger hippocampi, this may well account for the stated age-related increases in HF volume.

The accuracy and reproducibility of HF volume measurements have improved greatly since the introduction of the technique. It is common for patients to be assessed using a ratio of ipsilateral HF volume to contralateral HF volume, since this is regarded as the most reliable interobserver measure (Bergin

et al., 1994). However, it has been noted that the use of a HF volume ratio as described above does not always identify patients with MTS, since patients with bilateral MTS will have normal ratios (Jackson et al., 1994). Using normalised absolute HF volumes can correct for this. Since current image acquisition sequences and measurement techniques have led to intraobserver variabilities of 1.2% and interobserver variabilities of 3.4% being cited (Cendes et al., 1993b) they can safely be assumed to be a valuable clinical tool for assessing the extent of hippocampal pathology.

1.6.2 T2 Relaxometry

Another feature of MTS is elevation of the MR T2 relaxation time, which is a parameter measured from the water protons that give rise to the MRI signal. While this elevation may enable abnormalities to be seen on visual inspection of conventional T2-weighted images, the sensitivity of detection of such abnormalities can be increased by quantifying this parameter using T2 relaxometry (Jackson et al., 1993b). Jackson and colleagues showed that an increase in T2 relaxation times from the normal range (99 - 106 ms) to 116 ms or more was a constant feature of MTS.

In a cell counting study, T2 has been shown to be associated with pathology in regions CA1 and the hilus of the hippocampus (Van Paesschen et al., 1997), which implies a different neuropathological basis for the HF volume and T2 changes seen in MTS (See Section 1.6.1). Since the study used a GD/ND ratio, the elevation of T2 could be due to changes in glia such as the density of their processes, their size, or the amount of glial fibrillary acidic protein (GFAP) (O'Callaghan, 1993; Hawrylak et al., 1993; Krishnan et al., 1994). All three glial

changes are indicative of neuronal damage in vivo, but GFAP in particular has been shown to be a sensitive quantitative marker of neuronal cell injury (O'Callaghan, 1993). However, when Van Paesschen and colleagues examined the relationship of T2 with GD and 1/ND separately, they found that T2 did not correlate with GD when the effects of 1/ND had been partialled out. This suggests that an elevated T2 is not a marker of gliosis, at least when GD is used as the measure. This is reflected in two patients in Van Paesschen and colleagues' study (Van Paesschen et al., 1997), who had normal T2 values despite markedly abnormal GD/ND ratios.

Despite this different neuropathological basis for the reduction of HF volume and the increase in hippocampal T2 relaxation time, the two measures of hippocampal pathology do closely correlate (Van Paesschen et al., 1995). This is not surprising, since both hippocampal volume loss and increased T2 signal are classic features of MTS on MRI (Jackson et al., 1993a). However, the correlation also holds for patients whose TLE is caused by pathology other than MTS, such as a foreign tissue lesion, amygdala sclerosis, or end-folium sclerosis (Van Paesschen et al., 1995).

Whilst the 1995 study of Van Paesschen and colleagues showed a clear association between T2 elevation and HF volume loss in TLE cases, it is by no means certain that this relationship will hold for other forms of pathology. For example, patients with Alzheimer's disease demonstrate severe hippocampal atrophy but only mild prolongation of T2 (Pitkänen et al., 1996), indicating that different pathologies may affect T2 in different ways, in this case by the accumulation of iron within the hippocampus. Furthermore, it should be noted that T2 reflects the integrity of residual tissue, which may or may not be

abnormal, whilst HF volumes are effectively measuring what has been lost. It is therefore feasible for the hippocampus to be atrophic but the remaining tissue to have a normal T2. In addition, at this centre (Great Ormond Street Hospital/Institute of Child Health) T2 is measured from a single slice only. This means that regions which show atrophy on volume measurements may not be those whose integrity is being assessed by T2 relaxometry.

T2 relaxometry has been shown to be a stable measure, unaffected by continued seizures (Grünewald et al., 1994). The T2 relaxation time also appears to be unaffected by a seizure occurring in the hour prior to scanning, which implies that it is a measure of chronic and fixed abnormalities rather than post-ictal oedema (Grünewald et al., 1994). Good interobserver reliability has also been demonstrated, both in normal and abnormal hippocampi (Jackson et al., 1993b).

Of the limited research so far conducted, T2 appears to be a good correlate of verbal memory in adult TLE patients, measured by immediate recall of the WMS Logical Memory subtest (LM-R) (Kälviäinen et al., 1997). T2 has also been used in a study of adult patients following temporal lobe surgery in conjunction with VPAL (Incisa della Rocchetta et al., 1995). This showed a verbal memory impairment following left-sided surgery as predicted by previous work, but also a verbal memory impairment in a subset of patients with *right*-sided surgery, although only after a delay (90 minutes). It transpired that this sub-group also exhibited left-sided T2 abnormalities that could account for their verbal memory deficits, and they presumably had pre-existing bilateral pathology. This study demonstrates the value of measuring the integrity of the

non-operated temporal lobe, since without this knowledge results such as these will lead to very misleading interpretations.

In another study using the VPAL, however, two unexpected groups were found (Loftus et al., 1997). These were patients with impaired VPAL performance but normal left T2, and a group with normal VPAL performance but highly abnormal T2. On investigating the aetiology of these cases it was discovered that the former group had a history of head injury or cerebral infection, whilst the latter group had febrile convulsions and early onset of seizures. The first group was presumed to have global diffuse damage which was affecting performance through mechanisms such as impaired attention. However, it was suggested that the second group represented patients who had reorganised their verbal memory owing to early insult, a suggestion which has since received more detailed support (Wood, Saling, O'Shea et al., 1998).

1.6.3 Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy (^{1}H MRS) is a technique that provides biochemical information about the tissue under examination. It has been reported previously that ^{1}H MRS can detect abnormalities preoperatively in the temporal lobes of patients with TLE (Ng et al., 1994; Connelly et al., 1994). The technique provides information about brain abnormalities through study of the signals from N-acetylaspartate (NAA), creatine and phosphocreatine (Cr), and choline-containing compounds (Cho). Since these metabolites are found in the brain in far smaller concentrations than the water that is used for structural imaging and for hippocampal volumes and T2 data, the spatial resolution of the technique is correspondingly lower. Information is therefore gathered from a

large (commonly 2 x 2 x 2 cm) voxel within the temporal lobe. It is widely believed that almost all the NAA in the brain is neuronal (Koller et al., 1984; Moffet et al., 1991; Urenjak et al., 1992; Urenjak et al., 1993), so it is accepted that a fall in the NAA signal reflects neuronal loss or damage. This is consistent with the changes observed in the spectra of children and adults with epilepsy (Connelly et al., 1994; Cross et al, 1996), where neuronal loss might be expected. In addition, investigations of patients with epilepsy have shown increases in Cr and Cho signals, which on the basis of cell studies (Urenjak et al., 1992; Urenjak et al., 1993) may reflect reactive astrocytosis (Connelly et al., 1994; Gadian et al., 1994). The NAA/(Cho+Cr) signal intensity ratio, therefore, provides an index of regional cellular pathology. For the studies described in this thesis, the voxel is positioned within the medial temporal lobe such that the hippocampus makes only a minor contribution. It is therefore valid to use the ^{1}H MRS ratio as a measure of diffuse temporal lobe pathology, which is over and above the hippocampal damage seen on volumetric analysis and T2 relaxometry.

Only a few studies have examined the relationship between cognitive function and ^{1}H MRS data in epilepsy, although there have been a number of investigations in other diseases (Meyerhoff et al., 1993; Hohol et al., 1997). The technique was used in the research with temporal lobe surgery patients outlined above (Incisa della Rocchetta et al., 1995), with similar results as found for T2. Recently ^{1}H MRS was used to investigate the relationship between temporal lobe pathology in unoperated children with TLE and performance on tests of verbal and nonverbal intelligence and memory function (Gadian et al., 1996). This study demonstrated a significant relationship between the observed NAA/(Cho+Cr) signal intensity ratios from the left temporal lobe and verbal IQ,

and likewise between the right temporal lobe and nonverbal IQ, such that the greater the degree of temporal lobe pathology, the lower the cognitive performance. In addition, a relationship was found between the VPAL test and the ^{1}H MRS ratio from the left temporal lobe, highlighting the role of the left temporal lobe in this task.

1.7 Aims of the Study

The main theme of this thesis is to determine whether children with TLE suffer from selective memory problems, and if so, whether this is related to different measures of hippocampal and more diffuse temporal lobe pathology.

The study of temporal lobe pathology has been transformed by the development of techniques which enable the quantification of damage non-invasively. Prior to the introduction of these methods, pathology was assessed using surgical specimens or was assumed following a diagnosis. Now it is possible to investigate both temporal lobes and to analyse any change in structure that may occur on the operated and non-operated side over time. Children with TLE are an understudied population and these techniques have made investigation of this group much easier.

The main questions to be asked are as follows:

1. What is the relationship between HF volumetry, T2 relaxometry and NAA/(Cho+Cr) ratios in children with TLE, and how does this compare to the relationship seen in adults?

HF volumes have not previously been reported in the paediatric TLE population, and it is not certain that the pre-existing adult norms will be of use with these subjects. In addition, it is unknown to what extent T2 and HFV will provide extra information about the pathological status of the temporal lobe, since it is predicted that there will be a high degree of correlation between T2 and HFV. The correlation between those two measures and NAA/(Cho+Cr) ratios is expected to be less strong, concomitant with the wider area being assessed by the latter measure.

2. Are specific memory deficits in children with TLE related to the extent and side of focal pathology, as evidenced by three quantitative measures of pathology (right and left hippocampal T2, right and left HF volume, right and left NAA/(Cho+Cr) ratios)?

To date only IQ and Verbal Paired Associate Learning have been correlated with pathology measures (the NAA/(Cho+Cr) ratio) in the paediatric TLE population. In addition, there have been no studies that have examined all three measures of pathology and their relationship to cognitive function, in either adults or children. This study therefore set out to identify such relationships.

3. Is there any change in brain tissue following surgery for relief from intractable seizures, and is this related to cognitive status?

It has been shown by Hugg and colleagues that there can be normalization of contralateral metabolic state (as measured by a Cr/NAA ratio) following temporal lobectomy (Hugg et al., 1996). The idea that previously dysfunctional tissue in the contralateral temporal lobe can recover is radical, and of considerable clinical and neuroscientific importance.

4. Does cognitive outcome from surgery vary with the aetiology, and thus the type of surgery performed (i.e. resection or lesionectomy)?

As mentioned above, little is known of the cognitive outcome of children following temporal lobe surgery. Identifying differences in neuropsychological outcome dependent on the extent of resection may tell us more about the brain regions that subserve specific functions, and also which aspects of cognition can be expected to improve following epilepsy surgery.

5. What are the differences and similarities between patients with TLE and a group of unaffected siblings, in terms of neuropsychological function and MR measures of the medial temporal lobe?

By assessing non-epileptic siblings of TLE patients it is hoped to obtain data which control for factors such as upbringing. However, this could also identify possible genetic factors that might throw light on the familial

inheritance of epilepsy. Both neuropsychological measures and quantitative MR techniques will be used to compare the two groups, and it is predicted that the patient group will be significantly different from the siblings on most of these measures. However, tests of global function such as IQ may not differentiate between the groups.

Chapter 2. Methodology

In this chapter, a description is given of the subject population studied and of the methods used for the acquisition and analysis of the data presented in the subsequent chapters.

2.1 Subjects

2.1.1 Patients

55 patients with a history of epilepsy unresponsive to anti-epileptic drugs were selected from a series of children investigated by the epilepsy team at Great Ormond Street Hospital over a period from 1991 to 1997 (23 male, 32 female; median age 12y 0m, range 2y 5m to 17y 8m; see Appendix I for clinical details). All were selected because of a diagnosis of temporal lobe epilepsy (TLE) on the basis of clinical and electroencephalographic (EEG) findings. Of these, 47 were old enough and had sufficient levels of cognitive function to undergo neuropsychological evaluation as described below (see Section 2.3). All had clinical MRI scans and most (n=52) were assessed using at least one of the quantitative MR techniques.

Thirty-one of the TLE patients went on to have temporal lobe surgery (eight right and 23 left), the extent of resection being dependent on clinical need. Post-operative MR scans showed a range of hippocampal removals from 0 mm to 24 mm in length.

At the time of pre-operative assessment, all patients but one were taking anticonvulsant medication, generally as combined therapy. For the first year of post-operative follow-up, medication levels were unchanged, apart from one case (JBro), who stopped her medication without medical consultation.

Not all patients provided data for every chapter. Appendix I indicates the participation of the patients in the different chapters.

2.1.2 Patient evaluation

Patients were seen in the epilepsy clinic by one of a number of neurologists involved in the epilepsy surgery programme. A medical history was taken, detailing the nature of the seizures and their onset, plus any family history of febrile convulsions and epilepsy, and a full neurological examination was undertaken.

In addition, patients had further investigations, including both ictal and interictal EEG, ictal and interictal single photon emission computerised tomography (SPECT), MRI and MRS, neuropsychological assessment and a neuropsychiatric appraisal.

In this thesis, the data presented are drawn from the neuropsychological and MR investigations. Lateralization of the seizure focus was achieved in these patients through the use of neurological and EEG data.

2.1.3 Control subjects

24 normal subjects (group AC - 13 female and 11 male, median age 29y 10m) were scanned to provide a normal data set for HF volumetry (see Section 2.2.4).

Nine siblings of patients with TLE (group SC - 4 female and 5 male, median age 11y 4m; range 7y 0m to 16y 2m) underwent HF volumetry, T2 mapping and ^{1}H MRS, seven cases also completing a shortened neuropsychological assessment, which is presented in Section 2.3. The data from this second group were used in Chapters 5 and 7.

Hippocampal volumes were also measured in nine normal children (group CC - five male, four female; median age 12y 0m; range 8y 3m to 16y 0m) and 10 children who were neurological patients at Great Ormond Street Hospital but did not have epilepsy (group NEP - seven male, three female; median age 10y 2m; range 1y 4m to 15y 1m). These non-epilepsy patients were selected because they did not have temporal lobe damage and were therefore unlikely to have hippocampal volume loss. However, they cannot be considered a true control group. Of the ten, one had a chiasmal astrocytoma, one a right inferior frontal lobe tumour, one a left inferior parietal DNET, one a pineal gland tumour, one a suprastellar tumour, one an abnormality of the pituitary gland with no temporal lobe lesion, and four were neurologically normal.

39 different normal children (17 male, 22 female; median age 12y 0m, range 6y 0m to 17y 0m), none of whom were investigated using MRI, were assessed with the Wechsler Intelligence Scale for Children (WISC) and the Wechsler Memory Scale (WMS) for use in Chapter 4. These subjects were tested by various members of the neuropsychology group as part of the collection of normative data, and to determine the relationship between IQ and memory function.

2.2 Magnetic resonance imaging and spectroscopy

2.2.1 The basic principles of magnetic resonance

Nuclear magnetic resonance is a technique that uses the magnetic properties of certain atomic nuclei to investigate the properties of the substance in question. For the purpose of clinical investigations, it is generally divided into two areas, namely magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). MRI can be used to provide images of living tissue with high spatial resolution and good contrast. The most important nuclei in obtaining these images are those of hydrogen (protons). Protons produce the greatest signal-to-noise ratio of any nuclei (other than tritium), and the protons of water (and of fat) form the basis of conventional MRI (Gadian, 1995). The concentration of water in tissue is of the order of 40 Molar, as a result of which good signal-to-noise ratios can be obtained from a small region of interest. This in turn makes for good spatial resolution.

Contrast in MRI is provided through variations in a number of parameters, including proton density, and two different relaxation times, known as T1 and T2. These relaxation times can generate better soft-tissue contrast than proton density (Gadian, 1995), but in order to study the images produced it is not necessary to understand exactly what gives rise to their variation. T1- and T2-weighted images can distinguish between different tissue types and between normal and pathological tissue, but the degree of contrast is highly dependent on the specific manner in which the images are derived (i.e. on which 'pulse sequence' is used). Because these images tend to provide good contrast between grey and white matter, they are used for visual inspection by neuroradiologists

and for the measurement of hippocampal (and other) volumes. In general, T1-weighted images are good for looking at brain anatomy, whilst T2-weighted images give detailed images of pathology. However, this is a rather simplistic division, since both are used for clinical evaluations in a number of ways.

^{1}H MRS is used to study brain metabolism by examining the protons associated with certain chemicals. The technique has a higher sensitivity than ^{31}P MRS, which has also been widely used for metabolic studies, and this means that the spatial resolution can be better. However, because ^{1}H MRS studies compounds which exist in the brain at much lower (10000- to 100000-fold) concentrations than water, this resolution is generally only 1 - 2 cm. ^{1}H MRS can provide valuable information about the metabolic integrity of the brain which is not available from MRI.

2.2.2 Standard clinical protocol

All subjects were scanned using a 1.5 Tesla (T) Siemens SP whole body scanner. The basic clinical routine consisted of both T1- and T2-weighted imaging in the coronal plane, followed by a standard protocol for the acquisition of hippocampal volumes, T2 maps and ^{1}H MRS.

Some patients were scanned whilst under sedation or general anaesthetic, but this was not the case for any of the controls.

2.2.3 Quantitative magnetic resonance: T2 Mapping

As mentioned in Section 1.6.2, T2-weighted images frequently show abnormalities in the medial temporal lobe in patients with TLE. However, these images are assessed qualitatively, and so in order to increase the objectivity of

inspection, T2 relaxometry (also known as T2 mapping) was introduced (Jackson et al., 1993b).

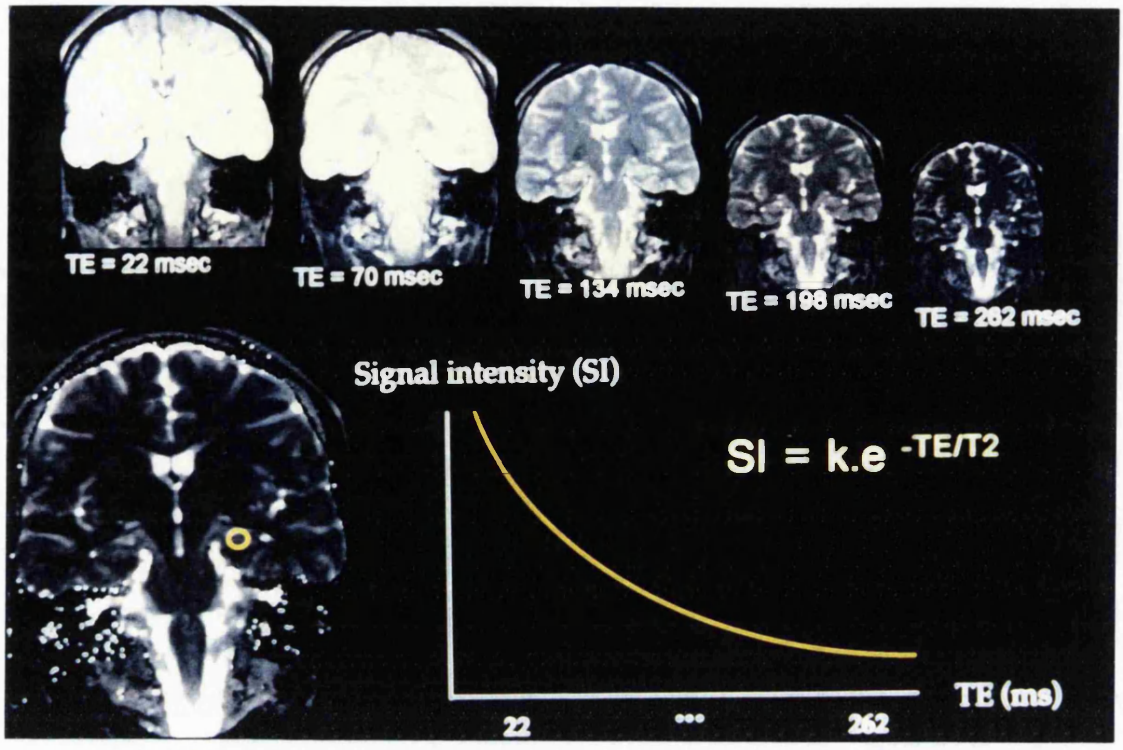

Figure 2.1 MR images showing the decay of T2-weighted signal and the decay curve.

At this centre, hippocampal T2 maps were calculated from 16 images obtained from the same slice position over a range of echo times (22 to 262 ms) (Figure 2.1). Single exponentials were then fitted to the image data of corresponding pixels from these 16 echoes. The thickness of the single slice used for T2 maps was 8 mm, and it was orientated in a tilted coronal plane perpendicular to the body of the hippocampus and placed along the anterior border of the brainstem (Figure 2.2a). The hippocampal T2 value (which is expressed in ms) was then measured by placing a circular region of interest within the hippocampus whilst avoiding the borders (Figure 2.2b). This was to prevent partial volume effects with CSF, which has a very much longer T2 relaxation time than grey or white matter. In general, the measurements were

performed by two independent observers, who were radiographers at Great Ormond Street Hospital.

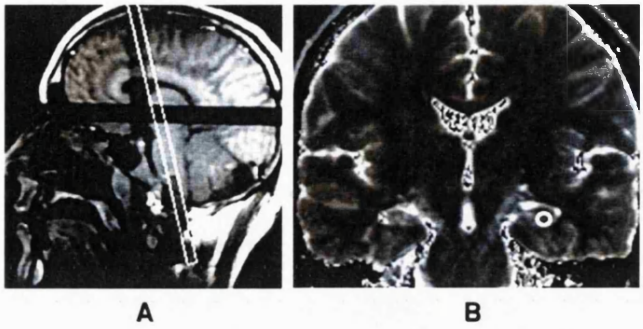

Figure 2.2 The positioning of the slice for T2 relaxometry (2.2a, left) and of the region of interest for measurement (2.2b, right).

At this centre, the mean T2 of 39 adult control subjects was 101.7 ± 3.1 ms (Van Paesschen et al., 1995). The upper limit of normal, which is 2 standard deviations (SD) above the mean, was 108 ms. A T2 of 116 ms or more is regarded as indicating MTS (Jackson et al., 1993b).

It has been shown that the repeatability of T2 maps is very good, with a mean difference between two consecutive measures of 0 ± 3 ms (Van Paesschen, 1997).

2.2.4 Quantitative magnetic resonance: HF volumetry

Images were obtained for analysis of hippocampal volumes using a 3-D Magnetization Prepared Rapid Gradient Echo (MPRAGE) sequence (Mugler & Brookeman, 1990), with a recovery time (TR) = 10 ms, echo time (TE) = 4 ms and an inversion time (TI) = 200 ms. The flip angle was 12 degrees and the matrix was 256 by 256 pixels. The MPRAGE sequence provides 128 images in the sagittal plane which are contiguous and 1.25 mm thick.

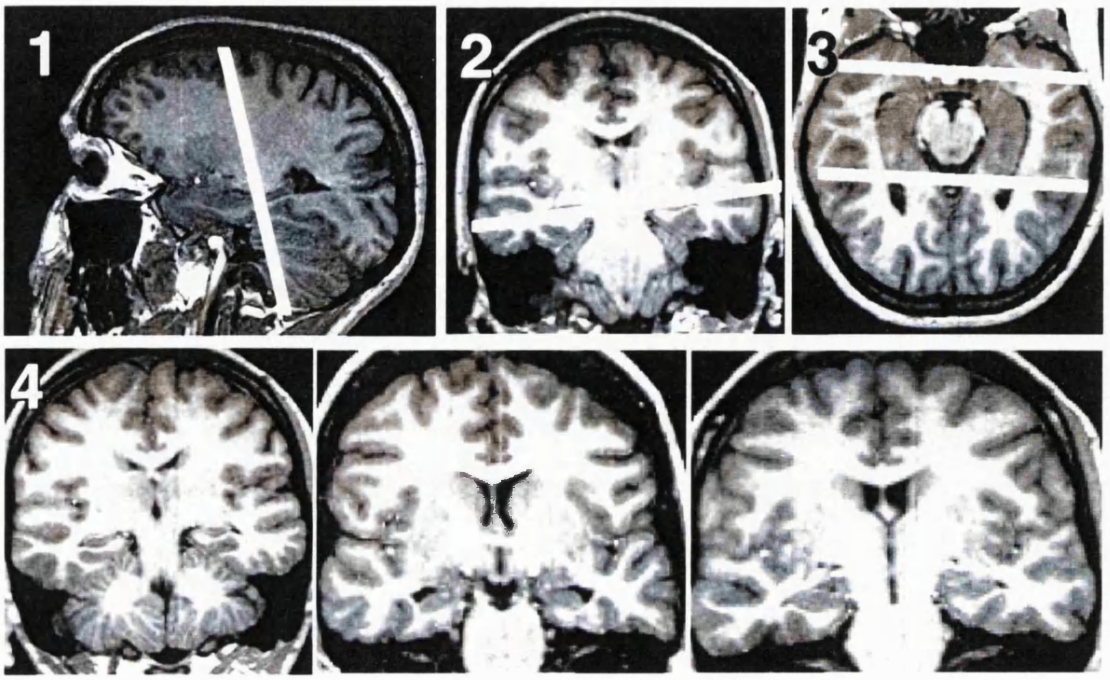

Figure 2.3 Reformatting procedure of the standard sagittally acquired MPRAGE into tilted coronal slices. (1) A section with the hippocampus visible is selected, and a slice made at right angles to the long axis of the hippocampus. This gives an image in a tilted coronal plane (2). Correction is then made for headtilt by selecting a slice through both hippocampi, resulting in an image in a tilted axial plane on which the full lengths of both hippocampi are visible (3). Finally, a set of contiguous 1mm slices is taken aligned at the posterior margin with the fornices. This gives a reformatted dataset in a tilted coronal plane (4)(from Van Paesschen, 1997).

This 3-D dataset was reformatted into 1 mm thick contiguous slices which were oriented perpendicular to the long axis of the hippocampus (Figure 2.3). These were then transferred to a SUN workstation and analysed using an image display and analysis program (Xdispim; Plummer, 1992). The boundaries of the hippocampus were as described by Watson and colleagues (Watson et al., 1992), and the hippocampus proper, dentate gyrus, fimbria, subiculum, intralimbic gyrus and uncinate gyrus were all included in the final volume measurement.

Measurement began at the point where the fornix was seen in full cross-section, and the full length of the hippocampus was measured. A one-in-three sampling strategy was employed such that from the first three slices one was chosen at random, and thereafter every third slice was measured (Van Paesschen, 1997). The total HF volume was calculated by summing the cross-sectional areas and multiplying this figure by the distance between the slices i.e. 3 mm (Cook et al., 1992; Oorschot, 1994).

2.2.4.1 Correcting for intracranial volume

It is accepted that larger people tend to have larger bodies, heads and hippocampi, and that there is a linear relationship between the size of the hippocampi and the total intracranial volume (ICV) (Jack et al., 1995a). In order to reduce the variance between normal subjects, and thus better identify patients with hippocampal atrophy, the measured hippocampal volumes were corrected to take account of head size. It has been shown that optimal volumetric normalization is achieved by using ICV, as opposed to a range of other parameters of head size (Free et al., 1995).

ICV was measured in the sagittal plane on the unreformatted MPRAGE dataset. The sampling strategy used for ICV measurement was one-in-ten (i.e. from the first ten slices one was chosen at random, and thereafter every tenth slice was measured) (Van Paesschen, 1997). The landmarks used were the dura mater (or the inside of the skull if the dura was not seen), the undersurface of the frontal and temporal lobes excluding the petrous bone, the clivus, and, at the craniovertebral junction, the attachment of the dura to the anterior and posterior

arch of the first cervical vertebra (C1). Figure 2.4 shows a specimen image from which the ICV can be measured.

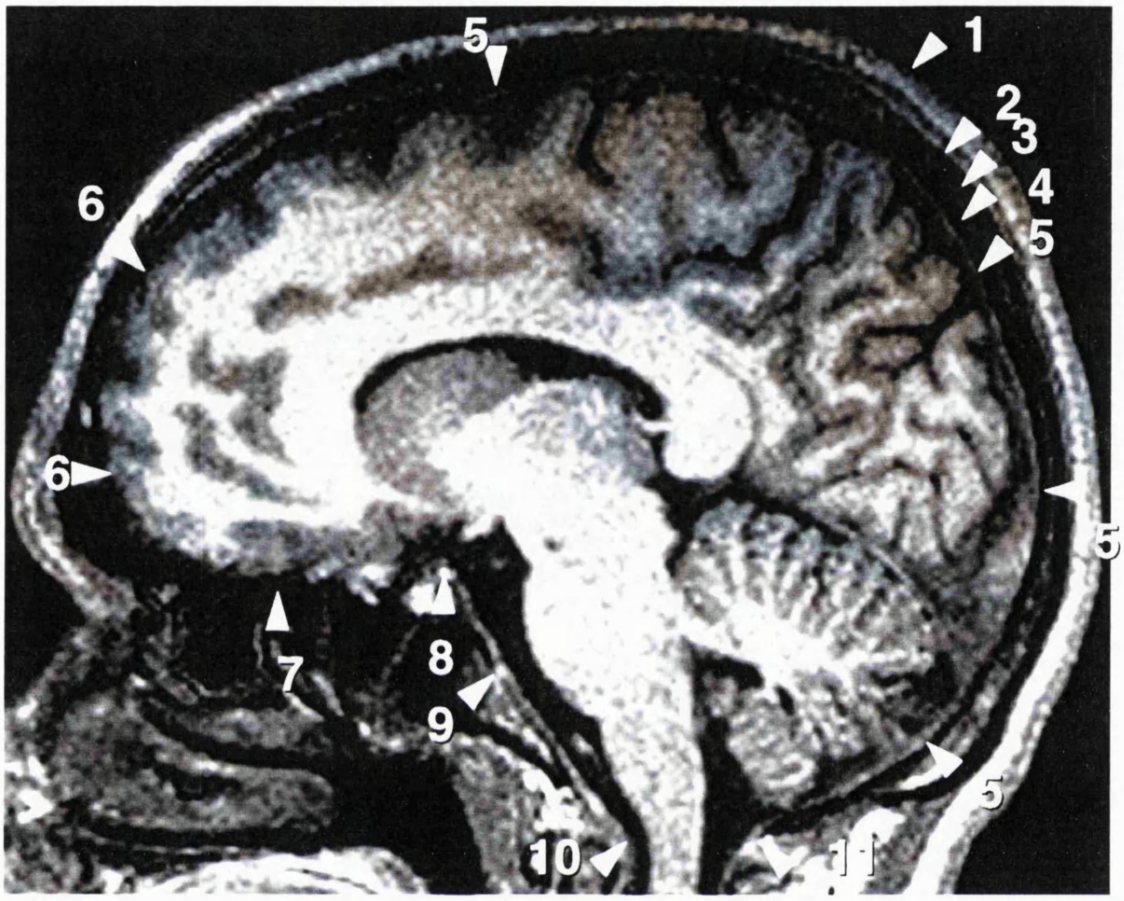

Figure 2.4 MR image showing landmarks for measurement of ICV. The scalp (1) is visible as a bright line, with the outer table of the skull immediately below it (2). The diploë (3) lies between the outer table and inner table (4). The dura mater (5) lies below the inner table and is generally visible as a white line. Where it is not, the cerebral contour (6) is outlined. Other landmarks are the undersurfaces of the frontal lobe (7), the dorsum sellae (8), clivus (9), and at the craniovertebral junction the attachment of the dura to the anterior (10) and posterior (11) arch of C1 (from Van Paesschen, 1997).

HF volume and ICV were assessed in 24 normal adult volunteers (group AC) on at least three trials and the mean of these measurements used. Figure 2.5 shows the graph of ICV against HF volume for these subjects. The Pearson's

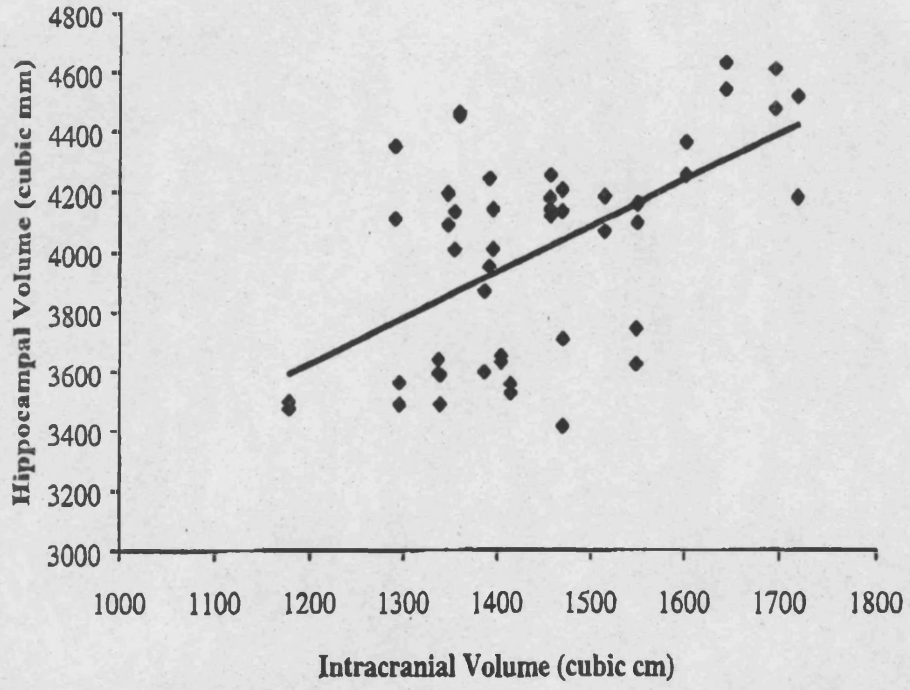

Figure 2.5 Graph of intracranial volume against measured HF volume in a group of 24 normal adult subjects (group AC).

A repeatability study was carried out using the normal controls to give the repeatability coefficient (RC). The RC was calculated by examining the differences between measurements of the same hippocampus (measure 1 - measure 2; measure 2 - measure 3; measure 3 - measure 1). These differences over the whole dataset were analysed and the RC computed by finding the standard deviation of the differences and doubling it to give a 95% confidence limit. This value was then divided by the mean control volume and multiplied by 100 to give a percentage error. For this thesis, the RC was found to be 7.9%. This compares well with previously reported RCs from this centre (Van Paesschen, 1997) and elsewhere (Jack, 1994).

2.2.4.2 HFV Distribution Graphs

Since HF volumes are measured by sequentially outlining the hippocampus along the posterio-anterior axis, it is possible to create graphs showing the cross-sectional areas at each slice position. This gives an outline of the hippocampus along its length, enabling visualisation of focal regions of atrophy (Cook et al., 1992). A control graph was plotted as previously described (Van Paesschen, 1997), displaying the 95% confidence limits at each section position. This is not directly calculated using the data for each section position. Instead, two SD of the control HFV is distributed among the section positions in proportion to their individual SD. Two SD of all the sections will therefore add up to two SD of the total volume. The plots for each individual patient were corrected for ICV by adding the following correction factors to each cross-sectional area (Figure 2.6):

correction factor = measured area x (cHFV - mHFV)/mHFV

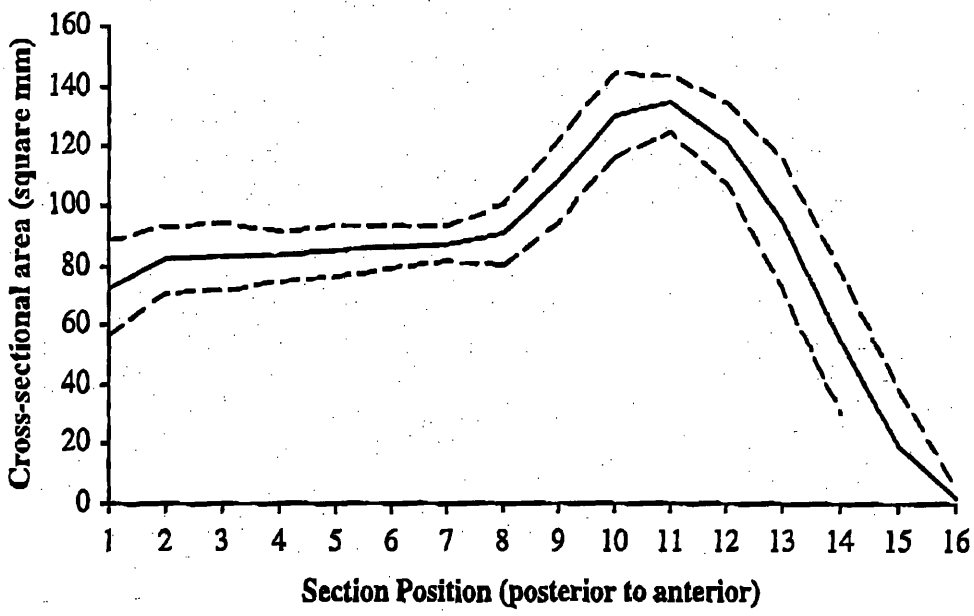

Figure 2.6 Graph of hippocampal cross-sectional area against hippocampal slice position in a group of 24 normal adult volunteers. The mean (solid line) and the ±2SD (dashed lines) are shown.

2.2.5 Quantitative magnetic resonance: Single volume ^{1}H MRS

^{1}H MR spectra were obtained from both right and left temporal lobes as previously described (Connelly et al., 1994). A 2 x 2 x 2 cm voxel was placed in the medial region of the temporal lobe, such that in the axial view it was centred on either side of the brainstem and in the coronal view it included the lateral part of the hippocampus. This is shown in Figure 2.7.

A 90°-180°-180° spin echo technique was used to achieve spatial localization, and water suppression was obtained by pre-irradiation using a 90° Gaussian pulse with a 60Hz bandwidth followed by a spoiler gradient. TR was 1600 ms and TE was 135 ms. Data were collected following global and local shimming, and water suppression optimization, in 2 to 4 blocks of 128 scans.

Non-water-suppressed data were used as a reference in order to correct the time domain data for eddy-current induced phase modulation. Exponential multiplication corresponding to 1 Hertz (Hz) line broadening was carried out prior to Fourier transformation, and a cubic spline baseline correction was performed.

Figure 2.7 MR image indicating the placement of regions of interest for single voxel ^1H MRS.

As mentioned in Section 1.6.3, proton spectra obtained in this way have three main peaks, relating to the concentrations of NAA, Cho and Cr. NAA is primarily neuronal, and Cho and Cr are found in neurons and glia, so the

Non-water-suppressed data were used as a reference in order to correct the time domain data for eddy-current induced phase modulation. Exponential multiplication corresponding to 1 Hertz (Hz) line broadening was carried out prior to Fourier transformation, and a cubic spline baseline correction was performed.

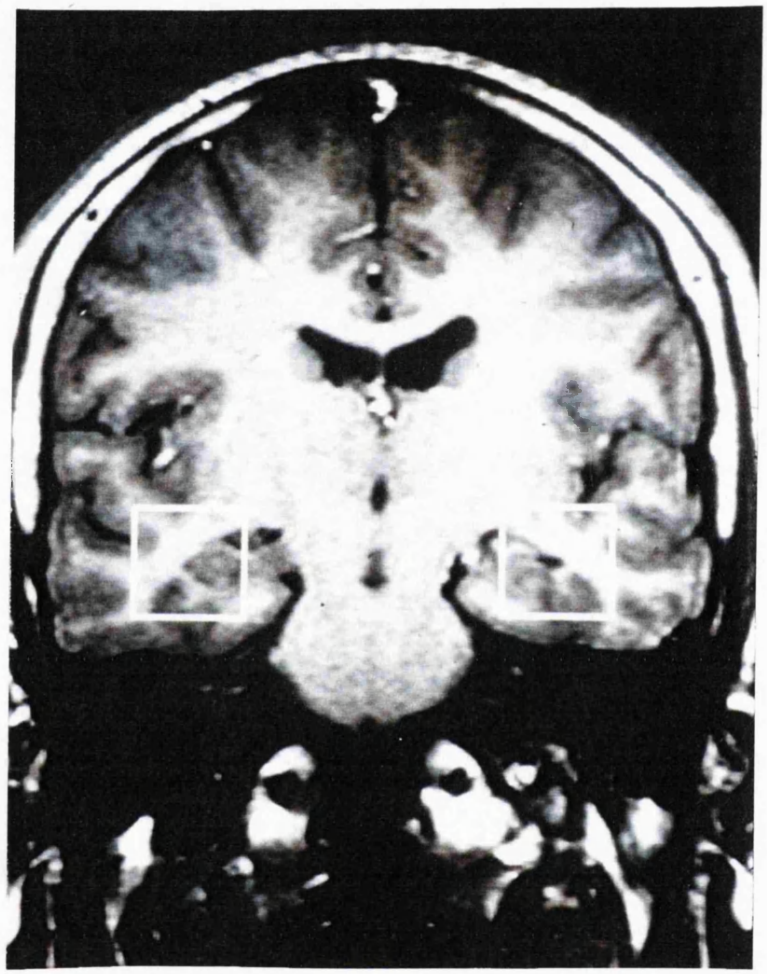

Figure 2.7 MR image indicating the placement of regions of interest for single voxel ^{1}H MRS.

As mentioned in Section 1.6.3, proton spectra obtained in this way have three main peaks, relating to the concentrations of NAA, Cho and Cr. NAA is primarily neuronal, and Cho and Cr are found in neurons and glia, so the

NAA/(Cho+Cr) signal intensity ratio should be an index of the neuronal integrity of the temporal lobe. Figure 2.8 shows two specimen spectra.

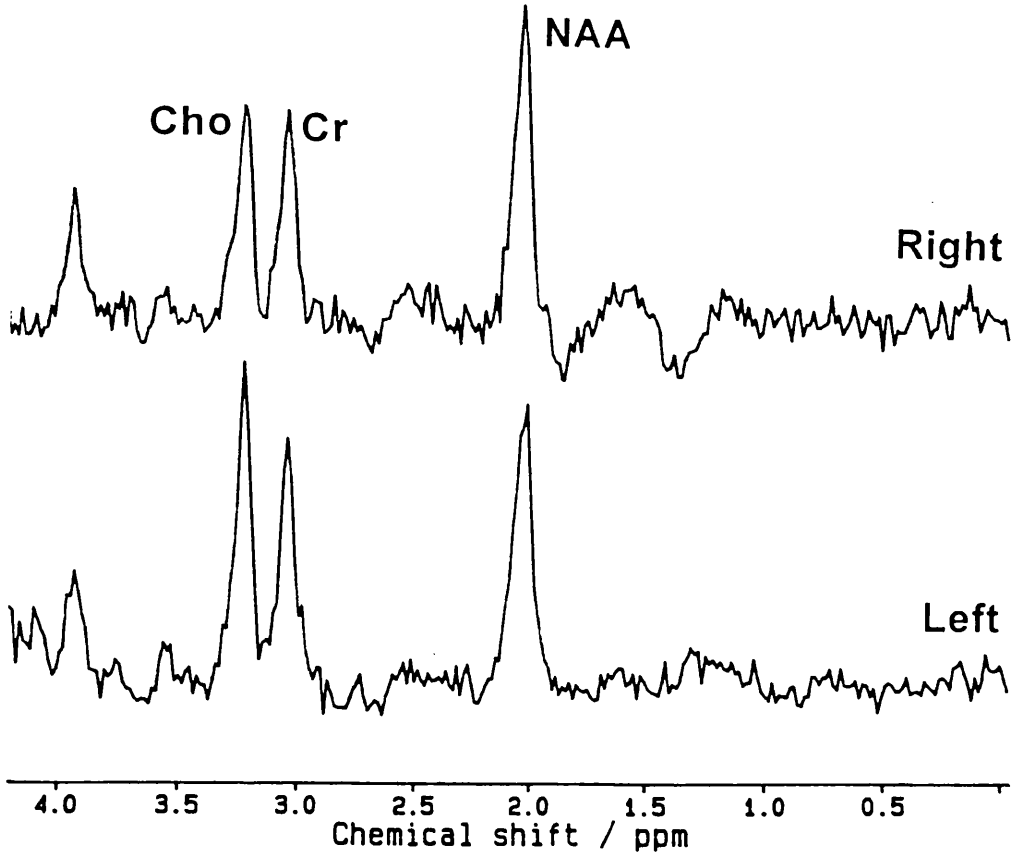

Figure 2.8 Normal (top) and abnormal (bottom) ^{1}H MR spectra. The bottom spectrum has a much lower NAA signal intensity and higher Cho and Cr signal intensities.

Signal intensities were measured at 2.0 parts per million (ppm) (primarily NAA), 3.0 ppm (Cr) and 3.2 ppm (Cho) by integration, but since the effects of T1 and T2 relaxation were not determined it was not possible to convert these intensities to concentration measurements. The ^{1}H MRS ratio (NAA/[Cho+Cr]) is a dimensionless figure, and a figure outside the 95% confidence interval was considered to be abnormal. In our control population, the lower cut-off figure was 0.72 (Connelly et al., 1994).

2.3 Neuropsychological Examination

Patients underwent a lengthy protocol that consisted of tests of intelligence, verbal and nonverbal memory, language ability, executive function, academic attainments and visuo-perceptual skills. From the outset this was a carefully chosen series of neuropsychological tests which were known to detect subtle deficits in function as a result of extensive work on adults following focal surgical procedures. Specifically, the protocol was anticipated to reveal lateralized memory deficits in TLE patients owing to the use of both verbal and nonverbal memory tests, and to dissociate between hippocampal and neocortical function. In addition, the use of tests sensitive to damage in other brain regions (such as the frontal lobes) was intended to ensure the selectivity of the memory deficits. The protocol was adapted in a number of ways to make it more suitable for the paediatric population, such as using children's versions of tests, and normative data were obtained from normal control children where possible.

Not all of the patients completed all of the protocol, either due to time constraints, fatigue, or the lengthening of the protocol over the years of the programme. Tests indicated with an asterisk (*) were also given to sibling controls.

The mean (± standard deviation) of the TLE population is shown for each test and subtest, along with the number of patients completing that test.

Table 2.1 displays the kinds of memory which were assessed by which test in this protocol, whilst Table 2.2 indicates the grouping of other tests used in the protocol.

Immediate Memory		Intermediate Memory		Delayed Memory		Recognition Memory	
Verbal	**Visual**	**Verbal**	**Visual**	**Verbal**	**Visual**	**Verbal**	**Visual**
Digit Span	Block Span	LM - I	D'	LM - D	D	WRMT - Words	WRMT - Faces
		VPA Score	Dot Location – Imm Rec	VPA Delayed	Emergent Complex Figure	CAVLT - Recognition	
		C'	CDLT - DLT	C	Dot Location – Del Rec		
		CAVLT – Lvl Lrn		CAVLT – Del Rec	CDLT – Del Rec		

Table 2.1 The types of memory assessed by the neuropsychological tests in the administered protocol (see below for details).

Language	Visual Perception	Executive Function
BPVS	Thurstone Closure	WCST
Wingfield-Oldfield Object Naming	Benton Facial Processing	Thurstone Written Fluency
Token Test	Benton Line Orientation	
TROG	Mooney Faces	

Table 2.2 Tests assessing language, visual perception and executive function in the administered protocol (see below for details).

The protocol consisted of the following:

2.3.1 Tests of Intelligence

**Age-appropriate Intelligence tests (Wechsler Intelligence Scale for Children [WISC-R/WISC-III^{UK}]; Wechsler, 1992: or Wechsler Adult Intelligence Scale [WAIS]; Wechsler, 1986).*

The Wechsler IQ tests are standardized tests of verbal and non-verbal intelligence. They are made up of a number of subtests testing functions as diverse as vocabulary and object assembly (jigsaw puzzles). There are six verbal subtests of which five make up the verbal IQ (VIQ; Mean = 87.8 ± 15.7; n = 46), and six non-verbal subtests of which five make up the performance IQ (PIQ; Mean = 94.8 ± 19.3; n = 46). The full-scale IQ (FSIQ; Mean = 89.7 ± 17.2; n = 46) uses all ten of these subtests to give a global score. The verbal subtests for the WISC-III^{UK} are as follows.

Information - a series of orally presented questions tapping the child's knowledge about common events, objects, places and people (Mean = 7.3 ± 3.2; n = 46).

Similarities - a series of orally presented pairs of words for which the child explains the similarity of the everyday objects or concepts they represent (Mean = 8.3 ± 3.5; n = 46).

Arithmetic - a series of arithmetic problems which the child solves mentally and responds to orally (Mean = 8.8 ± 3.0; n = 45).

Vocabulary - a series of words which are read to the child who then has to define them as accurately as possible (Mean = 7.2 ± 2.6; n = 44).

Comprehension - a series of orally presented questions that require the child to solve everyday problems or to show understanding of social rules and concepts (Mean = 7.8 ± 3.0; n = 45).

