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Medical and psychological outcomes following epilepsy surgery

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Medical and psychological outcomes following epilepsy surgery

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Declaration

I hereby declare that this thesis is the results of my own investigations, except where otherwise stated. All other sources are acknowledged by bibliographic references. This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree unless, as agreed by the University, for approved dual awards.

Chapter 7, *Temporal Lobectomy Impairs Spatial Binding in Visual Working Memory*, was written in collaboration with the following people:

• Mamdouh Alenazi, Neil M. Dundon, Mohammad Zia Ul Haq Katshu and Giovanni d'Avossa contributed to the design, development, and writing of the manuscript.

• Mamdouh Alenazi and Haya Al-Joudi collected the data.

• Faisal Alotaibi and Martyn Bracewell revised the manuscript.

• Mamdouh Alenazi, Haya Al-Joudi and Faisal Alotaibi contributed to patient recruitment.

Abstract

The predictors of postoperative seizure freedom are not clearly defined in the literature. The proposed predictive variables, e.g., age at seizure onset, duration of epilepsy and gender, have not been uniformly agreed upon as useful prognostic tools and there is a need for a large-scale study to identify suitable predictors. An understanding of such predictors would be useful in counselling patients in the preoperative work-up, with a view to create an economically efficient healthcare service in which patients have optimal post-operative outcomes. Many scientific papers reduce postoperative outcomes to seizure freedom exclusively, with limited papers evaluating the impact of epilepsy surgery on depression and anxiety, which can also have profound impacts on quality of life.

Epilepsy surgery grants researchers an opportunity to assess how brain functions are affected in the absence of particular cerebral structures. Knowledge of how brain function is affected by a lobectomy is important when consenting patients before surgery and informing them of possible post-operative deficits. One brain region in particular, the mesial temporal lobe, is of particular interest given it houses several structures that are alleged to help in memory formation and spatial cognition. However, there is contrasting evidence about the role of the mesial temporal lobe and the extent to which the mesial temporal lobe is involved in representing the environmental layout, the objects within in, as well as binding to the former to the latter (known as feature binding). In particular, it is not clear whether impairments of visual working memory are specifically spatial or rather generalize across visual feature dimensions (e.g., location, colour and shape) following focal temporal lobe lesions.

This thesis attempts to address aforementioned gaps in the literature. Firstly, I provide a comprehensive literature review of epilepsy, including the role of epilepsy surgery in its management. Thereafter, I provide a systematic review of the literature exploring post-operative psychiatric and neuropsychological outcomes in patients who undergo epilepsy

surgery in the absence of any pre-operative lesion/s on structural magnetic resonance imaging. Subsequently, I present original data showing the factors that predict post-operative seizure freedom in patients who have undergone resective surgery for epilepsy. The following chapter looks at the predictors of post-operative anxiety and depression in patients who have undergone resective epilepsy surgery. The penultimate chapter explores the factors that predict post-operative changes in working, visual and verbal memory in patients who have undergone resective epilepsy surgery. Finally, in a bench-side study conducted in Saudi Arabia, I studied a cohort of patients who had undergone temporal lobectomies for medically resistant temporal lobe epilepsy to establish whether impairments of visual working memory binding are specifically spatial or generalise across visual feature dimensions following focal mesial temporal lobe lesions.

With regards to seizure freedom, I found that pre-operative generalised seizures are less likely to exhibit seizure-freedom than patients without pre-operative generalised seizures. I also found that patients with temporal lobectomies were more likely to exhibit seizure-freedom than patients with extra-temporal. Patients with a unilateral local focus on electroencephalogram and those with a lower frequency of pre-operative seizures were more likely to be seizure free at two years. With regards to anxiety, I showed that postoperative anxiety is improved if patients were female, underwent right-sided cerebral resections or had lateral temporal lobe resections. With regards to depression, patients with pre-operative generalized seizures were less likely to exhibit depression than patients with other seizure types. Patients with left-sided hemisphere laterality were more likely to manifest postoperative depression than patients with right-sided hemisphere laterality. Finally, pre-operative non-generalised seizures were associated with an improved post-operative verbal memory whilst no pre-operative factors were independently associated with improved visual or working memory. With regards to the bench-side study, we showed that mesial temporal lobe pathology is associated with binding impairments that are spatially specific. Our results were in keeping with the idea that the left rather than right mesial temporal lobe structures were specifically involved in spatial binding.

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Glossary of abbreviations

AED	Anti-epileptic drug
BOLD	Blood Oxygenation Level Dependent
DNET	Dysembryoplastic neuroepithelial tumours
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
ETLE	Extratemporal lobe epilepsy
FDG	Fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
GSE	General Severity Index
HADS	Hospital Anxiety and Depression Scale
ILAE	International League Against Epilepsy
ITLE	Lateral (neo-cortical) temporal lobe epilepsy
MRI	Magnetic Resonance Imaging
mTLE	Mesial temporal lobe epilepsy
SPECT	Single-photon emission computerised tomography
vWM	Visual working memory
WMS	Wechsler Memory Scale

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Chapter 1. Introduction

Epilepsy is a chronic, non-communicable, neurological disease characterised by recurrent seizures: paroxysmal alterations of neurological function caused by the excessive, hypersynchronous discharge of neurons in the brain (Stafstrom & Carmant, 2015). According to the International League Against Epilepsy (ILAE), a clinical diagnosis of epilepsy can be made when any one of the following criteria can be met: (a) at least two unprovoked (or reflex) seizures occurring >24 hours apart; (b) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (c) diagnosis of an epilepsy syndrome (Krauss, 2014), **see table 1.** Globally, epilepsy is thought to affect approximately 70 million people (Ngugi et al., 2010) and epilepsy patients have been shown to have higher rates of mortality and morbidity (Hamilton et al., 2020; Levira et al., 2017; Thurman et al., 2017), including more physical and psychological co-morbidities, compared to the general population (Rai et al., 2012). In high income countries, epilepsy patients have been shown to have mortality rates 1.6-3.0 times higher than the general population (Thurman et al., 2017), and up to 7.2 times higher in low- and middle income countries (Levira et al., 2017).

Conceptual definition of epilepsy, from the International League Against Epilepsy
An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.
Operational (practical) definition of epilepsy, from the International League Against Epilepsy
Epilepsy is a disease of the brain defined by any of the following conditions 1. At least two unprovoked (or reflex) seizures occurring >24 h apart 2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years 3. Diagnosis of an epilepsy syndrome Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

Table 1. The conceptual and operational definitions of epilepsy. From Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*. 2014;55(4):475-482. doi:10.1111/epi.12550

1.1 Classification of epilepsy

In 2017, the ILAE revised the terminology and classification of seizures (Brodie et al., 2018), see **figure 1.** There are three layers to classifying epilepsy: (a) seizure type(s) – defined by the type of onset (focal, generalised, unknown); (b) epilepsy type (focal, generalised, combined generalised and focal, unknown), and (c) epilepsy syndrome. The ILAE have defined focal seizures as “originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures” (Berg et al., 2010). Generalized from onset seizures have been defined as “originating at some point within, and rapidly engaging, bilaterally distributed networks” (Berg et al., 2010). Focal seizures can be further stratified according to whether a person has retained awareness and by the earliest prominent motor onset or nonmotor onset features. Generalised and unknown onset seizures may be optionally subdivided into motor or nonmotor

onset, see **figure 2.** The epilepsy type and epilepsy syndrome diagnoses are made using a cluster of clinical features, including the seizure type, electroencephalogram (EEG) changes, brain imaging abnormalities, and genetic analyses that add up to a recognisable pattern (Brodie et al., 2018).

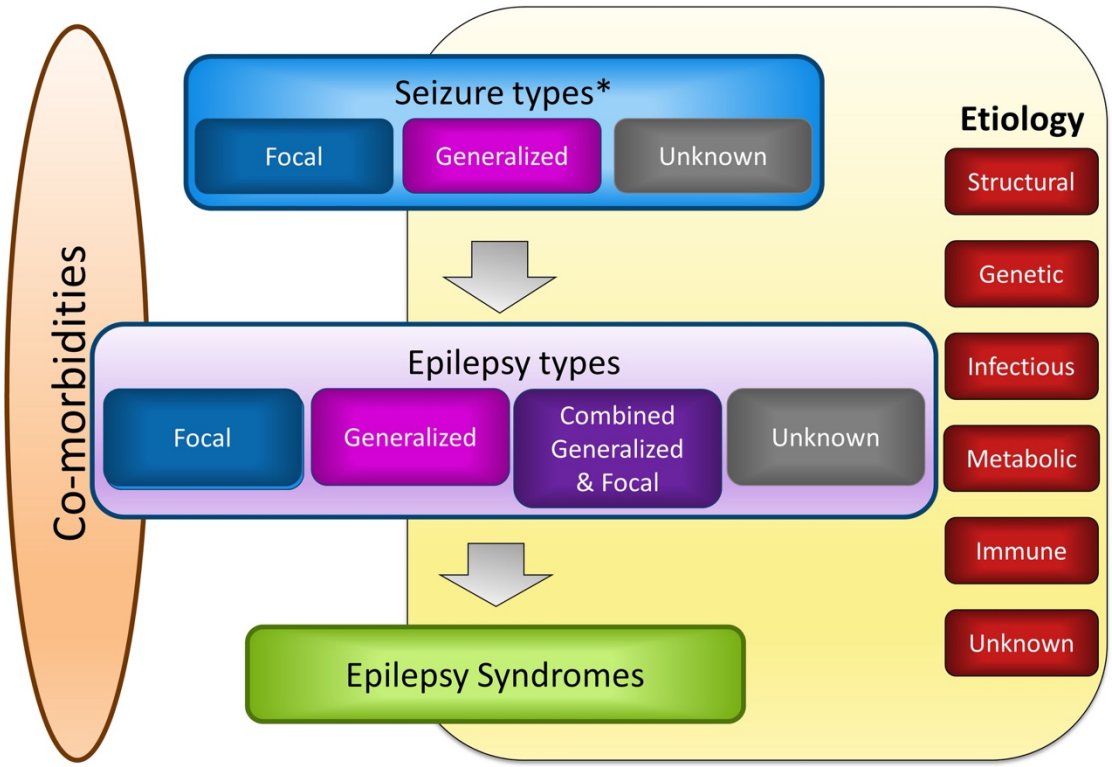


Figure 1. Framework for the classification of the epilepsies. * Denotes onset of seizure. From Scheffer, I.E., Berkovic, S., Capovilla, G., Connolly, M.B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G.W., Moshé, S.L., Nordli, D.R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y.-H. and Zuberi, S.M. (2017), ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia, 58: 512-521. doi:10.1111/epi.13709

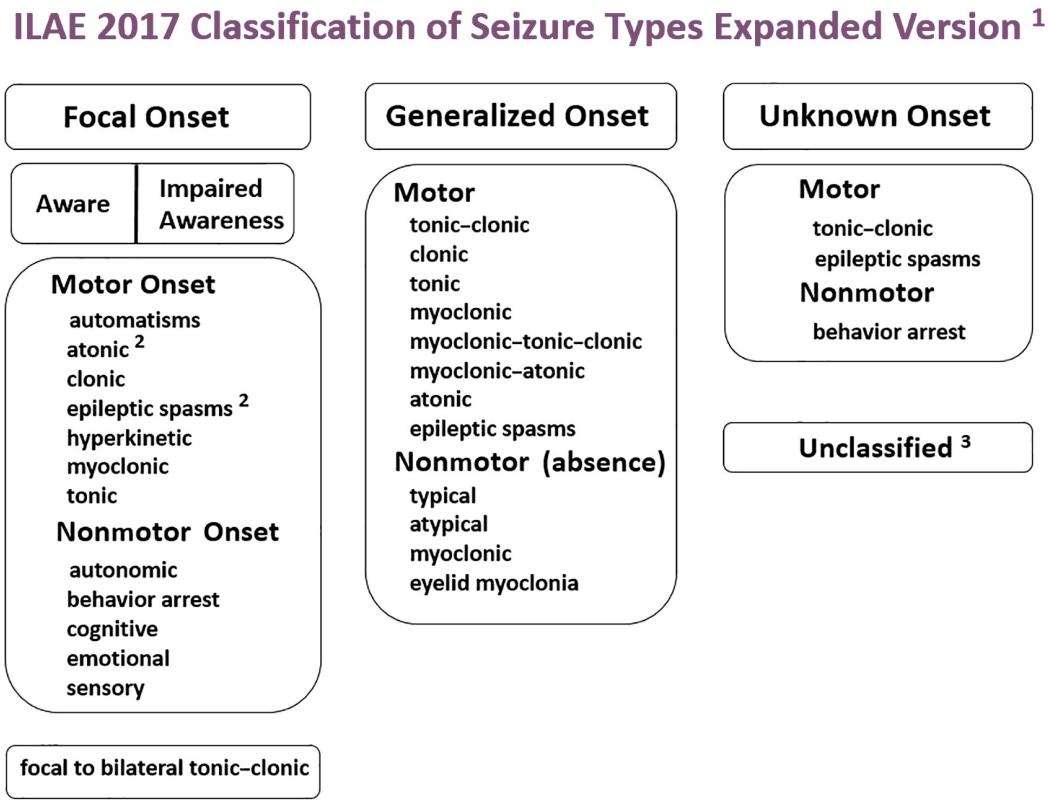


Figure 2. The expanded ILAE 2017 operational classification of seizure types. From Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):522-530. doi:10.1111/epi.13670

1.1.1 Temporal Lobe Epilepsy

Temporal lobe epilepsy is the most common form of focal epilepsy in adults (Téllez-Zenteno & Hernández-Ronquillo, 2012), and is thought to comprise approximately 30-35% of all epilepsies (Panayiotopoulos, 2005). Temporal lobe epilepsy can be broadly differentiated into two subtypes: (a) mesial temporal lobe epilepsy (mTLE) and (b) lateral (neocortical) temporal lobe epilepsy (lTLE).

Hippocampal sclerosis has been shown to affect approximately 60% of patients with mTLE (Kanda, 2016; Thom, 2014), and may be histopathologically identified as segmental pyramidal cell loss in CA 1, CA 3, and CA 4 regions (Blümcke et al., 2012; Nayak & Bandyopadhyay, 2020). The 2013 ILAE classification segregates hippocampal sclerosis into typical (type 1) and atypical (type 2 and 3) groups, based on the histological patterns of

subfield neuronal loss and gliosis (Thom, 2014). A childhood history of febrile seizures is a strong risk factor for the development of MTLE (French et al., 1993; Harvey et al., 1995). The causes of LTLE are more varied and can include benign tumours, malformations of cortical development, cavernous angiomas, glioma and gliosis from encephalitis or meningitis. LTLE generally has a less favourable surgical outcome compared to MTLE, which may be a result of poor localisation and resection of the epileptogenic zone (Kennedy & Schuele, 2012; SV et al., 1996). A comparison of the ictal semiology between MTLE and LTLE is outlined in **table 2.**

Sign/symptom	mTLE	LTLE
Seizure duration	>1 minute	<1 minute
Ambiguous onset/offset	No	Yes
Visceral/epigastric sensation	More likely	Less likely
Nonspecific auras	Less likely	More likely
Auditory hallucination	Less likely	More likely
Oral automatism	More likely	Less likely
Manual automatism	More likely	Less likely
Leg movements	Yes	No
Dystonic posturing	Yes	No
Clonic movement	Less likely	More likely
Body shifting	More likely	Less likely
Hyperventilation	Yes	No
“Dreamy state”	Yes	No
Fear	Yes	No
Searching	More likely	Less likely
Postictal cough/sigh	More likely	Yes

Table 2. A comparison of ictal semiology between MTLE and LTLE. From Kennedy JD, Schuele SU. Neocortical temporal lobe epilepsy. *J Clin Neurophysiol*. 2012;29(5):366-370. doi:10.1097/WNP.0b013e31826bd78b

Auras are commonly defined as *“a subjective sensation experienced by the patient during a seizure”* and are a cardinal feature of mesial temporal lobe epilepsy (Ferrari-Marinho et al., 2012). In order of prevalence, auras can include ascending epigastric sensation, experiential

symptoms, fear, déjà vu or jamais vu, auditory hallucinations and illusions, and olfactory hallucinations (Panayiotopoulos, 2005). Oro-alimentary automatisms are typical of MTLE only if preceded by epigastric aura, fear and mental symptoms, alone or in combination (Panayiotopoulos, 2005). Over 90% of patients with mTLE report feeling physical symptoms, often an epigastric sensation that has a rising character (Elger & Schmidt, 2008). Awareness is generally preserved at the onset of an MTLE seizure, but loss of full consciousness occurs shortly afterwards, with an initial motionless stare, and automatisms, which typically are oro-alimentary, vocal or gestural.

Behavioural automatisms that point to a seizure originating in the MTLE tend to be oro-alimentary in nature and can include chewing, swallowing or lip-smacking, although gestural actions such as fidgeting, repetitive motion, walking, running or sexual actions are also common and prolonged (Baxendale et al., 2020). Automatisms in the limbs are typically ipsilateral to the epileptogenic focus, with contralateral dystonic posturing. Headaches and confusion are commonly reported, as can post-ictal nose rubbing which occurs ipsilateral to the epileptogenic zone (Baxendale et al., 2020; Geyer et al., 1999)

The semiological features of lateral temporal lobe epilepsy (or neocortical temporal lobe epilepsy) include auditory, vestibular and complex visual hallucinations, and aphasia and focal sensory-motor phenomena (Blair, 2012; ILAE, 1989). As LTLEs are relatively less common that MTLE seizures they are not as well characterised (Blair, 2012). Some of the most common causes of LTLE include hamartoma, glioma, cavernoma, DNET, post-traumatic change and neuronal migration defect (Blümcke, 2009; Tassi et al., 2002). Unlike mTLE however, lateral temporal lobe epilepsy is not linked to febrile convulsions (Baxendale et al., 2020).

Interictal scalp, according to the evidence, is not particularly effective at differentiating between LTLE and mTLE (Bercovici et al., 2012). In a study published by Lee et al., (2005), the effectiveness of the interictal EEG was investigated in patients with LTLE and was reported to only be of value in 9 out of 17 of patients (52%) with LTLE. O'Brien et al., (1996) compared 46 patients with MTLE vs. LTLE by EEG and reported that patients with MTLE had more rapid rhythmic activity (>4 Hz). In contrast, lTLE patients were more prone to develop bilateral ictal EEG changes (O'Brien et al., 1996).

1.1.2 Extratemporal lobe epilepsy

The epileptogenic foci in extratemporal lobe epilepsy are located outside the temporal lobe (Dash & Tripathi, 2014). There is no robust evidence that patients with different seizure foci have any significant differences in long-term seizure freedom (Mohan et al., 2018).

Frontal lobe seizures

Statistically, frontal lobe seizures are the second commonest seizure type in adults after temporal lobe (Dash & Tripathi, 2014). Frontal lobe epilepsy can be further broadly stratified into dorsolateral frontal (further subdivided into central lobe, prefrontal and premotor cortex), mesial frontal (further subdivided into the primary motor cortex for the lower limb, the supplementary sensorimotor area (SSMA), the anterior cingulate cortex and the prefrontal cortex), and bifrontal seizures. Generally, auras are less common in frontal lobe seizures compared to temporal lobe seizures (Dash & Tripathi, 2014; Palmini & Gloor, 1992). Repetitive, proximal upper extremity movements and loss of consciousness are reportedly more common in the frontal lobe seizures vs. mesial temporal lobe seizures (Kotagal et al., 2003). Interestingly, a meta-analysis, Téllez-Zenteno et al., (2005) showed that frontal lobe resections produce the worst long-term seizure free rates among the resective surgeries (mean 27%, median 34%), as compared to temporal and other extratemporal surgical procedures. Several postulates have been forwarded to explain these poorer outcomes,

including inability to surgically resect the entire epileptogenic zone due its proximity to eloquent cortex. Moreover, the epileptogenic zone may be larger in the frontal lobe and seizure spread may be particularly extensive (Téllez-Zenteno et al., 2005).

Occipital lobe seizures

Occipital lobe epilepsies account for approximately 5 to 10% of all epilepsies (Adcock & Panayiotopoulos, 2012) and the ictal symptoms are typically visual (e.g. visual hallucination, visual illusion, blindness, or a field defect) and oculomotor (Kun Lee et al., 2005). Unlike temporal lobe epilepsy, scalp EEG has limited diagnostic utility in identifying occipital lobe epilepsy and formulating a management plan (Appel et al., 2015). In one study, only 17% of patients with occipital lobe epilepsy had scalp EEG showing occipital onset of seizure activity (Salanova et al., 1992). Harward et al., (2018) conducted a meta-analysis of 27 prospective or retrospective case series reporting postoperative seizure outcomes and associated factors in patients undergoing surgery for drug-resistant occipital lobe epilepsy were analysed. Surgical resection for occipital lobe epilepsy was associated with favourable outcomes with approximately 66% of patients achieving postoperative seizure freedom, but there was a substantial risk of visual decline following surgery.

Parietal lobe seizures

Approximately 2% of epilepsy patients are thought to experience parietal lobe seizures (Salanova, 2012; Semah et al., 1998). The auras associated with parietal lobe epilepsy typically include contralateral somatosensory sensory abnormalities, such as numbness or tingling (Salanova, 2012). Infrequently, patients may experience disturbances of body image or a feeling that an extremity has spatial displacement (Salanova, 2012). In a study of 50 patients (temporal, n=17; parietal. N=16; frontal, n=17) with pharmacoresistant focal

epilepsy, (Ristić et al., 2012) reported that scalp EEG readings of parietal lobe epilepsy patients had greater variable scatter of interictal discharges and a lower localisation value of ictal recordings compared to the other two epilepsy subtypes, suggesting an increased probability of misidentification and mislocalisation of parietal lobe epilepsy (Ristić et al., 2012). In a case series of forty patients (23 females and 17 males) with pharmacoresistant parietal lobe epilepsy, satisfactory surgical outcome – defined as Engel Classes I and II – were obtained in 67.5% of patients (Binder et al., 2009).

1.2 Psychiatric sequelae of epilepsy

Epilepsy is associated with profound psychiatric morbidity (Au et al., 2002; Baxendale et al., 2020). Multiple factors leading to the neuropsychiatric features of the condition have been put forward, including the chance that epileptiform discharges originate from within the central nervous system and trigger an emotional response due to limitations imposed by seizures, social stigma and side-effects from antiepileptic drug treatments (Baxendale et al., 2020). Approximately 50-60% of sufferers experience mood disorders, particularly anxiety and depression (Beyenburg et al., 2005; Fiest et al., 2013). Compounding the issue is the fact that epilepsy sufferers face higher levels of unemployment, lower marriage rates and social isolation (Jacoby, 1995; Mlinar et al., 2016; Riasi et al., 2014).

Psychopathological disorders are considered to be more frequent in patients with temporal lobe vs. extratemporal lobe epilepsy, but results are not always consistent (Garcia, 2012). In a study investigating a range of neuropsychiatric disorders (including depression and psychosis) in a sample of 319 Australian patients no significant difference was noted in the prevalence of neuropsychiatric disorders between patients with temporal and extratemporal lobe epilepsy (Adams et al., 2008). Sanchez-Gistau et al., (2010) investigated 308 patients

who were classified as having temporal or extratemporal epilepsy. These patients then underwent structured interviewing and their psychopathological disorders, if any, were stratified according to the DSM IV. The investigators showed that temporal lobe epilepsy patients had a 22% lifetime prevalence of major depressive disorder, and a previous one-year prevalence of 14.6%. Extra-temporal lobe epilepsy sufferers had a lifetime prevalence of 14.6% and a previous one-year prevalence of 6.5%. Several psychiatric disorders were assessed (including somatoform disorders, anxiety disorders, mood disorders, psychotic disorders and substance abuse disorders) and only previous year prevalence of major depressive disorder was shown to be significantly different between the two groups, with temporal lobe epilepsy sufferers having a higher rate of major depression.

Interestingly, in a UK study of temporal lobe epilepsy patients with a range of comorbid pre-surgical psychiatric diagnoses (mood disorders, postictal psychosis, anxiety disorders, non-epileptic seizures and interictal psychosis) those with an underlying pre-surgical psychopathology were less likely to be seizure free after epilepsy surgery (Cleary et al., 2012). A pre-operative history of secondary generalised tonic–clonic seizures has was shown to be independent predictor of de novo psychopathology (Cleary et al., 2012).

1.2.1 Depression

Modern research has shown a bi-directional relationship between depression and epilepsy. Not only are epilepsy sufferers more likely to develop depression, but patients with depression face a higher risk of developing epilepsy (Frucht et al., 2000; Gnanavel, 2017; Hesdorffer et al., 2000). It has been suggested that this relationship could be caused by an underlying pathology in the serotonin (5-HT) system of epilepsy patients which can lowers the threshold for seizures, while also increasing the risk of depression and sudden death

(Richerson & Buchanan, 2011).

In a systematic review (Macrodimitris et al., 2011) of 13 studies, the baseline prevalence of depression in patients undergoing epilepsy surgery was shown to range between 24-38%, but no higher than epilepsy patients treated medically. De novo depression post-surgery has also been well-documented and prevalence rates have been shown to range from a high of 18.2% of interictal dysphoric disorder cases ten months post-surgery (Blumer et al., 1998) to a low of 4% de novo depression cases one year post-surgery (Reuber et al., 2004).

With regards to postoperative depression, studies have not found any effects of laterality, age, sex or age of onset (Altshuler et al., 1999; Meldolesi et al., 2007; Spencer et al., 2003). Seizure freedom has inconsistently been shown to be a predictor of improvement in depression post-operatively (Spencer et al., 2003). Moreover, studies have shown a relationship between cognition and depression, particularly pre-surgical depression as a predictor of post-surgical memory change in adults who underwent temporal lobe resections (Busch et al., 2011). Busch et al., (2011) studied Wechsler Memory Scale-III and Beck Depression Inventory-II before and after temporal lobe resection (left = 110, right =101 and patients were divided into two groups: clinically elevated depressive symptoms or not depressed. The results indicated that elevated pre-surgical mood depressive symptomatology was a risk factor for post-surgical memory decline, which was independent of seizure outcome. Interestingly, in a seminal study conducted by Pope et al., (2019) pre-surgical cognitive and behavioural measures of frontal lobe dysfunction were reported to be significant predictors of poor psychiatric outcome following temporal lobe epilepsy surgery. Indeed, increased Wisconsin Card Sorting Test perseveration errors and self-reported dysexecutive behaviours prior to surgery were independently predictive of increased depressive morbidity postoperatively (Pope et al., 2019). Other studies have also reported

an interaction between depressive symptoms and cognitive impairment in non-surgical candidates with left, but not right-sided, seizure foci (Dulay et al., 2004; Helmstaedter, 2004; Paradiso et al., 2001)

1.2.2 Anxiety

The prevalence of anxiety symptoms is reportedly higher in patients with epilepsy compared to the general population and patients with several chronic medical disorders (Beyenburg et al., 2005). Seizure frequency has been linked with severity of anxiety in some (Jacoby et al., 1996) but not all studies (Choi-Kwon et al., 2003), and the risk of anxiety disorders seems to be higher in patients with focal temporal lobe seizures compared to other subtypes (Beyenburg et al., 2005). γ-aminobutyric acid, or GABA, is a well-recognised inhibitory neurotransmitter in the central nervous system, and abnormalities in GABA receptors have been hypothesises to be the 'missing link' in the connection between anxiety and epilepsy (Chapouthier & Venault, 2001; Möhler, 2006). This hypothesis is supported by the observation that some agents, including the GABAergic antiepileptic drugs (e.g., gabapentin and sodium valproate), as well as benzodiazepines have antiepileptic as well as anti-anxiolytic effects (Ashton & Young, 2003; Beyenburg et al., 2005).

The prevalence of anxiety disorders in candidates for epilepsy surgery has been reported to be between 10 and 30% (Beyenburg et al., 2005; Manchanda et al., 1996). Some studies have reported that pre-operative anxiety is a risk factor for poor seizure control after epilepsy surgery (Cleary et al., 2012; Kanner et al., 2009), but many of these studies are retrospective and classed as Class IV evidence. Interestingly, a prospective, five-year study showed that pre-surgical anxiety does not have any substantial impact on postsurgical seizure outcome for up to five years after surgery (Altalib et al., 2018). In one study, Prayson et al., (2017)

investigated the potential role of side *and* site of surgery in anxiety symptom change after epilepsy surgery in 228 patients and determined the base rate of psychological change at the individual level. Patients with left temporal lobe epilepsy showed greater anxiety symptoms prior to surgery than patients with left frontal lobe epilepsy. Similar differences in pre-operative psychological status were not apparent in patients with right-sided seizure foci. Following surgery, patients who underwent left temporal lobe resection reported a reduction in symptoms of anxiety, while those who underwent left frontal lobe resection did not show substantial post-operative changes in anxiety. Anxiety outcomes were shown to reduce significantly after right-sided surgery and were similar in temporal lobe and frontal lobe resection patients.

1.3 Cognitive sequelae of epilepsy

According to the literature (Martin et al., 2011; Wang et al., 2020) cognition is broadly defined as the brain's ability to perceive the objective world, including the environment and people, attention, judgement, performing complex mathematical calculation, language ability and executive function, etc. Cognitive dysfunction has been reported in epilepsy patients compared to healthy controls who are of similar age (Hermann & Seidenberg, 2007). Epilepsy patients may suffer from transient epileptic amnesia and progressive long-term forgetting, in which newly acquired memories fade over weeks to months (Butler & Zeman, 2008; Holmes, 2015). Perhaps because of its complex nature, memory dysfunction is reportedly the most common cognitive problem in epilepsy sufferers (Hendriks et al., 2002; Leritz et al., 2006) and the frequency of memory problems in patients with refractory epilepsy is estimated to be between 20-50%

Patients with temporal lobe epilepsy are particularly vulnerable to cognitive decline, including

memory dysfunction, compared to extratemporal lobe epilepsy patients (Hendriks et al., 2004; Stretton & Thompson, 2012). Given the associated underlying neuroanatomy involved in temporal lobe seizures, such as the hippocampus and surrounding medial temporal lobe structures, these findings are unsurprising. The lateralisation of the epileptogenic focus has been shown to be a significantly risk factor in determining both the severity and nature of memory dysfunction (Hendriks et al., 2004). Patients with a unilateral left temporal lobe epileptic focus, they argue, face significantly increased risks of experiencing memory difficulties compared to patients with right temporal lobe epilepsy. In one study (Fong et al., 2011) the pre- and post-operative scores for the Wechsler Memory Scale III and Boston Naming tests were assessed for 29 patients, of which 18 patients underwent mesial temporal lobe resections (10 left, 8 right). These cerebral structures were not resected in the remaining patients (nine left, two right). The investigators showed that patients were more likely to decline on memory measures following removal of the mesial temporal lobe structures, notably worse on the left-hand side, compared to operations that preserved the mesial temporal lobe structures (Fong et al., 2011). Other studies have shown that verbal memory deficits are most common in patients with left mesial temporal lobe epilepsy, while in right mesial temporal lobe epilepsy patients, visual memory deficits are the most frequent observations (Oddo et al., 2012).

Cognitive dysfunction can have several causes, the most important being brain lesions, seizures, epileptic dysfunction, and treatment (Christoph Helmstaedter, 2013). Whereas problems originating from lesions are mostly static and irreversible, problems associated with seizures and treatment are more dynamic and generally reversible (Christoph Helmstaedter, 2013). In one study, Wang et al., (2020) investigated the risk factors for cognitive impairment in 257 adult epileptic patients. The investigators showed that the specific cocktail of antiepileptic drugs, depression, education level and seizure frequency affected cognitive function. Interestingly, good seizure control, healthy psychological states,

single-drug treatment and high education attainment, were shown to be antidotes to neurocognitive decline.

