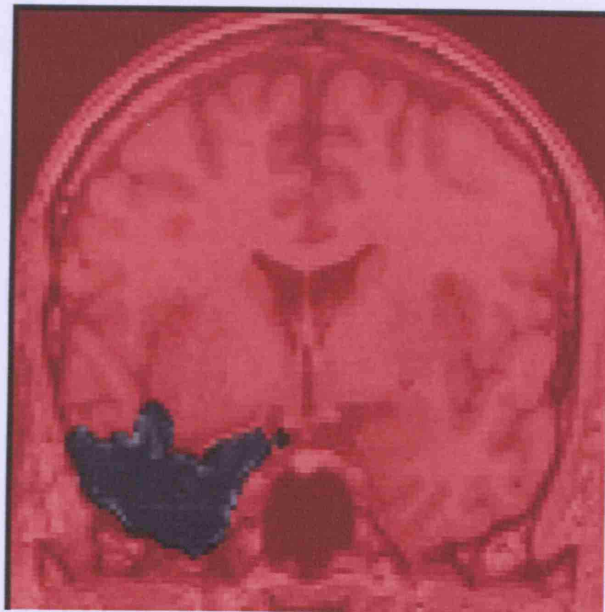




# Long-term Cognitive Effects of Temporal Lobectomy for Intractable Epilepsy in Children

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## 2. ABBREVIATIONS

ATL – Anterior Temporal Lobectomy  
LHS – Left Hippocampal Sclerosis  
RHS – Right Hippocampal Sclerosis  
TLE – Temporal Lobe Epilepsy  
lTLE – left Temporal Lobe Epilepsy  
rTLE – right Temporal Lobe Epilepsy  
LTL – Left Temporal Lobectomy  
RTL – Right Temporal Lobectomy  
DNET – Dysembryoplastic NeuroEpithelial Tumor  
WAIS – Wechsler Adult Intelligence Scale  
WISC – Wechsler Intelligence Scale for Children  
FSIQ – Full Scale Intelligence Quotient  
VIQ – Verbal Intelligence Quotient  
PIQ – Performance Intelligence Quotient  
WMS – Wechsler Memory Scale  
fMRI – functional Magnetic Resonance Imaging  
EPI – Echo-Planar Imaging  
ROI – Region Of Interest  
LI – Laterality/Lateralization Index (used interchangeably)  
IAP – Intracarotid Amobarbital Procedure  
ANOVA – ANalysis Of VAriance

### 3. INTRODUCTION

#### 3.1 Epilepsy

Epilepsy is defined as the propensity to have seizures. Seizures are synchronous, excessive discharges of synaptic activity in the brain. Epilepsy is a significant neurological condition that affects 50 million people worldwide every year and has a prevalence of 5-10 people in 1000 (Bell & Sander 2002). Its aetiology is complex: it can arise from developmental abnormalities, trauma, asphyxia during childbirth, underlying tumours and strokes and it is also often associated with dementia. It is a bimodal disease, afflicting primarily the young and the old.

#### 3.2 Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) is one of the most common types of epilepsy. It is characterized by seizures that originate from one or both of the temporal lobes (see *Figure 1*). Of the two forms of TLE – mesial and lateral – mesial is the more common and affects up to 80% of patients with TLE (Duchowny 1995; Bocti et al 2003). Mesial TLE arises in the hippocampus, parahippocampal gyrus and amygdala whereas lateral TLE arises in the neocortex.

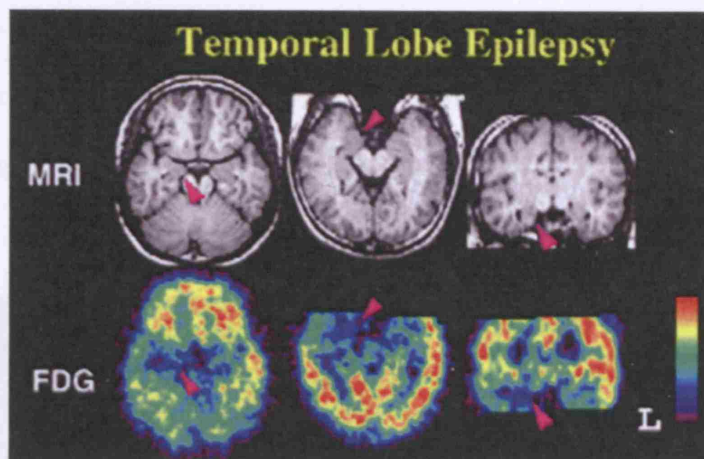


Figure 1: PET scans showing seizure activity in Temporal Lobe Epilepsy (TLE)

From Tokyo Metropolitan Institute of Gerontology

### 3.3 Hippocampal sclerosis

A common cause of TLE is hippocampal sclerosis (HS). HS is characterised by the dissemination of the granular layer of the hippocampus and a general cell loss and atrophy of the hippocampus (See Figure 2) and its associated structures (Bernasconi et al 2005). It is still unclear whether the sclerosis is causative of the epilepsy or is a result of the condition.

As an anatomical structure, the hippocampus is known to be important in learning and memory and has also been shown to have a crucial role in language and in verbal memory. The medial temporal lobe has furthermore been identified as having a role in maintaining the coherence of incoming information and consequently allowing it to pass into long-term memory form. Numerous neural connections originate and target the hippocampus from both proximal and distal areas (Van Hoesen 1995). An epileptogenic hippocampus can therefore be thought to affect distant areas both structurally and

functionally. As a consequence, damage to the hippocampus by chronic seizures and resection of part, or all of the hippocampus, can be thought to have an impact on memory, learning and language functions.

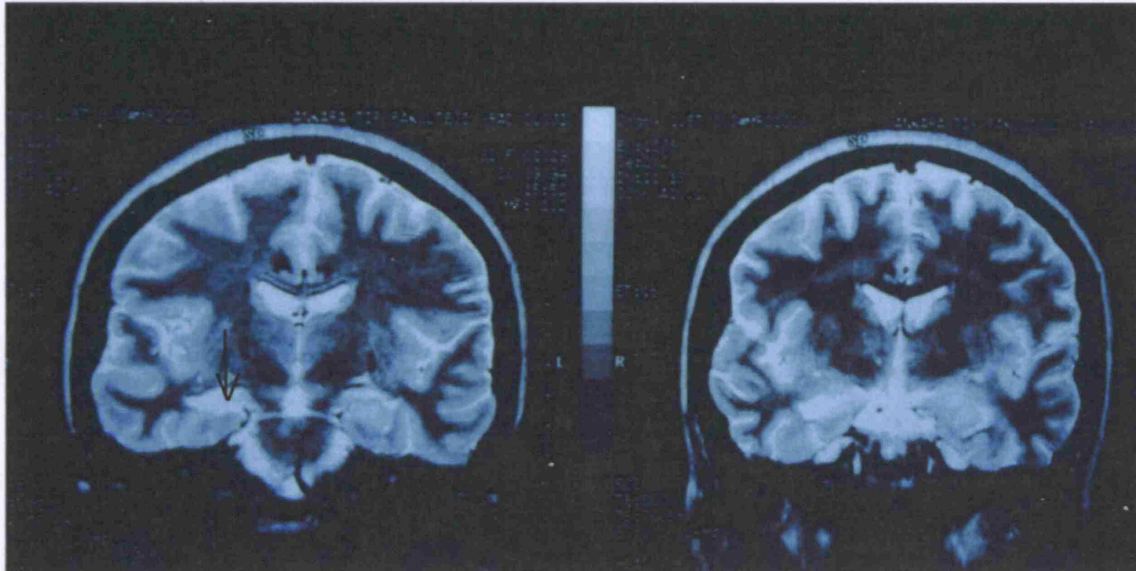


Figure 2: Right hippocampal atrophy (arrow) of patient with complex partial seizures

From Erdem et al 2002

### 3.4 Chronic drug-resistant epilepsy

Epilepsy is successfully treated with drug therapy in a majority of cases but 20-30% of all epilepsies are refractory, which means they do not respond to medication. It is thought that intractable, chronic epilepsy is connected to disturbances and imbalances in brain neurochemistry. Studies have furthermore suggested that the frequency of seizures as well as the subsequent pathological brain activity and metabolic disturbances of these seizures cause primary damage believed to then result in secondary neurophysiological

and structural degeneration (Hermann et al 1996; Jokeit & Ebner 1999).

In their paper, Devinsky et al (2005) emphasized that temporal lobe epilepsy is a dynamic epileptic disorder that in its chronic form can cause progressive structural, cognitive and behavioural changes. Fuerst et al (2001) showed that an earlier age of onset, greater seizure severity and longer duration of epilepsy in unilateral HS patients leads to more severe HS and greater hippocampal volume asymmetry. Greater overall hippocampal volume loss in patients with intractable TLE has also been shown to be correlated with a longer duration of epilepsy as well as an earlier age of onset (Hermann et al 2002). This was echoed by various other studies that showed that the age of onset of epilepsy is an important predictor of TLE outcome (O'Leary et al 1981, 1983). Previous studies have also shown that repeated seizures over years can contribute to progression of temporal lobe epilepsy (Tasch et al 1999; Bernasconi et al 2002; Kalviainen and Salmenpera 2002), in agreement with Gower's adage "Seizures beget seizures".

### **3.5 Cognitive effects of TLE**

Various factors have been seen to have debilitating effects on the cognitive outcome of patients. Jokeit et al 1999 showed that patients with a long history of intractable TLE were at higher risk of generalised cognitive impairment than patients with a shorter duration of TLE. They also posited that duration of epilepsy and educational levels were the best predictors for psychometric intelligence in the sample.