Digit Span - a series of orally presented number sequences which the child repeats verbatim for Digits Forward and in reverse order for Digits Backward (see below for a fuller description). This subtest score does not contribute to the VIQ but is instead used, with the Arithmetic subtest, to derive a measure of distractibility (Mean = 9.0 ± 3.0; n = 45).

The non-verbal subtests for the WISC-III^{UK} are as follows.

Picture Completion - a set of colourful pictures of common objects and scenes, each of which is missing an important part which the child identifies (Mean = 8.8 ± 3.5; n = 46).

Coding - a series of single digit numbers, each paired with a simple symbol. The child draws the symbol under its corresponding number according to a key (Mean = 8.8 ± 2.9; n = 44).

Picture Arrangement - a set of pictures presented in mixed up order, which the child identifies and rearranges to create a storyboard (Mean = 8.1 ± 3.1; n = 40).

Block Design - a set of geometric patterns presented in two dimensional form which the child replicates using two-colour cubes (Mean = 9.8 ± 4.0; n = 45).

Object Assembly - a set of jigsaw puzzles of common objects which the child assembles to form a meaningful whole (Mean = 10.2 ± 3.4; n = 45).

Symbol Search - a series of paired groups of symbols, each pair consisting of a target group and a search group. The child scans the two groups and indicates whether or not a target symbol appears in the search group. This subtest score

does not contribute to the PIQ but is instead used, with the Coding subtest, to derive a measure of processing speed (Mean = 9.2 ± 2.9; n = 33).

The subtests for the WAIS and the WISC-R are broadly the same as those for the WISC-III^{UK}, although there is no Symbol Search on either. The WISC-III^{UK} was given to almost all of the children in the studied population. All three tests are age-standardized, with a mean of 100 ± 15. Each subtest is also standardized with a mean of 10 ± 3.

2.3.2 Tests of Memory

**Wechsler Memory Scale (WMS; Wechsler & Stone, 1945) with adaptations: Children's stories for the under twelves, delayed recall conditions for logical memory, verbal paired-associate learning and visual reproduction subtests, and age corrections for those under twenty.*

In its original form this can be considered as a test of intermediate memory. It comprises seven subtests - orientation, information, mental control, digit span, logical memory (also known as story recall), visual reproduction of designs and verbal paired-associate learning. The last three subtests are frequently given alone. Some of these subtests tap attentional orientation (orientation, mental control), whilst others assess intermediate memory (logical memory, visual reproduction, paired-associate learning) or acquired world knowledge (information). In its original form there was no measure of delayed memory, but this has since been introduced - a 90 minute delay for story recall and paired-associates and a 40 minute delay for designs (Milner, 1975).

From this test a number of scores are obtained. The most global is the Memory Quotient (MQ; Mean = 90.0 ± 15.9; n = 46), which is a measure of

overall memory ability, comparable to FSIQ, in that in the normal population, the MQ is intended to give more or less the same score as FSIQ. In practice it is used less and less since memory is no longer regarded as a unitary system, but it is still sometimes compared with VIQ as a rough and ready test for amnesia. A discrepancy of 15 points of more between the MQ and the VIQ is generally regarded as being a mark of significant memory problems. This formula does not work all the time, because there is only one nonverbal subtest and that is very easy. In addition, the original MQ score was calibrated using the 1939 version of the Wechsler-Bellevue scale, and each subsequent revision of the Wechsler Intelligence Scales has resulted in normal subjects achieving a higher MQ for the same IQ (Lezak, 1995). Therefore, the link between MQ and IQ is not only dangerous from a theoretical point of view, but the relationship between the two has changed over the years.

Logical memory (or story recall) consists of two short passages of prose which are read to the subject, who immediately after each passage is presented must try to repeat it verbatim to the tester. After a 90 minute delay, the subject (without prior warning that this will happen) is again asked to recall the passages. There are 24 'units' of information in the first story and 22 in the second, and scoring is by giving a point for each unit recalled verbatim. Half a point is given for recalling the gist of a unit correctly, such that the basic idea has not been altered. The total for each story is summed and averaged, giving a measure of both immediate (LM-I; Mean = 7.2 ± 2.8; n = 46) and delayed (LM-D; Mean = 4.4 ± 3.3; n = 46) story recall, and the maximum score is therefore 23. In addition, a retention score as a percentage of LM-I (LM-%; Mean = 56.7 ± 28.8; n = 46) can be obtained using the following expression:

$$LM\text{-}\% = 100 \times (1 - [(LM\text{-}I - LM\text{-}D)/LM\text{-}I]$$

There is a set of children's stories for subjects between the age of six and twelve to avoid floor effects, with a different number of units (18 in both).

In the verbal paired-associate learning subtest (VPAL), a list of ten pairs of words is read to the subject. Following this, the first of each pair is given and the subject is asked to say the other. If the answer given is wrong, the subject is reminded of the correct answer. The list is re-presented and tested twice more, and after ninety minutes, unalerted delayed recall is obtained without prior presentation of the list of pairs.

The items are split into two unequal groups. There are six 'easy' pairs, where the second word is a semantic associate of the first (e.g. up - down, or fruit - apple), and four 'hard' pairs where there is no obvious semantic association (e.g. cabbage - pen, or crush - dark). The same list of pairs is used for all age groups, from six years upwards.

A number of scores are then derived from this test. The weighted score (VPA Score; Mean = 13.8 ± 4.1; n = 46) is equal to the total number of correct easy pairs over the three trials divided by two, plus the total number of correct hard pairs over the three trials. It therefore has a maximum score of 21. In addition, total correct easy pairs (VPA Easy; Mean = 15.8 ± 3.0; n = 46) and total correct hard pairs (VPA Hard; Mean = 5.8 ± 3.0; n = 46) over the three trials are scored, and also the number of correct pairs out of ten on the delayed recall trial (VPA Del; Mean = 7.7 ± 2.3; n = 46).

A composite measure of immediate verbal memory can be obtained by adding the average immediate recall of the stories to the total number of correct word pairs on trial three of the VPAL. This score is known as C prime, and has a

maximum score of 33 using the adult stories and 28 using the children's stories (C'; Mean = 15.8 ± 4.0; n = 46). The composite delayed recall measure, the C score (C; Mean = 12.1 ± 4.9; n = 46), is the sum of the average delayed recall of the stories plus VPA Del. A measure of how much information has been retained is given by the expression: 100 x (1 - [(C' - C)/C']). This is known as the percent retention score (%C; Mean = 75.2 ± 18.2; n = 46).

Non-verbal memory is assessed by the visual reproduction subtest, which consists of four geometric designs. These are presented over three trials, such that there is one design on each of the first two cards, and two presented simultaneously on the third. Each card is displayed for 10 seconds, and immediately afterwards the child is asked to draw the design presented (D'; Mean = 9.2 ± 3.1; n = 45). After a 40 minute delay, the child is asked to draw the designs again (D; Mean = 6.7 ± 3.6; n = 45). A measure of the retention of this information can be obtained using a similar equation to that used for the Composite score (D%; Mean = 70.8 ± 25.4; n = 45).

Unpublished norms (n=392) on these measures have been obtained by this centre for children ranging in age from 5 to 16.

**Children's Auditory Verbal Learning Test - 2nd edition (CAVLT-2; Talley, 1992).*

This is a standardized children's version of the widely used word list free-recall paradigm e.g. the Rey Auditory-Verbal Learning Test (RAVLT) or the California Verbal Learning Test (CVLT). The CAVLT-2 consists of three word lists: two free recall word lists and a recognition list. The words are all simple nouns of one or two syllables and should be within the normal vocabulary of

primary school children. All the words fall into one of four semantic categories; parts of the body, animals, articles of clothing, or parts of a house.

The first list consists of 16 common nouns which are read to the child at a rate of about one per second. The child is then asked to recall as many as possible in any order. This procedure is repeated a further four times. A second list of 16 words is then read once and recall obtained to determine the effects of interference. Immediate and delayed recall of the first list are then obtained, delayed recall following 20 minutes after immediate recall. Four age-standardized memory measures are then derived from the test;

Immediate Memory Span - The recall of both the first and second list after just one presentation. This is a measure of supraspan learning (Mean = 104.8 ± 20.9; n = 29).

Level of Learning - The sum of the recall of list one on trials three, four and five (Mean = 104.8 ± 16.3; n = 29).

Immediate Recall - Recall of list one immediately following list two (Mean = 102.1 ± 18.3; n = 29).

Delayed Recall - Recall of list one after a twenty minute delay (Mean = 102.1 ± 18.3; n = 29).

This test is age standardized so that comparisons can be made across age groups. The mean for all these scores is 100 ± 15 and norms are available from age 6 up to and including the age of 17.

In addition, measures of recognition memory and intrusions can be obtained, but these are not age standardized. Recognition memory (Mean = 29.5 ± 3.3; n = 23) is assessed following the Delayed Recall trial using a list of 32 words which are read to the child. The child is asked whether the words were in

the first list which was read, all of which are present in the recognition list. In addition, there are eight words from the interference list, and a further eight are novel words but from the same semantic categories. The intrusion score is merely the number of incorrect words from all the recall trials (i.e. not the recognition trial). Perseverative correct words are not considered as intrusions (Mean = 2.8 ± 3.8; n = 29).

**Design Learning Test (Coughlan & Hollows, 1985).*

This is a subtest taken from the Adult Memory and Information Processing Battery (AMIPB), and is a test of non-verbal learning which is broadly analogous to the CAVLT-2 (although the authors used their own verbal list learning test in this battery). It is therefore intended to measure the supraspan learning of non-verbal information and examine susceptibility to interference.

The test consists of two simple nine-line designs. In a similar manner to the CAVLT-2, one design is presented five times to give a measure of learning ability, with a maximum score of 45 (DLT; Mean = 32.5 ± 10.1; n = 26). Intrusions (incorrect lines) are also counted on these five trials (DLI; Mean = 8.2 ± 7.8; n = 26). This is followed by a second (interference) design, and immediate recall of the first design (ImmRec; Mean = 6.8 ± 2.5; n = 26). In its original form there was no delayed recall, but this has been added by this centre (DelRec; Mean = 6.8 ± 2.3; n = 24). In addition, a measure of immediate learning has been obtained by summing the score on the initial presentation of the two designs (ImmLrn; Mean = 9.7 ± 3.4; n = 26). This gives a score analogous to the Immediate Learning score of the CAVLT-2. However, there is no recognition trial.

Pre-published norms are available for the adult (n = 184; age 18 – 75 years) but not the childhood population. This test is explained further and norms for children presented in Appendix III.

**Emergent Complex Figure Learning (Jones-Gotman, 1986).*

This is a test designed to measure the subject's long-term memory for an emergent complex geometric figure. It is similar to the more commonly used Rey-Osterrieth Complex Figure in that it consists of a geometric figure to be copied, followed by an unalerted recall trial after 40 minutes. It differs in that a specific copying order is imposed on the subject. There are 18 figural items which are presented sequentially in such a manner that each subsequent item is seen in the context of the overall design up to that point. Therefore, the first item is presented on its own and is required to be copied by the subject. Then the second item is added to the first and must also be copied, followed by the third with the first two items, and so on until the whole figure has been displayed and copied.

The Emergent Complex Figure is also different from the Rey in the way that it is scored. Two points are given for an item which is correctly drawn and in the correct place (i.e. the maximum score is 36). For an item that is correctly drawn but in the wrong place, $1^1/_2$ points are given. One point is given for a badly drawn item in the right place and $^1/_2$ a point if it is in the wrong place. A percentage recall as a proportion of the copy score is then calculated in order to control for poor drawing skills (Mean copy score = 30.9 ± 3.1; n = 39; Mean recall score = 36.4% ± 13.4%; n = 39).

This test has been shown to be sensitive to right hippocampal damage, since patients with large right hippocampal removals perform worse on this test than those with small right hippocampal removals. Both do worse than patients with left hippocampal removals and normal controls, who are not significantly different from each other (Jones-Gotman, 1986).

**Warrington Recognition Memory Test (WRMT; Warrington, 1984).*

This consists of two subtests, one containing 50 written words and the other 50 faces. The words are all of moderate frequency and one or two syllables in length, whilst the faces are all unfamiliar, male and in black and white. In each test, both words and faces, the items are shown one after the other for 3 seconds each and the subject has to make a decision about whether the item is pleasant or unpleasant. This is to ensure that the item has been processed, and does not materially affect recognition scores (Delbecq-Derouesné & Beauvois, 1989). Once all the items have been presented there immediately follows a forced choice recognition, where 50 pairs are shown containing an item previously seen, and a novel distractor. The targets are in a different order to that in which they were presented. Both tests are scored out of 50, and a score of 25 indicates a performance no better than chance (Mean Words = 44.9 ± 6.1; n = 35; Mean Faces = 36.1 ± 6.5; n = 35). There are no children's norms for this test, and so the performance of patients is evaluated in relation to chance. In young adults (the 18-39 age range), this test has a significant ceiling effect (Leng & Parkin, 1990), which is presumably also the case for children at the top end of the age range (16-17).

The presentation time of this test of around 3 seconds per item means that there is about three minutes between presentation and recognition. This means that the test is one of intermediate rather than immediate memory. Interpretation must also take into account the subject's more global cognitive functioning since the test has been found to correlate with both the WAIS Vocabulary subtest and Raven's Matrices (Warrington, 1984).

However, this test has only inconsistently demonstrated material-specific memory deficits, since patients with left-sided lesions often do poorly on the recognition of faces as well as of words (Lezak, 1995).

**Dot Location (Incisa della Rocchetta et al., unpub.).*

This test was designed to measure memory for spatial location without verbal labels. The test consists of a display panel bearing an A3 size sheet of white paper, delimited by a black frame, and covered in clear plastic. On the white sheet, six red dots (diameter 3mm) have been drawn in a random arrangement. The child is first asked to copy the pattern onto a blank A3 sheet of paper (Copy; Mean = 98.3 ± 39.7 mm; n = 31), and then reproduce it without the display panel (Immediate Recall; Mean = 151.3 ± 38.5 mm; n = 31). After a 40 minute delay, the child is asked to recall the pattern without prior warning that this will happen (Delayed Recall; Mean = 169.4 ± 40.3 mm; n = 31). The test is scored using a target system. The scoring sheet is a clear acetate film with the six dots each surrounded by concentric circles 5 mm apart, up to a maximum of 40 mm from the actual dot. The dot drawn by the child is then given a score based on the circle in which it falls, so that the score is a measure of the amount of error in the reproduction. The maximum error score for all three trials is 240

mm. Norms have been obtained for children between the ages of 6 and 11 years (N = 150), and the graph of normal children's performance on this task against their age is shown in Appendix IV.

**Digit span (Wechsler, 1945)*

This is a test of immediate memory span for auditory-verbal information, which is also dependent on auditory attention. On each trial, a short string of digits is presented to the child who is requested to recall it immediately. The number of items in the string begins at two and lengthens one item at a time, theoretically without maximum. Each level has two trials of different sequences. Only if the subject fails both trials is the test discontinued. Once the child has reached maximum span, the test is repeated (with different strings), but this time the child is asked to recall the digits in reverse order. Three scores can be obtained - the maximum forwards span, the maximum backwards span, and a weighted score for the two together which is only used in IQ tests. This is calculated by awarding one point for each string correctly recalled, so that for each length of string the maximum score is two. However, for the WMS and measures of working memory, only the Forward Span and Backward Span are used (Mean Forwards Span = 5.7 ± 1.2; n = 45; Mean Backwards Span = 4.3 ± 1.4; n = 43).

The adding together of the forwards and backwards digit spans implies that the tests are measuring the same behaviour, but it has been shown that this is not true in aged subjects or subjects with brain damage (Lezak, 1995). Digit span in the forwards direction is affected more by left hemisphere damage than it is by right hemisphere or diffuse damage (Lezak, 1995). The backward span is also

affected more by left hemisphere damage than right. However, there appears to be no difference between patients with left or right temporal lobectomies and normal controls (Canavan et al., 1989).

**Block span (Milner, 1971)*

This is a test of immediate memory span for spatial location. It has a similar method of administration to the Digit Span, in that strings of information are presented for immediate recall, and those strings increase in length one item at a time. For the Block Span the information is a visual presentation of a tapping sequence on a set of nine blocks, which are fastened in a random order to a black board. As for the Digit Span, the sequence length begins with two items, and increases until two trials at that length are failed (Mean Forwards Span = 5.6 ± 1.3; n = 34; Mean Backwards Span = 5.2 ± 1.6; n = 28).

In adults, it has generally been found that block span is one unit smaller than digit span (Lezak, 1995). This also seems to be the case in children for forward span, but not for backward span where, if anything, block span exceeds digit span (Isaacs & Vargha-Khadem, 1989). Canavan and colleagues (Canavan et al., 1989), however, showed that there was no significant difference between controls and either left or right temporal lobectomy patients.

2.3.3 Tests of Language Function

**British Picture Vocabulary Scale (BPVS; Dunn et al., 1982).*

This is designed to measure a subject's receptive (or hearing) vocabulary for English words, and as such is a measure of the vocabulary comprehension level of the child. Four pictures are shown to the child and the tester says a

word. The child must then point to the picture that best fits the word. The words decrease in frequency of usage as the test goes on and also become more abstract. The test is discontinued once six out of eight items are answered incorrectly. This test has age-standardized norms from age 2 to adult, with a mean of 100 and standard deviation of 15 (Mean = 82.0 ± 13.0; n = 11).

**Object Naming Test (Oldfield & Wingfield, 1965).*

This consists of 36 cards showing line drawings of objects, ranging from easy objects such as a key, to hard items such as a gyroscope. These are presented to the child who is instructed to name them as quickly as possible. The test is designed to pick up subtle signs of word retrieval problems and was initially used in patients with focal missile wounds (Lezak, 1995). Two measures are generally obtained from this test. The first is the total number of objects named correctly (Mean = 27.0 ± 3.8; n = 41), and the second is the mean time to first utterance (Mean = 2.1 ± 0.7 s; n = 40). In the original study (Newcombe, Oldfield, Ratcliff et al., 1971), a cut off of twenty correct responses was used, given that the first ten pictures were used for practice. Only 4% of controls scored below the cut-off compared with 16% of those with left brain damage. The control group also had shorter latencies than the patients did.

At this centre, the full 36 items are used with a cut-off of 26 indicated naming problems. Unpublished norms have been obtained by this centre for children between the ages of 5 and 16 (n = 120).

Token test (De Renzi & Vignolo, 1962).

This is an extremely easy test to administer, and for most subjects to perform with few errors. However, it is highly sensitive to impaired linguistic processes (Lezak, 1995).

Twenty 'tokens' made of plastic are placed before the child. These are ten circles and ten squares, each of which consist of five large and five small tokens. Each token is further distinguished by being coloured - red, black, green, yellow and white. The tokens are laid out in parallel rows by shape and size (large circles, large squares, small circles, small squares) and the child is given oral instructions. There are 62 commands altogether, divided into five sections which increase in complexity. All the tokens are on the table only for sections 2 and 4; otherwise only the large tokens are used. The first level has simple orders such as, "Touch the red circle", whilst the fifth examines the understanding of grammatical relations within sentences, e.g. "Touch - with the black circle - the red square." Because both the small and the large tokens are also used for sections 2 and 4, these sections have an increased memory load in terms of the length of the instructions. The maximum score on this test is 62 (Mean = 55.7 ± 5.4; n = 30).

Test for Reception of Grammar - 2nd edition (TROG; Bishop, 1989).

This is a multiple-choice test to assess the understanding of grammatical constructs. The original intention was to assess whether children whose speech contained grammatical abnormalities also had problems in understanding grammatical contrasts (Bishop, 1989). In administration it is a forced choice paradigm not unlike the BPVS, since each item consists of four pictures and the

child is required to point to the picture which best suits the sentence spoken by the examiner. The test is composed of 20 blocks, each block containing four items. Each block is designed to test the understanding of a specific grammatical contrast, such that block A (the easiest) tests the understanding of nouns, whilst block T (the hardest) tests the comprehension of embedded sentences. Each item in a block must be answered correctly in order for that block to be passed to ensure that the child really does understand the contrast being tested (Mean Blocks passed = 16.7 ± 2.9; n = 38).

The test is appropriate only for children between the ages of 4 and 12 years, since by the upper age limit ceiling has been reached. Because of this, published norms are only available for this age range, although the test can prove very useful with dysphasic adults (Bishop, 1989).

2.3.4 Tests of Visuo-perception

**Thurstone closure (Thurstone & Jeffrey, 1984).*

This test is used to examine perceptual closure capacity, and poor performance is generally associated with right hemisphere damage (Lezak, 1995). In the test, the child is presented with 24 pictures which are degraded line drawings of common objects or scenes. The shadows and highlights have been exaggerated to make identification difficult. The total number of correctly named pictures is scored (Mean = 12.3 ± 4.5; n = 30), as is the total time taken to do the test (Mean = 314 ± 107 s; n = 25). Unpublished norms for this test have been collected by this centre (n = 143; age 6 – 12 years).

**Benton Facial Processing Test (Benton & Van Allen, 1968; Benton et al., 1983).*

This tests the ability of the child to match faces correctly and demonstrates facial processing without either a memory or a motor component. For the first six trials, six numbered faces and a test face are presented. The child is asked to say the number of the face which matches the test face.

There are a further 16 trials, which still have six numbered faces and a test face. However, the child is now asked to pick three faces which match the test face. These matching faces are pictures of the same person, but taken with different lighting conditions or from a different orientation. One point is given for each correctly matched face, giving a maximum score of 54. Any score below 39 is regarded as showing impairment (Mean = 41.5 ± 4.6; n = 22).

Patients with lesions to the right parietal lobe tend to do poorly on this task, whereas those with right temporal lobe lesions do not (Warrington & James, 1967; Wasserstein et al., 1984). However, there appears to be a linguistic component, because aphasic patients with comprehension problems do as poorly as patients with right hemisphere lesions (Hamsher et al., 1979).

**Benton Judgment of Line Orientation (Benton et al., 1975; Benton et al., 1983).*

This test requires matching of lines in different spatial orientations without a motor component. A template, which consists of eleven lines displayed as a fan, is presented with each line numbered. Five practice items are given, in which the child is shown a pair of unnumbered lines the same length as those on the template, and must say which of the template's lines they match. The test pairs, of which there are 30, are presented in an identical fashion, although the

lines to be matched are much shorter than those on the template. Both lines must be matched correctly for a point to be given, so the test is marked out of 30. Scores below 19 are indicative of a deficit, although this is derived from adult norms (Benton et al., 1978; Mean = 22.8 ± 6.2; n = 17).

Right hemisphere damaged patients do more poorly on this test than do patients with left hemisphere damage (Benton et al., 1975). However, cerebral blood flow increases bilaterally in temporo-occipital areas during this test, although the increase is greater on the right (Hannay et al., 1987).

Mooney Closure Faces Test (Mooney & Ferguson, 1951).

In this test, 22 degraded drawings of unfamiliar faces are presented to the child. The contrast is exaggerated to make identification of the faces difficult. The pictures are of both male and female faces, from three age groups (children, adults and old people). The child is asked to identify both the gender of the face and the age range. The time it takes to do this is noted. A number of scores are then obtained. The first is the number of correctly identified faces (Mean = 14.3 ± 4.5; n = 20), and then two mean reaction times, one for all the correct responses (Mean = 6.7 ± 2.6 s; n = 17) and another for all the wrong responses (Mean = 12.8 ± 16.9 s; n = 17).

This test has demonstrated sensitivity to damage in right temporo-parietal areas (Lezak, 1995), but it has not been shown to distinguish between patient groups on the basis of side of lesion (Wasserstein et al., 1987). However, patients with right temporal lobe removals have been shown to perform poorly on this task, making significantly more errors than those with left temporal

resections (Milner, 1990). This appears to be related, not to hippocampal excision, but rather to the posterior extent of the neocortical removal.

Unpublished norms have been collected by this centre for children between the ages of 6 and 12 (n = 143).

2.3.5 Tests of Executive Function

Wisconsin Card Sorting Test (WCST; Berg, 1948).

This test assesses abstraction and problem solving abilities and is believed to be sensitive to damage to the frontal lobes, particularly the dorsolateral prefrontal cortex (Milner, 1963; Weinberger et al., 1986). This is particularly pronounced on the left, since impairments are noted in patients with left frontal lobe epilepsy both before and after surgery. Patients with right frontal lobe epilepsy are only impaired post-operatively (Milner, 1963). Subjects are required to sort 128 cards according to three simple rules (colour, shape and number). However, they are not informed which rule to follow and must work it out from the information given by the tester ("right" or "wrong"). After they have obviously learnt a rule (ten correct responses in a row) the rule changes without warning. If the subject correctly sorts six times (i.e. goes through the three categories twice) the test is discontinued. Scores obtained from the test include the time taken to complete it (Mean = 742 ± 401 s; n = 32), the total number of categories achieved (Mean = 3.9 ± 2.3; n = 33), and the number of errors (Mean = 42.3 ± 30.9; n = 33), with particular emphasis placed on the number of perseverative errors. These occur when the subject fails to change from one set of responses because they have not taken feedback into account.

Norms for children between the ages of 6 and 16 have been collected for this test by this centre (n = 120).

Thurstone written fluency (Thurstone & Thurstone, 1962).

The child is asked to write as many words as possible in five minutes which begin with the letter S. He/she is then asked to write as many words as possible in four minutes, this time beginning with the letter C, with the added restriction that the words may only be four-letters long. For both conditions, the subject may not use plurals, nor more than one verb form. The total number of words produced for the two conditions are summed (Mean S words = 22.4 ± 11.7; n = 33; Mean C words = 7.3 ± 5.5; n = 32). Patients with left frontal lobectomies are seriously impaired on this task (Milner, 1975), when compared with left temporal lobectomy patients or those with right-sided resections. There are published norms available for this test for children between the ages of 6 and 18 (Kolb & Wishaw, 1996).

2.3.6 Other Tests

Dichotic Digits (Kimura, 1961).

This tests the auditory capacity of each ear separately but simultaneously, and is used as a way of determining lateralisation of speech and language functions. Using a dual-track sound system and listening through headphones, the subject hears three pairs of digits in rapid succession, one to each ear at precisely the same time. He/she is then asked to report the digits heard in any order. This is done six times with an interval between the pairs of digits of half a second, and another six times (with different pairs) with the interval lengthened

to 1.5 seconds. Normally, both digits are heard, but when one is missed it is generally in the ear ipsilateral to language dominance i.e. there is a right ear advantage for patients with left hemisphere dominance (Kimura, 1961; Kimura, 1967). A laterality index can therefore be obtained, demonstrating the likely dominant hemisphere of the subject. This asymmetry is thought to be due to the anatomy of the auditory system. Under normal circumstances, projections from the ears are sent to both hemispheres for processing. However, when different stimuli are presented simultaneously to each ear, it is thought that the ipsilateral pathway is suppressed. This means that information presented to the ear contralateral to the non-dominant hemisphere would first have to pass through that hemisphere and then across the cerebral commissures to reach the language processing regions of the brain. Information arriving in the dominant hemisphere in such a way would be likely to arrive with a slightly greater latency than information that is sent directly to the dominant hemisphere. This could explain the right-ear advantage seen in most people.

That this is a true reflection of hemispheric asymmetry is shown by the finding that subjects with reversed hemispheric dominance (i.e. in the right rather than the left) also have a reversed ear advantage (Zatorre, 1989).

In addition, the original study by Kimura (1961) showed that patients with damage to the left temporal lobe did more poorly than those with right temporal lobe damage. This test can therefore be used not only as an indication of the lateralization of language dominance, but also as a way of assessing the lateralization of brain damage.

Children below the age of 12 are given a somewhat simpler version of this test, which starts with only one pair of digits presented at a time, then two pairs

and finally three pairs. The same number of pairs are presented in total as in the adult test (36) but it is spread over three groups of six rather than two.

2.3.7 Academic Attainments

Wechsler Objective Reading Dimensions (WORD; Psychological Corporation, 1993)

This is an age-standardized test of scholastic achievement as it relates to reading ability. There are three subtests, basic reading, spelling, and reading comprehension. The basic reading subtest consists of single word reading, followed by a written spelling subtest. The child is read a word, followed by the word in a sentence to provide context cues. The child must then write the word. The final subtest consists of short passages of text which the child reads aloud. A comprehension question is then asked without removing the passage. This means that there is little or no memory contribution to this test (Mean Basic Reading = 99.0 ± 13.7; n = 22; Mean Spelling = 98.5 ± 14.9; n = 22; Mean Reading Comprehension = 91.5 ± 12.2; n = 22).

The subtests all have a mean score of 100 ± 15, but it is also possible to predict the subtest scores on the basis of Full Scale IQ from either the WISC-III^{UK} or from the WAIS-R. This allows for evaluation of the reading and spelling abilities of the child in comparison to his/her global cognitive function.

Wechsler Objective Numerical Dimension (WOND; Psychological Corporation, 1996)

This is an age-standardized test of scholastic achievement as it relates to numeracy and mathematical ability. The WOND contains two subtests;

mathematics reasoning and numerical operations. Mathematics reasoning consists of written questions (which are also read to the child by the examiner) which to a large extent are presented without mathematical signs. An example of the type of question in this subtest would be to order five fractions from least to greatest. The child is permitted to use a pencil and paper if they feel it will help. The numerical operations subtest is a sheet bearing a number of maths questions presented in symbol form, such as 42 + 125 = ___. The child is allowed to do rough work to assist in working out the answer.

As with the WORD, the subtests of the WOND have a mean of 100 ± 15, and can also be predicted from the child's WISC-III^{UK} Full Scale IQ. Again, this allows for an evaluation of the mathematical skills of the child in comparison to his/her cognitive abilities.

However, this test has only relatively recently been introduced to the protocol. Prior to this, the test used was the Number skills subtest of the British Ability Scale. This is basically the same as the numerical operations subtest of the WOND, but the norms are percentiles rather than standard scores.

2.4 Statistics

Statistical analysis was performed using SPSS for Windows 7.1.5 (SPSS Inc., Chicago, Ill., USA). Pearson's correlation coefficients (r), Spearman's rank-order correlation coefficients (ρ) were used to compare the relation of variables. Chi-square analyses (χ^2), non-parametric tests of variance (Kruskal-Wallis), one- and two-way analyses of variance (ANOVA) and Student's t-test

(both for paired and unpaired data) were used to compare the means of groups. Post-hoc analysis was performed with either Tukey's honestly-significant-difference (h-s-d), Dunnet's T3 analysis or simple planned contrasts. Finally, linear stepwise regression analyses were used to model the relationship between variables.

Chapter 3. The Relationship Between ^{1}H MRS, Hippocampal Volumetry and T2 Relaxometry in Patients with Temporal Lobe Epilepsy

3.1 Abstract

51 patients with a diagnosis of temporal lobe epilepsy were scanned using three quantitative MR techniques. The number of patients with mass lesions was noted and the incidence of bilateral pathology was assessed. The quantitative pathology scores were then correlated with each other to assess the degree of association between them for both patient groups (i.e. mass and non-mass lesions). A significant positive association between all three scores was noted for the non-mass lesion group, such that increased pathology on one score was associated with increased pathology on the others; for example, a decrease in hippocampal volume was associated with an increase in T2. In the mass-lesion group this was only the case for T2 and the NAA/(Cho+Cr) ratio, but there was also a trend for hippocampal volume to increase as T2 increased. This latter regression line proved to be significantly different from that for the non-mass lesion group on an analysis of variance. This difference has important implications for the interpretation of quantitative MR data.

3.2 Introduction

It is well known that surgical removal of a focal abnormality that is responsible for seizures can provide a cure for intractable temporal lobe epilepsy (TLE) in a significant proportion of patients. The resection of a definite lesion (either on pre-operative MRI or in the pathologic specimen) is associated with good seizure outcome in 60 to 90% of cases (Engel et al., 1993; Cascino et al., 1992). The identification of lesions to provide a target for surgery is therefore of great importance.

It is also important to identify lesions in as non-invasive a fashion as possible. This generally means using magnetic resonance (MR) techniques in preference to prolonged electroencephalographic (EEG) recordings using depth electrodes. This kind of invasive monitoring has declined dramatically over the past years, since it is now considered unnecessary in patients with clearly defined unilateral lesions on MR whose scalp-recorded EEG shows ictal changes on the same side (Jack, 1996).

As outlined in Section 1.6, a number of quantitative magnetic resonance methods have been developed for the evaluation of hippocampal and temporal lobe pathology, and these methods can greatly aid the identification of epileptogenic regions. The methods include hippocampal volumetry (Cook et al., 1992; Jack et al., 1990) and T2 relaxometry (Jackson et al., 1993b) for assessment of hippocampal pathology, and ^{1}H MRS (Connelly et al., 1994) for assessment of diffuse temporal lobe pathology. The most commonly seen pathology in TLE is medial temporal sclerosis (MTS), and its most common

appearance on MR measures is a hippocampus with an increased T2 and a small HFV.

Hippocampal volumetry has been shown to be a more sensitive technique for identifying hippocampal atrophy than visual inspection (Reutens et al., 1996), and the amount of neuronal loss from the hippocampus has been shown to correlate with hippocampal atrophy (Cascino et al., 1991; Lencz et al., 1992; Van Paesschen et al., 1997). In addition, hippocampal volumetry has been shown to be a specific marker for MTS, since seizures originating at extrahippocampal sites do not cause hippocampal atrophy or gliosis (Watson et al., 1997). Conversely, in patients with TLE, MTS has been shown to be associated with bilateral extrahippocampal and extratemporal volume deficits which may or may not be a result of epileptic seizures (Marsh et al., 1997). Hippocampal volumes generally have been shown to correlate well with the clinical and EEG lateralization of seizures (Ashtari et al., 1991; Bronen et al., 1991), and as such are now a widely used clinical tool in the investigation of patients with intractable TLE.

T2 relaxometry has also been shown to improve identification of hippocampal sclerosis (Jackson et al., 1993b), and is stable over a 12 month period even in chronic epilepsy (Grünewald et al., 1994). At Great Ormond Street Hospital/Institute of Child Health, a T2 greater than 108 ms is indicative of hippocampal pathology, whilst MTS is characterized by an elevation of the hippocampal T2 relaxation time to 116 ms or more (Jackson et al., 1993b). Jackson and colleagues (Jackson et al., 1993b) also noted that 29% of their subjects had bilateral hippocampal abnormalities when assessed with T2 relaxometry. This figure is very close to the 31% of cases of bilateral MTS

reported by Margerison and Corsellis (1966) in a study of post-mortem tissue from patients with intractable TLE. Elevated T2 may be indicative of increased tissue-free water (Jack, 1996), but there are a number of changes which can result in an increase or decrease of T2 relaxation time and it is not certain exactly what causes the increase in T2 seen in MTS. It is possible that other disease processes which are also characterized by hippocampal damage will not show the same lengthening of T2, and this has in fact been demonstrated for patients with Alzheimer's disease (Pitkänen et al., 1996). In addition, T2 has been shown to be no different when measured immediately after a single seizure and again following 72 hours with no seizures (Grünewald et al., 1994). This implies that there were no seizure-induced changes in hippocampal tissue water, and that the relaxation time measured was a feature of the chronic abnormalities seen in MTS.

The study of more diffuse temporal lobe pathology with ^{1}H MRS has been useful in aiding lateralization of the seizure focus of patients with TLE (Connelly et al., 1994; Ng et al., 1994; Cross et al., 1996). By using a ratio of NAA/(Cho+Cr), these studies have revealed a high incidence of bilateral pathology of around 40% of patients. This too is consistent with adult post-mortem studies which showed that around half of the specimens had bilateral temporal lobe pathology, with additional neuronal loss frequently identified in the cerebral cortex, thalamus and cerebellum (Margerison & Corsellis, 1966).

In a recent study of adult patients with TLE (Van Paesschen et al., 1995), it was shown that ipsilateral T2 correlated with HFV ratio (ipsilateral/contralateral), such that a high T2 was associated with a smaller ratio. This held whether the patient had MTS, a mass lesion such as a

dysembryoplastic neuroepithelial tumour (DNET), amygdala sclerosis, or end-folium sclerosis. However, there was a tendency towards a large HFV ratio (greater than one) in patients with a temporal lobe mass lesion (i.e. the ipsilateral HFV tends to be high and the T2 tends to be low). If this asymmetry were large enough, it could be regarded as a discordant result suggesting MTS in the contralateral temporal lobe. This in turn would reduce the probability of the patient being offered surgery, on the grounds that seizure reduction would be unlikely and that cognitive function could be gravely impaired post-operatively. However, it is possible that the enlarged HFV seen on the ipsilateral side could be a result of infiltration of the tumour into the hippocampus. Knowledge of this could materially affect the chances of surgical intervention.

In this chapter the relationship between the NAA/(Cho+Cr) ratio and hippocampal pathology is examined in children with TLE. Since the region of interest selected for ^{1}H MRS is placed such that the hippocampus makes only a small contribution to the observed ^{1}H MRS signals, we would predict that the correlation between NAA/(Cho+Cr) and T2 or HFV would not be as good as that between the two measures of hippocampal pathology. In addition, we might expect a discrepancy in the relationships between the pathology scores depending on the precise pathology being examined. Patients with MTS should display a highly significant relationship such that T2 and HFV are closely related (Van Paesschen et al., 1995; Van Paesschen et al., 1997), whilst in patients with temporal lobe mass lesions this may not be so.

3.3 Methods

3.3.1 Subjects

51 subjects (21 males, 30 females; median age 12y 0m) were scanned as part of investigations for possible epilepsy surgery (see Appendix I for patient data). The only selection criterion was a diagnosis of temporal lobe epilepsy, based on clinical and EEG findings. The identification of the neurological lesion was made by a neuroradiologist on the basis of visual inspection of standard clinical images.

3.3.2 Magnetic Resonance

All subjects were scanned as outlined in Section 2.2. MR measures included T2 relaxometry (n=43), hippocampal volumetry (n=38) and NAA/(Cho+Cr) signal intensity ratios (n=45). Results from all three measures were available in 32 cases. In addition, correlations between T2 and NAA/(Cho+Cr) were possible in 37 cases, between T2 and HFV in 38 cases, and between HFV and NAA/(Cho+Cr) in 32 cases.

3.3.3 Statistics

Although the quantitative MR scores are normally distributed in the normal population, this is not the case for the pathological data to be presented. Because of this, it was more appropriate to use a non-parametric measure of correlation, the Spearman's rank-order correlation coefficient (ρ). In addition, chi-squared (χ^2) analysis of frequency, t-tests and analyses of variance were carried out where indicated to identify significant differences between groups.

3.4 Results

3.4.1 Bilateral pathology

Of the 51 patients examined with quantitative MR techniques, 15 were found to have a mass lesion (e.g. a DNET) in one temporal lobe. Of these 15, nine (60%) showed bilateral damage on at least one measure of pathology, compared with 18 of the remaining 36 (50%), which is not a significant difference (χ^2 crit. = 3.84; χ^2 calc. = 0.43). The groups were therefore collapsed across lesion type.

Of all patients, 13/45 showed bilateral pathology on NAA/(Cho+Cr) ratios (28.9%), 11/43 showed bilateral hippocampal abnormalities on T2 relaxometry (25.6%) and 12/38 had bilaterally small hippocampi (31.6%). Only one patient showed bilateral abnormalities on all three measures.

3.4.2 Correlations between pathology scores

Table 3.1 shows the correlations between pathology scores for two different groups (mass lesions and non-mass lesions) using a one-tailed Spearman's rank-order correlation.

	Temporal lobes with mass lesions	**Temporal lobes without mass lesions**
T2 against HFV	$\rho = 0.367$; p = 0.098	$\rho = -0.644$; **p < 0.001**
T2 against NAA/(Cho+Cr)	$\rho = -0.618$; **p = 0.021**	$\rho = -0.395$; **p = 0.001**
NAA/(Cho+Cr) against HFV	$\rho = -0.195$; p = 0.295	$\rho = 0.367$; **p = 0.005**

Table 3.1 Spearman's rank-order correlation data for groups with and without mass lesions

On examining the regression lines of the two pathology groups for T2 against HFV (Figure 3.1) there appears to be a difference between the two distributions. This was confirmed by a two-way analysis of variance (ANOVA). In this test, the two pathology groups (mass lesions and non-mass lesions) were split into two, depending on whether their T2 was 109 ms or more (i.e. more than two standard deviations above the mean) or below this figure. The aim of this test was to determine whether there was a significant difference between the pathology groups in terms of their HFV, a difference between the T2 groups in terms of their HFV, and/or if there was an interaction between them.

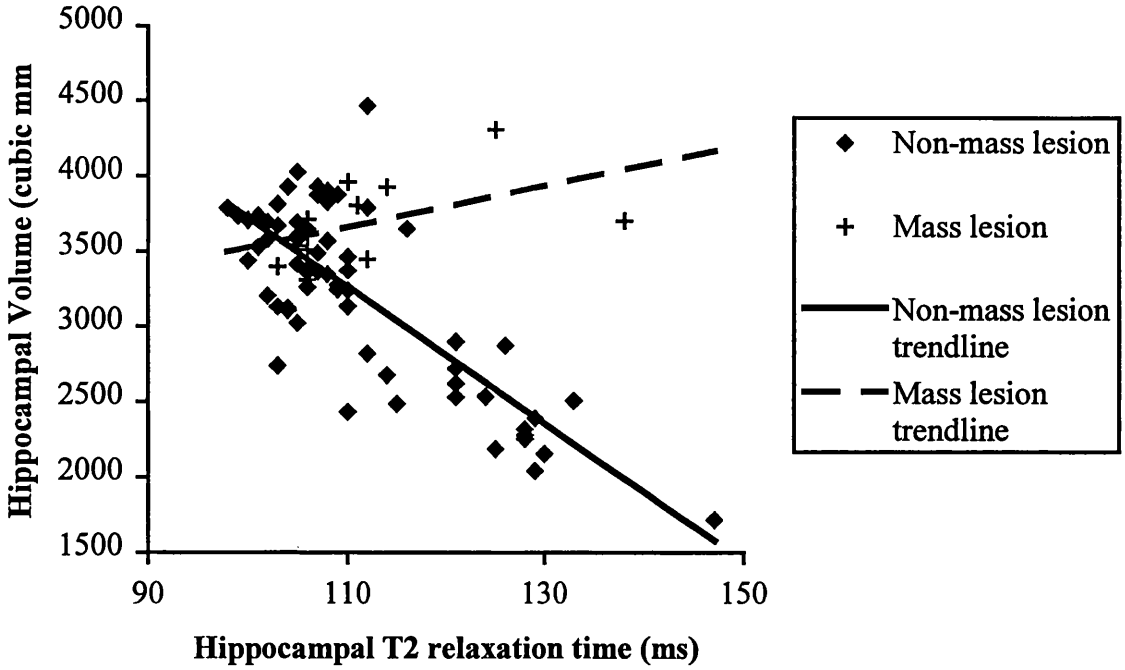

Figure 3.1 Graph showing HFV against T2 for patients with and without mass-lesions.

The ANOVA revealed a significant difference in HFV by pathology (F (1, 75) = 12.18, **p = 0.001**), but not one by T2 (F (1, 75) = 1.53, p = 0.221). However, there was a significant interaction between the groups (F (1, 75) = 13.21, **p = 0.001**). On investigation with a two-tailed t-test assuming unequal variances, a significant difference was found between the HFVs of the patients with mass lesions and those without when both groups had an abnormal (high) T2 (t = 6.22, **p < 0.001**). This was not so when both had a normal T2 (t = -0.26, p = 0.797). This is shown in Figure 3.2.

No such relationship exists between T2 and NAA/(Cho+Cr), or between HFV and NAA/(Cho+Cr).

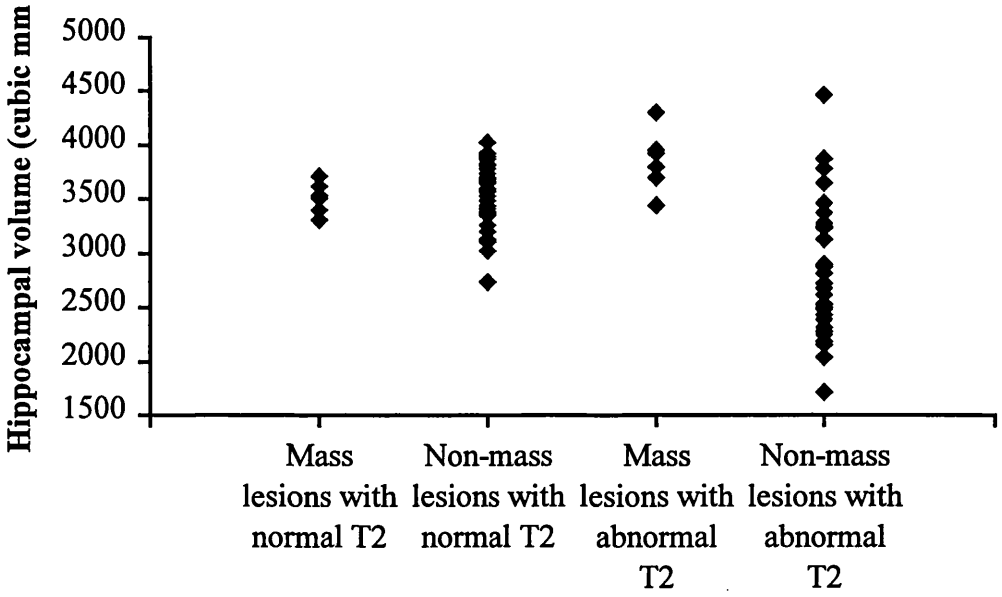

Figure 3.2 Graph showing the HFV for both pathology groups, the groups being divided into those with normal and those with abnormal T2 values.

3.5 Discussion

The results shown above demonstrate that the relationship between hippocampal pathology as measured by T2 and as measured by HFV is different depending on the type of pathology being examined. Temporal lobes with no mass lesion show a highly significant decrease in HFV with an increase in T2, whilst those containing a mass lesion show a trend towards a greater HFV as T2 increases.

The results also show a high degree of bilateral pathology. This supports the findings of Jackson and colleagues (Jackson et al., 1993b), who found that 29% of patients had bilateral hippocampal abnormalities as measured by T2 (compared with 26% of this population). However, the number of patients with bilaterally low MRS ratios was below that previously reported. In this

population there were only 29% with bilateral abnormalities, compared with 45% in the population studied by Cross and colleagues (Cross et al., 1996). This difference is most likely due to chance; an intermediate number (40%) have been found in adult studies (Connelly et al., 1994).

The correlation between hippocampal pathology measures and NAA/(Cho+Cr) is not surprising, even though MTS is primarily a disease of the hippocampus, since the finding is consistent with previous studies (Connelly et al., 1994; Ng et al., 1994; Cross et al., 1996). However, the association is weaker than the correlation between T2 and HFV. This is an indication of the value of using both techniques, since it demonstrates that the NAA/(Cho+Cr) ratio is detecting pathology that is not being shown by measures of hippocampal damage and vice versa. Clearly, though there is frequently an association between MTS and NAA/(Cho+Cr) abnormalities, there does not have to be one (as, for example, in patient WW who has a right cortical dysplasia with an abnormal right NAA/(Cho+Cr) ratio but normal right T2 and HFV). In addition, the pathology which gives rise to ^{1}H MRS abnormalities is often not visible directly with MRI, which adds to its usefulness (Connelly et al., 1994).

The difference in the relationship between T2 and HFV depending on the lesion-type is important, since it has implications for the interpretation of these data in the clinical setting. In one study that examined this relationship (Van Paesschen et al., 1995), a good inverse association was found between the hippocampal volume ratio and T2. In four patients with mass lesions, however, there was little increase in T2 and only mild volume asymmetry (although the hippocampus tended to be larger on the side of the lesion). The results shown above suggest that, in general, patients with mass lesions show only mild

abnormalities on T2, but this is associated with maintained, or even increased HFV. This may be a result of infiltration of the lesion into the hippocampus, returning an elevated T2 signal and an unchanged (or slightly elevated) HFV. Tumour infiltration of the hippocampus and surrounding regions is known to differ widely between patients (Mathern et al., 1995), which may explain the weaker relationships between the MR measures for the mass lesion group.

Even in the non-mass lesion group, though, there is not a one-to-one correspondence between T2 and HFV. There are at least three reasons why this might be so. Firstly, it is possible that what is left of an atrophied hippocampus may be fully functional and appear normal on T2 relaxometry; secondly, since T2 is only measured on a single slice, it can miss focal atrophy which is more posterior and/or anterior than the slice position; and thirdly, there is simply more variability in HFV than there is in T2, both between subjects and due to intrarater error (this can be seen from the standard deviations for the two measures - for T2, it is slightly less than 3%, but for HFV it is more than 7%). The former reason would suggest that HFV is providing information only on what has been *lost* rather than on the integrity of what remains, whilst T2 reflects the functional status of the residual hippocampus. There is the further possibility that T2 and HFV are measuring different pathologies within the hippocampus. T2 is associated with pathology in layers CA1 and the hilus, whilst HFV is associated with pathology in CA1, CA2, CA3 and the hilus (Van Paesschen et al., 1997).