1.4 Management of epilepsy

Antiepileptic drugs are the mainstay of epilepsy treatment (Scheffer et al., 2017; Thijs et al., 2019) and operate by increasing inhibition, decrease excitation or prevent the aberrant burst-firing of neurons. The overall goal of pharmacological treatment is to eliminate seizures or reduce their frequency to the maximum degree possible, to evade the adverse effects associated with long-term treatment, and to aid patients in maintaining or restoring their usual psychosocial and vocational activities, and in maintaining a normal lifestyle (Goldenberg, 2010). As stipulated by the National Institute of Clinical Excellence (Chadwick et al., 2009), the safety, cost, ease of use, pharmacokinetics are considered before treatment begins. The range of antiepileptic agents and their side effect profiles are outlined in **table 3.** Monotherapy is often the treatment of choice as it reduces teratogenicity, long-term toxic effects, and is simple meaning patients are more likely to comply with the treatment (Browne et al., 2000; St Louis et al., 2009).

Approximately 20% to 30% of patients have epilepsy that is resistant to medical therapy despite efforts to find an effective combination of antiepileptic drugs (Goldenberg, 2010). Although there is no uniformly accepted definition of pharmaco-resistance (Pati & Alexopoulos, 2010), the International League Against Epilepsy (ILAE) has defined pharmacoresistance as the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Sheng et al., 2018). In one prospective study, Kwan & Brodie (2001) demonstrated that 47% of patients with new-onset epilepsy

became seizure-free on the first antiepileptic drug, 32% on the second antiepileptic drug, and 9% on the third antiepileptic drug. Forth and subsequent antiepileptic drugs had at most a 5% chance of bringing seizure remission.

For some individuals with medically refractory epilepsy, neurosurgery represents the best treatment option available to them (Spencer & Huh, 2008). Resective surgery is a consideration in patients with drug-resistant, uncontrolled, disabling focal epilepsy if the seizures originate from a region that can be removed with minimal risk of disabling neurologic or cognitive dysfunction (Miller & Hakimian, 2013). In one USA-based, multicenter, controlled, parallel-group clinical trial of 38 participants (18 men and 20 women) resective surgery in addition to antiepileptic drug treatment for pharmacoresistant mesial temporal lobe epilepsy resulted in a lower probability of seizures during a two year follow up compared to continued antiepileptic drug treatment alone (Engel et al., 2012). Early surgery has also been shown to provide the best opportunity for seizure remission, minimizing adverse social and psychological consequences and premature death (Janszky et al., 2005; Vakharia et al., 2018). A thorough and extensive pre-surgical evaluation is necessary to ensure optimal outcomes following epilepsy surgery.

Adverse events	**GBP**	**TPM**	**LTG**	**LEV**	**RFN**	**VGB**	**OXC**	**PER**	**LCM**
CNS effects									
Somnolence	+	++	+	+	+	+		++	
Insomnia								+	
Sedation/psychomotor slowing		(+)							
Depression				(+)		+			
Behavioural problems		++		+	+	++			
Psychotic episodes	+	+		+		++		+	
Cognitive impairment		+					+		
Ataxia								+	+
Dizziness	+	++	+	+	+	+	++	++	++
Encephalopathy						++			
General issues									
Hypersensitivity		+	+				+		
Rash			+				+		
Fatigue		+			+			+	
Weight gain	+					+		+	
Weight loss		+			+				
Seizure aggravation	+				(+)	++		+	
Splanchnic and humoral system									
Leukopoenia							(+)		
Hyponatremia							+		
Gastrointestinal	(+)			(+)			+		
Pancreatitis	(+)								

Table 3. Adverse effects of antiepileptic drugs. From Hanaya, R., & Arita, K. (2016). The New Antiepileptic Drugs: Their Neuropharmacology and Clinical Indications. *Neurologia medico-chirurgica*, *56*(5), 205–220. https://doi.org/10.2176/nmc.ra.2015-0344

1.5 Pre-surgical evaluation of epilepsy surgery

The goal of the pre-surgical evaluation of drug-resistant epilepsy patients is the localisation of the epileptogenic substrate that can be surgically resected.

1.5.1 Electrophysiological investigations

There are four overall aims of scalp video electroencephalography (VEEG) (Mani, 2014):

1. To confirm that the individual has true epileptic seizures (4-10% of patients in surgical programs have co-morbid psychogenic non-epileptic seizures; if untreated before surgery, non-epileptic attacks often become more florid and present a major management problem).
2. To characterize electroclinical features and to establish whether these are concordant with other data magnetic resonance imaging (MRI, functional imaging, psychometry).
3. To demonstrate epileptogenicity of the presumed pathological substrate of refractory epilepsy.
4. To identify other potential epileptogenic foci.

The aim is to record ictal (seizure-related) and interictal epileptic activity (from the irritative zone) and demonstrate the correlation between the signs and symptoms of seizures and their corresponding EEG pattern (Bromfield et al., 2006; Miller & Hakimian, 2013). Unfortunately, the electrical current recorded by scalp EEG can be distorted by high-resistance tissues such as the skull, meninges, and skin (Enatsu & Mikuni, 2016). Therefore, scalp VEEG may limited in its detection, precise localization, and determination of the extent of epileptogenic zones.

Stereotactically-inserted depth electrodes (stereoelectroencephalography) is indicated when there is a lack of a potentially epileptogenic structural lesion, multiple putative epileptogenic lesions (zones), scalp EEG with multifocal or no interictal epileptiform discharges, indeterminate or multifocal ictal onset zone(s), discordant non-invasive findings, or if the ictal onset zone is in close proximity or overlaps with eloquent cortex (Siegel, 2004)

1.5.2 Magnetoencephalography

Magnetoencephalography (MEG) is a non-invasive technique that maps interictal magnetic dipole sources onto MR imaging to produce a magnetic source image (Tovar-Spinoza et al., 2008). The question of whether MEG has advantages over EEG has been widely discussed (Iwasaki et al., 2005; Tovar-Spinoza et al., 2008). The advantage of MEG over scalp EEG is that it has greater resolution owing to the lack of distortion of the magnetic signal by the meninges or skull (Singh, 2014).

1.5.3 Brain imaging

Various methods of brain imaging are available, such as structural / functional magnetic resonance imaging, positron emission tomography and single-photon emission computerised tomography (SPECT).

Structural magnetic resonance imaging (MRI)

Structural MRI is the main neuroimaging technique for identification of an epileptogenic lesion (Duncan et al., 2016). The presence of a lesion on structural MRI has been shown to be positively predict seizure freedom after surgery (de Tisi et al., 2011; Téllez-Zenteno et al., 2010), and approximately 15–30% of patients with refractory focal epilepsy do not have distinct lesions on MRI (Bien et al., 2009). The principal pathologies identified on structural MRI are hippocampal sclerosis, malformations of cortical development such as focal cortical dysplasia, cavernomas, dysembryoplastic neuroepithelial tumours (DNETs), low-grade tumours (gliomas), arteriovenous malformations and focal cerebral damage (Téllez-Zenteno et al., 2010).

Functional magnetic resonance imaging (fMRI)

Functional MRI is a technique that maps the physiological or metabolic consequences (blood oxygenation and flow) of altered electrical activity in the brain (Beers & Federico, 2012; Kesavadas & Thomas, 2008). The most common fMRI technique detects blood flow-related changes in venous deoxyhemoglobin content, the so-called Blood Oxygenation Level Dependent (BOLD) contrast technique, to generate functional maps of neural activation and deactivation (Beers & Federico, 2012).

The main use of fMRI in pre-surgical evaluations is the delineation of brain substrates for specific functions, such as the motor cortex, as well as expressive and receptive language areas, and their anatomical relation to areas where surgery is planned (Duncan, 1997). The sensitivity and specificity of fMRI for language lateralisation is 80%–90% and has replaced Wada testing (intracarotid sodium amobarbital procedure) in nearly all cases (Duncan, 2019). If planned resection margins are close to eloquent cortex, functional mapping techniques such as language and motor fMRI may help to delineate the boundaries of a safe resection (Duncan, 2019).

Positron emission tomography

Positron emission tomography (PET) is a technique that measures physiological function by looking at blood flow, metabolism, neurotransmitters, and radiolabelled drugs (Berger, 2003). Various PET studies, such as measurements of glucose, serotonin and oxygen metabolism, cerebral blood flow and receptor bindings are available for epilepsy (Sarikaya, 2015), see **table 4.** Accumulation of the radiolabelled glucose analogue 18-fluorodeoxyglucose (FDG) allows measurement of the rate of consumption of glucose (Berger, 2003). A meta-analysis performed by Willmann et al., (2007) showed that ipsilateral PET hypometabolism was a possible indicator for good postoperative outcome in presurgical evaluation of drug-resistant TLE, although the actual diagnostic added value was found to be questionable and unclear. PET was found not appear to add value in patients localized by ictal scalp EEG and MRI (Willmann et al., 2007).

PET study	**Findings**
Interictal ^{18}F-FDG	Usually reduced metabolism
Ictal ^{18}F-FDG	Increased and decreased metabolism (complex pattern)*
Post-ictal ^{18}F-FDG metabolism**	Complex pattern, increased or decreased
GABAA-cBZR receptor	Reduced binding
Opioid receptor	Increased mu and delta receptor bindings
Serotonin receptor	Reduced binding
Dopamine receptor	Reduced binding
^{11}C-alpha-methyl-L-tryptophan	Increased uptake
Interictal ^{15}O-H_2O	Usually reduced perfusion
Ictal ^{15}O-H_2O	Increased perfusion
* due to long brain uptake period of FDG; ** depending on the time of injection after seizure	

Table 4. PET findings in the area of seizure focus in patients with epilepsy. From Sarikaya I. (2015). PET studies in epilepsy. *American journal of nuclear medicine and molecular imaging*, *5*(5), 416–430.

Single-photon emission computerised tomography

Single-photon emission computerised tomography (SPECT) is employed to localise the ictal onset zone by administering a tracer during or immediately following a seizure (ictal SPECT) (Mullan et al., 1995).

1.6 Post-operative outcomes following epilepsy surgery

1.6.1 Neuropsychological assessment

Neuropsychological testing is recognised as an extension of the neurological examination applied to higher order cortical function, since each cognitive domain has an anatomic substrate (Zucchella et al., 2018). A neuropsychological work-up in patients with epilepsy typically involves the administration of a battery of tests investigating a variety of cognitive domains, including general intellectual ability, memory function, expressive and receptive language skills, executive function and perceptual abilities (Baxendale, 2018). Neuropsychological testing is useful in assessing pre-morbid function. The pattern of performance is often related to the lateralisation and localisation of cerebral pathology, although this is no longer the primary role of testing in an epilepsy population (Baxendale & Thompson, 2010).

Of the studies that have compared surgical outcomes, only a limited number have addressed neuropsychological outcomes. In one study (Fong et al., 2011), the pre- and post-operative scores for the Wechlser Memory Scale III and Boston Naming tests were assessed for 29 patients, of which 18 patients underwent temporal lobe surgeries that included resection of mesial temporal structures (10 left, 8 right). These structures were spared in the remaining patients (nine left, two right). The investigators showed that patients were more likely to decline on memory measures following surgery if they had resections that included removal of mesial temporal lobe structures, notably worse on the left-hand side, compared to operations that preserved the mesial temporal lobe structures (Fong et al., 2011). Other studies have shown that verbal memory deficits are most common in patients with left mesial

temporal lobe epilepsy, while in right mesial temporal lobe epilepsy patients, visual memory deficits are the most frequent observations (Oddo et al., 2012).

1.6.2 Psychiatric assessment

Many epilepsy centres in the world do not have a psychiatric assessment for every presurgical epilepsy patient (Sawant et al., 2016). A thorough assessment of a patient's presurgical psychiatric status allows investigtors to investigate exacerbations of presurgical complications and de novo development of psychiatric conditions (Ring et al., 1998). If a psychiatric evaluation is not offered in the epilepsy care program, then failure to treat can allow psychiatric comorbidity to persist or psychological difficulties to develop as the patient adjusts to life after surgery (Rayner & Wilson, 2012; Sawant et al., 2016). Importantly, psychiatric co-morbidities have been shown to be significant predictors of seizure outcome after surgery, with research demonstrating that the presence of psychiatric disorders may be associated with worse prognosis post operatively (Macrodimitris et al., 2011). The Hospital Anxiety and Depression Scale (HADS) is a commonly used tool to assess pre=operative and postoperative depression and anxiety (Zigmond & Snaith, 1983). The HADS is a fourteen-item scale. Seven of the items relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety or depression.

Several factors, including lateralisation of the epilepsy focus has been shown to affect depression and anxiety. There is evidence that depression and anxiety are not affected by the location of the epilepsy focus in the temporal lobe (Sanchez-Gistau et al., 2012), but psychiatric outcomes have hitherto been largely neglected in post-surgical cohorts. It is possible that patients with left mesial temporal lobe involvement may specifically have worse postsurgical outcomes vs. extratemporal and lateral temporal lobe sclerosis. For instance, de

Oliveira et al., (2010) have reported that patients with left mesial temporal sclerosis were at greater risk of depression. However, only 73 TLE patients, subdivided into four groups (right mesial, left mesial, bilateral mesial and temporal without mesial sclerosis) were included, thus increasing the likelihood of type II error (Sanchez-Gistau et al., 2012). With regards to anxiety, previous studies have failed to find a specific target region for anxiety disorders (Sanchez-Gistau et al., 2012), hence the effects of lateralisation may not have significant effects on post-surgical anxiety status.

1.6.3 Seizure control

The probability of a 'good' surgical outcome relies on the above investigations. The Engel and ILAE classifications are commonly used to measure freedom from seizures.

Engel classification

Two scales are commonly used to classify seizure recurrence after surgery. The Engel classification has been widely used for decades (Rodgers et al., 2012), and has been both complimented and criticised for including subjective patient opinion (Durnford et al., 2011). Based upon these disadvantages and the principle of designing a more objective system, a new classification was proposed by the ILAE Commission on Neurosurgery in 2001 (Durnford et al., 2011; Engel, 2001). Durnford et al., (2011) evaluated the inter-rater agreement of both the Engel and ILAE seizure outcome classification systems in a consecutive series of adults and children treated by a UK epilepsy surgery service. one observer classified 88% (n = 67) and a second observer classified 87% (n = 66) of patients as either Engel I or II (free from or rare disabling seizures) after a median follow up of 36 months (range 12–92 months); comparably, both observers classified 84% (n = 64) as ILAE 1–3. Correlation for Engel versus ILAE for observer 1 was 0.933 ($p < .0005$) and for observer

2 was 0.931 ($p < .0005$). Both ILAE (k 0.81, 95% confidence intervals 0.69, 0.91) and Engel (k 0.77, 95% CI 0.65, 0.87) classifications have very acceptable inter-rater reliability as well as significant correlation.

Class I: Free of disabling seizures

A. Completely seizure free since surgery
B. Non disabling simple partial seizures only since surgery
C. Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D. Generalized convulsions with AED discontinuation only

Class II: Rare disabling seizures ("almost seizure free")

A. Initially free of disabling seizures but has rare seizures now
B. Rare disabling seizures since surgery
C. More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D. Nocturnal seizures only

Class III: Worthwhile improvement

A. Worthwhile seizure reduction
B. Prolonged seizure-free intervals amounting to greater than half the followed-up period, but not <2 years

Class IV: No worthwhile improvement

A. Significant seizure reduction
B. No appreciable change
C. Seizures worse

ILAE classification

The ILAE scale has six outcomes based on a more objective scale of number of seizures after surgery (Engel, 2001).

1. Completely seizure free; no auras
2. Only auras; no other seizures
3. One to three seizure days per year; ± auras
4. Four seizure days per year to 50% reduction of baseline seizure days; ± auras
5. Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; ± auras
6. More than 100% increase of baseline seizure days; ± auras

Chapter 2. Aims and Hypotheses

The aims of this thesis are five-fold:

1. To conduct a systematic review of literature investigating the psychiatric and neuropsychological sequalae of epilepsy surgery in patients who do not have a lesion on structural magnetic resonance imaging, including the prognostic markers for favourable outcomes in this cohort of patients.
2. To identify the pre-operative factors that are associated with seizure freedom in patients who have undergone resective epilepsy surgery
3. To identify the pre-operative factors that predict post-operative anxiety and depression in patients who have undergone resective epilepsy surgery
4. To identify the pre-operative factors that predict post-operative changes in working, visual and verbal memory in patients who have undergone resective epilepsy surgery
5. To identify whether impairments of visual working memory binding are specifically spatial or rather generalize across visual feature dimensions following focal mesial temporal lobe lesions

Hypotheses

Hypotheses for aim 2: to identify the pre-operative factors that are associated with seizure freedom in patients who have undergone resective epilepsy surgery

I hypothesise that patients with extratemporal epilepsy will have poorer seizure outcome than temporal lobe epilepsy patients. In general, studies have reported less favourable seizure freedom outcomes for extratemporal resections (Hwaang et al., 2018). In one systematic review and meta-analysis of 76 resective epilepsy surgery studies, (Téllez-Zenteno et al.,

2005) showed that frontal lobe resections produce the worst long-term seizure free rates among the resective surgeries (mean 27%, median 34%), as compared to temporal and other extratemporal surgical procedures. Two main postulates have been forwarded to explain these poorer outcomes: it is challenging to localise the seizure onset focus because most cases have >1 triggering point with widespread location over the cortical surfaces (Téllez-Zenteno et al., 2005), and seizure foci may overlap with eloquent areas to a great extent thus making the lesions unresectable. It should be noted that some studies have shown no difference in long-term seizure outcomes between patients who have undergone extratemporal and temporal lesionectomies (Mohan et al., 2018).

I hypothesise that patients with MRI negative epilepsy will have a poorer prognosis as regards to seizure freedom compared to patients with MRI positive epilepsy. This hypothesis is supported by a meta-analytic review of 40 publications (n=697, non-lesional epilepsy; n=2860 lesional epilepsy) conducted by Téllez-Zenteno et al., (2010). In this study, the odds of being seizure free post-operatively were 2.5 times higher in patients with lesions on MRI (OR 2.5, 95%CI 2.1, 3.0, $p<0.001$). In patients with temporal lobe epilepsy surgery the odds were 2.7 times higher in those with lesions (OR 2.7, 95%CI 2.1, 3.5, $p<0.001$). In patients with extratemporal epilepsy surgery the odds were 2.9 higher in those with lesions (OR 2.9, 95%CI 1.6, 5.1, $p<0.001$). Muhlhofer et al., (2017) postulated that the poorer outcomes in patients with MRI negative epilepsy patients may be due to the presence of an intrinsically more widespread epileptogenic network, inadequate epileptogenic zone resections, or presurgical localisation error.

I hypothesise that patients with left-sided resections will have worse seizure outcomes compared to right-sided resections. This is supported by a Cochrane systematic review and meta-analysis, summarising all evidence published since the introduction of MRI to pre-operative surgical assessment in 1984. The prognostic impact of left-sided surgical resections was assessed in 36 studies (n=2933) and the risk ratio (0.94 [CI 0.90 – 0.98] confirmed that

left-sided resections were associated with poorer prognosis (West et al., 2019). Similar conclusions have been reported in other reports (Malmgren & Edelvik, 2017; Tonini et al., 2004). It is possible that the worse prognostic outcomes following left hemispheric procedures is because of a more conservative approach on the part of neurological surgeons who may not wish to perturb the language centres principally housed in the left hemisphere, including, in most cases, Broca's and Wernicke's areas (Fujii et al., 2016).

I hypothesise that patients with mesial temporal lobectomies will have better post-operative outcomes compared to lateral temporal lobectomies, which is supported by several published papers (Ficker et al., 1999; Spencer et al., 2003; Wass et al., 1996). This is also supported by a recent multicentre study of 339 patients in which two-year remission was achieved in 68% of patients who had medial temporal lobe resections vs. 50% of those who had neocortical resections (Spencer et al., 2005), although the differences did not reach statistical significance. However, it should be noted that a recent study of 285 patients who underwent epilepsy surgery with a prospective median follow-up time of 5 years (range 1 – 27 years) showed no difference in long-term seizure freedom between mesial and lateral temporal lobectomies (Mohan et al., 2018).

I hypothesise that patients with generalised seizures will have a poorer prognosis as regards to seizure freedom, which is supported by several published studies (Janszky et al., 2005; McIntosh et al., 2004; Schwartz et al., 2006; Spencer et al., 2005) It has been proposed that generalised seizures may source from a widespread epileptogenic zone, thus making it less amenable to surgical resection (Spencer et al., 2005). However, it should be noted that some studies have not shown any evidence associating seizure outcome and preoperative generalised seizures, even after multivariate analysis (Aull-Watschinger et al., 2008; Dupont et al., 2006; Lazow et al., 2012).

I hypothesise that patients with a high baseline seizure frequency will be less likely to experience seizure freedom at follow-up. In a population-based, prospective study in patients who were followed up as part of the Swedish National Epilepsy Surgery Register, multivariate analysis identified >30 seizures/month at baseline (pre-operatively) to be a negative predictor of long-term seizure freedom (Edelvik et al., 2013). In another study (Foldvary et al., 2000) showed that a preoperative monthly complex partial seizure frequency of <20 was associated with a higher likelihood of seizure freedom.

I hypothesise no difference in seizure outcomes between males and females. There is no biological a priori suggestion that either sex has better seizure outcomes (Bianchin et al., 2007), and sex has not been shown to influence outcomes in several clinical studies (Briellmann et al., 2000; Burneo et al., 2008; Helmstaedter et al., 2004; McIntosh et al., 2001). In one study of 368 epilepsy medically intractable temporal lobe epilepsy patients who underwent anterior temporal lobectomy, obtained from the discharge database of the University of Alabama between 1985 – 2001, Kaplan-Meier analysis revealed no association between gender and seizure recurrence at 7 days, 2 months, 6 months, 1, 2, 3, 4, 5, and 6 years following surgery (Burneo et al., 2008).

I hypothesise that age at seizure onset will not influence seizure outcomes, which is supported by several studies in the literature (Baxendale, Thompson, McEvoy, et al., 2012; d' Orio et al., 2017; Kanchanatawan et al., 2014; McIntosh et al., 2001). Although many authors support the argument showing no association between age at seizure onset and postoperative outcomes, some papers have shown better postoperative outcomes with an earlier age at seizure onset (Jutila et al., 2002), whilst others have shown that a young age at onset may predict a less favourable seizure outcome (Jayalakshmi et al., 2016).

I hypothesise that patients with unilateral localised discharges on electroencephalography (EEG) will be most likely to be seizure free at two years, which is consistent with the literature,

including systematic and meta-analytic reviews (Ebersole & Pacia, 1996; Ivanovic et al., 2017; Jeha et al., 2006; Lau et al., 2014; Tatum et al., 2008; Wang et al., 2016; Zhang et al., 2013). Indeed, in one meta-analytic review, (Wang et al., 2016) a pooled analysis showed that better seizure outcomes were more common when the EEG demonstrated no contralateral epileptic discharges (OR = 3.38, 95% CI = 1.57–7.25, $p < 0.05$, $I^2 = 0$). The most likely explanation for this finding is that a unilateral localised EEG permits better planning of the epileptic zone resection, thereby reducing the residual epileptogenic tissue (Ivanovic et al., 2017).

Hypotheses for aim 3: to identify the pre-operative factors that predict post-operative anxiety and depression in patients who have undergone resective epilepsy surgery

I hypothesise that patients with MRI negative epilepsy would have worse postoperative affective symptoms compared to patients with MRI positive scans. It is recognised that one of the best prognostic factors for "excellent" postoperative psychiatric outcomes is the presence of a discrete structural lesion on MRI, in an area that can be safely removed without interference with non-epileptogenic tissue (Bell et al., 2017). As described in my chapter *neuropsychological and psychiatric outcomes in patients with MRI-negative epilepsy*, few studies have investigated psychiatric outcomes in MRI-negative epilepsy cohorts (Guangming et al., 2009; Hellwig et al., 2012; B. P. Hermann et al., 1992; Kanemoto et al., 1998; Kanner et al., 2009; Reuber et al., 2004). At present, there is inconsistent evidence that MRI-negative epilepsy patients are at a relatively heightened risk of post-operative psychiatric decline compared to MRI-positive patients. In temporal lobe epilepsy cohorts, large resections may disturb limbic structures, such as the amygdala, hypothesised to be involved in the modulation and expression of mood (Janak & Tye, 2015). Neuroanatomically, post-surgical mood disorders may arise from limbic dysfunction (Cleary et al., 2013), and evidence shows a

correlation between the severity of mood disturbance (Anhoury et al., 2000; Paparrigopoulos et al., 2008) and the extent of hippocampal and amygdala resection. In the absence of a lesion, patients with MRI-negative epilepsy tend to have wider resection margins (Noe et al., 2013), reflecting the difficulty in localising the likely epileptogenic zone.

I hypothesise an association between pre-operative generalised seizures and worse postoperative anxiety and depression. Few studies have included seizure type in the logistic regression model for post-operative psychiatric morbidity. In one study (n=16), Carran et al., (2003) found that temporal lobectomy patients with mania and depression, as determined by criteria in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), were more likely to have preoperative generalised seizures compared to healthy controls (n=16, with no postoperative mood or anxiety disorder). However, evidence is conflicting. Indeed, in another study, patients with complex partial seizures were compared to patients with dual complex partial and simple partial seizures, and the authors found no differences in psychological functioning (Cankurtaran et al., 2005).

I hypothesise no relationship between age at seizure onset and post-operative psychiatric morbidity. Studies have not shown a relationship between an earlier age of seizure onset and the likelihood of poor post-operative psychiatric outcomes (Spencer et al., 2003). In one such study, there was no statistical difference in the age at onset between patients with depression, mania and healthy controls (Carran et al., 2003). In a sample of 276 epilepsy patients who underwent structured clinical interview for the full spectrum of DSM-IV Axis I diagnoses, researchers found no statistical difference in the age of onset of epilepsy in patients who did not have any psychiatric morbidities at baseline vs. patients with any DSM-IV Axis I diagnosis nor any difference at 1, 6 and 12 months following surgery (Pintor et al., 2007). In a longitudinal analysis of pre- and postsurgical psychopathology (presence vs. absence), (Inoue & Mihara, 2001) showed no significant difference in the age at onset of epilepsy in either group. Lastly, in a sample of 94 temporal lobe epilepsy patients, Reuber et al., (2004) showed that changes

in depression (Beck Depression Inventory) and anxiety scores (Self-Rating Anxiety Scale) were not associated with age at onset of surgery over a mean duration of 16 months.

I hypothesise that patients who are seizure free at two years will have less psychiatric morbidity compared to patients with continuing seizures postoperatively. Studies have revealed a mixed picture regarding the association between postoperative seizure freedom and psychiatric morbidity. Some have shown no association between both variables (McLellan et al., 2005; Meldolesi et al., 2007; Pintor et al., 2007; Smith et al., 2004; Spencer et al., 2003) whilst others have shown seizure freedom and improved postoperative psychiatric status (Altshuler et al., 1999; Blumer et al., 1998; Devinsky et al., 2005; Hermann et al., 1989; B. P. Hermann et al., 1992; Macrodimitris et al., 2011; Reuber et al., 2004).

It is not unreasonable to hypothesise a relationship, albeit indirectly, between fewer preoperative seizures and better postoperative psychiatry morbidity. In one study (n=110, mesial temporal lobe epilepsy patients with hippocampal sclerosis), multivariate analysis revealed a preoperative seizure frequency >10 / month to be associated with poor prognosis in terms of seizure frequency and control following surgical resection (Sànchez et al., 2014). These findings are consistent with earlier studies (Hitiris et al., 2007; Kwan & Brodie, 2000; MacDonald et al., 2000). Given the evidence favouring an association between seizure freedom and improved postoperative psychiatric status as discussed above, and also see (Macrodimitris et al., 2011), it is possible that fewer pre-operative seizures could indirectly be associated with improved postoperative psychiatric status.

I hypothesise that patients with temporal lobe epilepsy will have worse postoperative psychiatric morbidity as compared to extratemporal lobe patients. The aetiology of mood disturbance following temporal lobectomy is thought to be a result of several interacting factors that broadly fall into psychosocial and neurobiological domains (S. Wilson et al., 2001; S. J. Wilson et al., 2001; Wrench et al., 2004). Some researchers postulate that postsurgical

removal, deafferentation or disruption of temporal limbic structures may result in affective disorders, but no detailed account has been published of the postsurgical mechanisms involved (Wrench et al., 2004). Some evidence shows that psychosocial factors, relating to the process of adjusting to life without epilepsy, may be involved in the genesis of affective disorders. Indeed, following epilepsy surgery, patients begin to recover from the sick role associated with their chronic illness and learn to become well (Jobst, 2012). There is also the anxiety and depression that is associated with meeting the demands of postsurgical life (Bladin, 1992). In one longitudinal study (N=60), patients with temporal lobectomies (n=43) and extratemporal lobectomies (n=17) were assessed before surgery, at discharge, 1 month and 3 months post-surgery using the Austin CEP Interview (Wrench et al., 2004). Patients with temporal lobectomies reported significantly higher levels of depression, anxiety and psychosocial adjustment difficulties at the one-month review vs. extratemporal patients. The site of surgery appeared to be a significant determinant of mood outcome, thus supporting the role of neurobiological factors specific to the temporal lobe (Wrench et al., 2004). Notwithstanding the above evidence, two other studies have compared the level of postoperative depression in focal epilepsies, and both have shown no significant difference between temporal and extratemporal groups (Quigg et al., 2003; Suchy & Chelune, 2001).

I hypothesise that patients with mesial temporal lobe resections will have worse post-operative depression and anxiety vs. lateral temporal lobe resection patients. Patients with mesial temporal lobe epilepsy are recognised to have higher rates of mood disorders as compared to non-mesial temporal lobe epilepsy (Perini et al., 1996). This might be because medial temporal lobe structures, which house the limbic system, are thought to have a greater influence on the genesis of mood disorders as compared to the lateral cortex (Jobst, 2012). Indeed, in one study, Wrench et al., (2004) noted that de novo depression occurred more frequently after removal of mesial temporal lobe structures. Nevertheless, it is increasingly recognised that the onset of depression is affected by psychosocial factors in addition to limbic

structures (Bladin, 1992), and that the limbic system works synchronously with non-temporal lobe brain structures, which may affect overall affect.

I hypothesise that patients with left-sided resections will have worse postoperative depression and anxiety symptoms as compared to patients with right-sided resections. In the valence model, it is recognised that positive emotions, such as happiness and euphoria, originate from the left hemisphere whilst negative emotions, such as sadness and anger, arise from the right hemisphere. This is supported by findings in healthy people and patient with brain lesions, as well as deactivation during Wada testing (Carran et al., 2003). According to the Valence model, excessive right temporal lobe activity with loss of counterbalancing activity of the resected left temporal lobe may result in depressed and anxious reactions. This is supported by a clinical study of 235 patients who had undergone temporal lobe resections, in which left sided resection was found to be a significant determinant of postoperative depression (as determined by the Beck Depression Index) (Doherty et al., 2020).

As regards to preoperative electroencephalogram (EEG) findings, I hypothesise that patients with epileptic discharges in a single lobe (unilateral local lobe involvement) would have better psychiatric outcomes compared to patients with multiple seizure foci. This hypothesis is supported by several studies which show better outcomes in patients with unilateral localised epileptic discharges on EEG as regards to seizure freedom, psychiatric and neuropsychological freedom (Holmes et al., 2003; Pustina et al., 2014; Schmeiser et al., 2017). The region showing the epileptiform EEG signals are often used a proxy for the epileptogenic zone in clinical practice (Müller et al., 2018). Indeed, evidence suggests that the best prognostic factor for optimal postoperative outcome following epilepsy surgery is the presence of a discrete ictal EEG, conforming with a discrete structural lesion on MRI, consistent with seizure semiology (Vakharia et al., 2018). A common misconception in epilepsy surgery communities is that bilateral EEG spikes are a contraindication to surgery,

which is incorrect as patients with unilateral seizure can have bilateral ictal spikes (Vakharia et al., 2018).

I hypothesise that sex will not influence postoperative changes in anxiety or depression. Although females tend to have higher rates of anxiety and depression compared to males (Devinsky et al., 2005; Pintor et al., 2007), there is no evidence that the evolution of affective symptoms following epilepsy surgery depends on sex (Wrench et al., 2011).

