Psychiatric and psychosocial comorbidity before and one year after epilepsy surgery

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I declare that this thesis, which I submit to RCSI for examination in consideration of the award of a higher degree MD (Doctor of Medicine), is my own personal effort. Where any of the content presented is the result of input or data from a related collaborative research programme this is duly acknowledged in the text such that it is possible to ascertain how much of the work is my own. I have not already obtained a degree in RCSI or elsewhere on the basis of this work. Furthermore, I took reasonable care to ensure that the work is original, and, to the best of my knowledge, does not breach copyright law, and has not been taken from other sources except where such work has been cited and acknowledged within the text.

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Table of Contents

List of tables........................................................................................................... 11
List of figures........................................................................................................... 12
List of abbreviations............................................................................................... 14
Summary.................................................................................................................... 16
Acknowledgements.................................................................................................. 18
Publications and presentations related to this thesis............................................... 19
Chapter 1: Introduction............................................................................................ 20
Overview................................................................................................................... 20
1.1 Introduction........................................................................................................ 20
1.2 Epilepsy and Psychopathology.......................................................................... 22
1.3 Mood disorders in epilepsy.............................................................................. 24
1.3.1 Mood disorders: prevalence in epilepsy...................................................... 24
1.3.1 Mood disorders: aetiology in epilepsy......................................................... 25
1.3.3 Mood disorders: treatment in epilepsy....................................................... 30
1.4 Suicide in epilepsy............................................................................................. 32
1.5 Anxiety disorders in epilepsy.......................................................................... 33
1.5.1 Anxiety disorders: prevalence in epilepsy.................................................. 33
1.5.2 Anxiety disorders: aetiology ..................................................................... 34
1.5.3 Anxiety disorders: treatment in epilepsy ............................................ 36
1.6 Psychosis in epilepsy .............................................................................. 37
1.6.1 Psychosis: prevalence in epilepsy ....................................................... 37
1.6.2 Psychosis: aetiology in epilepsy ......................................................... 37
1.6.3 Psychosis: treatment in epilepsy ......................................................... 42
1.7 Auras .................................................................................................... 44
1.8 Personality disorders in epilepsy .......................................................... 45
1.9 Psychogenic Non Epileptic Seizures (PNES) ........................................... 46
1.10 Quality of life in epilepsy ..................................................................... 46
1.11 Surgical treatment of epilepsy .............................................................. 50
1.11.1 Surgery and psychopathology ........................................................... 50
1.11.2 Surgical treatment and mood disorders ............................................. 52
1.11.3 Surgical treatment and psychosis ....................................................... 53
1.11.4 Surgical treatment and anxiety .......................................................... 53
1.11.5 Surgical treatment and personality disorders .................................... 56
1.11.6 Surgical treatment and quality of life outcomes ............................... 57
1.12 Summary ............................................................................................. 60

Chapter 2: The prevalence of psychosis in epilepsy: a systematic review and meta-analysis ................................................................. 62

2.1 Introduction ......................................................................................... 62
2.2 Methods ............................................................................................. 63
2.3 Results ............................................................................................... 66
Chapter 3: The prevalence of psychosis in post-operative epilepsy surgery patients: a systematic review and meta-analysis.

Chapter 4: Methods for experimental chapters 5 and 6.

4.1 Study setting.

4.2 Recruitment of the cohort sample.

4.3 Ethical approval.

4.4 Study design.

4.5 Baseline Assessments.

4.6 Proforma.

4.7 Structured Clinical Interview for DSM IV (SCID I).

4.8 Structured Clinical Interview for DSM IV Personality Disorder (SCID II).

4.9 Hospital Anxiety and Depression Scale (HADS).

4.10 Quality of life in Epilepsy 89 (QOLIE-89) scale.

4.11 Follow up assessments.
5.12 Hospital Anxiety and Depression Scale (HADS) ........................................... 126
5.13 Quality of life in Epilepsy-89 (QOLIE-89) ..................................................... 127
5.14 Correlations between HADS, QOLIE-89, seizure frequency and SCID Diagnosis in medically refractory epilepsy sample ........................................ 127
Chapter 6: Surgical cohort results ................................................................... 134
Overview ........................................................................................................... 134
6.1 Demographic data ....................................................................................... 134
6.2 Psychiatric history ....................................................................................... 135
6.3 Psychiatric family history ............................................................................ 136
6.4 Birth complications and developmental delay ........................................... 137
6.5 Febrile convulsions .................................................................................... 137
6.6 Handedness and hemisphere of seizure origin .......................................... 137
6.7 Age of seizure onset .................................................................................. 139
6.8 Epilepsy diagnosis according to site of origin ............................................ 137
6.9 Seizure classification .................................................................................. 138
6.10 Seizure frequency ...................................................................................... 139
6.11 Psychiatric diagnosis ................................................................................ 142
6.11.1 All psychiatric diagnoses ........................................................................ 142
6.11.2 Pre and post-operative changes in mood disorders status .................. 143
6.11.3 Pre and post-operative changes in psychotic disorders status .......... 143
6.11.4 Pre and post-operative changes in anxiety disorders status ............ 143
List of tables
Table 5.1 Patient demographic data ................................................................. 115
Table 5.2 Psychiatric history .............................................................................. 116
Table 5.3 Family history of mental health problems ........................................... 117
Table 5.4 Seizure classification according to ILAE 1989 guidelines ................. 120
Table 5.5 Frequency of seizures grouped .......................................................... 121
Table 5.6 Psychiatric diagnosis of medically refractory epilepsy sample ......... 122
Table 5.7 Mood disorders in medically refractory epilepsy sample ................. 123
Table 5.8 Anxiety disorders in medically refractory epilepsy sample .............. 124
Table 5.9 Psychotic disorders in medically refractory epilepsy sample ............ 125
Table 5.10 Personality disorders in medically refractory epilepsy sample ....... 126
Table 6.1 Surgical cohort demographic data .................................................... 135
Table 6.2 Psychiatric history of surgical cohort ............................................... 136
Table 6.3 Surgical cohort: seizure classification according to the ILAE Guidelines 1989 ................................................................. 139
Table 6.4 Surgical cohort: change in number of seizures experienced Pre-operatively versus post-operatively ....................................................... 140
Table 6.5 Surgical cohort: psychiatric diagnosis .............................................. 142
Table 6.6 Psychiatric diagnoses pre and post-operatively ................................ 142
Table 6.7 De novo psychiatric illness post-operatively .................................... 145
Table 6.8 Surgical cohort Hospital Anxiety and Depression Scale pre and Post-operative assessment ................................................................. 146
Table 6.9 Surgical cohort QOLIE-89 scores pre and post operatively ............ 147
List of figures

Figure 2.1 PRISMA flow diagram.............................................................79
Figure 2.2 Pooled prevalence of psychosis in individuals with epilepsy...80
Figure 2.3 Prevalence of psychosis in Temporal Lobe Epilepsy.............81
Figure 2.4 Pooled odds ratio for students with controls.......................82
Figure 3.1 Pooled prevalence rate for post-operative psychosis in
Epilepsy patients.............................................................................93
Figure 3.2 Pooled prevalence rate for pre-operative psychosis in epilepsy
patients.........................................................................................94
Figure 3.3 Pooled prevalence rate of post-operative psychosis in epilepsy
Patients in which studies had a per-operative rate also....................95
Figure 3.4 Pooled prevalence rate of new onset psychosis in epilepsy
Patients after surgery....................................................................96
Figure 3.5 Pooled prevalence rate of pre-operative psychosis in temporal
lobe epilepsy patients..................................................................97
Figure 3.6 Pooled prevalence rate of post-operative psychosis in temporal
lobe epilepsy patients..................................................................98
Figure 3.7 Pooled prevalence rate of de novo psychosis in temporal lobe
Epilepsy post-surgery...................................................................99
Figure 4.1 Flow diagram: recruitment of participants..........................103
Figure 5.1 Bar chart of epilepsy diagnosis by category.......................119
Figure 5.2 Scatterplot showing seizure frequency with overall HADS
score.............................................................................................128
Figure 5.3 Scatterplot showing seizure frequency with QOLIE-89 overall
Score.............................................................................................129
Figure 5.4 Scatterplot showing correlation between QOLIE-89 and HADS
.......................................................................................................131
Figure 5.5 Bar chart showing the breakdown of SCID diagnosis present
v's absent for each seizure group.................................................................132

Figure 5.6 Boxplot to show the distraction of QOLIE-89 scores in patients
with and without a mood disorder..............................................................133

Figure 6.1 Surgical cohort: frequency of epilepsy diagnosis by site of
origin..................................................................................................................138