In summary, the relationship between T2, HFV and NAA/(Cho+Cr) ratios has been shown in a population of children with temporal lobe epilepsy. These demonstrated significant associations in patients without temporal lobe mass

lesions, such that an increase in pathology as measured by one technique was associated with an increase in the pathology measured by both the other techniques. This was not the case in those patients with mass lesions, but there was a trend towards a positive correlation between T2 and HFV. Analysis of variance showed that there was a significant difference between the two patient populations for this comparison. This has implications for the interpretation of quantitative MR data when making diagnoses for temporal lobe epilepsy.

Chapter 4. A Comparison Between Patients With Left and Right Temporal Lobe Epilepsy and Normal Controls using the WISC-III^{UK} Intelligence Test and the Wechsler Memory Scale

4.1 Abstract

Epilepsy is known to be detrimental to learning and memory. Much of the literature suggests that the exact nature of the cognitive deficit is dependent on the location of the seizure focus, such that left-sided seizures result in a verbal learning and memory deficit, whilst right-sided seizures adversely affect non-verbal functions. However, these studies have concentrated on adults, and it is not certain that children suffer in a similar fashion.

25 young patients with temporal lobe epilepsy and 25 age-matched normal controls were compared using the Wechsler range of intelligence tests and the Wechsler Memory Scale. 17 of the patients had left-sided seizures, whilst the remaining 8 had right-sided seizures.

There were no significant differences between the IQ scores of the three groups, but significant differences between the groups were identified on tests of delayed recall and retrieval. However, this was usually due to the fact that the normal group performed significantly better than the left TLE group, with the right TLE group falling between the two and not being significantly different

from either. Whilst this gives support to studies that have found impaired verbal functioning in patients with left-sided seizures, it also raises the possibility that bilateral pathology may be a confounding variable. This might be clarified through the use of quantitative MR methods.

4.2 Introduction

There has long been an acknowledged association between epilepsy and memory impairment in adults (Gowers, 1881; Milner, 1975), and this can be a cause of slow learning (Loiseau et al., 1982) and even amnesia (Engel et al., 1978). Group studies have indicated that, in general, epilepsy contributes to poor intelligence through the occurrence of seizures in early childhood (Glosser et al., 1997), although MTS is also significantly associated with a generalized cognitive impairment (Hermann et al., 1997). This impairment does not appear to have a lateralizing component in that patients with either right- or left-sided TLE are equally impaired, although in one study left-sided TLE patients scored significantly lower on the Vocabulary subtest of the WAIS (Hermann et al., 1995b).

A number of studies have shown that TLE can affect memory function dependent on the side of seizure lateralization (Delaney et al., 1980; Loring et al., 1988a), but this is not a consistent finding. Although left-sided TLE almost always results in a verbal memory deficit, non-verbal memory deficits and right-sided TLE have less frequently been associated (Barr, 1997; Barr et al., 1997; Hermann et al., 1997).

Most studies of cognitive functions in children with epilepsy have concentrated only on general intelligence and behaviour (Seidenberg et al., 1986; Camfield et al., 1984). One of the few studies to examine memory function in children with right and left temporal lobe epilepsy (TLE) indicated a material-specific dissociation in memory abilities, as described in Section 1.1, such that patients with left-sided TLE had a verbal memory impairment whilst patients with right-sided TLE had a non-verbal memory impairment (Fedio & Mirsky, 1969). This is consistent with the pattern of lateralization observed in adults both following temporal lobectomy (Milner, 1958; Milner, 1975) and also prior to possible surgical intervention (Delaney et al., 1980). A later study by Jambaqué and colleagues also found that epilepsy may contribute to memory deficits in children as it does in adults (Jambaqué et al., 1993). By using the Signoret Memory Battery, they were able to identify lateralized memory deficits in children with right and left TLE. They concluded, therefore, that children show hemispheric specialization for cognitive functions from at least the age of seven. However, they did not find that measures of general intelligence discriminated between these two groups in terms of their overall verbal or non-verbal cognitive function.

However, another study failed to find this hemispheric specialization when investigating children with an experimental memory test (Cohen, 1992). Although children with left-sided TLE performed lower than controls on tests of verbal memory, and children with right-sided TLE performed lower than controls on tests of non-verbal memory, in general the right and left TLE groups did not significantly differ. The exact nature of the lateralization of function in children remains uncertain.

In this study, children with well-lateralized epilepsy of either right or left temporal lobe onset were compared with normal child controls on tests of general intelligence and memory function. It was predicted that the TLE patients would exhibit a similar pattern of memory lateralization to that discovered in adults, although it was uncertain whether the same would be found for tests of intelligence.

4.3 Methods

4.3.1 Subjects

26 patients (10 male, 16 female) were recruited from the epilepsy programme at Great Ormond Street Hospital on the basis of their inclusion in Chapter 5. More specifically, only these 26 patients had all of the three MR measures of temporal lobe pathology discussed in the Chapter 3. However, one (NW) was then excluded since she did not have definitively lateralized TLE. The median age at assessment of the remaining 25 was 13y 11m (range 6y 3m to 17y 8m). On the basis of clinical and EEG investigations, they were divided into two groups; one with left-sided epilepsy (n = 17; median age 13y 8m) and another with right-sided epilepsy (n = 8; median age 15y 9m).

In addition, 25 normal children (8 male, 17 female; median age 12y 11m, range 6y 8m to 16y 5m) were also investigated. These children were matched as far as possible with the TLE group on the basis of age and IQ. This meant that the same number of subjects in both the control group and the TLE group received the children's stories on the WMS.

4.3.2 Neuropsychological evaluation

All children were tested with the WISC-III^{UK} to assess global cognitive function and the WMS to assess memory abilities (see Section 2.3 for descriptions). However, results were not always obtained from all subjects for all measures.

All patients were right-handed. Since the dichotic digits laterality index was not administered to all patients, it was not possible to use it to classify their hemispheric specialization.

4.4 Results

The three groups did not significantly differ in terms of their ages (χ^2 (2, 50) = 2.27, p = 0.322; Kruskal-Wallis test).

4.4.1 Comparison of IQ scores

The data from the three subject groups for the WISC-III^{UK} intelligence test are shown in Table 4.1.

	Left TLE Patients	Right TLE Patients	Normal Controls
VIQ	87.4 ± 12.9	97.6 ± 21.4	99.0 ± 14.1
PIQ	97.5 ± 21.4	94.0 ± 17.1	105.9 ± 11.4
FSIQ	90.6 ± 16.9	95.5 ± 20.2	102.2 ± 11.7

Table 4.1 Mean IQ scores (± standard deviations) for the three subject groups.

A single-factor analysis of variance (ANOVA) was performed on the IQ data. There was no significant difference between the groups for either VIQ (F (2, 47) = 3.15, p = 0.052), PIQ (F (2, 47) = 2.25, p = 0.116) or FSIQ (F (2, 47) = 3.09, p = 0.055), although both VIQ and FSIQ were very close to significance. However, a two-tailed one-sample t-test found that the performance of the normal controls was significantly higher than the population mean of 100 for PIQ (VIQ; t (24) = -0.35, p = 0.727: PIQ; t (24) = 2.57, **p = 0.016**: FSIQ; t (24) = 0.96, p = 0.347). The same test was then performed for both the left and right TLE patients. Those with left TLE did not have PIQ scores which were significantly different from 100 (t (16) = -0.48, p = 0.641), although both their VIQ scores (t (16) = -4.02, **p = 0.001**) and FSIQ scores (t (16) = -2.30, **p = 0.035**) were. The patients with right TLE did not have scores significantly different from 100 for any of the three IQ measures (VIQ; t (7) = -0.31, p = 0.763: PIQ; t (7) = -0.99, p = 0.355: FSIQ; t (7) = -0.63, p = 0.548).

It can be seen from Table 4.1 that the difference between VIQ and PIQ is much larger for the patients with left TLE than it is for either of the other two groups. In order to assess this, a two-way ANOVA was performed, with IQ as a repeated measure. This indicated that there was no significant group difference as would be expected (F (2, 47) = 2.80, p = 0.071), but also no significant interaction between IQ and group (F (2, 47) = 2.23, p = 0.119). This shows that though the left TLE group has a larger VIQ - PIQ discrepancy than both the right TLE group and the normal controls, it is not significantly so.

A single-factor ANOVA was also performed on the data from each subtest of the VIQ (shown in Table 4.2). These indicated a significant group difference for the Information, Vocabulary and Comprehension subtests only (Information;

F (2, 47) = 4.64, **p = 0.015**: Similarities; F (2, 47) = 1.00, p = 0.374: Arithmetic; F (2, 46) = 0.27, p = 0.762: Vocabulary; F (2, 46) = 3.72, **p = 0.032**: Comprehension; F (2, 46) = 4.43, **p = 0.017**: Digit Span; F (2, 46) = 0.09, p = 0.915). Post-hoc analyses using Tukey's h-s-d test revealed that the patients with left-sided TLE performed significantly below the normal controls on the Information, Vocabulary, and Comprehension subtests ($p < 0.05$).

	Left TLE Patients	**Right TLE Patients**	**Normal Controls**
Information	6.6 ± 2.4	9.6 ± 4.9	9.7 ± 3.3
Similarities	8.6 ± 2.7	9.9 ± 4.6	9.9 ± 2.5
Arithmetic	9.3 ± 3.4	9.6 ± 3.0	10.0 ± 3.1
Vocabulary	6.9 ± 1.9	8.5 ± 3.5	9.1 ± 2.7
Comprehension	7.6 ± 2.8	10.6 ± 3.8	10.1 ± 2.8
Digit Span	8.8 ± 2.6	9.3 ± 3.2	8.8 ± 2.7

Table 4.2 Mean verbal IQ subtest scores (± standard deviations) for the three subject groups.

However, a two-tailed one-sample t-test found that the scores of the normal controls were significantly lower than the population mean of 10 for the Digit Span subtest (t (24) = -2.25, **p = 0.034**). When the patients were examined with the same test, it was found that those with left TLE were significantly different from 10 on three subtests (Information; t (16) = -5.65, **p < 0.001**: Vocabulary; t (15) = -6.73, **p < 0.001**: Comprehension; t (16) = -3.51, **p = 0.003**). Those with right TLE were not significantly different from 10 on any subtest.

Table 4.3 shows the data from the three subject groups for the PIQ subtests.

	Left TLE Patients	Right TLE Patients	Normal Controls
Picture Completion	9.5 ± 4.1	8.8 ± 2.4	10.9 ± 2.4
Coding	9.2 ± 3.3	8.8 ± 2.7	10.8 ± 3.2
Picture Arrangement	8.1 ± 3.0	7.3 ± 4.1	10.2 ± 2.7
Block Design	10.1 ± 4.5	10.6 ± 4.2	10.5 ± 2.6
Object Assembly	10.6 ± 3.9	9.8 ± 2.1	11.2 ± 2.6
Symbol Search	10.2 ± 3.2	8.0 ± 2.2	11.7 ± 2.3

Table 4.3 Mean performance IQ subtest scores (± standard deviations) for the three subject groups.

Single-factor ANOVA demonstrated significant group differences for the Picture Arrangement and Symbol Search subtests (Picture Completion; F (2, 47) = 2.47, p = 0.095: Coding; F (2, 45) = 1.86, p = 0.168: Picture Arrangement; F (2, 45) = 3.85, **p = 0.029**: Block Design; F (2, 46) = 0.10, p = 0.905: Object Assembly; F (2, 46) = 0.79, p = 0.459: Symbol Search; F (2, 43) = 5.77, **p = 0.006**).

Post-hoc Tukey's h-s-d analyses revealed that right TLE patients performed significantly more poorly than normal controls on the Symbol Search subtest ($p < 0.05$), but that there was no significant difference for the Picture Arrangement subtest.

Again, a two-tailed one-sample t-test was carried out using the normal controls. This time it was found that they scored significantly higher than the population mean of 10 on only two PIQ subtests, Object Assembly and Symbol

Search (Object Assembly; t (24) = 2.37, **p = 0.026**: Symbol Search; t (24) = 3.59, **p = 0.001**).

When the patients were examined with the same test, it was found that the mean scores of those with left TLE were only significantly different from 10 for the Picture Arrangement subtest (Picture Arrangement; t (15) = -2.49, **p = 0.025**). The mean scores of those with right TLE, however, were only significantly different from 10 for the Symbol Search subtest (Symbol Search; t (6) = -2.45, **p = 0.050**).

4.4.2 Comparison of memory scores

Initially, the influence of IQ on the memory function was investigated. IQ could conceivably have a large effect on the performance of these memory scores, which would then need to be factored out using a covariance method. Strictly speaking, in order to do this the regression lines of each memory variable against the relevant IQ score must be the same for all three groups. This is to ensure that there is no interaction between groups and IQ. It has already been indicated above (Section 4.4.1) that though there is a difference across the groups, this interaction is not significant.

Six scores from the WMS were found to be dependent on overall intellectual function (MQ, D', D, VPA Score, VPA Hard and C'), and these scores were covaried for FSIQ. A further three were found to be dependent on the level of verbal function (LM-I, LM-D and C), and so these scores were covaried for VIQ. The remaining five scores (LM-%, D%, VPA Easy, VPA Del and C%) were not covaried for any of the IQ scores.

Single-factor ANOVA covarying for either FSIQ or VIQ were therefore performed on the overall Memory Quotients and the subtests of the WMS. Table 4.4 presents both the raw means with standard deviations, and also the adjusted means, for certain scores derived from the WMS. These are the MQ, Logical Memory and Visual Reproduction subtests. Only LM-% and D% showed significant group differences (MQ; F (2,46) = 2.00, p = 0.147: LM-I; F (2,46) = 1.07, p = 0.352: LM-D; F (2,46) = 2.02, p = 0.145: LM-%; F (2,47) = 4.20, **p = 0.021**: D'; F (2,46) = 0.89, p = 0.419: D; F (2,46) = 3.01, p = 0.059: D%; F (2,47) = 6.29, **p = 0.004**).

	Left TLE Patients	**Right TLE Patients**	**Normal Controls**
MQ (Adj. for FSIQ)	87.4 ± 18.2 (Adj. = 90.4)	95.9 ± 10.5 (Adj. = 96.2)	102.4 ± 14.2 (Adj. = 99.0)
LM-I (Adj. for VIQ)	6.3 ± 3.1 (Adj. = 6.9)	7.8 ± 3.1 (Adj. = 7.6)	8.6 ± 3.0 (Adj. = 8.3)
LM-D (Adj. for VIQ)	3.7 ± 3.2 (Adj. = 4.2)	5.6 ± 3.7 (Adj. = 5.3)	6.8 ± 3.5 (Adj. = 6.4)
LM-%	52.9 ± 29.2	64.6 ± 25.4	77.9 ± 27.1
D' (Adj. for FSIQ)	9.1 ± 3.3 (Adj. = 9.6)	10.6 ± 3.0 (Adj. = 10.6)	11.1 ± 2.3 (Adj. = 10.6)
D (Adj. for FSIQ)	7.1 ± 4.0 (Adj. = 7.6)	7.8 ± 4.1 (Adj. = 7.8)	10.5 ± 2.4 (Adj. = 9.9)
D%	72.8 ± 29.4	70.9 ± 21.9	93.2 ± 12.2

Table 4.4 Mean raw MQ, Logical Memory and Visual Reproduction scores (± standard deviations) and means adjusted for IQ (Adj.) for the three subject groups.

Post-hoc analyses were then performed. These indicated that for the LM-% score, only left TLE patients performed significantly below normal controls (p <

0.05) whilst left and right patients were not significantly different from each other (Tukey's h-s-d). In contrast, on the D% measure, both left and right TLE patients performed significantly below normal controls ($p < 0.05$; Tukey's h-s-d). However, there was no significant difference between the two patient groups.

Table 4.5 shows the raw means and standard deviations from the three subject groups for the VPAL and Composite Score subtests, and also the means adjusted for either FSIQ or VIQ.

	Left TLE Patients	**Right TLE Patients**	**Normal Controls**
VPA Score	13.0 ± 4.5	16.1 ± 2.0	16.4 ± 3.4
(Adj. for FSIQ)	(Adj. = 13.4)	(Adj. = 16.1)	(Adj. = 15.9)
VPA Easy	14.8 ± 3.2	17.9 ± 0.4	16.5 ± 1.9
VPA Hard	5.5 ± 3.2	7.1 ± 2.0	8.2 ± 2.6
(Adj. for FSIQ)	(Adj. = 5.9)	(Adj. = 7.2)	(Adj. = 7.8)
VPA Del	7.3 ± 2.6	9.3 ± 1.2	9.2 ± 1.3
C'	14.5 ± 4.4	17.3 ± 3.2	18.1 ± 3.4
(Adj. for FSIQ)	(Adj. = 15.0)	(Adj. = 17.4)	(Adj. = 17.5)
C	11.0 ± 4.9	14.8 ± 4.5	16.0 ± 3.8
(Adj. for VIQ)	(Adj. = 11.7)	(Adj. = 14.5)	(Adj. = 15.6)
C%	73.7 ± 17.7	84.3 ± 13.7	88.6 ± 12.1

Table 4.5 Mean raw VPAL and Composite scores (± standard deviations) and means adjusted for IQ (Adj.) for the three subject groups.

Single-factor ANOVAs were performed on the data. These revealed significant group differences for the VPA Easy, VPA Del, C and C% scores only (VPA Score; F (2,46) = 2.75, p = 0.075: VPA Easy; F (2,47) = 5.36, **p = 0.008**: VPA Hard; F (2,46) = 2.43, p = 0.099: VPA Del; F (2,47) = 6.43, **p =**

0.003: C'; F (2,46) = 2.55, p = 0.089: C; F (2,46) = 4.16, **p = 0.022**: C%; F (2,47) = 5.40, **p = 0.008**).

Post-hoc simple planned contrasts indicated that for the C score, left TLE patients scored significantly lower than normal controls (t = -2.87, **p = 0.006**) whilst patients with right TLE did not (p = 0.524). The TLE patients were not significantly different from one another (t = 1.59, p = 0.119). Post-hoc Tukey's h-s-d analyses on VPA Easy, VPA Del and C% were also performed. These showed that the patients with right TLE scored significantly better than those with left TLE on both VPA Easy and VPA Del, but the control group outscored the left TLE group only on VPA Del ($p < 0.05$). For the C% score, the control group scored significantly higher than the left TLE group, whilst the two patient groups were not different ($p < 0.05$).

4.5 Discussion

The results presented above show a number of differences between children with lateralized epilepsy, and normal controls. In particular, patients with left TLE had low VIQ scores and low scores on tests of recall, especially of verbal information, when compared to normal children. However, they tend not to show significant differences from those patients with right TLE, and indeed for some scores (D%), patients with right TLE also perform significantly lower than controls.

Neither left nor right TLE patients performed significantly below the level of the normal controls on the Wechsler Intelligence Scale. This is unsurprising,

since the control population was IQ-matched as far as possible. However, those with left-sided TLE did perform significantly below the population mean of 100 on VIQ and FSIQ. It therefore appears that left TLE results in an impairment of general verbal functioning but that right TLE does not result in a significant impairment of non-verbal functions or overall cognitive functions (i.e. FSIQ).

These findings show significant differences from the results of studies of adult patients with TLE, in that the impairments in verbal and performance IQ appear related to the side of seizure onset (Glosser et al., 1997; Hermann et al., 1997). The analyses of the performance on the subtests of the verbal IQ scale also reveal a difference between adults and children. It has already been shown in adults that performance on the Vocabulary subtest reliably distinguishes left TLE patients from those with right-sided seizures, whilst performance on the other subtests shows no difference between the groups (Hermann et al., 1995b). In the results presented in this chapter, however, patients with left TLE performed significantly worse than controls on the Information and Comprehension subtests, as well as the Vocabulary subtest. In addition, on none of these three subtests was the performance of those with right and left TLE significantly different. Indeed, the mean score of the right TLE group on the Vocabulary subtest was the lowest of all the verbal subtests. However, this description hides the fact that on all verbal subtests, left TLE patients scored lower than right TLE patients. Equally, the non-significant differences between TLE patients on the performance subtests disguise the fact that it is the right TLE patients who score lowest on these tasks.

The failure to find significant differences between the two patient groups is likely to be due to one or more of three factors. Firstly, there are fewer patients

with right-sided TLE, meaning that there is less statistical power to find significant differences; secondly, there are likely to be factors which are similar between the two groups which affect cognitive performance, such as the presence of seizures and the consequent need to take medication. The deleterious effects of anti-epileptic medication on cognitive performance have been well documented, but the methodology used in many past studies has been criticized for a number of reasons (see Meador & Loring, 1991 for a review). These are selection bias, lack of attention to drug blood serum levels, a tendency to compare different drugs across studies, and the use of numerous statistical tests in order to 'disprove' the null hypothesis. A number of studies have now indicated that there might be no great effect of medication on cognitive performance (Aman, Werry, Paxton et al., 1994; O'Dougherty, Wright, Cox et al., 1987), and indeed one found that subjects showed improvement under peak concentrations (Aman, Werry, Paxton et al., 1990). Another multicentre study of 83 patients indicated a slight improvement in performance following withdrawal of medication, but since this improvement was also found in the control group it is likely to be a practice effect (Tonnby, Nilsson, Aldenkamp et al., 1994). It seems likely that impaired performance at higher dosages (and thus higher concentrations) may be indicative of more severe epilepsy rather than an effect of the drug per se.

The third, and possible most important factor, is that the two groups of patients are likely to contain significant numbers of subjects with bilateral pathology (Cross et al., 1996). This bilateral pathology may be responsible for the low scores of both groups of patients when compared to the normal controls.

The finding of preserved Digit Span in both right and left TLE supports the findings of Canavan and colleagues in adults (Canavan et al., 1989). In addition, it implies that the group is well selected in terms of the specificity of TLE without more posterior involvement. This is because Digit Span is a test of working memory involving the articulatory loop, which includes a subvocal rehearsal system and a phonological store. Functional imaging using positron emission tomography (PET) has suggested a temporo-parietal location (the left supramarginal gyrus) for the phonological store, whilst the rehearsal system was associated with Broca's area (Paulesu et al., 1993). This has since been replicated using functional MRI (Paulesu et al., 1995).

The finding that patients with left-sided TLE perform poorly on tests of verbal memory is unsurprising, since this has been reported frequently in the past in adults (Delaney et al., 1980; Loring et al., 1988a), and less frequently but consistently in children (Fedio & Mirsky, 1969; Cohen, 1992; Jambaqué et al., 1993). The failure of the visual reproduction subtest to distinguish between patients with right- or left-sided TLE is also found in the adult literature, most recently in a multi-centre study (Barr et al., 1997). It is true that the small number of subjects in the right TLE group will have resulted in reduced statistical power on that side, as mentioned previously. This means that it would be harder to find a significant difference between performance on the visual reproduction subtest by right TLE patients and by normal controls, because the difference between groups would need to be higher. However, both right and left TLE groups scored more or less identically on this subtest, indicating that the poor performance exhibited by both groups is more likely to be a factor of chronic epilepsy or medication than a hemisphere-dependent deficit. A

significant, and more likely, explanation is that the test is not sophisticated enough to tap into the underlying specialization of the hemispheres.

Nonetheless, in general both groups of patients performed below the level of the normal controls, a finding that may well be the result of bilateral pathology in the patient groups. A similar finding (that the scores of patients with left or right TLE did not differ) has previously been reported in children (Cohen, 1992), which could also be attributed to a high frequency of bilateral pathology. The results of Chapter 3 indicated that bilateral pathology was a feature of this subject population. In order to take this into account, quantitative MR techniques could be used to identify patients who have bilateral pathology. These patients could then either be excluded from the analysis, or used in an alternative way to explain the neuropsychological test findings. There are two ways in which this might be done. The first would be to create two new groups of TLE patients with bilateral pathology (left TLE with right-sided pathology and vice versa), while the second would involve using a statistical technique such as stepwise regression to discern the contribution of both temporal lobes to the variable in question. Both have been used successfully, the former in adults (Incisa della Rocchetta et al., 1995), and the latter in children (Gadian et al., 1996). The following chapter uses both techniques to assess the role of temporal lobe pathology in the neuropsychological performance of the patient group assessed here.

Chapter 5. The Relationship Between Pre-operative Cognitive Function and Temporal Lobe Pathology

5.1 Abstract

33 young, right-handed subjects (26 with a clinical diagnosis of temporal lobe epilepsy and 7 normal siblings of patients with temporal lobe epilepsy) were assessed with both quantitative magnetic resonance techniques and tests of cognitive function. Magnetic resonance measures included T2 relaxometry and hippocampal volumetry to assess hippocampal pathology, and magnetic resonance spectroscopy to assess diffuse temporal lobe pathology. All the children were given tests of language ability, executive function and verbal and nonverbal memory. Scores on several memory tests considered to be sensitive to left temporal lobe damage were associated with measures of left temporal, and particularly left hippocampal, pathology. Memory tests believed to be sensitive to right temporal lobe damage were not associated with any pathology measure. This study extends previous work linking cognitive function to brain pathology as measured by quantitative magnetic resonance methods.

5.2 Introduction

It has been shown in Chapter 4 that patients with TLE show significant impairments on certain tests of cognitive function (most notably tests of delayed recall). However, the pattern of these impairments is not such that those with epilepsy of right temporal lobe onset can be distinguished from those of left temporal lobe onset with any great degree of reliability. In addition, it seems likely that certain memory functions are predominantly subserved by the hippocampus whilst others are subserved by temporal neocortex (Helmstaedter, Grunwald, Lehnertz et al., 1997). Without knowing something about the integrity of both the hippocampi and the temporal lobes more generally, it is hard to investigate this.

The advent of quantitative MR techniques has led to an improvement in the investigation of patients with epilepsy and refinements to research paradigms investigating memory abilities. One major reason for using these techniques to investigate memory function is that they provide a means of discriminating between hippocampal and more diffuse temporal lobe pathology, and also of defining bilateral pathology. This is important because of the high incidence of bilateral pathology seen in TLE cases, even in cases when the seizures are well lateralized (Connelly et al., 1994; Jackson et al., 1993b; Cross et al., 1996). It has been shown that it is important to be aware of bilateral pathology when attempting to analyse neuropsychological data from pre- or post-surgical epilepsy patients (Incisa della Rocchetta et al., 1995), as this can be a confounding variable masking hemisphere-dependent material-specific memory problems. Thus, the use of quantitative techniques allows investigation of the

relationship between extent of pathology and level of cognitive performance. This has been possible before using cell counting of hippocampal subfields (Sass et al., 1992a; Sass et al., 1992b; Rausch & Babb, 1993), but this has not given information about diffuse pathology in the rest of the medial temporal lobe. Of course, since these analyses were on surgical specimens, there has been no investigation of the contralateral temporal lobe.

Quantitative MR techniques have been used in some adult studies to demonstrate a correlation between left hippocampal pathology and either the Logical Memory (Lencz et al., 1992; Kälviäinen et al., 1997) or the verbal paired associate learning (VPAL) subtests (Incisa della Rocchetta et al., 1995; Loftus et al., 1997) from the Wechsler Memory Scale (WMS). A link between verbal paired associate learning and left temporal lobe pathology has also been shown in children (Gadian et al., 1996). A verbal supraspan learning task, the verbal Selective Reminding Test, has also been shown to correlate with left temporal lobe volume as measured by MR techniques (Lencz et al., 1992). Indeed, in at least one study, nonmnemonic abilities such as confrontation naming and intellectual function have been linked with hippocampal volumes (Shear et al., 1997). However, none of these studies utilised the three measures of temporal lobe pathology together (^{1}H MRS, HFV and T2) and so were unable to make fully informed judgments about the different aspects of memory function which were under investigation. This is because the three techniques each provide different information about the pathology the temporal lobe has sustained (see Chapter 3). In addition, certain statistical steps must be taken into account to clarify the relationship between overall cognitive ability or age at testing and specific memory impairment. One example of this is partialling out

the effects of IQ on memory performance. Since the verbal IQ of the subject influences performance on many tests of verbal memory, this is an important step, and without it results can be misleading.

There has been little attempt in children, however, to link degree of temporal lobe damage to the severity of cognitive deficit, because in the past there was no way of measuring the pathology without opening the cranium or using ionizing radiation. In recent years, various non-invasive magnetic resonance (MR) techniques have been developed to define the pathological basis of specific cognitive deficits, and in particular memory functions. In a previous study, for example, proton magnetic resonance spectroscopy (^{1}H MRS) was used to assess diffuse temporal lobe pathology in children (Gadian et al., 1996). The cognitive function of 22 children with TLE was assessed using the WISC-III^{UK}, which has both a verbal (Verbal IQ, or VIQ) and a non-verbal (Performance IQ, or PIQ) scale. By using stepwise regression it was determined that left-sided pathology was associated with a loss of verbal cognitive functions (as measured by verbal IQ), whilst right-sided pathology was associated with a loss of non-verbal functions (as measured by performance IQ). Pathology in the left temporal lobe did not significantly affect PIQ and likewise pathology in the right temporal lobe did not affect VIQ. This finding is consistent with results from studies of adults, showing lateralization of brain function to the cerebral hemispheres. However, this is a particularly interesting study because it implies that there is a relationship between the extent of diffuse temporal lobe pathology (as measured by ^{1}H MRS) and the extent of cognitive dysfunction. In addition, Gadian and colleagues showed that there was an association between poor

verbal paired associate learning and left temporal lobe pathology. The impact of VIQ on the association, however, was not analysed.

This chapter describes investigations of the relationships between temporal lobe pathology and memory dysfunction using three different measures of brain pathology. Two of the techniques quantitatively assess hippocampal pathology (T2 relaxometry and hippocampal volumetry) and the third (^{1}H MRS) examines diffuse temporal lobe pathology. This gives a four compartment model (two regions of interest, the hippocampus and the medial temporal lobe, on the left and the right) which can be used to examine the functional organisation of memory in children with TLE.

5.3 Methods

5.3.1 Subjects

Subjects were 33 right-handed children between the ages of 6y 3m and 17y 8m (see Appendix I). Twenty-six had a diagnosis of TLE (17 left, 8 right, 1 bilateral) on the basis of clinical and EEG findings (11 male, 15 female; median age at assessment was 13y 10m), whilst 7 were sibling controls (4 male, 3 female; median age at assessment was 10y 11m). The TLE patients were selected because they had all three quantitative MR measures. The comparisons of these patients with control subjects were described in Chapter 4.

5.3.2 Magnetic Resonance

All subjects were assessed with quantitative MR techniques using a 1.5 T Siemens whole body system with a standard circularly polarized head coil as described in Section 2.2. MR measures included T2 relaxometry and hippocampal volumetry, which are measures of hippocampal pathology, and NAA/(Cho+Cr), which reflects more diffuse temporal lobe damage. Results from all three measures were available in all cases.

5.3.3 Neuropsychology

All the children were given a range of neuropsychological tests including the age-appropriate Wechsler Intelligence Scale, tests of language, executive function and verbal and non-verbal memory as described in Section 2.3. However, not every child received all the tests, owing to time constraints, the unsuitability of the test for the child or because the test was not in use at Great Ormond Street at the time of the child's assessment.

5.3.4 Statistics

As part of the initial investigation, the subjects were divided into five groups. These consisted of (1) the sibling controls, (2) patients with TLE whose hippocampi were normal bilaterally by both T2 and HFV measurement criteria, (3) patients with TLE whose left hippocampus was abnormal by either T2 or HFV criteria, (4) patients with TLE whose right hippocampus was abnormal by either T2 or HFV criteria, and (5) patients with TLE whose hippocampi were abnormal bilaterally by either T2 of HFV criteria. Analyses-of-variance were then performed on the neuropsychological test performance of the five groups to

discern any significant differences, covarying for IQ where appropriate. Any post-hoc tests were either Tukey's h-s-d, or in the case of the covaried analyses, simple planned contrasts.

Following this, the subjects were redistributed amongst the groups, this time on the basis of their NAA/(Cho+Cr) ratio. For example, a patient with an abnormal left NAA/(Cho+Cr) ratio would be a member of group 3. The ANOVAs were then repeated.

As a result of these investigations, it was also decided to analyse scores on all of the neuropsychological tests using stepwise multiple-regression for the 26 TLE patients i.e. without the sibling controls. The advantage of this method of analysis is that it avoids the problem of small group sizes and provides information on the relative contributions of each independent variable to the dependent variable. As such this can be a powerful technique.

The hypothesis for these analyses was that pathology within the left and right temporal lobes would be linearly associated with selective deficits in memory function. Specifically, pathology in the left temporal lobe was expected to be associated with poor scores on tests of verbal memory such as Verbal Paired Associates, whilst pathology in the right temporal lobe was expected to be associated with poor scores on tests of non-verbal memory such as the recall of the Emergent Complex Figure. It was also hoped that tests such as the Visual Reproduction subtest from the WMS might exhibit contributions from both the left and right temporal lobes, since it is capable of being performed in both a verbal and a spatial manner. However, medial temporal lobe pathology was not expected to be related to poor scores on measures of executive function, language function, or tests of visuo-perception.

Because of this, all six pathology scores were used as independent variables. Age was also used as an independent variable to allow for the improvement commensurate with age in non-standardised tests. The entry value was $p_{in} = 0.05$ and the removal value was $p_{out} = 0.10$. For all regressions other than those concerning the WISC-III^{UK}, FSIQ was also used as an independent variable. The model was then checked by forcing all independent variables into the regression ($p_{in} = 0.99$). This was because stepwise regression requires that one variable be significant in its own right in order for a model to be created. By having a high entry value, models which required two variables to enter together to be significant would be discovered.

Stepwise regression analyses all the independent variables with respect to the dependent variable, and the variable that can explain the most significant amount of variance is used to form a model. The remaining variables are then examined, with the effect of the one in the model partialled out. If one of these contributes significantly to the model, then it is added to it, and the remaining variables are again examined, this time with both variables already in the model partialled out. This continues until no variable reaches the p_{in} value. There is a parallel analysis which checks that the variables in the model are still significant, since the p values will change as each new variable is added to the regression equation. If the p value for a variable becomes higher than p_{out}, then that variable is removed from the equation.

The outcome measures shown below are as follows.

r^2 - The r^2 value is the square of the product moment (Pearson's) correlation coefficient, and it can be adjusted (**r^2 adj.**) to take into consideration the sample

size and the number of degrees of freedom. It shows the percentage of the variance in the dependent variable which is explained by the model.

ANOVA- An analysis of variance is performed to test the null hypothesis that there is no linear relationship between the neuropsychological test performance and the independent variables. The degrees of freedom, F value and probability are shown.

b - The b values are partial regression coefficients. These can be used to construct the actual regression equation for the dependent variable.

β - The β values are standardized partial regression coefficients. The β value can be compared between variables to establish which is the more important factor - this means that the larger the value, the greater the weight of the variable.

The probability of entry (p value) for each independent variable is also shown.

Constant - The constant for each regression equation is shown at the foot of each column.

The complete equation for a dependent variable would therefore be of the kind:

$$\text{Dependent variable} = \Sigma\, \mathbf{b}\,(\text{Independent variable}) + \text{Constant}$$

5.4 Results

Table 5.1 displays the number of patients with normal, unilateral and bilateral pathology on each of the quantitative measures for those with left TLE,

right TLE and bilateral TLE. This demonstrates the difficulty of defining groups with three measures that tap different pathologies and indicates just how heterogeneous the groups are if they are determined merely on the basis of the side of ictal onset.

T2	**Normal**	**Abnormal left only**	**Abnormal right only**	**Bilateral pathology**
Left TLE	4	12	0	1
Right TLE	3	0	4	1
Bilateral TLE	0	1	0	0
HFV				
Left TLE	3	8	0	6
Right TLE	5	0	2	1
Bilateral TLE	0	0	0	1
T2 or HFV				
Left TLE	3	8	0	6
Right TLE	3	0	3	2
Bilateral TLE	0	0	0	1
AA/(Cho+Cr)				
Left TLE	4	7	1	5
Right TLE	0	1	6	1
Bilateral TLE	0	0	0	1

Table 5.1 Distribution of normal, unilateral and bilateral pathologies on each of the three quantitative MR measures.

5.4.1 Analyses of variance using hippocampal pathology

The patients were divided into groups on the basis of their hippocampal pathology, such that if *either* the T2 *or* the HFV on one side was abnormal, they were assumed to have pathology on that side. Therefore, a patient could be in the bilateral group because of a high T2 on the left, and a low HFV on the right.

This division gave five groups as follows:

Group 1: Sibling controls (SC; n = 7; median age 11y 4m)

Group 2: Patients with TLE and normal hippocampi bilaterally (TLE N (HF); n = 6; median age 13y 10m)

Group 3: Patients with TLE and an abnormal left hippocampus (TLE L (HF); n = 8; median age 13y 2m)

Group 4: Patients with TLE and an abnormal right hippocampus (TLE R (HF); n = 3; median age 15y 11m)

Group 5: Patients with TLE and abnormal hippocampi bilaterally (TLE Bi (HF); n = 9; median age 12y 0m)

The groups did not significantly differ in terms of their age, as assessed using the Kruskal-Wallis test (χ^2 (4, 33) = 5.74, p = 0.219).

One-way ANOVA were performed for all the neuropsychological tests, covarying for IQ where necessary, to try to identify significant differences between the five groups. The complete analysis is shown in Appendix II.i - only the significant group effects and relevant negative findings are shown in full here.

Group	VIQ	PIQ	FSIQ
SC	98.3 ± 10.6	94.6 ± 14.1	96.0 ± 10.4
TLE N (HF)	89.8 ± 13.7	84.3 ± 10.5	85.7 ± 13.3
TLE L (HF)	84.0 ± 15.3	88.9 ± 18.9	84.4 ± 17.6
TLE R (HF)	107.7 ± 30.4	109.7 ± 13.3	110.0 ± 22.5
TLE Bi (HF)	93.6 ± 11.4	108.1 ± 19.7	99.4 ± 14.2

Table 5.2 IQ scores (Means ± standard deviations) for the five subject groups divided by hippocampal pathology.

Table 5.2 displays the mean IQ scores for the five subject groups. One-way ANOVAs on these scores only showed a significant group difference for PIQ (VIQ; $F(4, 28) = 1.76$, $p = 0.164$: PIQ; $F(4, 28) = 2.82$, **$p = 0.044$**: FSIQ; $F(4, 28) = 2.45$, $p = 0.069$). However, post-hoc analysis using Tukey's h-s-d test failed to identify significant differences between the groups. In addition, a two-way ANOVA using VIQ and PIQ as repeated measures failed to find a significant interaction between group and IQ ($F(4, 28) = 2.17$, $p = 0.098$).

The scores from each of the subtests of the IQ scale were also analyzed using a one-way ANOVA. There were no significant group differences except for the Vocabulary subtest from the Verbal scale ($F(4, 27) = 3.04$, **$p = 0.035$**), and the Block Design subtest from the Performance scale ($F(4, 27) = 3.29$, **$p = 0.026$**). Once again, though, there were no significant differences between the groups when a post-hoc Tukey's h-s-d analysis was performed. The means for these subtests are shown in table 5.3.

Group	Vocabulary	Block Design
SC	9.6 ± 2.7	8.0 ± 3.2
TLE N (HF)	8.0 ± 2.0	7.5 ± 3.3
TLE L (HF)	6.0 ± 2.1	8.8 ± 4.4
TLE R (HF)	10.3 ± 4.9	14.0 ± 2.0
TLE Bi (HF)	7.4 ± 1.1	12.5 ± 3.7

Table 5.3 Vocabulary and Block Design subtest scores (means ± standard deviations) for the five subject groups divided by hippocampal pathology.

The scores from the WMS were analysed in a similar fashion, using a one-way ANOVA. With the effects of VIQ covaried out, no significant differences

between the five groups were found for MQ, LM-I, LM-D, C', C, D', VPA Score or VPA Hard. The remaining scores from the WMS (LM-%, D, D%, C%, VPA Easy and VPA Del) were not affected by VIQ and so that was not covaried. However, only C% (F (4, 28) = 5.09, **p = 0.003**) and VPA Del (F (4, 28) = 4.79, **p = 0.005**) showed significant group differences. Post-hoc Tukey's h-s-d analysis was performed for the C% score, and indicated that the scores of the TLE L (HF) group were significantly lower than those of the TLE N (HF) and SC groups, but not different from those of the TLE R (HF) or the TLE Bi (HF) groups ($p < 0.05$). The Dunnet T3 test was used to assess group differences for the VPA Del score, since the group variances were not homogenous. This did not indicate any significant differences, possibly as a result of the large standard deviation of the TLE L (HF) group. Table 5.4 shows the means for the five groups on the C% and VPA Del scores.

Group	C%	VPA Del
SC	91.3 ± 10.9	9.6 ± 0.8
TLE N (HF)	93.8 ± 11.8	9.2 ± 1.0
TLE L (HF)	66.2 ± 16.8	6.0 ± 3.0
TLE R (HF)	80.7 ± 8.3	9.7 ± 0.6
TLE Bi (HF)	75.8 ± 14.1	8.3 ± 1.6

Table 5.4 C% and VPA Del scores (means ± standard deviations) for the five subject groups divided by hippocampal pathology.

The only other scores to show significant differences between the five groups were the forwards digit span (F (4, 28) = 3.81, **p = 0.013**), and the backwards block span (F (4, 20) = 3.54, **p = 0.024**). Post-hoc Tukey's h-s-d analysis showed that for the block span, the performance of the TLE R (HF)

group was significantly higher than that of the TLE N (HF) group. There were no significant post-hoc differences for the digit span. Presumably the differences are predominantly a factor of the low group numbers. Table 5.5 shows the mean scores for these tests.

Group	Digits Forward	Digits Backward	Blocks Forward	Blocks Backward
SC	5.7 ± 1.0 n = 7	4.0 ± 1.3 n = 7	5.1 ± 1.6 n = 7	5.9 ± 0.9 n = 7
TLE N (HF)	5.0 ± 1.1 n = 6	3.8 ± 0.8 n = 6	6.3 ± 1.3 n = 4	4.3 ± 1.5 n = 4
TLE L (HF)	5.1 ± 1.3 n = 8	3.8 ± 1.9 n = 8	5.4 ± 1.5 n = 5	4.8 ± 1.0 n = 4
TLE R (HF)	7.0 ± 0.0 n = 3	5.7 ± 1.5 n = 3	7.0 ± 1.4 n = 2	7.5 ± 0.7 n = 2
TLE Bi (HF)	6.4 ± 0.9 n = 9	4.3 ± 1.5 n = 9	5.8 ± 1.0 n = 8	5.6 ± 1.2 n = 8

Table 5.5 Digit and Block Span scores (means ± standard deviations) for the five subject groups divided by hippocampal pathology.

No other test of neuropsychological function demonstrated a significant group difference when tested with one-way ANOVAs (see Appendix II.i for details).

5.4.2 Analyses of variance using the NAA/(Cho+Cr) measure of pathology

The patients were divided into groups on the basis of their NAA/(Cho+Cr) ratio, such that if it was lower than 0.72 on one side, they were assumed to have pathology on that side. Therefore, a patient would be in the bilateral group because of a low ratio in both temporal lobes.

This division gave five groups as follows:

Group 1: Sibling controls (SC; n = 7; median age 11y 4m)

Group 2: Patients with TLE and normal NAA/(Cho+Cr) ratios bilaterally (TLE N (MRS); n = 4; median age 12y 10m)

Group 3: Patients with TLE and an abnormal left NAA/(Cho+Cr) ratio (TLE L (MRS); n = 9; median age 14y 6m)

Group 4: Patients with TLE and an abnormal right NAA/(Cho+Cr) ratio (TLE R (MRS); n = 7; median age 15y 8m)

Group 5: Patients with TLE and abnormal NAA/(Cho+Cr) ratios bilaterally (TLE Bi (MRS); n = 6; median age 12y 2m)

The groups did not significantly differ in terms of their age, as assessed using the Kruskal-Wallis test ($\chi^2 = 2.35$, $p = 0.671$).

One-way ANOVA was performed for all the neuropsychological tests, covarying for VIQ where necessary, to identify any significant differences between the five groups. The complete analysis is shown in Appendix II.ii.

Group	VIQ	PIQ	FSIQ
SC	98.3 ± 10.6	94.6 ± 14.1	96.0 ± 10.4
TLE N (MRS)	93.5 ± 18.4	100.3 ± 24.2	95.7 ± 21.4
TLE L (MRS)	87.0 ± 11.8	91.3 ± 20.8	87.1 ± 16.0
TLE R (MRS)	95.0 ± 25.1	90.7 ± 13.7	92.3 ± 22.0
TLE Bi (MRS)	92.3 ± 10.7	110.2 ± 18.0	100.2 ± 13.0

Table 5.6 IQ scores (Means ± standard deviations) for the five subject groups divided by NAA/(Cho+Cr) ratio.

Table 5.6 displays the mean IQ scores for the five subject groups. One-way ANOVAs on these scores failed to show a significant group difference for any of them (VIQ; F (4, 28) = 0.54, p = 0.709: PIQ; F (4, 28) = 1.28, p = 0.300: FSIQ; F (4, 28) = 0.63, p = 0.643). However, the TLE L (MRS) group had the lowest mean VIQ, whilst the TLE R (MRS) group had the lowest mean PIQ. Interestingly, the TLE Bi (MRS) group did not have especially poor IQ scores.

On further analysis, it was found that there were no significant differences between the performance of the five subject groups on any neuropsychological measure (see Appendix II.ii).

5.5 Regression Analysis

The previous sections have considered the data on a group basis. Chapter 4 was concerned with the comparison of the TLE group on the basis of side of onset, and against a group of matched controls. The earlier parts of this chapter have focused on dividing the patients on the basis of their pathology, as determined by quantitative MR methods. We now move onto another type of analysis, stepwise regression, which allows the data to be examined as a whole rather than by comparison. This allows a comparison of the relative contributions of the independent variables. In addition, it is possible to find relationships which rely on both the hippocampus and the temporal lobe more generally, which could not be identified by the preceding analyses.

Stepwise linear regression was performed using the 26 patients and excluding the sibling controls. This was done for methodological reasons, since

it was expected that the SC group would be qualitatively different and therefore not suitable to be modeled with the epilepsy group.

All the results shown below (Tables 5.7 to 5.9) are, with one exception, the significant associations only, obtained with a $p_{in} = 0.05$ and a $p_{out} = 0.1$. However, the use of $p_{in} = 0.99$ identified a significant association between LM-% and the independent variables, and so that relationship is displayed here.

By their nature, some of the models do not lend themselves to graphical display. Therefore, those that are shown are amenable to display in a two-dimensional manner.

5.5.1 IQ Scores

Table 5.7 shows the results of the regression analyses for IQ scores and certain subtest scores obtained from the WISC-III^{UK}.

	VIQ	Verbal IQ Subtests			
		Information	Similarities	Vocabulary	Comprehension
r^2	0.166	0.162	0.166	0.256	0.229
r^2 adj.	0.131	0.127	0.131	0.224	0.195
ANOVA	$F(1,24) =$ 4.784 p= 0.039	$F(1,24) =$ 4.647 p = 0.041	$F(1,23) =$ 4.782 p = 0.039	$F(1,23) =$ 7.925 p = 0.010	$F(1,23) =$ 6.815 p = 0.016
NAA/(Cho+Cr)$_{[L]}$	b = 43.608	b = 9.491	b = 9.086	b = 8.186	-
	β= 0.408	β = 0.403	β = 0.408	β = 0.506	-
	p= 0.039	p = 0.041	p = 0.039	p = 0.010	-
T2$_{[L]}$	-	-	-	-	b = -0.145
	-	-	-	-	β = -0.478
	-	-	-	-	p = 0.016
Constant	61.178	1.195	2.898	1.801	25.066

Table 5.7 Results of the linear multivariate regression analyses for the WISC-III^{UK}.

Verbal IQ (VIQ) scores showed an association with left NAA/(Cho+Cr) (NAA/(Cho+Cr)$_{[L]}$) ratios, and with no other pathology measure, suggesting that increased temporal lobe damage is associated with poorer performance on this measure of verbal intelligence. PIQ was not significantly associated with any of the pathology measures.

From the above information, it is possible to construct the regression equation for VIQ as follows

$$VIQ = 43.608\ (NAA/(Cho+Cr)_{[L]}) + 61.178$$

Figure 5.1 shows the graph of NAA/(Cho+Cr)$_{[L]}$ against VIQ score for all 26 patients with TLE, with the addition of the seven sibling controls. From this

it can be seen that, firstly, there is a very obvious outlier (JS) who may be contributing to skew the data, and secondly, that in general the siblings lie on the regression equation.