Hypotheses for aim 4: to identify the pre-operative factors that predict post-operative changes in working, visual and verbal memory in patients who have undergone resective epilepsy surgery

I hypothesise that patients who have undergone mesial and lateral temporal lobe resections will both have a similar decline in memory functions. Memory dysfunction is a common neuropsychological manifestation of patients who have undergone temporal lobe resections (Meador, 2002). Specifically, structures within the mesial temporal lobe have been shown to be critical for encoding memories (Oddo et al., 2003). In a study (Fong et al., 2011) investigating cognitive decline following temporal lobe surgery on measures of memory and confrontation naming, patients were most likely to decline on memory measures following surgery if they had resections that included removal of mesial temporal lobe structures, notably worse on the left hand side, compared to operations that preserved the mesial temporal lobe. This study measured cognitive decline using three modalities: Wechlser Memory Scale III and Boston Naming test. In contrast, Joo et al., (2005) investigated post-operative memory decline in temporal lobe patients who had either undergone resections of mesial temporal lobe structures (such as the hippocampus) vs lateral neocortex. In this study, patients with greater resections of the left inferior or basal temporal gyri in left temporal lobe epilepsy patients

experienced greater postsurgical memory decline, but the resection length of the hippocampus was not related to memory decline in either right or left temporal lobe epilepsy patients. This supports evidence that the temporal neocortex provides a repository of stored information (Giovagnoli, 1999; Skirrow et al., 2015). In sum, both of these studies support the conclusion that resections of either the lateral neocortex or mesial lobe can result in memory decline. Hitherto, a consensus regarding the impact of the extent of resection of the lateral temporal neocortex on postoperative memory has not been reached (B.P. Hermann et al., 1992; Joo et al., 2005).

I hypothesise that left-sided resections will result in verbal memory decline, but this will not be seen in non-verbal memory. Meta-analytic reviews generally support the finding that left-sided lobectomies, specifically affecting the temporal lobe, can result in verbal memory deficits whilst right temporal lobe seizures resulted in visuospatial memory impairments (Funk & Connor, 2019; Lee et al., 2002; Vaz, 2004). In one meta-analysis Sherman et al., (2011), weighted estimates indicated a risk to verbal memory with left-sided temporal surgery of 44%, twice as high as the rate for right-sided surgery (20%). However, there is growing evidence that these observations should be considered in the context of Wada testing, as patients will tend to manifest memory impairments depending on the language-dominant hemisphere. In brief, the WADA procedure involves the infusion of a fast-acting barbiturate into each carotid artery separately, which results in brief inactivation of the tissues supplied by the middle and anterior cerebral arteries. During this brief inactivation, cognitive domains are tested to determine the functional reserve of the hemisphere contralateral to the side that is impaired (Alpherts et al., 2000; Baxendale et al., 2008). Although I did not include Wada testing results in the present study, there is a growing body of evidence suggesting that Wada memory asymmetry index has little bearing on post-operative memory decline (J. R. Binder et al., 2008; Funk & Connor, 2019; Joo et al., 2005).

The neuropsychological sequalae of epilepsy surgery has been described elsewhere in this thesis (see chapter: *Neuropsychological and psychiatric outcomes in patients with MRI-negative epilepsy).* I hypothesise that patients with MRI negative epilepsy will have a more significant decline in memory compared to MRI positive epilepsy patients, which is supported by studies indicating a trend, albeit weak and inconsistent, toward MRI- patients experiencing greater cognitive decline vs. MRI+ patients (Bell et al., 2009; Berger et al., 2018; Helmstaedter et al., 2011; Immonen et al., 2010; Mariani et al., 2019; Seidenberg et al., 1998). The likely neurobiological reason for this phenomenon is that the resection margins for MRI negative patients tend to be larger (Noe et al., 2013), reflecting the difficulty in localising and reflecting the epileptogenic zone. Therefore, researchers have postulated that there is a greater probability of damaging eloquent cortex (Ives-Deliperi & Butler, 2012).

I hypothesise that both temporal and extratemporal lobe epilepsy patients will experience similar declines in memory. Few, if any, researchers have systematically investigated the cognitive risks of extratemporal resections (Sherman et al., 2011), and the majority of studies have neglected measuring neuropsychological sequelae in favour of seizure outcomes (Noe et al., 2013). For instance, it has been suggested that verbal memory may be vulnerable after extra-temporal surgery (Lah, 2004), whilst at least two studies have shown that extra-temporal resections do not result in any memory decline (Lendt et al., 2002; Mabbott & Smith, 2003). The cognitive sequelae associated with resection of temporal, frontal, parietal and occipital seizure foci have been comprehensively described by Dulay & Busch (2012), and include a range of overlapping visual, working and verbal memory deficits. At present, deficits cannot be reliably correlated to resections of specific lobe as the available studies are generally based on small sample sizes with heterogeneous patient populations (D. K. Binder et al., 2008; Dulay & Busch, 2012). Just as it is increasingly recognised that epilepsy is a disorder of cerebral networks (Wilson & Baxendale, 2014), so we have moved away from a phrenological approach of assigning specific cognitive functions to the role of specific cerebral structures

(Baxendale, 2018). Indeed, memory formation should be thought of as the interconnectedness between different cerebral structures.

I hypothesise no relationship between pre-operative seizure type and cognitive decline. To my knowledge, no study has systematically investigated the relationship between neuropsychological outcomes and preoperative seizure type. In one study, Sveikata et al., (2019) showed that postictal memory is the most effective non-invasive test that can predict postoperative decline and this was independent of (a) focal, (b) secondary bilateral tonic-clonic or (c) unspecific preoperative seizure types, suggesting weak evidence that preoperative seizure type does not greatly influence postoperative memory decline. In non-surgical cohorts, there is an argument that patients with generalised tonic-clonic seizures tend to have worse memory scores (Dodrill, 2004). As such, it is possible that patients with generalised tonic-clonic seizures, who have poor preoperative, baseline neuropsychological scores, will have less margin to deteriorate, or less function to lose, and progress down standard deviations compared to those with higher scores (Baxendale et al., 2006, 2007). Moreover, there is evidence that patients who have generalised tonic-clonic seizures are less likely to be seizure free post-operatively (Bell et al., 2017), and there is evidence of a relationship between continuing seizures and poor memory outcomes (Sherman et al., 2011). In sum, there is indirect evidence supporting a relationship between generalised tonic-clonic seizures and poor neuropsychological outcomes.

I hypothesise that an older age of seizure onset will result in worse neuropsychological outcomes. This is supported by several studies in the literature which show that memory decline tends to be greater with older age at seizure onset (J. R. Binder et al., 2008; Gleissner et al., 2004; Jokeit et al., 1997). In a classical study conducted by (Hermann et al., 1995), patients who underwent left n=50) or right (n=51) anterior temporal lobectomy were administered verbal and non-verbal memory tests, both preoperatively and 6 months postoperatively. Following a process of stepwise regression analysis, the investigators found

that later age at seizure onset was a significant predictor of decreased verbal and non-verbal memory decline.

I hypothesise that a higher preoperative seizure frequency will result in a less significant decline in memory outcomes. Patients with higher preoperative seizures tend to have poorer baseline (preoperative) memory functions, and patients with a low baseline level of memory tend to show less significant postoperative memory declines (Sherman et al., 2011). One possible explanation for this phenomenon is that the better preoperative performers have more function to lose i.e., the poor performers show less decline due to a psychometric “floor effect” (J. R. Binder et al., 2008).

For similar reasons, women with epilepsy are at greater risk than their male counterparts for widespread cognitive deficits (Baxendale et al., 2010), for unknown reasons (Funk & Connor, 2019). Therefore, I hypothesise that women will experience less postoperative cognitive decline compared to men.

Hypotheses for aim 5: to identify whether impairments of visual working memory binding are specifically spatial or rather generalize across visual feature dimensions (e.g., location, colour and shape) following focal mesial temporal lobe lesions

I hypothesise that visual working memory – visual memory held in short term, working memory – will be poorer in patients who have mesial temporal lobe resections for epilepsy surgery compared to healthy controls. Classical and contemporary studies in rodents and humans

have concluded that mesial temporal lobe lesions can instead produce substantial working memory deficits (Hannula et al., 2006; Olton et al., 1979). A suggestion, based on lesion work carried out mainly in non-human primates (Eacott & Gaffan, 2005; Ranganath, 2010), is that the mesial temporal lobe is involved in representing the environmental layout, the objects within it, as well as binding the latter to the former. A growing body of evidence suggests that the perirhinal cortex codes information about an object's identity and the parahippocampal cortex codes an object's location and its context, and these two streams are subsequently bound in the hippocampus (Libby et al., 2014; Pertzov et al., 2013; Watson et al., 2013; Yee et al., 2014).

I hypothesise that patients with left-sided mesial temporal lobe resections will see the most significant decline in visual spatial binding. This is supported by a study from Kessels et al., (2004) who found that patients who had undergone left, but not right temporal lobectomies, were impaired in spatial binding, confirming lateralization effects previously observed in a sample of patients with vascular pathology (Kessels et al., 2002).

Chapter 3. Neuropsychological and psychiatric outcomes in patients with MRI-negative epilepsy: a systematic review

3.1 Introduction

Magnetic resonance imaging (MRI) is a non-invasive neuroimaging technique that may be employed pre-surgically to locate the likely epileptogenic zone (Beers & Federico, 2012). Surgery may be offered to patients with no lesion demonstrated on MRI, on the bases of clinical and electroencephalogram (EEG) data. However, seizure outcomes for patients with normal pre-operative MRI findings (also referred to as MRI-negative and non-lesional epilepsy) are poorer than in MRI positive patients, reflecting the difficulty in localising the epileptogenic zone (Noe et al., 2013).

Epilepsy can be broadly stratified according to the region/s affected: temporal and/or extratemporal epilepsy. In temporal lobe epilepsy – the commonest form of epilepsy (Muhlhofer et al., 2017) – seizures may originate from the mesial or lateral temporal regions (or simultaneously from both), sometimes with extension of the epileptogenic zone to the neighbouring lobes ("temporal-plus" epilepsy) (Muhlhofer et al., 2017). Patients with normal pre-operative MRI findings generally include those denoted as cryptogenic or idiopathic temporal lobe with no mesial temporal sclerosis (Engel, 1996). In MRI-positive epilepsy, hippocampal sclerosis is the commonest pathology identified; other pathologies include tumours, vascular malformations, postinfectious or ischaemic damage (Muhlhofer et al., 2017). Approximately 30% patients with drug-resistant temporal lobe epilepsy are MRI-negative (Cascino et al., 1991; Muhlhofer et al., 2017). Extratemporal lobe epilepsies have

epileptogenic foci outside the temporal lobe, and can arise from the frontal, parietal, occipital lobes and from hypothalamic hamartomata (Dash & Tripathi, 2014).

The reported rate of excellent surgical outcome for non-lesional partial epilepsy range from 41-65% for the temporal lobe (Bell et al., 2009; Holmes et al., 2000; Noe et al., 2013; Radhakrishnan et al., 1998; Sylaja et al., 2004), 37% for mixed mesial temporal and neocortical sites (Blume et al., 2004), and 29-56% for extra-temporal epilepsy (Bien et al., 2009; Chapman et al., 2005; Jeha et al., 2007; Mosewich et al., 2000; Smith et al., 1997). Outcomes in non-lesional extratemporal epilepsy, however, are from relatively small numbers of highly select patients (Bien et al., 2009; Noe et al., 2013) with 1-year follow-up. Hitherto, several systematic reviews and meta-analyses have addressed seizure outcomes in patients with non-lesional epilepsy (Jobst & Cascino, 2015; Téllez-Zenteno et al., 2010; Wang et al., 2016). A pooled analysis of published studies between 1995 and 2010 reported the proportion of seizure-free patients as 51% after temporal lobes surgery among patients with non-lesional temporal lobe surgery, which is higher than the rate after epilepsy surgery among MRI-negative extratemporal epilepsy patients (35% seizure-free) (Téllez-Zenteno et al., 2010). Epilepsy duration >20 years and a well-defined epileptic focus in a unilateral temporal lobe have been shown to be favourable prognostic factors in MRI negative epilepsy, whilst PET localisation and specific pathology have not been shown to predict seizure outcome in patients with MRI-negative temporal lobe epilepsy (Wang et al., 2016).

Although seizure outcomes in non-lesional epilepsy surgery have been well studied, there is a paucity of evidence looking at neuropsychological and psychiatric outcomes following epilepsy surgery in MRI-negative cohorts. Indeed, only 3% of all epilepsy studies have reported psychiatric outcomes (Cleary et al., 2013; Jobst & Cascino, 2015). Cognitive deficits are of concern following epilepsy surgery and several systematic reviews have assessed the relationship between cognition and resection (Ives-Deliperi & Butler, 2012), but little attention has been paid to MRI negative cohorts.

Hitherto, to my knowledge, no article has summarised the up-to-date psychiatric and neuropsychological sequalae in MRI-negative epilepsy patients. Therefore, the overall aim of this review article is to provide an overview of the studies that have explored this landscape, including the prognostic markers for favourable post-surgical psychiatric and neuropsychological outcomes. I performed a systematic search of the PubMed®/MEDLINE®/EMBASE®/EMBASE® Classic/ Google Scholar databases, without language restriction and no additional filters, from inception to June 2020, using the following search terms: MRI negative epilepsy OR temporal lobe epilepsy, and the mesh terms: 'seizures' OR 'epilepsy'. In order to avoid missing relevant studies, references of the retrieved studies were also screened. As there was only one reviewer, I was unable to follow the PRISMA guidelines for systematic reviews and meta-analyses in this PhD (Liberati et al., 2009).

3.2 Neuropsychological outcomes in patients with MRI-negative epilepsy

Neuropsychological testing is recognised as an extension of the neurological examination applied to higher order cortical function (Zucchella et al., 2018). A neuropsychological work-up in patients with epilepsy typically involves the administration of a battery of tests investigating a variety of cognitive domains, including general intellectual ability, memory function, expressive and receptive language skills, executive function and perceptual abilities (Baxendale, 2018). Neuropsychological testing is useful in assessing pre-morbid function. The pattern of performance is often related to the lateralisation and localisation of cerebral pathology, although this is no longer the primary role of testing in an epilepsy population (Baxendale & Thompson, 2010). Common applications of neuropsychological assessment in the diagnosis, treatment and management of epilepsy are described in **table 5.** The limitations

of neuropsychological testing are numerous and include issues with validity, inadequate normative data, length of time for administration and patient motivation (Baxendale & Thompson, 2010; Howieson, 2019).

Use	Description
Assess and monitor medication effects	Some antiepileptic medications can have significant cognitive side effects. A neuropsychological assessment can be used to assess the cognitive cost/benefits of these medications, particularly for young people with respect to their education.
Aid in the differential diagnosis of epilepsy/ psychogenic non-epileptic attack disorder	A grossly abnormal profile may indicate the presence of a functional disorder.
Provide the basis for a cognitive rehabilitation programme	The results of a neuropsychological assessment can be used to create a tailor-made rehabilitation programme to reduce the impact of any cognitive deficits with an organic basis on everyday function.
Provide the basis for counselling regarding employment/educational options	People with epilepsy and their carers can develop altered expectations regarding the likely impact of their condition on their life opportunities. A neuropsychological assessment can provide a basis to ensure someone can function at their full potential.
Specialist applications in epilepsy surgery	• Lateralising/localising seizure focus in MRI-negative cases • Preoperative prediction of postoperative cognitive changes • Ensuring informed consent • Implementation of prehabilitation [a] for patients at high risk of a postoperative cognitive decline.
Foot notes: [a] Prehabilitation is cognitive rehabilitation implemented before the loss of a function. Epilepsy surgery patients are unique among neurological patients as we can predict both the nature and extent of the neuropsychological deficit they are likely to experience before the surgery that will cause it. A patient's intact memory functions can be exercised pre-emptively, to reduce the impact of postoperative cognitive decline.	

Table 5. Common applications of a neuropsychological assessment in the diagnosis, treatment and management of people with epilepsy. Adapted from: Baxendale S. Neuropsychological assessment in epilepsy. *Practical Neurology* 2018; **18:**43-48.

Neuropsychological evaluation can be useful to confirm the site of the epileptogenic zone in MRI-negative epilepsy patients; although distinct, lobe-specific neurocognitive profiles are difficult to identify given the natural spread of epileptogenic activity across the neural substrate (Esteller et al., 2015). Neuropsychological outcomes have been more systematically studied in patients with temporal lobe epilepsy – the commonest epilepsy subtype amenable to surgical resection (Wiebe, 2004) – and few studies have studied frontal, parietal and occipital epilepsies. Frontal lobe epilepsy patients have been shown to experience more difficulties with the organisational aspects of learning, which can lead to problems with both encoding and retrieval of information, while recognition recall may remain intact (Esteller et al., 2015; McDonald et al., 2001; Nolan et al., 2004). While both temporal and frontal lobe epilepsy patients have been shown to suffer from auditory fluency problems (Martin et al., 1990), frontal lobe epilepsy patients have been reported to have greater improvement when offered structured cueing on such tasks (Drane et al., 2006; Esteller et al., 2015). A complete neuropsychological profile of pre-surgical deficits in patients with temporal and extratemporal epilepsy is provided in **tables 6** and **7**, respectively.

Few studies (Bell et al., 2009; Berger et al., 2018; Helmstaedter et al., 2011; Immonen et al., 2010; Mariani et al., 2019; Seidenberg et al., 1998) have analysed post-surgical neuropsychological outcomes in patients with MRI-negative epilepsy. Generally, neuropsychological outcomes are a secondary enquiry, hence data for such outcomes are not systematically collected and the lack of power makes statistical analysis challenging (Mariani et al., 2019). Nevertheless, a selection of studies that have systematically investigated neuropsychological outcomes are discussed below.

Helmstaedter et al., (2011) investigated verbal and figural memory outcomes after temporal lobe surgery in 15 MRI- and histopathologically negative patients (MRH-) and these were compared to those obtained in 15 MRI- and histopathologically positive patients (MRH+). In the MRH- cohort, histopathologic workup of the resected tissue revealed no distinct

epileptogenic lesion (*i.e.,* a neuropathologist reported normal or nonspecific findings such as "gliosis" or "microglial activation"). Preoperatively, memory was found to be significantly better and less frequently impaired in MRH- as opposed to MRH+ patients. Postoperatively, memory losses in MRH- were more severe as opposed to MRH+ patients who did not change, on average. Losses in individual test parameters were seen in between 27% and 80% in MRH- patients as compared to between 13% and 47% in MRH+ patients. Overall, findings were strongest for verbal memory decline in left MRI-negative patients, but significant declines were also observed in visual memory for right MRI-negative patients. This study highlights that the absence of an MRI lesion significantly worsens postoperative neuropsychological outcomes.

Immonen et al., (2010) studied neuropsychological outcomes in 38 Finnish patients who had undergone surgery for MRI-negative temporal lobe epilepsy. Neuropsychological evaluation of intellectual ability, memory, and language was performed prior to surgery and repeated at 1 year postoperatively. Intellectual ability was assessed with the Wechsler Adult Intelligence Scale or the Wechsler Adult Intelligence Scale-Revised, and Verbal and Performance IQs were estimated. Verbal memory was evaluated with the Logical Prose Subtest from the Wechsler Memory Scale and visual memory was assessed with WMS Visual Reproduction Test. Verbal ability was evaluated with the Object naming test, the Token test, and the Verbal Fluency Test. Preoperative cognitive performance was not significantly different between left and right temporal lobe epilepsy patients before surgery. In the patients with operated right temporal lobe epilepsy the cognitive performance did not change significantly from preoperative to postoperative evaluation, but in left temporal lobe epilepsy patients both immediate and delayed recall of logical prose were impaired compared to preoperative performance. When the groups were compared, the performance was significantly different in immediate recall of logical prose; the patients after left temporal lobe epilepsy surgery showed impaired verbal immediate memory, whereas other tests did not show any difference. Generally, studies reporting the long-term follow-up of epilepsy surgery have shown that 50% of medically treated and 60% of surgically treated temporal lobe epilepsy patients experience

significant memory decline (Helmstaedter et al., 2003). Interestingly, (Immonen et al., 2010), reported that no more than 27% of MRI-negative patients experienced a decline in individual memory and less than 50% of patients had a decline in their verbal or visual performance, hence neuropsychological outcomes in MRI-negative cohorts may not be any worse than those in MRI-positive cohorts. An important weakness of this study (Immonen et al., 2010) is that it did used a limited range of cognitive measures, and did not include tasks that have been proven to be especially sensitive to hippocampal function, such as associated learning tasks (Esteller et al., 2015).

The finding of impaired verbal memory is consistent with the findings from a systematic review (Sherman et al., 2011) investigating neuropsychological outcomes after epilepsy surgery in MRI negative and positive cohorts. In this review (Sherman et al., 2011), the pooled estimates indicated a risk to verbal memory with left-sided temporal surgery occurring in 44% of patients, twice as high as the rate for right-sided surgery. There is evidence (Helmstaedter et al., 2008) that preservation of the temporal stem or the connections between the temporal stem or the connections between the temporal and frontal areas are important for verbal memory outcome after left-sided resections, whereas sparing of temporal neocortical structures appears crucial for figural memory after right-sided resections.

Presurgical deficit	**Laterality**	**Areas to emphasise during assessment of neurocognitive domain**	**Possible tests to consider**
Language: – naming (auditory/visual)	L. Naming deficits are common (proper nouns often worse than common nouns). L & R. Semantic fluency.	• Naming (e.g., visual, auditory/ naming to description, category related) • Common and proper noun semantic fluency categories	• Boston Naming Test, Columbia Auditory Naming Test, category-related naming tests • Various semantic fluency paradigms
Memory and learning: – Material-specific memory deficits	L. Common auditory/ verbal memory deficits. R. Sometimes visual memory deficits.	• Auditory/verbal learning, memory retention, and recognition: o List learning tasks o Contextual memory o Associative learning (with both easy and hard word-pairs) • Visual learning, memory retention, and recognition: o Simple geometric designs o Face recall o Complex visual designs Route learning	• Rey Auditory Verbal Learning Test, California Verbal Learning Test, Verbal Selective Reminding Test • Logical Memory Subtest (Wechsler Scales), Reitan Story Memory • Verbal Paired Associates (VPA) subtest (Wechsler Scales; WMS-III VPA appears less helpful than other versions, as it eliminated the easier word pairs) • Visual reproduction (Wechsler Memory Scales: older versions appear to be more useful for lateralization than the 3rd edition) • Face recall/hospital facial recognition task • Rey Complex Figure Test, MCG complex figures

Object recognition: –Category-related object recognition deficits	R. Recognition deficits often present for famous persons/faces, landmarks, & animals with anterior TL dysfunction.	Object recognition	• Famous faces test, category-related object recognition tests
Executive control processes: – Complex problem solving – Response inhibition	L & R. Frequent in one or more of these areas (likely caused by the disruption of temporofrontal networks secondary to onset activity).	• Complex problem solving • Response inhibition • Generative fluency tasks	• Wisconsin Card Sorting Test, Brixton Spatial Anticipation Task, Iowa Gambling Task • Color-word interference (Stroop) Test, Haylings Test, go/no-go tasks • Various verbal and design fluency tasks

Table 6. Neuropsychological profiles of presurgical deficits in temporal lobe epilepsy. Permissions: Esteller, R., Drane, D., Meador, K., & Loring, D. (2015). Neuropsychological issues in MRI-negative focal epilepsy surgery: Evaluation and outcomes. In E. So & P. Ryvlin (Eds.), *MRI-Negative Epilepsy: Evaluation and Surgical Management* (pp. 223-236). Cambridge: Cambridge University Press.

Presurgical deficit	Laterality	Areas to emphasise during assessment of neurocognitive domain	Possible tests to consider
Frontal lobe epilepsy			
Motor: – Motor functioning	L & R. Frequent motor deficits contralateral to side of seizure focus (e.g., gross motor speed, fine motor speed, and dexterity)	• Handedness • Gross motor speed • Fine motor speed • Grip strength • Psychomotor speed	• Edinburgh Handedness Scale • Finger tapping test • Grooved pegboard test • Hand dynamometer • WAIS subtests (e.g., symbol search, digit symbol)
Executive control processes: – Response inhibition – Complex problem solving	L & R. Frequent deficits	• Response inhibition • Complex problem solving • Generative fluency tasks – visual and verbal • Sequencing tasks	• Color-word interference (Stroop) Test, Haylings test, go/no-go tasks • Wisconsin card sorting Test, Brixton Spatial Anticipation Task, Iowa Gambling Task • Controlled oral word association (letter fluency), semantic fluency paradigms (cued and uncued) Action (verb) fluency, 5-point design fluency • Trail making test – Part B
Attention	L & R. Frequent deficits in primary and complex attention	• Primary attention (auditory & visual) • Complex attention	• Digit span forward (WAIS), Picture completion (WAIS) • Digit span backwards & letter–number sequencing (WAIS), trail-making tests, spatial span
Constructional praxis	Frequently have deficits on constructional tasks due to poor organization & planning	• Graphomotor copying tasks • Assembly tasks	• Copying simple shapes (e.g., Greek cross, Necker cube), Rey Complex Figure Test (Copy)

Posterior cortical epilepsies (Occipital lobe epilepsies and parietal lobe epilepsies)			
Language	L PLE. Possible deficits in naming, repetition, comprehension R PLE & R & L OLE. Unlikely language deficits	• Naming	• Boston Naming Test • Sentence repetition test (multilingual aphasia exam) • Token test (various versions)
Visual processing: – Visuoperception, acuity, visual fields – Visual–spatial processing	L & R OLE. Possible problems w/visuoperception L & R OLE. Sometimes visual-field cuts (particularly w/mesial dysfunction L & R OLE. Possible deficits in color processing & object localization R PLE. Often issues w/ visual–spatial processing	• Visuoperception • Visual acuity and visual field • Visual–spatial	• Visual Object Space Perception Battery (VOSP), facial recognition • Snellen Eye chart, visual field Examination • Judgment of line orientation, VOSP • Category-related object recognition tests
Sensory functioning	L & R PLE. May exhibit issues w/sensory discrimination or other sensory-perceptual issues	• Visual, auditory, and tactile acuities	• Snellen Eye Chart • Extinction to double simultaneous stimulation • Tactile form recognition • reitan–klove Sensory Examination

Table 7. Neuropsychological profiles of presurgical deficits in extratemporal lobe epilepsy. Permissions: Esteller, R., Drane, D., Meador, K., & Loring, D. (2015). Neuropsychological issues in MRI-negative focal epilepsy surgery: Evaluation and outcomes. In E. So & P. Ryvlin (Eds.), *MRI-Negative Epilepsy: Evaluation and Surgical Management* (pp. 223-236). Cambridge: Cambridge University Press.

In a retrospective review, Bell et al., (2009) identified 44 MRI-negative temporal lobe epilepsy patients who underwent anterior temporal lobectomy between January 1997 and June 2005 at the Mayo Clinic, Rochester. Neuropsychological testing of memory, language, and intelligence was obtained prior to temporal lobectomy and repeated at 6 months post-surgery. The battery of neuropsychological tests included: verbal comprehension quotients from a Wechsler intelligence scale, a test of lexical verbal fluency (Controlled Oral Word Association), Trail Making Test, a semantic fluency test, Boston Naming Test, and the Auditory Verbal Learning Test. The pre- and post-operative neuropsychological tests demonstrated that patients with right and left temporal lobe epilepsy were neuropsychologically different, with left temporal lobe patients tending to have lower verbal abilities compared to right temporal patients at presentation, which declined after surgery. Patients with left temporal lobe epilepsy had deficits on measures of semantic fluency and confrontation naming. Delayed verbal memory also declined after surgery, but the data for this observation were limited. Lexical fluency and rapid executive function were not different between patients with left and right temporal lobe epilepsy and seemed stable across evaluations.

[^{18}F] fluorodeoxyglucose positron emission tomography (FDG-PET) uses a radiolabelled glucose analogue to assess regional cerebral glucose metabolism (Sarikaya, 2015). FDG-PET is a useful tool in the pre-operative work-up when structural MRI and electroencephalograms are unclear as to the location of the epileptogenic foci (Berger et al., 2018; Peter et al., 2016). Interestingly, there is evidence that frontal lobe FDG-PET hypometabolism is related to executive dysfunction in MRI-negative frontal lobe epilepsy (McDonald et al., 2006), and that FDG-PET hypometabolism of the temporal lobe can be found in patients with extratemporal epilepsy and is associated with memory deficits (Knopman et al., 2014).

In one preliminary investigation (Berger et al., 2018), 68 patients with refractory unilateral temporal lobe epilepsy (35 left temporal lobe epilepsy, 33 right temporal lobe epilepsy) were

divided into three groups: (1) no evidence of pathology in either MRI or FDG-PET studies (MRI−/PET-), (2) temporal FDG-PET determined hypometabolism with normal MRI findings (MRI−/PET+), and (3) evidence of temporal abnormalities in both MRI and FDG-PET studies (MRI+/PET+). Patients with MRI+/PET+ were found to have worse verbal memory than patients with MRI−/PET−, regardless of the seizure focus position. Verbal memory performance of patients with MRI−/PET+ was between patients with MRI+/PET+ and MRI−/PET−, although group differences did not achieve statistical significance. No group differences were found for nonverbal memory. The investigators concluded that there may be an interactive negative effect of metabolic and structural temporal lobe abnormalities on verbal memory, such that both structural and metabolic alterations should be present in combination before verbal memory deteriorates.

In contrast, a study by Yang et al., (2014) revealed a statistically significant difference in the postoperative verbal memory decline (using the Auditory Verbal Learning Test) between MRI-/PET+ patients and MRI+ mesial temporal sclerosis patients (p=0.114). In this study, the long-term efficacy of anterior temporal lobectomy for the treatment of medically refractory temporal lobe epilepsy in 28 patients who presented with ipsilateral temporal PET hypometabolism and non-lesional MRI (PET+/MRI−) was compared to 87 patients who had mesial temporal sclerosis on MRI. Neuropsychological testing of memory, language, and intelligence was obtained prior to temporal lobectomy and then repeated at three months following surgery. The following neuropsychological tests were performed: verbal comprehension quotients from a Wechsler intelligence scale, a test of lexical verbal fluency (Controlled Oral Word Association Test), Trail Making Test, a Semantic Fluency Test (animals, fruits, vegetables), Chinese naming test, and the Auditory Verbal Learning Test. Only verbal comprehension scores were significantly different between the PET+/MRI− group and group with MTS prior to surgery (92.6 ± 7.7 vs. 88.3 ± 7.0). The PET+/MRI− group had a lower verbal comprehension score but higher Controlled Oral Word Association Test and Trail Making Test scores that the group with mesial temporal sclerosis. In the PET+/MRI− group, the Auditory Verbal Learning Test score

decreased following surgery. Interestingly, in the group with mesial temporal sclerosis, the Controlled Oral Word Association Test, Trail Making Test, Chinese naming test, and Auditory Verbal Learning Test scores improved following surgery.

In both of the aforementioned FDG-PET studies the investigators failed to perform a head-to-head study of MRI+/PET- vs. MRI+/PET+ patients. Therefore, it is unclear whether MRI structural damage alone (MRI+/PET-) or an interaction between hypometabolism and structural damage (MRI+/PET+) are responsible for the above results. vs. MRI+/PET- patients.

Predictors of post-operative neuropsychological decline have significant value in the pre-operative counselling of patients. In one study (Baxendale et al., 2006) employing a multivariate model, postoperative deterioration in verbal learning significantly associated with higher levels of preoperative function in both right and left temporal lobe resection groups. Older age at the time of the operation and a lower verbal IQ were additional significant predictors for the right temporal lobe resection group. Given MRI negative epilepsy patients have been shown to have higher pre-operative neuropsychological scores (Helmstaedter et al., 2011), it would not be unreasonable to hypothesise that this cohort of patients is at higher risk of cognitive decline.