Figure 6.2 Histogram of change in seizure frequency from pre-operative
To post-operative............................................................................................141
List of Abbreviations

ADPEAF-Autosomal Dominant Partial Epilepsy with Auditory Features
AED-Anti-Epileptic Drugs
APA-American Psychiatric Association
CBT-Cognitive Behavioural Therapy
CI-Confidence Interval
CNTNAP2-Contactin-Associated-Protein-Like-2
CNV-Copy Number Variant
DNIT-Dysembryoplastic Neuroepithelial Tumour
DSM IV-Diagnostic and Statistical Manual of Mental Disorders Version 4
ECT-Electroconvulsive Therapy
EEG-Electroencephalogram
EMU-Epilepsy Monitoring Unit
FDA-Food and Drug Administration
FDG-Fludeoxyglucose
GABA-Gama-AminoButyric Acid
GAD-Generalised Anxiety Disorder
GMC-General Medical Condition
HADS-Hospital Anxiety and Depression Scale
HPA-Hypothamic-Pituitary-Axis
HRQOLs-Health Related Quality of Life
I²-I Squared Statistic
IDD-Interictal Dysphoric Disorder
ILAE-International League Against Epilepsy
IQ-Intelligence Quotient
LGI-Leucine-rich Glioma Inactivated
MRI-Magnetic Resonance Imaging
MRS-Magnetic Resonance Spectroscopy
MTS-Mesial (or Medial) Temporal Sclerosis
NOS-Not Otherwise Specified
OCD-Obsessive Compulsive Disorder
OR-Odds Ratio
PET-Position Emission Tomography
PNES-Psychogenic Non-Epileptic Seizures
PRISMA-Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PTSD-Post Traumatic Stress Disorder
QOL-Quality of Life
QOLIE 89-Quality of Life In Epilepsy 89
RR-Relative Risk
SCID-Structured Clinical Interview for DSM IV
SF-36-Short Form 36 Health Survey
SSRI-Selective Serotonin Re-uptake Inhibitor
SNRI-Serotonin Noradrenaline Re-uptake Inhibitor
SPECT-Single Photon Emission Computed Tomography
TLE-Temporal Lobe Epilepsy
Summary

Introduction
Epilepsy is a common disease with a prevalence of 0.5-1% of the population. The literature on psychopathology in refractory epilepsy is conflicting. In refractory epilepsy, surgical intervention is considered to reduce seizure frequency and in some cases prevent seizures. It has been reported that neurosurgical intervention for epilepsy is associated with significant undesirable psychiatric consequences. This study looked at psychiatric and psychosocial comorbidity in a sample of pre-operative epilepsy surgery candidates and also examined patients who proceeded to surgery at one year post-operatively to see whether surgery had positive or negative consequences on patients' mental health.

Methods
This study examined a sample of patients with medically refractory epilepsy and a prospective cohort study was conducted on a sub-group of this sample who underwent surgery and had psychiatric follow-up at one year postoperatively. This study used the Structured Clinical Interview for DSM IV (SCID I) to examine for an Axis I psychiatric diagnosis and the presence of a personality disorder was assessed for using SCID II. The Hospital Anxiety and Depression Scale (HADS) and Quality of Life In Epilepsy 89 (QOLIE 89) were the subjective rating scales utilized.

Results
The findings of this study demonstrated the high prevalence of psychiatric comorbidity (54.4%) in patients with medically refractory epilepsy. A total of 48 patients had pre-operative and post-operative assessments at one
year. There was a highly significant reduction post-operatively with the number of patients with a psychiatric diagnosis (p<0.021). There was a reduction in the number of patients with psychosis post-operatively. There was a marked improvement in the subjective quality of life scores post-operatively (p<0.002).

Conclusions
Overall, this study demonstrated that undergoing surgery for medically refractory epilepsy had an overall positive impact on mental health with a significant reduction in the prevalence of psychiatric symptoms and an improved quality of life for patients.
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Clancy M, Clarke M, Cotter D, Cannon M. Prevalence of psychosis in post-operative epilepsy patients; a systematic review and meta-analysis

13th International Congress on Schizophrenia Research, Colorado Springs, Colorado, April 2011
Chapter 1 Introduction

Overview
This introductory chapter provides an overview of the clinical features of epilepsy and its association with psychiatric illness, considers its prevalence based on epidemiological studies, examines aetiological theories for the associated psychiatric disorders and considers the evidence base for treatment options. The current literature findings and their limitations are discussed. The main question relates to current understanding of the association between epilepsy and psychopathology with a particular focus on depression, psychosis, anxiety and personality disorders in the medication refractory epilepsy population.

1.1 Introduction
The definition of an epileptic seizure according to the International League Against Epilepsy (ILAE) is '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 neurobiological, cognitive, psychological and social consequences of this condition'. The lifetime prevalence of epilepsy is approximately 0.5-1% (MacDonald et al., 2000). The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epilepsy is not one single condition but more an umbrella term for a variety of conditions in which seizures occur. In 2010, the ILAE published updated new guidelines on classification replacing the 1989 guidelines. The new guidelines take into account advances in aetiology, seizure types and foci. Seizures are broadly divided into generalised encompassing tonic-clonic, absence, myoclonic, clonic, tonic and atonic and also into focal seizures with additional descriptors-with or without impairment of consciousness or awareness. Further classification can be used based on the underlying aetiology-genetic, structural/metabolic or unknown cause.
There are many varied definitions of medically refractory epilepsy. Many clinical researchers define medically refractory epilepsy as seizures that are not controlled after an adequate trial of two different first line Anti-Epileptic Drugs (Kwan et al., 2010). (AEDs) A consensus proposal by the Task Force of the International League Against Epilepsy (ILAE) Commission created an operational definition of medically refractory epilepsy. The ILAE defines medically refractory epilepsy as ‘the failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Some experts advocate at least 3 regimens including one trial of 2 drug therapy. If three trials of monotherapy with first line drugs are unsuccessful, the chances that the patient will respond to a fourth drug as monotherapy or polytherapy is only 5%. The term ‘seizure free’ refers to freedom from all seizures including auras. The concept of intractable epilepsy also requires an understanding of how seizures affect patient’s quality of life in terms of their psychological, interpersonal and occupational functions. Patient’s satisfaction extends beyond measurement of seizure control, adverse effects or quality of life scores and may be influenced by a broad range of internal and external variables such as in the case of epilepsy surgery, pre-operative expectations, post-operative effect, ability to discard the sick role, obtaining employment and perceived success (Chin et al., 2006).

Seizure freedom is defined as freedom from all types of seizures for 12 months or three times the pre-intervention inter-seizure interval, whichever is the longer. (eg if prior to the intervention, the patient had intervals without seizures of up to 6 months, a seizure-free period of 18 months would be required to reasonably conclude that the seizure frequency is lower to prior to the intervention) (Kwan et al., 2010).
Examination of epilepsy and comorbid psychiatric disorders has been complicated by a lack of clarity of the phenomenology in both fields. The most useful classification which has emerged is to link psychopathology according to its temporal relationship with seizures ie pre (hours before seizure), post (hours or days following seizure), peri (during seizure) and interictal (phase between seizures when the electroencephalogram (EEG) is returned to baseline). Psychopathology for the purpose of this chapter will be discussed using the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) categories of Mood, Anxiety and Psychotic disorders diagnostic classifications (APA, 2000).

1.2 Epilepsy and Psychopathology
There has long been a historical association between epilepsy and mental illness. The first written account of epilepsy and pericital psychiatric symptoms was by the ancient Babylonians circa 2000 BC (Reynolds and Kinnier Wilson, 2008). The term epilepsy is derived from the Greek term epilepsia which means 'falling sickness'. The ancient Greeks considered epilepsy a sacred disease as they believed that the gods controlled people with epilepsy. In the middle ages, seizures and mental illness both were considered to be demonic possession. In the nineteenth century, considerable attention began to be paid by psychiatrists and neurologists towards cataloguing, describing and understanding disorders at the interface of epilepsy and psychiatry.

It was only with the development of clinical research methods that helped to operationalize concepts and classifications that neuroscientists were able to explore and try to understand the mechanisms that drive seizures and psychopathology. The advent of modern diagnostic techniques e.g. in brain imaging and neurophysiology have also contributed significantly to the studies of disorders at this interface (Krishnamoorthy, 2001).

Numerous studies have been conducted in which epidemiological, pathophysiological and therapeutic aspects of the comorbidities between
these entities have been evaluated. The results although variable because of differences in methodology and heterogeneity of patients, have confirmed a bidirectional relationship between psychiatric disorders and epilepsy which appears to play a role in the course of the disease (Garcia-Morales et al., 2008, Hesdorffer et al., 2000, Kanner and Balabanov, 2002).