The literature has also shown that early onset of epilepsy is an important predictor in determining cognitive outcome and impairment (Vasconcellos et al 2001, Hermann et



al 2002, Smith et al 2002). The findings suggest that epilepsy occurring in early childhood is frequently associated with considerable cognitive and behavioral deterioration. Vargha-Khadem et al 1994 showed that during the first two years of life in particular, brain abnormalities associated with epilepsy may result in severe cognitive impairment.

In studying memory function in subjects with TLE, Blake et al (2000) found that patients with left temporal lobe epilepsy (lTLE) perform normally in short-term memory testing but poorly in long-term verbal memory tasks, compared to those subjects with right temporal lobe epilepsy (rTLE) and normal controls. Their findings point to the left temporal lobe as the critical region for long-term memory consolidation of verbal material.

In two recent large cohort studies of the long-term outcome of childhood-onset epilepsy, Geelhoed et al (2005) determined that predicting outcome of childhood epilepsy tends to be incorrect in about one of every three subjects. This emphasizes the individualistic nature of the progression of epilepsy. The debilitating effects of chronic seizures on cognitive outcome do stress, however, that an early arrest of seizures may lead to the best outcome for the children; their developing brains may exhibit enough plasticity and compensatory mechanisms to mediate any cognitive effects of brain damage caused by TLE.

### **3.6 Epilepsy Surgery**

The potential damage to the immature brain by repetitive seizure activity and the

associated decline in cognition and social abilities has made resective surgery an increasingly important and viable option. The option was made possible, in part, by the advent of Magnetic Resonance Imaging (MRI) and other diagnostic tools. MRI enables diagnosis of pathology (Salmenpera & Duncan 2005; Scott 2001) as well as the localization and detection of the epileptogenic origin, or foci. Seizures in patients with intractable epilepsy are often caused by tumours or brain abnormalities that can be entirely removed by surgical resection. The most common and successful epilepsy surgery has been anterior temporal lobectomy (ATL). In 70-80 percent of cases where this surgery is performed for pharmaco-resistant epilepsy in both children and adults, ATL results in either a significant reduction in seizure frequency or complete seizure remission. For cases of unilateral HS, it is furthermore associated with a good prognosis for seizure control (Wyllie et al 1998, Olivier 1996). Continuation of seizures following surgery for the remaining 20-30% percent may be due to the inaccurate localization of the foci, or the presence of additional lesions that have gone undetected.

### **3.7 Impact of surgical intervention**

Resection of the temporal lobe may damage eloquent areas of the brain important for memory and language, despite extensive pre-operative language and memory testing (Hermann et al 1994, Langfitt and Rausch 1996, Clusmann et al 2002). When hippocampal sclerosis is diagnosed as the epileptic pathology, less post-operative difficulties are found compared to other pathologies underlying epilepsy. This may be due to reorganization of function as the condition progresses and healthy brain tissue

degenerates into a sclerosis. Affected neural circuits may already pre-operatively reorganize to distant brain regions, both intra- and inter-hemispherically.

### **3.8 Cognitive outcome after temporal lobectomy: Intelligence**

Patients may experience complex cognitive effects after surgery that may be a consequence of surgery or may equally be due to the effects of prolonged, repetitive seizures. The long-term cognitive effects of temporal lobectomy on intelligence have been assessed in adults (Alpherts et al 2004): limited effects on intelligence were found in the long term after surgery. The changes that were found were furthermore attributed to retest effects. Cognitive outcome in children, which has been less well evaluated, may differ a great deal from that in adults because of developmental factors. It is thought, for example, that relief of intractable seizures and the increased plasticity of the young brain can potentially result in accelerated cognitive development, and compensation for earlier injury post-surgically; however, several previous studies have found little or no change in children's IQ postoperatively (Gleissner et al 2006, Korkman et al 2005, Williams et al 1998; Westerveld et al 2000).

### **3.9 Cognitive outcome: Verbal memory**

Temporal lobectomy patients often complain about problems with memory that may not become apparent during conventional memory tests; this is particularly true of left temporal lobectomy subjects. Studies about memory in childhood temporal

lobectomy have been more uncommon and have also yielded controversial results (Mabbott et al 2003; Baxendale et al 1998; Chelune et al 1995; Jokeit et al 1997). In a long-term study of cognitive function, Rausch et al (2003) found that temporal lobe surgery is associated with language-associated cognitive declines and deficits in verbal memory in left temporal lobectomy patients. Alpherts et al (2006) also found verbal memory difficulties in LTL patients in a long-term (6 year follow up) study. In their study they propose that the hippocampal system acts as a relay and that its loss may therefore have wide-reaching effects on the rest of the brain. Furthermore, after the resection of the hippocampus, the remaining connections and structures may continue to degenerate and explain the gradual decline seen in many subjects postoperatively.

An earlier study by Gleissner et al (2002) found a functional association of verbal memory with the left temporal lobe in children similar to previous findings in adult patients. They found, however, that the post-operative verbal memory values recover over time after an initial decline, suggestive of the plasticity of the developing brain of children compared to adults.

### **3.10 Language lateralization**

The left hemisphere is typically dominant for language function; in 1-2% the right hemisphere is dominant and in about 20% of healthy subjects, language is represented bilaterally (Loring et al 1990; Springer et al 1999; Knecht et al 2000). Previous studies have shown more frequent atypical language representation – either bilateral or right-dominant – in subjects with focal epilepsy compared to healthy controls. This is thought

to be explained by compensatory neuronal reorganisation due to the early trauma that is caused to the left hemisphere by both lesions and seizures. The mechanism by which this occurs is still poorly understood and more investigation is necessary but studies show that functional reorganization allows the right hemisphere to assume language functions when epileptic pathology occurs early in life (Helmstaedter et al 1997).

It is well established that damage to the left hemisphere can result in severe and language deficits in adults but lesions of the left hemisphere that occur in children do not necessarily have the same consequences on language abilities (Vargha-Khadem et al 2000). The ability of the brain to compensate for early damage to the brain has been attributed to the brain's ability to reorganize when it is not yet fully developed. This, as a result, can lead to compensatory neurological development both ipsi- and contralaterally. It has furthermore been shown that this type of reorganisation is true not only when language areas or extensive areas are affected but also when lesions are remote to the main language areas (Duchovny 1996). Weber et al (2006) furthermore studied whether lesions that are closer to classic language-related areas, like Broca's or Wernicke's areas, result in greater shifts in language dominance than lesions to the hippocampus and found that subjects with hippocampal sclerosis showed greater levels of language reorganisation than patients with other pathologies. This indicates that the hippocampus is an important structure in determining language dominance. Neuroimaging studies (Muller et al 1999b and Duncan et al 1997, Muller et al 1998) have furthermore shown that atypical language lateralization occurs more frequently when the injury is early as opposed to late.

### 3.11 Purpose of study

Various studies have investigated the long-term effects of temporal lobectomy on intelligence in adults but have not assessed these effects in children, and specifically verbal memory in children. In this study we hope to evaluate the long-term cognitive effects of epilepsy surgery in children by measuring intelligence using the WAIS, verbal memory using the WMS, and comparing word retrieval by auditory or visual cues using the Auditory and Visual Naming Task.

We wanted to assess intelligence in both a cross-sectional and longitudinal manner, by comparing individuals' development over time as well as to determine whether any overall trends could be observed within and between groups (eg LHS, RHS).

We also wanted to see whether other factors were statistically significant when characterizing long-term cognitive outcome in children who have temporal lobectomies for intractable surgery. These factors include the extent and volume of resection, the extent of seizure control following surgery, age at onset, the side of surgery and seizure duration.

The goal was furthermore to assess verbal memory in a similar manner as to intelligence – to determine whether any cross-sectional or longitudinal findings would be apparent from the WMS test and specifically from the subtests that evaluate verbal memory. We wished to analyze the lateralization of language in patients with LHS and RHS and evaluate the effect that temporal lobe surgery has on verbal memory. We furthermore wanted to determine whether a correlation could be found between the side of the surgical lesion and the resulting change in language dominance (Knecht 2004,

Liegeois 2004) and compare it to healthy controls. The hypothesis is that LHS and left temporal surgery of the temporal lobe will lead to a greater reorganization of language function than in a group of matched healthy controls. The hypothesis is furthermore that when no language reorganisation occurs, the activation patterns should be independent of the resection side.

We wished to combine these findings with any changes found in neuropsychological data through comparison of pre-operative data with long-term post-operative data. Comparing these factors may allow us to determine the effects of plasticity in the immature brain as well as evaluate how comparable the literature for adults is to children.

### 3. METHODS

#### 3.1 Subjects

Subjects included 17 individuals with left temporal lobectomies (LTL) and 9 with right temporal lobectomies (RTL). All of the subjects had a history of drug-resistant epilepsy with hippocampal sclerosis pathology. They underwent extensive pre-surgical assessments including neuropsychological testing and subsequent temporal lobectomy surgeries at Great Ormond Street Hospital at least five years prior to the study (average time since surgery = 113.1 months with a range of 59 to 176). Written informed consent to participate in a larger study on long-term cognitive outcome of surgery for refractory epilepsy was obtained from all subjects as outlined by Great Ormond Street Hospital for Children/Institute of Child Research Ethics Committee. Data about the age of seizure onset, past and current seizure frequency, past and current medication as well as pre-operative neuropsychological scores were collected from questionnaires given to the patients and retrospectively from medical records.

For two subjects – one RTL and one LTL subject – it was not possible to collect pre-operative neuropsychological data. For two other LTL patients, it was not possible to conduct the fMRI part of the project: one due to insufficient safety information and one due to bilateral hearing difficulties.