3.3 Psychiatric outcomes in patients with MRI-negative epilepsy

There is a relative paucity of evidence for the psychiatric complications of epilepsy surgery compared to neuropsychological and neurological sequalae. Epilepsy patients have an increased risk of developing psychiatric disorders, such as mood, anxiety and psychotic disorders (Iranzo-Tatay et al., 2017). These psychiatric sequalae can also present de novo or

worsen following epilepsy surgery (Cleary et al., 2013), and may tarnish an otherwise good surgical outcome, resulting in significant distress for patients and their families (Cleary et al., 2013; Moss et al., 2009). Depression – which can occur as early as one month postoperatively (Wrench et al., 2009) – is the commonest psychiatric morbidity in patients with epilepsy, followed by anxiety (García-Morales et al., 2008; Iranzo-Tatay et al., 2017; LaFrance et al., 2008; Reynolds & Trimble, 2009). A systematic review found inconsistent findings in the studies comparing depression/anxiety score before and after epilepsy surgery (Cleary et al., 2013). Indeed, several studies have reported a reduction in the number of patients with self-reported depressive symptomatology or clinically confirmed depression (Altshuler et al., 1999; Kanner et al., 2009; Ring et al., 1998; Wrench et al., 2011), whilst some have reported no change in the prevalence of mood disorders pre- and post-surgery (Anhoury et al., 2000). For anxiety, studies have shown reduced (Cankurtaran et al., 2005; Kanner et al., 2009), no change (Cleary et al., 2013) or increased rates (Anhoury et al., 2000; Kohler et al., 2001; Malmgren et al., 2002) of anxiety following epilepsy surgery.

Limited studies have attempted to describe psychiatric outcomes in MRI-negative, cryptogenic epilepsy cohorts (Guangming et al., 2009; Hellwig et al., 2012; B. P. Hermann et al., 1992; Kanemoto et al., 1998; Kanner et al., 2009; Reuber et al., 2004). In some cases, researchers have not intentionally sampled MRI-negative patients (Kanemoto et al., 1998), whilst in others the post-operative psychiatric status is not described, presumably because of the small sample size and lack of statistical power (Hellwig et al., 2012). In other cases, patients with MRI-negative verified lesion, except for mesial temporal sclerosis – which accounted for 13% of patients in one series (B. P. Hermann et al., 1992) – were excluded, hence the results were grossly generalisable to those patients with chronic, intractable epilepsy not attributable to a mass lesion.

In one study (Hellwig et al., 2012), the pre-operative evaluation of baseline characteristics for 26 epilepsy patients revealed no significant difference in the rate of any psychiatric morbidity

(including affective disorder, dysphoric disorder, interictal dysphoric disorder, postictal dysphoric disorder, psychosis, organic brain syndrome and personality disorder) in cryptogenic vs. non-cryptogenic epilepsy cohorts. The group did not perform multivariate regression to tease out whether the presence of an MRI lesion predicted change in psychiatric morbidity post-operatively.

Systematic exploration of pre- and post-operative outcomes in MRI-negative epilepsy patients have been described infrequently. In one study (Guangming et al., 2009), investigators employed the Symptom Checklist-90-R (SCL-90): a self-report psychometric instrument from which a General Severity Index (GSI) can be calculated, which is an average score for all responded items and an serves as an overall score of psychiatric distress (Rytilä-Manninen et al., 2016). In this study, 62 patients with mesial temporal lobe epilepsy had undergone corticoamygdalohippocampectomy (anterior temporal lobe resection plus amygdalohippocampectomy) and no statistically significant difference was found in the pre-surgical and post-operative GSI scores (calculate 1 and 2 years postoperatively) between patients with MRI+ and MRI- patients. In another investigating post-operative depression (Beck Depression Inventory) in epilepsy patients who had undergone resective surgery (n=76), multivariate regression showed that an abnormal MRI status did not influence post-operative depression scores measured at approximately 16 months (mean).

Some studies have assessed cohorts of patients that may be generalisable to MRI-negative cohorts. In one tertiary centre study, the investigators noted that most patients with identifiable brain lesions were treated in the preceding medical facilities with the result that only patients without apparent MRI lesions were recruited in the study. In this Japanese study, researchers studied the pre-operative risk factors for post-surgical mood disorders – diagnosed using the DSM – in patients (n=38) who had undergone inferior (or inferior and middle) temporal lobectomy with hippocampoamygdalotomy. The incidence of pre-operative episodes of postictal psychosis were five times more frequent in the mood disorder group (38%) than in

the non-mood disorder group (7%). Patients with a left sided lobectomy predominated in the patients with post-operative mood disorders (88% v 50%). The simultaneous presence of these two factors predisposed the patients operated on to subsequently develop mood disorders with a significantly higher frequency.

Due to the lack of an identifiable MRI lesion, patients with MRI-negative epilepsy may have a larger extent of surgical resection of mesial structures, and this has been shown in one study (Kanner et al., 2009) to be independently associated with a seizure free status (Engel Classification 1A). Due to the bi-directional link between seizure-free status and improvement in psychiatric status, it may be plausible that MRI-negative patients who have undergone large resections have improved psychiatric status. However, it has been suggested that large resections may damage limbic structures, such as the amygdala – which is known to be involved in the modulation and expression of mood (Janak & Tye, 2015). It has been hypothesised that post-surgical mood disorders may arise form limbic dysfunction (Cleary et al., 2013), and evidence shows a correlation between the severity of mood disturbance (Anhoury et al., 2000; Paparrigopoulos et al., 2008) and the extent of hippocampal and amygdala resection.

3.4 Conclusion

In sum, there is inconsistent evidence that MRI-negative epilepsy patients are at a relatively heightened risk of post-operative cognitive decline compared to MRI-positive patients, and no evidence to suggest that pre- and post-operative psychiatric domains are different. The absence of adequately powered prospective research studies looking at psychiatric and neurocognitive domains at consecutive time-points over a long-term period makes it challenging to fully appreciate the impact of epilepsy surgery on these outcomes. There is also a need for more studies to explore the evolution of psychiatric morbidity and neurocognitive decline in extratemporal epilepsy. To my knowledge, no study has hitherto evaluated post-

operative neuropsychological and psychiatric outcomes, including the interrelationship between both domains, in MRI negative cohorts compared to MRI positive cohorts, which may be an interesting area of exploration in an adequately powered sample. Future studies looking at this landscape should employ a wider range of neuropsychological questionnaires and potential confounding variables – such as epilepsy duration, medications, education level and type of seizures – using a multivariate regression model.

Chapter 4. A retrospective study of prognostic markers for seizure freedom in patients following epilepsy surgery

4.1 Introduction

The efficacy and tolerability of neurosurgery for refractory epilepsy, defined as resistance to treatment with two appropriately chosen antiepileptic drugs, is well established in the literature (Liu et al., 2018; Téllez-Zenteno et al., 2005). For instance, in one classical randomised controlled trial of surgery for refractory temporal lobe epilepsy (Wiebe et al., 2001), the cumulative proportions of patients who were free of seizures impairing awareness at one year were 58 percent in the surgical group and 8 percent in the medical group (P<0.001) The proportions who were free of all seizures, including auras, were 38 percent in the surgical group and 3 percent in the medical group (P<0.001) (Wiebe et al., 2001). The quality of life was better among the patients in the surgical group than among those in the medical group (P<0.001), and it improved over time in both groups (P=0.003) (Wiebe et al., 2001).

Some studies estimate the delay between the onset of epilepsy to surgery to be in the region of 20 to 30 years, which can result in significant impairment in quality of life (Berg et al., 2003). Although surgery is highly efficacious for the treatment of refractory epilepsy it is commonly underutilised as physicians are unclear as to the predictors of short- and long-term success and the types of patients who may be suitable candidates (Engel, 2016).

The success of epilepsy surgery is usually defined by the postoperative seizure freedom as determined by the Engel classification (Vakharia et al., 2018). Several factors have been shown to potentially affect seizure freedom, including but not limited to the presence of a lesion on structural MRI (Foldvary et al., 1997; Muhlhofer et al., 2017; Pfänder et al., 2002), age at

seizure onset (Abou-Khalil et al., 1993; Ficker et al., 1999; Foldvary et al., 1997; Mathern et al., 1995), extratemporal epilepsy (Téllez-Zenteno et al., 2005), seizure type (McIntosh et al., 2004; Yoon et al., 2003), pre-operative epilepsy frequency (Edelvik et al., 2013; Foldvary et al., 2000; Mohan et al., 2018).

4.2 Aims and hypotheses

4.2.1 Primary aim

1) To assess the factors that predict post-operative seizure freedom in patients undergoing resective surgery for epilepsy

4.2.2 Hypotheses

1) I hypothesise that patients who have undergone extratemporal surgery for drug-resistant epilepsy will be less likely to be seizure-free at two years compared to patients who have undergone temporal lobectomies.
2) I hypothesise that patients with MRI-negative, drug-resistant epilepsy who have undergone lobectomy will be less likely to be seizure-free at two years compared to patients with MRI-positive epilepsy.
3) I hypothesise that drug-resistant epilepsy patients who have who have undergone left-sided resections will be less likely to be seizure-free at two years compared to those who have had right-sided resections.
4) I hypothesise that drug-resistant epilepsy patients who have undergone mesial temporal lobe resections will be more likely to be seizure-free at two years compared to those who have undergone lateral (neocortex) temporal lobe resections.

5) I hypothesise that drug-resistant epilepsy patients with pre-operative generalised seizures will be less likely to be seizure-free at two years compared to those without pre-operative generalised seizures.
6) I hypothesise that drug-resistant epilepsy patients with a higher number of pre-operative seizures will be less likely to be seizure-free at two years.
7) I hypothesise that sex will not influence whether drug-resistant epilepsy patients are seizure free at two years following lobectomy
8) I hypothesise that age at onset of seizures will not influence whether drug-resistant epilepsy patients are seizure-free at two years following lobectomy
9) I hypothesise that patients with unilateral lobe spikes on an electroencephalogram will be more likely to be seizure free at two years following lobectomy compared to those who do not.

4.3 Methodology

4.3.1 Study setting and inclusion criteria

Consecutive patients with medically refractory epilepsy who had undergone epilepsy surgery at the Walton Centre NHS Foundation Trust, Liverpool were included in the present retrospective study. The Walton Centre NHS Foundation Trust is a tertiary referral centre covering a catchment area of approximately 3 million people in the North West of England and additionally treats people with refractory epilepsy referred from Northern Ireland, North Wales and Yorkshire. A registry of patients who had undergone resective surgery for drug-resistant epilepsy between 2006 – 2017 was interrogated by the PhD student (Mamdouh Alenazi) who was supported by the project supervisor (Martyn Bracewell).

Patients met the following inclusion criteria:

1. Aged 18 – 65
2. Underwent resective surgery from 2006-2017
3. Two-point data (i.e. pre- and post-operative) on seizure outcomes
4. Epilepsy surgery with temporal or extratemporal resection
5. Clear onset of seizure by video telemetry
6. Failed to respond to antiepileptic medications for a minimum of two years (i.e., drug-resistant epilepsy).

Patients were excluded from the study if they met the following criteria:

1. Refused surgery
2. Did not have resective epilepsy surgery (i.e., received deep brain stimulation or vagal nerve stimulation).
3. Did not have two-point data for seizure outcomes
4. Had psychogenic seizures
5. Had seizures of unknown onset

4.3.2 Presurgical evaluation

All patients underwent a comprehensive standardised presurgical evaluation which included: (1) sex, (2) age at onset of seizures, (3) seizure frequency / month, (4) type of seizure and (5) MRI status (positive or negative). All patients had dedicated MRI scans with coronal gradient echo T1 sequence with continuous slices in the highest available resolution and T2 imaging perpendicular to the longitudinal axis of the hippocampus. The various parameters used to localise the lesion are listed in **table 8.**

T2 FLAIR SPACE SAG (Siem or IMRI)
T1 MPRAGE SAG (Siem or IMRI)
T2 Volume Spaave (Siemens or IMRI)
SAG CUBE FLAIR (MR2)
FSPGR COR 3D (MR2)
T2 Volume Cube (MR2)

Table 8. Parameters used in the study to localise the lesion

4.3.3 Operative details

Epilepsy surgery was performed by functional neurosurgeons who specialised in the surgical treatment of epilepsy.

4.3.4 Follow-up

Patients attended a follow-up consultation two years after the procedure. Seizure outcome was the only variable that was uniformly collected in all patients; hence this was the primary outcome of interest in our analysis. Patients were assigned an Engel seizure classification score, which was as follows: Class I, free of disabling seizures; class II, rare disabling seizures, 'almost seizure-free'; class III, worthwhile improvement; and class IV, no worthwhile improvement.

4.3.5 Ethical approval

Approval to conduct this study was obtained from Walton Centre NHS Foundation Trust, Liverpool and The Research Ethics Committee, Bangor University. This is a non-interventional, retrospective study thus was exempt from requiring individual patient consent.

4.3.6 Data labelling

Epileptic seizures

According to the international classification of epileptic seizures (ILAE, 2017), seizure types were divided into focal aware seizures, focal impaired awareness seizures and generalised seizures (Scheffer et al., 2017). For the purpose of statistical analysis, patients were divided into two groups: generalised seizures and focal seizures (with or without impaired awareness).

Structural MRI status

The MRI data were classed as positive and negative according to whether a lesion was identified on the scan.

Seizure outcomes

Regarding seizure outcome, patients were divided into two categories: (a) seizure-free group (Engel classification I) and (b) continuing seizure group (Engel classification II-IV). Seizure-freedom was defined as those patients that were seizure free until the assessment for at least 2 years post-surgery.

4.3.7 Statistical analysis

Descriptive statistics were initially used to summarise the data in order to identify the underlying patterns in the preliminary stage of the analysis.

Tests of associations were used to determine the statistically significant relationships between the dependent and independent variables. The relationship between seizure outcome (dependent variable) with gender (male or female), presence of unilateral ictal spikes on EEG,

presence of generalised seizures, laterality (left or right hemisphere), MRI status (positive or negative), location (temporal or extratemporal) and position on the temporal lobe (mesial or lateral temporal lobe) were analysed using the chi square test. An independent sample t test has been used to determine the association between the seizure outcomes with age at seizure onset and preoperative seizure frequency.

Because the dependent variable “seizure outcome” is nominal with two levels of outcomes, binary logistic regression was used to ascertain the effects of the dependent variables on the independent variable.

The Statistical Package for the Social Sciences (SPSS) version 27.0.1.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis and $P < 0.05$ was considered a statistically significant difference.

4.4 Results

4.4.1 Descriptive statistics

A total of 83 patients were included in the sample. Among the respondents 48 (57.8%) of them were female and 35 (42.2%) of them were male **(Figure 3).** The mean seizure frequency was 23.24±20.98 per month with the range of 1 to 70. The mean age of onset was 15.05±9.17 years with the range of 1 to 47 years. According to the video EEG, 11 (13.3%), 6 (7.2%) and 67 (80.7%) of them had positive results on bilateral lobes (spikes on both hemispheres), multi focal lobes (spikes on several lobes in a single hemisphere) and unilateral local lobe (spikes on a single lobe) respectively **(Figure 4).** Considering seizure types, 17 (20.5%) respondents had generalised seizures, 68 (81.9%) respondents had focal impaired awareness seizures and 20 (24.1%) had focal aware seizures **(Figure 4).** Fifty (60.2%) out of 83 patients have left-sided resections while 33 (39.8%) of them have right-sided resections. Among the temporal

and extra temporal lobe epilepsy patients 49 (40.6%) and 19 (15.7%) of them were MRI positive, respectively. 22 (26.5%) were extra temporal epilepsy patients while 61 (73.5%) of them were temporal lobe epilepsy patients.; of these, 41 (67.2%) respondents were mesial temporal sclerosis patients while 20 (32.8%) respondents were lateral patients. 40 (48.2%) patients had continuing seizures at two years and 43 (51.8%) patients were seizure free after two years **(Figure 5).**

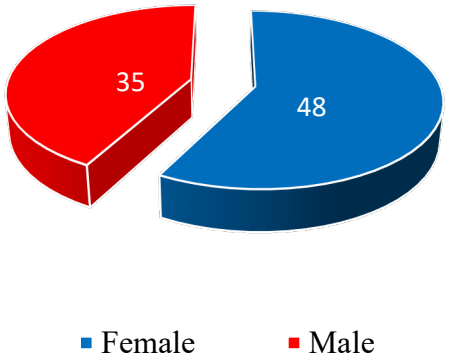


Figure 3. Gender

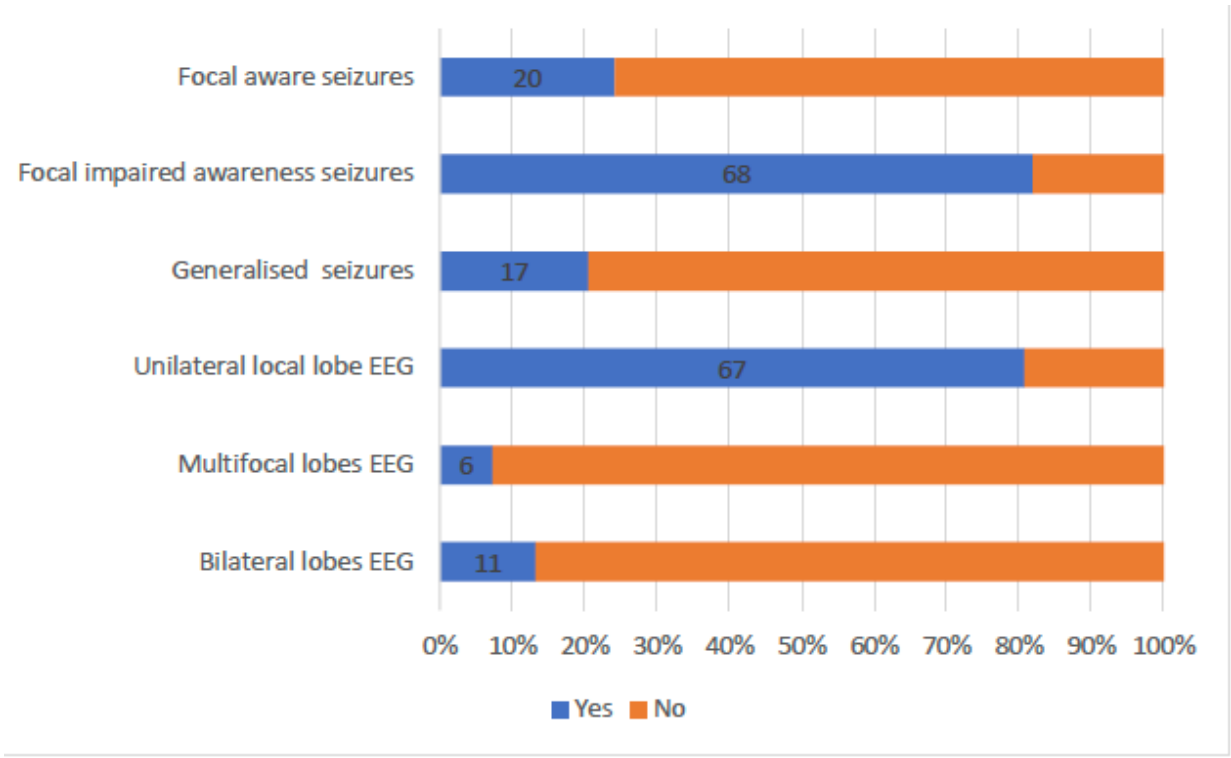


Figure 4. Video EEG results and seizure types

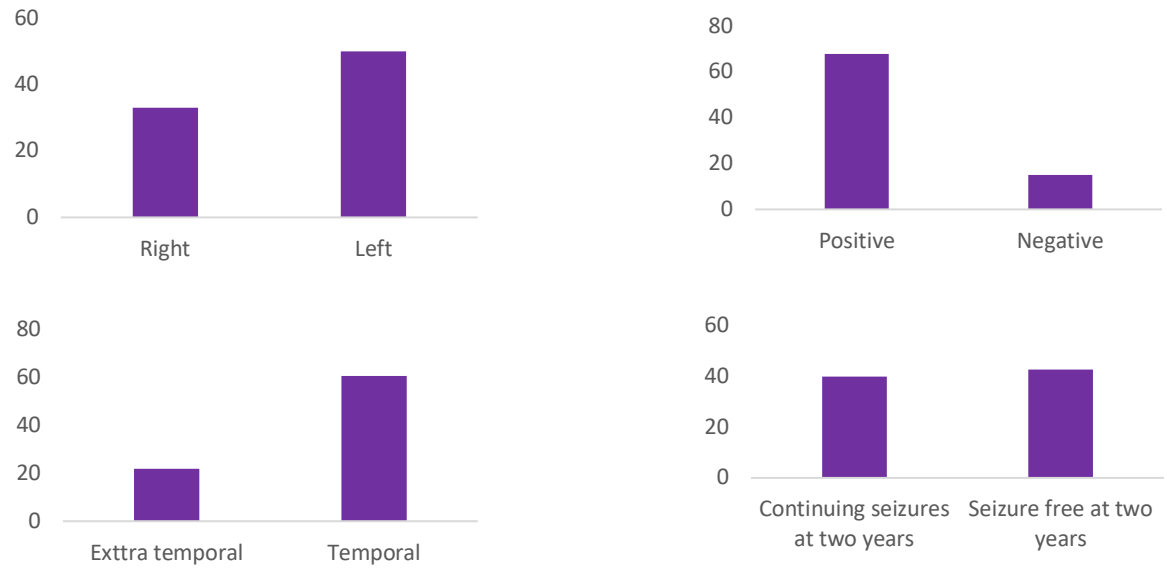


Figure 5. Hemisphere laterality (top left), MRI status (top right), Location (bottom left) and seizure outcome (bottom right)

4.4.2 Association between seizure outcome and independent variables

Age at onset of epilepsy

The p-value of Levene's test is 0.340: there is not enough evidence to reject the null hypothesis of the Levene's test and concludes that equal variance assumed should be considered. Therefore, there was a significant difference in mean age between patients who continuing seizures at two years and patients were seizure free after two years with $t_{81} = -2.736$, p-value

= 0.008 <0.05. Hence, our results show that patients with an earlier age at onset of epilepsy have worse post-operative seizure outcomes.

Pre-operative seizure frequency

The p-value of Levene's test is 0.136, thus there is not enough evidence to reject the null hypothesis of the Levene's test and concludes that equal variance assumed should be considered. Therefore, there was a significant difference in mean preoperative seizure frequency between patients who had continuing seizures at two years and patients who were seizure free after two years with $t_{81} = 4.124$, p-value <0.001. Hence, our results show that patients with a higher number of pre-operative seizures have a greater chance to continue to suffer seizures at two years.

Gender

There is no statistical significant association between gender and seizure outcomes with $X^2(1) = 0.69$, p-value = 0.406 > 0.05. Therefore, both male and females equally had chances to have seizures post epilepsy surgery.

Pre-operative video EEG

I compared patients with unilateral local lobe involvement with patients with either multifocal lobe or bilateral involvement. There is a statistically significant association between having unilateral local lobe involvement and good seizure outcome with $X^2(1) = 8.675$, p-value = 0.003 <0.05. The strength of the association is moderate (Phi =0.323).

Preoperative seizure type

I compared patients with generalised and focal (with or without impaired awareness). There is a statistically significant association between patients with generalised seizures and poor seizure outcomes with $X^2(1) = 13.729$, p-value <0.001. The strength of the association is moderate (Phi =0.407).

Laterality (hemisphere affected)

There is no statistically significant association between laterality and seizure outcomes with $X^2(1) = 0.002$, p-value = 0.965 > 0.05. Therefore, patients with both left-sided and right-sided resections equally had chances to have seizures post epilepsy surgery.

MRI status (positive vs. negative)

There is no statistically significant association between MRI status and seizure outcomes with $X^2(1) = 0.492$, p-value = 0.483 > 0.05. Therefore, patients with both positive and negative status equally had chances to have seizures post epilepsy surgery.

Temporal vs. extratemporal lobectomy

There is a statistically significant association between temporal and extra temporal epilepsy patients and seizure outcomes with $X^2(1) = 13.556$, p-value <0.001. The strength of the association is moderate (Phi =0.404). Extratemporal patients have a worse outcome.

Mesial vs. lateral temporal lobe epilepsy

There is no statistically significant association between mesial and lateral temporal sclerosis patients and seizure outcomes with $X^2(1) = 0.200$, p-value = 0.655 > 0.05. Therefore, patients

with both mesial and lateral temporal sclerosis equally had chances to have seizures post epilepsy surgery.

4.4.3 Model building

Variables that were associated with seizure outcome (age at onset of seizures, preoperative seizure frequency, unilateral local lobe spikes on EEG, generalised seizures and temporal/extra temporal epilepsy) were used for the model building process.

Model – Seizure outcome

Parameter	Estimate	Standard error	Wald	df	Sig.	Exp (B)
Age onset	0.030	0.035	0.726	1	0.394	1.030
Frequency	-0.028	0.015	3.530	1	0.060	0.972
Un_Lob=Y	1.412	0.819	2.973	1	0.085	4.103
Gen_S.z=Y	-2.202	0.880	6.265	1	0.012	0.111
Location Temp=Y	1.838	0.727	6.395	1	0.011	6.281
Constant	-1.897	1.072	3.131	1	0.077	0.150

Table 9. Parameter estimation. [Age onset] is age at onset of seizures; [Frequency] is preoperative seizure frequency; [Un Lob=Y] is unilateral local lobe on (EEG) ;[Gen S.z= Y] is presence of generalised seizure; [Location Temp=Y] is temporal lobe seizure.

The model explained 50.8% (Nagelkerke R^2) of the variance in seizure outcomes and correctly classified 79.5% of cases. Increasing seizure frequency was associated with a decreased likelihood of exhibiting seizure-freedom with p-value =0.060 <0.1. Patients with unilateral local lobe were 4.103 times more likely to exhibit seizure freedom than patients without unilateral local lobe with p-value =0.085 <0.1. Patients with generalised seizures were 0.111 times less likely to exhibit seizure freedom than patients without generalised seizures with p-value =0.012 <0.05. Patients with temporal lobe resections were 6.281 times more likely to exhibit seizure freedom than patients with extra temporal with p-value =0.011 <0.05 **(Table 9).** The goodness of fit test, $X^2(8) = 5.396$, p-value = 0.715 > 0.05 suggests that the fit of the model is adequate **(Table 10).**

Chi-Square	df	Sig.
5.396	8	0.715

Table 10. Hosmer and Lemeshow test

4.5 Discussion

In my study, the following factors were associated with seizure freedom: (1) lower frequency of pre-operative seizures; (3) unilateral local focus; (4) non-generalized seizures; (5) temporal lobe resections

My binary logistic regression uncovered a significant relationship between seizure type and postoperative seizure freedom at two years. Patients with generalised seizures were 0.111 times less likely to exhibit seizure-freedom than patients without generalised seizures, p-value =0.012. In general, the published literature suggests that patients with generalised seizures tend to have the worst prognosis postoperatively compared to other seizure subtypes. In one study, after adjustment for preoperative pathology, only the presence of preoperative secondarily generalised seizures (new terminology: focal to bilateral seizures) had a significant association with seizure recurrence (McIntosh et al., 2004). To add to this, in a study of 396 operated patients who were followed-up over a period of two years, the absence of generalised seizures was significantly and independently associated with remission, but only in the mesial temporal resection group (Bergen, 2006). Patients who had a history of tonic-clonic seizures still had a 64.6% chance of achieving a two-year seizure remission, as opposed to a 79.4% chance for those with no such history (Bergen, 2006). The reason for the poor prognosis in patients with secondary generalized seizures is unknown, but it would not be unreasonable to hypothesise that these seizures are a manifestation of a more widespread epileptogenic zone or of secondary epileptogenesis (McIntosh et al., 2004; Yoon et al., 2003). Therefore, it is possible that the complete epileptogenic circuit is not removed in epilepsy surgery and that the residual epileptogenic zone could precipitate further seizures.

My binary logistic regression showed that patients with temporal lobectomies were 6.281 times more likely to exhibit seizure freedom than patients with extra temporal with p-value =0.011 <0.05. Few studies have explored the long-term outcomes of patients who have undergone temporal lobe epilepsy surgery (Elsharkawy et al., 2008; Noe et al., 2013). A previous study showed no significant differences in the probability of seizure freedom between extratemporal and temporal lesionectomies (Mohan et al., 2018). Other studies have reported better prognosis for patients who undergo temporal vs. extratemporal lesionectomies, although the differences are not particularly marked. For example, extratemporal lobe epilepsy is reported to have a 29%-56% success rate whilst for temporal lobe epilepsy surgery is approximated to have a 41%-65% success rate (Noe et al., 2013). One systematic review and meta-analysis of 76 resective epilepsy surgery studies (Téllez-Zenteno et al., 2005) concluded that the long term seizure freedom for extratemporal (i.e., occipital, parietal and frontal lobes) was lower than temporal lobe epilepsy. The effectiveness of temporal lobe epilepsy is thought to be related to the fact that temporal lobe epilepsy commonly originates from the anteriomesial temporal lobe (anterior temporal neocortex, amygdala, and hippocampus), a network commonly involved in epileptogenesis that is entirely resected in a standard anterior temporal lobectomy (Noe et al., 2013).

In univariate analysis I showed a significant difference in the mean age at seizure onset between patients who had continuing seizures at two years vs. patients who were seizure free after two years with $t_{81} = -2.736$, p-value = 0.008. My results are consistent with findings from (d' Orio et al., 2017) who showed a strong correlation between poor seizure outcome and early age at seizure onset (median age of Engel class I and Engel class II–IV was 26 years and 16.5 years, respectively; p = 0.0381), although regression did not show a relationship between age of seizure onset and seizure outcome. In another study, Aguglia et al., (2011) showed that patients (n=190, normal MRI) achieving 24-month seizure freedom had a significantly older age at onset of epilepsy (33.5 ± 19.9 vs 17.2 ± 14.4 years).

On the other hand, some earlier studies have reported no association between age of onset of epilepsy and seizure freedom following epilepsy surgery (Abou-Khalil et al., 1993; Ficker et al., 1999; Foldvary et al., 1997; Mathern et al., 1995). As an example, in a study of 366 patients who underwent anterior temporal lobectomy in an Australian centre, age of seizure onset was not found to be associated with seizure recurrence (McIntosh et al., 2004). Similarly, Asadi-Pooya & Sperling (2015) showed that patients with childhood-onset (i.e., age at onset of the first afebrile habitual seizure below ten years), medically refractory mesial temporal sclerosis and temporal lobe epilepsy fared similarly to patients with adult-onset disease (i.e. age at onset of the first afebrile habitual seizure age 20 years or above).

In univariate analysis I show that patients with a higher number of pre-operative seizures had a greater probability of having seizures at two years with $t_{81} = 4.124$, p-value <0.001. These results are consistent with the literature (Edelvik et al., 2013; Foldvary et al., 2000; Mohan et al., 2018). For instance, in one nationwide prospective study conducted in Sweden, multivariate analysis identified a higher baseline frequency of seizures to be a negative predictor of post-operative seizure-free days (Edelvik et al., 2013).

In my study, the presence of a lesion on structural MRI was not shown to have any effect on seizure freedom at two years. This result is, at first glance, unexpected. In a systematic review and meta-analysis of 40 studies (Téllez-Zenteno et al., 2010), the odds of being seizure-free after resective surgery (minimum one year follow-up) were 2.5 times higher in patients with lesions on MRI (OR 2.5, 95%CI 2.1, 3.0, $p < 0.001$). In patients with temporal lobe epilepsy surgery the odds were 2.7 times higher in those with lesions (OR 2.7, 95%CI 2.1, 3.5, $p < 0.001$). In patients with extratemporal epilepsy surgery the odds were 2.9 higher in those with lesions (OR 2.9, 95%CI 1.6, 5.1, $p < 0.001$). The pathophysiological basis underpinning the worse seizure outcomes in non-lesional resective epilepsy surgery is thought to be a result of the presence of a more widespread epileptogenic network, inadequate epileptogenic zone resections, or presurgical false localisation error (Foldvary et al., 1997; Muhlhofer et al., 2017;

Pfänder et al., 2002). The poorer clinical outcomes in MRI-negative vs MRI-positive cohorts are thought to be a result of the presence of a more widespread epileptogenic network, inadequate epileptogenic zone resections, or presurgical false localisation error (Muhlhofer et al., 2017; Pfänder et al., 2002).