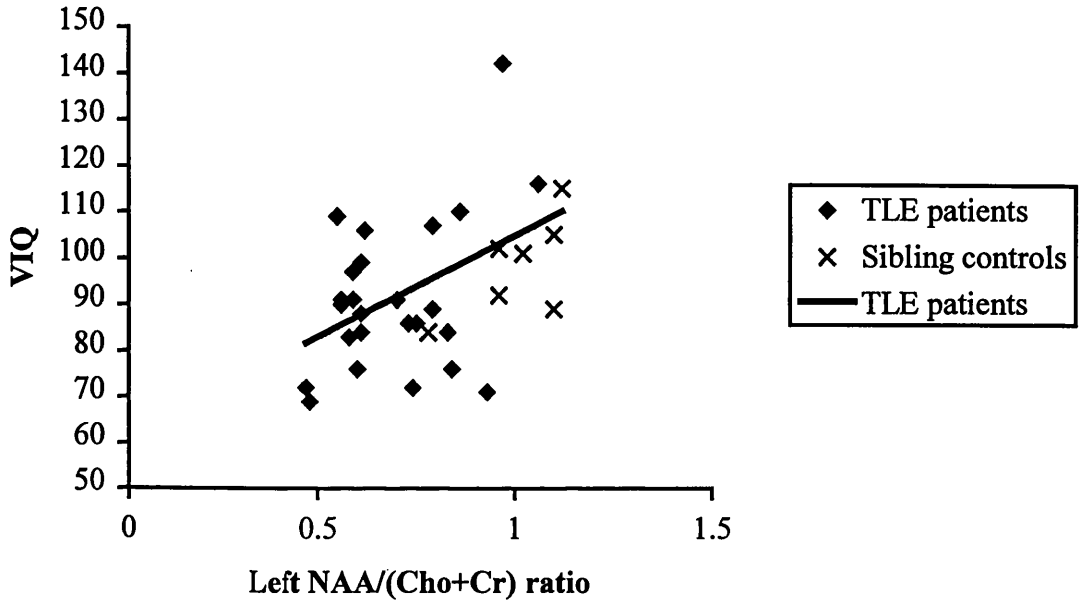

Figure 5.1 Scatter graph of left NAA/(Cho+Cr) ratio against VIQ for both TLE patients and sibling controls.

Subsequent investigation within a larger population of patients who had both IQ scores and NAA/(Cho+Cr) ratios (but not necessarily T2 maps or HFV measurements; n = 43, including the seven sibling controls) revealed that the relationship with VIQ was maintained, but there was still no association for PIQ (see Appendix II.iii).

Stepwise regressions between the subtests of the WISC-III^{UK} and pathology scores were also performed. These demonstrated that the subtest which was most significantly associated with NAA/(Cho+Cr)$_{[L]}$ (and therefore may contribute the most to the relationship between VIQ and NAA/(Cho+Cr)$_{[L]}$) was Vocabulary, such that poor performance on this subtest was associated with a greater degree of left temporal lobe damage. However, it also showed that the

Information and Similarities subtests were associated with NAA/(Cho+Cr)$_{[L]}$, albeit more weakly than the association between Vocabulary and NAA/(Cho+Cr)$_{[L]}$. In addition, the Comprehension subtest scores were associated with T2$_{[L]}$, such that a greater degree of hippocampal pathology resulted in a poorer score.

None of the VIQ subtests were significantly associated with NAA/(Cho+Cr)$_{[R]}$, and neither that score nor NAA/(Cho+Cr)$_{[L]}$ showed any association with a subtest from the Performance scale.

Figures 5.2, 5.3 and 5.4 display the relationships between NAA/(Cho+Cr)$_{[L]}$ and Vocabulary, Similarities and Information respectively, whilst Figure 5.5 displays the relationship between T2$_{[L]}$ and Comprehension. Both the patients with TLE and the sibling controls are shown on each graph.

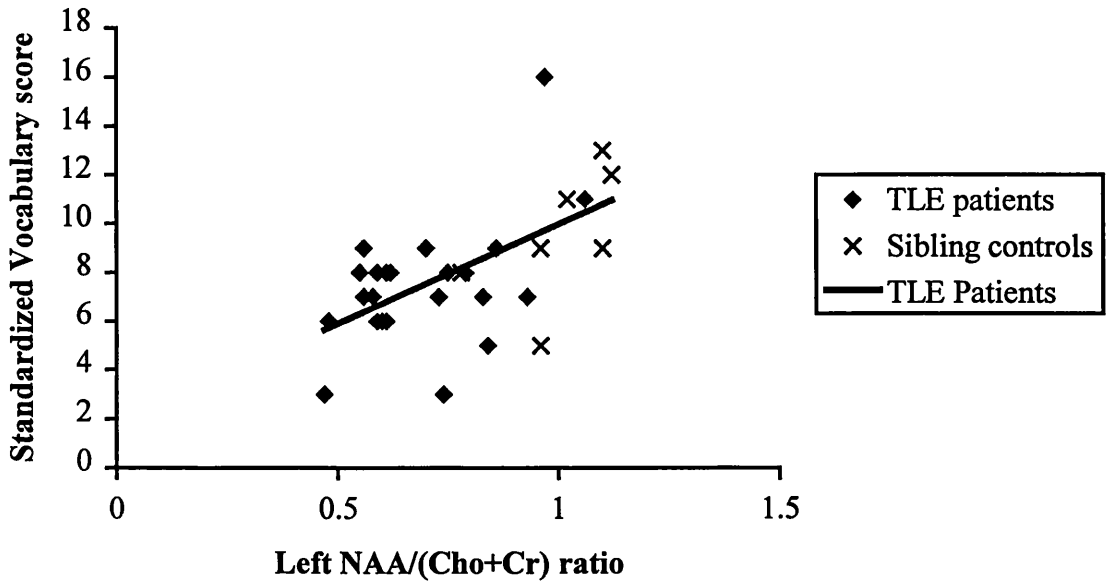

Figure 5.2 Scatter graph of left NAA/(Cho+Cr) ratio against Vocabulary score for both TLE patients and sibling controls.

Again it can be seen that there is a significant outlier (JS), but the sibling controls do fit with the regression equation calculated from the scores of the patients with TLE.

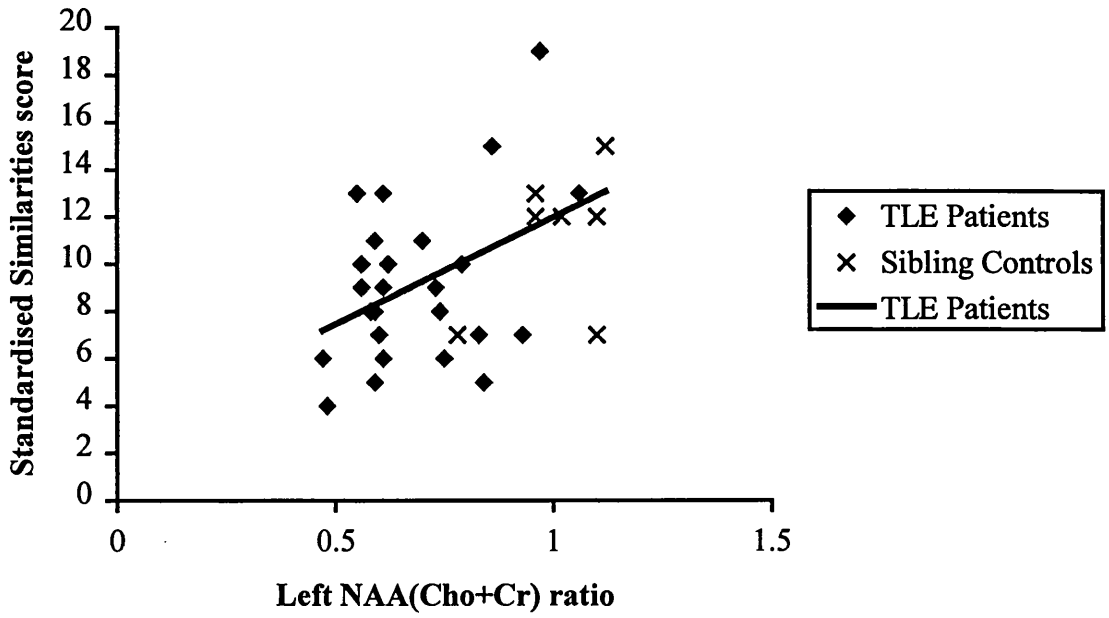

Figure 5.3 Scatter graph of left NAA/(Cho+Cr) ratio against Similarities score for both TLE patients and sibling controls.

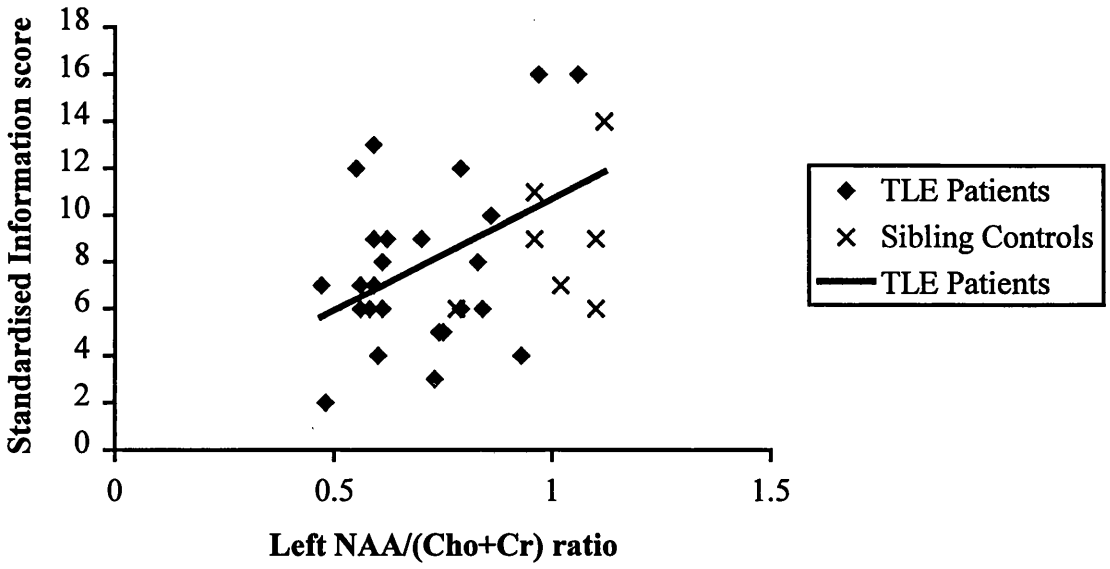

Figure 5.4 Scatter graph of left NAA/(Cho+Cr) ratio against Information score for both TLE patients and sibling controls.

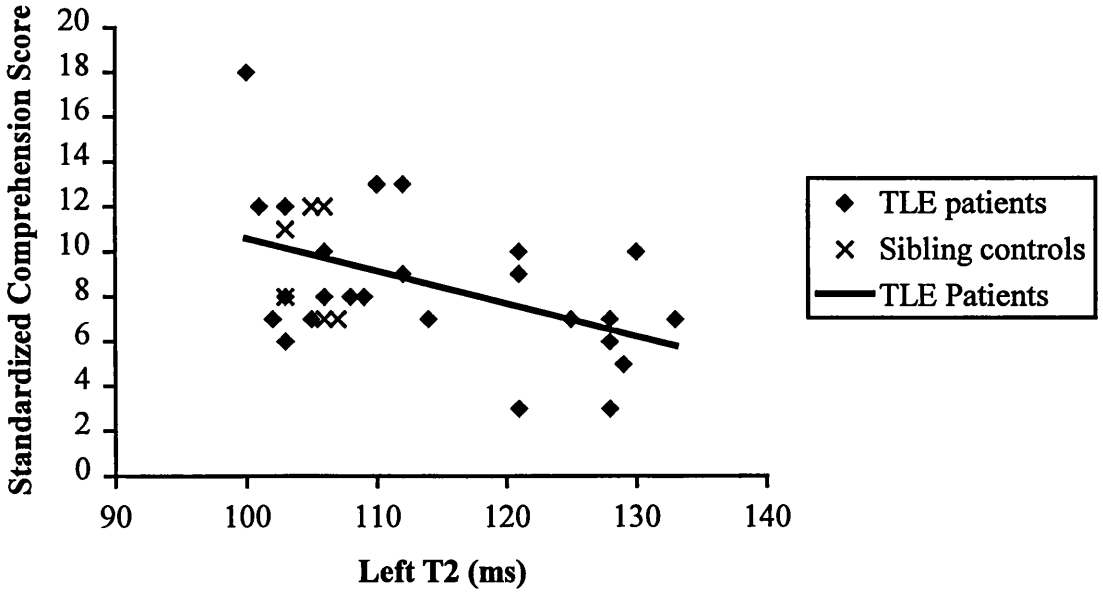

Figure 5.5 Scatter graph of left T2 against Comprehension score for both TLE patients and sibling controls

5.5.2 Scores from the Wechsler Memory Scale

As might be expected, most of the scores derived from the WMS showed significant associations with age and/or VIQ. Only four measures were also associated with measures of left temporal pathology. These were the percentage recall of the stories (LM-%), the percentage recall of the Composite score (C%), and two scores from the VPAL (VPA Easy and VPA Del) (Table 5.8). The delayed measure from the VPAL score was associated with VIQ but did not show an association with age, whilst the LM-% and VPA Easy scores associated with age but not VIQ. The C% score did not associate with either.

As shown in Table 5.8, LM-% and C% associated significantly with $T2_{[L]}$, whilst the VPA Del score was significantly associated with $HFV_{[L]}$. These associations imply that as left hippocampal pathology increases, performance decreases. However, the VPA Easy score associated with $NAA/(Cho+Cr)_{[L]}$, with no significant contribution from measures of hippocampal pathology.

Neither the MQ score nor the Visual Reproduction scores showed any significant associations with any measure of temporal lobe pathology.

	LM-%	VPA Easy	VPA Del	C%
r^2	0.331	0.394	0.319	0.222
r^2 adj.	0.239	0.341	0.260	0.189
ANOVA	$F(3,22) =$ 5.681 p = 0.010	$F(2,23) =$ 7.473 p = 0.003	$F(2,23) =$ 5.383 p = 0.012	$F(1,24) =$ 6.840 p = 0.015
VIQ	-	-	b = 0.052	-
	-	-	β = 0.362	-
	-	-	p = 0.049	-
Age	b = -4.625	b = 0.458	-	-
	β = -0.500	β = 0.470	-	-
	p = 0.010	p = 0.008	-	-
$NAA/(Cho+Cr)_{[L]}$	-	b = 7.836	-	-
	-	β = 0.406	-	-
	-	p = 0.020	-	-
$HFV_{[L]}$	-	-	$b = 1.4 \times 10^{-3}$	-
	-	-	β = 0.381	-
	-	-	p = 0.039	-
$T2_{[L]}$	b = -1.203	-	-	b = -0.729
	β = -0.463	-	-	β = -0.471
	p = 0.016	-	-	p = 0.015
Constant	255.467	4.453	-1.071	160.668

Table 5.8 Results of linear multivariate regression analyses for Logical Memory and the Composite Score from the WMS.

Figure 5.6 displays the graph of C% against $T2_{[L]}$ for both TLE patients and sibling controls.

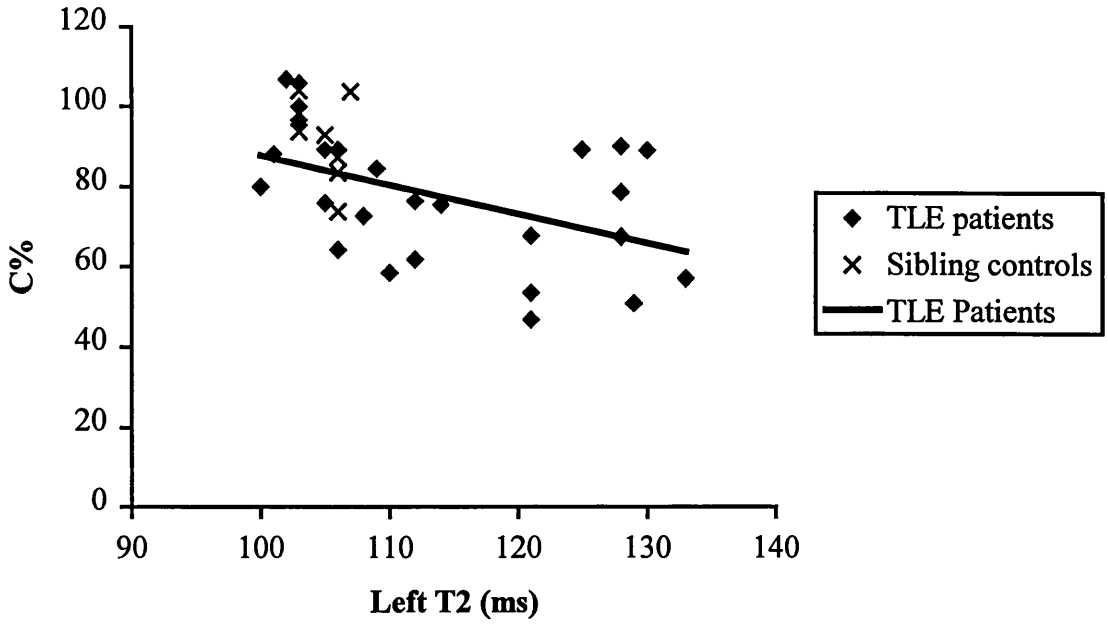

Figure 5.6 Scatter graph of left T2 against the C% score for both TLE patients and sibling controls.

5.5.3 Scores from the CAVLT-2

As can be seen from the analyses shown in Table 5.9, this age-standardized test of verbal supraspan learning was significantly associated with a measure of left hippocampal pathology (T2), whilst measures of right-sided pathology did not make a significant contribution. Immediate Learning and Level of Learning both showed significant associations with $T2_{[L]}$ and VIQ, whilst Delayed Recall and the total number of Intrusions showed a significant association with $T2_{[L]}$ only.

The Intrusions score of the CAVLT-2 is not age-standardized, and so it is perhaps surprising that age does not make any contribution to this relationship.

	Immediate Learning	Level of Learning	Delayed Recall	Intrusions
r^2	0.559	0.462	0.195	0.241
r^2 adj.	0.513	0.406	0.155	0.203
ANOVA	$F(2,19) =$ 12.058 $p < 0.001$	$F(2,19) =$ 8.172 $p = 0.003$	$F(1,20) =$ 4.838 $p = 0.040$	$F(1,20) =$ 6.340 $p = 0.020$
VIQ	$b = 0.560$	$b = 0.427$	-	-
	$\beta = 0.435$	$\beta = 0.398$	-	-
	$p = 0.012$	$p = 0.033$	-	-
$T2_{[L]}$	$b = -1.014$	$b = -0.767$	$b = -0.923$	$b = 0.176$
	$\beta = -0.514$	$\beta = -0.466$	$\beta = -0.441$	$\beta = 0.491$
	$p = 0.004$	$p = 0.015$	$p = 0.040$	$p = 0.020$
Constant	164.875	150.188	202.958	-17.017

Table 5.9 Results of the linear multivariate regression analyses for the CAVLT-2.

Figure 5.7 displays the graph of Delayed Recall on the CAVLT-2 against $T2_{[L]}$ for both TLE patients and sibling controls.

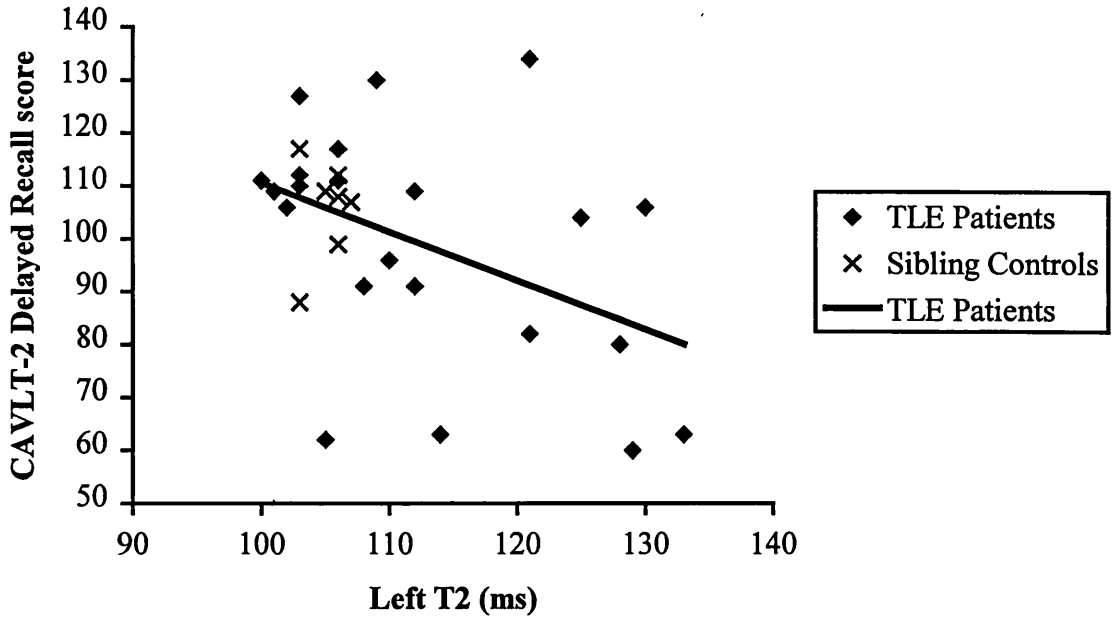

Figure 5.7 Scatter graph of left T2 against the Delayed Recall score from the CAVLT-2 for both TLE patients and sibling controls.

From this graph it can be seen that the association is not strong, as would be expected with an r^2 of only 0.195. There are at least two obvious outliers (RG and JL). The sibling controls are clustered heavily at one end of the distribution.

Figure 5.8 shows the relationship between $T2_{[L]}$ and the total number of intrusions for both TLE patients and sibling controls. This appears to have a strong ceiling effect, in that many subjects are scoring 0 or 1. The siblings do not appear to fit the distribution particularly well.

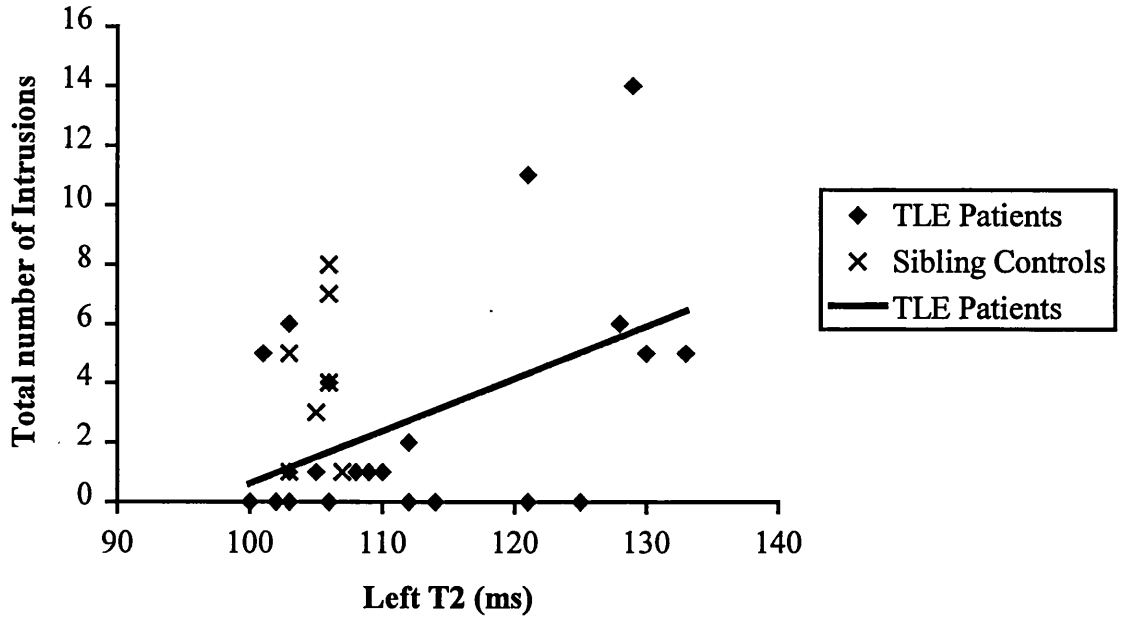

Figure 5.8 Scatter graph of left T2 against the total number of Intrusions on the CAVLT-2 for both TLE patients and sibling controls.

Both the Immediate Recall score and the Recognition Memory score failed to show associations with any measure of temporal lobe pathology.

5.5.4 Negative findings

Memory tests believed to be sensitive to right temporal lobe damage (e.g. memory for an Emergent Complex figure (Jones-Gotman, 1986) or the Face subtest of the WRMT) did not show significant associations with any measure of temporal lobe pathology. In addition, the use of a very high value for p_{in} (0.99) did not reveal any near-significant relationships between right temporal lobe pathology and tests of nonverbal memory.

Scores on tests of language such as the TROG, subtests of the WORD, naming to confrontation and the token test showed no association with the pathology measures. The same was true of scores on tests of visuoperception

(eg. Benton Face Matching, Thurstone Closure, Mooney Closure test) and executive function (eg. Wisconsin Card Sorting Test, Thurstone written fluency).

5.6 Discussion

This discussion will begin with a summary of the relative findings of the three major types of analysis; TLE lateralization, pathology lateralization, and regression analyses.

TLE lateralization

This analysis indicated that patients with left TLE scored significantly lower than controls on the Information, Vocabulary and Comprehension subtests of the WISC-III, and on the LM-%, D%, C, VPA Del and C% subtests of the WMS. Patients with right TLE scored significantly below controls for the Symbol Search and D% subtests only.

Pathology lateralization

This analysis only identified significant differences when the patients were grouped on the basis of hippocampal pathology. There were suggestions of differences between the groups for PIQ, Vocabulary and Block Design, but no one group was significantly poorer than another was. On the WMS, only the C% subtest revealed a significant difference between the groups, with those patients with left hippocampal pathology scoring below those without such damage, and also the sibling controls.

Regression analysis

This analysis showed that poor VIQ, Vocabulary, Information and Similarities scores were all associated with diffuse left temporal pathology. In addition, the scores on the Comprehension subtest were associated with left hippocampal pathology. Four subtests from the WMS were associated with pathology scores – these were LM-%, VPA Del and C%, all of which were associated with left hippocampal pathology, and VPA Easy, which was associated with diffuse left temporal pathology. A number of scores from the CAVLT were also associated with left hippocampal pathology scores.

The three methods of analysis differ in a number of specific ways in their findings, but there are two common factors. These are firstly that left-sided pathology is associated with impaired retrieval of verbal information, and secondly, that measures expected to associate with right temporal lobe pathology have failed to do so.

Where the analyses are discordant, it seems likely that part of the reason is that group sizes in the first two analyses were low. This results in low statistical power. The final regression analyses are probably statistically the most valid, since they utilize the full range of the data. Even so, an increase in the group size would have increased the likelihood of models being discovered which relied on both a hippocampal pathology score and the NAA/(Cho+Cr) ratio rather than solely on one or the other. There are a number of more complex statistical methods (e.g. discriminant analysis, factor analysis) which in principle might have been able to identify such relationships, but the sample sizes required for

such methods are higher than those that were obtainable over the time span available for data collection.

With such small sample sizes and so many statistical comparisons, it is important not to put too much weight on a significant association that has a probability of, say, only 0.04. Given the large number of statistical tests performed, the occurrence of Type I errors cannot be ruled out.

The major findings of the above results suggest that verbal learning is impaired by left temporal lobe pathology. They also suggest that verbal supraspan learning is dependent on the left hippocampus, since damage to it results in poor performance. In addition, they reaffirm the relationship found previously between diffuse left temporal lobe pathology and VIQ, although they do not support the relationship found between diffuse right temporal lobe pathology and PIQ (Gadian et al., 1996). This discussion will now go on to consider the findings in more detail.

5.6.1 IQ Scores

The confirmation of the relationship between diffuse left temporal lobe pathology and impaired verbal cognitive function supports the view that the left temporal lobe plays an important role in verbal abilities. Multivariate regression (Table 5.7) demonstrates that about one seventh of the variance in VIQ is accounted for by changes in $NAA/(Cho+Cr)_{[L]}$. It is perhaps surprising, given this finding, that the patients with abnormal $NAA/(Cho+Cr)_{[L]}$ did not have significantly lower VIQ scores than the other groups when analysed with one-way ANOVA. However, this can be attributed to the fact that a patient would be

placed in this group with a ratio of 0.71, i.e. only just within the abnormal range, which, judging by the regression equation, would not mean a particularly low VIQ. In addition, some patients with highly abnormal ratios in the left temporal lobe would have been placed in the TLE Bi (MRS) group, because their NAA/(Cho+Cr) ratio on the right was only just abnormal. The regression analysis implies that diffuse pathology in the right temporal lobe does not contribute significantly to poor VIQ scores, which is consistent with the finding that the TLE Bi (MRS) group are not more impaired than those with unilateral pathology on this measure.

By examining the associations between $NAA/(Cho+Cr)_{[L]}$ and the subtests of the VIQ scale, it can be seen that the subtest that is most significantly affected by diffuse left temporal lobe damage is Vocabulary. The finding in Section 5.4.1 that the TLE L (HF) group perform more poorly on this test than the SC group suggests that there may also be a hippocampal contribution to this subtest. However, this has not been supported by the use of stepwise regression analysis. The former result is consistent with the hypothesis that this subtest is likely to make use of semantic memory, which may be subserved by the cortex surrounding the hippocampus (Vargha-Khadem et al., 1997). In that study, the three subjects all suffered severe bilateral hippocampal damage (in two cases at a very early age) with other medial temporal lobe areas relatively unaffected. This bilaterality of pathology, not seen to the same extent in the TLE patients studied in this chapter, may result in different mechanisms of information processing. It is not unlikely, therefore, that patients with TLE are impaired on this subtest by both hippocampal and more diffuse temporal lobe pathology.

Scores from the Information and Similarities subtests, which are also assumed to rely on semantic memories, are also weakly related to measures of diffuse left temporal pathology. By contrast, the score on the Comprehension subtest is associated with left hippocampal pathology ($T2_{[L]}$), although presumably it too has a semantic contribution.

No significant association was found between PIQ and $MRS_{[R]}$, in contrast to that reported previously (Gadian et al., 1996). The finding relating PIQ to hippocampal pathology in Section 5.4.1 is probably spurious, since it seems to imply that damage to the right hippocampus results in a higher PIQ score. This is probably a factor of the small group sizes, resulting in skewed data. Unlike previously published work (Gadian et al., 1996), this study indicates that there is no significant contribution of the right temporal lobe to PIQ performance. This is despite one of the subtests of the Performance scale (Block Design) showing a significant group difference on ANOVA. However, this is also likely to be an effect of small group sizes, since it implied that right hippocampal damage was beneficial to the performance of this test.

Overall these results provide partial support for the work of Gadian et al. (1996), in that there is a good association between verbal abilities (as tested using the VIQ test) and left temporal pathology (as measured by the NAA/(Cho+Cr) ratio). The present results have been strengthened by a small increase in the subject numbers (26 versus 22) compared to that previous work and the inclusion of measures of hippocampal pathology. The results are also maintained in a larger population (see Appendix II.iii). In addition, it has been shown that the association between VIQ and $NAA/(Cho+Cr)_{[L]}$ is due mostly to performance on the Vocabulary subtest, but that there are also significant

associations between the Information and Similarities subtests and $NAA/(Cho+Cr)_{[L]}$. It has also been shown that there is no association between $NAA/(Cho+Cr)_{[R]}$ and PIQ.

5.6.2 Logical memory

The associations between logical memory and pathology scores demonstrate that, when Age is allowed for, there is a significant relationship between the percentage of material retained over a delay and left hippocampal pathology. That there are no significant pathology contributors for logical memory in the immediate recall condition is not surprising, since the scores obtained are heavily dependent on attention. This would mean little or no involvement of the medial temporal lobes in this function, but rather of the lateral temporal neocortex. An earlier study based on cell counting of post-surgical specimens has indicated that the immediate recall of the stories is not related to the degree of left hippocampal cell loss (Rausch & Babb, 1993). In addition, the children's stories may be too easy for the higher end of the age range to which they are given. This would mean that an eleven-year-old might score highly (as many as twelve or thirteen points) but a twelve-year-old, given the adult stories, might only score seven or eight points. This may further explain why the significant relationship between immediate story recall and left hippocampal pathology shown in adults by Kälviäinen and colleagues (Kälviäinen et al., 1997) is not seen here.

Using the LM-% score, however, could solve these problems. By using this measure, it should no longer be absolute performance that is tested, but the storage and retrieval ability of the subject. This means for example, that getting

three points on immediate and delayed recall is as good as getting twelve points both times, in that both would have a retention score of 100%. However, this still shows an association with age that is negative, i.e. performance falls as age increases. This may be because an older child, with an LM-I score which is already fairly low (e.g. five points) will have a fairly insensitive LM-% score. This is because the LM-D score can only drop in $^1/_2$ point intervals, which in this example would equate to 10%. A younger child, scoring more points on the children's stories, would have a lower percentage fall in LM-% for each $^1/_2$ point fall in LM-D.

Nonetheless, the LM-% score is significantly associated with $T2_{[L]}$. This supports previously reported relationships between the number of neurons in CA3 and the hilus of the left hippocampus and the LM-% score (Sass et al., 1992a), and also the role of the lateral neocortex in data acquisition and the hippocampus in long term retrieval (Helmstaedter et al., 1997).

5.6.3 Verbal Paired-Associate Learning

The regression equations relating pathology and VPAL scores indicate that the learning of the semantically-associated ('easy') word-pairs is predominantly dependent on the left medial temporal cortex, whilst their delayed recall appears to rely more on the left hippocampus. This only provides slight support to the previously reported relationship between $NAA/(Cho+Cr)_{[L]}$ and VPA score (Gadian et al., 1996), since VPA Score was not associated with temporal lobe pathology in this analysis. However, although the relationship between $T2_{[L]}$ and VPA Delayed Recall (Incisa della Rocchetta et al., 1995) has not been supported, there is an association with $HFV_{[L]}$, indicating that the hippocampal

formation is involved in the performance of this test. As has been pointed out in Chapter 3, there is a large degree of correlation between T2 and HFV which would imply that either will associate with the VPA Del score if the other is not utilized in the statistical analysis.

The finding for VPA Del mirrors the significant group difference found in Section 5.4.1. In that analysis, however, no one group was significantly poorer than another, possibly as a result of the high variance of the TLE L (HF) group. Nonetheless, the patients in the TLE L (HF) group did have the lowest mean score.

It might be expected that performance on the VPA Easy Pairs should correlate with neocortical damage, since the easy pairs are based on semantic associations. As mentioned above, it has been suggested that regions other than the hippocampus subserve semantic knowledge, and this would give weight to the hypothesis that it is subserved by temporal neocortex.

In addition, the degree of left hippocampal cell loss has been shown to be associated with poor delayed recall (Rausch & Babb, 1993). This supports the finding of the stepwise regression equation for VPA Delayed Recall, which found that $HFV_{[L]}$ was the only significant contributor. Possible reasons why $HFV_{[L]}$ should be the only contributor are discussed in Chapter 8. However, it is by no means the case that a subject with a normal $HFV_{[L]}$ and abnormal $NAA/(Cho+Cr)_{[L]}$ ratio would achieve a normal VPA Del score. If they could not learn the associations initially (which are related to $NAA/(Cho+Cr)_{[L]}$) then it is difficult to believe they would get the perfect delayed recall score commensurate with their non-atrophied hippocampus.

The failure to find a relationship between greater left temporal lobe damage and poorer performance on the hard pairs was not predicted. Because there is no semantic relationship between the words of each pair, one might assume that the hippocampus was required to form a new association between the words. It has been suggested that the learning of these arbitrary associations is an excellent measure of hippocampal integrity (Saling et al., 1993). Amnesics with hippocampal damage tend to do badly on the hard pairs, and Loftus and colleagues (Loftus et al., 1997) suggested that left hippocampal damage (as measured by T2) was related to hard pair performance. However, examination of the graph of $T2_{[L]}$ against VPA Hard (see Appendix II.iii), shows that, as in the study of Loftus and colleagues, some of the patients with high $T2_{[L]}$ do well on the hard pairs. This could indeed be an indication of transferred memory in response to early injury, as Loftus and colleagues suggested, but the regression analysis (also shown in Appendix II.iii) indicates that VIQ and Age alone are able to explain the variability in this measure.

5.6.4 C', C Score and Percent Retention of C

The results of regression equations using these memory scores showed that only the C% score was significantly associated with $T2_{[L]}$, whilst both C' and C were associated only with VIQ. This supports the findings of the ANOVA in Section 5.4.1, in which a significant group difference was found between those with left hippocampal pathology and those with no hippocampal pathology only for the C% score.

Given that these measures are composite scores of memory tasks which are almost certainly performed in different ways, it is perhaps surprising that there

should be such a convincing relationship between C% and $T2_{[L]}$. This is especially the case since LM-D was not significantly associated with $T2_{[L]}$ (although LM-% was), and only VPA Del significantly associated with $HFV_{[L]}$. However, this suggests that the composite score is a good way of assessing verbal memory in a non-specific fashion (though one would expect to see an association between the scores from which it is calculated and hippocampal pathology if larger groups were used).

This implies a fairly major role for the left hippocampus in verbal memory storage and retrieval, which is consistent with the vast majority of published research to date. It does not, of course, imply that the medial temporal neocortex makes no contribution to these functions, but it does suggest that it plays a lesser role. In addition, age does not make a significant contribution to the model, despite its role in Logical Memory. This implies that the percentage of the originally recalled information which can be retained over a delay does not change with increasing age. Of course, this would need to be confirmed in a normal population, rather than in this pathological one.

5.6.5 CAVLT-2

Although the memory tests which have been discussed above have proved useful in assessing verbal learning and memory ability, they leave other aspects of memory function untapped (Hermann et al., 1987). One test of much interest to cognitive psychologists is the free recall of a list of related or unrelated words (Cermack, 1972), which allows investigation of the rate of verbal learning, interference effects and retrieval efficiency (Hermann et al., 1987). An example of such a test is the CAVLT-2. A number of studies have been published which

have used free recall lists to assess memory performance in patients with epilepsy or following temporal lobectomy, with mixed results, most probably due to variations in subject populations. For example, when investigating immediate free recall (roughly analogous to the Immediate Learning score from the CAVLT-2) in patients following temporal lobe surgery, Weingartner (1968) and Fedio and colleagues (Fedio et al., 1984) demonstrated that patients with left-sided removals performed worse than those with right-sided lesions. Similar results were obtained by Hermann and colleagues (Hermann et al., 1987) studying patients with TLE. However, in a different study of patients with TLE, no laterality effects were observed, although both groups were reported to be worse than controls (Loiseau et al., 1983). A subsequent study, again using nonsurgical TLE patients, found no impairments and no laterality effects (Mungus et al., 1985).

Verbal learning ability, as measured by the Level of Learning score on the CAVLT-2, has not been frequently investigated. When this ability was defined as the number of words recalled on the last learning trial minus the number recalled on the first learning trial, patients with left TLE performed worse than both those with right TLE and normal controls (Hermann et al., 1987). However, Mungus and colleagues, using the same measure, found no impairments (Mungus et al., 1985).

On measures of delayed free recall, however, left temporal lobe patients have been uniformly shown to perform more poorly than normal controls (Delaney et al., 1980; Mungus et al., 1985), although Hermann and colleagues (1987), using a short delay, failed to identify significant differences between groups.

The results presented in this chapter, using the CAVLT-2, demonstrate that there is a significant relationship between verbal supraspan learning and left hippocampal pathology, broadly agreeing with the results from the 1987 publication of Hermann and colleagues. In addition, the fact that the Immediate Recall score shows no such relationship (also a concordant finding with that study) shows the effect of the interference trial. This is because the interference list is made up of words which are semantically associated with words on the original list, so immediately after presentation there is some confusion over which word was on which list. Although patients with temporal lobe lesions are not especially susceptible to interference (Smith et al., 1995), lateralized epileptic discharges may affect the temporal lobes' ability to inhibit interference (Giovagnoli & Avanzini, 1996). This could mean that the score on the Immediate Recall trial was not necessarily affected by the extent of pathology, but by possible subclinical discharges causing increased interference.

There has been recent work which has indicated that in TLE cases the increase in T2 may reflect the loss of neurons from layer CA1 and the hilus of the hippocampus (Van Paesschen et al., 1997), which would imply that performance on the CAVLT-2 relies on these two regions. However, work by Sass and colleagues (Sass et al., 1990) has identified cell loss in regions CA3 and the hilar region as being responsible for the pre-operative deficit seen in adult TLE patients (without structural lesions) on a verbal Selective Reminding Test (vSRT), which is similar to the CAVLT-2. In a follow-up study examining adult TLE patients with structural lesions (eg a glioma or astrocytoma), they found a correlation with CA1 and CA2 (Sass et al., 1995), but they suggested no reason for this difference. It may, however, be due to pathology-induced

shrinkage in the tissue specimen, a problem that was circumvented by Van Paesschen and colleagues (Van Paesschen et al., 1997) since they used a dimensionless ratio of glial to neuronal density.

Somewhat surprisingly, a study investigating associations between MR-derived volumes of the hippocampus and the temporal lobe and the vSRT indicated that left temporal lobe volume significantly associated with vSRT performance, whereas left HF volume did not (Lencz et al., 1992).

It might be expected that measures of immediate memory span (the Immediate Learning score) would not be associated with measures of left hippocampal pathology. The high significance of the association which was found, however, is presumably related to the fact that this is a *supraspan* learning task, i.e. to achieve a good Immediate Learning score the child must recall words not just from the end of the list, but from the beginning and middle as well. Functional imaging using positron emission tomography (PET) has indicated that both hippocampi are required to recall these middle words, and indeed, that the increase in blood flow within the hippocampus is proportional to the degree of retrieval success (Grasby et al., 1993).

The fact that the Delayed Recall score shows the weakest association with hippocampal pathology may be a consequence of the subjects learning the semantic association between the words (there are four categories with four words each - parts of a house, animals, parts of the body and items of clothing). This means that once one word of a category has been recalled, it cues recall of others from that category by association, resulting in 'clustering' of responses into semantic groups. This may be more likely to use the neocortex in addition to the hippocampus. However, it has been found that left temporal lobectomy

patients tend not to 'cluster' their responses in semantic groups (Weingartner, 1968) as much as right temporal lobectomy patients. A similar pattern has also been shown for pre-surgical TLE patients (Hermann et al., 1987), but the left TLE subjects were only significantly different from normal controls, and not from patients whose epilepsy was localised to the right temporal lobe. This could well produce the results presented in this chapter. Since the patients in the study of Hermann and colleagues (Hermann et al., 1987) were not investigated with quantitative MR techniques, it is not possible to know whether the impairment shown by left TLE patients' was due to diffuse temporal lobe or hippocampal pathology. The CAVLT-2 does not have a measure of semantic clustering.

The significant associate for the Delayed Recall score is $T2_{[L]}$, and not $HFV_{[L]}$. This is the reverse of the association shown for delayed recall of the VPA, and may indicate a difference between these two tests in terms of their demands on the hippocampus. This is further discussed in Chapter 8.

It has been suggested that the reason for the variable performance of patients with intractable left TLE on tests of verbal learning and memory (specifically the California Verbal Learning Test which is roughly analogous to the CAVLT-2) is due to variations in language competence (Hermann et al., 1988). Hermann and colleagues wanted to understand why a significant minority of patients (33% in their earlier study (Hermann et al., 1987)) exhibited relatively unimpaired memory. By using a brief aphasia battery (the Multilingual Aphasia Examination) they showed that Oral Word Association and Visual Naming were the best overall predictors of memory performance (Hermann et al., 1988). Only the degree of retroactive interference failed to

correlate with language performance, indicating that it might be the best pure indicator of memory function. However, in their earlier study, it had failed to be significantly different between groups, although significantly more left TLE patients scored below the cut-off than did patients with a right-sided focus (Hermann et al., 1987).

This raises the question of whether the associations seen here between performance on the CAVLT-2 and $T2_{[L]}$ are a result of language rather than memory impairment. To a degree this should be controlled for because VIQ was used as an independent variable, and this obviously has a large verbal contribution. But a number of other studies have also identified associations between temporal lobe damage and language difficulties (Mungas et al., 1985; Schnider et al., 1992). In addition, Ojemann & Dodrill (1985) found a correlation between postoperative dysphasia and postoperative memory loss.

However, there is at least one factor which suggests that the results presented in this chapter are a reflection of memory problems and not language difficulties. If the Wingfield-Oldfield Object Naming test score (similar to the Visual Naming test used by Hermann and colleagues [Hermann et al., 1988]) is used as an independent variable in the regression analyses, it replaces VIQ as a significant contributor. However, despite improving the unadjusted r^2 of the model (from 0.462 to 0.639 in the case of the Level of Learning subtest), the Object Naming score does not replace $T2_{[L]}$ as the best single predictor. This implies that left hippocampal pathology is still the best predictor of impaired free recall ability, though clearly there is a strong role for language competence.

5.6.6 General Points and Negative Findings

A simple understanding of the way in which the temporal lobe is connected is enough to know that one cannot suggest that because a task is only significantly associated with one pathology measure, that is the only region of the temporal lobe which is important for that task. Indeed, the entire temporal lobe may not be sufficient for the task, which may require visual input, perceptual interpretation, and/or a motor output. Therefore, tasks such as the Delayed Recall from the CAVLT-2, which appears solely dependent on $T2_{[L]}$, rely upon a whole train of other regions in order for them to be performed successfully.

In addition, the close correlation between the three quantitative measures of pathology makes it harder to discover a model in which more than one will significantly associate with a neuropsychological variable. That does not mean that the medial temporal lobe (as measured by ^{1}H MRS) is inactive for tasks which associate solely with measures of hippocampal pathology, just that the contribution is not strong enough to be seen with the low statistical power available in this study. Additional data from future patients with TLE will enable better models to be constructed, and a better idea of the contributions of the different temporal lobe regions to be obtained.

5.6.6.1 Right temporal lobe function

So far no association has been observed between right temporal lobe pathology and tests thought to be sensitive to right temporal lobe damage. However, this patient population has only a very small number of children who

display right hippocampal damage as their primary pathology (just three with right MTS), which may be a reflection of the increased sensitivity of the left hemisphere to seizure onset before the age of five (Taylor, 1969a; Strauss et al., 1997). With such a small group, statistical power is low. Increased numbers in this patient subgroup may enable us to establish whether any tests are sensitive to right hippocampal damage. It has been noted, however, that although the accepted theory states that the left temporal lobe subserves verbal memory and the right temporal lobe subserves nonverbal memory, it has proved hard to replicate the latter finding reliably (Rausch, 1991; Incisa della Rocchetta et al., 1995; Barr et al., 1997). The lack of any correlation between right hippocampal pathology and memory scores may merely reflect this difficulty. The question is, therefore, why this should be so. There are two possible reasons. The first is that the subjects are simply verbalising the 'non-verbal' stimuli. This is highly likely for the Visual Reproduction subtest of the WMS, which consists of geometrical figures such as rectangles and squares which can be memorized both as the shape and as the word. The finding from Chapter 4 that both left and right TLE patients were equally impaired at this task may be related to this suggestion.

The second possible reason is that non-verbal memory tests do not put a high enough demand on the right medial temporal lobe. Most verbal memory tests are auditory, and in order to do well the brain must process each piece of information quickly and move on to the next. With non-verbal memory, usually tested in the visual domain, there is no such necessity to process quickly since the design is present for at least ten seconds. It has been proposed that the medial temporal lobe is best adapted for fast and time-limited consolidation of memory processes (Squire, 1992; Squire et al., 1993; Eichenbaum et al., 1994),

which may imply a preference for extrahippocampal structures for memory tasks with a longer presentation. In order to find tasks which correlate with right hippocampal damage, the task needs to be highly spatial, difficult, and embedded in the real world, such as topographical memory involving learning a route (Maguire, Burke, Philips et al., 1996), or a test of spatial mapping and memory in a Nine-box maze (Abrahams, Pickering, Polkey et al., 1997). The former study showed that both right and left temporal lobectomy patients were impaired on a number of measures of topographical learning, with right-sided patients always poorer. This was in marked contrast to the lack of impairment of the right-sided cases on any of the widely used and standardized tests of non-verbal memory such as the Rey-Osterrieth Complex Figure, design learning and maze learning. In addition, increased right hippocampal blood flow has been shown using PET imaging during a topographical learning task in a virtual environment (Maguire, 1997). This underlines the difference between testing non-verbal memory using a real environment and extrapolating from table-top tests (Maguire et al, 1996). This is further discussed in Chapter 8.