The prevalence rates of psychiatric comorbid disorders vary widely among the different studies published in the literature. Swinkels et al explained the variability of data by the following factors-group heterogeneity, lack of standardised analysis instruments and the absence of adequate controls (Swinkels et al., 2005). The difference among studies in terms of the type and severity of epilepsy markedly influence results and are probably partially responsible for the reported incidence rates between 19% and 80%. The highest prevalence had been reported in patients evaluated for epilepsy surgery and especially those with temporal lobe epilepsy (TLE) (Manchanda et al., 1996, Perini et al., 1996, Victoroff et al., 1994). The lowest prevalence rates have been reported in population-based studies. In spite of the variability of the data, there is a general consensus that psychiatric disorders are more prevalent in patients with epilepsy than in the general population (Jalava and Sillanpaa, 1996, Swinkels et al., 2001).

The spectrum of psychiatric disorders in epilepsy appears fairly constant across culture, across gender and across age (Trimble and Krishnamoorthy, 2003, Hermann et al., 2000). Mood disorders, predominately major depression and anxiety have the highest frequency followed by psychosis (Victoroff, 1994). The resulting impact on quality of life (QOL) for patients suffering from both epilepsy and psychiatric illness is potentially profound and the importance of frequent and regular consultation between neurologists and psychiatrists treating patients who have epilepsy cannot be overstated (Boro and Haut, 2003).
1.3 Mood disorders in epilepsy

1.3.1 Mood disorders: Prevalence in epilepsy

Depression is one of the most frequently reported comorbid psychiatric conditions in patients with epilepsy. Prevalence figures ranging from 20-55% in patients with recurrent seizures and 3-9% in patients with controlled seizures have been reported (Jacoby et al., 1996). It is more prevalent among patients with partial seizure disorders of temporal or frontal lobe origin and among patients with poorly controlled seizures. A population based survey investigating the lifetime prevalence of depression in epilepsy, asthma and diabetes reported 29% of patients with epilepsy having at least one episode of depression as compared with 16% and 17% prevalence in patients with diabetes and asthma respectively and 8.7% in healthy respondents (Blum D, 2002). The reported prevalence of depression in people with epilepsy ranges between 12% and 37% in community settings (Ettinger et al., 2004) (Mohammadi et al., 2006). This wide range of estimates may be due to heterogeneity in study design, population demographics, lack of standardised assessments or the operational criteria used to diagnose depression and epilepsy. A recent systematic review and meta-analysis by Fiest et al found that people with epilepsy had an overall prevalence of active depression of 23.1% (95% CI 20.6-28.31) (Fiest et al., 2013). For lifetime depression (i.e. a depressive episode occurring at least once during a person’s life), an overall prevalence of 13% was found (Fiest et al., 2013). Otherwise ‘depression’ is one sustained episode of prominent depressive symptoms and associated features as per ICD 10 or DSM IV diagnostic criteria. A Canadian community population study found a lifetime rate of major depressive disorder of 17.4% in patients with epilepsy compared to 10.7% in the general population (Tellez-Zenteno et al., 2007b). A lifetime prevalence has been estimated at up to 50% among patients followed up in tertiary centres. Despite higher prevalence rates, depression remains under-recognized and under-treated in patients
with epilepsy. Kanner et al found that in a study of patients with epilepsy and a depressive disorder severe enough to warrant pharmacotherapy, that referral for psychiatric treatment was suggested after more than a year from the onset of symptoms in 63% of patients with a spontaneous mood disorder and in 54% with an iatrogenic episode (Kanner et al., 2000).

In recent years, a bidirectional relationship between depressive disorders and epilepsy has been demonstrated, as not only are people with epilepsy at greater risk of developing depression but patients with depression have a 3-7 fold higher risk of developing epilepsy (Forsgren and Nystrom, 1990) (Hesdorffer et al., 2000, Hesdorffer et al., 2006).

The concept of interictal dysphotic disorder (IDD) must also be mentioned. IDD was first described by Blumer and is characterised by a constellation of eight symptoms which require the presence of any three of the following: depressed mood, fear, paroxysmal irritability, anergia, anxiety, euphoric mood, pain and insomnia (Blumer et al., 1995). IDD is typically of short duration and symptoms occur at various intervals and tend to last from hours to two to three days. Blumer reported that between a third and a half of patients with epilepsy seeking medical care suffer IDD of sufficient severity to require intervention (Blumer et al., 2004). As IDD is not recognised under DSM criteria, patients presenting with these symptoms which are milder than those required to diagnose major depressive disorder may have to be classified under atypical depressive disorder or depression not otherwise specified.

1.3.2 Mood disorders: aetiology in epilepsy
The aetiology of depression in patients with epilepsy remains complex and is multifactorial in origin. Neurobiological factors, patient factors, medication related effects and psychosocial factors have all been implicated. Various causative mechanisms have been proposed.
Neurobiological factors

A hyperactive hypothalamic-pituitary-adrenal axis was identified in patients with TLE without depression which was of comparable magnitude to that of patients without epilepsy with depression (Zobel et al., 2004) (Kondziella et al., 2007). In humans with depression, a hyperactive HPA has been postulated as one of the operant pathological mechanisms mediating the atrophy of hippocampi and frontal lobes including the cingulate gyrus and orbitofrontal and dorsolateral cortex demonstrated by multiple investigators (Coffey, 1994, Bremner et al., 2000, Bremner et al., 2002, Sheline, 2006).

In epilepsy, the pathogenic role of the excitatory and inhibitory neurotransmitters glutamate and GABA (Gamma-Aminobutyric Acid) has been long established. In depression, the pathogenic mechanisms of these neurotransmitters are now being recognised in studies of experimental models of depression and in pharmacological, neuropathological and neuroimaging studies in humans (Kanner, 2011, Toro et al., 2007). Three lines of evidence support a pathogenic role of glutamate and GABA in depressive disorders: 1) dysfunction of glutamate transport proteins 2) abnormal concentrations of cortical glutamate and GABA identified with functional neuroimaging studies using proton magnetic resonance spectroscopy (H1-MRS) and neuropathological studies and 3) antidepressant effects of glutamate receptor antagonists (Brambilla et al., 2003, Kugaya and Sanacora, 2005).

Pineda et al examined whether a commonly used model of TLE in rats could be used as a model of comorbidity between epilepsy and depression suitable for both mechanistic studies and for the development of mechanism based antidepressant therapies (Pineda et al., 2010). Rodents that had been subjected to lithium chloride and pilocarpine status epilepticus and developed spontaneous recurrent seizures exhibited a set of impairments congruent with a depressive state, behavioural
equivalents of anhedonia and despair, dysregulation of the HPA axis and compromised raphe-hippocampal serotonergic transmission. Pharmacological studies have suggested that depressive impairments following status epilepticus develop as a result of enhanced interleukin -1 Beta signalling in the hippocampus which leads to depression via inducing perturbations in the HPA axis and subsequent deficit in the raphe-hippocampal serotonergic transmission (Vezzani et al., 2008).

Structural and functional abnormalities of the same neuroanatomical regions in primary depression and in epilepsy disorders that are frequently associated with comorbid depression have been found (Kanner, 2005, Kanner and Balabanov, 2002, Sheline, 2006). Structural changes in epilepsy and depression present as atrophy of temporal and frontal lobe structures (identified by high resolution MRI) in the amygdala, hippocampus, entorhinal cortex, temporal lateral neocortex, as well as in the prefrontal, orbitofrontal and mesial-frontal cortex and to a lesser degree, the thalamic nuclei and basal ganglia. Depression has also been associated with FDG-PET (fludeoxyglucose positron emission tomography) hypometabolism in subjects with temporal lobe epilepsy (Gilliam et al., 2004). Functional abnormalities in both depression and epilepsy have been identified by PET and SPECT (single photon emission computed tomography) in temporal and frontal lobes, consisting of decreased 5-HT 1A binding in the mesial structures, raphe nuclei and cingulate gyrus. SSRIs have been shown to abolish or reduce seizures in animal models in epilepsy (Richman and Heinrichs, 2007) and serotonergic mechanisms are presumed to be directly involved in these anticonvulsant effects (Kanner, 2005). However, higher doses of SSRIS may have a pro-convulsive effect due to emergent GABAergic and glutamergic disturbance (Jobe and Browning, 2005).
Patient factors

The majority of studies have found men with epilepsy to be at increased risk of depression as compared to women with epilepsy (Altshuler et al., 1990, Mensah et al., 2006, Septien et al., 1993). This is particularly significant because studies of people with depression without epilepsy have demonstrated an increased prevalence in women (Piccinelli and Wilkinson, 2000). Lund found in a study of patients with learning disability that twice the percentage of patients with epilepsy had a psychiatric disorder compared to patients with a learning disability without epilepsy (Lund, 1985). Psychiatric disorder was more common in patients with epilepsy in the last year and was inversely proportional to IQ. Family history of psychiatric illness usually depression and suicide has been associated with an increased incidence of depression (Robertson et al., 1994).