Why did I not find a comparable result? It is possible that the small sample size of MRI - negative patients (nine in the seizure-free group and six in the seizure group) limited robust analysis of the effects of MRI status on seizure outcomes. It is also plausible that, in the absence of an MRI-defined lesion, patients were subject to more stringent selection before being offered surgery: thus, only the patients with clearly defined epileptogenic foci on electroencephalography had resective surgery.

Chapter 5. A retrospective study of prognostic markers for psychiatric outcomes in patients following epilepsy surgery

5.1 Introduction

Anxiety and depression are the most common psychiatric disorders in epilepsy patients, and their prevalence is higher than in the general population (Kwon & Park, 2014; Reuber et al., 2004). There is also evidence of a putative biological gradient between depression severity and the risk of epilepsy, as well as the odds of worse seizure outcome (Josephson et al., 2017).

Depression and anxiety are co-morbid in many non-epilepsy patients and are managed by similar pharmacological and psychosocial strategies (Coplan et al., 2015). The prognosis for patients with comorbid anxiety and depression is thought to be worse than patients with anxiety alone e.g. patients with co-existing conditions are thought to have a greater intolerance of uncertainty, poor problem orientation, cognitive avoidance, and beliefs about worry (Dupuy & Ladouceur, 2008). This observation extends to people with epilepsy in whom co-morbid depression and anxiety is thought to impair quality of life more significantly as compared to patients with a single diagnosis (Kwon & Park, 2014).

Studies have reported an improvement (Blumer et al., 1998; Derry et al., 2000; Devinsky et al., 2005; Reuber et al., 2004), deterioration (Altshuler et al., 1999), or no change in postoperative depression and anxiety scores (Macrodimitris et al., 2011; Spencer et al., 2003) following surgery for drug-resistant epilepsy.

5.2 Aims and hypotheses

5.2.1 Primary aim

1) To assess the factors that predict post-operative anxiety and depression in patients undergoing resective surgery for epilepsy

5.2.2 Hypotheses

1) I hypothesise that MRI-negative drug-resistant epilepsy patients will have worse psychiatric outcomes (anxiety and depression) than MRI-positive patients.
2) I hypothesise that patients with preoperative generalised seizures will have worse psychiatric outcomes (anxiety and depression) than focal seizure patients.
3) I hypothesise no relationship between age at seizure onset and post-operative psychiatric morbidity.
4) I hypothesise that patients who are seizure-free at two years will have better psychiatric outcomes compared to patients with ongoing seizures.
5) I hypothesise that patients with a lower preoperative seizure frequency will have better postoperative psychiatric outcomes.
6) I hypothesise that patients with temporal lobe resections will have worse postoperative psychiatric outcomes compared to extratemporal lobe resections.
7) I hypothesise that patients with mesial lobe resections will have worse postoperative psychiatric outcomes compared to patients with lateral resections.
8) I hypothesise that patients with left-sided resections will have worse postoperative psychiatric outcomes compared to patients with right-sided resections.
9) I hypothesise that patients with unilateral hemispheric discharges on electroencephalogram will have worse postoperative psychiatric outcomes vs. patients who do not following epilepsy surgery.

10) I hypothesise that sex will not influence postoperative psychiatric outcomes following epilepsy surgery.

5.3 Methodology

5.3.1 Study setting and inclusion criteria

See section 4.3.1 for study setting

Inclusion and exclusion criteria as detailed in section 4.3.1 in addition to the following;

Two-point data (i.e., pre-and post-operative) on anxiety and depression scores

5.3.2 Presurgical evaluation

See section 4.3.2.

5.3.3 Psychiatric assessment

The Hospital Anxiety and Depression Scale (HADS) was used to assess depression and anxiety during the pre-operative workup and two years following epilepsy surgery. The HADS provides scores for anxiety and depression symptom severity. It is a validated fourteen item scale stratified into three meaningful, validated and clinically distinct ranges. Seven of the items on the scale relate to anxiety and seven relate to depression. Each item on the questionnaire is scored from 0-3 and this means that a person can score between 0 and 21 for either anxiety or depression. A score within the range 0-7 is normal, a score within the range 8-10 is borderline abnormal (borderline case) and a score within the range 11-21 is abnormal (case), **see table 12.** Anxiety and depression status were assessed by a consultant neuropsychologist at two timepoints: (a) in the pre-operative workup and (b) two years following epilepsy surgery. The neuropsychologist assessed the pre- and post-operative HADS scores.

Range on Hospital Anxiety and Depression Scale	Diagnosis
0 – 7	Normal
8 – 10	Borderline abnormal (borderline case)
11 – 21	Abnormal (case)

Table 12. The clinical ranges for the hospital anxiety and depression scale.

5.3.4 Operative details

See section 4.3.4

5.3.5 Follow-up

Patients attended a follow-up consultation two years after the operation. Psychiatric status (depression and anxiety) was the primary outcome of interest.

5.3.6 Ethical approval

See section 4.3.6

5.3.7 Data labelling

Epileptic seizures

According to the international classification of epileptic seizures ILAE (2017), seizure types were divided into focal aware seizures, focal impaired awareness seizures and generalised seizures (Scheffer et al., 2017). For the purpose of statistical analysis, patients were divided into two groups: generalised seizures and focal seizures (with or without impaired awareness).

Structural MRI status

The MRI data were classed as positive and negative according to whether a lesion was identified on the scan.

Psychiatric outcomes

Patients were divided into three categories: (a) improvement (b) deterioration and (c) no change. In this study, 'improvement' was assigned when a patient improved on the clinical range of the HADS scale **(see table 12)** e.g., a patient transitioned from "abnormal case" to "borderline case" or "borderline case" to "normal". The term "deterioration" was assigned when a patient deteriorated on the clinical range of the HADS scale **(see table 12)** e.g., a patient transitioned from "normal" to "borderline case" or "borderline case" to "case". The term "no change" was assigned when a patient remained within the same clinical range **(see table 12).** Therefore, the dependent variables are ordinal.

Seizure outcomes

Regarding seizure outcome, patients were divided into two categories: (a) seizure-free group (Engel classification I) and (b) continuing seizure group (Engel classification II-IV). Seizure freedom was defined as being seizure-free until the assessment for at least ≥ 2 years post-surgery. Therefore, these independent variables are categorical.

5.3.8 Statistical analysis

Descriptive statistics were initially used to summarise the data in order to identify the underlying patterns in the data in the preliminary stage of the analysis.

Univariate analysis was performed to identify the relationship between the dependent and independent variables. The relationship between anxiety and depression scores (independent variables) with sex (male / female), electroencephalogram (EEG) findings (presence or absence of a single focus on EEG), preoperative generalised seizures (presence or absence), presence of a structural lesion on MRI (presence or absence), temporal lobe resection (presence or absence), mesial or temporal lobe resection, and post-operative seizure status (ongoing or freedom) were analysed using the Mann Whitney U test. Kendall's Tau-b was used to determine the association between the depression and anxiety score change with age at seizure onset and pre-operative seizure frequency (number/month).

The ordinal regression method was used in the study as the dependent variables "anxiety score change" and "depression score change" are ordinal. The test of parallel lines was used to check the validity of the proportional odds assumption. Likelihood ratio deviance and Pearson chi-square statistics were used to measure the fitness of the model.

The Statistical Package for the Social Sciences (SPSS) version 27.0.1.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis and $P < 0.05$ was considered a statistically significant difference for the statistical methods.

5.4 Results

5.4.1 Descriptive statistics

50 patients satisfied the criteria for inclusion in the study. Twenty-six (52%) of them were female and 24 (48%) of them were male **(Figure 6).** The mean seizure frequency was 22.92±20.91 months with the range of 1 to 68 months. The mean age of onset was 14.88±8.42 years with the range of 2 to 40 years.

Regarding the video EEG data, 6 (12%), 2 (4%) and 43 (86%) had involvement of bilateral lobes, multifocal lobes and unilateral local lobe respectively **(Figure 7).**

Considering seizure types, 12 (24%) had generalized seizures, 38 (76%) had focal impaired awareness seizures and 13 (26%) had focal aware seizures **(Figure 7).**

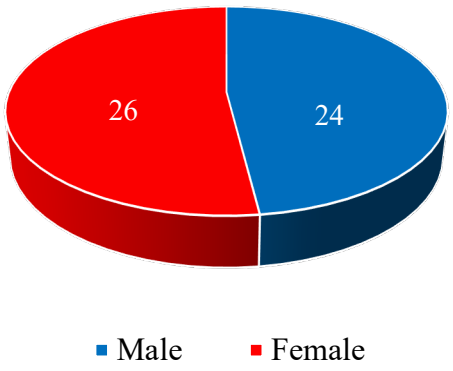


Figure 6. Gender

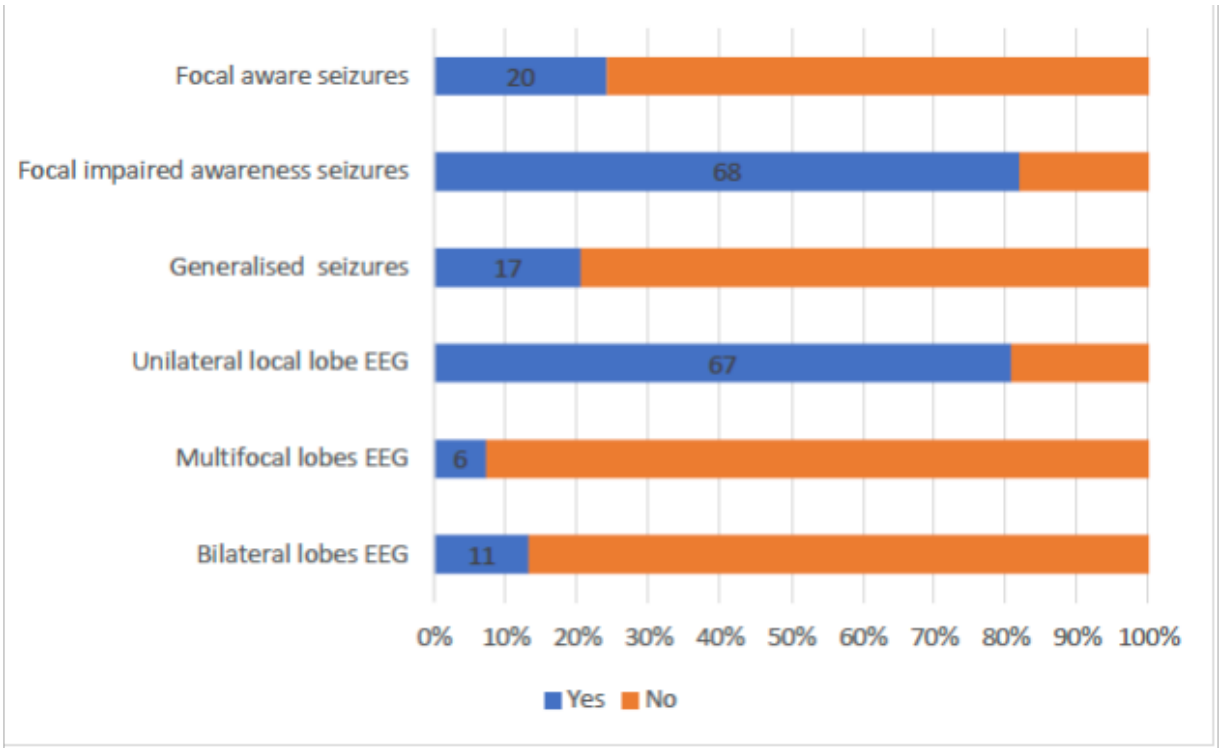


Figure 7. Video EEG results and seizure types

Thirty (60%) out of 50 patients had left-sided resections while 20 (40%) patients had right-sided resections. Among the temporal and extra-temporal lobe epilepsy patients 28 (56%) and 10 (20%) were MRI positive respectively. Twelve (25.5%) patients had extra temporal epilepsy while 35 (74.5%) had temporal lobe epilepsy. Of these, 26 (70.3%) patients had mesial temporal resection and 11 (29.7%) had lateral temporal lobe resection. Twenty-four (48%) patients had continuing seizures at two years and 26 (52%) patients were seizure free after two years **(Figure 8).**

Seventeen (34%), 22 (44%) and 11 (22%) patients had an improvement, no change and deterioration respectively in the anxiety scores. Twelve (24%), 27 (54%) and 11 (22%) patients had an improvement, no change and deterioration respectively in the depression scores **(Figure 9)**. With regards to left-sided resections (n=30), 8/30 (26.7%) patients had worse anxiety outcomes, 14/30 (46.7%) had similar pre-operative and post-operative anxiety scores whilst 8/30 (26.7%) had improved anxiety outcomes. With regards to right-sided resections (n=20), 3/20 (15.0%) patients had worse depression outcomes, 8/20 (40.0%) had similar pre- and post-operative depression outcomes, and 9/20 (45.0%) had an improvement in depression outcomes.

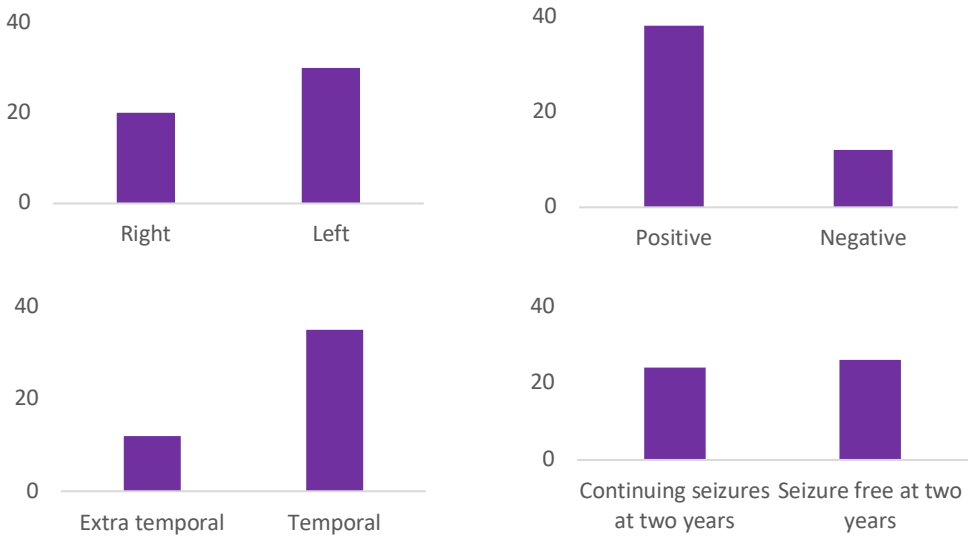


Figure 8. Laterality (top left), MRL status (top right), Location (bottom left) and seizure outcome (bottom right)

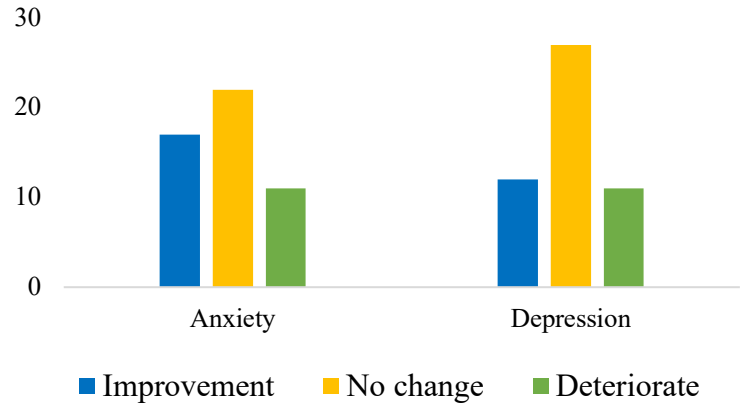


Figure 9. Anxiety and depression

5.4.2 Association between psychiatric status (anxiety, depression) and independent variables

The Mann Whitney U Test was used to assess the relationship between changes in anxiety and depression scores with gender, unilateral local lobe involvement on EEG, generalised seizures, temporal lobe involvement, mesial or lateral temporal lobe resection, presence of a lesion on structural MRI and seizure outcome. Kendall's Tau-b was used to identify the relationship between the continuous dependent variables (age at seizure onset and preoperative seizure frequency) with the change in depression and anxiety scores. The results of univariate analysis are presented in **table 13.**

Following univariate analysis, only those variables that were associated with a change in anxiety and depression at the 20% level were included in the model building process.

Anxiety

The variables that were significant at the 20% level were gender, unilateral local lobe involvement or not on EEG, generalised or focal seizures, extratemporal/temporal lobe involvement, mesial/lateral temporal lobe, and seizure outcome.

In ordinal logistic regression female patients were less likely to exhibit anxiety than male patients, p-value =0.017 <0.05. Patients with left-sided laterality were more likely to exhibit anxiety than patients with right-sided laterality, p-value =0.082 <0.1. Patients with mesial temporal lobe more likely to exhibit anxiety than patients with lateral temporal lobe, p-value = 0.050 <0.05 **(Table 14).**

The chi-square statistics indicates that the final model for anxiety gave a significant improvement over the baseline intercept-only model with $X^2(6) = 17.877$, p-value = 0.007 < 0.05 **(Table 15).** The significance value of the test is over the preferred 5% level of significance; $X^2(6) = 18.977$, p-value = 0.004 > 0.001 **(Table 15).** Hence, the test concludes that the model holds proportional odds assumptions. Pearson and Deviance tests have p-values values greater than 0.05 suggesting that the fit of the model is adequate **(Table 15).**

Depression

The variables that were significant at the 20% level were gender, generalised seizures, laterality, mesial/lateral temporal lobe, and seizure outcome **(see table 13).**

In ordinal logistic regression I show that patients with generalized seizures were less likely to exhibit depression than patients with other seizure types, p-value =0.018 <0.05. Patients with left-sided laterality were more likely to exhibit depression than patients with right-sided laterality with p-value =0.049 <0.05 **(table 16).**

The chi-square statistics indicates that the final model gives a significant improvement over the baseline intercept-only model with $X^2(5) = 20.948$, p-value =0.001 < 0.001 **(Table 17).** The significance value of the test is over the preferred 5% level of significance; $X^2(5) = 10.993$, p-value = 0.052 > 0.05 **(Table 17).** Hence, the test concludes that the model holds proportional odds assumptions. Pearson and Deviance tests have p-values values greater than 0.05 suggesting that the fit of the model id adequate **(Table 17).**

Outcome	Variable	P-value	Conclusion
Anxiety	Gender	0.110***	Association
	Age at onset of seizures	0.625	No association
	Preoperative seizure frequency	0.928	No association
	Unilateral local lobe on EEG	0.125***	Association
	Generalised seizures	0.044*	Association
	Laterality	0.160***	Association
	Lesion on structural MRI	0.558	No association
	Temporal lobe involvement	0.553	No association
	Mesial or lateral temporal lobe	0.034*	Association
	Seizure outcome	0.069**	Association
Depression	Gender	0.150***	Association
	Age at onset of seizures	0.462	No association
	Preoperative seizure frequency	0.352	No association
	Unilateral local lobe on EEG	0.497	No association
	Generalised seizures	0.003*	Association
	Laterality	0.019*	Association
	Lesion on structural MRI	0.555	No association
	Temporal lobe involvement	0.892	No association
	Mesial or lateral temporal lobe	0.127***	Association
	Seizure outcome	0.153***	Association

Table 13. Univariate analysis for psychiatry scores
Levels of statistical significance are as follows:
*:- Variable is significant at 5% level
**:- Variable is significant at 10% level
***:- Variable is significant at 20% level

Parameter	Estimate	Standard error	Wald	df	Sig.
Anx_change = Imp	1.305	1.590	0.674	1	0.412
Anx_change = Det	4.047	1.722	5.525	1	0.019
Gender=F	-1.866	0.780	5.719	1	0.017
Un_Lob=N	0.858	1.130	0.576	1	0.448
Focal S.z	0.460	1.118	0.170	1	0.680
Laterality=L	1.405	0.809	3.017	1	0.082
Mesial	1.756	0.896	3.838	1	0.050
S.z Outcome=Con	1.352	0.839	2.594	1	0.107

Table 14. Parameter estimation for anxiety. [Anx_change=Imp] is improvement in anxiety state; [Anx_change=Det] is deterioration in anxiety state; [Gender=F] is female; [Un_Lob=N] is multilobe or bilateral involvement on EEG; [Focal S.z] is the presence of focal seizures; [Laterality=L] is left-sided resections; [Mesial] is mesial temporal lobe involvement; [S.z Outcome=Con] is continuing seizures.

Model

	Chi-Square	df	Sig.
Model fitting information			
	17.877	6	0.007
Test of parallel lines			
	18.977	6	0.004
Goodness of fit test			
Pearson	25.552	30	0.698
Deviance	29.783	30	0.477

Table 15. Model fitting information for anxiety.

Parameter	Estimate	Standard error	Wald	df	Sig.
Dep_Change = Imp	-3.335	1.714	3.786	1	0.052
Dep_Change = Det	0.080	1.705	0.002	1	0.963
Gender=F	-0.585	0.744	0.618	1	0.432
Focal S.z	-3.296	1.392	5.605	1	0.018
Laterality=L	1.572	0.800	3.859	1	0.049
Mesial	0.622	0.800	0.605	1	0.436
Outcome=Con	0.209	0.840	0.062	1	0.803

Table 16. Parameter estimation for depression. [Dep_Change = Imp] is improvement in depression state; [Dep_Change = Det] is deterioration in depression state; [Gender=F] is female; [Focal S.z] is the presence of focal seizures; [Laterality=L] is left-sided resection; [Mesial] is mesial temporal lobe resection; [S.z Outcome=Con] is continuing seizures.

	Chi-Square	df	Sig.
Model fitting information			
	20.948	5	0.001
Test of parallel lines			
	10.993	5	0.052
Goodness of fit test			
Pearson	22.388	25	0.613

Deviance	23.359	25	0.557

Table 17. Model fitting information for depression

5.5 Discussion

In this study, ordinal logistic regression revealed that female patients were less likely to exhibit anxiety postoperatively than male patients with a p-value =0.017. Patients with left-sided laterality were more likely to exhibit anxiety than patients with right-sided laterality with p-value =0.082. Patients with mesial temporal lobe resections are more likely to exhibit postoperative anxiety than patients with lateral temporal lobe, p-value =0.050. Patients with generalized seizures were less likely to exhibit postoperative depression than patients with other seizure types, p-value =0.018. Patients with left-sided laterality were more likely to exhibit depression than patients with right-sided laterality with p-value =0.049.

Women in general have a markedly greater prevalence of anxiety disorder than men (Hantsoo & Epperson, 2017): the causes for this are thought to be multifactorial. However, in people with epilepsy and those in epilepsy surgery cohorts, there is no robust evidence to suggest an independent relationship between gender and postoperative anxiety (Devinsky et al., 2005; Macrodimitris et al., 2011). In a sample of 70 patients who underwent surgery for temporal lobe epilepsy, female patients were found to be at greater risk of developing anxiety over the first year after surgical treatment (Pintor et al., 2007). Our results may be explained by the fact that females are both likelier and have a greater severity of preoperative anxiety compared to males, which has previously been shown by Devinsky et al., (2005). Therefore, any improvement in anxiety that arises from epilepsy surgery will be more marked for females compared to males.

Patients with left-sided laterality were demonstrated to be at greater risk of depression than patients with right-sided laterality with p-value =0.049 <0.05. Logistic regression also suggested that patients with left-sided seizure laterality were more likely to exhibit postoperative anxiety compared to patients with right-sided resections, p-value =0.082, but this failed to reach statistical significance. Several studies have examined the effects of laterality on depression and anxiety, but no clear, consistent pattern has been emerged. Some studies have suggestion that right sided resections are a greater risk factor for postoperative psychopathology (e.g. depression and anxiety) (Glosser et al., 2000; Kohler et al., 1999; Quigg et al., 2003; Taylor, 1972), whilst others have suggested that left sided resections are a greater risk factor for this complication (Malmgren et al., 2002; Quigg et al., 2003). Other studies have shown no relationship between laterality and postoperative psychopathological status (Devinsky et al., 2005; Macrodimitris et al., 2011; Meldolesi et al., 2007; Rayner & Wilson, 2012). These mixed findings have also been replicated in cohorts that have undergone surgery for tumour resection (Irle et al., 1994; Pringle et al., 1999). In one study conducted at the Cleveland Clinic, Prayson et al., (2017) investigated the relationship between the exact cerebral lobe and postoperative anxiety and depression. Patients who underwent left temporal lobe resections reported a reduction in symptoms of anxiety and depression, whilst those who underwent left frontal lobe resections did not report significant post-operative anxiety and depression changes. On the other hand, psychological outcomes after right-sided resections were no different in temporal and frontal lobe resection patients, with reported improvements in depression and anxiety postoperatively (Prayson et al., 2017).

My logistic regression demonstrated that patients with mesial temporal sclerosis experience higher postoperative rates of anxiety compared to those with neocortical lesions. Patients with mesial temporal sclerosis have been reported to experience greater rates of preoperative anxiety and depression compared to patients with neocortical lesions (Quiske et al., 2000). There is also evidence that patients with mesial temporal lobe sclerosis experience a greater

frequency of mood disorders when treated with antiepileptic drugs (Mula et al., 2003). Consistent with my findings, several studies have reported worse psychiatric status in patients with mesial temporal sclerosis (Garcia, 2012; Georgiadis et al., 2013; Wrench et al., 2011). In one study of 73 patients who underwent temporal lobe epilepsy at a Brazilian tertiary service (de Oliveira et al., 2010), patients with left mesial temporal sclerosis were shown to have more psychopathologic features, mainly anxiety disorders ($p = 0.006$), and scored higher on the Hamilton Anxiety Scale and Hamilton Depression Scale ($p < 0.05$ in both). The increased rate of psychopathology in patients who have undergone mesial temporal lobe resections is most likely due to disturbance of the limbic structures, such as the amygdala and hippocampus, which have been found to play an important role in the genesis and maintenance of depression and anxiety (de Oliveira et al., 2010; Satishchandra et al., 2003). Mesial temporal lobe resection was not found to have any impact on postoperative depression. This is interesting as anxiety and depression are thought to have a common neurobiological substrate and that depression may be an expected 'precursor syndrome' in the development of at least some forms of anxiety (Paul, 1988).

In my study, logistic regression revealed that patients with preoperative generalised seizures were less likely to exhibit depression than patients with other seizure types. The relationship between preoperative seizure type and post-operative psychiatric status has not been thoroughly studied in the literature. There is evidence that patients with preoperative generalised seizures are at increased risk of continuing seizures post-surgery (see the previous chapter), and poorer seizure control is thought to associated with worse psychiatric outcomes (McIntosh et al., 2004; Mohan et al., 2018; Schwartz et al., 2006; Spencer et al., 2005). My results, however, go to the contrary.

In my study, seizure outcome was not shown to be independently associated with an improvement in anxiety or depression. Some studies have suggested that depression improves not because of epilepsy surgery *per se*, but because of improved seizure control

which is more commonly achieved by surgery than medical treatment (Reuber et al., 2004). In one study (Hamid et al., 2011), five years after resective epilepsy surgery, significant differences in mean change from baseline Beck Depression Inventory scores were demonstrated between excellent and poor seizure control ($p = 0.006$) as well as between excellence and fair seizure control ($p = 0.02$). This study controlled for seizure location (including laterality), age, race, and education. However, the relationship between seizure-freedom and depression is still unclear; some cross-sectional studies have shown no relationship between seizure frequency and depression score (Boylan et al., 2004). These findings bring into question the highly simplistic notion that psychiatric outcome is primarily driven by seizure frequency.

Chapter 6. A retrospective study of prognostic markers for verbal, working and visual memory outcomes in patients following epilepsy surgery

6.1 Introduction

Although epilepsy surgery is generally a safe procedure it is not without risks, some of which pertain to cognitive decline. In particular, there are concerns about the deleterious effects of epilepsy surgery on visual, working and verbal memory (Alpherts et al., 2006; Baxendale et al., 2006; Lee et al., 2002; Lineweaver et al., 2006; Meador, 2002; Stroup et al., 2003; Tanriverdi et al., 2010). Longitudinal studies have shown that approximately 30-60% of patients experience cognitive decline following temporal lobe resection, which may be associated with pre-operative MRI findings, lateralisation of the epileptogenic focus, resection of mesial temporal lobe structures and age of epilepsy onset (Baxendale, Thompson, & Duncan, 2012; J. R. Binder et al., 2008; Helmstaedter et al., 2018; Helmstaedter et al., 2003). Conversely, some authors have reported that epilepsy surgery may have a positive impact on cognitive domains (Baxendale et al., 2008; Kim et al., 2007).

Neuropsychological investigations are important when a clinician is assessing patients' baseline memory status before an operation (Helmstaedter & Witt, 2012), and are commonly used following surgery to assess for any post-operative memory decline or improvement. Some factors that have previously been reported to determine neuropsychological outcomes following epilepsy surgery are listed in **table 18.**

Extent, side, and site of surgery
Degree of surgical selectivity in terms of sparing functional tissues beyond the eliptogenic lesion Collateral damage Complications of surgery
Functional integrity of resected (and surgically affected) tissues As estimated by the degree of pathology and the respective presurgical neuropsychological performance
Individual reserve capacities Functional integrity of the remnant brain or homologue contralateral structures
Degree of functional plasticity Age at surgery Gender
Postsurgical control of epileptic activity Epileptic seizures Interictal epileptic discharges
Changes in antiepileptic treatment

Table 18. Determinant of neuropsychological outcome after surgical treatment of epilepsy. From Vakharia, V.N., Duncan, J.S., Witt, J.-A., Elger, C.E., Staba, R. and Engel, J., Jr (2018), Getting the best outcomes from epilepsy surgery. Ann Neurol., 83: 676-690. doi:10.1002/ana.25205

6.2 Aims and hypotheses

6.2.1 Primary aim

1) To assess the factors that predict post-operative changes in working, visual and verbal memory in patients undergoing resective surgery for epilepsy

6.2.2 Hypotheses

1) I hypothesise that patients with both mesial and lateral temporal lobe resections will have a similar decline in memory (verbal, visual and working) outcomes

2) I hypothesise that patients with left sided resections will have a significant verbal memory decline, but non-verbal memory abilities will remain intact.
3) I hypothesise that patients with MRI negative epilepsy will have worse memory (verbal, visual and working) outcomes than MRI positive patients
4) I hypothesise that patients with temporal and extra-temporal lobectomies will have a similar decline in memory (verbal, visual and working) outcomes
5) I hypothesise no association between preoperative seizure type and postoperative memory (verbal, visual and working) outcomes
6) I hypothesise that an earlier age at seizure onset will result in worse postoperative memory (verbal, visual and working) outcomes
7) I hypothesise that patients with a higher frequency of preoperative seizures will have less significant declines in postoperative memory (verbal, visual and working) outcomes

6.3 Methodology

6.3.1 Study setting and inclusion criteria

See section 4.3.1 for study setting.

The inclusion criteria outlined in section 4.3.1 in addition to the following:

Two-point data (i.e. pre- and post-operative) on neuropsychological outcomes

6.3.2 Presurgical evaluation

All patients underwent a comprehensive standardised presurgical evaluation which included: (1) sex (2) age of onset, (3) seizure frequency, (4) type of seizure, (5) MRI status, (6) verbal memory score, (7) visual memory score and (8) working memory score. All patients had

dedicated MRI scans with coronal gradient echo T1 sequence with continuous slices in the highest available resolution and T2 imaging perpendicular to the longitudinal axis of the hippocampus. The various parameters used to localise the lesion are listed in **table 19.**

T2 FLAIR SPACE SAG (Siem or IMRI)
T1 MPRAGE SAG (Siem or IMRI)
T2 Volume Spaave (Siemens or IMRI)
SAG CUBE FLAIR (MR2)
FSPGR COR 3D (MR2)
T2 Volume Cube (MR2)

Table 19. Parameters used in the study to localise the lesion

6.3.3 Neuropsychological assessment

The Wechsler Memory Sale (Kent, 2013) was the neuropsychological test employed in this study to measure pre- and post-surgical memory function. The Wechsler Memory Scale IV is composed of seven subtests: spatial addition, symbol span, design memory, general cognitive screener, logical memory (I & II), verbal Paired Associates (I & II), and visual reproduction (I & II). A patient's performance is reported as five index scores: auditory memory, visual memory, visual working memory, immediate memory, and delayed memory. In this study, I specifically chose to analyse outcomes for visual memory, verbal (or auditory) memory and immediate (or working) memory, as outcomes for the other memory subtests were not available. Memory status was assessed by a consultant neuropsychologist at two time points: (a) in the pre-operative workup and (b) 24 months after epilepsy surgery. The index scores were then converted to the validated qualitative descriptors: (a) impaired range, (b) below average range, (c) average range, (d) high average range, (e) superior range.