5.6.6.2 Recognition memory

It is also of interest to note that there is no association between hippocampal pathology and recognition memory (as measured by the WRMT), and indeed, none between recognition memory and temporal lobe pathology as measured by the NAA/(Cho+Cr) ratio. This supports the suggestion that recognition memory is spared when there are selective lesions to the hippocampus or its diencephalic targets (Aggleton & Shaw, 1996), and fits with results from an amnesic patient with pure hippocampal pathology (Vargha-

Khadem, pers. comm.). It also corresponds well with work using hippocampectomized monkeys, who are unimpaired on tests of one-trial object recognition (Murray & Mishkin, 1996), but are severely impaired following perirhinal/entorhinal cortex removal (Murray et al., 1993; Meunier et al., 1993). However, although there is unlikely to be a precise relationship between the NAA/(Cho+Cr) ratio and damage to the rhinal cortices, pathology in those areas will probably be reflected in a lower NAA/(Cho+Cr) ratio. This makes it somewhat surprising that no relationship was seen between this ratio and recognition memory scores, but for the words subtest of the WRMT, this can be attributed to a ceiling effect. The fact there is no relationship for the faces subtest either may be the result of a number of reasons, not least that the faces are not appropriate for children. They are all black and white photographs of men (generally middle-aged and wearing suits) which children may find rather uninteresting. In addition, the most memorable part of many of the photographs is not the face, but the tie the man is wearing, or the hairstyle, both of which are easily verbalisable and may contribute to the lack of an association between face recognition memory and pathology. It has been pointed out that patients with left-sided lesions often do poorly on the Faces subtest (Lezak, 1995), although in the present study there was no association between left temporal lobe pathology and poor Face recognition performance either. However, it is clearly possible to obtain a significant relationship between right temporal lobe pathology and face recognition impairments (Milner, 1968b; Barr, 1997). This may indicate that it is the test which is failing to show a laterality effect, but it may equally well be a reflection of the small group and especially of the small numbers who have right-sided TLE.

5.6.6.3 Methods of analysis

Both techniques used in this chapter have successfully been used in the past for the analysis of neuropsychological and quantitative pathology scores (Incisa della Rocchetta et al., 1995; Gadian et al., 1996). However, in this chapter it is clear that the method of stepwise regression analysis has provided the most comprehensive information about the associations between temporal lobe pathology and neuropsychological deficits. There are at least two reasons for this. Firstly, the group sizes for the analyses of variance are low, resulting in low statistical power and the increased likelihood that the null hypothesis would be confirmed. Secondly, by grouping the data in this way, resolution is lost. Specifically, if patients are to be grouped on the basis of a criterion, beyond which he/she is regarded as having 'pathology', then the use of quantitative MR techniques can be little better than standard visual methods of classification. It is true, however, that the use of the NAA/(Cho+Cr) ratio allows the investigation of metabolic status not available by MR imaging, so there is some use in the technique. Nonetheless, when the patients were grouped on the basis of their MR pathology, no significant differences were found for any neuropsychological test. Presumably this is due to the placing of patients with low left NAA/(Cho+Cr) ratios in the bilateral group as a result of their marginally low right ratios. Patients whose data support the relationship between abnormal left MRS ratios and low VIQs would then be split between two groups, the TLE L (MRS) group and the TLE Bi (MRS) group.

Admittedly the imposition of linear relationships on the variables is limiting, but the regression analysis has not found any unlikely associations. On

the contrary, the results shown in this chapter (even those for non-verbal memory tests) confirm existing ideas about the functioning of the medial temporal lobe.

In summary then, this work provides qualified support for, and also considerably extends, the findings of both Gadian and colleagues (Gadian et al., 1996) and Jambaqué and colleagues (Jambaqué et al., 1993). Diffuse left temporal lobe pathology has been found to be associated with a loss of semantic knowledge characterized by vocabulary and general knowledge, but also by the impairment of the learning of semantically associated word-pairs. Left hippocampal pathology, in contrast, has been shown to be associated with poor recall of complex verbal material and a poor performance on a verbal supraspan learning task. In addition, left hippocampal pathology seems to be highly sensitive to performance on delayed recall, an association which appears to be a factor of storage and/or retrieval rather than encoding.

Chapter 6. An Analysis of Change in Quantitative MR and Neuropsychology Measures in Temporal Lobectomy Patients

6.1 Abstract

A subgroup of 19 patients from a group of 23 surgical cases were examined both before and after epilepsy surgery using quantitative magnetic resonance techniques (^{1}H MRS, T2 relaxometry and hippocampal volumetry). This was in an attempt to identify any post-operative changes in the contralateral hemisphere, and also to ascertain any differences as a consequence of the type of epilepsy surgery (lobectomy versus lesionectomy). All 19 were seizure-free post-operatively. It was found that there was a significant increase in both the contralateral hippocampal T2 ($p = 0.030$), and the contralateral HFV ($p = 0.012$) after surgery. However, both also showed significant interactions dependent on the type of surgery, such that it was the lesionectomy patients who showed the greater increase in T2, but the lobectomy patients who showed the greater increase in HFV. There was also a trend towards a significant increase in the NAA/(Cho+Cr) ratio ($p = 0.060$), which did not show an interaction. These results can best be explained in terms of the reliability of the measures.

A second subgroup, this time of 16 patients (including three who did not have quantitative MR investigations), were assessed pre- and post-temporal lobe surgery, using neuropsychological tests. All underwent left temporal lobe

surgery, and only two had continued seizures post-operatively. It was found that scores from tests of executive function (Word Fluency and the WCST) were significantly improved following temporal lobe surgery in both temporal lobectomy and lesionectomy patients. These improvements were seen with the effects of VIQ and age covaried out, implying a change in performance attributable to improved concentration and attention following relief from seizures. In addition, certain scores obtained from memory tests indicated a post-operative improvement for the lesionectomy patients, but a decline for the lobectomy patients.

6.2 Introduction

Temporal lobectomy in children has been an effective treatment for medically refractory epilepsy for over twenty years (Davidson & Falconer, 1975; Whittle et al., 1981; Adams et al., 1990; Duchowny et al., 1992). What is not known is effect of focal removal of tissue on the remaining brain in terms of both structure and function. Outcome following temporal lobe surgery can be measured in a number of ways, the most usual (and generally the most important) being the degree to which the patient has become seizure-free. By this criterion, surgical success rates are good, with as many as 80% of operated children being relieved of seizures (Polkey, 1996). It is, however, not true to say that seizure outcome is the only factor which matters. There are, of course, a number of other ways of assessing the success or otherwise of temporal lobe surgery, such as psychosocial outcome (which is not dealt with in this thesis, but

see Taylor (1996) for a discussion of its importance in caring for children with epilepsy) and neuropsychological outcome, particularly in terms of memory function.

Although the differential effects of left and right temporal lobectomy in adults have been well documented, such that left-sided removal results in a verbal memory deficit and right-sided resection in a non-verbal one (Milner, 1968a; Milner, 1968b; Novelly et al., 1984), there is still some uncertainty about the effect that this type of surgery has on the development of lateralization of function. This has been compounded by methodological problems in the published studies to date, such as the combining of patients with temporal lobe resections with patients who have had extra-temporal resections. In addition, memory has not always been investigated in these studies, and where it has the protocol has not always been ideal. Memory assessment in children is not easy, since there are few tests available which are age-standardized and suitably developmentally sensitive. It has also proved difficult to compare performance before surgery with performance during follow-up (Adams et al., 1990).

Adams and colleagues (Adams et al., 1990) set out to try to address some of these problems in 44 children under the age of sixteen who underwent a temporal lobectomy (20 left and 24 right). The verbal memory of all the patients was assessed, using the Paired Associate Learning Test and the Logical Memory subtests from the WMS, both immediately and after a one hour delay. In addition, the recall of the Rey-Osterrieth figure was used to assess non-verbal memory. In both domains adequate normative data were either collected or already available.

Prior to surgery, all patients performed relatively poorly on tests of verbal memory, a finding that is supported by the results shown in Chapter 4. After surgery, however, patients who had a left-sided resection deteriorated in terms of both initial learning and delayed recall. Patients who underwent a right-sided resection showed no such deterioration. Post-operatively, non-verbal memory performance was found to be unrelated to side of resection, and nor were there changes in performance as a result of surgery. In addition, no difference was found between pre- and post-operative assessment for either Verbal or Performance IQ scores.

This is broadly in line with the majority of published studies of adults following temporal lobectomy, indicating the risk of a post-operative decline in memory function (Chelune, 1995). The extent of this decline has been shown to be related to the preoperative abilities of the individual patient, with those with relatively preserved memory abilities most at risk of a large fall in performance as a result of surgery (Chelune, 1995). Further support for this comes from recent study of 14 preadolescent children (Szabó, Wyllie, Stanford et al., 1998). In this group there was no change in IQ following surgery, but immediate verbal memory performance decreased significantly in those who performed above the median preoperatively.

An understanding of the differing memory contributions of the temporomedial and temporolateral structures can been obtained through the investigation of patients who have had different types of temporal lobe surgery. Initial results suggested that a selective amygdalo-hippocampectomy (SAH) did not result in memory impairment when compared to a standard two-thirds anterior temporal lobectomy (ATL) (Wieser & Yasargil, 1982). More recently

(Goldstein & Polkey, 1993), it has been shown that ATL results in a greater memory impairment for verbal paired associates than does SAH.

It has been suggested that delayed memory decline following surgery is a result of the excision of the hippocampus, since a delayed recall impairment is a consistent problem in patients with TLE preoperatively. However, the decline in immediate recall post-surgery is much greater, and has been interpreted as being a result of the lateral cortical resection during ATL (Helmstaedter & Elger, 1996).

This has been supported recently by work using patients who went on to have SAH, ATL, or temporal cortical lesionectomy. The preoperative differences in verbal memory performance and the specific patterns of postoperative impairment suggested that data acquisition and working memory was mediated by the temporal lateral cortex, whilst long-term consolidation and retrieval was a function of the medial temporal lobe (Helmstaedter et al., 1997).

However, a number studies have actually identified improvements in memory and intelligence following temporal lobe surgery. There is general agreement that in adult patients there is some modest increase in intelligence scores post-operatively, especially if it is the non-dominant hemisphere which is resected (Dodrill et al., 1993). Changes in memory ability were initially shown in a patient with right hemisphere speech, who showed an improvement in verbal memory $7^1/_2$ years after a left temporal lobectomy (Milner, 1975). This has also been shown for patients with left hemisphere speech (Rausch & Crandall, 1982), but the reverse occurrence, that of showing improvements in non-verbal memory following dominant hemisphere temporal lobectomy has only been reported in patients who had undergone temporal lesionectomy for a

tumour (Cavazzuti et al., 1980). This improvement in memory ability seems to be related to the seizure outcome of the patient - indeed, continued seizure activity following temporal lobectomy may even result in a global memory decline (Novelly et al., 1984). This has been suggested to be because a reduction of seizure frequency is associated with a non-specific enhancement of cerebral function (Hebb & Penfield, 1940; Milner, 1975), but since no consistent global cognitive improvement (as measured by IQ) has been reported, this does not seem to be supported. It is suggested by Novelly and colleagues (Novelly et al., 1984) that the reason for the seizure-related improvement in memory may be that commissural fibres travelling from one temporal lobe to the other result in the selective disruption of specific memory functions during epileptic attacks. When these fits are abolished by surgery, there is no longer any memory disruption.

An understanding of the neuropathological condition of the contralateral temporal lobe in post-operative patients could in principle help our understanding of the various memory changes seen in these subjects. Silent pathology in this lobe can be responsible for a relatively poorer cognitive outcome post-operatively, as was demonstrated by Incisa della Rocchetta and colleagues (Incisa della Rocchetta et al., 1995). They showed that pathology in the left temporal lobe (as measured by T2 relaxometry and ^{1}H MRS) was associated with a verbal memory deficit following right temporal lobectomy, but this was unrelated to seizure outcome.

However, bilateral pathology identified pre-operatively using quantitative MR techniques does not always result in a poor seizure outcome (Quigg et al., 1997) or a poor cognitive outcome (Trenerry et al., 1996). But, in neither case

was the contralateral temporal lobe assessed using the same techniques *following* surgery, because it was assumed that there could be no improvement in pathology status post-operatively. An alternative hypothesis might be that there was some recovery of previously dysfunctional tissue in the contralateral temporal lobe that contributed to the good outcome.

Recently there have been suggestions that the non-operated temporal lobe may show 'normalization' of metabolic function following temporal lobectomy (Hugg et al., 1996; Cendes et al., 1997). The study by Hugg and colleagues looked at five patients both before and after temporal lobectomy using proton magnetic resonance spectroscopic imaging (MRSI), which, like single voxel ^{1}H MRS, has been shown to reliably lateralise the epileptic focus in TLE (Cendes et al., 1994). It was found that the two patients who had bilaterally abnormal MRSI ratios (Cr/NAA) showed significant improvement in metabolic state one year after surgery with seizure-free recovery. However, this study is somewhat constrained by the very limited number of subjects, and in addition, one of the remaining three patients actually showed a worsening of the MRSI ratio. These data therefore need careful consideration, and would be strengthened by replication in a larger population.

Cendes and colleagues (Cendes et al., 1997) showed a single patient with bilateral MRSI abnormalities (measured as NAA/Cr) who showed metabolic improvement in the contralateral temporal lobe following temporal lobectomy. This was the only patient with bilaterally low NAA/Cr ratios who became seizure-free (out of five) whereas six out of eight patients with low ratios only in the ipsilateral temporal lobe became seizure-free. However, it was shown that the ipsilateral temporal lobe also had significantly improved MRSI ratios,

implying that this possible metabolic normalization could also occur ipsilateral to the seizure focus. These outcomes did not differ as a result of the type of surgical approach (temporal lobectomy or amygdalo-hippocampectomy).

It is important to avoid placing too much weight on these studies, however, since methodological and statistical implications must also be considered. Change, whether it be in memory performance or in temporal lobe pathology, is assessed by taking the difference between the preoperative and the postoperative score on the same measure, but any change thus observed may be due to a number of factors. Firstly, and most obviously, there are the specific effects of the treatment, i.e. the removal of one or other temporal lobe. Secondly, there may be effects that are transient and uncontrolled, e.g. EEG abnormalities (Binnie & Marston, 1992). Finally, regression to the mean may occur (Hermann et al., 1991; Yudkin & Stratton, 1996). This states that the probability of improving in a retest is low when the initial score was already good, and vice versa.

In the present study, the pre- and post-operative quantitative MR data from a series of epilepsy patients were compared to identify any significant changes in the contralateral, non-operated side. In addition, the changes were compared between patients who had had an en bloc lobectomy, and those who had had a lesionectomy. Any post-operative changes in the pathological state of the contralateral temporal lobe may help explain the differing outcomes from temporal lobe surgery described in the literature.

In addition, a group of patients with left-sided temporal lobe removals were investigated with neuropsychological measures, in an attempt to discover any changes in cognitive function as a result of surgery, either lobectomy or

lesionectomy. Any changes thus identified could be compared with changes in the MR data.

6.3 Methods

6.3.1 Subjects

Investigations were carried out with a total of 23 patients (11 male, 12 female; median age at surgery 14y 6m; range 4y 6m to 18y 5m) who underwent epilepsy surgery at Great Ormond Street Hospital for relief from intractable seizures (see Appendix I for patient data). All patients were diagnosed on the basis of clinical and electroencephalographic (EEG) findings and underwent a full investigatory programme prior to surgical intervention. Nineteen patients had left-sided temporal lobe resections whilst four had right-sided resections.

Nineteen of the 23 patients were investigated with quantitative MR measures both before and after surgery. All were seizure-free at the time of post-operative scanning. Sixteen of the patients underwent both pre- and post-operative ^{1}H MRS (six male, ten female); 15 were studied using T2 relaxometry (eight male, seven female); finally, 13 were assessed with HF volumetry (six male, seven female).

Sixteen of the 23 patients, all of whom had left-sided resections, were evaluated both before and after surgery using neuropsychological techniques (eight male, eight female; median age at first assessment 13y 6m; at surgery 14y 6m; at follow-up 15y 9m). Three of them had no pre-operative quantitative MR investigation. Of these 16, eight had en bloc temporal lobectomies (four male,

four female; median age at first assessment 13y 7m; at surgery 14y 8m; at follow-up 16y 8m), whilst the other eight had temporal lesionectomies (four male, four female; median age at first assessment 13y 2m; at surgery 13y 8m; at follow-up 14y 7m). All but two of the 16 were seizure-free after the operation, one from each surgical procedure group.

6.3.2 Magnetic Resonance

Patients were scanned as stated in Chapter 2. All were scanned in the six months prior to surgery. Post-operative scans were performed between six and twelve months following surgery, although in one case the scan took place earlier (at four months) and in five cases later (maximum five years).

^{1}H MRS and T2 data were measured as described in Section 2.2, but a more elaborate procedure was required for the measurement of HFVs. Because of the level of subjectivity involved in this last technique, measurements were made blind to the identity of the patient and also to the surgical status (whether control, pre- or post-operative). This was done by presenting only one temporal lobe on the computer screen at a time. Following repeated measurement of this hippocampus, the side previously hidden was revealed and also measured. Intracranial volume (ICV) was measured for both sets of scans, so the correction for ICV was slightly different for the pre- and post-operative measurements.

6.3.3 Neuropsychology

All of the 16 patients were assessed with the age-appropriate Wechlser intelligence scale and the Wechsler memory scale both pre- and post-surgery, as described in Section 2.3. However, the complete test battery was not

administered in full on both occasions in some patients. On the basis of previous literature it was predicted that there would be little change in the overall neuropsychological status of the patients, but that there was more likely to be a decrease in verbal memory in the patients who had a lobectomy. This was because those patients' left hippocampus was resected, whilst this was left intact in the lesionectomy patients.

6.4 Results

6.4.1 ^{1}H MRS

Table 6.1 shows the pre- and post-operative contralateral NAA/(Cho+Cr) ratios for the 16 patients. A two-way ANOVA with repeated measures was used to compare the pre-operative contralateral NAA/(Cho+Cr) ratio with that obtained post-operatively.

Patient Group	Contralateral NAA/(Cho+Cr) ratio	
	Pre-op	Post-op
Lobectomy	0.80 ± 0.09	0.84 ± 0.15
Lesionectomy	0.79 ± 0.10	0.88 ± 0.10

Table 6.1 Pre- and post-operative mean contralateral NAA/(Cho+Cr) Ratios(± standard deviations) for the two temporal lobe surgery groups.

The two groups did not show an overall significant difference (F (1, 14) = 0.14, p = 0.717), but there was a very nearly significant trend towards an increase in the mean NAA/(Cho+Cr) ratio following temporal lobe surgery (F

(1, 14) = 4.18, p = 0.060). There was no significant interaction between the groups (F (1, 14) = 0.44, p = 0.517). 69% of the patients showed some increase, and in some patients (such as BJB) these were very large. There were, however, also some large decreases in the ratio (e.g. LC).

There was no significant difference in the mean size of change in NAA/(Cho+Cr) ratio between those who underwent left-sided surgery and those who underwent right-sided surgery (mean change for left (n = 13) = 0.05 ± 0.13; mean change for right (n = 3) = 0.11 ± 0.08; t = -1.02, p = 0.353; two-tailed unpaired t-test assuming unequal variances). In addition, there were no significant differences in mean NAA/(Cho+Cr) ratio change as a factor of sex (mean change for males (n = 6) = 0.05 ± 0.15; mean change for females (n = 10) = 0.07 ± 0.12; t = -0.33, p = 0.748), age at onset of seizures (mean change for those whose first seizure occurred below five years (n = 11) = 0.06 ± 0.14; mean change for those whose first seizure occurred at age five or over (n = 6) = 0.06 ± 0.09; t = 0.03, p = 0.975), or the presence or absence of MTS (mean change MTS (n = 9) = 0.06 ± 0.15; mean change no MTS (n = 7) = 0.07 ± 0.08; t = -0.17, p = 0.864). All of these analyses used a two-tailed unpaired t-test assuming unequal variances.

The absolute signal intensity data that went to make up the NAA/(Cho+Cr) ratio was then examined. Neither the mean NAA nor the mean (Cho+Cr) signal intensities demonstrated a significant change between pre- and post-operative measurement (using a two-way ANOVA with repeated measures). Both did show a slight trend towards an improvement in the metabolic status of the contralateral temporal lobe (pre-op mean NAA = 19.3 ± 3.4; post-op mean NAA = 20.0 ± 2.9; F (1, 14) = 0.39, p = 0.545: pre-op mean Cho+Cr = 24.5 ± 5.3;

post-op mean Cho+Cr = 24.0 ± 5.2; F (1, 14) = 0.77, p = 0.394). In neither case was there a significant interaction (NAA; F (1, 14) = 0.04, p = 0.846: Cho+Cr; F (1, 14) = 1.77, p = 0.204) or group difference (NAA; F (1, 14) = 1.01, p = 0.332: Cho+Cr; F (1, 14) = 0.10, p = 0.760).

6.4.2 T2 relaxometry

Table 6.2 displays the pre- and post-operative T2 data for each of the 15 patients. A two-way ANOVA with repeated measures was used to compare the pre-operative contralateral hippocampal T2 map with that obtained post-operatively, and to contrast the patients who had temporal lobectomies with those who had temporal lesionectomies.

Patient Group	**Contralateral T2 (ms)**	
	Pre-op	**Post-op**
Lobectomy	106.3 ± 3.9	106.0 ± 3.8
Lesionectomy	105.2 ± 4.9	109.4 ± 3.9

Table 6.2 Pre- and post-operative mean contralateral T2 scores (± standard deviations) for the two temporal lobe surgery groups.

There was no significant difference between the two patient groups overall (F (1, 13) = 0.59, p = 0.586), but there was a significant overall difference in mean T2 as a result of surgery, which was a slight increase (F (1, 13) = 5.94, **p = 0.030**). On further investigation, a significant interaction was shown (F (1, 13) = 7.91, **p = 0.015**), which indicated that the increase in mean T2 post-operatively came from the lesionectomy patients (mean pre-op T2 = 105.2 ± 4.9 ms; mean post-op T2 = 109.4 ± 3.9 ms). The lobectomy patients actually showed little

change in mean T2 after surgery (mean pre-op T2 = 106.3 ± 3.9 ms; mean post-op T2 = 106.0 ± 3.8 ms).

6.4.3 Hippocampal Volumes

Table 6.3 shows the pre- and post-operative contralateral HFV for the 13 patients. A two-way ANOVA with repeated measures was used to compare the pre-operative contralateral hippocampal volume with that obtained post-operatively, and to contrast the patients who had temporal lobectomies with those who had temporal lesionectomies.

Patient Group	**Contralateral HFV (mm^3)**	
	Pre-op	**Post-op**
Lobectomy	3470 ± 419	3747 ± 286
Lesionectomy	3648 ± 226	3671 ± 216

Table 6.3 Pre- and post-operative mean contralateral HFV scores (± standard deviations) for the two temporal lobe surgery groups.

The ANOVA indicated that there was a significant increase (of 5.1%) in mean contralateral HFV following epilepsy surgery regardless of group (F (1, 11) = 8.97, **p = 0.012**). However, despite there being no significant difference between the groups overall (F (1, 11) = 0.16, p = 0.694), there was a significant interaction (F (1, 11) = 6.45, **p = 0.027**). This indicated that the increase in mean HFV post-operatively came mostly from the lobectomy patients (mean pre-op HFV = 3470 ± 419 mm^3; mean post-op HFV = 3747 ± 286 mm^3; equivalent to an increase of 8.0%). The lesionectomy patients showed only a slight increase in

mean HFV after surgery (mean pre-op HFV = 3648 ± 226 mm^3; mean post-op HFV = 3671 ± 216 mm^3; equivalent to 0.6%).

There was also a trend towards a fall in the mean ICV between the two scans, of 1.6% of the mean pre-operative ICV (mean pre-op ICV = 1409 ± 179 cm^3; mean post-op ICV = 1387 ± 167 cm^3; F (1, 11) = 4.00, p = 0.071). ICV was not significantly different between the groups (F (1, 11) = 0.01, p = 0.909), and neither was there a significant interaction (F (1, 11) = 0.14, p = 0.720). The loss of ICV after surgery (which could contribute to the apparent increase in contralateral HFV, since a smaller ICV leads to a larger correction factor) was equivalent to an increase in HFV of only 34 mm^3.

6.4.4 IQ Scores

Table 6.4 shows the mean IQ scores from the WISC-III^{UK} for the left temporal lobe surgery groups. Right temporal lobe surgery groups were not analysed because there were only three cases with both pre- and post-operative neuropsychological assessments. The data were analysed using a two-way ANOVA to assess whether there was a significant difference in scores as a result of temporal lobectomy or lesionectomy.

Group	VIQ		PIQ		FSIQ	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Left temporal lobectomy	88.1 ± 21.0	87.4 ± 20.0	105.5 ± 19.1	105.0 ± 23.0	95.0 ± 21.3	94.9 ± 21.0
Left temporal lesionectomy	82.9 ± 8.2	83.9 ± 9.6	93.0 ± 15.7	97.6 ± 11.3	85.8 ± 11.3	88.8 ± 9.8

Table 6.4 Pre- and post-operative mean IQ scores (± standard deviations) for the two left temporal lobe surgery groups.

Two-way ANOVA showed that there was no significant change in mean IQ scores following left temporal lobe surgery (VIQ; F (1, 14) = 0.003, p = 0.959: PIQ; F (1, 14) = 0.48, p = 0.499: FSIQ; F (1, 14) = 0.35, p = 0.566). There were also no significant changes between the groups (VIQ; F (1, 14) = 0.34, p = 0.571: PIQ; F (1, 14) = 1.40, p = 0.257: FSIQ; F (1, 14) = 0.92, p = 0.353), nor any significant interaction between the groups and the pre- and post-operative mean IQ scores (VIQ; F (1, 14) = 0.13, p = 0.722: PIQ; F (1, 14) = 0.74, p = 0.403: FSIQ; F (1, 14) = 0.41, p = 0.533).

Two-way ANOVA also failed to indicate any significant change in the mean score of any subtest as a result of surgery (Information; F (1, 14) = 1.65, p = 0.219: Similarities; F (1, 14) = 0.21, p = 0.653: Arithmetic; F (1, 14) = 2.61, p = 0.128: Vocabulary; F (1, 13) = 1.84, p = 0.198: Comprehension; F (1, 14) = 1.19, p = 0.294: Digit Span; F (1, 14) = 0.45, p = 0.511: Picture Completion; F (1, 14) = 0.04, p = 0.854: Coding; F (1, 14) = 2.89, p = 0.111: Picture Arrangement; F (1, 12) = 0.82, p = 0.384: Block Design; F (1, 13) = 1.41, p = 0.257: Object Assembly; F (1, 13) = 0.03, p = 0.865: Symbol Search; F (1, 7) = 0.16, p = 0.699). There were also no significant differences between the groups, although two subtests showed significant interactions. These were the Arithmetic subtest (F (1, 14) = 4.94, **p = 0.043**) and the Coding subtest (F (1, 14) = 7.3, **p = 0.017**). Both indicated an increase in the mean subtest scores of the lesionectomy group following surgery, whilst the lobectomy group did not change. These are shown in Table 6.5.

Group	Arithmetic		Coding	
	Pre-op	Post-op	Pre-op	Post-op
Left temporal lobectomy	9.4 ± 4.0	9.0 ± 3.2	10.3 ± 2.6	9.6 ± 3.1
Left temporal lesionectomy	7.0 ± 1.4	9.4 ± 2.1	7.3 ± 3.2	10.0 ± 2.9

Table 6.5 Pre- and post-operative mean Arithmetic and Coding scores (± standard deviations) for the two left temporal lobe surgery groups.

6.4.5 Memory Scores

Two-way ANOVA with pre- and post-operative VIQ and age covaried out were performed on all the memory scores on the protocol, including the WMS, the CAVLT-2, the emergent complex figure, the WRMT, and the Dot Location test. These indicated no significant changes for any subtest of the WMS as a result of surgery, and neither was there any significant difference between the groups except for the mean LM-% score (F (1, 10) = 11.38, **p = 0.007**). However, there was a significant interaction between the groups and the mean MQ score (F (1, 10) = 5.62, **p = 0.039**). This was such that the mean MQ of the lesionectomy group increased following surgery, whilst that of the lobectomy group decreased. A similar pattern was noted for the mean LM-% score, although this did not quite reach significance (F (1, 10) = 4.92, p = 0.051). Table 6.6 shows the mean scores on these two measures, the MQ and the LM-%.

Group	LM-%		MQ	
	Pre-op	Post-op	Pre-op	Post-op
Left temporal lobectomy	47.7 ± 35.2	47.3 ± 33.1	95.4 ± 16.5	89.3 ± 11.9
Left temporal lesionectomy	67.9 ± 26.0	78.2 ± 11.5	88.3 ± 10.6	95.5 ± 11.6

Table 6.6 Pre- and post-operative mean LM-% and MQ scores (± standard deviations) for the two left temporal lobe surgery groups.

Examination of the three scores which contribute most to the MQ (LM-I, D' and the VPA Score) indicates that, whilst the changes were not significant once the effects of Age and VIQ were covaried out, the mean scores which declined in the lobectomy group were the LM-I (Interaction; F (1, 10) = 3.23, p = 0.103) and the VPA Score (Interaction; F (1, 10) = 0.55, p = 0.474), whilst the mean score which improved in the lesionectomy group was the D' (Interaction; F (1, 10) = 0.50, p = 0.495). Table 6.7 shows the means and standard deviations for these three measures.

Group	LM-I		D'		VPA Score	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Left temporal lobectomy	7.8 ± 2.9	4.9 ± 2.6	10.5 ± 2.3	10.9 ± 1.8	14.1 ± 4.5	12.8 ± 4.2
Left temporal lesionectomy	7.1 ± 2.4	7.2 ± 2.9	8.6 ± 3.3	11.0 ± 1.8	14.0 ± 3.2	14.8 ± 4.1

Table 6.7 Pre- and post-operative mean scores (± standard deviations) for the LM-I, D' and VPA Score measures for the two left temporal lobe surgery groups.

No other memory test score showed any significant change as a consequence of surgery, although there was a nearly significant improvement in mean forwards Digit Span (F (1, 10) = 4.21, p = 0.067). There was only one significant group difference, for the mean Level of Learning score from the CAVLT-2 (F (1, 4) = 12.87, **p = 0.023**). However, there were two significant interactions, between the groups and the mean copy score of the Dot Location test, and the mean immediate recall score of the same test (Copy; F (1, 4) = 10.50, **p = 0.032**: Immediate Recall; F (1, 4) = 14.99, **p = 0.018**). Both of these measures indicated an improvement in the performance of the lesionectomy patients following surgery, but a decline in that of the lobectomy patients. Table 6.8 shows the means for all four of these scores.

Group	Forwards Digit Span		CAVLT-2: Level of Learning		Dot Location: Copy		Dot Location: Immediate Recall	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Left temporal lobectomy	5.8 ± 1.5 (n = 8)	6.3 ± 2.0 (n = 8)	104.0 ± 20.0 (n = 5)	86.6 ± 23.9 (n = 5)	80.8 ± 45.4 (n = 6)	115.0 ± 36.5 (n = 6)	113.3 ± 56.8 (n = 6)	151.7 ± 28.2 (n = 6)
Left temporal lesionectomy	5.5 ± 1.3 (n = 8)	6.3 ± 1.4 (n = 8)	117.0 ± 7.0 (n = 3)	119.0 ± 3.0 (n = 3)	81.3 ± 21.4 (n = 4)	57.5 ± 22.5 (n = 4)	160.0 ± 15.8 (n = 4)	142.5 ± 39.7 (n = 4)

Table 6.8 Pre- and post-operative mean scores (± standard deviations) on the digit span, CAVLT-2 and Dot Location tests for the left temporal lobe surgery groups.

6.4.6 Other tests

Of the other scores evaluated with two-way ANOVAs (still covaried for VIQ and Age), only the mean number of 'S' words produced on the Word

Fluency test and the mean length of time taken on the WCST showed a significant change as a result of surgery. In addition, the change in the mean number of four-letter 'C' words produced approached significance. In all cases, the change was an improvement ('S' words; F (1, 6) = 9.53, **p = 0.021**: 'C' words; F (1, 6) = 4.80, p = 0.071: WCST Time; F (1, 5) = 7.40, **p = 0.042**). However, none of these test scores showed a significant group difference ('S' words; F (1, 6) = 1.04, p = 0.348: 'C' words; F (1, 6) = 0.14, p = 0.720: WCST Time; F (1, 5) = 0.80, p = 0.412), nor a significant interaction, although this was nearly significant in the case of the WCST Time score ('S' words; F (1, 6) = 0.26, p = 0.631: 'C' words; F (1, 6) = 2.42, p = 0.171: WCST Time; F (1, 5) = 5.92, p = 0.059). Table 6.9 displays these scores for both temporal lobe surgery groups.

Group	Number of 'S' words		Number of 'C' words		Time on the WCST (seconds)	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Left temporal lobectomy	23.0 ± 11.8 (n = 7)	28.1 ± 6.6 (n = 7)	8.6 ± 5.9 (n = 7)	7.9 ± 4.3 (n = 7)	715.2 ± 473.2 (n = 6)	442.0 ± 236.7 (n = 6)
Left temporal lesionectomy	22.8 ± 5.8 (n = 5)	35.4 ± 14.7 (n = 5)	7.0 ± 4.4 (n = 5)	11.8 ± 6.7 (n = 5)	472.4 ± 236.7 (n = 5)	472.0 ± 181.4 (n = 5)

Table 6.9 Pre- and post-operative mean scores (± standard deviations) on Word Fluency and the WCST for both left temporal lobe surgery groups.

There were no other significant changes in the neuropsychological test scores.

6.5 Discussion

The above results demonstrate significant increases in both the mean volume and T2 relaxation time of the HF in the contralateral hemispheres of patients who have undergone temporal lobe surgery. However, these increases were not consistent across surgical procedures, such that it was patients who had a temporal lobectomy who showed an increase in HFV, but those who had a temporal lesionectomy who showed an increase in T2. In addition, although there was not a significant group change, there was a trend towards an improvement in the mean contralateral temporal lobe NAA/(Cho+Cr) ratio. However, the bases for both the improvements (HFV and NAA/(Cho+Cr) ratio) and the decline (T2) are uncertain.

Although there were some significant changes in certain neuropsychological test scores following left temporal lobe surgery, most test scores did not differ between pre- and post-surgery. Scores from tests of executive function such as the Word Fluency test and the WCST showed significant improvements post-operatively across both surgical groups. In contrast, a number of memory scores (the MQ and the copy and immediate recall of the Dot Location) showed significant improvements in the lesionectomy group but declines in the lobectomy group. However, these results were obtained from multiple comparisons with small group sizes, so it is quite possible that these may prove to be Type I errors.

6.5.1 MR measures

It should be borne in mind that there are a number of methodological factors that must be taken into consideration when attempting to understand the results presented in this thesis. Firstly, the NAA/(Cho+Cr) ratio is not an entirely objective measure in that it depends to some extent on the judgment of the rater in deciding the limits of each peak and the best way to present the spectra for measuring. There can also be technical problems present in one scan that are not present in another. These can result in poor repeatability. It should be borne in mind that the increase in NAA/(Cho+Cr) ratio is not significant ($p = 0.060$), though it occurs in a majority of patients, the majority of whom show a sizeable rise. Also, any changes in the NAA/(Cho+Cr) signal intensity ratio could occur as a result of changes in the NMR relaxation times of the protons in NAA, Cho and Cr, rather than any change in their concentrations (Cendes et al., 1997; DeStefano et al., 1995). However, this would require large changes in relaxation time to occur selectively, which seems unlikely.

Secondly, the increase in mean HFV (which is significant) can be accounted for by a number of technical features. The results could be explained by a change in the T1 relaxation time in the unoperated hippocampus. If this signal change was such that a region which was dark on the pre-operative scan (and therefore excluded as probably cerebrospinal fluid) became lighter post-operatively, it could be included in the post-operative measurement, giving a volume increase. More simply, the results may be a feature of the quality of the images used to measure the volumes, which whilst good, may not be sufficient to accurately resolve the fairly small changes in cross-sectional area indicated by the average increase. HF volumetry is a reliable measure, but this reliability may

introduce a bias towards only measuring what is confidently believed to be hippocampus. Poor image quality on a number of pre-operative scans could conceivably account for the apparent increases in HFV. Given the small number of subjects studied, a repeatability study is indicated, particularly now that much better quality images are obtainable from a new generation of MR scanners.

The increase in mean T2 relaxation time in the lesionectomy patients appears to represent a decline in the pathological status of the contralateral hippocampus in these subjects. However, changes in T2 can be caused by a number of effects, such as changes in the quantity of water or iron in the region of interest. Whilst these could be the consequence of pathological factors, they may also be unrelated to the neuronal integrity of the hippocampus.

However, it is probably unwise to discount the results as mere artifacts. Given the current literature (Hugg et al., 1996; Cendes et al., 1997), we must also attempt an explanation which supposes that the increases seen in both mean HFV and NAA/(Cho+Cr) are real and may represent an improvement in the neurological nature of the contralateral temporal lobe.

6.5.1.1 T2 Relaxometry

The increase in the mean T2 of the lesionectomy patients implies that their contralateral hippocampi are slightly more abnormal following surgery than they were before. This is despite the relief from seizures in every case. However, the increase in mean T2 time from 105 ms to 109 ms is fairly small, and only just places the group as a whole outside the normal range. Only one patient (MR) showed an increase greater than 6 ms which is the upper limit of repeatability.

This suggests that this finding may be the product of random fluctuations, in the low group size of five.

6.5.1.2 ^{1}H MRS

An increase in the mean NAA/(Cho+Cr) ratio may reflect an increase in the NAA peak, or a decrease in the Cho and Cr peaks, or both. Indeed Cendes and colleagues (1997) found a highly significant increase in the NAA peak, but no change in either the Cho or the Cr peaks. However, in this chapter there is no significant change in either of these measures as a result of temporal lobe surgery, though both show slight trends in the aforementioned directions. This lends support to the use of the ratio rather than the absolute values, since it appears to be more sensitive. It may also be that for different subjects the recovery of metabolites is different. In some there may be a reduction of the Cho and Cr peaks, and in others an increase in the NAA peak. Both sets of patients would show an increase in NAA/(Cho+Cr) ratio, whilst their combination would make it impossible to see significant changes in the metabolite peaks alone.

It is assumed that a low NAA/(Cho+Cr) ratio is a measure of neuronal loss or damage (through the use of the NAA peak) and of reactive gliosis (through the use of the Cho and Cr peaks) (Connelly et al., 1994; Ng et al., 1994). It follows that when the ratio increases it is because of a reversal of these pathologies. However, this is not necessarily the case. There is little real understanding of the function of NAA in neurons, and though it is true that if neurons die the level of NAA in that brain region falls, it is also highly likely that neuronal dysfunction is related to a drop in NAA concentrations. Therefore, seizure-related metabolic changes which impair neuronal function could well

cause the observed changes in the NAA/(Cho+Cr) ratio, a hypothesis supported by at least one clinical study (DeStefano et al., 1995). It is, however, not possible to say whether the fall in NAA is a cause of dysfunction, or an effect. Whilst it seems certain that it is related to the primary pathology of epilepsy, it may also be a marker of secondary changes in response to epileptic activity (Cendes et al., 1997). It may also be that an increase in NAA indicates a return to more normal function.

Equally, although increased Cho+Cr has been interpreted as an indication of gliotic change (Connelly et al., 1994; Ng et al., 1994), the finding that it may show a decrease following surgery indicates a more complex explanation. This may be related to changes in the metabolism of glia or neurons as a result of the cessation of seizures (Cendes et al., 1997).

There is also a case for neuronal sprouting accounting for the increases seen in the NAA/(Cho+Cr) ratio. Assuming that NAA is within axons as well as cell bodies, there could be an increase in this metabolite within the temporal lobe by an increase in axons. As a result, glial cells may be displaced out of the area of measurement, causing a drop in the Cho and Cr peaks. An alternative hypothesis is based on the finding that deafferentation may lead to a transsynaptic decrease in NAA (Rango et al., 1995). This decrease may be reversible when synaptogenesis occurs. However, it is by no means certain that axonal sprouting can occur fast enough to explain the increases seen here. BJB, for example, shows the largest increase in NAA/(Cho+Cr) ratio of 0.23 only eight months after his surgery.

Nine of the eleven patients (82%) showing an increase in contralateral NAA/(Cho+Cr) ratio had contralateral ratios in the normal range prior to surgery

(albeit below the mean control value of 0.92 in all but one case). In other words, by normal standards they did not have a damaged contralateral temporal lobe before temporal lobectomy, yet it 'improved' subsequently. This is different from the cases that showed normalisation in the work by Hugg and colleagues (Hugg et al., 1996), both of whom had abnormal ratios prior to surgical intervention. It is not inconsistent, however, with the results of Cendes and colleagues (1997). In that study, although the seven seizure-free cases did not show significantly improved NAA/Cr ratios in the contralateral temporal lobe, there was an overall increase. In all but one case, these ratios were in the normal range prior to surgery. It is not necessarily true however, that the NAA/(Cho+Cr) ratio of a temporal lobe which is within the average range is undamaged - pathology may exist which has reduced the NAA/(Cho+Cr) ratio below the mean but not enough to put it below 0.72. Therefore an increase from a low-average level may still represent improvement in metabolic status.

6.5.1.3 Hippocampal Volumetry

The apparent increase in mean contralateral HFV is not an artifact of the correction for ICV. Although there is a significant loss of ICV as a result of surgery, this would only increase HFV by about 34 mm^3, whereas the average increase across the group is 179 mm^3.

However, the increase in MR-derived hippocampal volume does not necessarily imply an increase in tissue. These results could be explained by increased water in the head of the contralateral hippocampus, although it is not obvious as to why this should occur. It is difficult to rule this out absolutely,

although if present it would still imply some kind of change in tissue characteristics following surgery.

If the volume change is real and consists of some increase in cell volume, this could reflect an increase in glial volume, sprouting of neurons or neurogenesis. An increase in glia in patients who are not having seizures seems unlikely, especially in the unaffected hippocampus. This is also not supported by the ^{1}H MRS results, which if anything would suggest that the neuron/glia ratio has increased, albeit in a somewhat different region. It is possible that T2 relaxation mapping could provide further information in this regard since the T2 maps are related to the neuron/glia ratio (Van Paesschen et al., 1997). Although the T2 data presented above did show an increase following surgery, this is not particularly helpful. The group that showed the increase in T2 (the lesionectomies) did not show much change in HFV. This makes it unlikely that the increase in HFV is related to an increase in glia. In addition, the T2 maps were obtained from just one slice in the body of the hippocampus (slices 6 to 8 on Figure 2.7). Since HFV covers the entire hippocampus, there is only a poor overlap between the two measures. Further work could be done to examine other regions using multi-slice T2 relaxometry.

Axonal sprouting has been shown to occur in the hippocampi of rats that have had entorhinal cortex lesions (Cotman & Nadler, 1978). The entorhinal cortex projects to the granule cells of the dentate gyrus of the ipsilateral hippocampus, but these cells also receive an input from the contralateral entorhinal cortex (Kolb, 1995). When the entorhinal cortex is removed unilaterally, there is an enormous loss of input to the dentate gyrus ipsilaterally, which leads to reorganization and an increased input from the contralateral

entorhinal cortex (Steward, 1991). However, the surgical procedure carried out in these patients means that few, if any, will have had unilateral entorhinal cortex lesions without removal of the ipsilateral hippocampus.

The possibility that axonal sprouting, which is generally regarded as deleterious in epilepsy, might be beneficial to the restitution of function after injury, has recently been raised (Prince, 1997). This seems more likely given the findings of Jones and colleagues (Jones et al., 1996), who made a unilateral lesion to the forelimb area of the rat sensorimotor cortex. Between ten and 30 days later, the rats were killed and the sensorimotor cortex contralateral to the lesion was examined using electron microscopy. This region showed increased synapse density and dendritic volume that was believed to be related to compensatory changes in the use of the non-impaired forelimb (Jones & Schallert, 1994). There seems to be no reason to believe that analogous changes would be impossible in the temporal lobe, although the hippocampus itself is a different kind of cortex and may well behave differently. In addition, the change in sensory motor cortex is use-dependent – there is no evidence of that here.

It is, however, possible that the significant improvement in contralateral HFV and the improvements seen in the NAA/(Cho+Cr) ratio of a large number of patients are an adaptive or compensatory change as a result of increased information processing workload in the intact temporal lobe. The improved performance on maze learning of rats living in a stimulating external environment was first noted by Hebb (1947). This enriched environment has since been shown to result in an increase in granule cell neurons in the dentate gyrus of rats (Kempermann et al., 1997). There is now some anatomical evidence for an increase in granule cells in the human hippocampus postnatally

(Mathern et al., 1996). Although it is not known whether neurogenesis continues for long following birth in humans, neurogenesis has been shown to continue throughout adult life in the rat (Altman & Das, 1965; Kaplan & Hinds, 1977). It may therefore be that following temporal lobectomy, there is more information processing demand (an "enriched" environment) on the remaining temporal lobe, possibly as a result of seizure relief, possibly as a consequence of temporal lobe removal. If so, in order to cope with this requirement, it may be that neurogenesis and/or neuronal sprouting in the hippocampus and the medial temporal lobe occur, resulting in the increase in contralateral HFV and NAA/(Cho+Cr) ratio shown above.

6.5.2 Neuropsychological measures

The finding of 'no change' in a large number of tests, particularly the IQ scores, is of interest because it implies that temporal lobe surgery does not have a significant effect on a large proportion of neuropsychological function. This is broadly in agreement with the findings of a number of studies on children following temporal lobectomy (Szabó et al., 1998; Adams et al., 1990; Meyer et al., 1986). This can either be taken to show that temporal lobe surgery holds few dangers to cognitive function, or that the selection of patients for this type of surgical procedure has resulted in only those patients unlikely to suffer significant post-operative cognitive declines being chosen as surgical candidates. An alternative conclusion is that the time between the two assessments (median 2y 3m) is simply too short for any meaningful change.

Despite these findings, there is a significant interaction between the pre- and post-operative mean MQ scores of the two groups of patients following left

temporal lobe surgery. This is clearly unrelated to IQ variations, since they were covaried out. However, it is unclear how much should be made of this finding, given that the p value was only 0.039 and also that there were multiple comparisons. Investigation of the three memory subtests which make the largest contribution to the MQ indicates that the decline in the temporal lobectomy patients is most likely to be a factor of a fall in LM-I, and also to a lesser extent the VPA Score. In addition, the improvement in the lesionectomy patients is not in these tests, but in the D' score.

The most likely explanation for the decline in LM-I in the lobectomy patients, is that a more of them (four) were given the children's stories before surgery and the adult stories afterwards than the lesionectomy patients (only two). This change from a test at which they were scoring high marks to one on which they were scoring low ones suggests that their decline is due to the increased difficulty of the material presented, rather than a result of temporal lobe surgery per se. For example, SWr, a lobectomy patient, scored an LM-I of 10.75 on the children's stories prior to surgery, but only 3.75 on the adult stories subsequently. In addition, the association found in Chapter 5 between LM-% and age indicated that the patients generally got lower scores as they got older. It might be thought that a solution to this would be to use percentage scores for the LM-I and LM-D, in place of the absolute values. This is fallacious, however, since there are fewer units to remember on the children's stories. This means that the percentage figure will be greater for the children's stories than for the adult ones, resulting in an exacerbation of the discrepancy already seen.

A different conclusion may be suggested by the literature. The MQ score is derived from the immediate recall scores of the component subtests (LM-I, D'

and VPA Score, as well as the digit span). This means that it is a test of immediate/intermediate memory, and certainly not one of delayed memory (although it also involves tests of orientation, information and mental control, making it also a test of current information and attention). It is believed that whilst the temporomedial system is involved in the fast processing of memory such as is required in long-term episodic memories, it is the neocortical structures which mediate short-term memories and act as an information store (Squire, 1992; Squire et al., 1993; Eichenbaum et al., 1994). This suggests that the decline in mean MQ seen in the temporal lobectomy patient group investigated in this chapter is due to the resection of lateral temporal neocortex. However, the temporal lesionectomy patients showed an increase in MQ despite losing some neocortex in the surgical procedure.