Medication factors

Antiepileptic medication has been shown to be associated with depression in patients with epilepsy (Mendez et al., 1993a, Fiordelli et al., 1993). There is some evidence for the following variables being relevant to the association of depressive symptoms with AED therapy: enhanced GABA transmission, folate deficiency, polytherapy, the presence of hippocampal sclerosis, forced normalization and a past history of affective disorder (Mula and Sander, 2007). In a study of 100 patients treated for depression in epilepsy, almost one third of patients were considered to have iatrogenic depression provoked by antiepileptic medication (Kanner et al., 2000). The antidepressants which have been most commonly reported as depressogenic are vigabatrin (10%), tiagabine (5%) and pheobarbitone (Trimble, 1996). Topiramate was implicated in affective disorders in 10.7% of patients (Mula et al., 2003a). Levetiracetam therapy was associated with depression in 2.5% of individuals; this was dose dependent and was also related to a past history of febrile seizures.
and status epilepticus (Mula et al., 2003b). A paradoxical ‘iatrogenic’
cause of psychopathology among patients with epilepsy includes the
phenomenon of ‘forced normalization’ (Akanuma et al., 2005). This
concept was first described by Landolt in the 1950’s (Landolt, 1957). This
phenomenon consists of the appearance of psychiatric illness associated
with the cessation of epileptict seizures. It is usually more widely
associated with psychosis in epilepsy. Thus an interictal depression may
exacerbate or present de novo in patients as better seizure control is
attained (Mula and Sander, 2007).

Psychological factors

Epilepsy is associated with repeated and unpredictable episodes of loss of
consciousness. This unpredictability and uncontrollability has been
compared with Seligman’s concept of ‘learned helplessness’ which occurs
when patients are exposed to adverse experiences on a random basis
(Seethalakshmi and Krishnamoorthy, 2007). Another concept used to
explain depression in patients with epilepsy is the ‘burden of normality’
that describes psychiatric decompensation in a person who is cured of a
chronic illness (Wilson et al., 2001). This may happen when a person
loses illness associated privileges and is forced to meet the everyday
challenges of a healthy person. In a study of in-patients with epilepsy,
limited social support, perceived stigma, external locus of control and
poor vocational adjustment were identified as significant predictors of
depression scores. Following multiple regression analysis, four key factors
were identified: increased stressful life events, female gender, poor
adjustment to epilepsy and less adequate financial status (Hermann and
Whitman, 1991). Higher levels of stigma predicted an increased risk of
depression (Reisinger and DiIorio, 2009). However, a recent systematic
review on psychosocial predictors of depression and anxiety in patients
with epilepsy found that the majority of studies did not support the
importance of attribution theory and stigma in the development of
depression in epilepsy (Gandy et al., 2012). There was inconsistent
support for the role of illness representations but likely support for the role of stress and self-efficacy.

1.3.3 Mood disorders: treatment in epilepsy
Treatment of psychiatric disorders in epilepsy is largely opinion-led with little evidence from systematic randomized controlled trials (Krishnamoorthy, 2003). There has been only one small double blind placebo controlled trial on the efficacy of antidepressants in patients with major depressive disorder and epilepsy. Amitriptyline was compared to nomifensine and placebo. At 6 weeks, all patients had improved with no significant differences between the active drugs and placebo. At 12 weeks, nomifensine was found to be superior (Robertson and Trimble, 1985).

Management of depression in epilepsy with antidepressants involve 3 major issues: 1) effect of antidepressant on seizure threshold, 2) antidepressant-anticonvulsant interactions 3) efficacy of antidepressants in this category of patient. (Seethalakshmi and Krishnamoorthy, 2007) In all patients, enquiry into suicidal ideation is mandatory. Alper compared the incidence of seizures between depressed patients randomized to SSRIs (Selective serotonin reuptake inhibitors), SNRIs (serotonin-noradrenaline reuptake inhibitors), mirtazapine and placebo in the course of multicentre placebo controlled studies submitted to the FDA (Food and drug Administration) for approval (Alper et al., 2007). Compared to the expected incidence of seizures in the general population, all depressed patients had a higher incidence. Nonetheless, patients randomized to placebo had a significantly higher incidence of seizures than the patients actually treated with the antidepressants (Alper et al., 2007). In general, the SSRI class of antidepressants except for fluoxetine and paroxetine are safe in epilepsy. Kanner found that sertraline definitely worsened seizures in only 1 out of 100 patients with refractory epilepsy (Kanner et al., 2000). Increased seizures have been identified in patients without epilepsy taking tricyclic antidepressants (Curran and de Pauw, 1998).
Most antidepressants are metabolized in the liver and their metabolism is accelerated in the presence of anti-epileptic medications with enzyme inducing properties which include phenytoin, carbamazepine, phenobarbital and at higher doses oxcarbazepine and topiramate. This pharmokinetic effect is not observed with the newer anticonvulsants gabapentin, lamotrigine, tiagabine, levetiracetam and zonisamide (LaFrance et al., 2008). Conversely, some of the SSRIS are inhibitors of one or more isoenzymes of the cytochrome P450 (CYP 450) system. These include fluoxetine, paroxetine and to a lesser degree sertraline. Citalopram on the contrary does not have pharmokinetic interactions with anticonvulsant medications.

The SSRI class should be considered as the first line treatment in depressed patients with epilepsy. They are safe with respect to seizure propensity, are less likely to have fatal consequences in overdose and generally they have a favourable side effect profile. Furthermore, their efficacy in dysthymic disorders and in symptoms of irritability and poor frustration tolerance make this class of antidepressants more attractive among patients that have atypical forms of depression.

In patients with epilepsy and comorbid mood disorder, use of anticonvulsants with known positive mood effects such as valproate, carbamazepine and lamotrigine should be considered. Leviteracetam, vigabatrin, topiramate and barbiturates should be avoided where possible. Caution however is advised with switching anticonvulsants as withdrawal reactions have been noted and in approximately 40% of patients with epilepsy, affective symptoms have been noted in the withdrawal phase (Ketter et al., 1994).

Several models of CBT (Cognitive Behavioural Therapy) ranging from more generic applications to more specific models based on original research have been applied in epilepsy. However a meta-analysis of psychological therapies in epilepsy concluded that ‘in view of the
methodological deficiencies and limited number of patients studied, we have found no reliable evidence to support the use of treatments and further trials are needed’ (Ramaratnam et al., 2008). There are no studies looking at the efficacy of combined pharmacotherapy and psychotherapy in patients with epilepsy.

Electroconvulsive therapy is not contraindicated in depressed patients with epilepsy. It is a well-tolerated treatment and is worth considering in patients with epilepsy with very severe depression that fails to respond to antidepressant medication. Lunde et al reviewed 43 patients treated with ECT. The procedure was found to be safe and adequate seizure induction was obtained. Eventual anticonvulsant dosage reduction was needed in some case. There was a moderate to marked improvement in psychiatric symptoms (Lunde et al., 2006).

1.4 Suicide in epilepsy
Patients with epilepsy have a significantly higher suicidal risk that the general population. In a Canadian based population study, lifetime prevalence of suicidal ideation was twice as high in patients with epilepsy (25%, 95% CI 17.4-32.5) compared to the general population (13.3% 95% CI 12.8-13.8) (Tellez-Zenteno et al., 2007b). A large population based case control study found that people with a history of epilepsy had a three times higher risk of suicide (RR 3.17 (95% CI 2.88-3.5 p<0.001) compared with people with no such history. The relative risk remained high even after excluding patients with a history of psychiatric disease and controlling for socio-economic factors. (RR 1.99 1.71-2.32, p<0.0001) The highest risk of suicide in patients with epilepsy occurred within 6 months of a new diagnosis being made and the risk of suicide declined with the duration of epilepsy (Christensen et al., 2007). An older meta-analysis gave a suicide risk five times higher than expected. Risk of suicide was eight times greater in patients with temporal lobe epilepsy (Harris and Barraclough, 1997). Higher risk was associated with previous
suicide attempts, alcohol and drug abuse and stigma. A more recent review identified psychiatric co-morbidity and presence of an Axis I disorder as primary risk factors for suicide (Verrotti et al., 2008). Other factors identified included temporal lobe epilepsy, surgical treatment, absence of seizures for a long time especially after being very frequent and early age of epilepsy onset. However, many patients with suicidal ideation can present as euthymic or with only mild depressive symptoms in a neurology out-patient clinic (Hecimovic et al., 2012).