6.3.4 Operative details

See section 4.3.4

6.3.5 Follow-up

Patients attended a follow-up consultation two years after the procedure. Memory status (working memory, visual memory and verbal memory) was the primary outcomes of interest.

6.3.6 Ethical approval

See section 4.3.6

6.3.7 Data labelling

Epileptic seizures

According to the international classification of epileptic seizures ILAE (2017), seizure types were divided into focal aware seizures, focal impaired awareness seizures and generalised seizures (Scheffer et al., 2017).

Structural MRI status

The MRI data were classed as positive and negative according to whether a lesion was identified on the scan.

Neuropsychological outcomes

Patients were divided into three categories: (a) improvement (b) no change or (b) deterioration in memory according to the validated ranges of the Wechsler Memory Scale. Patients' neuropsychological status were assessed by the same consultant neuropsychologist. In this study, the term 'improvement' was defined as an increase in the Wechsler Memory Scale score (e.g., shift from "below average range" to "average range" OR "high average range" to

"superior range"), 'deterioration' was defined as a decrease in the Wechsler Memory Scale score (e.g., shift from "average range" to "below average range OR "superior range" to "high average range"), and 'no change' was defined as the same pre- and post-operative Wechsler Memory Scale range.

Seizure outcomes

Regarding seizure outcome, patients were divided into two categories: (a) seizure-free group (Engel classification I) and (b) continuing seizure group (Engel classification II-IV). Seizure freedom was defined as those patients that were seizure free until the assessment for at least ≥ 2 years post-surgery.

6.3.8 Statistical analysis

Descriptive statistics were used to summarise the data in order to identify underlying patterns in the preliminary stage of the analysis.

Univariate analysis was performed to identify the relationship between the dependent and independent variables. The relationship between verbal, working and visual memory scores with gender (male or female), EEG limited to unilateral lobe, presence of generalised seizures, laterality (left or right hemisphere), MRI status (positive or negative), location (temporal or extratemporal) and position on the temporal lobe (mesial or lateral temporal lobe) were analysed using the Mann Whitney U test. Kendall's Tau-b was used to determine the association between the verbal, working and visual memory scores with age at seizure onset and preoperative seizure frequency.

The ordinal regression method was used in the study as the three dependent variables: “verbal memory score change”, “working memory score change” and ‘visual memory score change”, are ordinal. The test of parallel lines was used to check the validity of the proportional odds assumption. Likelihood ratio deviance and Pearson chi-square statistics were used to measure the fitness of the model.

The Statistical Package for the Social Sciences (SPSS) version 27.0.1.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis and $P < 0.05$ was considered a statistically significant difference for the statistical methods.

6.4 Results

6.4.1 Descriptive statistics

50 patients satisfied the criteria for inclusion in this study. Among the respondents 26 (52%) of them were female and 24 (48%) of them were male **(Figure 10).** The mean seizure frequency was 22.92±20.91 months with the range of 1 to 68 months. The mean age at seizure onset was 14.88±8.42 years with the range of 2 to 40 years. According to the video EEG results, 6 (12%), 2 (4%) and 43 (86%) had involvement of bilateral lobes, multifocal lobe and unilateral local lobe, respectively **(Figure 11).** Considering seizure types, 12 (24%) respondents had generalized onset seizures, 38 (76%) respondents had focal impaired awareness seizures, and 13 (26%) had focal aware seizures **(Figure 11).**

Thirty (60%) out of 50 patients have left-sided resections while 20 (40%) of them have right-sided resections. Among the temporal and extratemporal lobe epilepsy patients 28 and 10 of them were MRI positive, respectively. Twelve (25.5%) of the patients had extratemporal lobe epilepsy while 35 (74.5%) of them were temporal lobe epilepsy patients – of these, 26 (70.3%)

patients had mesial temporal epilepsy and 11 (29.7%) patients had lateral temporal lobe epilepsy.

Twenty-four (48%) patients had seizures at two years and 26 (52%) patients were seizure-free after two years **(Figure 12).**

Considering memory assessment, 10 (20%), 22 (44%) and 18 (36%) had an improvement, no change and deterioration respectively in the verbal memory assessment. Nine (18%), 23 (46%) and 18 (36%) patients had an improvement, no change and deterioration respectively in the working memory assessment. Nine (18%), 28 (56%) and 13 (26%) patients had an improvement, no change and deterioration respectively in the visual memory assessment **(Figure 13).**

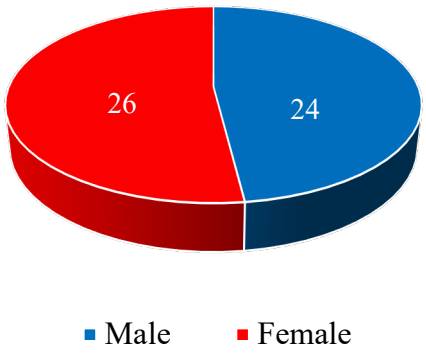


Figure 10. Gender

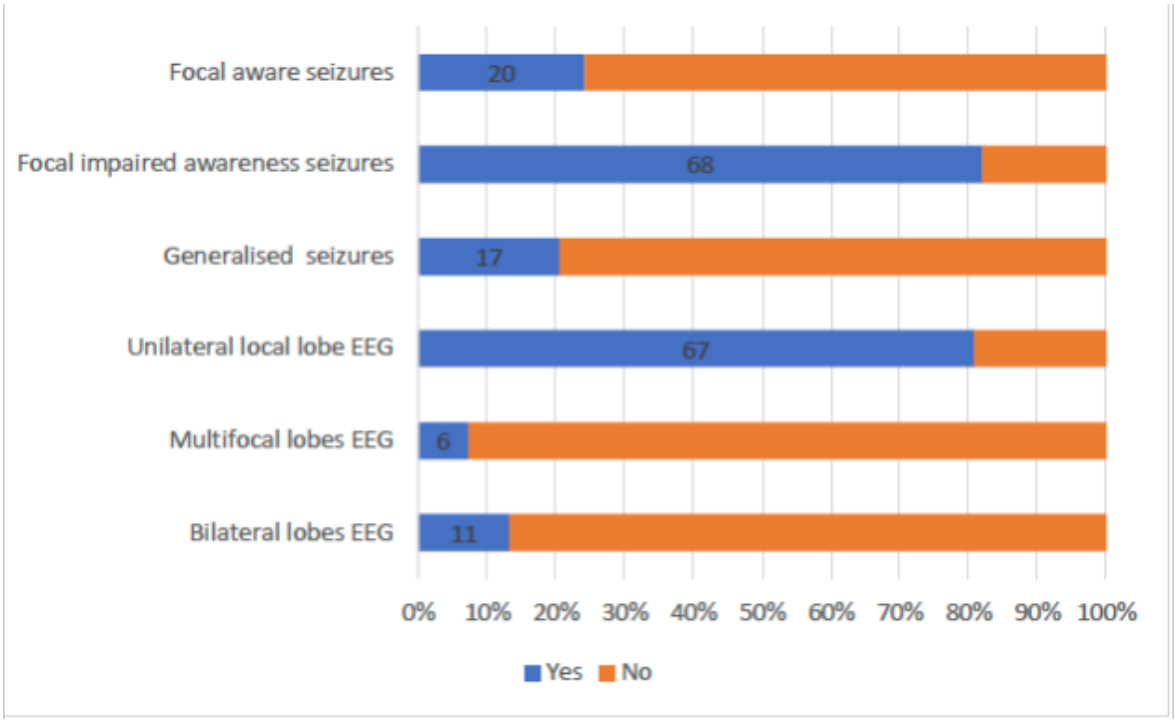


Figure 11. Video EEG results and seizure types

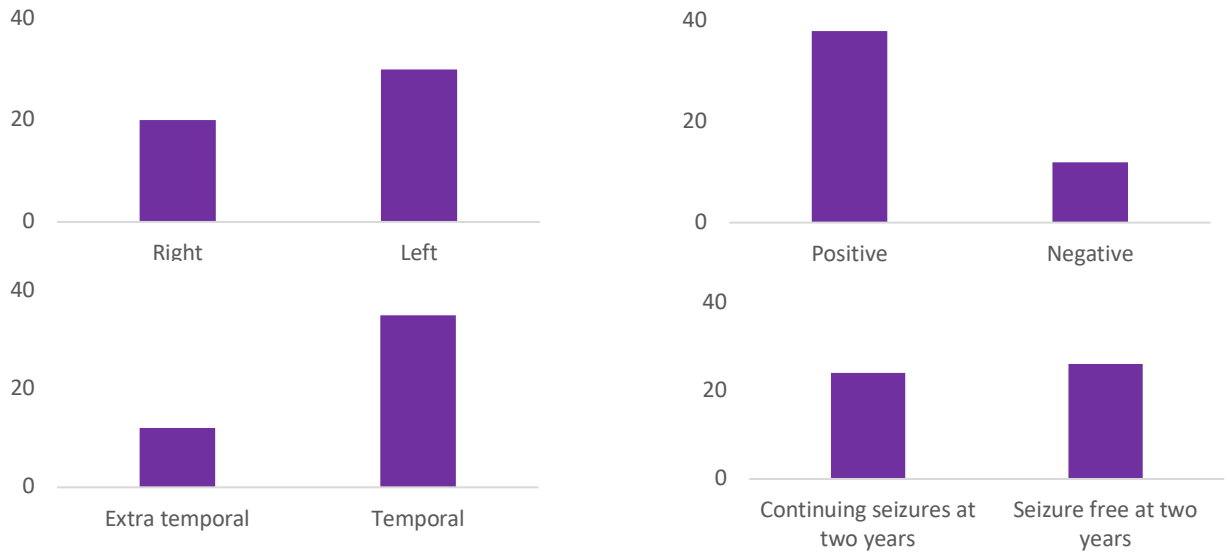


Figure 12. Laterality (top left), MRL status (top right), Location (bottom left) and seizure outcome (bottom right)

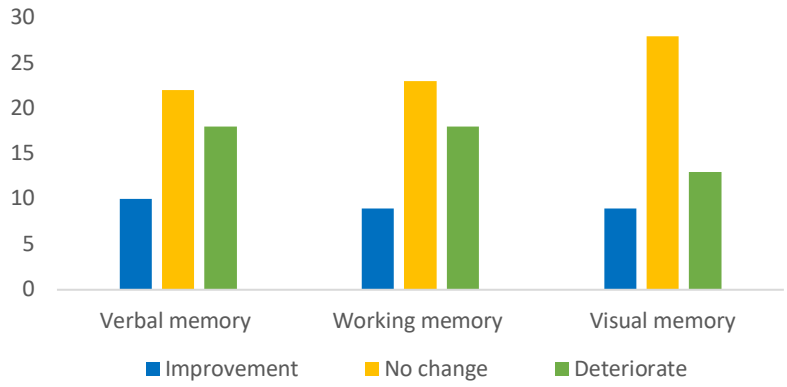


Figure 13. Memory

6.4.2 Association between memory (verbal, working and visual) and independent variables

The Mann Whitney U Test was used to assess the relationship between changes in verbal, working and visual memory scores and gender (male or female), age at seizure onset, seizure frequency, unilateral local lobe involvement on EEG, generalised seizures, laterality (left or right hemisphere), MRI status (positive or negative), location (temporal or extratemporal), mesial or lateral temporal lobe and seizure outcome. Kendall's Tau-b has been used to identify the relationship between the continuous variables: age at seizure onset and preoperative seizure frequency with the change in verbal, working and visual memory scores. The results of univariate analysis are presented in **table 20.**

Following univariate analysis, only those variables that were associated with a change in verbal, visual and working memory at the 20% level were included in the model building process. In the case of verbal memory scores, the variables that were significant at the 20% level were generalised seizures and laterality. In the case of working memory scores, the variables that were significant at the 20% level were unilateral local lobe on EEG and

generalised seizures. In the case of visual memory scores, the variables that were significant at the 20% level were generalised seizures and mesial/lateral temporal lobe.

Verbal memory

In ordinal logistic regression patients with generalized seizures were more likely to exhibit verbal memory decline postoperatively than patients with other types of seizures, p-value =0.073 <0.1 **(Table 21).** The chi-square statistics indicates that the final model gives a significant improvement over the baseline intercept-only model with $X^2(2) = 6.172$, p-value = 0.046 < 0.05 **(Table 22).** The significance value of the test is over the preferred 5% level of significance; $X^2(2) = 0.117$, p-value = 0.943 > 0.05 **(Table 22)**. Hence, the test concludes that the model holds proportional odds assumptions. Pearson and Deviance tests have p-values values greater than 0.05 suggesting that the fit of the model is adequate **(Table 22).**

Working memory

Ordinal logistic regression did not show any variables that were independently associated with changes in working memory **(Table 23).** The chi-square statistics indicates that the final model gives a significant improvement over the baseline intercept-only model with $X^2(2) = 5.084$, p-value = 0.079 < 0.1 **(Table 24).** The significance value of the test is over the preferred 5% level of significance; $X^2(2) = 1.777$, p-value = 0.411 > 0.05 **(Table 24).** Hence, the test concludes that the model holds proportional odds assumptions. Pearson and Deviance tests have p-values values greater than 0.05 suggesting that the fit of the model is adequate **(Table 24).**

Visual memory

Ordinal logistic regression did not show any variables that were independently associated with changes in visual memory **(Table 25).** The chi-square statistics indicates that the final model

gives a non-significant improvement over the baseline intercept-only model with $X^2(2) = 2.751$, p-value = 0.253 > 0.05 **(Table 26).** The significance value of the test is over the preferred 5% level of significance; $X^2(2) = 1.709$, p-value = 0.426 > 0.05 **(Table 26).** Hence, the test concludes that the model holds proportional odds assumptions. Pearson and Deviance tests have p-values values greater than 0.05 suggesting that the fit of the model is adequate **(Table 26).**

Outcome	Variable	P-value	Conclusion
Verbal memory	Gender	0.802	No association
	Age at onset of seizures	0.525	No association
	Seizure frequency	0.479	No association
	Unilateral local lobe	0.278	No association
	Generalised seizures	0.063**	Association
	Laterality	0.105***	Association
	MRI status	0.378	No association
	Location	0.958	No association
	Mesial or lateral temporal lobe	0.315	No association
	Seizure outcomes	0.402	No association
Working memory	Gender	0.681	No association
	Age at onset of seizures	0.891	No association
	Seizure frequency	0.942	No association
	Unilateral local lobe	0.095**	Association
	Generalised seizures	0.070**	Association
	Laterality	0.209	No association
	MRI status	0.423	No association
	Location	0.720	No association
	Mesial or lateral temporal lobe	0.561	No association
	Seizure outcomes	0.792	No association
Visual memory scores	Gender	0.610	No association
	Age at onset of seizures	0.714	No association
	Seizure frequency	0.645	No association
	Unilateral local lobe	0.365	No association
	Generalised seizures	0.128***	Association
	Laterality	0.774	No association
	MRI status	0.970	No association
	Location	0.290	No association
	Mesial or lateral temporal lobe	0.133***	Association
	Seizure outcomes	0.983	No association

Table 20. Univariate analysis for memory scores
Levels of statistical significance can be mentioned as follows.
*:- Variable is significant at 5% level
**:- Variable is significant at 10% level
***:- Variable is significant at 20% level

Model

Parameter	Estimate	Standard error	Wald	df	Sig.
Mem_Verbal = Imp	-1.888	0.729	6.701	1	0.010
Mem_Verbal = Det	0.258	0.686	0.141	1	0.707
Focal S.z	-1.195	0.667	3.208	1	0.073
Laterality=L	0.880	0.561	2.457	1	0.117

Table 21. Parameter estimation for verbal memory. [Mem_Verbal = Imp] is improvement in verbal memory; [Mem_Verbal = Det] is deterioration in verbal memory; [Focal S.z] is presence of focal seizures; [Laterality=L] is left sided resections

	chi-Square	df	Sig.
Model fitting information			
	6.172	2	0.046
Test of parallel lines			
	0.117	2	0.943
Goodness of fit test			
Pearson	1.979	4	0.740
Deviance	2.390	4	0.664

Table 22. Model fitting information for verbal memory

Parameter	Estimate	Standard error	Wald	df	Sig.
Mem_Work = Imp	-2.188	0.709	9.530	1	0.002
Mem_Work = Det	0.045	0.633	0.005	1	0.943
Un_Lob=0	1.166	0.888	1.722	1	0.189
Focal S.z	-0.923	0.688	1.802	1	0.180

Table 23. Parameter estimation for working memory score. [Mem_Work= Imp] is improvement in working memory; [Mem_Work = Det] is deterioration in working memory; [Un_Lob=0] is multilobe involvement on EEG; [Focal S.z] is presence of focal seizures

	Chi-Square	df	Sig.
Model fitting information			
	5.084	2	0.079
Test of parallel lines			
	1.777	2	0.411
Goodness of fit test			
Pearson	3.993	4	0.407
Deviance	4.182	4	0.382

Table 24. Model fitting information for working memory score

Parameter	Estimate	Standard error	Wald	df	Sig.
Mem_Vis = Imp	-1.467	1.100	1.779	1	0.182
Mem_Vis = Det	1.662	1.122	2.191	1	0.139
Mesial	1.004	0.799	1.580	1	0.209
Focal S.z	-0.526	0.888	0.351	1	0.554

Table 25. Parameter estimation for visual memory score. [Mem_Vis = Imp] is improvement in visual memory; [Mem_Vis = Det] is deterioration in visual memory; [Mesial] is presence of mesial lobe resection; [Focal S.z] is presence of focal seizures.

	Chi-Square	df	Sig.
Model fitting information			
	2.751	2	0.253
Test of parallel lines			
	1.709	2	0.426
Goodness of fit test			
Pearson	1.186	2	0.553
Deviance	1.709	2	0.426

Table 26. Model fitting information for visual memory score

6.5 Discussion

In this study there is a trend which fails to reach significance for an association between generalised seizures and poor visual, verbal and working memory. There is a dearth of studies in the literature that have examined the relationship between seizure type and cognitive outcomes (Sherman et al., 2011). Helmstaedter et al., (2003) conducted a longitudinal study investigating the changes in memory and non-memory functions in 147 surgically and 102 medically treated patients with temporal lobe epilepsy. All patients were evaluated at baseline and after two to ten years. The authors reported a relationship between fewer tonic-clonic seizures and better cognitive outcomes as measured by the Verbaler Lern und Merkfähigkeitstest (English translation: Verbal Learning and Memory Test) and Diagnostikum

für Zerebralschädigung (English Translation: Diagnostic test for cerebral damage) revised for figural memory.

Hermann et al., (2007) determined whether distinct cognitive phenotypes could be identified in temporal lobe epilepsy. Cluster analysis revealed three distinct cognitive profile types: (i) minimally impaired; (ii) memory impaired (24%); and (iii) memory, executive, and speed impaired (29%). The group reported a greater proportion of patients with generalised seizures in group iii compared to all other groups, suggesting an association between memory, executive and speed impairment and generalised seizures. A systematic review of the literature assessing the relationship between seizure type and memory outcomes suggested an association between progressive cognitive decline and the presence of generalised seizures in non-surgical and surgical epilepsy cohorts (Dodrill, 2004).

There is also a trend which fails to reach significance for an association between the side of resection and verbal memory outcomes, which is consistent with the literature (Alpherts et al., 2006). Pooled estimates suggest verbal memory decline in left-sided temporal surgery occurring in 44% of patients, which is twice as high as the rate for right-sided resections (Sherman et al., 2011). In a paediatric cohort, Law et al., (2017) reported that children who underwent left-sided resections were the only group to show a decline in verbal memory vs. right-sided resections. Amongst the patients who were treated for left-sided resections those with excised mesial structures showed the most significant decline. Unsurprisingly, better verbal memory scores have been reported in patients who have greater postoperative residual hippocampal volumes, particularly for those who have had left-sided resections (Skirrow et al., 2015).

There is trend which fails to reach significance for an association between mesial lobe resection and poorer cognitive outcomes, which is consistent with the literature. In one study (Fong et al., 2011), the pre- and post-operative scores for the Wechlser Memory Scale III and Boston Naming tests were assessed for 29 patients, of which 18 patients underwent temporal lobe surgeries that included resection of mesial temporal structures (10 left, 8 right). These structures were spared in the remaining patients (nine left, two right). The investigators showed that patients were more likely to decline on memory measures following surgery if they had resections that included removal of mesial temporal lobe structures, notably worse on the left-hand side, compared to operations that preserved the mesial temporal lobe structures (Fong et al., 2011). Other studies have shown that verbal memory deficits are most common in patients with left mesial temporal lobe epilepsy, while in right mesial temporal lobe epilepsy patients, visual memory deficits are the most frequent observations (Oddo et al., 2012).

Of note, I did not find an association between seizure-freedom and cognitive prognosis. Generally, patients who are seizure-free after epilepsy surgery are thought to have better cognitive outcomes (Baxendale, Thompson, & Duncan, 2012; Helmstaedter et al., 2018; Helmstaedter et al., 2003), although these findings have not been replicated in all studies (Alpherts et al., 2006; Andersson-Roswall et al., 2010). Several hypotheses have been proposed to explain the conflicting reports regarding the relationship between postoperative verbal memory function and seizure freedom. For many patients in these studies, poor preoperative function, or indeed the initial postoperative decline, may have put them near the bottom of the traditional memory test, thus making any further decline impossible (Baxendale, Thompson, & Duncan, 2012). Indeed, patients with higher preoperative test scores generally tend to show larger declines in post-operative verbal memory outcomes (J. R. Binder et al., 2008). Also, large resection might result in both fewer seizures and greater cognitive loss.

I did not find an association between later age of seizure onset and risk of memory (visual, working and verbal) decline. Later age of seizure onset has been associated with a greater risk for memory decline, as individuals who have seizures that begin in adulthood are more likely to develop adequate memory abilities prior to the onset of seizures (Dulay & Busch, 2012).

Male sex has also been shown to be a poor prognostic marker for memory deterioration and this is hypothesised to result because females are thought to have a more bilateral representation of memory (Trenerry et al., 1995).

In the paragraphs below, I summarise chapters 4,5 and 6. I outline the relationship between the independent variables (predictors) and the dependent variables (post-operative seizure freedom, anxiety, depression and verbal memory, visual memory and working memory).

Female patients were more likely to have improved post-operative anxiety outcomes, but sex did not affect the likelihood of seizure freedom, post-operative depression, or neuropsychological outcomes (verbal, visual or working memory).

Patients with right-sided resections were more likely to have improved post-operative anxiety, improve post-operative depression, but side of resection did not affect the likelihood of seizure freedom or neuropsychological outcomes (verbal, visual or working memory).

Patients with non-generalised seizures were more likely to experience seizure freedom post-operatively and improved post-operative verbal memory. However, the presence of generalised seizures was associated with improved post-operative depression outcomes. The seizure type was not associated with post-operative anxiety or post-operative visual or working memory.

Patients with a lower frequency of pre-operative seizures were more likely to experience post-operative seizure freedom. However, the number of pre-operative seizures was not reported

to affect post-operative anxiety, post-operative depression or post-operative neuropsychological outcomes (verbal, visual or working memory).

Patients with unilateral local lobe focus on electroencephalogram were more likely to have post-operative seizure freedom. However, the locus on electroencephalogram was not associated with post-operative anxiety, post-operative depression or neuropsychological outcomes (verbal, visual or working memory).

Patients with temporal lobe resections were more likely to have post-operative seizure freedom. However, temporal lobe involvement was not associated with post-operative anxiety, post-operative depression or neuropsychological outcomes (verbal, visual or working memory).

Patients with lateral temporal lobe seizures were more likely to have improved post-operative anxiety outcomes, but temporal lobe laterality did not impact seizure freedom, post-operative depression or neuropsychological outcomes (verbal, visual or working memory). Mesial/lateral temporal lobe involvement was assessed in greater detail in **chapter 7**, wherein the association between mesial/lateral temporal lobe involvement and visual working memory was examined.

Chapter 7. Temporal Lobectomy Impairs Spatial Binding in Visual Working Memory

7.1 Introduction

One brief, but useful definition of Memory is “faculty of encoding, storing, and retrieving information” (Squire, 2009a). The definition highlights three processes that logically required for information to be retained and retrieved across time. Declarative memory is traditionally divided in short-term and long-term **(see figure 14),** which differ in two fundamental ways. First short-term memory demonstrates temporal decay, second it has limited capacity limits (Cowan, 2008). Working memory includes short-term memory and other processing control mechanisms that help us make efficient , purposeful use of the information stored in short-term memory (Cowan, 2008). Long-term memory is divided into explicit (conscious) and implicit (unconscious) memory **(see figure 14).**

The mesial temporal lobe is composed of the entorhinal, parahippocampal and perirhinal cortices and houses the hippocampal and parahippocampal regions. These structures have been shown to play an important role in the encoding and storage of episodic memory (Squire, 2009b), as evidenced by the anterograde amnesia that occurs following damage to the mesial temporal lobe (Corkin et al., 1997; Dundon, et al., 2018; Scoville & Milner, 1957).

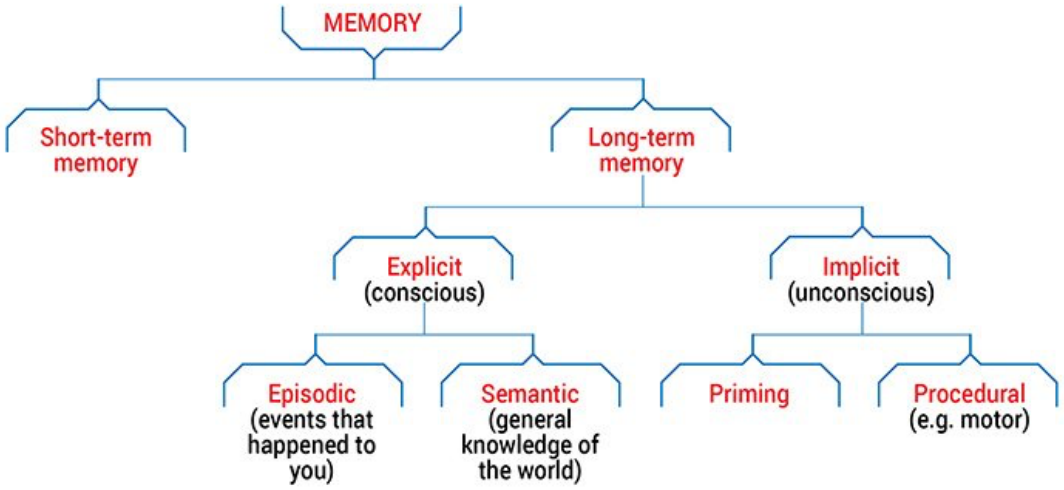


Figure 14. Stratification of memory in the brain

The role of the medial temporal lobe (MTL) in episodic, long-term memory is well established (Squire, 2009a). Despite initial reports of preserved immediate memory span in temporal lobectomy patients (Drachman & Arbit, 1966), later animal and human studies found that MTL lesions also engender substantial working memory (WM) deficits (Hannula et al., 2006; Olton et al., 1979). Functional imaging in healthy controls provided evidence that MTL structures are activated by recall of the sensory impressions associated with a personal event, regardless of its remoteness (Gilboa et al., 2004). These findings may suggest that the MTL is crucial for storing detailed sensory data. Which WM processes the MTL specifically supports is nevertheless a matter of ongoing investigation.

An early, seminal model suggested that visual WM (vWM) contains few discrete “slots” and that each slot is used to store one and only one object with high fidelity (Luck & Vogel, 1997; Zhang & Luck, 2008). Despite its simplicity, the slot model made non-trivial predictions. First, the complexity of memorised objects should not affect recall accuracy. Second, recalling conjunctions should carry no additional cost over remembering features, since features are *ipso facto* stored as part of objects already bound, when encoded into vWM. (Wheeler & Treisman, 2002) found instead that simple objects were recalled more accurately than

complex ones, and that recall accuracy was equalised for sample displays containing the same number of features, rather than the same number of objects. They concluded that memory limitations reflect feature rather than object-based storage mechanisms. Moreover, observers were worse at detecting changes of feature conjunctions than features, indicating that conjunctions are stored or recalled less efficiently than features. Later studies confirmed that recall of features is more robust to interference than recall of their conjunction (Allen et al., 2006), leading to the suggestion that dimensionally specific registers store features, while an “episodic buffer” is dedicated to holding bound object representations in vWM (Baddeley et al., 2011). The idea that separate binding processes in vWM are needed follows logically from the suggestion that visual features are stored in dimensionally specific, limited resolution stores (Bays et al., 2009). Clearly, if different visual dimensions (e.g., location, colour and shape) are stored separately, then a binding process is required to ensure that features belonging to the same object are identified as such (Wheeler & Treisman, 2002).

While there is not yet unanimous agreement that binding is required to preserve object identity in vWM (Luck & Vogel, 2013), specific proposals regarding the nature of binding processes have been put forward. Treisman & Zhang (2006) concluded that binding of non-spatial features is automatic, facilitated initially by their shared location, but that feature binding eventually becomes independent of location. Schneegans & Bays (2017) proposed instead that binding in vWM always requires location information, because visual features are stored in separate retinotopic maps, whose only shared dimension is location.

Investigators examining the neurological underpinnings of declarative memory largely embraced the idea that space plays a crucial role in indexing declarative memories and binding. Animal lesion and patient studies (Brown & Aggleton, 2001; Chalfonte et al., 1996; Eacott & Gaffan, 2005; Libby et al., 2014; Piekema et al., 2006; Ranganath, 2010) documented a functional parcellation of the MTL with different structures involved respectively in representing the environmental layout, the objects within it, as well as binding the latter to

the former. This proposal suggests that space is crucial for establishing the context for memorised objects, but not for binding object features. Olson et al., (2006) for example, reported that patients with post-anoxic or post-encephalitic MTL pathology had impaired object-location binding in a WM task. This impairment was not accounted by either diminished recognition or spatial memory. These findings are in broad agreement with animal studies, which demonstrated that lesions to MTL structures, such as the Perirhinal and Parahippocampal cortex, produce impairments in vWM. Other haves reported increased BOLD responses in the right Parahippocampal cortex instead during both encoding and maintenance of object-location information compared to objects (Benjamin et al., 2014; Luck et al., 2010) raising the possibility that MTL contributions to spatial binding are lateralised. In laboratory animals MTL lesions can be followed by dissociated impairments in object recognition and object-location conjunctions, suggesting that recognition and spatial binding depend on distinct MTL processes (Malkova & Mishkin, 2003; Meunier et al., 1993; Murray & Mishkin, 1998). Similarly, studies in patients with temporal lobe epilepsy (TLE) have reported deficits in spatial recall, spatial binding and visual recognition tasks (Abrahams et al., 1997; Bohbot et al., 1998; Stepankova et al., 2004). However, whether spatial binding impairments following MTL lesions should be attributed to a spatial deficit (Kolarik et al., 2016) or a binding one (Zokaei et al., 2019) still remains to be established, including the extent to which binding impairments, when present, generalise across visual dimensions (Hannula et al., 2006; Pertzov et al., 2013) or, rather, are specifically spatial. The latter possibility would be in keeping with findings reported by Dundon et al., (2018) in a patient with strokes involving the Parahippocampal cortex of both hemispheres. who showed prominent impairments in spatial binding, but not non-spatial binding. Ultimately, whether spatial binding depends on dedicated neural circuits, separate from those involved in non-spatial binding, is crucial for understanding its role in organising declarative memories.