The phenomenon of improved non-verbal memory following dominant temporal lobe surgery has only previously been reported in patients with mass lesions (Cavazzuti et al., 1980), so the suggestion of an increase in D' in the lesionectomy group would seem to support this. It has been shown in Chapters 4 and 5 that the scores on the Visual Reproduction subtest are not related to temporal lobe pathology, but rather to the condition of TLE. However, the data indicate that the increase in the lesionectomy group brings them to the level of the lobectomy group, who remain stable. This seems to indicate that there is a specific deficit in the lesionectomy cases pre-operatively which is abolished following surgery. This may take the form of increased neo-cortical abnormalities impairing the processing and reproduction of these figures, but it is difficult to understand the exact way in which this might occur. The significant interaction in the Dot Location subtest analyses also suggested that

the immediate processing of visual information may be improved following left temporal lesionectomy. Again, one must be cautious about reading too much into results with small group sizes and multiple comparisons. Further work is clearly warranted.

The improvement seen in tests of executive function (the number of 's' words produced, and the time taken to complete the WCST) may be a result of the relief from seizures in the majority of these patients, allowing greater concentration and flexibility of thought. With the effects of age covaried out, this cannot be attributed to the expected improvement in performance commensurate with age. A role for the hippocampus in the performance of the WCST has been suggested (Corcoran & Upton, 1993). The evidence for this was based on data showing that preoperative patients with MTS took longer to perform the WCST and made more errors than TLE patients without MTS. The patients with MTS were also more impaired on these measures than patients with unilateral frontal epilepsy. Word fluency was not affected by the presence of MTS. The findings presented in this chapter do not appear to support a role for the hippocampus in the WCST. This is because left hippocampal removal results in a large improvement in the time taken to perform the task.

As yet the behavioural and MR data from these patients are not well enough matched to allow meaningful comparisons. It is therefore not known whether the post-operative improvement in the NAA/(Cho+Cr) ratio of some patients, and/or the significant increase in the hippocampal volume of the contralateral temporal lobe has a functional correlate.

This study therefore needs further prospective work, firstly to confirm or refute the quantitative MR changes suggested here and by others, and secondly

to identify any behavioural changes which are a consequence of the presumed neuronal changes in the temporal lobe.

In summary, this work greatly extends the work previously published (Hugg et al., 1996; Cendes et al., 1997) by investigating a larger series of patients and showing post-operative improvements in two separate MR measures of temporal lobe pathology, as well as one post-operative decline. It appears likely that the more abnormal mean contralateral T2 of patients with lesionectomies is the result of normal measurement error compounded by the small group size. The apparent increase in HFV is requires further validation, as does the suggested increase in the NAA/(Cho+Cr) ratio.

This chapter also demonstrates that there are significant changes in some neuropsychological test scores following left-sided surgery, although the reasons for these may not be entirely due to the surgical procedure. It appears that the significant changes in MQ are not necessarily a result of changes in memory abilities, but due to changes inherent in the test. The improvement in the scores from the Word Fluency and the WCST, however, may be the result of seizure relief enabling better information processing and concentration.

Chapter 7. The Relationship Between Children with TLE and Their Unaffected Siblings on Measures of Temporal Lobe Pathology

7.1 Abstract

There is known to be a strong genetic contribution to the occurrence of prolonged febrile convulsions. In order to investigate this, the temporal lobes and hippocampi of eight children with histologically confirmed MTS and a history of a prolonged febrile convulsion and seven normal siblings of children with TLE were examined with three quantitative MR techniques. Comparison of the T2 relaxation times of the hippocampus contralateral to the seizure focus in the TLE cases with those of the siblings showed no significant difference. However, there was a significant difference in NAA/(Cho+Cr) ratios, with those of the contralateral temporal lobes of the TLE cases being lower (0.78 ± 0.08 cf. 0.93 ± 0.13). This was attributed to neuronal dysfunction as a consequence of either the initial febrile convulsion or the subsequent chronic epilepsy. When the hippocampal volumes were compared, however, it was found that there was no significant difference between the mean volumes of the contralateral hippocampi of the TLE cases and the siblings (3560 ± 279 mm^3 and 3328 ± 325 mm^3). This was investigated further using an additional three groups, one of adult controls (n = 24), one of child controls (n = 11) and another of non-epilepsy patients (n = 10). It was found that the hippocampi of the siblings were

significantly smaller than those of either normal adult or child controls on average (4000 ± 294 mm^3 and 3939 ± 280 mm^3 respectively), and also smaller than those of a group of patients without epilepsy (3935 ± 507 mm^3). Although the contralateral hippocampi of the TLE cases were not significantly smaller than those of any of the three control groups, in all cases they were near significance (in the case of the adult controls, $p = 0.051$). It is suggested that this may indicate some genetic factor leading to smaller hippocampi, which may predispose the child to developing a febrile convulsion.

7.2 Introduction

The genetic basis of childhood epilepsy has become of major interest with recent advances in neuroepidemiological and molecular biological techniques. As many as 70% of all epilepsies occur before the age of 20, and epidemiological data indicate that 50% of these cases may have a genetic basis (Hauser & Hesdorffer, 1990).

Although the generalised epilepsies have proved the most productive in terms of the identification of genetically acquired syndromes (Buchhalter, 1994), temporal lobe epilepsy (TLE) has also been reported to have a genetic basis (Currie et al., 1971; Falconer, 1971; Jensen, 1975). This is somewhat surprising, since TLE is generally believed to result from an acquired lesion, but studies have suggested that between 11 and 30% of the family members of TLE sufferers also had epilepsy (Currie et al., 1971; Falconer, 1971; Jensen, 1975). A subsequent review (Ottman, 1989) suggested, however, that some of the patients

in these studies did not have TLE at all, but actually had benign epilepsy of childhood (characterized by centrotemporal spikes on EEG), 70% of whom have a family member with childhood epilepsy (Heijbel et al., 1975). This had resulted in an apparently increased familial incidence of epilepsy in TLE patients, and when these patients were removed the incidence of epilepsy in the families of children with TLE was reduced to just one to three percent above that seen in controls. This seems to imply that TLE has only a slight genetic contribution.

Febrile convulsions, however, which are known to be associated with the later onset of TLE, do have a significant genetic component (Brett & Neville, 1997). Febrile convulsions are one of the most common kinds of seizure in young children, with 2 to 5% of all children likely to have at least one before the age of five (O'Donohoe, 1992). These seizures are associated with fever but without any obvious cause such as intracranial infection. They are denoted as 'complex' if certain criteria, such as focality, more than 30 minutes duration or recurrence within 24 hours are met (Buchhalter, 1994). Complex febrile convulsions are associated with an increased incidence of afebrile seizures, and the more febrile convulsions the child has, the greater the probability of developing subsequent epilepsy (Annegers et al., 1987). There is frequently a family history of febrile seizures, which could suggest either a genetic or an environmental basis for their occurrence. Twin studies have shown concordance rates for developing febrile seizures to range from 31 to 70% in monozygotic twins (Schiottz-Christensen, 1972; Tsuboi & Okada, 1985; Lennox-Buchthal, 1971; Lennox-Buchthal, 1973) with a significantly lower occurrence in dizygotic twins (14 to 18%). A recent study in two families with a history of

febrile seizures has suggested a possible structural basis for this (Fernandez, Effenberger, Vinz et al., 1998). All 11 subjects who had had a febrile convulsion without developing TLE and six of the 10 who had not had hippocampi which were smaller on the left than the right. In addition, the internal structure of the left hippocampus was abnormal in these subjects. This implies an inherited hippocampal abnormality which might produce a predisposition to febrile seizures. However, febrile seizures are not always (indeed, perhaps not usually) followed by the onset of chronic epilepsy (Tsai & Hung, 1995), so this would imply that some other factor or factors are involved in the aetiology of TLE, which could also have a genetic basis.

Various models of genetic transmission and inheritance patterns of epilepsy have been proposed, including autosomal recessive or dominant inheritance to a polygenic or multifactorial model (Gardiner, 1990). Linkage analysis has identified an association between familial febrile convulsions and a gene(s) on chromosome 8 (Wallace et al., 1996). Candidate genes in this region include corticotrophin releasing hormone and calbindin, and rat models have shown that both of these proteins may have a role in seizures (Smith & Dudek, 1994; Tønder et al., 1994). In addition, a complex segregation analysis has been conducted, examining the families of children who had febrile convulsions (Rich et al., 1987). This concluded that for a heterogeneous group of families (the children may have had one or more febrile convulsion), the most parsimonious model was a polygenic one with a large (68%) heritable component. This supports previous work which investigated 6706 Japanese children and concluded that febrile convulsions were most likely to be associated with a multifactorial model of inheritance (Tsuboi, 1977).

It is therefore likely that there are many individual components which can affect the incidence of febrile convulsions which may all be under separate genetic control (Buchhalter, 1994). These components include age of onset, a predisposition to hyperexcitability and gender. What is not known, however, is why some children develop chronic epilepsy in later life. Prophylaxis does not appear to improve the long-term outcome (Knudsen, 1996), and so presumably there is something different about the children who develop TLE as a consequence of febrile convulsions, at the time of their seizure. What this is remains to be discovered.

In this study, children with TLE following a prolonged febrile convulsion in early childhood and unaffected siblings of patients with TLE were compared using measures of temporal lobe pathology, to investigate whether there were similarities between them. If found, these would be of great interest to those involved with the treatment and counseling of people with epilepsy, since it may be possible to show that these similarities predispose the child to developing the condition.

7.3 Methods

7.3.1 Subjects

Eight children with TLE (three male, five female; median age 14y 11m; range 6y 3m to 17y 8m) and seven children with no neurological history who had siblings with TLE (four male, three female; median age 10y 11m; range 7y 0m to 16y 2m) were examined using quantitative MR techniques (see Appendix

I for details). All eight TLE cases had well lateralized epileptic foci, a history of prolonged febrile convulsion and subsequently underwent temporal lobectomy. The presence of MTS was confirmed by post-operative histological analysis. Three of these patients had brothers or sisters in the sibling group.

Ten non-epilepsy patients (seven male, three female; median age 10y 2m; range 1y 4m to 15y 1m) underwent hippocampal volumetry as part of their radiological investigation. These patients were not necessarily neurologically normal, but they did not have any temporal lobe pathology or any epileptic history. Commonly they suffered from a tumour (e.g. chiasmal astrocytoma or pineal region tumour), but four patients had no visible lesion on MRI (see Chapter 2.1.3).

In addition to the normal adult controls collected and measured in Chapter 2.2.3, eleven normal children (six male, five female; median age 12y 0m; range 8y 3m to 16y 0m) were investigated using hippocampal volumetry. These were made up of Group CC plus two sibling controls (TM and GB). These two children had siblings who did not have a prolonged febrile convulsion as their initial epileptic event, and so were regarded as qualifying for the normal control group.

7.3.2 Magnetic Resonance

Magnetic resonance examination included ^{1}H MRS, T2 relaxometry and the acquisition of a 3D dataset for measuring hippocampal volumes, as described in Section 2.2. One sibling control did not undergo spectroscopy owing to technical difficulties, and one TLE patient did not have hippocampal volumetry. All TLE patients were scanned prior to surgery.

7.3.3 Statistics

The statistics used were t-tests and one-way analyses of variance with post-hoc Tukey's h-s-d analysis. These were performed as necessary to test for significant differences between groups.

7.4 Results

7.4.1 T2 Relaxometry

The T2 relaxation times of the hippocampi of the sibling controls were compared with the T2 relaxation times from the hippocampi of the TLE patients, using a one-way ANOVA (Table 7.1). In the TLE patients, the ipsilateral hippocampus can be expected to have an abnormal T2, while, at least in some cases, the contralateral T2 can be expected to have normal values.

Hippocampal T2 of TLE Cases		**Hippocampal T2 of Sibling Controls**	
Ispilateral	Contralateral	Left	Right
129	107	106	102
128	106	103	101
128	108	102	103
123	111	92	98
133	107	106	101
126	108	106	104
110	98	103	111
125	102		

Table 7.1 Pre-operative T2 of eight TLE patients and the T2 of seven normal siblings.

There was a significant group difference in mean T2 (F (2,27) = 53.55, **p < 0.0001**). Post-hoc analysis with Tukey's h-s-d test indicated that the mean ipsilateral T2 of the patients with TLE was significantly higher than both the mean contralateral T2 and the T2 of the sibling controls ($p < 0.05$). However, the mean contralateral T2 and the mean T2 of the sibling controls were not significantly different (mean ipsilateral TLE T2 = 125.3 ± 6.8 ms; mean contralateral TLE T2 = 105.9 ± 4.1 ms; mean sibling T2 = 102.7 ± 4.4 ms; cf. adult controls 101.7 ± 3.1 ms).

7.4.2 ^{1}H MRS

The NAA/(Cho+Cr) ratios of both temporal lobes from the sibling controls were compared with the NAA/(Cho+Cr) ratios from the contralateral and ipsilateral temporal lobes of the TLE patients, using a one-way ANOVA (Table 7.2).

NAA/(Cho+Cr) ratio of TLE Cases		NAA/(Cho+Cr) ratio of Sibling Controls	
Ipsilateral	Contralateral	Left	Right
0.60	0.69	1.02	1.10
0.62	0.89	1.10	0.94
0.93	0.85	0.85	0.77
0.60	0.77	1.12	0.79
0.61	0.80	0.96	0.87
0.71	0.83	0.78	0.86
0.86	0.72		
0.56	0.66		

Table 7.2 Pre-operative NAA/(Cho+Cr) ratio of TLE patients and the NAA/(Cho+Cr) ratio of normal siblings.

There was a significant group difference in the mean NAA/(Cho+Cr) ratio (F (2, 25) = 10.30, **p = 0.0005**). Post-hoc Tukey's analysis showed that the siblings had a significantly higher mean NAA/(Cho+Cr) ratio than either that of the contralateral or ipsilateral temporal lobes of the TLE patients ($p < 0.05$). The ipsilateral and contralateral mean ratios were not significantly different from each other (mean ipsilateral TLE NAA/(Cho+Cr) ratio = 0.69 ± 0.14; mean contralateral TLE NAA/(Cho+Cr) ratio = 0.78 ± 0.08; mean sibling NAA/(Cho+Cr) ratio = 0.93 ± 0.13; cf. adult controls 0.92 ± 0.16).

7.4.3 Hippocampal Volumes

The hippocampal volumes of the seven sibling controls, the ipsilateral and contralateral HFVs of the seven TLE patients, the HFVs of the 10 non-epilepsy patients and the HFVs of both the 24 normal adult controls and the 11 normal children were compared using a one-way analysis of variance. This showed a

significant difference of group (F (5, 112) = 35.47, $\mathbf{p < 0.0001}$; Table 7.3). Figure 7.1 shows all the data points for the six groups. Post-hoc analysis revealed that the mean ipsilateral HFV of the TLE patients was significantly different from all other groups ($p < 0.05$). In addition, the mean HFV of the sibling controls was significantly below that of the normal controls, both adults and children, and also that of the non-epilepsy patients ($p < 0.05$). The mean contralateral HFV of the TLE patients was not significantly lower than that of the controls, although it was nearly significant in the case of the adults ($p = 0.051$).

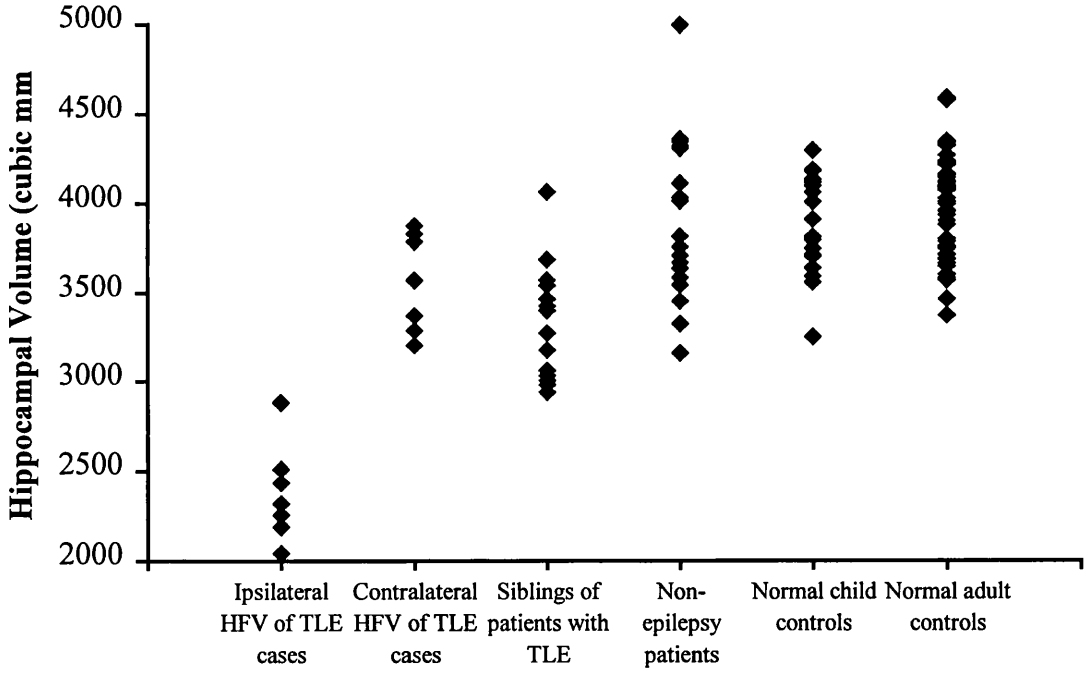

Figure 7.1 Chart showing the HFVs for all subjects in each of the six subject groups.

Group	Mean HFV	Standard Deviation
Ipsilateral HFV of TLE patients	2374 mm^3	270 mm^3
Contralateral HFV of TLE patients	3560 mm^3	279 mm^3
Siblings of patients with TLE	3328 mm^3	325 mm^3
Non-epilepsy patients	3935 mm^3	507 mm^3
Normal child controls	3939 mm^3	280 mm^3
Normal adult controls	4000 mm^3	294 mm^3

Table 7.3 Means and standard deviations for the hippocampal volumes of the six subject groups.

7.5 Discussion

In all analyses it was shown that, as expected, the ipsilateral temporal lobes of the TLE patients had greater mean pathology scores than those of the siblings. This finding is a demonstration of the specificity of the particular measures used to assess temporal lobe pathology. However, there are interesting results with respect to the contralateral temporal lobes of these patients in comparison to the siblings. These show that whilst mean T2 and mean HFV do not differ between these two groups, the mean NAA/(Cho+Cr) ratios of the two groups are significantly different.

That the T2 relaxation times of the two groups are not significantly different is not surprising. There is unlikely to be any serious hippocampal pathology in the side contralateral to the epileptogenic focus, because all of the TLE patients continued to surgery. Temporal lobectomy is very unlikely to be undertaken if there is evidence of severe bilateral hippocampal pathology.

The cause of the lower mean NAA/(Cho+Cr) ratio in the TLE group may be either chronic seizure activity, or an effect of the initial febrile convulsion. Indeed, a large proportion of children with TLE do show bilateral temporal lobe pathology as measured by the NAA/(Cho+Cr) ratio (see Chapter 3; Cross et al., 1996). It is therefore possible that there is a degree of temporal lobe pathology in many of the TLE patients, even those whose ratios are within the normal range.

The major interesting result concerns the hippocampal volumes. The data demonstrate that there is no significant difference between the hippocampal volumes of the siblings and the volumes of the contralateral hippocampi of TLE patients. However, they are both significantly lower than the volumes of normal controls.

It is clear that this is not a factor of age (the idea that despite the correction for ICV, there is an age dependent increase in HFV), because although the mean HFV of the normal child controls is lower than that of the adults (though not significantly), it is still significantly higher than that of the siblings. In addition, the use of the non-epilepsy patient group which contains patients as young as one year old indicates that there is not an age-related increase in HFV.

It has recently been suggested (Quigg et al., 1997) that most patients with TLE have some bilateral hippocampal atrophy, quite apart from any volume asymmetry. However, this bilateral atrophy appears to have no impact on the success of any subsequent temporal lobe surgery (Quigg et al., 1997; Jack et al., 1995b). The results reported in this chapter suggest, instead, that patients whose primary insult was a prolonged febrile convulsion do not necessarily have bilateral atrophy, since siblings with no neurological basis for pathology have

hippocampi of equivalent size. It is, however, true that the TLE patients have small hippocampi on the side contralateral to the epileptogenic focus. The results may point to a genetic heritability for small hippocampi, which could be a predisposing factor to the development of temporal lobe epilepsy, as suggested by Fernandez and colleagues (Fernandez et al., 1998). This could explain why apparent bilateral pathology had no effect on surgical outcome - there was no 'pathology' as such, but the hippocampus was naturally smaller than the average.

One mechanism by which smaller hippocampi could be a predisposing factor for TLE is through complex febrile convulsions. Many febrile convulsions are benign, with no long lasting consequences (Tsai & Hung, 1995), although the nature of those convulsions which are and those which are not associated with later epilepsy is not significantly different (Wallace et al., 1996). A small hippocampus may actually be a predisposing factor to the development of febrile convulsions in childhood, although which children go on to have chronic seizures subsequently is likely to be dependent on other factors, both genetic and environmental. However, there is an alternative explanation that is that small hippocampi are more susceptible to damage caused by febrile seizures, resulting in later recurrent epilepsy. Those children who have no epileptic sequelae following a febrile seizure may be those whose hippocampi are of a normal size.

These hypotheses could be tested by prospectively measuring the hippocampal volumes of a group of children as soon as possible after early complex febrile convulsions, and comparing them with age-matched controls. If having small hippocampi predisposes the child to febrile convulsions, we would

expect to find that the average HFV of the febrile convulsion group would be lower than that of the controls. Alternatively, if HFV affects the outcome of the febrile convulsion, it may be that by following the febrile convulsion group over time we will be able predict those children who will develop chronic TLE. For example we may find that those patients with HFVs in the range of the sibling controls would be more likely to develop TLE than patients whose HFVs are in the normal range. This would imply some cut-off level for hippocampal volume, below which the damage sustained is great enough to result in seizures.

It may also be the case that the siblings whose epileptic brothers and/or sisters did not have a febrile convulsion as their initial episode would have volumes far closer to the mean. In this study only two siblings, GB and TM, were in this category, and both were used as a normal child controls. GB had hippocampal volumes which were 4010 mm^3 on the left, and 4121 mm^3 on the right, which are both greater than the mean HFV from the adult normal controls, whilst for TM they were 4121 mm^3 on the left and 3910 mm^3 on the right. This clearly needs further investigation using a new population of siblings, both of epileptics with a history of febrile convulsions and those without. Presumably one could also investigate the hippocampi of the parents of children with TLE, since if there really is an inherited characteristic of small hippocampi, then they should show it too.

In summary then, this chapter has shown that the siblings of children with TLE have significantly smaller hippocampal volumes than both normal controls and patients without epilepsy. This may indicate a genetic factor that predisposes the child to develop smaller hippocampi, and this may be a risk factor for TLE in later life.

Chapter 8. General Discussion and Directions for Further Research

This thesis has shown the use of investigating the brain with quantitative MR techniques. In contrast to most previous studies, it has been possible to examine both temporal lobes pre-operatively, and also to assess the integrity of the remaining tissue following temporal lobe surgery for relief from seizures. This has increased the understanding of the extent and nature of the pathology, which has in turn enabled meaningful conclusions to be drawn from neuropsychological data.

The three most important results are (i) the increased understanding of the impact of left medial temporal lobe pathology on the performance on a number of neuropsychological tests (Chapter 5); (ii) the possible improvement in the pathological status of the contralateral temporal lobe following epilepsy surgery (Chapter 6); and (iii) the similarities between the hippocampi of siblings of patients with TLE and the contralateral hippocampi of patients with a history of febrile convulsions in terms of their volumes (Chapter 7).

However, this research has resulted in a number of further questions, which are detailed below.

- **What might result in an improvement in the quantitative MR scores of the contralateral temporal lobe?**

These questions were dealt with to some extent in Chapter 6. However, there are a number of factors that are worth discussing. Firstly, the patient groups examined with ^{1}H MRS and those examined with HFV were not identical, making it difficult to compare the increases statistically across measures. Anecdotally, patient CA showed a slight fall in both measures, which might indicate a link between the two. However, patient NB showed a large increase in HFV but a fall in ^{1}H MRS ratio. This fits rather well with the results of the correlation work shown in Chapter 3 - whilst there is some correlation between ^{1}H MRS and measures of hippocampal pathology, it is only weak. Therefore we would not expect to see a strong relationship between post-operative increase in one pathology measure and increase in the other.

This further implies that the pathological basis for the poor scores and the manner of recovery are different. In the case of ^{1}H MRS improvement, much of the volume being investigated is made up of temporal lobe white matter, whilst the hippocampus is grey matter. It may well be that an increase in ^{1}H MRS reflects an improvement in axonal integrity rather than an increased number of neurons as such.

Secondly, we would like to consider the possible benefits of this improvement in the contralateral temporal lobe. These can be divided into clinical benefits and cognitive benefits. It may be that an increase in the NAA/(Cho+Cr) ratio is associated with relief from seizures. However, it does not follow that these increases result in seizure relief - indeed, it is more likely to be the reverse, in that relief from seizures results in conditions which allow the

contralateral medial temporal lobe to improve. Continued seizures would be likely to impair the processing capability of the remaining temporal lobe, and thus prevent the environment necessary for the neurochemical and neuroanatomical changes to occur.

From a behavioural point of view, little is known. As was mentioned in Chapter 6, there have been a number of published studies detailing post-operative improvements in memory functions believed to be subserved by the non-operated temporal lobe (Rausch & Crandall, 1982; Cavazzuti et al., 1980). It is possible that those patients exhibiting the greatest memory improvement in these studies would also be the ones exhibiting the greatest increase in either HFV or the NAA/(Cho+Cr) ratio. However, the results presented in Chapter 6 indicate that for this group of patients there is no significant overall change in most forms of memory function as a result of left temporal lobe surgery, although of course some patients show a loss of function after surgery whilst others appear to show improvements. Because the groups studied on the MR measures and the neuropsychology are not the same, it is not possible to show precise relationships between memory change and changes in the contralateral temporal lobe.

The phenomenon of 'no change' in material-specific memory function following temporal lobectomy has been noted for some time, along with evidence showing that some patients show large material-specific memory decrements after surgery (Chelune, 1995). However, it has been difficult to identify which patients will suffer memory loss and which will remain unchanged. Current theory suggests that a postoperative loss of memory function is dependent on the functional adequacy of the to-be-resected tissue

(Chelune, 1995). This means that those patients who exhibit the best memory function prior to surgery are the group at greatest risk for developing memory decrements after temporal lobectomy.

However, a recent study by Seidenberg and colleagues (Seidenberg et al., 1997) indicated that this does not have to be the case. They presented data from a group of patients with severe left medial temporal sclerosis who became seizure-free following anterior temporal lobectomy. This group showed at least adequate preoperative verbal memory abilities which did not decline as a result of surgery. These patients were suggested to have reorganised their verbal memory functions away from their damaged hippocampus, probably soon after the initial insult in early childhood. This was in marked contrast to another group of patients with severe left MTS who did not become seizure-free after temporal lobe resection. The authors concluded that the continued seizures were a sign of more diffuse pathology, which limited the neuronal resources available for reorganisation. They were unable to say, however, whether the reorganisation in the former group was inter- or intrahemispheric.

What would be useful in these patients is an understanding of whether there really is more diffuse pathology in the latter group. Clearly these patients should be investigated with quantitative MR methods in order to elucidate the status of both temporal lobes, but more importantly a prospective study is required to identify similar subjects. The use of functional imaging may also cast some light on the mechanisms by which some patients seem able to preserve verbal memory function even when the left hippocampus is badly damaged. This does depend, however, on the development of reliable paradigms which activate the left hippocampus in normal subjects.

There has recently been a suggestion that the hippocampal formation is not actually a material-specific structure, but it is lent that specificity by the lateral cortex of the temporal lobe (Helmstaedter et al., 1997). This means that the left hippocampus is involved with the consolidation of verbal memory because it is delivered verbal information by the left temporolateral neocortex, and not because it is specifically organised for verbal processing. Indeed, Helmstaedter and colleagues explicitly state:

'The bilateral arrangement of the hippocampal formation provides for the possibility of compensability of left hippocampal functioning by the right hippocampal formation, and thus a higher plasticity as compared to highly specialized unilaterally disposed neocortical structures.'

This concurs with the findings of Delacour (1994), who considered that from anatomical and physiological data it was unlikely that the hippocampus would show material-specificity.

Finally, the question arises as to whether these findings are only found in children. This is a particularly important point if we are postulating some kind of reorganisation in these patients, since this is believed to only occur in young children. However, we are not suggesting that the reorganisation is particularly efficacious, and certainly not that it results in normal or near-normal function postoperatively.

Two lines of evidence suggest that the neurochemical and neuroanatomical changes at least can be found in adults. The first are the studies by Hugg and colleagues (Hugg et al., 1996), which shows improvement in MRSI ratio in two adults patients, and Cendes and colleagues (Cendes et al., 1997), which shows

improvement in NAA in one adult patient. The second is the fact that most of the patients used in Chapter 6 were aged 12 or over at the time of surgery.

Previously it has been impossible to show these changes in temporal lobe pathology, because the unoperated temporal lobe was not examined. Neither pre- nor post-operative data were available. In addition, the great strength of the study is its ability to examine the same patient both before and after surgery to investigate change. This is harder to do in animals (unless MR techniques are used) because two groups of animals are needed. One would be killed following temporal lobectomy and the other after a sham lesion. The mean volumes of the groups would then have to be compared. In order to allow for the natural variance of the hippocampi, large numbers of animals would be required.

Therefore, MR studies of animals are required in order to determine the nature of the improvement in the contralateral temporal lobe. It has been shown (Kempermann et al., 1997) that it is possible to identify new neurons in the dentate gyrus of mice by immunohistochemistry, and Jones and colleagues (Jones et al., 1996) have demonstrated the use of electron microscopy to show synaptogenesis and dendritic growth in the motor cortex of the rat. These techniques could be extended to mice or rats after temporal lobectomy. Animal work could also discover whether the prior existence of epilepsy is necessary for HFV increase to occur.

- **Why is T2 a better predictor of memory performance than HFV?**

The fact that $T2_{[L]}$ is a better predictor of memory performance than $HFV_{[L]}$ (for everything apart from delayed recall on the CAVLT-2 and the VPA) requires explanation, since both are measures of hippocampal pathology. Indeed,

this is despite the limitation that, at Great Ormond Street Hospital, T2 is only measured from a single slice (see Section 2.2.2). There are at least three reasons why $HFV_{[L]}$ might not be as good a predictor as $T2_{[L]}$. Firstly, it is possible that what is left of an atrophied hippocampus may be fully functional and appear normal on T2 relaxometry; secondly, the regions which have atrophied may not be those required for the task; and thirdly, there is simply more variability in HFV than there is in T2, both between subjects and due to intrarater error.

That the third reason is true is shown by the relative standard deviations for each measure, as reported in Chapter 3. However, it also seems likely that the relationship between $T2_{[L]}$ and verbal learning and retention is dependent on the nature of the pathology being measured, and may only hold for patients with TLE. For example, patients with Alzheimer's Disease show grave memory deficits, and concomitant hippocampal atrophy, but they do not show greatly lengthened T2 relaxation times (Pitkäanen et al., 1996). Similarly, a group of amnesic children studied at this centre show very small hippocampi with only relatively moderate increases in T2 (Vargha-Khadem et al., 1997).

As also mentioned in Chapter 3, there is the further possibility that T2 and HFV are measuring different pathologies within the hippocampus. T2 is associated with pathology in layers CA1 and the hilus, whilst HFV is associated with pathology in CA1, CA2, CA3 and the hilus (Van Paesschen et al., 1997). It may be, therefore, that relationships which demonstrate that T2 is the significant contributor are showing that the memory function relies more on CA1 and/or the hilus than CA2 or CA3. This has been shown in a number of cell counting studies, demonstrating that poor Logical Memory is associated with a loss of cells in specific subregions (Rausch & Babb, 1993; Sass et al., 1992a;

Baxendale et al., 1997). Equally, the delayed recall scores from the VPAL and the CAVLT-2, which are most strongly related with $HFV_{[L]}$, may require CA2 and/or CA3 to be intact, either in addition to or instead of CA1 or the hilus.

As has been pointed out previously, it has been found that bilateral damage to just one subfield of the hippocampus (CA1) can cause global and lasting amnesia (Zola-Morgan et al., 1986). This would seem to indicate that damage to a single region of the hippocampus is enough to impair all kinds of cognitive memory functions, and thus that there are no functional differences between the subfields. However, this may be due more to CA1's position in the flow of information through the hippocampus than its function alone. As with all lesion studies, what is actually being examined is not the function of the damaged area, but the function of the brain without the lesioned area. In this case, the loss of CA1 cells themselves may be devastating to memory abilities, because they are a stage from the dentate gyrus to the subiculum.

However, as pointed out in Section 1.2, CA3 does have output projections that do not pass through other subfields of the hippocampus. This could make it possible for CA3 to operate without CA1, and thus for hippocampal function to occur in the presence of circumscribed pathology.

Perhaps though, it would be more likely for hippocampal functional units to be arranged in terms of the lamellae perpendicular to the long axis of the hippocampus, rather than each subfield independently (Anderson et al., 1971). As described in section 1.2, this functional unit would be a narrow strip of entorhinal cortex projecting to the dentate gyrus, which in turn is linked to another narrow strip of CA3 and CA1. Hippocampal slices used for in vitro experiments are always sections taken perpendicular to the long axis of the

hippocampus, which follows the path of the neuronal projections between subfields. However, since there are also significant connections organised longitudinally, it is unlikely that the lamellae are functionally distinct (Amaral, 1987; Amaral & Witter, 1989).

One must then ask whether the hippocampus is functionally organised in a longitudinal fashion. There are obvious macroscopic changes along the long axis of the hippocampus, from the tail, through the body to the head, with its digitations and the uncus. Focal atrophy has been shown in patients with TLE, sometimes limited to the posterior portion, sometimes to the anterior portion (Cook et al., 1992). This appears to be associated with seizures, since patients with generalized seizures were more likely to have widespread atrophy. It may then be possible to analyze the performance of patients with differing focal atrophy on tests of memory function.

It is most likely though, that the hippocampus functions as a unitary structure, functioning more or less as a whole. This could result in memory deficits which are graded depending on the extent of hippocampal damage. It is unlikely, however, that a model would ever be generated in which both T2 and HFV contributed, because the correlation between them is so high. One must be wary, therefore, of overinterpreting the results of Chapter 5.

- **What is the relationship between genetics, febrile convulsions and the hippocampi of TLE patients?**

In Chapter 7 it was noted that there seems to be a genetic basis for certain types of epilepsy, and that febrile convulsions in particular appear to have an

inherited quality. But how might this occur? And in what way might having a small hippocampus affect the likelihood of later epilepsy?

Evidence gained from in situ hybridisation methods has indicated that there is a range of gene expression induced by seizures, both early and delayed (Noebels, 1992). These effects vary from the expression of immediate early genes such as c-fos and c-jun to the selective increase in certain growth factors (e.g. nerve growth factor (NGF)) and neurotransmitters (e.g. neuropeptide Y) (Noebels, 1992). There is also a selective decrease in kainate receptors (Gall et al., 1990). The overall effect of these changes in gene expression is presumably to increase the excitability of the cells in which they occur - NGF is selectively upregulated in the dentate gyrus, for example (Gall et al., 1991).

It is not too difficult to envisage that a seizure or repeated seizures might give rise to a pattern of abnormal gene expression which could reinforce the cycle of excitability and gene expression. It has been suggested that the mutation of any of these seizure-inducible genes could be regarded as causative of epilepsy, and that these are thus candidate genes (Noebels, 1992).

How, though, might a small hippocampus be more vulnerable to developing epilepsy, since this is clearly not a reflection of a candidate gene of the type presented above? It has been noted by a number of workers (Dichter & Spencer, 1969; Traub & Wong, 1982; McKinney et al., 1997) that sprouting of injured axons from the pyramidal cells of the hippocampus can lead to the formation of a hyperexcitable network. One of the ways in which axons can be damaged is by febrile convulsion, since kainate-induced status epilepticus has been shown to cause apoptosis in the mouse (McNamara, 1992). If there needs to be a certain percentage of the pyramidal cells lost to apoptosis before

recurrent epilepsy is caused, then this will mean that a smaller number of neurons need to die if the hippocampus is small.

Fernandez et al (1998) have stated that the findings from their group of subjects, which also showed smaller hippocampal volumes in subjects with a family history of febrile convulsions, are compatible with impaired migration of hippocampal neurons. It is known that migrational defects can lead to increased susceptibility to seizures (Palmini, Gambardella, Andermann et al., 1995), and there are several cases where these are hereditary (Andermann & Andermann, 1996). In addition, it has been noted that disturbed hippocampal neuronal migration in immature rats lowers the threshold to temperature-induced seizures (Germano, Zhang, Sperber et al., 1996). This then may be a mechanism whereby a genetically inherited hippocampal malformation may lead to increased frequency of febrile convulsions.

- **How can right temporal lobe function best be tested?**

No test of non-verbal memory function was found to be associated with right temporal lobe damage in this thesis, whilst performance on many verbal memory tasks were linked to the extent of left temporal lobe pathology. It is important to identify material-specific memory deficits in TLE patients in order to provide good information to clinicians concerning the likely lateralization of seizures and any possible unfavourable surgical outcome. It is widely agreed that verbal memory is impaired in patients with left temporal lobe foci and that there are a number of neuropsychological tests which can be used to show this (Chelune, 1995). However, there does not appear to be the same consensus for tests of non-verbal memory (Lee et al., 1989). Specifically, there appears to be

no comprehensive account of the type of memory which is affected by right temporal lobe damage (Barr, 1997). Current definitions extend to an impairment in information which is not readily verbalised, but which is not modality-specific (Smith, 1989; Milner, 1990).

The most commonly used tests of non-verbal memory are the visual reproduction subtests from the Wechsler Memory Scale, and the Rey-Osterrieth Complex Figure Test. Despite the wide usage of the WMS, there is no consistency of results. There have been studies which showed impairments in the immediate and delayed recall of designs of right TLE patients when compared to normal controls (Delaney et al., 1980) or unilateral left temporal EEG findings (Jones-Gotman, 1991). However, it is also been noted that right TLE patients can score significantly higher than left TLE patients on the same designs (Ivnik et al., 1987). The revision of the designs and their scoring criteria in 1987 (Wechsler, 1987) does not appear to have improved their reliability as a test of right temporal lobe function (Bornstein et al., 1988; Chelune et al., 1991; Barr et al., 1997).

The Rey figure has been suggested to be a suitable alternative to the Wechsler designs to identify memory impairments associated with right temporal lobe damage (Milner, 1975). Both Taylor (1969b) and Fedio and Mirsky (1969) reported that patients with right TLE were more impaired on the recall of the Rey figure than those with left TLE, but some more recent studies have failed to support this. Many research studies have shown no difference in performance between those with left or right epileptic foci (Mayeux et al., 1980; Powell et al., 1985; Lee et al., 1989). In addition, a multi-centre study with 355

subjects also failed to identify any significant differences between left TLE and right TLE patients on this test (Barr et al., 1997).

It has been noted, however, that the administration and scoring criteria for both the WMS designs and the Rey figure are rather lax (Lezak, 1995; Loring et al., 1990; Helmstaedter et al., 1995). This could well cause variations in the length and nature of the delay period, plus the time of exposure of the original, the orientation of the paper and whether multi-coloured pencils are allowed. The variability in WMS designs and Rey figure recall scores that this gives has been shown in the recent multicentre study by Barr and colleagues (Barr et al., 1997). The same study, however, did not show such variation in scores from the revised WMS. This implies that the criteria for administration and scoring have been improved, without altering the task's capability to discriminate the laterality of seizure onset.

The scoring of the Rey tends to emphasize the aspects of the task subserved by the left hemisphere, in that the presence of a particular figural detail is of greater importance than its spatial location (Loring et al., 1988b; Piguet et al., 1994). Studies which have concentrated on distortion or misplacement errors have tended to find that the right TLE group perform significantly worse than the left TLE group (Loring et al., 1988b; Piguet et al., 1994). It is possible that had the Emergent Complex Figure been scored in a similar fashion, associations would have been seen between measures of right temporal lobe pathology and the recall score in the patient population described in this thesis.

However, the use of figural reproduction measures does not appear to be a particularly good measure of right temporal lobe function, and has called into

question the whole idea of a critical link between the right medial temporal lobe and nonverbal memory (Barr et al., 1997). It has been pointed out that valid clinical measures of nonverbal memory are difficult to find (Barr et al., 1997) and there has been much debate over the years about the validity of a nonverbal, imaginative memory system (Anderson, 1978; Kosslyn, 1980).

Performance on design learning tasks has also been assessed in a number of studies. Despite consistent findings in pre-operative right TLE patients of a memory deficit (Helmstaedter et al., 1991; Giovagnoli et al., 1995), studies of patients following temporal lobectomy have not always supported this (Jones-Gotman, 1986; Lee et al., 1989). In contrast, the use of recognition paradigms for both nonsense figures and faces have been successful when studying post-surgical samples (Kimura, 1963; Milner, 1968b), but results have been mixed when the subjects were studied prior to surgery (Delaney et al., 1980; Hermann et al., 1995a; Naugle et al., 1994). Spatial learning deficits have also not consistently been shown in patients with right temporal lobe resections (Corsi, 1972; Smith & Milner, 1981; Rausch & Ary, 1990; Malec et al., 1991).

It is in contrast to findings of verbal memory impairments, which have proved highly robust, that there is still no single test which can reliably be said to identify nonverbal memory impairments in patients with right temporal lobe damage (Barr, 1997). Whilst it is true to say that part of the reason for the failure of some studies to replicate the results of others is due to variables such as patient selection and surgical procedure, it is also true to say that the theory behind nonverbal memory function has not always been the emphasis of the research (Barr, 1997). Right hemisphere processing is not just spatial and non-verbal, it is also holistic, simultaneous and novelty seeking, and these latter

attributes have received relatively little attention (De Renzi, 1982). In addition, our understanding of the nature of visual processing may help our understanding of the way in which the right hemisphere represents spatial and object information (Barr et al., 1997).

A number of studies have identified two independent visual systems which are anatomically distinct - the ventral stream, and the dorsal stream (Mishkin et al., 1983). The ventral stream, also known as the 'what' system, passes forward from the occipital lobe to the inferior temporal lobe. This system encodes and stores the properties of an object such as colour or shape. The dorsal stream, by contrast, is a 'where' system that extends to the posterior parietal lobe superiorly from the occipital lobe. This system codes for location, size, and other spatial properties. Although the first evidence for these systems was obtained in the primate (Mishkin et al., 1983), there have since been a number of functional imaging studies in human subjects, including one which demonstrated dissociated activation in the temporal and parietal regions during concurrent facial recognition and dot localization (Haxby et al., 1991).

One recent study used the concept of the dorsal and ventral processing streams when choosing nonverbal memory tests with which to study presurgical TLE patients (Barr, 1997). A facial recognition test was used as a test of the 'what' system, whilst a test of spatial design learning similar in construction to the Coughlan Design Learning Test used in this thesis was used to test the 'where' system. Since right TLE patients were only impaired on the facial recognition test when compared to left TLE patients, it was concluded that epileptogenic pathology in the right temporal lobe selectively impairs the functioning of the 'what' system. However, the design learning test used by Barr

suffers from a pronounced ceiling effect which may affect its ability to measure the functioning of the dorsal system. In addition, a weakness of the study was that both of the tasks used to examine the patients were not designed as tests of the ventral or dorsal processing systems. In this respect, it has been suggested that the facial recognition test is a 'good' test of the ventral system, but the spatial design learning test is not a 'good' test of the dorsal system (Barr, 1997). This remains to be evaluated with further studies using tests specifically designed for the purpose.

However, two recent studies may point to a way forward in terms of non-verbal memory testing, following O'Keefe and Nadel's theory of the hippocampus as a cognitive map (O'Keefe & Nadel, 1978). The first used a Nine-box Maze (analogous to the radial arm maze) to investigate spatial memory in both TLE patients and those who had undergone temporal lobectomy (Abrahams et al., 1997). The distinction was made between observer-independent (allocentric) information and that which relates to the body axes (egocentric), as initially suggested by O'Keefe and Nadel (1978). In order to test this in the human subject, a number of objects are hidden in containers on a board, which remains fixed with respect to the surroundings. The subject is then required to use cues from the room to assist in remembering the locations of each object, since he/she does not remain in the same place throughout the test, thus making this a test of allocentric memory. A deficit in this was found in both the TLE and the lobectomy groups with right-sided damage.

The idea of allocentric memory is also used in the second study (Maguire et al., 1996), which investigated topographical memory in temporal lobectomy patients. Topographical memory is the ability to learn to find one's way from

one place to another in the environment, and though it is by no means a unitary process there are definite mnestic components. The manner by which Maguire and colleagues investigated this was to use a real-world setting to assess the acquisition of knowledge about the environment. In particular, they looked at the progression from an egocentric system in which landmarks are encoded in relation to self to an allocentric representation, where even routes that have never personally been crossed are included.

The study used a video containing footage of an urban area, through which two overlapping routes were traversed. Testing consisted of simple tasks, such as deciding which of two landmarks seen on the video was closest to a target landmark, through to more difficult tasks such as drawing a sketch map of the street network including landmarks. Overall, the results showed that both right and left temporal lobectomy patients were impaired when compared to a control group (though on every task the right temporal lobe group was more impaired than the left). This suggests that both verbal and visual strategies are used when learning to way-find successfully.

This has been further evaluated using functional imaging. In this study, using positron emission tomography, right hippocampal and parahippocampal activation were shown in response to the learning of an urban environment. There was also left parahippocampal activation. In a subsequent study (Maguire, 1997; Maguire, Burgess, Donnett et al., 1998), it was stated that left-sided activation was seen in subjects whose recall of the route was not good, and thus found the target in a roundabout way. This may imply that verbal encoding is not as efficient as non-verbal encoding, but both are necessary for topographical learning.

Since these studies clearly indicate that the hippocampus is involved in allocentric spatial mapping, as postulated by O'Keefe & Nadel (1978), the challenge is to develop tests such as those described above for use with children. These tests would hopefully improve our ability to diagnose material-specific memory deficits associated with right temporal lobe epilepsy.

- **Would different results be seen with larger groups?**

Relatively small sample sizes often reduce the probability of rejecting the null hypothesis, and increase the susceptibility to selection bias (Barr et al., 1997). This means that the results presented here are more likely to suggest that there are no significant associations or differences when there really are some. Even so, many highly significant effects have been found, all of which generally fit with what would be predicted.

The regression equations suffer most because of the small sample. With a big population, more sophisticated multivariate statistics could have been used. In particular, the regressions forced a linear relationship on the data which may not be completely true - a linear relationship would be likely for only a small region, because of ceiling and floor effects for both the neuropsychological measures and for the pathology scores. Nonetheless, many of the linear regression models can explain a large amount of the variance in the dependent variables - as much as 56% in the case of the Immediate Learning subtest from the CAVLT-2.

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Appendix I. Patient population

The subjects who participated in each chapter are presented in the table below. An 'x' implies that the child provided data for that chapter. For Chapter 6, an '(a)' mean that that child's data were used in the postoperative neuropsychological analysis.

Subject	Sib/TLE	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
AA	TLE	x	x	x		
CA	TLE	x	x	x	x (a)	x
KBa	TLE	x				
NB	TLE	x	x	x	x (a)	x
JBri	Sib			x		x
KBri	TLE	x	x	x		x
RB	Sib			x		x
SB	Sib					x
GB	Sib			x		x
JBro	TLE	x	x	x	x (a)	
BJB	TLE	x			x (a)	x
EB	TLE	x				
MC	TLE	x			x	
SC	TLE	x				
LC	TLE	x	x	x	x (a)	
RC	TLE				(a)	
IC	TLE	x			x (a)	
KD	TLE	x			x	
ID	TLE	x				
DF	TLE	x			x (a)	
TG	TLE	x				
RG	TLE	x	x	x		
EGi	TLE	x				
MG	TLE	x				
AGo	TLE	x				
AGr	TLE	x			(a)	
EGr	TLE				x	
LG	TLE	x				
JH	TLE				(a)	

Subject	Sib/TLE	Chapter 3	Chapter 4	Chapter 5	Chapter 6	Chapter 7
CH	TLE	x				
AJ	TLE	x	x	x	x	x
SJ	TLE	x				
BJ	TLE	x	x	x		
EJ	TLE	x				
KLam	TLE	x	x	x	x (a)	
KLaw	TLE				(a)	
RL	TLE	x	x	x		
HL	TLE	x	x	x		
JL	TLE	x	x	x		
OM	TLE	x	x	x		
SMa	TLE	x	x	x		
SMK	TLE	x			x	
EM	TLE	x	x	x		
TM	Sib			x		x
SMo	TLE	x	x	x		
GOB	TLE	x				
AP	TLE	x	x	x		
NR	TLE	x				
MR	TLE	x			x (a)	
CS	TLE	x			x (a)	
JS	TLE	x	x	x	x	
AWa	Sib					x
CW	TLE	x				
JW	TLE	x				
EW	Sib			x		x
NW	TLE	x	x	x		
PW	Sib			x		x
SWe	TLE	x	x	x	x	x
TW	TLE	x	x	x	x (a)	x
FWS	TLE	x	x	x		
AWi	TLE	x	x	x		
DW	Sib			x		x
SWr	TLE	x	x	x	x (a)	x
WW	TLE	x	x	x		

The following table details the clinical information for all the epilepsy patients.