It is important also to recognise the bidirectional relationship between suicidality and epilepsy. Suicide attempt was associated with a 3.5 fold increased risk for developing epilepsy after adjusting for age, gender, socio-economic status, major depression and cumulative alcohol consumption in a population based case control study (Hesdorffer et al., 2006). A matched longitudinal cohort study examining whether psychiatric disorders associated with suicide were more common in incident epilepsy than in matched controls without epilepsy before and after epilepsy diagnosis, found that the prevalence rate was increased for suicide attempt before epilepsy onset (prevalence rate 2.6-5.2) and after epilepsy onset (prevalence rate 2.4-5.6) (Hesdorffer et al., 2012). These relations suggest common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk for psychiatric disorders and suicide.

1.5 Anxiety Disorders in Epilepsy

1.5.1 Anxiety disorders: Prevalence in epilepsy

Much attention on psychiatric comorbidity in epilepsy has focused on depression despite high prevalence rates of anxiety disorders which can be equally disabling. Depending on the study population, anxiety rates can vary from 10% to 32% in cases of intractable epilepsy (Victoroff, 1994). A study of epilepsy in-patients with all types of epilepsy using a standardised diagnostic interview found a 25% one year prevalence of
anxiety disorders (Swinkels et al., 2001). Social phobia and generalised anxiety disorder were the most common anxiety disorders. One tertiary out-patient study using SCID interviews found an anxiety disorder in 30.4% of patients with almost half the patients with anxiety disorders meeting criteria for 2 more anxiety disorders (Jones et al., 2005). In one large cross sectional population based study on patients with epilepsy, 11% of patients with epilepsy had an anxiety diagnosis compared to 5.6% of the general population without epilepsy (Gaitatzis et al., 2004a). Another population study found the lifetime prevalence of any anxiety disorder in patients with epilepsy was 22.8% versus 11.8% in non-epilepsy subjects (Tellez-Zenteno et al., 2007b). A study of patients with epilepsy attending their GPs found an anxiety rate of 15% (Edeh and Toone, 1987)

1.5.2 Anxiety Disorders: Aetiology

Risk factors

Seizure frequency has been linked with severity of anxiety in studies (Jacoby et al., 1996). This does not necessarily imply ictal fear but rather that as the burden of epilepsy increases, so does the anxiety. Anxiety symptoms can be attributed to the unpredictable nature of epilepsy with lack of control, sudden onset of seizures and the possibility of injury or embarrassment. The patient’s perception of danger eg falling or injuring themselves during a seizure is critical. The risk of anxiety disorders appears to be higher in focal especially temporal lobe epilepsy than in generalised epilepsies (Marsh and Rao, 2002, Vazquez and Devinsky, 2003). The highest rates of psychiatric morbidity including anxiety are found in patients with chronic refractory seizure disorders (Hermann et al., 2000, Kanner, 2003, Kanner et al., 2004). In these disorders, psychiatric variables are strong predictors of poor quality of life (Boylan et al., 2004). Patients with seizures originating in the left temporal lobe may
be more prone to anxiety than people originating in the right (Andelman et al., 2001).

**Neurobiological mechanisms**

The theory of a common pathophysiological mechanism of anxiety attacks and epilepsy is based on the observation that epileptic activity in certain parts of the brain directly causes paroxysmal anxiety usually in the form of panic (Charney, 2003, Satishchandra et al., 2003). The amygdala is a particularly important structure for the production of anxiety symptoms and epilepsy discharges in temporal lobe epilepsy. It is responsible for processing and relaying emotional stimuli to limbic and other cortical structures, basal ganglia, hypothalamus and the brainstem. It is therefore central to the generation of affective, autonomic, cognitive and endocrine components of the clinical symptoms of anxiety (Beyenburg et al., 2005). Electrical stimulation of the amygdala causes anxiety states, déjà vu phenomenon, hallucinations and disturbance of autonomic functions (Halgren et al., 1978).

In vivo structural and functional magnetic resonance imaging (MRI) studies confirm the association of abnormalities of the amygdala and anxiety or panic disorders (Cendes et al., 1994). More than 50% of patients with MRI confirmed amygdala atrophy on the same side as the seizure focus have some form of ictal fear (Van Paesschen et al., 2001). The central role of GABA receptors in both epilepsy and anxiety is a further pathophysiological similarity between the two disorders (Lydiard, 2003). This concept is supported by the observation that some substances including the GABAergic antiepileptics drugs gabapentin, vigabatrin, valproate and pregabalin as well as benzodiazepines have antiepileptic as well as anxiolytic properties (Beyenburg et al., 2001).
1.5.3 Anxiety disorders: treatment in epilepsy

The most important substances for the medical therapy of anxiety disorders are antidepressants including SSRIs, SNRIs, tricyclics and to a lesser extent benzodiazepines. To date, there have been no controlled studies of the medical therapy of anxiety disorders in patients with epilepsy. As with treating depression, the main concern is the risk of inducing or exacerbating seizures. Practically, SSRIs are often the drug of choice because of their advantageous side effect profile, their relatively small effect on neuronal excitability and their favourable pharmokinetic properties with a low potential for drug-drug interactions (Marsh and Rao, 2002, Scicutella and A, 2002). There is no good evidence from studies of possible anxiolytic effects of anticonvulsants in patients with epilepsy. However GABAergic drugs can reduce anxiety in animal experiments and this ‘side effect’ can therefore be put to good therapeutic use. The GABA analogues pregabalin and gabapentin have proven effects in anxiety disorders and focal epilepsies (Beyenburg et al., 2005, Beyenburg et al., 2004). Benzodiazepines have been used in the past for management of anxiety disorders in epilepsy but are not recommended because of the development of tolerance, sedating adverse effects and the potential for withdrawal seizures.

Other treatments include counselling and Cognitive Behavioural Therapy. It should be noted that deep breathing (hyperventilation) is contraindicated in CBT for panic disorder in patients with epilepsy (Kerr et al., 2011).
1.6 Psychosis in epilepsy

1.6.1 Psychosis: prevalence in epilepsy
See chapter 2 for (Systematic review and meta-analysis) a description of postictal and interictal psychosis.

1.6.2 Psychosis: aetiology in epilepsy
As with depression in epilepsy, the aetiology of psychosis in epilepsy is most likely multifactorial. The seminal works of Gibbs, Slater and Beard and Flor-Henry in the 1940s and 1960s on schizophrenia-like-psychosis of epilepsy have formed the foundation for the modern view that temporal lobe epilepsy and psychotic illness are closely related (Gibbs, 1948, Slater et al., 1963, Flor-Henry, 1969). Neurobiological, neuropathological, neuroimaging, genetic, medication and environmental factors have been implicated (Cascella et al., 2009).

Neurobiological factors

Chronic subictal activity in the temporal lobe with possible changes in monoamines particularly postsynaptic dopamine receptor sensitivity has been proposed as a potential mechanism for TLE psychosis (So et al., 1990, Devinsky et al., 1995a). SPECT (single photon emission computed tomography) studies showing low levels of striatal dopamine D2 receptors in perictal psychosis support this hypothesis (Ring et al., 1994). Other potential mechanisms proposed include increased GABA turnover, reduction in cerebral aspartate and glutamate, changes in endorphins, peptides, brain adenosine and the second messenger system (Meldrum, 1991).

The neurotoxic effects of epilepsy may explain the association between epilepsy and psychosis. Various effects on how this may be brought about have been postulated. A 'kindling' process whereby acute seizure discharges may cause changes in brain function perhaps through receptor-based changes and changes in cerebral blood flow has been
implicated (Cascella et al., 2009). The concept of a 'forced normalisation' process whereby an inverse relationship exists between seizure control and psychotic symptoms has been recognised (Kristensen and Sindrup, 1978, Landolt, 1957). This describes a 'normalization' of EEG recordings with the appearance of psychiatric symptoms. On-going subictal activity in the limbic system that is undetectable on EEG but which leads to brain changes that result in psychosis may also occur (Cascella et al., 2009, Elliott et al., 2009a).

Neuropathology factors

The neuropathological studies have not supported lateralization of pathology (Bruton et al., 1994, Roberts et al., 1990). Larger ventricles, more periventricular gliosis, more focal damage, and more periventricular white matter softening have been reported in patients with psychosis in epilepsy (Bruton et al., 1994). Other neuropathological studies examining post-lobectomy tissue has been conflicting. Taylor et al found that patients with psychosis are more likely to have 'alien tissue' such as hamartomas and focal dysplasias whereas more recently Roberts et al found a greater preponderance of patients with psychosis having medial temporal sclerosis (MTS) (Taylor, 1975, Roberts et al., 1990).