In light of contrasting evidence about the MTL's role, we tested patients who had undergone temporal lobectomies for medically resistant TLE, to establish whether impairments of vWM

binding are specifically spatial or rather generalize across visual feature dimensions (e.g., location, colour and shape) following focal MTL lesions. To this end, we employed two tasks used in a previous investigation of the binding impairments in a stroke patient (Dundon et al., 2018). The first task probed participants' ability to perceptually estimate the average position of three visible dots, thus assessing the integrity of spatial perception. The second used identical sample displays in trials of spatial and non-spatial binding. As this task places minimal demands on feature memory and distinguishes recall errors due to incorrect binding from those due to guessing, vWM binding performance could be interpreted while minimizing confounds stemming from impaired feature memory.

7.2 Methodology

The aim of the present study was to compare non-spatial and spatial binding performance in TLE patients' with medically refractory epilepsy who had undergone temporal lobectomy and healthy controls. Participants recruitment and testing took place at the Neuropsychology section of the Department of Neurosciences, King Faisal Specialist Hospital and Research Centre (KFSHRC), Riyadh, Saudi Arabia in accordance with the relevant guidelines and regulations. The experimental protocol was approved by the KFSHRC Ethics committee. Participants gave written informed consent prior to engaging in any experimental procedure.

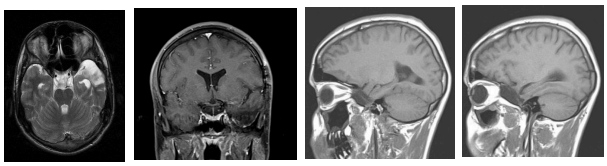
7.2.1 Study participants

Over a three-month period, patients attending the Neurology and Neurosurgical Clinics at King Faisal Specialist Hospital and Research Centre (KFSHRC) were invited to participate in the study. All had been diagnosed with TLE on the basis of clinical presentation and instrumental diagnostic procedures, inclusive of ambulatory EEG and neuroimaging, and after failing medical therapy, had undergone surgical treatment. All patients had normal or corrected to normal visual acuity. Those with an estimated full-scale IQ of less than 75, as assessed

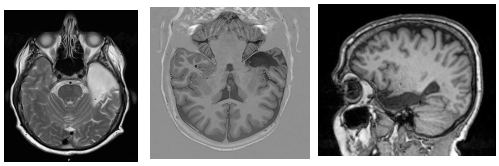
with an Arabic version of the Wechsler Abbreviated Scale of Intelligence Second Edition (Al-Joudi et al., 2019), were excluded, as well as those with a history of traumatic brain injury or major psychiatric disorders. Patients who suffered a seizure in the preceding 48 hours had the testing session postponed. Thirteen patients took part in this study, who were representative of the least cognitively impaired portion of the population. The study's neurosurgeon (FA) identified the anatomical structures involved by the resection on the basis of the surgical record and post-surgical MRI scans. **Figure 15** shows postsurgical axial and sagittal and coronal multimodal MRI slices for each of the patients.

Fifteen healthy participants were concurrently recruited from the local community as controls. Potential participants were excluded if they had a history of a major neurological or psychiatric disorder, an uncorrected visual impairment, or an estimated IQ less than 75.

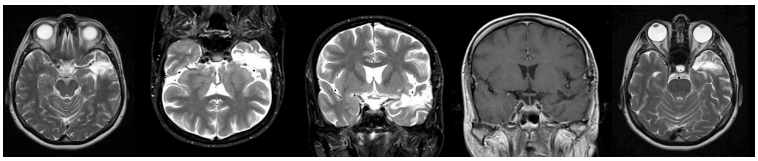
P1 –Temporal pole and Perirhinal cortex



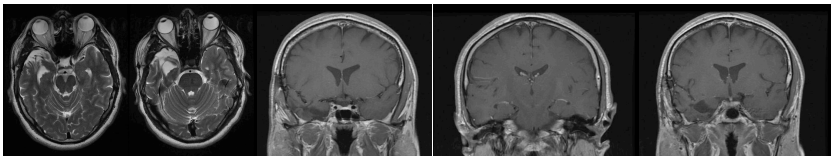
P2 –Temporal, amygdala and hippocampus



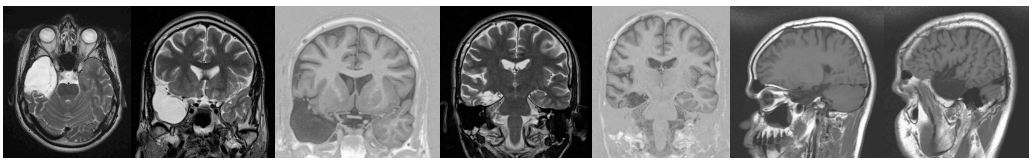
P3 – Temporal pole and perirhinal cortex



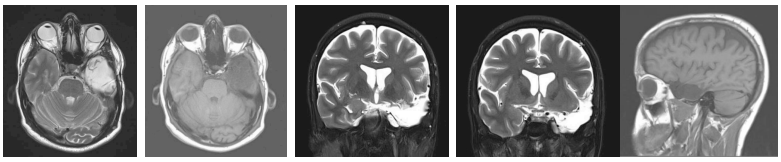
P4 – Perirhinal and entorhinal cortex



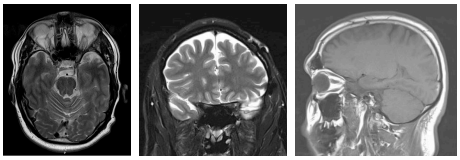
P5 – Temporal neocortex, mesial hippocampus, amygdala and entorhinal cortex



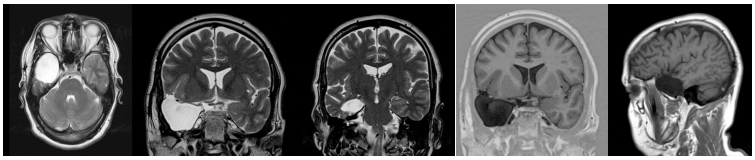
P6 – Temporal cortex, hippocampus, amygdala and entorhinal cortex



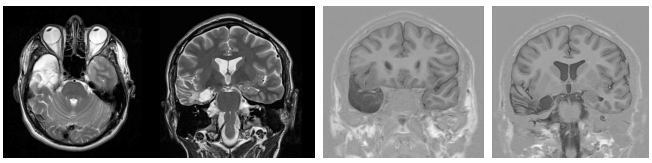
P7- Temporal tip cortex



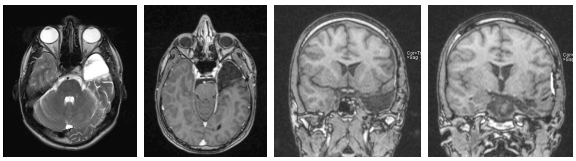
P8 – Temporal cortex, hippocampus, amygdala and entorhinal cortex



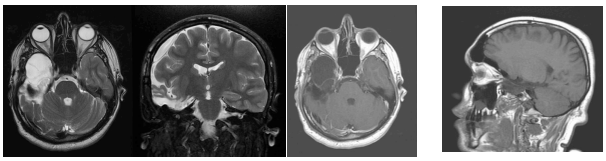
P9 – Temporal cortex, hippocampus, amygdala and entorhinal cortex



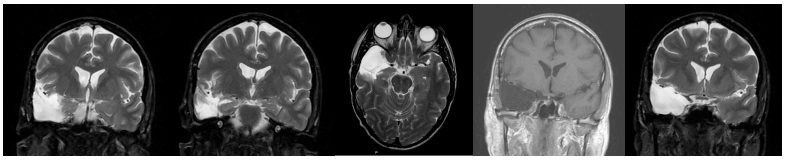
P10 – Temporal cortex, hippocampus, amygdala and entorhinal cortex



P11 –Temporal cortex, hippocampus, amygdala and entorhinal cortex



P12 – Anterior temporal, entorhinal cortex



P13 – Temporal cortex, hippocampus, amygdala and entorhinal cortex

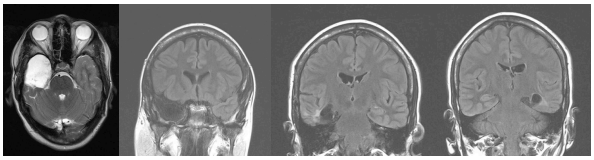


Figure 15. Post-surgical anatomical MRI. Each of the patients underwent a post-surgical scan to assess the extension of the surgical lesion. The images are presented in radiological coordinates.

7.2.2 Testing protocol

Testing took place in a quiet, dimly lit room. Participants sat comfortably at a distance of approximately 70cm from a 15.4-inch Radeon Pro 555 2048 MB graphics screen, set at a resolution of 1680x1050 pixels. Custom-coded Matlab (Mathworks, Natick, Massachusetts) scripts used a set of freely available routines (Brainard, 1997) to control the timing of the displays. Two tasks were conducted using the computerized set-up.

7.2.3 Cued colour recall

Figure 16A illustrates the event structure of a cued colour recall trial. In each trial, an equilateral triangle and a square, whose side lengths are 1.29° and 0.92° respectively, appear side-to-side in the lower half of the screen. The shapes are centered at an eccentricity of 2.27° along the main diagonals and remain visible for 2.0s. The two shapes are of different colours, either red, blue or green. The sample display is followed by a 0.2s long pattern mask and a 1.3s blank screen. The recall screen contains three coloured rectangles, 0.53° wide and 1.59° high, whose lower edges are aligned 1.39° above the screen centre and spaced horizontally 4.81° apart. A bright cross (location probe) or the outline of one of the polygons (shape probe) identifies the target. The location probe, which also includes a dark cross, appear at the locations occupied by the two shapes. The shape cue appears 3.0° below the screen centre. Participants report the target colour by placing the cursor over the corresponding-coloured rectangle and clicking the mouse button. The mouse click prompts the beginning of a new trial, after a 1.0s delay, during which the screen is blank. Participants practiced the task over 16 trials and then completed two blocks of 96 trials each, including both shape and location cued recalls. Trial order was randomised, minimizing participants' ability to predict whether a shape or location probe would follow the sample display. To ensure that patients had not forgotten the task instructions, at the end of each block they were asked to describe what they had done.

7.2.4 Centroid Estimation

This task assesses the accuracy and precision of estimates of the average location of three visible white discs, which is illustrated in the **figure 16b.** The discs' diameter is 0.27°. Participants place a crosshair shaped cursor at the estimated centroid location and clicks the mouse. Following a 1.0s interval, a novel set of discs appears and the procedure is repeated. Discs can occupy any three of seven canonical locations, including the screen center and the vertices of a virtual concentric hexagon, with a side length of 3.67°. All permutations of three canonical locations, less any resulting in a collinear configuration, are used as sample arrays. Each possible permutation appears twice, for a total of 64 trials. Pseudorandom, zero mean, independent circular Gaussian distributions, with a standard deviation of 0.6°, are sampled to jitter each disc's position. Prior to testing, instructions were read to the participants. The centroid was defined as the point in space where the triangle, whose vertices coincided with the discs' locations, would balance in the horizontal plane (Baud-Bovy & Soechting, 2001).Participants completed 25 practice trials, without feed-back.

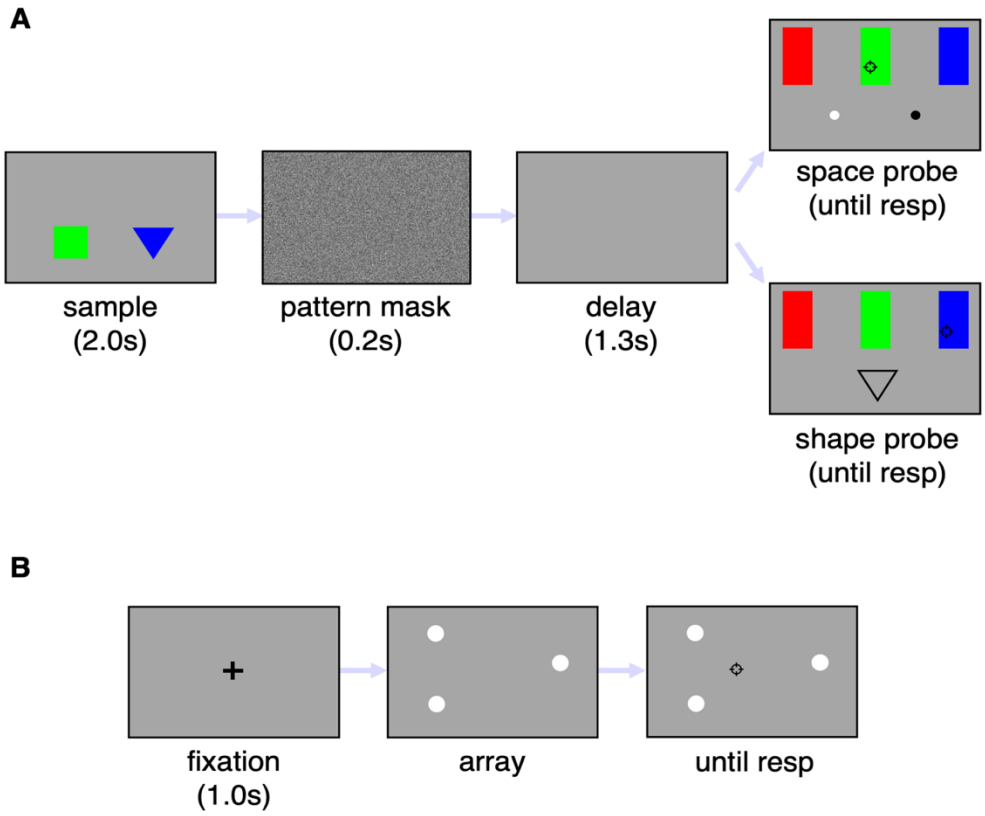


Figure 16. Tasks structure. **Panel A** shows the event sequence in the color recall task. Participants had to recall the color of a triangle and a square displayed side by side. The sample display was followed by a pattern mask and a blank screen. The recall target was identified either by a space probe, consisting a bright cross displayed at the location previously occupied by the target, or by a shape probe, consisting of the outline of the target shape. The color was reported by placing the cursor over the corresponding colored rectangle and clicking the mouse button. **Panel B** shows the centroid estimation task. The visual display contained 3 bright dots and the participant had to indicate the location of the center of mass of the imaginary triangle whose vertices corresponded to the dots location, by dragging the cursor and clicking.

7.2.5 Neuropsychological tests

Three neuropsychological instruments were used to assess participants: 1) Hopkins Verbal Learning Test – Revised (HVLT-R), 2) Brief Visuospatial Memory Test – Revised (BVMT-R), and 3) Colour Trails Test (CTT). The Arabic version of these tests was recently validated (Al-Joudi *et al.*, 2019).

7.2.6 Analysis

In the recall task, participants could either report 1) the colour of the target, that is indicate the correct choice, 2) the colour of the non-target item, that is make a swap error, or 3) the colour absent from the previous sample, that is make a generic error. In trials in which participants forgot the sample and guessed, we assumed they were equally likely to be correct, make a swap error or a generic one. The distribution of correct reports, swap and generic errors counts ***x,*** is multinomial:

$$f(\boldsymbol{x}|n,\boldsymbol{p}) = \frac{n!}{\prod_{i=1}^{k} x_i} \prod_{i=1}^{k} p_i^{x_i}$$

where ***p*** is the probability of each of the *k* (=3) possible outcomes and *n* is the number of trials. Separate estimates of ***p***, i.e. the report probabilities, were obtained for the two levels of the probe dimension, i.e. shape vs. space, and group, i.e. patient vs controls, respectively. Each participant's data were considered a separate observation. We assigned ***p*** an uninformed prior, i.e., a Dirichlet parameter matrix with all values equal to 1 (i.e., the prior assumes that all possible trial outcomes are initially equally probable). ***p*** was updated by the observed data using Bayesian Markov chain Monte Carlo (MCMC). The distribution of the posterior was sampled using No U-Turn sampling (NUTS), implemented with the PyMC3 package (Salvatier et al. 2016) in Python 3.8. Posterior distributions were sampled across 4 chains of 10000 samples (40000 total), with an additional initial 10000 samples per chain (40000 total) discarded after tuning the sampler's step-size (80000 samples combined). To assess differences between the estimated parameters of ***p***, we created deterministic distributions on each step of the MCMC, corresponding to the pairwise differences between the twelve elements of matrix *p* estimated on that step (n=132 pairwise contrasts). Parameters can be considered different if the central 95% of highest density interval (HDI95%) of the relevant pairwise contrast did not include zero. The Bayesian approach is inherently conservative with respect to multiple comparisons; in the absence of a true effect in any given pairwise contrast, our choice of identical priors for each element of ***p***. In our results section, we report the

posterior mean (μ), and the lower (*lb*) and upper bound (*lb*) of the HDI95% using the convention "μ, HDI94=[*lb,ub*]".

We also tested whether the hemispheric laterality of the lesion affected performance on the recall task. This model was fitted using the same approach outlined above and included the six patients who had undergone left temporal lobectomy and seven with a right one. The estimates was run 13 times, each time leaving out one patient (leave-one-out jackknife). These results are reported in the supplementary materials.

Model convergence was assessed using three metrics: (i) the number of times the sampler diverged after tuning, that is how often the sampler transitioned to a region of the parameter space in violation of ergodicity. (ii) the range of values of the ratio $\hat{R}$ whose numerator is the average variance within the four posterior chains, while W is the variance of the pooled chains. $\hat{R}$ = 1 indicates convergence, while $\hat{R}$ exceeding 1 suggests that at least one chain failed to converge (see Vehtari et al., 2020). (iii) The median of the mean effective sample size (ESS). Higher ESS reflects greater estimation precision.

The analysis of the centroid task was carried out by fitting the following regression model to each participants' reports:

$$r_x = a_0 + a_1 C_x + a_2 C_y + a_3 I_x + a_4 I_y + e_x$$

$$r_y = b_0 + b_1 C_x + b_2 C_y + b_3 I_x + b_4 I_y + e_y$$

where r_x and r_y are the *x*-*y* coordinates of the centroid estimates produced by each participant, C_x, C_y, I_x and I_y are the centroid and incenters coordinates of the three visible dots and e_x and e_y are the residual errors. These regressors were chosen since healthy participants have been previously reported to show a systematic incenter bias, when estimating the centroid of dot displays (Baud-Bovy & Soechting, 2001), although this effect may show substantial inter-individual differences (Drew *et al.*, 2010). In order to quantify accuracy and precision in the

centroid estimation task we computed, in each participant, two variables, namely the average incenter bias (IB) and the variable error (VE):

$$IB = \frac{(a_3 + b_4)}{2}$$

$$VE = \sqrt{\frac{Var(e_x) + Var(e_y)}{2}}$$

Where *V*ar is the variance of the residuals.

7.3 Results

Participants' demographic, clinical and neuro-psychometric characteristics.

Table 27 reports the demographic characteristics of the patients and healthy controls. The two groups were matched on age, gender and educational level. Patients had a lower full-scale IQ that healthy controls, but the difference was not statistically significant. **Table 28** reports sex, years of educations and performance on the neuropsychometric battery for each of the thirteen patients. Both raw scores as well the values normalised on the basis of a reference sample of healthy controls whose first language is Arabic (Al-Joudi et al., 2019), are shown. **Table 29** summarizes the location of the MTL lesion, the post-surgical tissue diagnosis and extent of anatomical damage.

		TLE (*n*=13)	Healthy controls (*n*=15)	*p*
Gender	% male	92.3%	93.3%	> .5
Age, years	Mean (*SD*)	33.08 (8.9)	32.6 (7.8)	> .5
Education, highest grade	Mean (*SD*)	14.38 (1.9)	13.6 (2.4)	> .5
Full Scale IQ	Mean (*SD*)	83 (10.9)	99.5 (15.3)	> .1
Epilepsy onset age, years	Mean (*SD*)	18.7 (13.8)	—	

Table 27. Demographic and clinical sample characteristics. Frequencies were compared with a χ^2 test. Continuous variables were compared with unpaired, two sample t-tests. SD = standard deviation.

Patient	Gender	Education (years)	WAIS II				HVLT			BVMT			CTT	
			block design	*vocabulary*	*matrix reasoning*	*similarities*	*immediate*	*delayed*	*discrimination*	*immediate*	*delayed*	*discrimination*	*CTT1 (sec)*	*CTT2 (sec)*
P1	M	16	16 *(-.59)*	18 *(-1.6)*	12 *(-.41)*	24 *(-.77)*	19 *(-1.43)*	6 *(-1.47)*	9 *(-1.9)*	12 *(-1.01)*	4 *(-1.22)*	4 *(-1.4)*	85 *(1.24)*	160 *(2.0)*
P2	M	14	18 *(-.46)*	27 *(-.83)*	12 *(-.41)*	23 *(-.88)*	26 *(.36)*	9 *(.11)*	12 *(1.1)*	10 *(-1.28)*	4 *(-1.22)*	4 *(-1.4)*	97 *(1.74)*	166 *(2.22)*
P3	F	16	12 *(-.88)*	25 *(-1.0)*	18 *(.53)*	28 *(-.31)*	24 *(-.15)*	7 *(-.95)*	10 *(-.9)*	9 *(-1.41)*	*6 (-.58)*	5 *(-.4)*	65 *(.41)*	130 *(.92)*
P4	M	14	16 *(-.59)*	26 *(-.91)*	14 *(-.09)*	26 *(-.54)*	22 *(-.67)*	7 *(-.95)*	11 *(.1)*	14 *(-.75)*	5 *(-.9)*	4 *(-1.4)*	66 *(.45)*	191 *(3.12)*
P5	M	12	14 *(-.74)*	28 *(-.74)*	10 *(-.72)*	25 *(-.66)*	24 *(-.15)*	8 *(-.42)*	8 *(-2.9)*	7 *(-1.68)*	3 *(-1.55)*	3 *(-2.4)*	65 *(.41)*	135 *(1.1)*
P6	M	16	24 *(-.0)*	20 *(-1.48)*	16 *(.22)*	22 *(-1.0)*	24 *(-.15)*	7 *(-.95)*	11 *(.1)*	*21 (.19)*	7 *(-.26)*	5 *(-.4)*	75 *(.82)*	150 *(1.65)*
P7	M	16	14 *(-.74)*	28 *(-.74)*	8 *(-1.03)*	25 *(-.66)*	19 *(-1.43)*	5 *(-2.0)*	7 *(-3.9)*	12 *(-1.01)*	5 *(-.9)*	4 *(-1.4)*	87 *(1.33)*	154 *(1.79)*
P8	M	16	39 *(1.09)*	45 *(.71)*	21 *(1.0)*	30 *(-.08)*	27 *(.62)*	10 *(.63)*	12 *(1.1)*	13 *(-.88)*	9 *(.39)*	5 *(-.4)*	32 *(-.97)*	85 *(-.7)*
P9	M	14	*27 (.21)*	32 *(-.4)*	18 *(.53)*	26 *(-.54)*	21 *(-.92)*	8 *(-.42)*	11 *(.1)*	*21 (.19)*	7 *(-.26)*	5 *(-.4)*	52 *(-.13)*	105 *(.02)*
P10	M	14	19 *(-.37)*	22 *(-1.26)*	9 *(-.88)*	24 *(-.77)*	18 *(-1.69)*	7 *(-.95)*	10 *(-.9)*	17 *(-.35)*	7 *(-.26)*	4 *(-1.4)*	94 *(1.62)*	165 *(2.19)*
P11	M	11	26 *(.14)*	22 *(-1.26)*	16 *(.22)*	24 *(-.77)*	20 *(-1.18)*	7 *(-.95)*	10 *(-.9)*	*15 (-.61)*	*6 (-.58)*	4 *(-1.4)*	80 *(1.03)*	151 *(1.68)*
P12	M	12	13 *(-.81)*	23 *(-1.17)*	12 *(-.41)*	22 *(-1.0)*	19 *(-1.43)*	5 *(-2.0)*	8 *(-2.9)*	12 *(-1.01)*	5 *(-.9)*	4 *(-1.4)*	86 *(1.28)*	153 *(1.75)*
P13	M	16	17 *(-.52)*	28 *(-.74)*	11 *(-.56)*	28 *(-.31)*	21 *(-.92)*	8 *(-.42)*	10 *(-.9)*	14 *(-.75)*	*6 (-.58)*	4 *(-1.4)*	83 *(1.16)*	158 *(1.94)*

Table 28. Demographic and neuro-psychometric performance of individual TLE patients. *Raw scores are reported for each test and participant (see methods). The corresponding normalised values are shown in paranthesis. Normalised values were computed by subtracting the mean score of a reference sample (Al-Joudi et al, 2019) and dividing by the standard deviation. To facilitate inspection of the table scores corresponding to better than mean performance are underlined*

	Age	Pathology	Lesion laterality	Temporal lobe structures								
				Hippocampus	Entorhinal cortex	Perirhinal cortex	Parahippocampal cortex	Inferotemporal gyrus	Middle temporal gyrus	Temporal pole	Superior temporal gyrus	Amygdala
P1	25	GGs	L	0	+	+	0	0	0	+	0	0
P2	25	MTS	L	++	0	0	0	0	0	+	0	++
P3	50	MG	L	0	0	+	0	0	+	+	0	0
P4	41	GGs	R	0	+	+	0	0	0	+	0	0
P5	31	MTS	R	++	+	0	+	0	+	+	+	++
P6	27	MTS	L	++	0	0	0	0	0	0	0	0
P7	40	MG	L	0	0	0	0	0	+	+	0	0
P8	32	MTS	R	++	0	0	0	+	0	++	0	+
P9	33	MTS	R	++	+	0	++	+	0	0	+	+
P10	22	MTS	L	+	+	0	0	++	0	0	+	0
P11	25	MTS	R	++	+	0	0	0	0	0	+	++
P12	47	GGs	R	0	+	0	0	0	++	++	+	0
P13	32	MTS	R	+	+	0	+	+	0	0	+	0

Table 29. Patients' lesion anatomy. ''0'' indicates an unaffected subregion, ''+'' a rostro-caudal lesion extent up to 20 mm, and ''++'' up to 40 mm.

Cued colour recall performance

In the cued recall task, participants completed two blocks of 96 trials each. Performance, namely the counts of the three possible outcomes, correct responses, swap or binding errors, was parametrized with a multinomial distribution. Bayesian estimates of the outcomes' posterior probabilities were obtained separately for each group and probe dimension. The estimates showed good convergence with $\hat{R}$ = 1 for all parameters and the median ESS across parameters= 55480. **Figure 17** displays the distribution posteriors for the report probabilities.

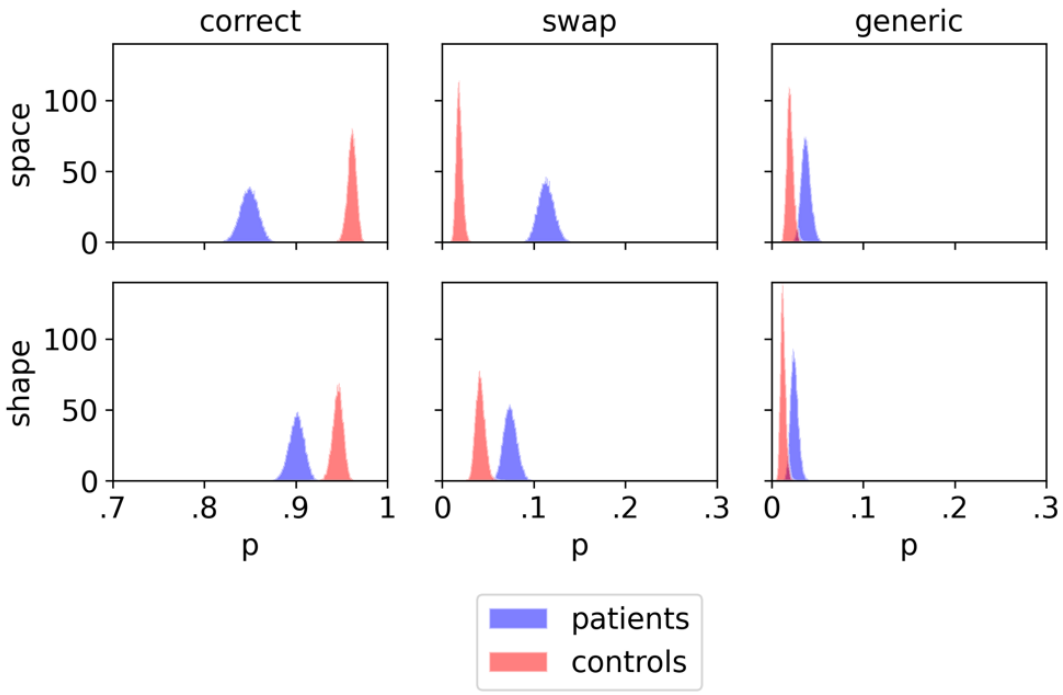


Figure 17. Distributions of report probability estimates in the recall task. The ordinate represents the posterior density. The left, middle and right panels are respectively the probability of a correct report, a swap and generic error for patients (blue) and controls (red). The upper panels are estimates obtained for trials in which the target was identified by a space probe, while the lower ones for trials in which the target was identified by a shape probe (bottom). Patients were less accurate than controls and were more likely to make a swap error following space than shape probes.

Patients were not as accurate as controls, following both space (patients: μ=0.849, HDI94=[0.830, 0.868]; controls: μ=0.961, HDI94=[0.952, 0.971]; contrast: μ=-0.112, HDI94=[-

0.133, -0.091]) and shape probes(patients: μ=0.901, HDI94=[0.885, 0.917]; controls: μ=0.946, HDI94=[0.934, 0.957]; contrast: μ=-0.045, HDI94=[-0.065, -0.026]). Patients were less accurate following space than shape probes (contrast: μ=-0.052, HDI94=[-0.076, -0.027]). On the other hand, controls were less accurate following shape than space probes (contrast: μ=-0.015, HDI94=[-0.030, -0.001]).

Patients made more swap errors than controls, following space (patients: μ=0.113, HDI94=[0.096, 0.130]; controls: μ=0.019, HDI94=[0.012, 0.026]; contrast: μ=0.095, HDI94=[0.076, 0.112]) and shape probes (patients: μ=0.074, HDI94=[0.060, 0.088]; controls: μ=0.042, HDI94=[0.032, 0.052]; contrast: μ=0.033, HDI94=[0.016, 0.050]). Patients were more likely to make swap error following space than shape probes (contrast: μ=0.039, HDI94=[0.017, 0.061]), while controls were less likely (contrast: μ=-0.023, HDI94=[-0.011, -0.035]).

Patients also made more generic errors than controls, following space (patients: μ=0.038, HDI94=[0.028, 0.048]; controls: μ=0.020, HDI94=[0.013, 0.027]; contrast: μ=0.017, HDI94=[0.005, 0.030]) and shape probes (patients: μ=0.025, HDI94=[0.017, 0.033]; controls: μ=0.012, HDI94=[0.007, 0.018]; contrast: μ=0.033, HDI94=[0.016, 0.050]). However, neither patients (contrast: μ=-0.013, HDI94=[-0.026, 0.000]) nor controls (contrast: μ=-0.008, HDI94=[-0.016, 0.001]) showed an effect of probe dimension on the probability of making a generic error.

We also examined the effects of lesion laterality on recall performance. The model showed very good convergence. The zero divergences post-tuning was = 1 for all parameters, median ESS across parameters was 47511. **Figure 18** displays the density of the posteriors for the report probabilities.