### **3.2 Controls**

10 healthy controls that matched the temporal lobectomy subjects for age and gender were recruited for the fMRI portion of the study. 9 of the controls were native English speakers, or had learned English before the age of 5 and were educated in English. 1 control spoke English as a second language and had been educated in English at secondary and university level.

### **3.2 Neuropsychological evaluation**

A battery of neuropsychological tests was performed for each of the subjects, to assess their intellectual, language and memory abilities. These test results were then compared to pre-operative and early post-operative data, where this information was available. The measures that were used for the purposes of this study include the Wechsler Adult Intelligence Scale, the Wechsler Memory Scale and a novel auditory and visual learning task (Hamberger et al 2003). These tests formed the primary basis for analysis of long-term changes in IQ, memory and language. For each included patient, one, or several, sets of pre-operative data were available, from which we could study the cognitive development of the patients.

For most subjects the Wechsler Intelligence Scale for Children (WISC-R UK and WISC-II UK) was used in the pre-operative tests and earlier post-operative tests. This was compared to the Wechsler Adult Intelligence Scale (WAIS-R and WAIS-III) used in adults above the age of 16. The different scales allow for comparisons between adults and children. The WAIS-III is an intelligence test based on a number of subtests. The tests

that were used in this study were 6 Verbal WAIS scales: Information, Digit Span, Vocabulary, Arithmetic, Comprehension and Similarities and 5 Performance WAIS scales: Picture Completion, Picture Arrangement, Block Design, Digit Symbol and Matrix Reasoning. From these tests, three IQ scores were obtained – Verbal IQ (VIQ), Performance IQ (PIQ) and Full Scale IQ (FSIQ). The separate IQ divisions of the WAIS-III can be useful to determine whether there are strengths or weaknesses in the different areas and each subtest may furthermore be used to isolate specific subject difficulties. These difficulties may then indicate which part of the brain has been affected.

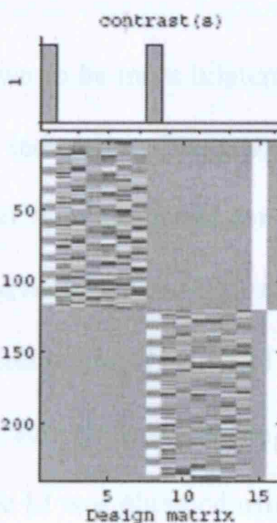
The Wechsler Memory Scale (WMS) is a test used to assess learning, memory and working memory. Special focus was placed in this study on two subtests that evaluate verbal memory: Story Recall and Paired-Associate learning. These subtests are scored both immediately and at a delayed timepoint. This enables analysis of the amount of retention of information over time, using one presentation of a story as in Story Recall or several presentations of paired words as in Paired-Associate learning.

The WMS and WAIS can be used together to evaluate correlations between intellectual performance and memory.

### **3.3 Magnetic Resonance Imaging**

MRI was performed on a 1.5-T Siemens Vision System (Erlangen, Germany). Anatomical images were obtained as axial multislice T1-weighted FLASH (fast low angle shot) images [TR (repetition time) = 31 ms, TE (echo time) = 11 ms, flip angle 40 degrees, matrix size 256 x 256 x 64, voxel size 0.75 x 0.75 x 3 mm]. Functional MRI data

were acquired using a whole brain gradient echo 3D EPI (echo-planar imaging) sequence [TR = 87 ms, TE = 40 ms, flip angle 30 degrees, matrix 64 x 64 x 64, 3 mm isotropic voxels]. For each participant, two consecutive runs of 120 verb generation data sets were collected. Each run consisted of 10 Task/Rest cycles with 6 data sets for each state (See *Figure 3*). The Task period consisted of the participants silently generating verbs in response to nouns presented via earphones every 2.8 s (approximately 12 nouns per Task period). During the Rest period, bursts of amplitude-modulated noise were presented every 2.8 s, during which time the subjects were asked to think of nothing. Scanning time was 12 mins per run and the total time for anatomical and functional images was approximately 40 min.



*Figure 3. Design paradigm for Verb Generation task*

The collected MR images were processed and analyzed using the Statistical Parametric Mapping software SPM2 and SPM5. The following steps were performed: the

Echo-Planar images were realigned using the first scan as a reference to correct for movement artefacts. The T1 3D-flash images and Echo-Planar images were then spatially normalized onto a standard, symmetric T1-weighted template to minimize any anatomical asymmetries that could interfere with accurate activity comparison of the right and left hemispheres. The images were spatially smoothed to three times the original voxel size using a Gaussian kernel. Masks were generated using the 3D tool in MRICro. The volumes of the resections were determined from analysis of these regions of interest (ROIs). The masks were furthermore co-registered, normalized and smoothed with the T1 structural image.

### **3.4 Lateralization Index**

The temporal lobe is known to be more bilaterally representative of language and Broca's region is said to be more indicative of language dominance. For each participant, several lateralization indices (LIs) were computed for selected regions of interest (ROIs) using overlay masks. The selected regions were Broca's area, the temporal lobe minus the mean resected areas and the cerebellum. The spmT image produced from the spm5 analysis of fMRI task for each subject was chosen as the contrast image for which laterality would be computed. The LI was obtained using an adaptive threshold: the value of  $(R - L)/(R + L)$  was computed where L and R are the number of activated voxels in the left and in the right hemisphere respectively that fall above the average intensity of all positive voxels. The adaptive threshold was furthermore used in the calculations to account for intersubject variability in the levels of overall activation. Participants with a

negative LI greater than -0.2 were considered left lateralized for language, while those with a positive LI greater than 0.2 were considered right lateralized. Subjects whose LI values ranged from -0.2 to 0.2 were considered to have bilateral language representation. Voxel value was chosen instead of voxel count in order to take into account the value, or strength, of a given voxel and thereby more accurately reflect the individual contribution of a given voxel. Broca's area, of the inferior frontal gyrus, was chosen as a region of interest because it has been shown in previous studies that lateralization of activation in this region best correlates with other established laterality methods, such as WADA. Broca's area is furthermore known to be involved in language processing and is found unilaterally in the left hemisphere of the brain. The temporal lobe was chosen because of its importance in various language processes, including both low-level perception and higher-level functions such as comprehension, naming and verbal memory. The mesial temporal lobe, and specifically the hippocampus, is thought to be important for episodic and declarative memory and in particular, for the transferral of memories from the short term to the long term. Lastly, the cerebellum was chosen as a region of interest because it shows activity contralateral to the dominant hemisphere. See *Figure 4* for the regions of interest used to determine the laterality index.

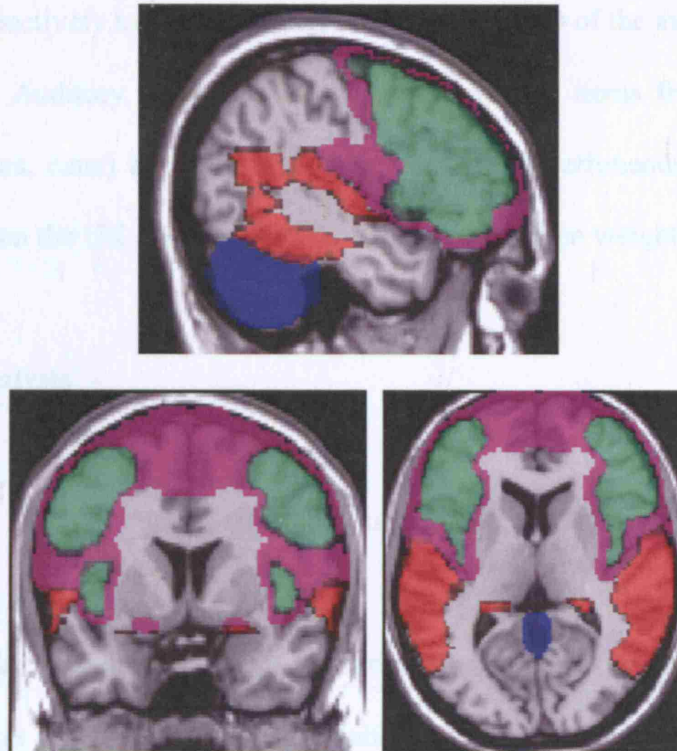


Figure 4. Regions of interest in sagittal, coronal and transverse images  
(blue=cerebellar, red=temporal, green=Broca's, pink=frontal)

### 3.5 Auditory and visual naming tests

A subset of the LTL subjects were furthermore tested with a novel Auditory and Visual Naming task described by Hamberger et al (2003). The Auditory Naming task consisted of 50 different descriptions of common-place nouns and the Visual Naming task consisted of 50 readily recognizable objects. The timing of the subject's response in naming each of the items was initiated when the last word of the description was spoken for the Auditory Naming Task, or when the page was turned for the Visual Naming Task. The average age and education of our LTL patient group (n=7) was lower than that of the LTL group in the normative study. The average IQ and WAIS-R Vocabulary score of our

subjects were respectively lower and higher but within one SD of the averages reported in the study. In the Auditory Naming Task we removed four items from the task (gas, resume, suspenders, cane) because these were consistently erroneous due to language differences between the UK and the USA. The results were then weighted accordingly.

### **3.6 Statistical analysis**

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software. ANOVAs and *t* tests were used in our study to assess demographic differences among groups. Bivariate correlations (Pearson and Spearman) were used to assess any two continuous variables (eg. LI with cognitive scores) that we were examining. Within and between group ANOVAs were performed when significant interactions were suspected between Groups (LTLE vs RTLE, low vs high preoperative FSIQ range). Multiple regression analysis was used to determine the relationship between WMS Paired Associate Retention and WMS Story Retention using FSIQ and WMS MQ as covariates.