Enlarged ventricles may help to explain the neurodevelopmental hypothesis of schizophrenia (Cascella et al., 2009). Neuronal migration defects have been proposed as a mechanism related to enlarged ventricles and this defect could be common to both schizophrenia and epilepsy, perhaps representing a shared susceptibility. Disorders of neuronal migration such as lissencephaly are associated with epileptic seizures (Dobyns et al., 1984) and lissencephaly has been thought of as a molecular model for schizophrenia (Ayala et al., 2007). Also interesting in this regard is the finding that enlarged ventricles are common to first episode schizophrenia and TLE subjects without psychosis (Barr et al., 1997).
Neuroimaging factors

One imaging study had found bilateral enlargement of the amygdala in patients with schizophrenia like psychosis in epilepsy (i.e. interictal psychosis) in comparison with patients with TLE without psychopathology and healthy volunteers (Tebartz Van Elst et al., 2002). In another neuroimaging study, patients with epilepsy and psychosis were compared with a group of patients with epilepsy alone, significant grey and white matter deficits were found in patients with temporal lobe epilepsy with psychosis (Sundram et al., 2010). These encompassed the medial temporal lobe structures but also extended to lateral temporal and extratemporal regions. Some of these deficits overlap with those found in schizophrenia.

Genetic factors

Linkage and association studies have yielded several candidate genes for schizophrenia and epilepsy but despite these successes, the genetic mechanisms underlying the comprehensive pathophysiology of these brain disorders remains poorly understood (Owen et al., 2005, Tan et al., 2004). Friedman et al confirmed an association between the CNTNAP2 gene for epilepsy in patients outside the Old Order Amish community in non-related patients and demonstrated an association between CHTNAP2 gene and schizophrenia (Friedman et al., 2008). They found evidence for CNTTAP2 as a strong candidate gene for epilepsy and schizophrenia and their results supported the notion that genome copy number variants (CNVs) are a potentially important source of genetic susceptibility to both epilepsy and schizophrenia. Mefford et al found that rare CNVs are likely to contribute to a broad range of focal and generalised epilepsies. They also found that 2.9% of patients carry deletions at 15q11.2, 15q13.3 or 16p13.11, genomic hotspots previously associated with intellectual disability, autism and schizophrenia. These findings suggest common aetiological findings for seemingly diverse diseases (Mefford et al., 2010).
Genes implicated in neurodevelopment may play a common role in both psychosis and epilepsy e.g. leucine-rich glioma inactivated (LG1) family gene. Autosomal dominant partial epilepsy with auditory features (ADPEAF) is a benign and rare form of epilepsy characterized by auditory auras that in part resemble the auditory hallucinations experienced by patients with schizophrenia (Winawer et al., 2000). The auditory hallucinations range from elementary sounds to fully formed voices talking to patients. Leucine-rich glioma inactivated 1 (LGI1), has been shown to be mutated in gliomas in autosomal dominant lateral temporal epilepsy (Kalachikov et al., 2002). The expression pattern of the LGI1 protein in the mouse is predominately neuronal and is consistent with the anatomic regions involved in temporal lobe epilepsy. In humans, LGI1 is expressed predominately in brain (frontal lobe, temporal lobe and putamen) and the spinal cord (Chernova et al., 1998). More recent data has shown that LGI1 is secreted in its N-terminal leucine rich repeat region is structurally similar to Slit proteins which may be involved in axonal path finding (Senechal et al., 2005). Thus, LGI1 might also function as a developmental morphogen or provide migration cues in the developing central nervous system. This raises the possibility that some forms of epilepsy may be neurodevelopmentally based.

Large studies have shown that genetic factors play a significant role in the development of psychosis in patients with epilepsy (Qin et al., 2005, Adachi et al., 2010). Qin et al found in a population based cohort study that epilepsy was associated with an increased risk of schizophrenia (RR 2.48) and schizophrenia-like-psychosis (RR 2.93). The effect of epilepsy was the same in men and women and increased with age. Family history of psychosis and a family history of epilepsy were significant risk factors for schizophrenia and schizophrenia-like-psychosis and the effect of epilepsy, both in cases and families was greater among people with no family history of psychosis (Qin et al., 2005).
Medication factors

Psychotic disorders as an expression of drug toxicity has been reported with several anticonvulsants most notably topiramate and leviteracetam (Mula et al., 2003a, Mula et al., 2003b). Psychotic disorders can occasionally follow the discontinuation of anticonvulsants, especially those with mood stabilizing properties such as valproate and carbamazepine (Ketter et al., 1994). In general terms, the frequency of psychoses during anticonvulsant treatment seems to be in the region of 1-2% and most cases described were difficult to treat patients undergoing add-on therapy (Mula and Monaco, 2009).

Environmental/other factors

There have been few studies looking at whether psychosis is a risk factor for epilepsy. One study found that the prevalence of epilepsy in patients with treated schizophrenia was not particularly increased compared to the general population (Gelisse et al., 1999). The opposite has been reported in a 28 year follow up study of a Finnish general population birth cohort which found that epilepsy was strongly associated with schizophrenia (OR= 11.1, 95% CI 4-31.6) (Makikyro et al., 1998). A more recent population based family study has found that individuals with a parental history of epilepsy had a 2-fold risk of developing psychosis compared with individuals without a parental history of epilepsy (Clarke et al., 2012).

The evidence for a preponderance of either left sided or right sided pathology in patients with epilepsy and psychosis is lacking. In EEG studies, both an excess of left and right temporal foci have been found (Shukla et al., 1979, Jensen and Larsen, 1979a, Sherwin, 1981). Laterality findings are complicated by the use of surface electrodes, the fact that foci on one side does not imply normal opposite side and the fact that left sided foci are generally more common in epilepsy (Currie et al.,
1971). Neuroimaging studies that examined laterality were inconclusive (Toone et al., 1982, Conlon et al., 1990).

De novo schizophrenia-like psychosis may develop post-operatively following temporal lobectomy and rates of 3-28% have been reported in older studies (Taylor, 1975, Shaw et al., 2004). Other risk factors reported for psychosis in epilepsy include a history of complex partial seizures especially those involving mesial temporal or limbic structures, severity of epilepsy with long duration, multiple seizure types and refractoriness in particular being implicated and age of seizure onset before or around adolescence (Torta and Keller, 1999).

Risk factors specifically for postictal psychosis include age above 30, localization related epilepsy, bilateral seizures, clustering of seizures, a history of encephalitis, secondary generalisation and a family history of mood disorders (Logsdail and Toone, 1988, Kanemoto et al., 1996, Alper et al., 2001). Postictal psychosis typically arises after more than 10 years of seizures and is most common equally in right and left temporal lobe epilepsy. As the frequency of postictal psychosis increases, so does the risk of developing chronic interictal psychosis (Tarulli et al., 2001).

1.6.3 Psychosis: treatment in epilepsy
Better seizure control and minimization of anticonvulsant associated side effects are treatment priorities in all cases of psychosis with epilepsy. Psychotropic medication is not recommended in the treatment of ictal psychosis of epilepsy, however antipsychotics are recommended in particular in cases of post-ictal and inter-ictal psychosis of epilepsy (Devinsky, 2003). There are special considerations such as interactions with anticonvulsants, the potential of all antipsychotic drugs especially clozapine to lower seizure threshold and their side effect profile and the polymorphism of the psychotic phenomena (Gaitatzis et al., 2004b, Koch-Stoecker, 2002). Interictal psychoses may require long-term treatment similar to treatment for primary schizophrenia and should be administered
long-term following remission (Kerr et al., 2011). Antipsychotic medications such as risperidone, olanzapine or haloperidol are least likely to have a major impact upon seizure threshold. The use of antipsychotics is empirical as there are no randomized double blind studies specifically examining the efficacy and tolerability of antipsychotics in patients with epilepsy. A Cochrane Systematic review was carried out looking at interventions for psychotic symptoms concomitant with epilepsy (Ferooq and Sherin, 2008). The authors found little evidence to inform the treatment of psychosis in people with epilepsy. Only one small RCT was found which lacked the power to test the efficacy of antipsychotics in patients with psychosis and epilepsy.