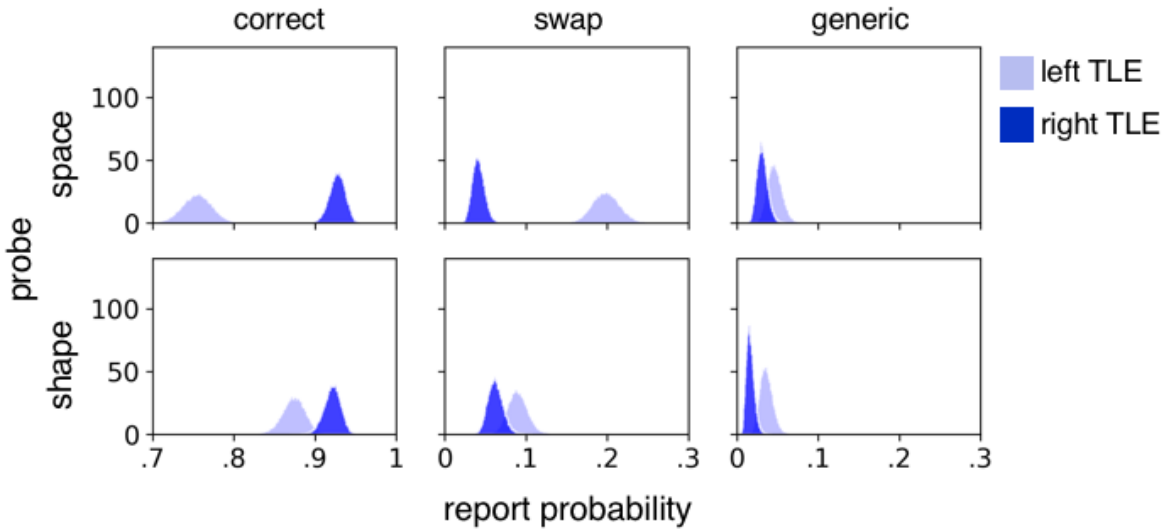


Figure 18. Distributions of report probability estimates for patients who had undergone a left (light blue) and right temporal lobectomy (dark blue respectively). The probability of correct reports (left), swap errors (middle) and generic errors (right), are shown separately when the target was identified by a space (top) or a shape probes (bottom). Left lobectomy patients were more impaired on the task and more likely to make a swap error following space than shape probes.

Left hemisphere patients were less accurate than right hemisphere patients, following space (left: μ=0.755, HDI94=[0.72, 0.788]; right: μ=0.927, HDI94=[0.908, 0.945]; contrast: μ=-0.173, HDI94=[-0.211, -0.135]) and shape probes (left: μ=0.874, HDI94=[0.848, 0.900]; right: μ=0.921, HDI94=[0.902, 0.941]; contrast: μ=-0.048, HDI94=[-0.080, -0.016]). Left lesion patients were less likely to register correct responses following space probes, relative to shape (contrast: μ=-0.119, HDI94=[-0.163, -0.077]), however right lesion patients showed similar performance for both probes (contrast: μ=0.006, HDI94=[-0.020, 0.033]).

Following a space probe left lesion patients were more likely to make a swap error than right lesion patients, (left: μ=0.199, HDI94=[0.168, 0.230]; right: μ=0.041, HDI94=[0.027, 0.056]; contrast: μ=0.157, HDI94=[0.123, 0.191]), but not when instructed by shape probe (left: μ=0.090, HDI94=[0.068, 0.112]; right: μ=0.062, HDI94=[0.045, 0.080]; contrast: μ=0.028,

HDI94=[-0.001, 0.056]). Left lesion patients were more likely to make a swap error following space than shape probes (contrast: μ=0.109, HDI94=[0.071, 0.148]), however right lesion patients were swap error rates following space and shape probes (contrast: μ=-0.021, HDI94=[-0.044, 0.002]).

Following space probes, left lesion patients were not appreciably more likely to make a generic error than right lesion patients (left: μ=0.047, HDI94=[0.030, 0.063]; right: μ=0.031, HDI94=[0.019, 0.044]; contrast: μ=0.015, HDI94=[0.005, 0.037]). However, following shape probes, left lesion patients were more likely to make a generic error than right lesion patients (left: μ=0.036, HDI94=[0.022, 0.051]; right: μ=0.016, HDI94=[0.008, 0.025]; contrast: μ=0.020, HDI94=[0.003, 0.037]). Neither left lesion (contrast: μ=0.010, HDI94=[-0.012, 0.033]) or right lesion patients (contrast: μ=0.015, HDI94=[-0.001, 0.030]) were appreciably more likely to make a generic error following a space than a shape probe.

Centroid estimation performance

Two indexes of performance, namely accuracy and precision, were calculated for each participant in the centroid estimation task. Accuracy was the defined as the incenter bias (IB), averaged over its x and y components, which were obtained from the fits of a regression model (see Methods). Precision was the standard deviation of the model residuals, averaged over the x-y components. The group difference in the incenter bias between controls (-0.02. $\pm$ .1) and patients (-0.23 $\pm$ .14) was not significant (t(26) = 1.31, p<.2). The estimation precision was also comparable: the group averaged error standard deviation was 0.33° $\pm$.03° in controls and 0.4° $\pm$.08° in patients (t(26)=-0.86, p<.4).

7.4 Discussion

In this study we compared performance of healthy controls and temporal lobectomy patients in two tasks, one probing binding in vWM, the other perceptual, spatial averaging of dot patterns. The vWM task required the recall of a target's colour, identified by either a location or a shape probe. Controls were more accurate than patients overall. Moreover, they made fewer swap errors following space than shape probes, while patients made more swap errors following space than shape probes. There was no appreciable group difference in the accuracy and precision of perceptual centroid estimates. The implication of these findings for the organization of binding and spatial processes in vWM is discussed in the next paragraph, following a brief overview of prior evidence.

MTL lesions specifically disrupt spatial binding in vWM

Previous studies addressed whether MTL pathology is associated with impairments in vWM binding. The ability to recall object-location conjunctions, as well as item-item conjunctions was found to be diminished in patients with anoxic/ischemic or infectious pathology involving the MTL, suggesting an impairment in "relational" binding (Hannula et al., 2006; Olson et al., 2006). (van Geldorp et al., 2014) compared patients, who had undergone anterior temporal lobectomies for medically refractory epilepsy, and healthy controls' performance in four match-to-sample tasks. The tasks were difficult and required participants to remember three separate frames, presented sequentially. Each frame contained the picture of a face and a building, which differed in location and colour. A cue, presented before the sample, indicated whether participants should only remember the identity of the items, or also their location (spatial binding condition), colour (colour binding condition) or the item they had been presented with (relational binding condition). Overall, recall was less accurate in patients compared to controls, and particularly so in the relational binding condition. Recall performance in the spatial and colour binding conditions were not differentially affected, suggesting that spatial and non-spatial WM binding were not differentially compromised in patients. Zokaei et al.,

(2019) found that patients, who had undergone a temporal lobectomy, made more swap errors when recalling the location of fractal patterns, compared to controls. Since neither fractal recognition nor memory for locations were found to be appreciably impaired in these patients, it was inferred that they suffered a primary binding deficit. Using a very similar paradigm pathology, Pertzov et al., (2013) documented both a spatial as well as a non-spatial binding deficit in individuals recovering from autoimmune encephalitis, suggesting that binding impairments due to MTL dysfunction are not dimensionally specific. Braun et al., (2011) concluded instead that TLE patients, who had undergone a right temporal lobectomy, were only impaired when the vWM task required spatial binding but performed similarly to healthy controls when it required binding of non-spatial features.

Our own findings contribute new, crucial evidence for understanding the role of MTL in vWM binding, by confirming the association between MTL pathology and spatial binding impairments, unaccounted by impairments of either spatial vision or feature memory. We found an increase in the proportion of swap errors in the TLE group. Crucially, while healthy participants made significantly more swap errors following the shape probe, patients made significantly more errors following the space probe. The results in control participants are therefore in keeping with the hypothesis that binding of non-spatial features is mediated by the features' shared location. The likelihood of swap errors should be greater following shape compared to space probes, because in the latter case both the target shape and colour need to be bound respectively to the target location before they can be bound to each other (Schneegans & Bays, 2017). However, patients did not make made appreciably more swap errors following shape probes, although they made significantly more swap errors following space probes than controls. A possible interpretation of this dissociation is that patients gained the ability to bind non-spatial features directly, without the mediation of a shared location, allowing them to achieve higher accuracies following shape than space probes. Whether this inference is warranted remains to be established. Regardless, the group level pattern of dimensionally specific binding impairments observed in the TLE patients, who took part in the

present study, replicates a previous observation in a patient with bilateral MTL strokes, found to be impaired only in vWM tasks requiring spatial binding, but not those requiring non-spatial binding (Dundon et al., 2018). These data allow us to draw the following conclusion: MTL pathology is associated with WM binding impairments that are spatially specific and reverse the spatial advantage characteristic of healthy controls. If processes underlying spatial binding in vWM are independent from processes devoted to binding of non-spatial features, then the role of space in organising vWM may extend beyond the need to provide a shared index for the binding of features from other visual dimensions.

Hemispheric lateralization and binding

Bohbot et al., (1998) found that patients who had undergone thermocoagulation of structures within the right, but not the left. MTL were more impaired in a delayed spatial estimation task than those who had not undergone surgery. However, both patients with left and right sided lesions were more impaired at an object-location memory task, which required identifying which items had swapped positions between the sample and test display. These findings were used to suggest that right MTL structures may play an overarching role in spatial memory, but that left MTL structures have a specific role in spatial binding. On the other hand, (Braun et al., 2011) compared patients with right temporal lobectomy and healthy controls' performance on a number of single feature and features conjunction recall tasks and concluded that these patients are specifically impaired in spatial binding. However, the tasks employed memory samples of different complexity, thus confounding the effects of dimensionality and load. Our own results are in keeping with the idea that left rather than right MTL structures are specifically involved in spatial binding, since patients who had undergone left temporal lobectomies showed greater spatial binding impairments than right lobectomies patients. While our results need to be interpreted cautiously, given the small sample size, they are in keeping with (Kessels et al., 2004), who found that patients who had undergone left, but not right temporal lobectomies were impaired in spatial binding. These findings confirmed

lateralization effects previously observed, by the same group, in a sample of patients with vascular pathology (Kessels et al., 2002).

It is important to note, with regard to the issue of localization and the nature of cognitive impairments encountered in TLE patients, that group level results belie substantial inter-individual differences **(see Figure 17).** Impairments in a range of cognitive functions, besides memory, including attention, sensorimotor, language and executive functions have been reported in TLE, consistent with our neuropsychometric assessment **(see Table 28).** This is not surprising given the fact that TLE patients show widespread structural abnormalities in cortical and subcortical structures outside the main epileptogenic focus (Bell et al., 2011). A host of factors, including the age of seizure onset, severity and frequency of seizures, neuropsychiatric complications and antiepileptic medications, have been shown to affect the nature and degree of cognitive impairments observed (Bell et al., 2011), which may explain the inter-individual variations reported in the literature and seen in our own sample **(Figure 17).** Furthermore, pre and postoperative functional reorganization in temporal as well as extra-temporal structures has been documented to shape cognitive outcomes in TLE patients (Sidhu et al., 2013; Sidhu et al., 2016). In view of this, we think reporting individual participant data along with group-level data is required to facilitate a more nuanced understanding of the relation between lesion anatomy and cognitive outcomes.

Chapter 8. Summary Chapter

8.1 Conclusion

I originally set out to address five aims listed below.

1. To conduct a systematic review of literature investigating the psychiatric and neuropsychological sequalae of epilepsy surgery in patients who do not have a lesion on structural magnetic resonance imaging, including the prognostic markers.
2. To identify the pre-operative factors that are associated with seizure-freedom in patients who have undergone resective epilepsy surgery
3. To identify the pre-operative factors that predict post-operative anxiety and depression in patients who have undergone resective epilepsy surgery
4. To identify the pre-operative factors that predict post-operative changes in working, visual and verbal memory in patients who have undergone resective epilepsy surgery
5. To identify whether impairments of visual working memory binding are specifically spatial or rather generalize across visual feature dimensions following temporal lobe resections.

We found that post-operative seizure freedom was more likely in the following cohort of patients:

1) Patients with a lower frequency of pre-operative seizures
2) Patients with a local focus on EEG
3) Patients with non-generalised seizures
4) Patients with temporal lobe resections.

We found that post-operative anxiety outcomes were improved in the following cohort of patients:

1) Patients who were female

2) Patients with right-sided resections
3) Patients with lateral temporal lobe resections

We found that post-operative depression outcomes were improved in the following cohort of patients:

1) Patients with generalised seizures
2) Patients with right-sided resections

We found that verbal memory outcomes were improved in the following cohort of patients:

1) Non-generalised seizures

We found no independent factors that could improve post-operative visual and working memory outcomes.

In sum, this thesis helps to identify patients who would benefit most from epilepsy surgery at a tertiary neurosurgical centre in the North of England and facilitates shared decision making. Shared decision making ensures that decisions on a treatment are orchestrated by both the patient and healthcare professional using the best available evidence (Pickrell et al., 2015; Shafer, 2015). The findings of this thesis contribute to the existing evidence base and shed more light on the patient groups who would most likely benefit from epilepsy surgery, which can enhance the decision-making process and ensure that patients and healthcare professionals can make more informed choices. Herein, I discuss the significant findings and the inter-relationship between different outcomes.

With regards to cognitive and psychiatric outcomes found no evidence that patients with structural lesions on MRI had different outcomes compared to those with no structural lesions on MRI. Many of the relevant studies that have studied this area have compared patients using a retrospective design or did not follow-up patients for periods longer than two years. These

limitations make it difficult to draw firm conclusions about the long-term cognitive and psychiatric outcomes specifically in patients without structural lesions on MRI. Importantly, there are limited data concerning the cognitive and psychiatric outcomes following extratemporal lobe resections. It would not be unreasonable to expect that MRI negative patients may have worse psychiatric and cognitive outcomes, because the absence of a visible lesion may limit the ability to reliably outline the margins between pathological and non-pathological cortex. This may either increase the likelihood of resecting physiologically healthy tissue, or conversely, inadvertently miss epileptogenic tissue in the resection margins. This would result in either more extensive lesions than otherwise warranted or more postoperative seizures, which have been associated with poorer postoperative psychological and psychiatric outcomes. In general, MRI negative epilepsy patients have been shown to have higher pre-operative neuropsychological scores (Helmstaedter et al., 2011), making them more vulnerable to cognitive decline – “more room to fall”. A more comprehensive understanding of the cognitive and psychiatric outcomes in MRI negative cohorts would be important for counselling patients, and future studies should consider potential confounding variables e.g., epilepsy duration, seizure type and antiepileptic medication type and dose.

Several studies have reported a relationship between low baseline seizure frequency and seizure freedom (Edelvik et al., 2013; Hitiris et al., 2007; Kwan & Brodie, 2000; MacDonald et al., 2000), but the strength of the association is still debatable. Indeed, in one study conducted in the Cleveland Clinic Epilepsy Unit, patients with <30 seizures per month were reported to have higher rates of seizure worsening compared to patients with >30 seizures per month (Sarkis et al., 2012). In another study, Foldvary et al., (2000) showed that a preoperative monthly complex partial seizure frequency of <20 was associated with a higher likelihood of seizure freedom. With the addition of my findings, there remains inconclusive evidence for an association between pre-operative (baseline) seizure frequency and post-operative seizure freedom. This study did not show an association between mood scores (depression and anxiety) and pre-operative seizure frequency. Seizure freedom, which I have demonstrated to

be more likely in patients with low baseline seizure frequency, has been shown to be associated with improved post-operative psychiatric status (Altshuler et al., 1999; Blumer et al., 1998; Devinsky et al., 2005; Hermann et al., 1989; B. P. Hermann et al., 1992; Macrodimitris et al., 2011; Reuber et al., 2004). Therefore, in my study, it is surprising that anxiety and depression outcomes were not influenced by pre-operative seizure frequency. Considering my observation that lower pre-operative seizure frequency can result in seizure freedom, patients with low pre-operative seizure frequency should theoretically have an improvement in neuropsychological outcomes. Indeed, one study has shown that cognitive outcomes more than five years after temporal lobe epilepsy surgery are most remarkable in the absence of seizures (Helmstaedter et al., 2018). However, patients with a higher pre-operative seizure frequency tend to have lower baseline levels of memory, and those with lower baseline levels of memory typically improve the least following surgery (Sherman et al., 2011).

Patients in this study were more likely to experience seizure freedom at two years if they had a unilateral local focus of epileptogenic activity on encephalography, which is consistent with the literature (Ebersole & Pacia, 1996; Ivanovic et al., 2017; Jeha et al., 2006; Lau et al., 2014; Tatum et al., 2008; Wang et al., 2016; Zhang et al., 2013). Unilateral localised EEG can allow for more focussed epileptic zone resections, thereby reducing the likelihood of residual epileptogenic tissue (Ivanovic et al., 2017). Ensuring functional tissue is spared has been shown to be important determinants of post-operative neuropsychological and psychiatric improvement (Vakharia et al., 2018). A more localised surgery with less “collateral damage” may also result in fewer post-operative complications, which can mean fewer re-admissions into hospital and ensuing psychological demise. Given the association between improved seizure freedom and better neuropsychological (Skirrow et al., 2015) and psychiatric outcomes (Macrodimitris et al., 2011), it is surprising that unilateral EEG was not found to be a predictor of improved neuropsychological or psychiatric outcomes.

I found that patients with non-generalised seizures were more likely to achieve seizure freedom in the postsurgical period compared to patients with generalised seizures, which is consistent with the literature (Bergen, 2006; McIntosh et al., 2004). Generalised seizures typically have a more widespread epileptogenic zone which cannot be resected entirely with surgery; hence the residual epileptogenic zone can precipitate further seizures in patients with pre-operative generalised seizures (McIntosh et al., 2004; Yoon et al., 2003). Interestingly, I also found that patients with pre-operative generalised seizures were more likely to see less post-operative depression compared to those with non-generalised seizures. There is evidence that patients with generalised seizures have worse psychiatric outcomes compared to patients with non-generalised seizures (Dodrill, 2004), hence patients with pre-operative generalised seizures (with higher psychopathology) may notice more dramatic improvements in their psychiatric status post-operatively compared to patients with non-generalised seizures. Interestingly, non-generalised seizures were found to be an independent predictor of improved post-operative verbal memory scores, but this was not observed for any other memory subtype. Hitherto, no study has directly explored the effects of seizure type on neuropsychological outcomes, and my finding was unexpected. This is because patients with generalised seizures tend to have worse neuropsychological scores (Dodrill, 2004), so successful epilepsy surgery would be expected to cause a more dramatic change (improvement) compared to pre-operative non-generalised seizures.

Patients with temporal lobe epilepsy were reported to have higher chances of seizure freedom compared to extra-temporal lobe epilepsy. This finding is inconsistent with another epilepsy surgery published in the Northwest of England in which the temporal locality of resection did not influence the likelihood of seizure freedom (Mohan et al., 2018). On the other hand, in keeping with our finding, one meta-analysis has demonstrated that extratemporal resections have less likelihood of resulting in seizure freedom compared to temporal lobe resections, which might be because seizure foci in multiple lobes may overlap with eloquent cortex to a greater extent, thus making lesions less amenable to resection (Téllez-Zenteno et al., 2005).

Interestingly, mesial or lateral temporal lobe involvement was not reported to affect seizure freedom. Mesial temporal lobectomies are generally recognised to have a greater likelihood of seizure freedom compared to lateral temporal lobectomies (Ficker et al., 1999; Spencer et al., 2003; Wass et al., 1996), but evidence is still inconclusive (Mohan et al., 2018; Spencer et al., 2005). Post-operative psychopathology (specifically depression) was found to be improved in patients with lateral temporal lobectomies compared to those with mesial lobe resections, which is in keeping with previously published reports (de Oliveira et al., 2010; Garcia, 2012; Georgiadis et al., 2013; Wrench et al., 2011). Lateral lobe resections do not disturb limbic structures, such as the amygdala and hippocampus, which may explain why psychopathology is better in this cohort of patients compared to those with mesial lobectomies. It is unclear why depression outcomes are not affected by mesial lobe involvement.

There is no robust evidence exploring the association between sex and postoperative anxiety in post-operative epilepsy surgery cohorts. In this study I showed that females were more likely to have less anxiety postoperatively compared to males. This is likely because females tend to have more severe pre-operative anxiety (Devinsky et al., 2005), so any improvement that arises from epilepsy surgery may be more marked in females compared to males. Sex was not found to affect seizure freedom which is consistent with the literature at large (Briellmann et al., 2000; Burneo et al., 2008; Helmstaedter et al., 2004; McIntosh et al., 2001). The evidence implicating an association between side of resection and postoperative psychopathology is inconsistent. Some studies have suggested that right sided resections are a greater risk factor for postoperative psychopathology depression and anxiety (Glosser et al., 2000; Kohler et al., 1999; Quigg et al., 2003; Taylor, 1972), whilst others have suggested that left sided resections are a greater risk factor for this complication (Malmgren et al., 2002; Quigg et al., 2003). Other studies have shown no relationship between laterality and postoperative psychopathological status (Devinsky et al., 2005; Macrodimitris et al., 2011; Meldolesi et al., 2007; Rayner & Wilson, 2012). Therefore, it is not possible to draw any consensus from the literature. In the majority of people in the healthy population, the left cortex

is responsible for the genesis and processing language and speech, so deficits in these domains may have a more profound effect on day-to-day living, resulting in downstream psychiatric impairment. Therefore, my finding of worse postoperative anxiety and depression in epilepsy patients with left-sided resections is broadly consistent with the current evidence base (de Oliveira et al., 2010; Garcia, 2012; Georgiadis et al., 2013; Quiske et al., 2000; Wrench et al., 2011). Whilst right-sided resections have been shown to associated with seizure freedom (Malmgren & Edelvik, 2017; Tonini et al., 2004; West et al., 2019), my study did not show a relationship between side of resection and chances of seizure freedom. My study did not elucidate an association between side of resection and neuropsychological outcomes (verbal memory, visual memory or working memory), which is broadly consistent with the literature (Sherman et al., 2011). However, there is evidence that left-sided resections may result in greater memory decline compared to right-sided resections (Law et al., 2017).

In this study, an improvement in verbal memory was associated with the absence of pre-operative generalised seizures, but no association was found with visual or working memory. The majority of studies that have investigated post-operative outcomes following resective surgery for epilepsy have focussed principally on seizure outcomes and, given the paucity of literature exploring cognitive outcomes, it is challenging to draw any meaningful conclusions. Systematic reviews and meta-analyses have shed some light the cognitive sequelae of epilepsy surgery. One systematic review investigating the relationship between seizure type and cognitive decline found a significant association between cognitive deterioration and the presence of preoperative generalised seizures (Dodrill, 2004). A major issue that I encountered in this study was the absence of adequate post-operative data for neuropsychological and psychiatric outcomes, which limited my sample size. The lack of an adequately powered sample with two-point data (pre and post-operative) is most likely responsible for the lack of statistically significant outcomes.

It is established that epilepsy patients who undergo temporal resection may develop visual memory deficits (see chapter 7). In chapter 7, I performed an in-depth study of visual memory in this patient group. I examined visual working memory in thirteen patients with varying forms of temporal lobe pathologies who had undergone resective surgery for epilepsy. Disorders of the medial temporal lobe adversely affect visual working memory, including feature binding. It is debated whether these impairments are specifically spatial or generalise across visual dimensions. To address this issue, I compared performance of patients who had undergone a temporal lobectomy and healthy controls in a visual working memory and a perceptual task. In the memory task participants had to remember the colour of two polygons, displayed side by side. After a brief blank delay, the target, whose colour had to be reported, was identified either by a location or a shape probe. In the perceptual task, participants estimated the centroid position of three visible disks. In the recall task, patients were less accurate following space than shape probes, because they reported the non-target instead of the target's colour (swap errors). Healthy controls made more swap errors following shape than space probes instead. Patients and controls performed similarly in the perceptual task. We conclude that mesial temporal lobe damage specifically impairs spatial binding in visual working memory, which does reflect on a visuo-spatial deficit.

I found that this cohort of patients makes a greater number of object-location binding errors compared with healthy controls. The major strength of this study was the fact that I had identified 13 patients who fit the tight inclusion criteria, carefully documented the extent of their mesial temporal lobe damage, provided them with a battery of psychological tests, and identified suitably matched control group patients. My results support the conclusion of a previous paper (Dundon et al., 2018). In that study, a 46-year-old man with lesions involving the parahippocampal cortex and hippocampal atrophy, but spared perirhinal cortex, was found to have a selective deficit in short-term spatial binding compared to a group of age matched healthy controls. In an identical protocol to the one I have described in this thesis (see chapter 7 methodology), when asked to recall the colour of one of two objects, the patient in question

misidentified the target when cued by its location, but not its shape. In contrast, the healthy control group showed comparable recall irrespective of the cue type, suggesting that the patient in question had a binding impairment that was specifically spatial in nature.

8.2 Limitations

Chapters 4,5 and 6 are retrospective studies, as is the case in the large majority of papers exploring this field. It would be unfeasible to undertake a prospective study within the timeframe of a PhD.

As alluded to in the conclusion (see section 8.1), a major issue that I encountered was inadequate postoperative data on several patients who would otherwise have been included in this study. The lack of two-point data (pre and post-operative) data was particularly obvious for patients who underwent cognitive and psychiatric assessments.

I did not take into consideration the effects of antiepileptic drugs on seizure outcome. Surgery may allow clinicians to reduce the dose of antiepileptic drugs but tapering down such drugs may cause seizure recurrence in approximately one in three patients (Kanchanatawan et al., 2014; Pimentel et al., 2012). Therefore, seizure-freedom (Engel classification I) in our study may have been a result of a change in the type, regime and dosage of antiepileptic drugs. In one study, investigators were able to discontinue one or more antiepileptic drugs in 48.7% of patients, while 13.2% of all patients were free of any antiepileptic drugs two years postoperatively (Kanchanatawan et al., 2014). In another study, approximately 30% of patients discontinued antiepileptic drugs two years after surgery and had remained seizure-free, suggesting no risk of seizure recurrence after antiepileptic drug discontinuation (Elsharkawy et al., 2009). In addition to influencing seizure outcome, antiepileptic drugs also have psychotropic properties **(see table 30)** and can be used as mood stabilisers (Melvin et al., 2008), anxiolytics (Mula et al., 2007) and in withdrawal regimes (Zullino et al., 2004). In

addition to effects on affect, anti-epileptic drugs have also been shown to affect short-term memory and may induce drowsiness or concentration effects (Eddy et al., 2011; C. Helmstaedter, 2013). In future, it would be useful to account for the type and dose of antiepileptic drug, which might have an effect on seizure outcome, psychiatric and cognitive profiles

	Negative	**Positive**
Barbiturates	Depression, hyperactivity	Anxiolytic, hypnotic
Carbamazepine-Oxcarbazepine	Irritability	Mood stabilising, antimanic
Ethosuximide	Behavioural abnormalities, psychosis	-
Felbamate	Depression, anxiety, irritability	-
Gabepentin	Behavioural problems in children	-
Lamotrigine	Insomnia, agitation	Mood stabilising, antidepressant
Levetiracetam	Irritability, emotional lability	Antimanic?
Phenytoin	Encephalopathy	Antimanic?
Pregabalin	?	Anxiolytic
Tiagabine	Depression (non-convulsive status epilepticus)	Anti-anxiety?
Topirimate	Depression, psychomotor slowing, psychosis	Mood stabilising
Valproate	Encephalopathy	Mood stabilising, antimanic (anxiolytic)
Vigabatrin	Depression, aggression, psychosis	-
Zonisamide	Agitation, depression, psychosis	Antimanic?

Table 30. Psychotropic effects of antiepileptic drugs. From Mula, M., & Schmitz, B. (2009). Depression in epilepsy: mechanisms and therapeutic approach. *Therapeutic advances in neurological disorders*, *2*(5), 337–344. https://doi.org/10.1177/1756285609337340

Another limitation of this study is the absence of any data related to antidepressant on medication use and cognitive behavioural therapy that could affect postoperative psychiatric and cognitive outcomes. There is also evidence that new-generation antidepressants can decrease seizure threshold (Hill et al., 2015), which may have influenced the proportion of patients in our cohort who were seizure-free at two years.

Furthermore, data on presurgical epilepsy duration were not available for all patients. A 2019 systematic review and meta-analysis of 12 studies concluded that *"duration of epilepsy is the only known modifiable factor that is associated with favourable seizure outcome after epilepsy surgery"* (Bjellvi et al., 2019).

My study is confined to adults, so it may not be generalisable to paediatric practice. My study is also skewed towards temporal lobe resections. With regards to the latter limitation, this is an inevitable limitation as anterior temporal lobe resections are always the most common form of epilepsy surgery (de Tisi et al., 2011).

With regards to the final chapter. I only studied two colours. Unfortunately, this design was not particularly taxing on working memory, as evidenced by the very high accuracy in the task for both patients and controls. Given the small study sample size, this experiment arguably does not heavily tax working memory. As such, to the extent that there is any deficit in performance here, it is challenging to attribute this entirely to working memory. Psychiatric morbidity has been reported to affect cognitive outcomes (see chapter 6), and the absence of formal DSM diagnostic assessments means that important confounding variables have not been included into the regression analysis. Moreover, as evidenced in **table 30** antiepileptic drugs can have debilitating neurocognitive side-effects and I did not systematically collect data on the postoperative antiepileptic medication, potentially important confounding variables. The small sample size (13 patients in the resection group) increases the risk of type I error.

8.3 Future directions

Researchers who intend to explore this field in future may wish to design a prospective, multi-centre study. Indeed, the outcomes from this PhD have provided a basis for our group to develop a protocol for a large scale, international, multi-centre study with sites in the United Kingdom and Saudi Arabia. Given the different populations, this should ensure that our results are reproducible to surgical cohorts across the globe.

In future, it would be worthwhile to analyse the socioeconomic status (stratified by education level and occupational status) of patients and its impact on seizure outcome, which have both been shown to independently result in a worse seizure outcome epilepsy patients. In previous studies, epilepsy has been shown to be associated with lower levels of employment and income (Andersson et al., 2020; Bautista & Wludyka, 2007; Burneo et al., 2009; Jennum et al., 2011). There is also evidence that the association between epilepsy-related morbidity and lack of employment is stronger in patients with low educational attainment (Andersson et al., 2020). However, interestingly, in a study investigating the relationship between median household income by residence postal code (used as a proxy for patient income), it has been shown that household income does not affect epilepsy outcomes (Burneo et al., 2006). One United Kingdom-based database that could be interrogated for this purpose could be the Swansea Secure Anonymised Information Linkage (SAIL) https://popdatasci.swan.ac.uk/centres-of-excellence/sail/ , which is a repository of anonymous medical and social data belonging to the population of Wales. The SAIL database has already been interrogated in research related to epilepsy surgery (Kansu et al., 2020). In that study, epilepsy surgery was associated with significant improvements in seizures, a reduced antiepileptic drug load and improved quality of life that correlate with reduced hospital admissions following surgery (Kansu et al., 2020).

Future studies should also take into consideration the effect of the histopathological substrate of the epileptogenic zone on postoperative outcomes. I had intended to study this but the number of patients with complete pre- and post-operative data was too small. It would not be unreasonable to hypothesise that patients with an underlying cortical dysplasia would have worse postoperative outcomes than patients diagnosed with hippocampal sclerosis. Cortical dysplasia has long been considered one of the major causes of symptomatic and refractory epilepsy and is generally considered less amenable to surgical management compared to hippocampal sclerosis (Sun et al., 2017). This being said, there is some evidence that

underlying histopathology does not have a significant effect on epilepsy outcomes (Chapman et al., 2005), so this should be further clarified in future studies. There are no studies that adequately address histopathology and cognitive and psychiatric outcomes.

Researchers who explore this landscape in future should ensure that data are analysed by the exact extratemporal lobe that was operated upon (parietal, frontal or occipital). This is because surgery on specific lobes has been shown to have different psychiatric manifestations (Prayson et al., 2017).

Unfortunately, my limited data set meant it was not possible to elucidate whether pre-existing psychopathology affected the chances of seizure freedom and whether epilepsy surgery could precipitate *de novo* psychiatric disturbances. Indeed, the most significant risk factor for post-surgical depression and anxiety has consistently been shown to be a lifetime psychiatric diagnosis (Cleary et al., 2013).

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