## 5. RESULTS

### 5.1 Long-term changes in cognitive functions – IQ

*Table 1* shows the demographic data and selected cognitive outcome scores of the left and right-sided hippocampal sclerosis patients. Of the 26 left and right hippocampal sclerosis patients, 21 (80.8%) are seizure-free post-operatively. Out of the 24 patients for whom we have relevant medical data, 11 (45.8%) are still taking anti-epileptic drugs. The age range of the patients is 16-31 with an average age of 23.1 (4.3). The average age of the clinical onset of seizures is 26.1 months (30.1) with a range of 3-120. The average volume of resection of the right or left temporal lobe is 17.5 (6.3) with a range from 8.9 to 33.7.

The average value of full score IQ for the overall left and right hippocampal sclerosis subjects was 85.7 (21.0) with a range of 53 to 128. This is reflected by the histogram in *Graph 1* which shows a bell curve that is centred around 85: this is considerably lower than the average population IQ which is standardized at 100. The average change in full score IQ of the subjects was 7.4 (n=24, with a range from -5 to 20). Missing values reflect incomplete pre-operative data. Of the 24 subjects with complete data, 6 exhibited a decrease in FSIQ score that ranged from -3 to -5. Of the remaining 18 subjects, 11 saw an improvement in their FSIQ of 10 or higher. *Graph 2* displays the longitudinal FSIQ progression of each left hippocampal sclerosis patient,



allowing a more detailed analysis of changes that occurred over time. Many patients demonstrated an initial drop in IQ during the first pre-operative years and for those patients where information was available at several pre-operative dates, a decline in scores was often seen prior to the surgery. In these subjects, the increase in IQ found post-operatively meant that their IQ scores had returned to levels that were similar to earlier pre-operative findings.

**Graph 1. FSIQ in Left and Right Temporal Lobectomy**

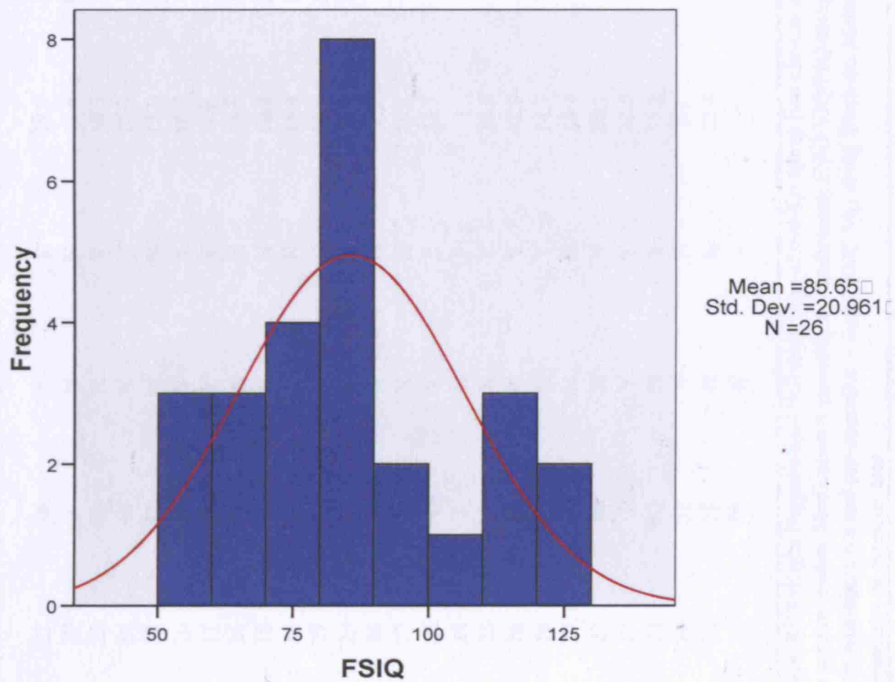


Table 1. Demographic data and cognitive scores of LHS and RHS subjects\*

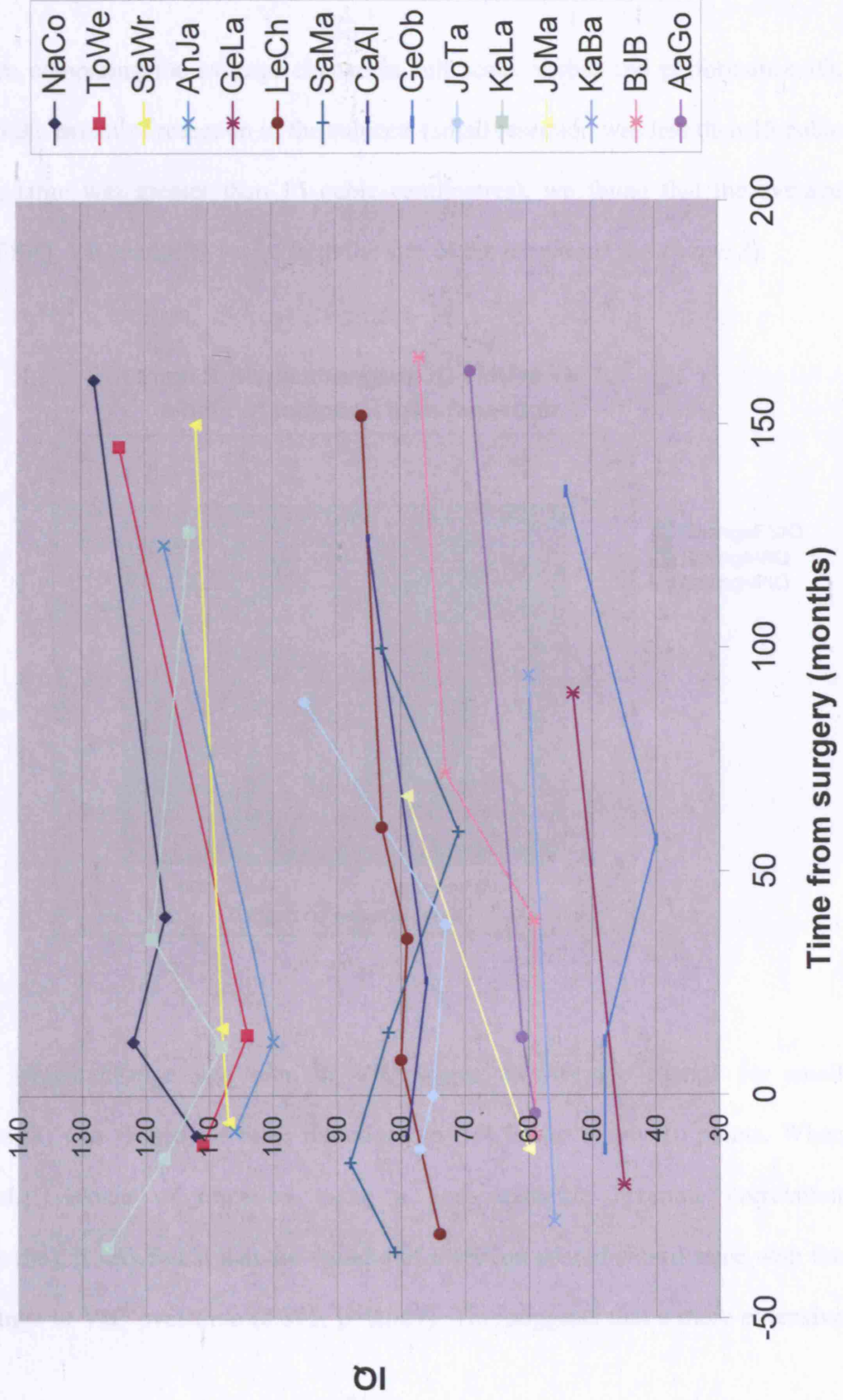
Subject no.	Side	Sex	Age	Age of onset	Seizures	Medication	Resection	FSIQ	VIQ	PIQ	ΔFSIQ	WMS MQ
1	LHS	F	22	36	Y	Y	19.9	86	75	57	6	62
2	LHS	M	29	9	N	N	15.8	113	105	102	12	94
3	LHS	F	23	60	N	Y	18.3	79	71	122	-4	114
4	LHS	M	24	10	N	Y	17.3	83	78	92	19	89
5	LHS	F	25	12	N	N	13.0	85	83	91	-5	99
6	LHS	F	26	24	Y	Y	16.7	60	62	90	6	89
7	LHS	F	17	18	Y	Y	9.9	77	71	64	4	59
8	LHS	M	26	24	N	N	24.5	95	87	87	18	81
9	LHS	F	18	23	N	N	10.8	128	124	106	20	93
10	LHS	F	31	120	N	N	15.4	124	125	127	16	140
11	LHS	M	29	10	N	N	18.9	112	103	117	13	118
12	LHS	F	23	10	N	N	16.3	117	116	124	7	113
13	LHS	M	26	6	N	N	9.2	87	93	116	11	126
14	LHS	F	17	8	N	N	18.1	89	79	79	-5	110
15	LHS	M	26	110	Y	Y	33.7	53	58	104	-	77
16	LHS	M	24	3	N	-	-	69	74	56	8	52
17	LHS	M	23	6	N	Y	28.2	62	66	69	10	84
18	RHS	M	16	23	N	Y	12.9	77	73	63	-5	58
19	RHS	M	19	13	N	Y	14.7	95	91	86	-4	101
20	RHS	F	27	10	N	N	18.4	81	75	100	7	97
21	RHS	M	23	48	N	N	28.1	58	58	92	10	81
22	RHS	M	17	7	Y	Y	23.5	104	100	67	-	59
23	RHS	M	24	9.5	N	Y	15.2	71	73	109	17	106
24	RHS	F	16	52	N	N	8.9	84	81	74	7	86
25	RHS	F	26	18	N	N	12.4	84	82	90	-3	108
26	RHS	F	24	10	N	-	-	54	60	87	12	101