A combination of a benzodiazepine and an atypical antipsychotic medication is often used to treat postictal psychosis (Devinsky, 2008). This should be carefully tapered off. For very short periods of psychosis, where symptom remission is rapid, this can occur after five days (Kerr et al., 2011). Early treatment can lead to rapid resolution of postictal psychosis. For longer episodes where symptoms remission takes longer than a few days, a period of 1-2 months following complete remission of psychosis is recommended before an attempt is made to taper off the antipsychotic medication.

The seizure rate associated with the use of anti-psychotic medication has ranged between 0.5%-1.2% among non-epileptic patients (Whitworth and Fleischhacker, 1995). In addition to pro-convulsant properties of antipsychotic medication, clinicians must also consider the pharmacokinetic and pharmacodynamic interactions between anticonvulsants and antipsychotics (LaFrance et al., 2008). Induction of hepatic enzymes upon the introduction of enzyme inducing anticonvulsants may result in an increase in the clearance of most antipsychotics.
1.7 Auras

Auras, or simple partial seizures frequently precede the onset of complex partial or secondary generalized seizures but may be seen independently and reflect abnormal stimulation of brain areas in close proximity to regions from which clinical seizures originate (Kohler et al., 2001). Auras of temporal lobe epilepsy include visceral sensations and experiential phenomenon such as fear, déjà vu and jamais vu illusions and olfactory, gustatory and visual hallucinations and illusions. The literature is limited in describing auras and their role in psychopathology.

Fear is a common ictal aura and it may contribute to interictal anxiety or panic disorder. Fear is reported as an aura in 10-15% of patients with partial seizures (Torta and Keller, 1999). Panic attacks may actually represent seizures which may complicate the treatment of patients with epilepsy and comorbid anxiety disorders (Feichtinger et al., 2001, Mintzer and Lopez, 2002). Admission for continuous video/EEG monitoring to capture and characterize this type of event is often useful though a simple partial seizure manifesting as fear or panic may not be apparent by surface EEG monitoring (Devinsky et al., 1989). Involvement of the amygdala in both temporal lobe epilepsy and panic disorder may explain the comorbidity between focal epilepsy with ictal fear and panic disorder.

One small study with limited numbers found that the presence of fear auras in TLE patients was associated with increased prevalence of mood and anxiety disorders following temporal lobectomy regardless of post-operative presence or absence of auras (Kohler et al., 2001). Guarneri et al found that the presence of pre-surgical anxiety disorder was associated with auras following temporal lobectomy in patients with TLE with hippocampal sclerosis (Guarnieri et al., 2009). There may also be a greater association between auras and postictal psychosis than auras with interictal psychosis (Kanemoto et al., 1996).
1.8 Personality disorders in epilepsy

Relatively little research is available on the comorbidity of personality disorders in epilepsy. Few studies have been conducted using standardised diagnostic tools. The majority of studies examining personality disorder use the Minnesota Multiphasic Personality Inventory which is a dimensional tool rather than a diagnostic one. Existing data on personality disorders in patients with epilepsy reveal a prevalence of between 4 and 38% (Fiordelli et al., 1993, Manchanda et al., 1996, Swinkels et al., 2003). In comparison the prevalence of personality disorders in the general population ranges between 6-13% (Samuels et al., 1994). Dependent, avoidant and obsessive-compulsive personality disorders are the most common personality disorders in patients with intractable epilepsy (Victoroff, 1994, Manchanda et al., 1996). It has been hypothesised that these personality disorders may be the result of the psychosocial consequences of living with epilepsy as a maladaptive reaction to a chronic disorder or the result of disrupted neuronal functioning or a combination of both (Swinkels et al., 2005). There has been considerable controversy about an 'epileptic' type personality in the past but this has now been discredited (Manchanda R, 2002, Devinsky, 2003). A better understanding of personality traits frequently seen in patients with epilepsy and in other neurological, psychiatric, and normal populations led to the abandonment of this concept. The most commonly described traits include preoccupation with philosophical and religious concerns, anger, excessive emotionality, viscosity, circumstantiality and hypergraphia (Waxman and Geschwind, 1975). It must be noted that these traits are not necessarily maladaptive and can occur independent of epilepsy. Bear and Fedio designed an inventory to assess and identify these and other traits and have postulated that they may result from a sensory limbic hyper-connection syndrome in which an epileptic focus leads to an enhanced association between affect and stimuli (Bear and Fedio, 1977).
1.9 Psychogenic Non Epileptic Seizures (PNES)
Patients with psychogenic non-epileptic seizures straddle the continuum of neurology to psychiatry and their presentation blurs the margins of the two disciplines. PNES are somatoform expressions of developmental or traumatic experiences and psychiatric comorbidities commonly occur in patients with PNES (Kanner et al., 2012). PNES resemble epileptic seizures presenting as sudden involuntary time limited alteration in behaviour, motor activity, autonomic function, consciousness or sensation. However, they are not accompanied by an epileptiform electrographic ictal pattern. At least 10-25% of patients with PNES have concurrent epileptic seizures or have had epileptic seizures before being diagnosed with PNES thus complicating diagnosis and treatment (Devinsky et al., 2011, LaFrance and Barry, 2005). Patients are usually female (80%) and are aged between 15 and 35 (Shen et al., 1990). There are no clinical features pathognomonic for PNES. When typical seizures can be recorded, video EEG is the diagnostic gold standard for PNES and in such cases a diagnosis can be made with high accuracy. Prognosis is variable with patients having recurrent or pervasive psychiatric disorders including depression and personality disorder or a history of chronic abuse having poor outcomes (Kanner et al., 1999). For management of PNES, an integrated biological, psychosocial, familial and social approach with the following goal is essential-establishing a sense of hope in patients and raising the patient’s awareness of triggers and reactions and changing their behaviours and beliefs (LaFrance and Barry, 2005). Comorbid depressive and anxiety disorders need to be treated with SSRIs and CBT being the mainstay of treatment (Goldstein et al., 2010).

1.10 Quality of life in epilepsy
Clinicians have long recognized the impact of seizure frequency on the well-being of patients with epilepsy (Birbeck et al., 2002). Seizure frequency had been found to be negatively associated with quality of life
functioning. Patients who are seizure free have HRQOLs (Health related quality of life) measures similar to that of the general population (Leidy et al., 1999). Boylan et al examined a cohort of refractory epilepsy patients and found that depression was a powerful predictor of quality of life while seizure related factors had no predictive value (Boylan et al., 2004). Other studies have shown that symptoms of depression and anxiety were independently associated with reduced health related quality of life measures. Psychiatric comorbidity explained more variance in HRQOL than did combined groups of clinical seizure or demographic variables in one study (Johnson et al., 2004). Interictal anxiety and depression exerted independent adverse effects on health related quality of life. Frequent, severe and chronic seizures reduce HRQOL but appear less powerful predictors than interictal psychiatric symptoms. Furthermore in other studies of pharmacoresistant TLE, symptoms of depression were found to be the strongest independent predictors of poor quality of life but not the seizure frequency or severity (Perrine et al., 1995, Gilliam, 2002, Pulsipher et al., 2006, Tracy et al., 2007). A robust ‘dose related’ or linear relationship between interictal depressive symptoms and HRQOL was found, such that the more frequent and severe the symptoms of depression, the poorer the patients’ HRQOL. (Gilliam, 2002) In addition to mood, adverse anti-epileptic medication side effects also was a significant predictor of reduced HRQOL, whereas traditional clinical variables such as seizure frequency were unrelated to patient-reported quality of life. More recently, sub-syndromic depression has been found to have a comparable negative impact on the quality of life of patients with epilepsy as major depression and anxiety disorders (Kanner et al., 2010) The worst impact on quality of life was found among patients with a mixed anxiety and depressive episode. It has to be noted that the relationship between depression and quality of life in epilepsy is likely bidirectional. On the one hand, the presence of depressive symptoms may affect quality of life; on the other, several epilepsy-related impairments such as lower independence and less social opportunities may influence mood and lead
to the development or exacerbation of depressive symptoms (Meldolesi et al., 2006).

A systematic review examining psychosocial difficulties in people with epilepsy found that the most frequent psychosocial difficulties were depressive symptoms, memory function, stigma, locus of control and cognitive and emotional functions in general (Quintas et al., 2012). Stigma plays a negative impact upon quality of life in epilepsy (Boro and Haut, 2003). Negative attitudes to stigma have spanned centuries and cultures and these attitudes have had significant impact on quality of life leading to low self-esteem hopelessness, anxiety and depression (Jacoby, 2002). Even patients with new onset of epilepsy report feeling stigmatized suggesting that the diagnosis alone creates an expectation of being treated differently. Discrimination in the workplace still occurs and despite improvements over time, the depiction of epilepsy in the media is frequently disparaging. It has been found that reported levels of stigma are associated with interactions of seizure worry and employment status, self-efficacy and social support, quality of care and age of seizure onset (Smith et al., 2009, Taylor et al., 2011a). A study looking at marital statistics in an epilepsy sample found that of a quarter of patients who divorced, the reason for divorce was epilepsy (Wada et al., 2004). Factors associated with having a resilient outcome in patients with epilepsy have also been examined (Taylor et al., 2011b). Significant predictors of a resilient outcome were absence of depression and fewer adverse treatment effects at 4 years and also good quality of life at baseline. Significant predictors of a vulnerable outcome were fair/poor health perception, presence of depression, reduced sense of mastery and more adverse treatment outcomes at follow up.