Name	Date of Birth	Age at onset	Febrile seizures?	Neurological signs	EEG focus	Histo-pathology
AA	2/3/85	4y 6m	No	Mild dyspraxia	Right temporal	Normal
CA	27/6/80	2y 6m	Yes	None	Left temporal	Left MTS
KBa	19/11/88	1y 6m	Yes	None	None	Left MTS
NB	13/6/75	10m	Yes	None	Left temporal	Left MTS
KBri	28/1/90	2y	Yes	None	Left temporal	Left MTS
JBro	3/3/79	12y 6m	No	Brisk reflexes on right	Left centro-parietal	Left temporal glioma
BJB	11/6/79	2y	Yes	None	Left temporal	Left MTS
EB	23/9/80	1y 3m	Yes	Nystagmus	Bilateral temporal	Left MTS
MC	6/3/87	5y	No	None	Right temporal	Right temporal hamatoma
SC	11/5/77	4y	Yes	None	Left temporal	Left MTS
LC	6/9/76	9m	No	None	Left temporal	Left MTS
RC	25/4/83	9y 4m	No	None	Left temporal	Left temporal DNET
IC	24/7/81	6y	No	None	No focal signs	Left temporal DNET
KD	21/1/81	2y 6m	Yes	None	Right temporal	Right MTS
ID	22/1/82	7m	No	None	Normal	Right temporal DNET
DF	27/6/84	5y	No	None	Left temporal	Left temporal DNET
TG	10/12/80	2y 6m	No	None	Right infero-frontal	Right temporal DNET
RG	29/6/83	11m	Yes with meningitis	Clumsy right finger/thumb	Left temporal	Left MTS
EGi	15/2/80	8m	Yes	None	Left temporo-parietal	Left MTS and left occipital glioma
MG	25/7/87	6y	No	Right inco-ordination	Left temporal	Left temporal lesion
AGo	1/9/83	3m	No	None	Left temporal	Left MTS
AGr	22/6/81	9y	Yes with encephalitis	None	Left temporal	Left MTS and encephalitis

Name	Date of Birth	Age at onset	Febrile seizures?	Neurological signs	EEG focus	Histo-pathology
EGr	2711/88	1y 3m	Yes	None	No focal signs	Left DNET
LG	18/8/88	3m	No	None	Bilateral temporal	Right temporal DNET
JH	6/7/80	12y	No	None	Left temporal	Left temporal DNET
CH	28/4/93	1m	No	Left signs	Right temporal	Right temporal DNET
AJ	19/4/81	6m	Yes	None	Bilateral temporal	Left MTS
SJ	10/4/78	10y	No	None	Left temporal	Left temporal arachnoid cyst
BJ	28/4/80	9y	No	None	Left temporal	Left temporal neocortical abnormalities
EJ	3/3/77	3y	No	None	Bilateral spiking	Right temporal hamatoma
KLam	24/3/83	5y	No	None	Left temporal	eft end-foliu sclerosis
RL	18/11/80	9y	No	None	Right temporal	Right temporal DNET
KLaw	15/5/81	13y	No	None	No focal abnormali ty	Left temporal DNET
HL	11/11/83	1y 1m	Yes	Right dyspraxia	Left centro-temporal	Left MTS
JL	22/6/83	8y 6m	No	None	Left temporal	Normal
OM	16/7/81	10m	Yes	None	Bilateral fronto-temporal	Right MTS
SMK	29/2/84	3y	No	None	Left temporal	Left temporal DNET
SMa	26/2/81	7m	No	None	Left temporal	Left MTS
EM	21/7/87	3m	No	Slow right hand	Left temporal	Left MTS
SMo	18/8/82	1m	Yes	Pes cavus	Left parieto-temporal	Left MTS
GOB	28/5/84	5m	No	None	Left posterior	Left MTS
AP	20/7/84	10m	No	None	Left temporal	Right temporal DNET
NR	27/7/77	4y 5m	No	None	Bilateral fronto-temporal	Bilateral atrophy

Name	Date of Birth	Age at onset	Febrile seizures?	Neurological signs	EEG focus	Histo-pathology
MR	28/9/80	1y	Yes	None	Left temporal	Left temporal DNET
CS	30/4/78	6y	No	None	Left temporal	Left temporal DNET
JS	22/9/79	5y	No	Left posturing	Right centro-temporal	Right temporal DNET
CW	5/8/86	4y	No	None	Right temporal	Right MTS
JW	28/9/83	2y 6m	Yes	None	Left temporal	Left MTS and left occipital heterotopia
NW	29/10/85	1y 1m	Yes	None	Right central, left temporal	Left MTS and right temporal arachnoid cyst
SWe	16/9/78	10m	Yes	None	Bilateral spikes	Right MTS
TW	27/7/78	10m	Yes	None	Left temporal	Left MTS
FWS	24/10/75	2y	Yes	None	Right temporal	Right MTS
AWi	31/1/86	3y	No	Mild right posturing	Left central	Left MTS
SWr	29/8/83	10m	Yes	Right facial weakness	Left temporal	Left MTS
WW	28/7/85	5m	No	None	Right temporal	Right temporal dyplasia

Appendix II. Complete analyses for Chapters 5 and 6

II.i Analysis of pre-operative neuropsychological measures with hippocampal pathology

All of the data that is presented below is shown as means plus or minus standard deviations. The exception is the data which has been covaried for IQ, in which case only the adjusted means are displayed.

II.i.i Scores from the Wechsler Intelligence Scale

	SC	TLE N (HF)	TLE L (HF)	TLE R (HF)	TLE Bi (HF)	Group effect
VIQ	98.3 ± 10.6 n = 7	89.8 ± 13.7 n = 6	84.0 ± 15.3 n = 8	107.7 ± 30.4 n = 3	93.6 ± 11.4 n = 9	F(4,28)=1.76 p = 0.164
PIQ	94.6 ± 14.1 n = 7	84.3 ± 10.5 n = 6	88.9 ± 18.9 n = 8	109.7 ± 13.3 n = 3	108.1 ± 19.7 n = 9	F(4,28)=2.82 p = 0.044
FSIQ	96.0 ± 10.4 n = 7	85.7 ± 13.3 n = 6	84.4 ± 17.6 n = 8	110.0 ± 22.5 n = 3	99.4 ± 14.2 n = 9	F(4,28)=2.45 p = 0.069
Information	8.9 ± 2.9 n = 7	7.8 ± 4.5 n = 6	5.9 ± 2.4 n = 8	11.0 ± 4.4 n = 3	8.3 ± 3.3 n = 9	F(4,28)=1.54 p = 0.219
Similarities	11.1 ± 3.0 n = 7	8.3 ± 3.2 n = 6	8.8 ± 3.6 n = 8	12.3 ± 6.1 n = 3	9.1 ± 2.3 n = 9	F(4,28)=1.27 p = 0.307
Arithmetic	10.1 ± 2.6 n = 7	8.3 ± 2.7 n = 6	9.3 ± 4.3 n = 8	11.0 ± 4.6 n = 3	10.2 ± 2.6 n = 9	F(4,28)=0.50 p = 0.733
Vocabulary	9.6 ± 2.7 n = 7	8.0 ± 2.0 n = 6	6.0 ± 2.1 n = 8	10.3 ± 4.9 n = 3	7.4 ± 1.1 n = 8	F(4,27)=3.04 p = 0.035
Comprehen-sion	9.1 ± 2.4 n = 7	9.0 ± 2.7 n = 6	7.4 ± 3.4 n = 8	13.0 ± 7.1 n = 2	8.2 ± 2.3 n = 9	F(4,27)=1.52 p = 0.225
Digit Span	9.3 ± 2.6 n = 7	6.7 ± 2.4 n = 6	8.7 ± 2.7 n = 7	11.3 ± 1.2 n = 3	10.2 ± 2.4 n = 9	F(4,27)=2.66 p = 0.055
Picture Completion	8.7 ± 3.0 n = 7	8.2 ± 3.8 n = 6	7.6 ± 3.9 n = 8	10.7 ± 1.5 n = 3	10.3 ± 3.3 n = 9	F(4,28)=0.96 p = 0.446
Coding	11.3 ± 3.7 n = 7	7.2 ± 2.9 n = 6	8.9 ± 2.2 n = 7	10.7 ± 2.1 n = 3	10.3 ± 3.4 n = 8	F(4,26)=1.77 p = 0.166
Picture rrangement	10.7 ± 2.6 n = 7	7.7 ± 4.0 n = 6	6.3 ± 2.4 n = 7	8.5 ± 2.1 n = 2	9.6 ± 3.4 n = 9	F(4,26)=2.11 p = 0.108
Block Design	8.0 ± 3.2 n = 7	7.5 ± 3.3 n = 6	8.9 ± 4.4 n = 8	14.0 ± 2.0 n = 3	12.5 ± 3.7 n = 8	F(4,27)=3.29 p = 0.026
Object Assembly	7.9 ± 2.4 n = 7	8.7 ± 1.4 n = 6	10.1 ± 4.7 n = 8	11.7 ± 1.5 n = 3	11.4 ± 3.0 n = 8	F(4,27)=1.65 p = 0.192
Symbol Search	11.0 ± 2.2 n = 7	8.0 ± 1.7 n = 6	9.7 ± 2.3 n = 6	8.5 ± 3.5 n = 2	11.1 ± 3.9 n = 8	F(4,24)=1.49 p = 0.238

II.i.ii Scores from the Wechsler Memory Scale

	SC	TLE N (HF)	TLE L (HF)	TLE R (HF)	TLE Bi (HF)	Group effect
MQ	94.5 (adj.) n = 7	91.6 (adj.) n = 6	87.7 (adj.) n = 8	97.6 (adj.) n = 3	95.1 (adj.) n = 9	F(4,27)=0.51 p = 0.732
LM-I	7.1 (adj.) n = 7	7.6 (adj) n = 6	7.0 (adj.) n = 8	5.1 (adj.) n = 3	7.7 (adj.) n = 9	F(4,27)=0.53 p = 0.717
LM-D	5.5 (adj) n = 7	6.4 (adj.) n = 6	4.3 (adj.) n = 8	2.4 (adj) n = 3	4.7 (adj.) n = 9	F(4,27)=0.87 p = 0.496
LM-%	75.8 ± 22.6 n = 7	78.1 ± 21.7 n = 6	48.9 ± 27.0 n = 8	50.6 ± 25.3 n = 3	54.7 ± 31.3 n = 9	F(4,28)=1.83 p = 0.151
D'	9.4 (adj.) n = 7	9.3 (adj.) n = 6	8.6 (adj.) n = 8	12.6 (adj.) n = 3	10.6 (adj.) n = 9	F(4,27)=1.28 p = 0.301
D	8.4 ± 3.7 n = 7	6.8 ± 4.4 n = 6	5.5 ± 3.7 n = 8	12.7 ± 1.0 n = 3	7.8 ± 3.2 n = 9	F(4,28)=2.38 p = 0.076
D%	84.1 ± 21.7 n = 7	72.7 ± 24.3 n = 6	65.7 ± 35.7 n = 8	93.8 ± 5.8 n = 3	71.7 ± 21.4 n = 9	F(4,28)=0.93 p = 0.459
VPA Score	16.5 (adj.) n = 7	15.2 (adj.) n = 6	12.9 (adj.) n = 8	16.6 (adj.) n = 3	14.4 (adj.) n = 9	F(4,27)=1.07 p = 0.392
VPA Easy	17.0 ± 0.8 n = 7	17.2 ± 1.6 n = 6	14.1 ± 3.4 n = 8	17.7 ± 0.6 n = 3	16.0 ± 3.2 n = 9	F(4,28)=1.99 p = 0.124
VPA Hard	8.0 (adj.) n = 7	6.5 (adj.) n = 6	5.5 (adj.) n = 8	8.0 (adj.) n = 3	6.4 (adj.) n = 9	F(4,27)=0.95 p = 0.450
VPA Del	9.6 ± 0.8 n = 7	9.2 ± 1.0 n = 6	6.0 ± 3.0 n = 8	9.7 ± 0.6 n = 3	8.3 ± 1.6 n = 9	F(4,28)=4.79 p = 0.005
C'	16.4 (adj.) n = 7	16.6 (adj.) n = 6	14.9 (adj.) n = 8	14.6 (adj.) n = 3	16.8 (adj.) n = 9	F(4,27)=0.51 p = 0.731
C	14.9 (adj.) n = 7	15.7 (adj.) n = 6	10.8 (adj.) n = 8	11.6 (adj.) n = 3	13.0 (adj.) n = 9	F(4,27)=1.66 p = 0.189
C%	91.3 ± 10.9 n = 7	93.8 ± 11.8 n = 6	66.2 ± 16.8 n = 8	80.7 ± 8.3 n = 3	75.8 ± 14.1 n = 9	F(4,28)=5.09 p = 0.003

II.i.iii Scores from other memory tests

	SC	TLE N (HF)	TLE L (HF)	TLE R (HF)	TLE Bi (HF)	Group effect
CAVLT-Immediate Learning	109.7 (adj.) n = 7	117.3 (adj.) n = 6	94.0 (adj.) n = 6	107.6 (adj.) n = 2	102.3 (adj.) n = 8	F(4,23)=1.80 p = 0.164
CAVLT - Level of Learning	113.1 (adj.) n = 7	112.1 (adj) n = 6	102.9 (adj.) n = 6	102.1 (adj.) n = 2	102.0 (adj.) n = 8	F(4,23)=0.87 p = 0.494
CAVLT - Imm. Recall	102.9 ± 8.9 n = 7	103.5 ± 20.1 n = 6	102.5 ± 22.7 n = 6	97.0 ± 28.3 n = 2	97.5 ± 21.5 n = 8	F(4,24)=0.14 p = 0.968
CAVLT - Del. Recall	105.7 ± 9.5 n = 7	105.2 ± 22.4 n = 6	94.5 ± 25.4 n = 6	101.0 ± 14.1 n = 2	96.8 ± 24.3 n = 8	F(4,24)=0.37 p = 0.829
CAVLT - Intrusions	4.1 ± 2.7 n = 7	2.2 ± 2.6 n = 6	3.8 ± 4.4 n = 6	0.5 ± 0.7 n = 2	3.3 ± 4.7 n = 8	F(4,24)=0.53 p = 0.712
CAVLT - Recognition	30.6 ± 1.0 n = 7	30.2 ± 1.6 n = 6	27.0 ± 6.0 n = 5	30.5 ± 0.7 n = 2	29.8 ± 2.5 n = 5	F(4,20)=1.16 p = 0.357
Emergent Figure - Copy	29.9 ± 3.2 n = 7	30.8 ± 3.3 n = 5	29.6 ± 4.3 n = 7	33.0 ± 0.9 n = 3	31.9 ± 1.6 n = 9	F(4,26)=1.09 p = 0.381
Emergent Figure - % Recall	46.7 ± 16.7 n = 7	37.3 ± 18.9 n = 5	34.4 ± 8.7 n = 7	46.0 ± 8.1 n = 3	31.0 ± 11.0 n = 9	F(4,26)=1.74 p = 0.172
Dot Location - Copy	134.3 ± 47.6 n = 7	101.0 ± 47.9 n = 5	99.2 ± 29.9 n = 6	77.5 ± 10.6 n = 2	114.7 ± 33.4 n = 8	F(4,23)=1.22 p = 0.328
Dot Location - Imm. Recall	157.9 ± 48.7 n = 7	164.0 ± 11.4 n = 5	140.8 ± 43.4 n = 6	150.0 ± 42.4 n = 2	158.1 ± 25.9 n = 8	F(4,23)=0.34 p = 0.851
Dot Location - Del. Recall	174.9 ± 43.7 n = 7	183.5 ± 26.3 n = 5	166.7 ± 33.7 n = 6	177.5 ± 17.7 n = 2	181.6 ± 31.0 n = 8	F(4,23)=0.23 p = 0.922
WRMT - Words	46.7 ± 3.7 n = 7	45.0 ± 4.7 n = 4	43.7 ± 6.6 n = 7	49.3 ± 1.2 n = 3	45.4 ± 4.5 n = 9	F(4,25)=0.85 p = 0.509
WRMT - Faces	36.4 ± 3.3 n = 7	38.0 ± 8.7 n = 4	31.9 ± 5.9 n = 7	38.3 ± 5.9 n = 3	37.6 ± 6.4 n = 9	F(4,25)=1.22 p = 0.326
DLT - DLT	34.3 ± 9.0 n = 7	28.4 ± 9.9 n = 5	29.8 ± 13.6 n = 6	43.0 ± 0.0 n = 2	35.7 ± 5.1 n = 7	F(4,22)=1.20 p = 0.339
CDLT - DLI	10.4 ± 11.2 n = 7	15.0 ± 11.4 n = 5	8.0 ± 7.3 n = 6	1.5 ± 0.7 n = 2	6.7 ± 5.5 n = 7	F(4,22)=1.12 p = 0.372
CDLT - Learning	9.7 ± 4.3 n = 7	10.4 ± 1.7 n = 5	7.7 ± 3.9 n = 6	15.0 ± 1.4 n = 2	10.3 ± 2.3 n = 7	F(4,22)=2.01 p = 0.129
CDLT - Imm. Recall	7.9 ± 1.7 n = 7	5.2 ± 2.5 n = 5	7.0 ± 3.5 n = 6	9.0 ± 0.0 n = 2	7.6 ± 1.4 n = 7	F(4,22)=1.49 p = 0.240
CDLT - Del. Recall	7.6 ± 2.2 n = 7	4.8 ± 1.5 n = 4	6.8 ± 3.4 n = 6	7.5 ± 2.1 n = 2	7.9 ± 1.1 n = 7	F(4,21)=1.42 p = 0.262
Forwards Digit Span	5.7 ± 1.0 n = 7	5.0 ± 1.1 n = 6	5.1 ± 1.3 n = 8	7.0 ± 0.0 n = 3	6.4 ± 0.9 n = 9	F(4,28)=3.81 p = 0.013
Backwards Digit Span	4.0 ± 1.3 n = 7	3.8 ± 0.8 n = 6	3.8 ± 1.9 n = 8	5.7 ± 1.5 n = 3	4.3 ± 1.5 n = 9	F(4,28)=1.06 p = 0.394
Forwards Block Span	5.1 ± 1.6 n = 7	6.3 ± 1.3 n = 4	5.4 ± 1.5 n = 5	7.0 ± 1.4 n = 2	5.8 ± 1.0 n = 8	F(4,21)=0.99 p = 0.434
Backwards Block Span	5.9 ± 0.9 n = 7	4.3 ± 1.5 n = 4	4.8 ± 1.0 n = 4	7.5 ± 0.7 n = 2	5.6 ± 1.2 n = 8	F(4,20)=3.54 p = 0.024

II.i.iv Scores from non-memory tests

	SC	TLE N (HF)	TLE L (HF)	TLE R (HF)	TLE Bi (HF)	Group effect
WORD - Reading	-	97.5 (Adj.) n = 4	96.0 (Adj.) n = 5	87.3 (Adj.) n = 2	101.5 (Adj.) n = 6	F(3,12)=0.61 p = 0.622
WORD - Spelling	-	90.8 (Adj.) n = 4	95.7 (Adj.) n = 5	96.4 (Adj.) n = 2	90.4 (Adj.) n = 6	F(3,12)=0.47 p = 0.708
WORD - Comprehen-sion	-	94.5 (Adj.) n = 4	99.8 (Adj.) n = 5	89.6 (Adj.) n = 2	102.1 (Adj.) n = 6	F(3,12)=0.41 p = 0.751
Word Fluency - S	-	21.4 (Adj.) n = 3	20.5 (Adj.) n = 6	22.1 (Adj.) n = 3	24.0 (Adj.) n = 7	F(3,14)=0.10 p = 0.959
Word Fluency - C	-	7.5 (Adj.) n = 3	5.2 (Adj.) n = 6	8.9 (Adj.) n = 3	9.7 (Adj.) n = 7	F(3,14)=0.82 p = 0.503
Line Orientation	22.8 ± 5.0 n = 4	19.7 ± 7.5 n = 3	22.5 ± 9.2 n = 2	26.0 ± 2.8 n = 2	25.8 ± 3.5 n = 5	F(4,11)=0.73 p = 0.590
Face Matching	40.1 ± 3.1 n = 7	40.5 ± 1.9 n = 4	41.6 ± 3.1 n = 5	46.5 ± 0.7 n = 2	37.8 ± 3.9 n = 6	F(4,19)=3.17 p = 0.037
Token Total	-	53.0 ± 5.7 n = 2	53.0 ± 8.8 n = 4	60.3 ± 2.1 n = 3	55.7 ± 7.1 n = 7	F(3,12)=0.78 p = 0.540
Token - Total 2&4	-	17.5 ± 2.1 n = 2	16.8 ± 3.8 n = 4	19.7 ± 0.6 n = 3	18.6 ± 2.2 n = 7	F(3,12)=0.87 p = 0.485
TROG - Blocks passed	-	17.5 ± 3.0 n = 4	15.8 ± 4.5 n = 8	19.7 ± 0.6 n = 3	17.3 ± 2.4 n = 7	F(3,18)=1.04 p = 0.397
TROG - otal correct	-	76.3 ± 4.5 n = 4	71.9 ± 8.9 n = 8	79.7 ± 0.6 n = 3	74.7 ± 4.3 n = 7	F(3,18)=1.23 p = 0.329
Object naming - otal correct	28.7 (Adj.) n = 7	27.9 (Adj.) n = 4	27.3 (Adj.) n = 8	27.6 (Adj.) n = 3	28.7 (Adj.) n = 8	F(4,24)=0.31 p = 0.869
Object naming - Reaction time	1.7 ± 0.3 n = 7	1.9 ± 0.3 n = 4	2.2 ± 0.8 n = 8	2.0 ± 0.4 n = 3	1.6 ± 0.3 n = 8	F(4,25)=1.59 p = 0.209
Thurstone closure - otal correct	12.7 ± 1.4 n = 7	14.0 ± 5.5 n = 5	12.8 ± 5.0 n = 6	15.5 ± 0.7 n = 2	10.9 ± 4.5 n = 7	F(4,22)=0.70 p = 0.601
Thurstone closure - Total time	320.9 ± 30.6 n = 7	284.4 ± 40.1 n = 4	343.0 ± 42.6 n = 4	426.2 ± 60.8 n = 2	282.2 ± 30.3 n = 7	F(4,18)=1.46 p = 0.235
WCST-time	467.3 ± 94.0 n = 4	555.0 ± 223.5 n = 2	840.3 ± 467.9 n = 6	387.5 ± 16.3 n = 2	825.9 ± 416.5 n = 7	F(4,16)=1.23 p=0.492
WCST-categories	4.8 ± 1.9 n = 4	5.2 ± 1.2 n = 2	2.7 ± 2.7 n = 6	6.0 ± 0.0 n = 3	3.6 ± 2.7 n = 7	F(4.17)=1.30 p=0.265
WCST - Total errors	47.0 ± 29.6 n = 3	28.5 ± 40.3 n = 2	59.8 ± 38.2 n = 6	7.3 ± 5.9 n = 3	43.7 ± 33.4 n = 7	F(4,16)=1.37 p=0.202

II.ii Analysis of pre-operative neuropsychological measures with diffuse temporal lobe pathology

All of the data which is presented below is shown as means plus or minus standard deviations. The exception is the data which has been covaried for VIQ, in which case only the adjusted means are displayed.

II.ii.i Scores from the Wechsler Intelligence Scale

	SC	TLE N (MRS)	TLE L (MRS)	TLE R (MRS)	TLE Bi (MRS)	Group effect
VIQ	98.3 ± 10.6 n = 7	93.5 ± 18.4 n = 4	87.0 ± 11.8 n = 9	95.0 ± 25.1 n = 7	92.3 ± 10.7 n = 6	F(4,28)=0.54 p=0.709
PIQ	94.6 ± 14.1 n = 7	100.3 ± 24.2 n = 4	91.3 ± 20.8 n = 9	90.7 ± 13.7 n = 7	110.2 ± 18.0 n = 6	F(4,28)=1.28 p=0.300
FSIQ	96.0 ± 10.4 n = 7	95.8 ± 21.4 n = 4	87.1 ± 16.0 n = 9	92.3 ± 22.0 n = 7	100.2 ± 13.0 n = 6	F(4,28)=0.63 p=0.643
Information	8.9 ± 2.9 n = 7	7.8 ± 3.9 n = 4	7.1 ± 2.9 n = 9	8.6 ± 5.3 n = 7	7.8 ± 2.8 n = 6	F(4,28)=0.28 p=0.887
Similarities	11.1 ± 3.0 n = 7	9.5 ± 4 n = 4	7.7 ± 2.8 n = 9	10.1 ± 4.6 n = 7	10.2 ± 2.0 n = 6	F(4,28)=1.21 p=0.331
Arithmetic	10.1 ± 2.6 n = 7	12.3 ± 0.6 n = 3	9.0 ± 4.0 n = 9	9.1 ± 3.4 n = 7	9.7 ± 2.9 n = 6	F(4,27)=0.70 p=0.599
Vocabulary	9.6 ± 2.7 n = 7	8.0 ± 1.0 n = 3	6.4 ± 1.6 n = 9	8.1 ± 4.3 n = 7	7.8 ± 1.2 n = 6	F(4,27)=1.45 p=0.244
Comprehen-sion	9.1 ± 2.4 n = 7	7.8 ± 4.1 n = 4	8.1 ± 1.5 n = 9	9.7 ± 4.8 n = 7	8.2 ± 3.3 n = 5	F(4,27)=0.39 p=0.811
Digit Span	9.3 ± 2.6 n = 7	10.7 ± 3.2 n = 3	8.1 ± 2.4 n = 9	9.1 ±3.4 n = 7	9.7 ± 2.5 n = 6	F(4,27)=0.60 p=0.664
Picture Completion	8.7 ± 3.0 n = 7	10.8 ± 5.7 n = 4	7.1 ± 2.6 n = 9	8.3 ± 2.1 n = 7	11.7 ± 2.9 n = 6	F(4,28)=2.31 p=0.082
Coding	11.3 ± 3.7 n = 7	9.7 ± 2.5 n = 3	7.8 ± 2.9 n = 8	9.0 ± 1.8 n = 7	10.8 ± 3.9 n = 6	F(4,26)=1.53 p=0.223
Picture rrangement	10.7 ± 2.6 n = 7	10.3 ± 1.5 n = 3	7.0 ± 2.7 n = 9	7.3 ± 4.1 n = 7	9.6 ± 3.5 n = 5	F(4,26)=2.05 p=0.117
Block Design	8.0 ± 3.2 n = 7	8.0 ± 3.0 n = 3	9.9 ± 4.4 n = 9	9.9 ± 4.4 n = 7	12.7 ± 4.3 n = 6	F(4,27)=1.24 p=0.317
Object Assembly	7.9 ± 2.4 n = 7	9.7 ± 1.2 n = 3	10.7 ± 4.9 n = 9	9.3 ± 1.8 n = 7	11.5 ± 2.4 n = 6	F(4,27)=1.26 p=0.309
Symbol Search	11.0 ± 2.2 n = 7	10.7 ± 3.8 n = 3	8.9 ± 1.7 n = 7	8.7 ±2.9 n = 7	11.4 ± 4.2 n = 5	F(4,24)=1.20 p=0.337

II.ii.ii Scores from the Wechsler Memory Scale

	SC	TLE N (MRS)	TLE L (MRS)	TLE R (MRS)	TLE Bi (MRS)	Group effect
MQ	93.4 (adj.) n = 7	89.1 (adj.) n = 4	87.7 (adj.) n = 9	93.5 (adj.) n = 7	96.9 (adj.) n = 6	F(4,27)=0.64 p = 0.641
LM-I	7.0 (adj.) n = 7	6.9 (adj.) n = 4	6.7 (adj.) n = 9	6.8 (adj.) n = 7	7.9 (adj.) n = 6	F(4,27)=0.20 p = 0.935
LM-D	5.4 (adj) n = 7	4.2 (adj.) n = 4	4.1 (adj.) n = 9	4.6 (adj.) n = 7	5.4 (adj.) n = 6	F(4,27)=0.23 p = 0.921
LM-%	75.8 ± 22.6 n = 7	62.5 ± 15.9 n = 4	51.1 ± 26.2 n = 9	58.2 ± 31.2 n = 7	64.4 ± 37.5 n = 6	F(4,28)=0.80 p = 0.535
D'	9.1 (adj.) n = 7	8.1 (adj.) n = 4	9.4 (adj.) n = 9	10.0 (adj.) n = 7	11.6 (adj.) n = 6	F(4,27)=1.22 p = 0.326
D	8.4 ± 3.7 n = 7	5.5 ± 5.1 n = 4	6.8 ± 3.4 n = 9	7.5 ± 3.6 n = 7	9.6 ± 4.5 n = 6	F(4,28)=0.85 p = 0.504
D%	84.1 ± 21.7 n = 7	54.2 ± 39.9 n = 4	76.3 ± 24.2 n = 9	73.5 ± 22.3 n = 7	78.6 ± 25.2 n = 6	F(4,28)=0.92 p = 0.466
VPA Score	16.2 (adj.) n = 7	14.0 (adj.) n = 4	13.2 (adj.) n = 9	15.5 (adj.) n = 7	14.7 (adj.) n = 6	F(4,27)=0.83 p = 0.520
VPA Easy	17.0 ± 0.8 n = 7	16.5 ± 2.4 n = 4	14.4 ± 3.7 n = 9	17.7 ± 0.5 n = 7	15.5 ± 3.1 n = 6	F(4,28)=2.00 p = 0.123
VPA Hard	7.8 (adj.) n = 7	5.5 (adj.) n = 4	5.9 (adj.) n = 9	6.7 (adj.) n = 7	6.9 (adj.) n = 6	F(4,27)=0.77 p = 0.552
VPA Del	9.6 ± 0.8 n = 7	6.8 ± 2.6 n = 4	7.3 ± 3.1 n = 9	9.0 ± 1.2 n = 7	8.5 ± 1.6 n = 6	F(4,28)=1.86 p = 0.145
C'	16.2 (adj.) n = 7	15.4 (adj.) n = 4	14.8 (adj.) n = 9	16.1 (adj.) n = 7	16.8 (adj.) n = 6	F(4,27)=0.35 p = 0.844
C	14.8 (adj.) n = 7	11.0 (adj.) n = 4	11.8 (adj.) n = 9	13.5 (adj.) n = 7	13.7 (adj.) n = 6	F(4,27)=0.71 p = 0.589
C%	91.3 ± 10.9 n = 7	71.6 ± 11.1 n = 4	74.2 ± 18.2 n = 9	82.4 ± 15.7 n = 7	81.0 ± 20.4 n = 6	F(4,28)=1.46 p = 0.241

II.ii.iii Scores from other memory tests

	SC	TLE N (MRS)	TLE L (MRS)	TLE R (MRS)	TLE Bi (MRS)	Group effect
CAVLT-Immediate Learning	108.0 (adj.) n = 7	100.0 (adj.) n = 4	99.5 (adj.) n = 6	109.7 (adj.) n = 7	100.0 (adj.) n = 5	F(4,23)=0.47 p = 0.755
CAVLT – Level of Learning	112.0 (adj.) n = 7	100.3 (adj) n = 4	101.0 (adj.) n = 6	112.4 (adj.) n = 7	97.1 (adj.) n = 5	F(4,23)=1.49 p = 0.239
CAVLT - Imm. Recall	102.9 ± 8.9 n = 7	94.5 ± 33.8 n = 4	99.5 ± 20.5 n = 6	107.0 ± 19.4 n = 7	97.2 ± 11.1 n = 5	F(4,24)=0.36 p = 0.832
CAVLT - Del. Recall	105.7 ± 9.5 n = 7	92.0 ± 28.9 n = 4	91.0 ± 24.9 n = 6	112.7 ± 14.1 n = 7	94.2 ± 20.4 n = 5	F(4,24)=1.51 p = 0.231
CAVLT – Intrusions	4.1 ± 2.7 n = 7	2.3 ± 2.5 n = 4	2.7 ± 4.6 n = 6	1.6 ± 2.1 n = 7	5.4 ± 5.4 n = 5	F(4,24)=1.09 p = 0.399
CAVLT – Recognition	30.6 ± 1.0 n = 7	27.0 ± 6.9 n = 4	29.0 ± 3.0 n = 3	30.9 ± 1.2 n = 7	28.8 ± 1.9 n = 4	F(4,20)=1.31 p = 0.299
Emergent Figure – Copy	29.9 ± 3.2 n = 7	32.8 ± 1.5 n = 3	30.0 ± 3.8 n = 9	31.4 ± 3.0 n = 7	31.8 ± 1.7 n = 5	F(4,26)=0.83 p = 0.521
Emergent Figure - % Recall	46.7 ± 16.7 n = 7	35.9 ± 12.0 n = 3	34.7 ± 11.4 n = 9	36.1 ± 13.8 n = 7	34.4 ± 16.1 n = 5	F(4,26)=0.91 p = 0.474
Dot Location – Copy	134.3 ± 47.6 n = 7	85.0 ± 7.1 n = 2	113.4 ± 32.6 n = 8	93.6 ± 41.2 n = 7	110.0 ± 36.7 n = 4	F(4,23)=1.19 p = 0.341
Dot Location - Imm. Recall	157.9 ± 48.7 n = 7	150.0 ± 7.1 n = 2	153.8 ± 46.0 n = 8	155.0 ± 20.0 n = 7	153.8 ± 16.5 n = 4	F(4,23)=0.02 p = 0.999
Dot Location - Del. Recall	174.9 ± 43.7 n = 7	165.0 ± 49.5 n = 2	184.4 ± 26.7 n = 8	168.2 ± 29.6 n = 7	185.8 ± 27.6 n = 4	F(4,23)=0.35 p = 0.843
WRMT – Words	46.7 ± 3.7 n = 7	48.5 ± 0.7 n = 2	44.0 ± 6.1 n = 9	46.5 ± 4.3 n = 6	45.2 ± 4.8 n = 6	F(4,25)=0.58 p = 0.683
WRMT – Faces	36.4 ± 3.3 n = 7	39.0 ± 5.7 n = 2	34.2 ± 8.4 n = 9	35.5 ± 6.3 n = 6	38.2 ± 5.2 n = 6	F(4,25)=0.49 p = 0.747
DLT - DLT	34.3 ± 9.0 n = 7	25.5 ± 15.5 n = 4	30.7 ± 4.8 n = 6	36.0 ± 10.1 n = 7	39.7 ± 1.2 n = 3	F(4,22)=1.33 p = 0.291
CDLT - DLI	10.4 ± 11.2 n = 7	9.5 ± 7.0 n = 4	11.8 ± 6.5 n = 6	8.3 ± 11.1 n = 7	2.0 ± 2.0 n = 3	F(4,22)=0.64 p = 0.642
CDLT – Learning	9.7 ± 4.3 n = 7	7.5 ± 4.4 n = 4	9.0 ± 2.2 n = 6	11.3 ± 3.2 n = 7	12.3 ± 1.5 n = 3	F(4,22)=1.27 p = 0.311
CDLT - Imm. Recall	7.9 ± 1.7 n = 7	5.5 ± 4.0 n = 4	6.8 ± 1.5 n = 6	7.1 ± 2.7 n = 7	8.7 ± 0.6 n = 3	F(4,22)=0.98 p = 0.437
CDLT - Del. Recall	7.6 ± 2.2 n = 7	5.0 ± 3.9 n = 4	7.4 ± 0.6 n = 5	6.6 ± 2.1 n = 7	9.0 ± 0.0 n = 3	F(4,21)=1.69 p = 0.191
Forwards Digit Span	5.7 ± 1.0 n = 7	5.8 ± 1.9 n = 4	5.6 ± 1.0 n = 9	5.6 ± 1.4 n = 7	6.3 ± 1.0 n = 6	F(4,28)=0.44 p = 0.778
Backwards Digit Span	4.0 ± 1.3 n = 7	4.0 ± 2.9 n = 4	3.8 ± 1.2 n = 9	5.1 ± 1.4 n = 7	3.8 ± 0.8 n = 6	F(4,28)=1.03 p = 0.410
Forwards Block Span	5.1 ± 1.6 n = 7	5.3 ± 1.2 n = 3	5.5 ± 1.6 n = 6	6.2 ± 1.2 n = 6	6.5 ± 0.6 n = 4	F(4,21)=0.90 p = 0.480
Backwards Block Span	5.9 ± 0.9 n = 7	4.0 ± 1.4 n = 2	5.2 ± 1.0 n = 6	5.5 ± 1.8 n = 6	6.0 ± 1.6 n = 4	F(4,20)=1.00 p = 0.430

II.ii.iv Scores from non-memory tests

	SC	TLE N (MRS)	TLE L (MRS)	TLE R (MRS)	TLE Bi (MRS)	Group effect
WORD – Reading	-	88.6 (Adj.) n = 2	96.5 (Adj.) n = 5	93.7 (Adj.) n = 7	102.9 (Adj.) n = 3	F(3,12)=0.65 p = 0.598
WORD – Spelling	-	84.8 (Adj.) n = 2	99.4 (Adj.) n = 5	95.4 (Adj.) n = 7	101.3 (Adj.) n = 3	F(3,12)=0.60 p = 0.629
WORD – Comprehen-sion	-	80.2 (Adj.) n = 2	90.6 (Adj.) n = 5	93.3 (Adj.) n = 7	94.4 (Adj.) n = 3	F(3,12)=1.64 p = 0.232
Word Fluency - S	-	21.0 (Adj.) n = 2	22.5 (Adj.) n = 8	18.1 (Adj.) n = 3	28.3 (Adj.) n = 6	F(3,14)=0.67 p = 0.583
Word Fluency - C	-	3.6 (Adj.) n = 2	7.9 (Adj.) n = 8	7.3 (Adj.) n = 3	11.9 (Adj.) n = 6	F(3,14)=1.81 p = 0.192
Line Orientation	22.8 ± 5.0 n = 4	24.5 ± 6.4 n = 2	22.0 ± 8.5 n = 2	23.8 ± 6.8 n = 5	24.3 ± 4.0 n = 3	F(4,11)=0.08 p = 0.988
Face Matching	40.1 ± 3.1 n = 7	41.5 ± 3.5 n = 2	38.6 ± 4.6 n = 5	42.3 ± 3.1 n = 7	39.0 ± 4.6 n = 3	F(4,19)=1.02 p = 0.423
Token Total	-	60.5 ± 2.1 n = 2	52.0 ± 9.1 n = 6	56.0 ± 6.2 n = 3	57.6 ± 3.1 n = 5	F(3,12)=1.10 p = 0.387
Token - Total 2&4	-	20.0 ± 0.0 n = 2	16.7 ± 3.3 n = 6	18.3 ± 2.1 n = 3	19.2 ± 1.1 n = 5	F(3,12)=1.49 p = 0.267
TROG – Blocks passed	-	14.0 ± 5.3 n = 3	16.9 ± 3.6 n = 8	18.2 ± 2.7 n = 5	18.0 ± 2.1 n = 6	F(3,18)=1.22 p = 0.332
TROG - otal correct	-	68.0 ± 12.2 n = 3	74.1 ± 6.0 n = 8	77.6 ± 3.3 n = 5	76.2 ± 4.1 n = 6	F(3,18)=1.70 p = 0.202
Object naming - otal correct	28.6 (Adj.) n = 7	26.9 (Adj.) n = 3	27.4 (Adj.) n = 8	28.0 (Adj.) n = 6	29.2 (Adj.) n = 6	F(4,24)=0.59 p = 0.677
Object naming – Reaction time	1.7 ± 0.3 n = 7	1.9 ± 0.8 n = 3	2.0 ± 0.8 n = 8	1.8 ± 0.4 n = 6	1.9 ± 0.2 n = 6	F(4,25)=0.38 p = 0.824
Thurstone closure - otal correct	Not performed since one or more of the patients groups had a group size of one or below					
Thurstone closure - Total time	Not performed since one or more of the patients groups had a group size of one or below					
WCST – Time	Not performed since one or more of the patients groups had a group size of one or below					
WCST- Categories	4.8 ± 1.9 n = 4	3.5 ± 3.5 n = 2	2.9 ± 2.7 n = 6	6.0 ± 0.0 n = 2	4.6 ± 2.3 n = 6	F(4.17)=0.92 p = 0.476
WCST - Total errors	47.0 ± 29.6 n = 3	36.0 ± 38.2 n = 2	54.0 ± 39.5 n = 8	8.5 ± 7.8 n = 2	37.2 ± 33.3 n = 6	F(4,16)=0.75 p = 0.574

II.iii Additional graphs and analyses from Chapter 5

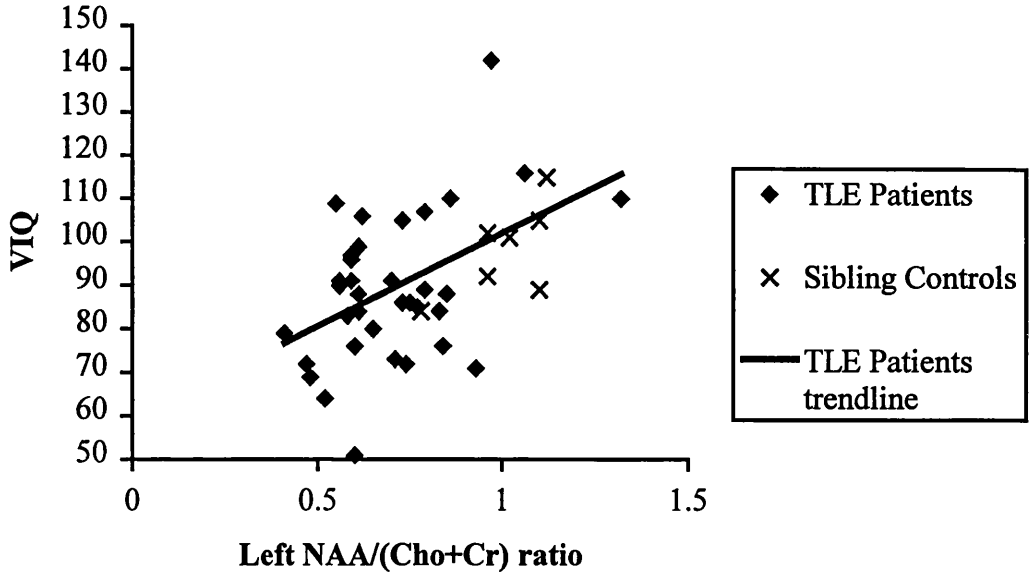

Figure II.i Graph of VIQ against left NAA/(Cho+Cr) ratio in enlarged data set (n = 43).

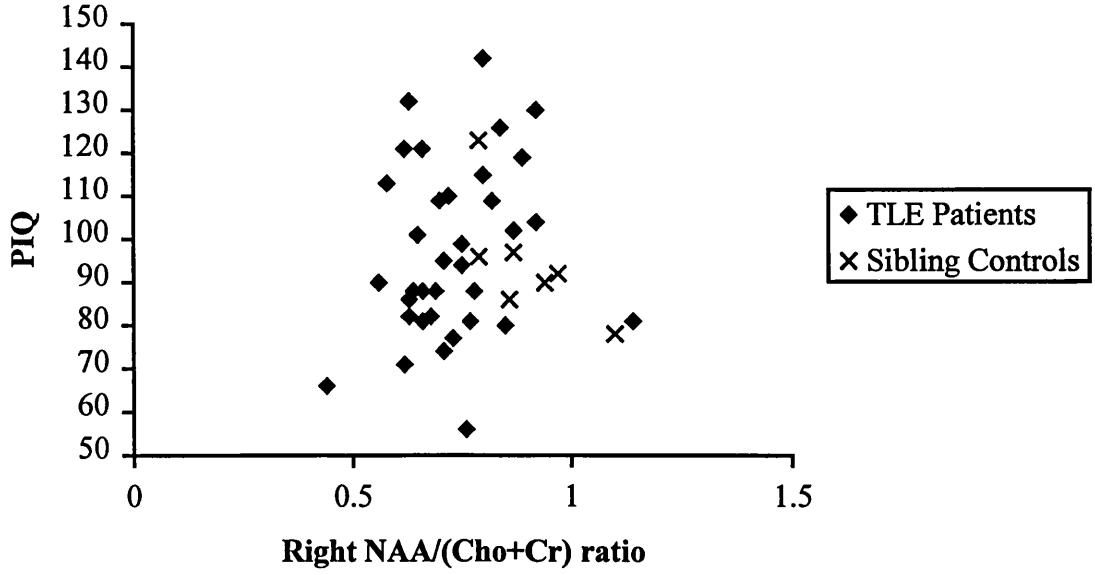

Figure II.ii Graph of PIQ against right NAA/(Cho+Cr) ratio in enlarged data set (n = 43).

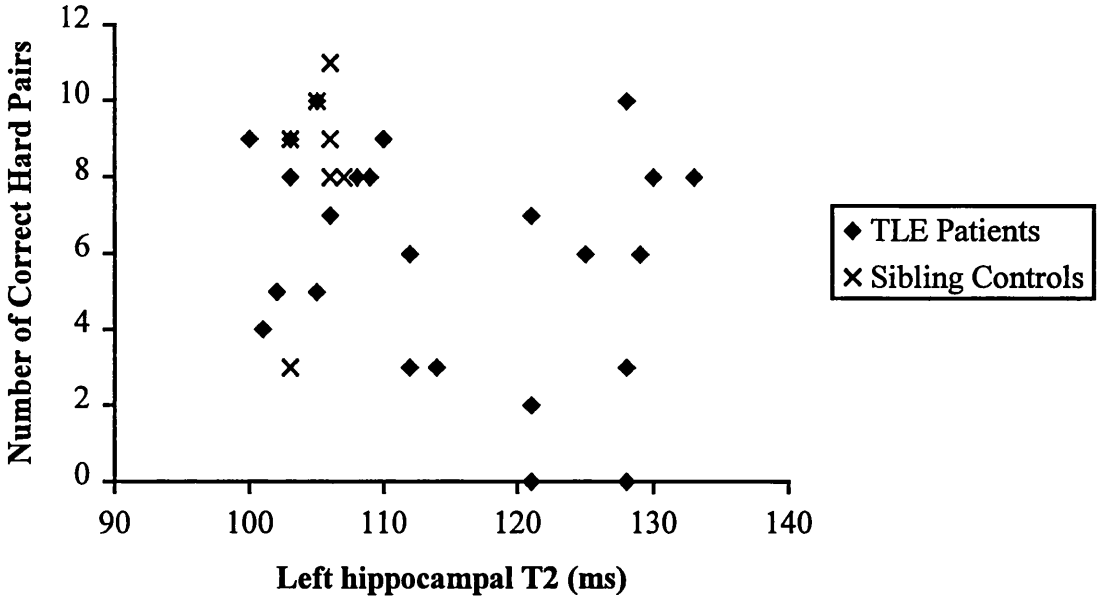

Figure II.iii Graph of left T2 against VPA Hard.

	VPA Hard
r^2	0.555
r^2 adj.	0.517
ANOVA	DF (2, 23)
	$F = 14.360$
	$p < 0.001$
VIQ	b = 0.084
	β = 0.482
	p = 0.003
Age	b = 0.441
	β = 0.468
	p = 0.003
Constant	-7.357

Table II.i Regression analysis for VPA Hard.

II.iv Analysis of pre- and post-operative neuropsychological measures not presented in Chapter 6

All the data presented below is shown as means plus or minus standard deviations. Only the data for which meaningful comparisons could be made has been presented. Therefore, some tests from the protocol are not displayed because the group sizes were too low.