Note LHS=Left Hippocampal Sclerosis, RHS=Right Hippocampal Sclerosis; Age of onset = age at first clinical seizure, in months; Resection = volume of resection in cubic centimeters; Seizures = current seizure burden; Medication = currently on medication; FSIQ/VIQ/PIQ using Wechsler Adult Intelligence Scale-Revised UK; ΔFSIQ = difference between long-term post-operative and pre-operative values; WMS MQ using Wechsler Memory Scale  
*Empty values represent missing pre-operative or medical data*

\*Data collected by Caroline Yaro and Johanna Gaiottino

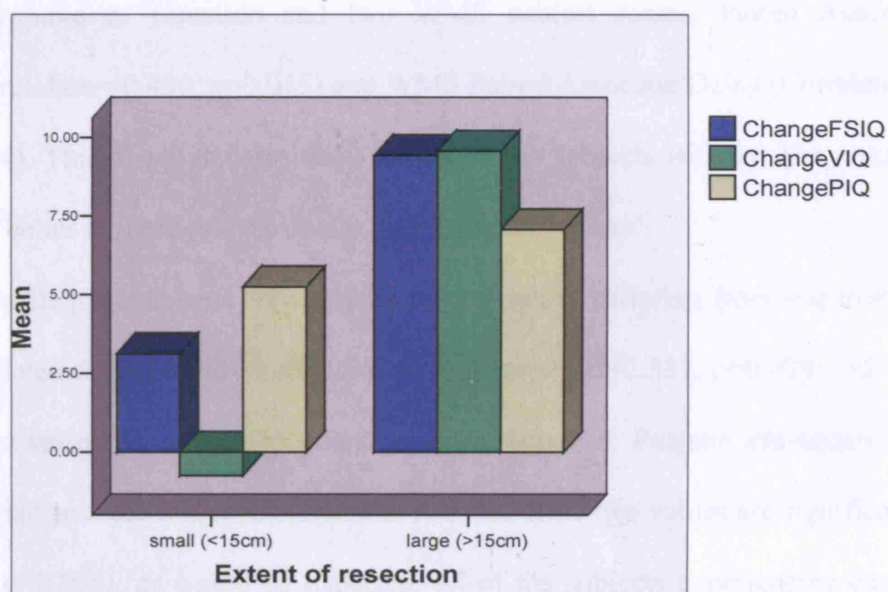
Graph 3.

### FSIQ over time - Left Temporal Lobectomy



When comparing the average change in full scale, verbal and performance IQ, compared to the extent of resection in the subjects (small resection was less than 15 cubic centimetres, large was greater than 15 cubic centimetres), we found that the average changes in FSIQ, VIQ and PIQ varied with the size of the resection (See *Graph 3*).

**Graph 3. Mean change in IQ values vs. extent of temporal lobe resection**



The largest change was seen in VIQ where the average change for small resections (n=8) was -1 and for large resections (n=16) it was nearly 10 points. When analyzing the volume of resection using a non-parametric bivariate correlation (Spearman's rho), it was found that the volume of resection neared significance with the average change in VIQ over time (0.395,  $p=0.069$ ). This suggests that a more extensive

resection acts as a positive predictor of verbal cognitive outcome. Selecting for right or left sided cases made this correlation less significant. Although this finding is based on small groups and is not quite significant, it is in contrast with those of Alpherts et al (2004) where no interaction was found between the extent of resection and post-operative IQ scores.

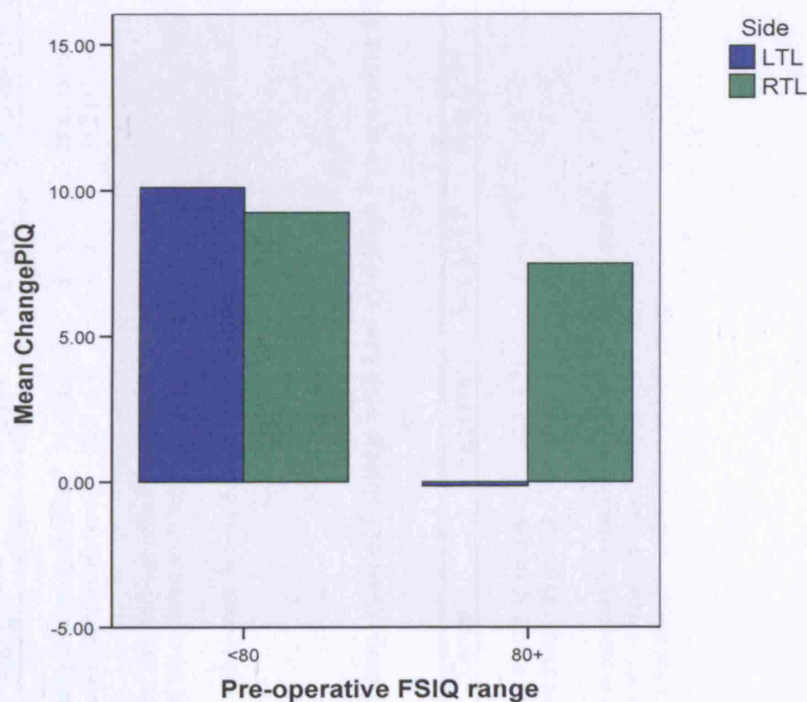
Further correlations between the volume of resection and cognitive scores were examined. The Pearson Correlation (2-tailed) showed a significant negative correlation between the volume of resection and two WMS subtest scores: Paired Associate Retention (Correlation=-0.490, p=0.015) and WMS Paired Associate Delay (Correlation=-0.459, p=0.024). This negative correlation indicates that subjects with smaller volumes of resection do better in these two particular verbal memory tasks.

Whether the patients were currently on medication or suffering from seizures was significantly related to full scale IQ values post-operatively (t=2.331, p=0.029; t=2.079, p=0.048) as measured by an independent samples t-test. A Pearson chi-square test comparing current seizures and medication showed that these two values are significantly linked (7.464, p=0.006); as would be expected, all of the subjects experiencing current seizures are on anti-epileptic medication.

The age at surgery was found to be significantly correlated with FSIQ (0.484, p=0.014), VIQ (0.439, p=0.028) and PIQ (0.483, p=0.015) as well as long-term change in FSIQ (0.431, p=0.036) and the WMS MQ (0.456, p=0.022). Age of onset of epilepsy and seizure duration were not significantly related with any of the cognitive scores we measured and checked correlations with.

The graphs comparing the mean change in FSIQ, VIQ and PIQ in subjects with low preoperative FSIQ values ( $\leq 80$ ) and those with high preoperative FSIQ values ( $>80$ ) show a large difference in each of the IQ values for left hippocampal sclerosis subjects, but not for right hippocampal sclerosis subjects (See *Graph 4* for PIQ value). An independent samples t-test (*Table 4*) analyzing for differences between the low and high pre-operative FSIQ groups showed a significant result for the change in performance IQ ( $t=2.303$ ,  $p=0.031$ ). This points to a lower pre-operative cognitive score being a predictor for post-operative PIQ performance.

**Graph 4. Mean change PIQ vs. pre-operative FSIQ in Left and Right Temporal Lobectomy subjects**



**Table 3. Comparison of Left and Right Hippocampal Sclerosis Subjects**

Group	Age*	Sex M:F†	Age at onset*	Seizure duration*	Age at surgery*	Resection*
Left Hippocampal Sclerosis (n=17)	24.1 (4.0)	8 - 9	28.8 (35.4)	148.1 (42.1)	171.8 (35.3)	17.9 (6.5)
Right Hippocampal Sclerosis (n=9)	21.3 (4.4)	5 - 4	21.2 (17.1)	136.7 (44.0)	157.9 (36.9)	16.8 (6.3)

\* Independent samples t-test revealed no differences between groups

† Chi-square test revealed no differences between groups

Note Age. Age at onset. Seizure duration. Age at surgery measured in months = Mean (SD). Resection measured in cubic centimeters

**Table 4. Comparison of Subjects with Low and High Pre-operative FSIQ**

Group	Age (years)*	Sex M:F†	Side L:R‡	Resection*	ChangeFSIQ*	ChangeVIQ* ChangePIQ‡
Pre-operative FSIQ ≤ 80 (n=13)	22.2 (4.2)	7 - 6	9 - 4	17.5 (6.9)	9.7 (6.8)	8.2 (9.0) 9.8 (7.2)
Pre-operative FSIQ > 80 (n=11)	24.6 (4.1)	4 - 7	7 - 4	15.4 (3.0)	4.5 (8.9)	3.9 (10.0) 2.6 (8.1)

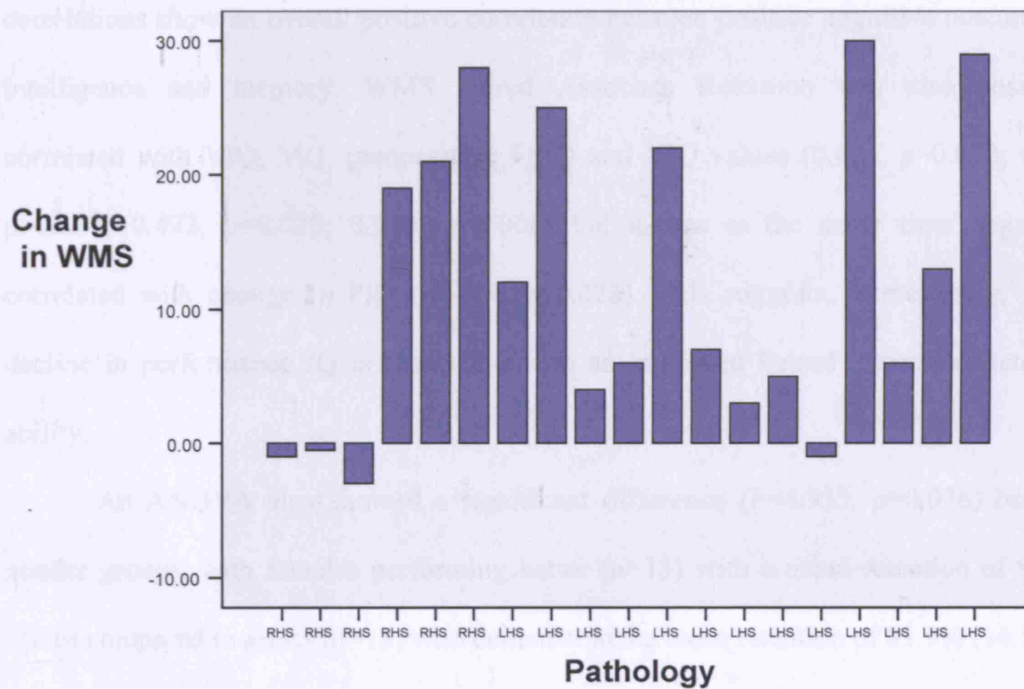
\* Independent samples t-test revealed no differences between groups

‡ t=2.303, p=0.031 Equal variances assumed

† Chi-square test revealed no differences between groups

## 5.2 Long-term changes in cognitive functions - Memory

**Graph 5. Long-term Changes in WMS Memory Quotient**



Graph 5 shows bars representing each of the cases for which pre- and post-operative WMS data is available. An overall improvement in the WMS memory quotient is seen over time ( $n=19$ , mean change in WMS = 11.8 with a range of -3 to 30). An ANOVA analyzing differences between the left and right sided hippocampal sclerosis subjects (LHS:RHS = 13:6) did not find any significant differences between any of the WMS subscores compared to the side of surgery.

The various verbal components of the WMS subtests (Story Immediate, Story Delayed, Story Retention, Paired Associate Immediate, Paired Associate Final, Paired



Associate Delayed) are all strongly positively correlated ( $p < 0.010$ ) with verbal, performance and full scale IQ values, WMS MQ and preoperative IQ values. These correlations show an overall positive correlation between positive cognitive outcomes of intelligence and memory. WMS Paired Associate Retention was also positively correlated with VIQ, MQ, preoperative FSIQ and VIQ values (0.426,  $p = 0.030$ ; 0.524,  $p = 0.006$ ; 0.473,  $p = 0.020$ ; 0.540,  $p = 0.006$ ) but it was at the same time negatively correlated with change in PIQ ( $-0.449$ ,  $p = 0.028$ ). This suggests, interestingly, that a decline in performance IQ is associated with an improved Paired Associate Retention ability.

An ANOVA also showed a significant difference ( $F = 4.955$ ,  $p = 0.036$ ) between gender groups, with females performing better ( $n = 13$ ) with a mean retention of 92.9% (10.6) compared to males ( $n = 13$ ) who demonstrated a mean retention of 81.9% (14.5).

Table 2

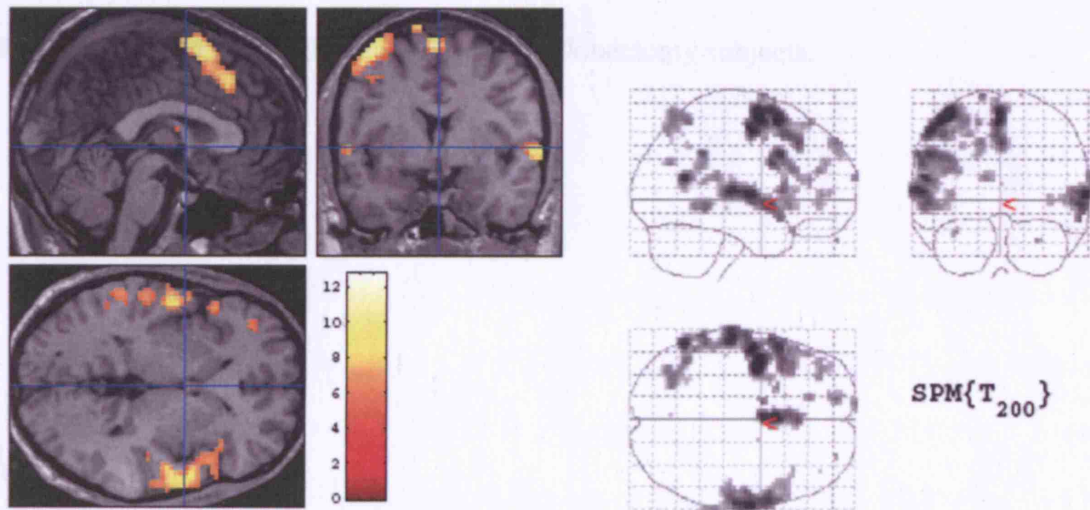
## Laterality Indices of LHS RHS and Controls

Subject no.	Side	Sex	Age	Broca LI	Temporal LI	Cerebellar LI	Laterality Index
1	LHS	F	22	-0.500	-0.517	0.627	R
2	LHS	M	29	0.256	0.409	0.005	L
3	LHS	F	23	0.451	0.372	-0.476	L
4	LHS	M	24	0.811	0.682	-0.289	L
5	LHS	F	25	0.403	0.095	-0.400	L
6	LHS	F	26	0.376	0.111	-0.641	L
7	LHS	F	17	-0.051	-0.299	-0.626	B
8	LHS	M	26	0.593	0.101	0.372	L
9	LHS	F	18	0.321	0.251	-0.080	L
10	LHS	F	31	0.628	-0.030	-0.501	L
11	LHS	M	29	0.944	0.275	-0.578	L
12	LHS	F	23	0.629	0.633	-0.889	L
13	LHS	M	26	0.386	0.169	-0.414	L
14	LHS	F	17	-0.044	0.137	0.321	B
15	LHS	M	26	0.490	0.121	-0.027	L
18	RHS	M	16	0.003	-0.410	-0.615	B
19	RHS	M	19	0.204	0.209	-0.708	L
20	RHS	F	27	0.284	0.129	-	L
21	RHS	M	23	-0.421	-	-	R
22	RHS	M	17	0.358	-0.471	-0.600	L
23	RHS	M	24	-0.007	-0.515	-	B
24	RHS	F	16	0.240	0.292	-0.593	L
25	RHS	F	26	-0.681	-0.346	0.496	R
26	RHS	F	24	0.418	0.095	-0.346	L
27	Ctrl	M	26	0.493	0.086	-0.209	L
28	Ctrl	M	24	0.757	0.285	-0.271	L
29	Ctrl	F	25	0.262	-0.089	-0.006	L
30	Ctrl	F	27	0.435	0.128	-0.129	L
31	Ctrl	F	23	0.444	0.053	-0.413	L
32	Ctrl	F	24	0.591	0.443	-0.458	L
33	Ctrl	F	28	0.417	0.180	-0.345	L
34	Ctrl	M	24	0.660	0.358	-0.275	L
35	Ctrl	M	24	0.161	0.331	-0.047	B
36	Ctrl	M	27	0.590	0.238	0.225	L

*Note* LHS=Left Hippocampal Sclerosis; RHS=Right Hippocampal Sclerosis; Ctrl=Healthy Control; Temporal LI=LI for temporal lobe mask minus resected areas; Broca LI=LI for Broca's extended; Cerebellar LI=LI for cerebellar mask; LI is defined by Broca LI where (L)eft lateralization is 0.2 to 1.0, (B)ilateral lateralization is -0.2 to 0.2 and (R)ight lateralization is 0.2 to 1.0. Missing values represent subthreshold activation in the region of interest

5.3 Lateralization Index

Table 2 shows the LI values calculated using the three different masks in left and right hippocampal sclerosis subjects compared to healthy controls. Figure 5 furthermore shows the lateralization of the verb generation activation from which the LI values are calculated in one healthy control and one LTL subject. Broca's area LI in the inferior frontal gyrus was chosen as the value by which to measure lateralization (Left lateralization = 0.2 to 1.0; Bilateral lateralization = -0.2 to 0.2; Right lateralization = -0.2 to -1.0). Of the 10 healthy controls, only 1 (10%) showed bilateral lateralization of language. 3 out of 15 LTL subjects (20%) showed bilateral or right dominant language representation and 4 out of 9 RTL subjects (44%) showed atypical dominant language representation (See Graph 6).