II.iv.i Subtests of the Wechsler Intelligence Scale

	Lobectomy		Lesionectomy		Group effect	Surgical effect	Interaction
	Pre-op	Post-op	Pre-op	Post-op			
Information	6.5 ± 3.9	6.4 ± 3.7	6.9 ± 1.6	5.9 ± 2.2	F(1,14)=0.002 p = 0.966	F(1,14)=1.65 p = 0.219	F(1,14)=1.00 p = 0.334
Similarities	8.3 ± 4.3	7.9 ± 3.9	7.8 ± 2.1	7.5 ± 3.5	F(1,14)=0.07 p = 0.793	F(1,14)=0.21 p = 0.653	F(1,14)=0.01 p = 0.928
Vocabulary	7.0 ± 2.6	6.0 ± 2.6	6.5 ± 2.3	6.1 ± 2.6	F(1,13)=0.02 p = 0.880	F(1,13)=1.80 p = 0.198	F(1,13)=0.38 p = 0.548
Comprehen-sion	7.6 ± 2.7	6.9 ± 2.6	7.4 ± 2.1	6.9 ± 2.4	F(1,14)=0.01 p = 0.910	F(1,14)=1.19 p = 0.294	F(1,14)=0.05 p = 0.830
Digit Span	8.8 ± 3.9	8.9 ± 3.3	8.3 ± 3.0	9.0 ± 2.4	F(1,14)=0.02 p = 0.900	F(1,14)=0.45 p = 0.511	F(1,14)=0.23 p = 0.638
Picture Completion	10.3 ± 4.1	9.4 ± 2.4	9.3 ± 2.2	10.4 ± 2.4	F(1,14)<0.001 p = 1.000	F(1,14)=0.04 p = 0.854	F(1,14)=2.25 p = 0.156
Picture rrangement	9.0 ± 3.4	8.4 ± 4.0	8.4 ± 0.8	8.0 ± 1.9	F(1,12)=0.13 p = 0.725	F(1,12)=0.82 p = 0.384	F(1,12)=0.02 p = 0.899
Block Design	10.4 ± 3.8	12.4 ± 6.2	9.9 ± 2.3	9.9 ± 1.2	F(1,13)=0.79 p = 0.390	F(1,13)=1.41 p = 0.257	F(1,13)=1.41 p = 0.257
Object Assembly	12.3 ± 1.8	12.4 ± 3.1	10.0 ± 4.0	10.1 ± 3.0	F(1,13)=2.66 p = 0.127	F(1,13)=0.03 p = 0.865	F(1,13)<0.001 p = 0.991
Symbol Search	12.8 ± 4.6	11.8 ± 1.5	8.0 ± 2.1	10.0 ± 2.2	F(1,7)=5.52 p = 0.051	F(1,7)=0.16 p = 0.699	F(1,7)=1.46 p = 0.266

II.iv.ii Scores from the Wechsler Memory Scale

All of the following analyses are covaried for both pre- and post-operative VIQ, and also for age at pre- and post-operative assessments.

	Lobectomy		Lesionectomy		Group effect	Surgical effect	Interaction
	Pre-op	Post-op	Pre-op	Post-op			
MQ	93.4 ± 16.5	89.3 ± 11.9	88.3 ± 10.6	95.5 ± 11.6	F(1,10)=0.86 p = 0.377	F(1,10)=0.02 p = 0.895	F(1,10)=5.62 p = 0.039
LM-I	7.9 ± 2.9	4.9 ± 2.6	7.1 ± 2.4	7.2 ± 2.9	F(1,10)=1.48 p = 0.252	F(1,10)=0.48 p = 0.505	F(1,10)=3.23 p = 0.103
LM-D	4.3 ± 3.6	2.7 ± 2.6	5.1 ± 2.9	5.6 ± 2.6	F(1,10)=4.61 p = 0.057	F(1,10)=1.68 p = 0.224	F(1,10)=3.82 p = 0.079
LM-%	47.3 ± 35.2	47.7 ± 33.1	67.9 ± 26.0	78.2 ± 11.5	(1,10)=11.38 p = 0.007	F(1,10)=3.00 p = 0.114	F(1,10)=4.92 p = 0.051
D'	10.5 ± 2.3	10.9 ± 1.8	8.6 ± 3.3	11.0 ± 1.8	F(1,10)=0.04 p = 0.839	F(1,10)=1.39 p = 0.266	F(1,10)=0.50 p = 0.495
D	7.5 ± 3.8	7.8 ± 3.9	6.3 ± 3.0	8.3 ± 3.3	F(1,10)=0.06 p = 0.805	F(1,10)=1.14 p = 0.311	F(1,10)=0.002 p = 0.962
D%	67.6 ± 27.5	70.1 ± 33.4	75.5 ± 22.8	73.4 ± 24.5	F(1,10)=0.74 p = 0.410	F(1,10)=0.16 p = 0.695	F(1,10)=0.44 p = 0.524
VPA Score	14.1 ± 4.5	12.8 ± 4.2	14.0 ± 3.2	14.8 ± 4.1	F(1,10)=0.62 p = 0.450	F(1,10)=0.37 p = 0.557	F(1,10)=0.55 p = 0.474
VPA Easy	15.8 ± 3.2	16.6 ± 1.3	16.8 ± 0.9	16.0 ± 2.1	F(1,10)=0.56 p = 0.470	F(1,10)=0.18 p = 0.682	F(1,10)=1.01 p = 0.338
VPA Hard	6.3 ± 3.0	5.8 ± 4.0	5.6 ± 2.8	6.8 ± 3.3	F(1,10)=0.46 p = 0.511	F(1,10)=0.44 p = 0.524	F(1,10)=1.14 p = 0.311
VPA Del	7.4 ± 2.2	6.5 ± 2.7	8.0 ± 2.1	7.9 ± 2.4	F(1,10)=1.36 p = 0.271	F(1,10)=0.004 p = 0.951	F(1,10)=0.88 p = 0.371
C'	16.6 ± 4.6	12.9 ± 3.5	16.4 ± 3.1	16.2 ± 3.4	F(1,10)=2.72 p = 0.130	F(1,10)=0.07 p = 0.801	F(1,10)=2.28 p = 0.162
C	11.7 ± 5.4	9.2 ± 4.7	13.1 ± 3.4	13.5 ± 4.0	F(1,10)=4.36 p = 0.063	F(1,10)=1.26 p = 0.288	F(1,10)=4.69 p = 0.056
C%	67.0 ± 19.1	69.2 ± 26.7	79.8 ± 15.4	82.7 ± 12.5	F(1,10)=4.12 p = 0.070	F(1,10)=2.60 p = 0.138	F(1,10)=3.61 p = 0.087

II.iv.iii Scores from other memory tests

The scores below were all covaried for both pre- and post-operative VIQ, and all but the CAVLT were also covaried for age at pre- and post-operative testing. This was partly because the CAVLT is age-standardised and so should not show any age-dependence, but also because the inclusion of age as a covariable reduced the degrees of freedom to (1, 2) for all subtest scores.

	Lobectomy		Lesionectomy		Group effect	Surgical effect	Interaction
	Pre-op	Post-op	Pre-op	Post-op			
CAVLT-Immediate Learning	109.8 ± 20.1	93.8 ± 13.9	117.7 ± 23.0	113.7 ± 23.5	F(1,4)=0.97 p = 0.380	F(1,4)=0.02 p = 0.910	F(1,4)=0.48 p = 0.525
CAVLT-Level of Learning	104.0 ± 20.0	86.6 ± 23.9	117.0 ± 7.0	119.0 ± 3.0	F(1,4)=12.87 p = 0.023	F(1,4)<0.001 p = 0.997	F(1,4)=0.99 p = 0.376
CAVLT-Immediate Recall	108.0 ± 19.2	87.8 ± 21.9	104.7 ± 11.2	113.0 ± 12.1	F(1,4)=3.49 p = 0.135	F(1,4)=0.22 p = 0.667	F(1,4)=6.31 p = 0.066
CAVLT-Delayed Recall	96.4 ± 25.2	84.8 ± 24.1	112.7 ± 15.0	121.0 ± 11.4	F(1,4)=3.41 p = 0.139	F(1,4)=0.56 p = 0.496	F(1,4)=1.93 p = 0.237
CAVLT-Intrusions	5.2 ± 6.4	6.0 ± 6.4	0.0 ± 0.0	0.3 ± 0.6	F(1,4)=3.61 p = 0.130	F(1,4)=1.55 p = 0.281	F(1,4)=0.26 p = 0.637
Emergent Figure - Copy	31.7 ± 2.4	30.2 ± 2.3	32.4 ± 1.6	32.0 ± 2.3	F(1,7)=0.88 p = 0.379	F(1,7)=0.44 p = 0.527	F(1,7)=0.01 p = 0.946
Emergent Figure - Recall	36.7 ± 11.8	40.3 ± 10.4	42.5 ± 12.8	86.7 ± 79.9	F(1,12)=0.13 p = 0.725	F(1,12)=0.82 p = 0.384	F(1,12)=0.02 p = 0.899
Dot Location - Copy	80.8 ± 45.4	115.0 ± 36.5	81.3 ± 21.4	57.5 ± 22.5	F(1,4)=6.46 p=0.064	F(1,4)=0.71 p=0.447	F(1,4)=10.50 p=0.032
Dot Location - Immediate Recall	10.4 ± 3.8	12.4 ± 6.2	9.9 ± 2.3	9.9 ± 1.2	F(1,13)=0.79 p = 0.390	F(1,13)=1.41 p = 0.257	F(1,13)=1.41 p = 0.257
Dot Location - Delayed Recall	12.3 ± 1.8	12.4 ± 3.1	10.0 ± 4.0	10.1 ± 3.0	F(1,13)=2.66 p = 0.127	F(1,13)=0.03 p = 0.865	F(1,13)<0.001 p = 0.991
WRMT - Words	43.9 ± 9.2	46.4 ± 4.8	47.2 ± 3.3	47.0 ± 3.5	F(1,7)=2.10 p=0.191	F(1,7)=0.001 p=0.972	F(1,7)=0.03 p=0.869
WRMT - Faces	38.5 ± 6.6	40.5 ± 7.6	38.4 ± 8.1	40.2 ± 4.1	F(1,7)=0.26 p=0.628	F(1,7)=0.53 p=0.491	F(1,7)=0.18 p=0.687
Forwards Digit Span	5.8 ± 1.5	6.3 ± 2.0	5.5 ± 1.3	6.3 ± 1.4	F(1,10)=0.85 p=0.378	F(1,10)=4.21 p=0.067	F(1,10)=3.04 p=0.112
Backwards Digit Span	12.8 ± 4.6	11.8 ± 1.5	8.0 ± 2.1	10.0 ± 2.2	F(1,7)=5.52 p = 0.051	F(1,7)=0.16 p = 0.699	F(1,7)=1.46 p = 0.266

II.iv.iv Scores from non-memory tests

	Lobectomy		Lesionectomy		Group effect	Surgical effect	Interaction
	Pre-op	Post-op	Pre-op	Post-op			
Token Total	57.0 ± 5.8	59.2 ± 2.9	55.0 ± 2.7	58.0 ± 3.2	F(1,4)=3.75 p = 0.125	F(1,4)=0.37 p = 0.578	F(1,4)=2.01 p = 0.229
Token - Total 2&4	18.3 ± 2.7	19.3 ± 0.8	18.8 ± 1.3	19.0 ± 1.2	F(1,4)=13.24 p = 0.022	F(1,4)=0.40 p = 0.564	F(1,4)=4.78 p = 0.094
TROG - Blocks passed	17.0 ± 1.7	18.5 ± 2.3	16.8 ± 1.8	18.7 ± 0.8	F(1,6)=0.001 p = 0.946	F(1,6)=1.00 p = 0.356	F(1,6)=0.27 p = 0.623
TROG - otal correct	73 ± 3.8	77.5 ± 3.8	76.2 ± 2.8	78.0 ± 1.7	F(1,6)=1.13 p = 0.328	F(1,6)=1.33 p = 0.293	F(1,6)=2.44 p = 0.169
Object naming - otal correct	28.7 ± 3.6	29.4 ± 3.6	26.6 ± 3.5	27.6 ± 3.1	F(1,8)=0.05 p = 0.838	F(1,8)=0.001 p = 0.971	F(1,8)=0.01 p = 0.911
Object naming - Reaction time	2.3 ± 1.1	2.4 ± 1.8	2.0 ± 0.3	2.0 ± 2.9	F(1,8)=1.00 p = 0.347	F(1,8)=0.42 p = 0.537	F(1,8)=0.30 p = 0.596
Thurstone closure - otal correct	13.2 ± 4.8	15.8 ± 2.6	14.0 ± 4.8	15.6 ± 3.3	F(1,5)=1.53 p = 0.271	F(1,5)=2.43 p = 0.180	F(1,5)=2.77 p = 0.157
WCST - Total categories	4.2 ± 2.5	5.2 ± 1.9	5.2 ± 1.8	4.2 ± 2.6	F(1,5)=0.03 p = 0.867	F(1,5)=0.06 p = 0.813	F(1,5)=3.31 p = 0.129
WCST - Total errors	34.2 ± 32.1	18.8 ± 26.7	26.2 ± 26.7	28.2 ± 26.1	F(1,5)=0.08 p = 0.795	F(1,5)<0.001 p = 0.998	F(1,5)=5.60 p = 0.064

Appendix III. Normative data for the Coughlan Design Learning Test and the Performance of Children With Temporal Lobe Epilepsy

III.i Abstract

126 normal schoolchildren between the ages of six and sixteen were assessed using a test of design learning (the Coughlan Design Learning Test from the Adult Memory and Information Processing Battery), in order to obtain normative data for comparison with performance by children with temporal lobe epilepsy. It was found that there was a significant improvement in performance with increasing age for all subtests, such that adult levels (judging by the adult norms published in the original manual) were achieved by the age of twelve at the latest. Testing using the Vocabulary subtest of the WISC-III showed that the subjects were indeed a representative sample from the normal population and in addition, there were no significant differences between age groups in terms of this measure.

III.ii Introduction

It is known that children improve in memory ability as they get older. How they do this, however, is still uncertain. It was initially suggested that there were two systems showing a different timetable of development - an early developing sensorimotor "habit" system, and a "cognitive memory" system which was dependent on the medial temporal lobe and developed later (Bachevalier & Mishkin, 1984). However, more recent work seems to suggest that the two-system theory cannot explain the data. This is due to evidence that the development of memory involves the graded increase of existing systems rather than the maturation of independent systems. For example, the differences between infant and adult memory processes appear to be quantitative (in terms of memory span and retrieval time) rather than qualitative (Rovee-Collier, 1993). In addition, novel looking (preferential looking at a novel stimulus) develops early in infants and in infant monkeys, whilst those with medial temporal lobe lesions do not do this (Bachevalier et al., 1993). This implies that this region makes a significant contribution to visual recognition, and further studies indicate that it is the hippocampus which plays the important role (Johnson, 1997).

Since the children who have been tested range in age from under six to over seventeen, it is helpful to know that a memory task is testing the same memory system for each age group. The research outlined above suggests that when a task is thought to be testing hippocampal function, it is doing so throughout the age range which is of interest. It is still unknown, however, how performance alters as a function of age.

Children have been shown to improve as they get older on a number of tests of visual memory (Akshoomoff & Stiles, 1995; Aliotti & Rajabiun, 1991), and there are also indications that spatial and verbal memory may develop differently (Isaacs & Vargha-Khadem, 1989).

The current study attempts to show this age-related improvement using the Coughlan design learning test (CDLT). The CDLT is a non-verbal memory test which is part of the Adult Learning and Information Processing Battery (AMIPB; Coughlan & Hollows, 1985) and in construction is similar to the CAVLT-2. Since verbal list learning has been shown to be reliant on the left hippocampus (Grasby et al., 1993), it was considered that a similar test in the visual domain might be a test of right hippocampal function. In addition, maze learning (which this test resembles to a certain extent) has been shown to be sensitive to right hippocampal damage (Corkin, 1965; Milner, 1965), and it was hoped that this test might be useful in assessing children with TLE for the purposes of lateralising their seizure focus.

Limited normative data were obtained by the authors of the CDLT and published in the AMIPB manual, but the lowest age group tested was 18-25 year-olds. Further data from normal children were therefore required in order to be able to evaluate the results from patients.

III.iii Methods

III.iii.i Subjects

Schools were selected at random from a directory of schools in the London area and asked if they would participate in this study. Those that responded were visited and children selected at random by the teachers were tested on a number of neuropsychological tests in addition to the CDLT. In total 126 children between the ages of 6 and 16 (median age 9 years 10 months) were assessed. These children were all in normal school classes and had no known neurological abnormality.

III.iii.ii Procedure

The test session took place in school in a quiet room away from other children. Other tests in the assessment included the WMS, the vocabulary subtest from the WISC-III^{UK}, and the Doors & People test (Baddeley et al., 1994). All tasks were administered within one testing session, with short breaks taken between tests when necessary. The vocabulary subtest was used to give an indication of the general intelligence of the child since it was impractical to try to administer even a shortened version of the WISC-III^{UK}.

The CDLT is administered in the following manner. A response sheet consisting of sixteen dots in a four by four pattern is given to the child who is told that he or she is going to be shown a design which connects up some of the dots for ten seconds (Figure III.i) which they should look at and try to remember. When the design is taken away they are to draw as much as they are able.

This is done five times, or until the child draws the correct design twice running. An interference design is then presented once, followed by recall. The child is then asked to draw the initial design, and after a 20 minutes delay filled with unrelated tasks, draw it again. A number of scores are then obtained.

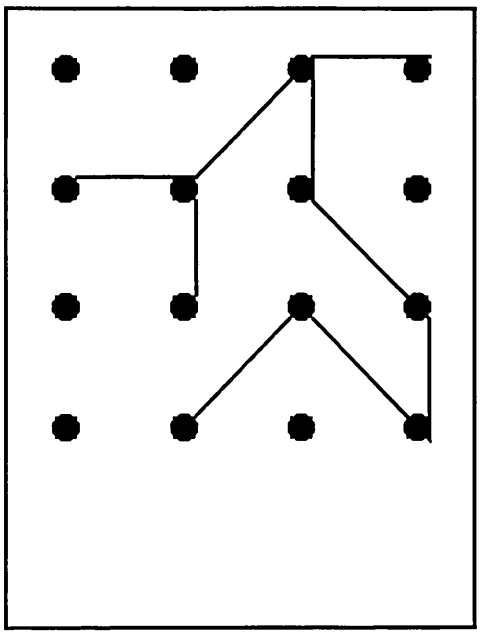

Figure III.i Design 1 of the Coughlan Design Learning Test.

The Design Learning Total (DLT) is the sum of the correct lines on the learning trials of the first design (ie trials one to five). If the child achieves the discontinue criteria then he/she is given credit for the remaining learning trials. The maximum score for the DLT is 45.

The Design Learning Intrusions (DLI) is the sum of the incorrect lines on the learning trials of the first design (ie. trials one to five). Obviously the maximum DLT score could be obtained by merely joining all the dots on the response sheet, so the DLI score is an important check on performance.

The Interference Trial score (Trial B) is the sum of the correct lines on the single trial of the interference design. The maximum score is therefore 9.

The Immediate Recall score (A6) is the sum of the correct lines on the immediate recall trial, with a maximum of 9.

In order to more closely approximate the CAVLT-2 with this test, two new scores were added, which did not have previously obtained adult norms. These were a measure of Immediate Learning, or short-term memory, and a test of Delayed Recall. Immediate Learning is the sum of correct lines on trial one of the learning trials of the first design and the correct lines on Trial B. Delayed recall is the same as trial A6, but obtained after a 20 minute delay.

III.iii.iii Statistics

All subjects were grouped according to their age, with those between 12 and 16 grouped together in order to make the group sizes more equal. Single-factor analyses of variance performed to identify significant differences in performance between the age groups. Post-hoc analyses were used to identify groups which were significantly different from others, with the type of analysis being dependent on whether the groups exhibited homogeneity of variance or not (using the Levene test). Those which did were analysed with Tukey's honestly-significant-difference (h-s-d) test, whilst those which did not were analysed with Dunnet's T3. Subjects for whom English was not their first language were excluded from the analysis of the Vocabulary subtest. In addition, not all children received the Delayed Recall trial of the CDLT, owing to time constraints during the testing session.

III.iv Results

III.iv.i Results from the WISC-III^{UK} Vocabulary Subtest

Performance on the vocabulary subtest of the WISC-III^{UK} demonstrated that the children tested were from a standard cross-section of the population (Table III.i). Single-factor analysis of variance was performed on the data, and revealed that there was no significant difference between the age groups ($p = 0.118$). It is therefore considered valid to use the results from the CDLT as a normative dataset for comparison with TLE patients.

AGE	Mean scaled Vocabulary score	SD	N
6	9.94	2.7	16
7	11.10	4.2	19
8	9.85	1.7	13
9	8.56	2.9	18
10	9.40	2.8	20
11	9.87	3.5	15
12 - 16	11.05	2.3	22

Table III.i Means and standard deviations for Scaled scores on the Vocabulary subtest for all age groups.

III.iv.ii Results from the CDLT

All of the scores on the CDLT showed a definite improvement in performance up to the age of ten. Table III.ii shows the mean scores and standard deviations for each age group for the DLT. Single-factor analysis of variance revealed a significant difference between the age groups ($p < 0.001$).

Post-hoc Tukey's h-s-d analysis revealed that the performance of the 10, 11 and 12-16 year-olds was significantly better that that of the six, seven, eight and nine year-olds on this measure ($p < 0.05$).

AGE	Mean DLT score	SD	N
6	19.69	7.6	16
7	23.00	6.7	19
8	25.85	7.0	13
9	26.67	8.6	18
10	34.10	8.5	20
11	33.00	5.1	16
12 - 16	36.48	5.6	25
18 - 25	36.80	6.7	-

Table III.ii Means and standard deviations for the DLT score from the CDLT, including the AMIPB mean for the 18 - 25 age group.

These results, and examination of the graph of DLT against age (Figure III.ii) shows that a plateau has been more or less reached by age 10. The mean DLT score for the 18-25 age group in the AMIPB manual was 36.8 ± 6.7.

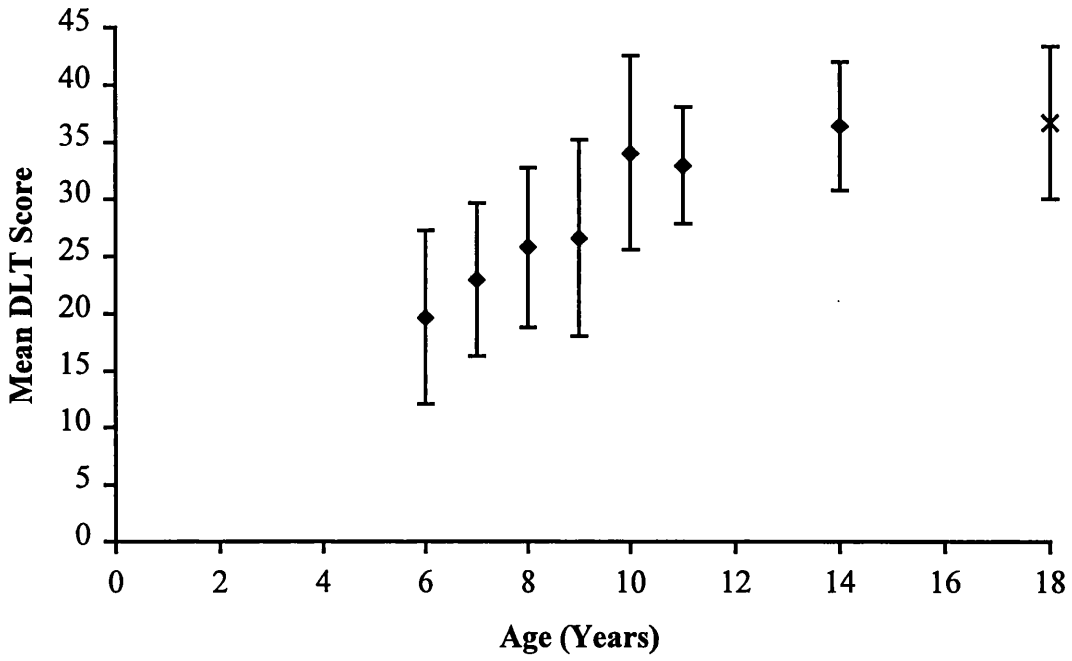

Figure III.ii Graph showing mean DLT score against age group (mean ± standard deviation), including the AMIPB mean for the 18 - 25 age group (X).

The same can be shown on examining the DLI score against age. Table III.iii shows the mean scores and standard deviations for each age group for the DLI. Single-factor analysis of variance revealed a significant difference between the age groups ($p < 0.001$). Post-hoc Tukey's h-s-d analysis again showed that six to nine year-olds did significantly worse than 10 to 16 year-olds ($p < 0.05$).

AGE	Mean DLI score	SD	n
6	20.06	8.3	16
7	17.58	8.1	19
8	14.23	9.7	13
9	16.28	7.8	18
10	8.75	10.4	20
11	7.94	4.7	16
12 - 16	6.04	4.3	25
18 - 25	6.00	5.5	-

Table III.iii Means and standard deviations for the DLI score from the CDLT, including the AMIPB mean for the 18 - 25 age group.

Examination of the graph of DLI against age (Figure III.iii) shows that, as for the DLT score, a plateau has been more or less reached by age 10, certainly by age 12. The mean DLI score for the 18-25 age group in the AMIPB manual was 6 ± 5.5, implying firstly that this group achieves similar levels of performance as the original normative sample, and secondly that adult levels are indeed achieved by age 12.

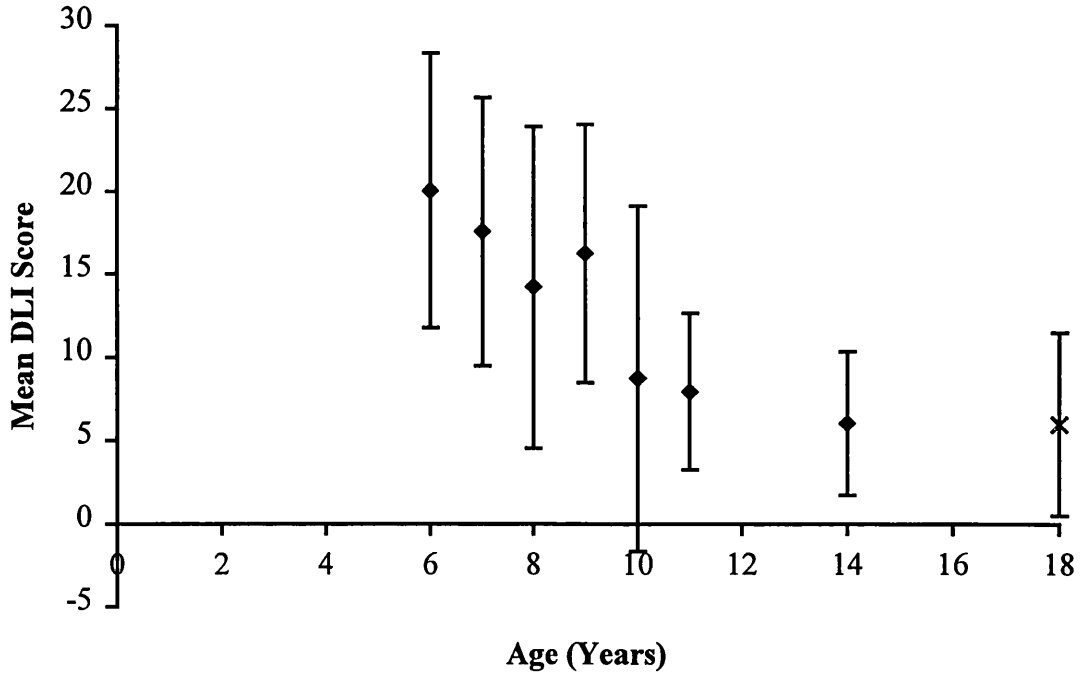

Figure III.iii Graph showing mean DLI score against age group (mean ± standard deviation), including the AMIPB mean for the 18 - 25 age group (X).

The score on the interference trial B also showed improvement with age. Table III.iv shows the mean scores and standard deviations for each age group for trial B. Single-factor analysis of variance revealed a significant difference between the age groups ($p < 0.001$). This time, post-hoc Tukey's h-s-d analysis showed that six year-olds scored significantly lower than those aged 10, 11 and 12-16 ($p < 0.05$).

AGE	Mean B score	SD	n
6	3.31	2.0	16
7	4.74	1.3	19
8	4.15	1.1	13
9	4.78	1.5	18
10	5.30	1.8	20
11	5.25	1.7	16
12 - 16	5.84	1.8	25
18 - 25	5.80	1.9	-

Table III.iv Means and standard deviations for the B score from the CDLT, including the AMIPB mean for the 18 - 25 age group.

These results and examination of the graph of trial B against age (Figure III.iv) shows that there appears to be a gradual increase in performance across the ages tested. The mean score for trial B for the 18-25 age group in the AMIPB manual was 5.8 ± 1.9.

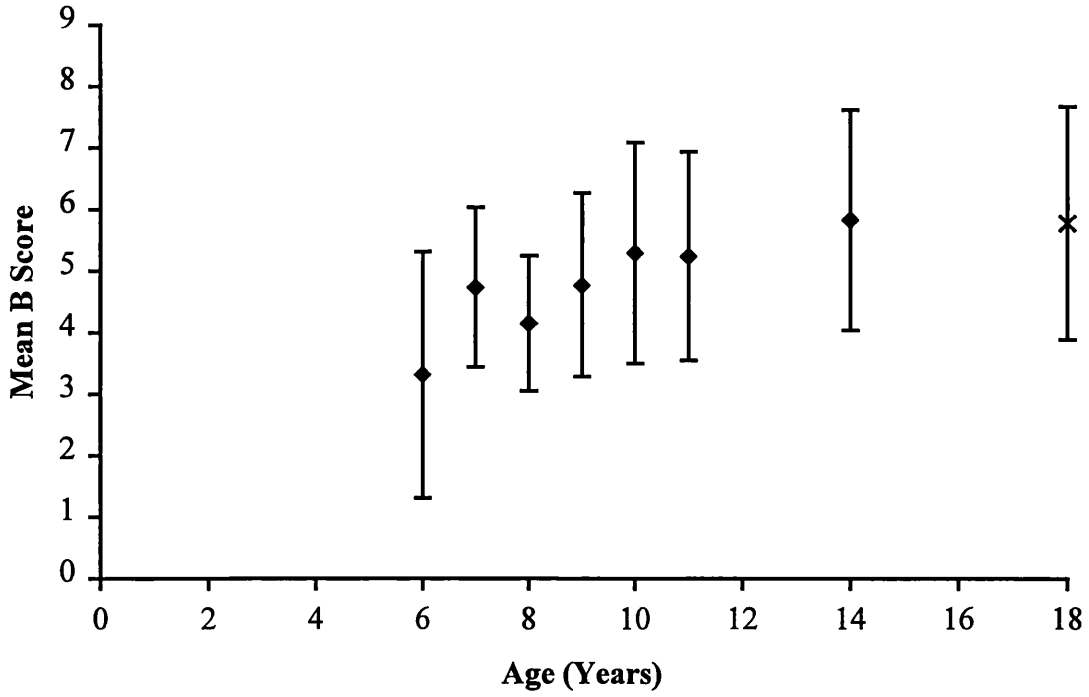

Figure III.iv Graph showing mean B score against age group (mean ± standard deviation), including the AMIPB mean for the 18 - 25 age group (X).

The Immediate Learning score also showed improvement with age. Table III.v shows the mean scores and standard deviations for each age group for the Immediate Learning score. Single-factor analysis of variance revealed a significant difference between the age groups ($p < 0.001$). Post-hoc Tukey's h-s-d analysis showed that six year-olds scored significantly lower than 12-16 year-old age group ($p < 0.05$).

AGE	Mean Imm Lrn score	SD	n
6	5.88	2.3	16
7	7.47	2.3	19
8	7.23	1.9	13
9	8.33	3.2	18
10	9.80	3.6	20
11	8.75	2.7	16
12 - 16	10.44	2.5	25

Table III.v Means and standard deviations for the Immediate Learning score from the CDLT.

The graph (Figure III.v) also indicates a gradual increase in score with increasing age. However, this score was not part of the original AMIPB and so there are no adult norms.

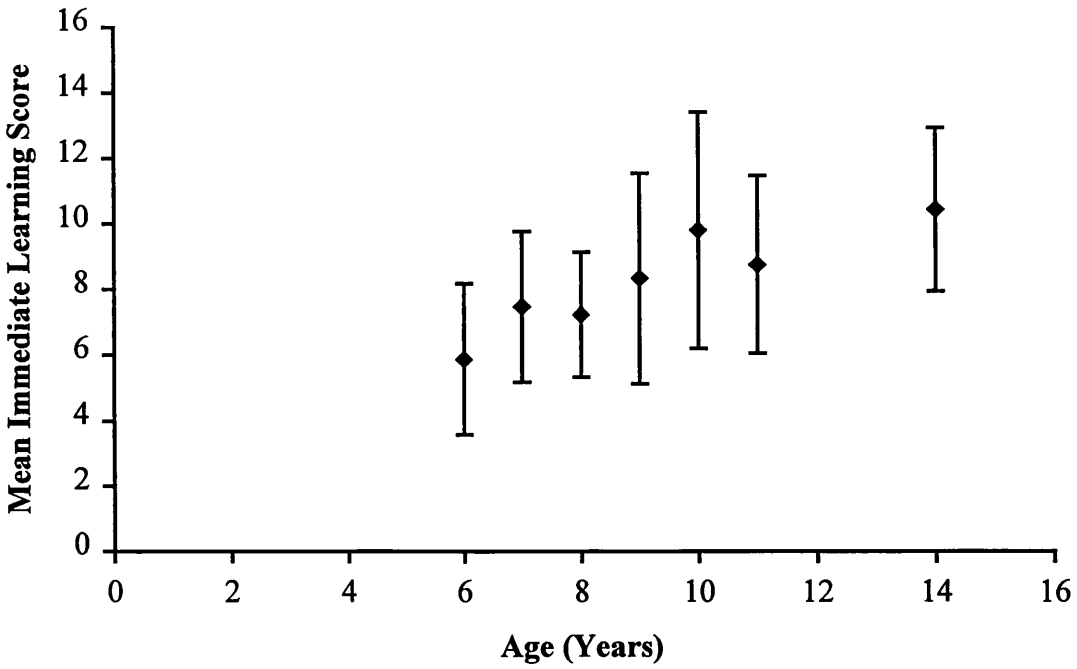

Figure III.v Graph showing mean Immediate Learning score against age group (mean ± standard deviation).

Analysis of the Immediate Recall (A6) scores indicated an age-related improvement in performance (Table III.vi). A single-factor analysis of variance revealed a significant difference between the age groups ($P < 0.001$). When investigated using a post-hoc Tukey's h-s-d analysis, it was shown that six and seven year-olds recalled significantly less than 10, 11 and 12-16 year-olds ($p < 0.05$).

AGE	Mean A6 score	SD	n
6	4.25	2.3	16
7	5.21	2.3	19
8	5.85	2.2	13
9	6.44	2.1	18
10	7.70	2.1	20
11	7.63	1.9	16
12 - 16	7.92	1.7	25
18 - 25	7.90	1.9	-

Table III.vi Means and standard deviations for the A6 score from the CDLT, including the AMIPB mean for the 18 - 25 age group.

These results and examination of the graph of trial A6 against age (Figure III.vi) shows that there appears to be a gradual increase to a plateau at about age ten. The mean score for trial A6 for the 18-25 age group in the AMIPB manual was 7.9 ± 1.9.

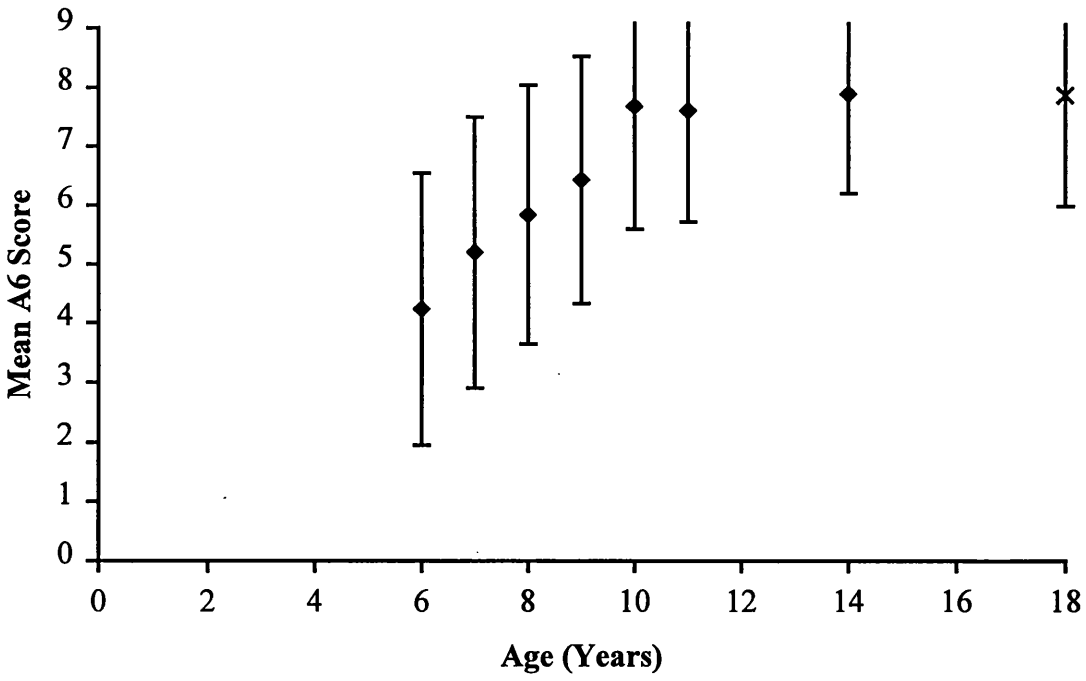

Figure III.vi Graph showing mean A6 (Immediate Recall) score against age group (mean ± standard deviation), including the AMIPB mean for the 18 - 25 age group (X).

Analysis of the Delayed Recall scores indicated an age-related improvement in performance (Table II.vii). A single-factor analysis of variance revealed a significant difference between the age groups ($P < 0.001$). When investigated using a post-hoc Tukey's h-s-d analysis, it was shown that six and seven year-olds recalled significantly less than those aged 10 to 16 ($p < 0.05$).

AGE	Mean Delayed Recall score	SD	n
6	3.87	2.3	15
7	5.17	2.3	18
8	5.92	2.1	13
9	6.50	2.0	18
10	7.80	2.2	20
11	7.75	1.8	16
12 - 16	7.80	1.9	25

Table III.vii Means and standard deviations for the Delayed Recall score from the CDLT.

These results and examination of the graph of the delayed recall trial against age (Figure III.vii) shows that there appears to be a gradual increase to a plateau at about age ten. This score was not part of the original AMIPB and so there are no pre-existing adult norms.

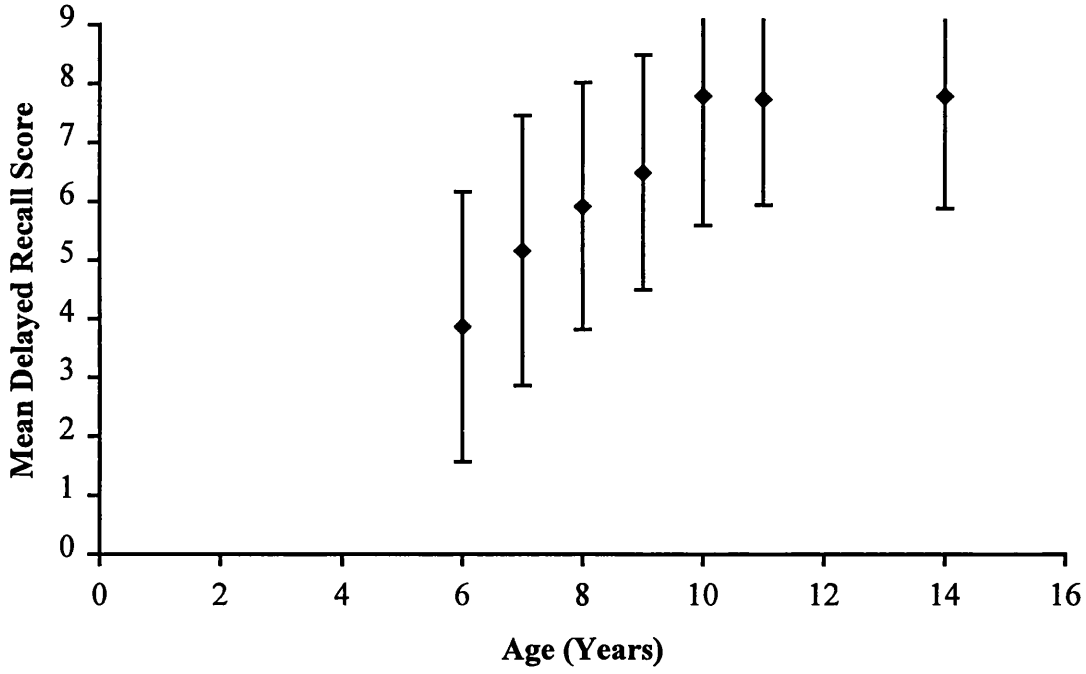

Figure III.vii Graph showing mean Delayed Recall score against age group (mean ± standard deviation).

III.v Discussion

The results of testing 128 normal children on the CDLT are displayed above and demonstrate that adult levels are generally attained between the age of ten and twelve. This supports previously produced data about the development of visuospatial function (Incisa della Rocchetta et al., unpub.), indicating a levelling off of performance between the age of ten and eleven.

Since there were no significant differences between the age groups when scaled score performance on the vocabulary subtest was examined, it can be inferred that no age group was significantly more intelligent than any other. In addition, the range of means about the standard score of ten indicated that this was a good sample of the normal population.

Following examination of the previously acquired adult norms presented in the AMIPB manual, it appears that the mean performance of the 18-25 year-old age group is not significantly different from that of children above the age of ten. It is therefore feasible to use the adult norms for all children aged ten and over, and the norms presented above for children younger than that age. These results therefore give support to the previously believed development of visuospatial memory in children, a study of which demonstrated a levelling off of performance at the age of ten (Incisa della Rocchetta et al., unpub.).

Appendix IV. Graphs of Dot Location performance against age in normal children

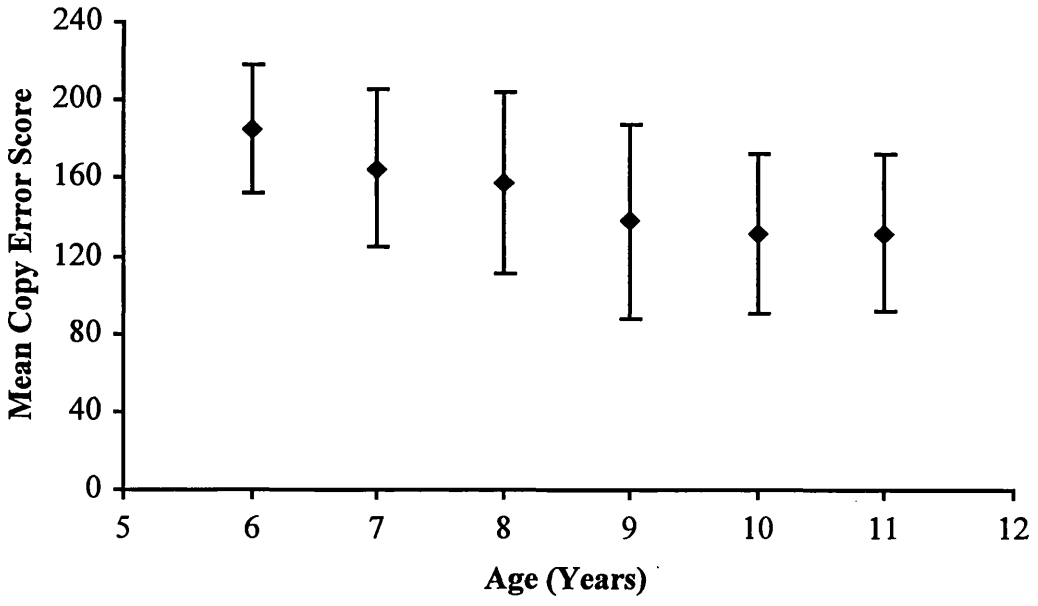

Figure IV.i Graph showing mean Copy error score (± standard deviations) of normal controls for the Dot Location test.

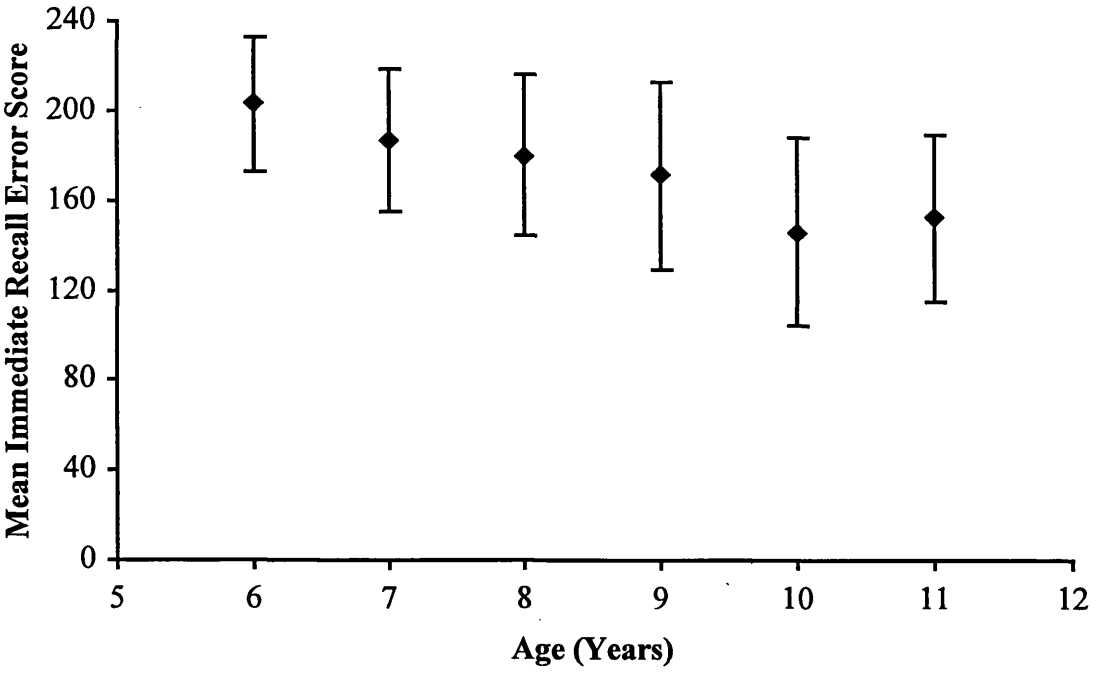

Figure IV.ii Graph showing mean Immediate Recall error score (± standard deviations) of normal controls for the Dot Location test.

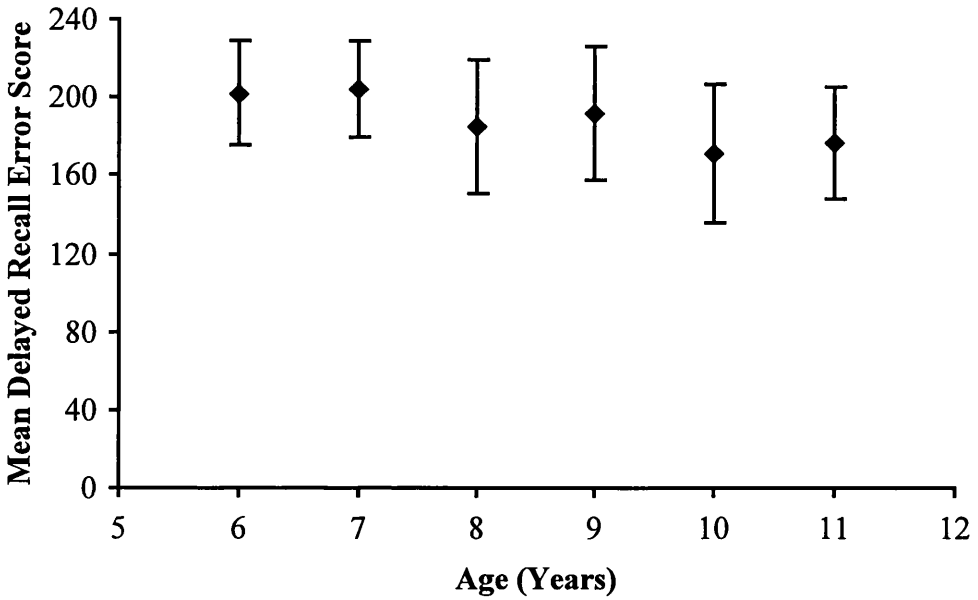

Figure IV.iii Graph showing mean Delayed Recall error score (± standard deviations) of normal controls for the Dot Location test.