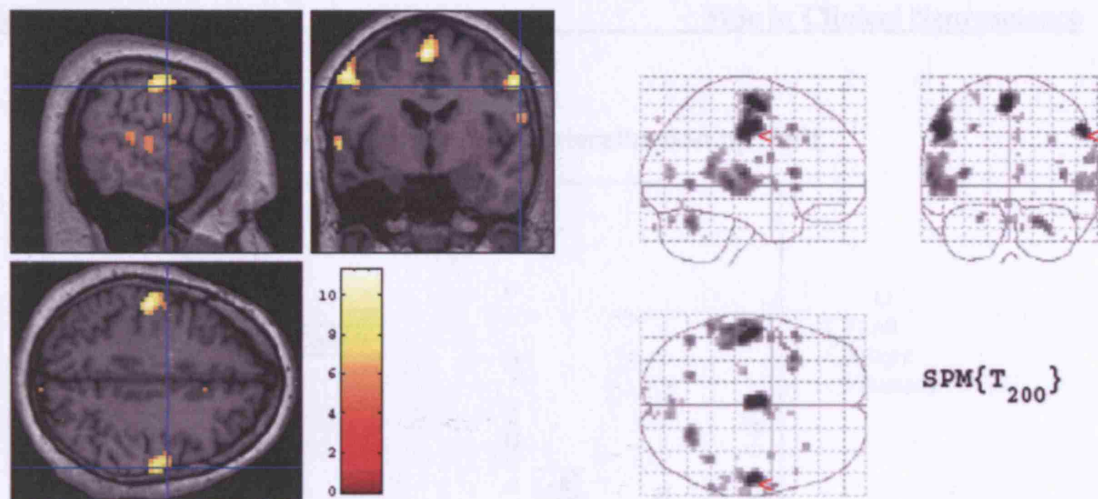
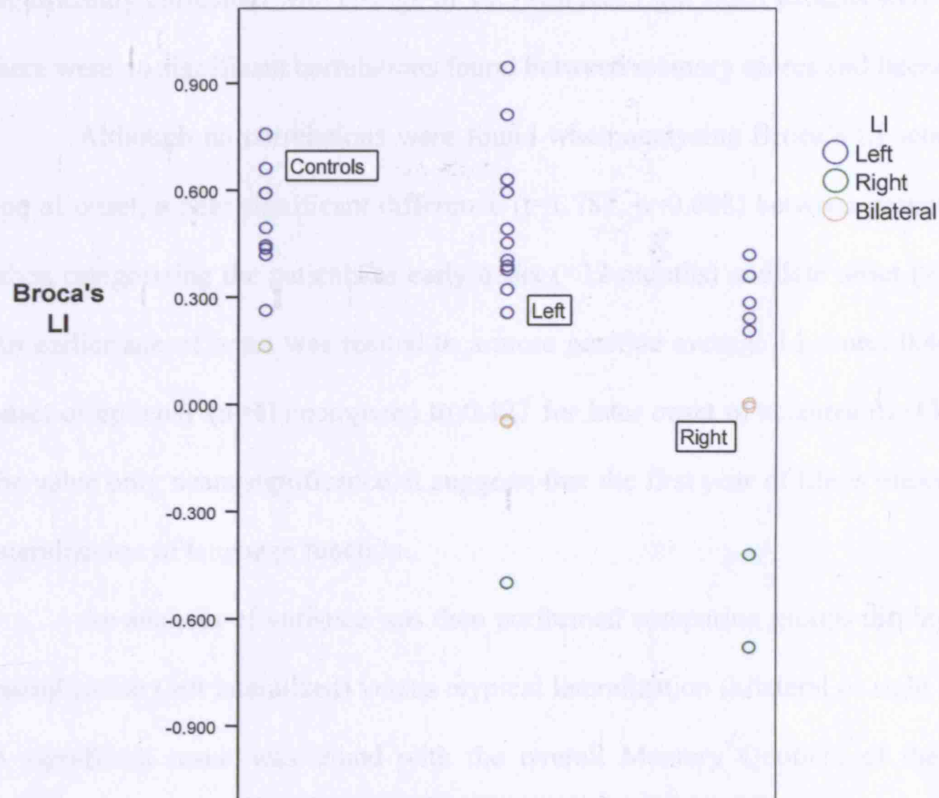


Figure 5. LI values calculated from fMRI activation –  
 Healthy control (previous page) and LHS subject (above)

Using the temporal lobe LI values to determine the lateralization of language results in a different number of subjects categorized as showing atypical language lateralization but the overall trend remains the same, i.e. controls show less atypical lateralization than both right and left temporal lobectomy subjects.

Graph 6. Language lateralization by fMRI



Broca's LI value was found to be strongly positively linked to the PIQ value (0.519,  $p=0.009$ ) and significantly related to FSIQ (0.491,  $p=0.015$ ), VIQ (0.429,  $p=0.037$ ) and change in VIQ (0.511,  $p=0.015$ ) using a Pearson's Correlation. It also neared significance with preoperative FSIQ values (0.384,  $p=0.078$ ) and change in FSIQ (0.407,  $p=0.060$ ). No significance was found when using the Temporal or Cerebellar LI scores. This suggests that normal lateralization is correlated with higher post-operative IQ scores and greater cognitive improvement following surgery and that atypical lateralization is linked with a poorer cognitive outcome. When analyzing the right and left sided subjects

separately for correlations between LI and cognitive output, left sided patients were significantly correlated with change in VIQ whereas right sided patients were not. Lastly, there were no significant correlations found between memory scores and lateralization.

Although no correlations were found when analyzing Broca's LI scores with the age of onset, a near significant difference ( $t=1.787$ ,  $p=0.088$ ) between groups was noted when categorizing the patients as early onset (<12 months) and late onset (>12 months). An earlier age of onset was related to a more positive average LI score: 0.403 for early onset of epilepsy ( $n=11$ ) compared to 0.127 for later onset of seizures ( $n=13$ ). Although the value only nears significance, it suggests that the first year of life is important for the lateralization of language function.

An analysis of variance was then performed comparing groups displaying normal lateralization (left lateralized) versus atypical lateralization (bilateral or right lateralized). A significant result was found with the overall Memory Quotient of the WMS test ( $F=4.704$ ,  $p=0.043$ ) and a near significant result was found with the full scale IQ ( $F=4.281$ ,  $p=0.052$ ). This supports the idea that positive cognitive outcome is linked to normal lateralization.

#### **5.4 Auditory and visual naming task**

The normative Hamberger (2003) test data reported scores of 48.7 out of 50 and for subjects with left TLE compared to 49.6 out of 50 for Control subjects in the Visual Naming Task and 45.4 for subjects with left TLE compared to 49.0 for Control subjects in the Auditory Naming Task. For the Visual Naming Task, we found that the left TLE

subjects had an average score of 43.3 and in the Auditory Naming Task their score was 39.6. Our preliminary findings were not quite comparable to the data found in the Hamberger test which can be explained by our small sample size as well as the great range in intellectual ability of the group. For example, excluding the lowest performing subject (FSIQ=53) gave scores of 44.6 for the Visual Naming Task and 45.7 for the Auditory Naming Task, which are much more comparable to the findings in Hamberger paper. The number of Tip-of-the-Tongues seen in the Hamberger trial were 1.9 and 3.7 for the Visual and Auditory Naming Tasks for healthy controls. The numbers for LTLE subjects in their paper were 5.0 and 10.5 respectively. In our study we found the numbers were 7.2 and 6.5 for Visual and Auditory Naming Tasks respectively, again excluding for the low functioning subject.

## 6. DISCUSSION

Previous studies have shown limited changes in intelligence at long-term follow-ups of temporal lobectomy compared to pre-operative data (Dlugos et al 1999; Alpherts et al 2004). In contrast to this, our findings show an overall average increase in FSIQ in both our right and left temporal lobectomy subjects. This improvement in IQ scores indicates that plasticity and compensatory mechanisms may be at work, allowing the affected areas of the brain to reorganize functionally, and to thereby return to pre-operative, or even pre-epileptic levels of performance. It is possible that a total remission of seizures, which is achieved by a majority of post-surgical subjects, has allowed for an accelerated cognitive trajectory in particular patients. This development is presumed to be highly individualistic and reliant on multiple factors, some of which are discussed in this study.

Previous literature has referred to two main components when discussing cognitive outcome: the 'functional integrity' of the tissue that is surgically resected, and the 'functional capacity' of the area symmetric to the damaged tissue, located in the contralateral hemisphere. Outcome can be said to be dependent, in these terms, on the essential nature, or integrity, of the tissue that is removed and the capacity of remaining structures to mediate and compensate for the removed tissue. Studies have, for example, shown that the volume of the hippocampal remnant and its subsequent shrinkage were correlated with postoperative memory outcome (Baxendale et al 2000; Sallie et al 2000; Jones 1987). These studies maintain that the amount and integrity of the hippocampus



that is spared during a resection is a significant factor in neuropsychological outcome. The processes by which functional areas reorganize and mediate may take years and may furthermore be paralleled by negative effects of surgery, such as the degeneration of remnant tissue and severed connections between the hippocampus and associated structures. Martin et al (1998), argue, for example, that dynamic processes within the remaining hippocampal structure can contribute to postoperative memory deterioration. Therefore, a long-term positive effect may be preceded by a decline in cognitive outcome, and specifically in those eloquent areas affected by the surgery. This type of cognitive trend is seen in many of our subjects, and in particular in those in the low pre-operative IQ range. Lower IQ value may reflect a history of more severe and diffuse epilepsy and more bilateral neurologic damage, as reported by Gleissner et al 2006. Chronic severe epilepsy may slow down or perhaps even essentially halt normal cognitive development; relief of the seizures and the right conditions for recovery may therefore allow the subject to resume normal cognitive development. In patients with high pre-operative IQ, the high IQ may already be indicative of a certain level of normal cognitive development and a general sparing of cognitive function by the seizure activity. The difference that we found between the pre-operative FSIQ groups may then signify that there is less 'room for improvement' for those with high pre-operative IQ compared to those with low pre-operative IQ.

Taking into account the effect of re-testing mentioned by some studies (Alpherts et al 2004) as well as the effect of using different, but comparable, tests to assess cognitive function in children compared to adults, the average change in FSIQ in our

study is substantial, and it speaks to an overall positive effect of surgery as an option in an increasing number of cases of intractable epilepsy in childhood.

In a further analysis of the intelligence scores, the literature (Blakemore et al 1967, Chelune et al 1993, Davies et al 1995, Ivnik et al 1987, Meier et al 1966, Selwa et al 1994) shows that a decrement of VIQ is seen in LTL patients in follow-up studies of 2 years. This decrement has furthermore been explained to be due to the removal of, or damage to, important areas for verbal intelligence and function, known to be located primarily in the left temporal lobe and hemisphere. Our results show instead that verbal intelligence improves post-surgically in the long-term. As was argued previously, it may take longer for this positive effect to become apparent than the 2 year follow-up that was used in some of these research papers. This was furthermore supported in a study by Alpherts et al (2004) where they reported that the largest gain in VIQ was seen 2 to 6 years after surgery. In their study they concluded that the initial decline seen in VIQ scores in LTL subjects is reversed over a longer time period and our findings are in line with their conclusion.

We also found that the size of resection showed a positive correlation with the change in VIQ over time; it furthermore seemed negatively associated with verbal retention memory measures from the WMS. These findings are interesting, if at first seemingly contradictory; the argument against more extensive resections is that the resection has a somewhat proportional impact on functional areas, which in left temporal lobectomy would primarily be language and memory. Our tentative results suggest that in the long-term analysis of outcome, subjects do both better and worse in those functional

areas dependent on the extent of resection. It could be thought that this correlation would differ between the side of resection because of the functional dominance of the hemispheres but when analysing the effect in left or right sided cases separately, the correlation became weaker. If more extensive surgery accounts for an improvement in verbal IQ but a decline in retention scores: firstly, what are the mechanisms behind this trade-off and second, what is the optimal compromise in terms of the extent of resection? A potential explanation to our findings could be that the original epileptogenic focus in those subjects with more extensive resections were more diffuse and affected more regions of the brain, therefore necessitating a larger resection originally and at the same time resulting in greater functional reorganization at an early stage. This would be in agreement with the ideas discussed previously: the removed tissue would be less essential, because of decreased functional integrity whereas the functional capacity of compensatory tissue would be increased.

It is difficult to assess the arguments for and against more comprehensive surgical resections. More extensive surgery would improve the chances of a seizure-free outcome and decrease the need for future medication, which have both been shown to be important in overall cognitive outcome. But more extensive surgery would also result in less obvious consequences in terms of memory, as indicated by the decreased WMS retention scores – effects often reported by post-surgical epileptic subjects but less readily defined by neuropsychological assessments.

It was also seen in our findings that when separating subjects into groups of low and high preoperative FSIQ ranges, the low-scoring pre-operative group saw a significant

increase in PIQ compared to the high functioning group. This again supports the idea that the patients who were already doing well pre-operatively and who had not suffered as much injury to eloquent areas did not need to recover as much as the patients in the low functioning group.

Age of surgery was found to be positively correlated with various measures of cognitive outcome, suggesting that greater post-operative IQ and WMS MQ scores were found in subjects who underwent surgery at an older age. Instead of being a positive predictor for cognitive outcome, this might instead reflect an inverse relationship between age of surgery and post-operative performance. Patients who did well pre-operatively and whose seizures did not greatly affect their cognitive function may have made the decision to postpone a major surgery because of the potential risks during development. This is perhaps something that could be addressed by detailed questionnaires and perusal of medical records.

The patients in our study represent an early average onset of seizures typical of hippocampal sclerosis pathology and onset of epilepsy was not a differential factor in cognitive outcome within our group. Seizure duration did not show significance with cognitive factors either but whether the subjects suffered from post-operative seizures and were still on medication were both found to be important in predicting cognitive outcome. This suggests that, for this rather small sample of hippocampal sclerosis patients, the most significant factor in long-term neuropsychological outcome is being seizure-free. Helmstaedter et al (2000) also found that this seemed true in adults, where both surgical and nonsurgical patients exhibited stable cognitive function on seizure remission.

The results of the fMRI studying brain activity following a verb generation task point to greater atypical lateralization in both left and right lobectomy subjects compared to controls. The left lobectomy subjects show the greatest spread in lateralization and the right temporal lobectomy subjects demonstrated the largest percentage of subjects with atypical lateralization. This does not fully agree with previous literature where predominantly left temporal lobectomy subjects experienced changed hemispheric dominance for language. Few studies have focused on lateralization of language in patients with right lobectomy, however.

Broca's LI scores showed a correlation with the IQ scores, suggesting that a larger positive LI score – indicative of left-sided dominance in language function – is associated with higher post-operative intelligence. Like previously discussed, this may signify that less injury and damage caused by the seizures has led to less reorganization of language function and less barriers to realizing full cognitive development.

A correlation was found for lateralization in left lobectomy patients and change in verbal IQ post-surgically. This may solely be an artefact of the small subject group of right sided subjects but may also be a real finding indicating that left lateralization is a predictor of good verbal intelligence outcome in patients with left, as opposed to right, lobectomy. It may reflect that a successful surgical operation was performed which did not interfere with eloquent areas related to verbal function and hence did not require functional reorganization and atypical lateralization of language. It is also the case that laterality assessments by fMRI have previously shown a tendency to suggest bilateral language representation in some studies (Kadis et al 2007; Vingerhoets et al 2004). In

those cases where fMRI suggests bilateral language representation, it may reflect that it shows overall activity and not only that which is specific to the task.

## **6.2 Limitations**

There were various limiting factors of this study. The LHS and RHS groups that were studied were small. This consequently makes the results and analysis more sensitive to data that is potentially not representative of the groups that we studied. It also sometimes precluded cross-sectional analysis between groups, especially when attempting to separate and categorize further within groups.

Handedness information was not collected for the temporal lobectomy subjects – this information could be important in future analysis of lateralization of language pre-surgically and post-surgically. Our fMRI data gave us an idea of the lateralization of language but pre-operative dominance by other measures, such as WADA or IAP would have provided an interesting comparison, especially considering the trend for atypical language lateralization seen in our results. Pre-operative data could have indicated whether subjects who showed atypical lateralization after surgery showed a similar organization before surgery and point to whether a change in lateralization was due to the effects of the epilepsy or was a consequence of surgery.

Another limitation of the study was its broad scope, in that it may have attempted to assess too many variables that could be of importance for determining long-term cognitive outcome. The large number of factors and possible directions for future

research do, however, highlight the multiple aspects that must be taken into consideration when recommending surgery for a child suffering from intractable epilepsy. Each variable needs to be studied in separation, if possible, from other variables to understand the true significance of various predictors and consequences of cognitive outcome of surgery.

### **6.3 Future directions**

There are many avenues to explore based on both the findings and the limitations of this study. Our results and discussion have posited that the extent and nature of the lobectomy are important in predicting patient outcome – both in terms of seizure control and long-term cognitive function. One interesting complement to the study would be to analyze the resected volume of each subject and to compare patient groups based on whether their entire hippocampus had been removed or whether they have remaining hippocampal and associated structures post-surgically. One relatively novel method that could help to evaluate the integrity of connections between important structures is DTI (diffuse tensor imaging) or tractography and is an area under current investigation for its potential in this field.

One of the main things to continue working with, additionally, would be a more detailed analysis of the various components of the Wechsler Memory Scale and what significance these scores have when compared longitudinally, as was done to a certain extent with the WAIS scores.

Our subjects all shared hippocampal sclerosis pathology. Another future direction, which is presently being undertaken by the co-contributors to this study, is not only to

determine the impact of right versus left lobectomy but to study other causes or pathologies underlying epilepsy, such as Dysembryoplastic Neuroepithelial Tumors (DNETs). Studying different neuropathologies would help clarify and differentiate between the progression of epilepsy, the success and impact of surgery as an option and would help identify the best treatment options for future patients.

Another important aspect of the long-term outcome in patients is the psychosocial impact that this surgery and epilepsy in general has on children. Our subjects completed various questionnaires evaluating quality of life and sociodevelopmental status. It would be interesting to evaluate the quality of life post-surgically compared to pre-surgically as well as to compare surgical with nonsurgical patients to determine whether surgery has a significant positive effect, as seen in adults (Jones et al 2002).

Further LI analysis could also be conducted where masks of both more broad – global comparison of activity within the two hemispheres – and more narrow – studying specific areas of the temporal lobe known for specific language and memory functions – regions of interest could be applied.

The findings from the Auditory and Visual Naming Tasks were preliminary and should be compared to non-surgical controls as well as right TLE subjects. The finding of Hamberger et al that there are separate auditory and visual naming centers in the temporal lobe could be an important factor in explaining certain lobectomy patients' specific memory difficulties post-surgically and highlights using this information in pre-surgical mapping of the volume to be resected.



## **6.4 Conclusion**

Temporal lobectomy has become an established and common-place surgical intervention for patients suffering from intractable epilepsy. A greater understanding of the factors that are important in determining long-term cognitive outcome of subjects that undergo surgery for intractable epilepsy holds the promise of fewer side effects of surgery, as well as providing us with academic insight into how the brain functions and compensates following seizures and surgical trauma.

Our study focused on the long-term cognitive effects of performing this surgery in children with a hippocampal sclerosis pathology underlying the epilepsy. Overall, the results of the study supports surgical resection in childhood patients who suffer from refractory epilepsy and suggests that surgery results in long-term stability and in some cases, improvement in cognitive outcome. The findings are furthermore supportive of the concept of plasticity and compensation in the immature brain following seizure remission and surgery.

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