An American national epidemiological survey found a net association of epilepsy with number of days of role impairment after controlling for physical and mental comorbidities to be the equivalent to an annualized 89.4 million excess role impairment days in adults with epilepsy (Kessler
et al., 2012). Role impairment alone is a major component of the societal costs of epilepsy rather than merely due to physical and mental disorders comorbid with epilepsy.
1.11 Surgical treatment of epilepsy

Approximately 50% of patients with epilepsy will achieve good seizure control on one anticonvulsant, 20-30% of non-responders will achieve control with addition of a further medication but up to 30% will fail to respond to medication and in this subgroup, surgery for refractory seizures should be considered. In patients with refractory epilepsy, advances in surgical procedures have offered considerable hope for improved outcomes giving seizure freedom in 50-80% of patients (Engel et al., 2003). Anterotemporal lobectomies and amygdalohippocampectomies are the most commonly performed operations. Pre-operative psychiatric assessment varies widely between individual surgical centres with some not offering them despite guidelines explicitly emphasising the importance (Kerr et al., 2011).

1.11.1 Surgery and psychopathology

There are methodological limitations in the literature on surgery and psychopathology as most reports have been cross sectional studies in small samples or heterogeneous groups of patients and are usually for a limited follow up. It is difficult to compare the studies due to different methods used in identifying or measuring psychopathology. In addition, the standard psychiatric measures have not been validated in patients with epilepsy. Few prospective studies involve large samples or long term follow up which are essential in providing further insights into the psychiatric sequelae following epilepsy surgery. It is also not known how the psychiatric outcome following epilepsy surgery compares to that following other neurosurgery e.g. surgery for brain tumours as the data is limited (Foong and Flugel, 2007). As already mentioned earlier, up to 70% of patients with refractory epilepsy can suffer from mental illness (Devinsky, 2003, Gaitatzis et al., 2004b). Psychiatric comorbidity has been associated with a worse surgical outcome after temporal lobectomy (Kanner et al., 2009, Anhoury et al., 2000, Guarnieri et al., 2009). A
more recent study found no significant associations between post-surgery seizure outcome and a current or lifetime history of any psychiatric disorder (Adams et al., 2012). The literature is unclear about improved psychiatric outcome following epilepsy surgery with earlier studies linking surgery to increased rates of depression, anxiety and psychosis (Blumer et al., 1998, Jensen and Larsen, 1979a, Glosser et al., 2000, Taylor, 1972, Trimble, 1992). Later studies have shown conflicting results (Devinsky et al., 2005, Pintor et al., 2007).

There has been to date one recent systematic review on the subject (Macrodimitris et al., 2011a). Macrodimitris et al found either improvements in psychiatric outcomes post-surgery or no changes in psychiatric outcome. Only one study demonstrated deterioration in psychiatric status after surgery with higher anxiety rates in the context of continued seizures post-operatively (Reuber et al., 2004). The two main predictors of psychiatric outcome were seizure freedom and pre-surgical psychiatric history. De novo psychiatric disorders occurred post-operatively at a rate of 1.1-18.2% with a milder psychiatric illnesses being more common. An important finding was that studies that included a structured clinical interview produced more definitive positive results compared to studies that employed rating scales which generally demonstrated more mixed or equivocal results. This suggests that although patients may not meet full criteria for a psychiatric disorder post-operatively, they may still struggle with symptoms. Psychiatric complications presenting as exacerbation or recurrence of pre-surgical psychiatric comorbidities are most frequent in the first postsurgical year as are psychosocial adjustment difficulties (Kerr et al., 2011).

The methodology of this study was therefore specifically designed to address the shortcomings in the studies mentioned above by being of prospective design using gold standard tools and having an adequate period of follow up.
1.11.2 Surgical treatment and mood disorders

The most commonly reported psychiatric complications following epilepsy surgery are mood disorders including emotionally lability and depression which is often transient and usually occurs in the first three months following surgery and is of brief duration (Ring et al., 1998, Blumer et al., 1998, Anhcury et al., 2000, Hellwig et al., 2012). Devinsky et al carried out a large multicentre prospective study which followed up patients for 2 years post-operatively and found that the overall rate of depression decreased significantly three months after surgery and further reduced to half the pre-surgical rate (22.5%) by the end of the 2 year follow up (11.7%) (Devinsky et al., 2005).

The reported rates prevalence of de novo depression post-operatively ranges from 4-18.2% (Altshuler et al., 1999, Blumer et al., 1998, Devinsky et al., 2005, Reuber et al., 2004, Hellwig et al., 2012). The literature is vague in terms of differentiating between depressive symptoms and depressive disorders. Pintor et al conducted a prospective study using operational diagnostic criteria and found a reduction in depression from 17.2% pre-operatively to 4.3% at 1 year post-operatively (Pintor et al., 2007). Patients with no pre-operative mental illness had lower rates of post-operative mental illness than those with a psychiatric history and a de novo rate of depression of 8.6% was found. Devinsky et al in the largest prospective study conducted found a similar de novo rate of 7.9%.

The presence of pre-operative depression is likely to be the strongest predictor of post-operative depression, (Malmgren et al., 2002, Altshuler et al., 1999) and has been reported in 20-38% of patients undergoing epilepsy surgery. Ongoing seizures post-operatively appear to be a risk factor for post-operative depression. A more favourable seizure outcome or complete seizure freedom post-operatively is associated with stabilization of depression (Blumer et al., 1998, Reuber et al., 2004). In terms of other predictors of post-operative depression, studies found no
laterality effects, (Meldolesi et al., 2007) and no effects of age, sex or age at epilepsy onset (Spencer and Huh, 2008). Poor post-operative family dynamics has also been associated with an increased likelihood of post-operative depression (Wrench et al., 2011). The underlying mechanisms for post-operative depression are not well understood. PET studies have reported orbitofrontal hypometabolism in patients with post-operative depression (Salzberg et al., 2006). It is important to consider that psychosocial factors such as disappointment about surgical outcome or adjustment to the sudden removal of chronic epilepsy may have some negative effect on the patient and the family post-operatively (Bladin, 1992). Few studies have examined family history, social supports or life stress events as predictors of outcome.

1.11.3 Surgical treatment and psychosis
Although many publications have investigated the prevalence rates and risks of developing post-operative psychosis, there are important methodological limitations in these studies similar to those I have mentioned in the surgery and psychopathology section. Most studies consist of cross-sectional studies involving relatively small numbers of patients with heterogeneous epileptic syndromes and groups followed up for limited periods of time. Few studies have used categorical diagnostic criteria following modern psychiatric nosology (Filho et al., 2012). The concept of auras as psychotic like symptoms have been poorly investigated and documented in the literature.

It is generally considered that after surgery, most patients who become seizure free also become free from postictal psychosis (Inoue and Mihara, 2001). The prevalence of de novo postictal psychosis following surgery is low with estimates of 1% (Manchanda et al., 1993, Christodoulou et al., 2002). Devinsky in a large post-operative sample found a de novo rate of only 1.1% for all types of psychosis.
In the past, patients with pre-existing chronic interictal psychosis were often unlikely to be considered for surgery by many epilepsy surgery centres and older studies suggested a worse outcome following surgery (Jensen and Larsen, 1979b, Roberts et al., 1990, Trimble, 1992). There was a wide range estimated in the incidence of interictal psychosis developing de novo post-operatively in a previous review, 3.8% to 35.7% with a mean of 7.6%. However this review was of studies published before 1992 (Trimble, 1992). The incidence of post-operative psychosis more recently has been estimated at 3-9% (Kanner, 2000). More recent studies found that patients with interictal psychosis had a favourable seizure and psychosocial outcome without worsening of their psychosis (Reutens et al., 1997, Marchetti et al., 2003).

A history of psychosis should not be considered a contraindication to epilepsy surgery provided that patients can co-operate during the pre-surgical evaluation and have a clear understanding of the nature of the surgical procedure, potential risks and benefits that would allow them to give informed consent (Reutens et al., 1997, Fenwich, 1994). In many instances, the patient is better off without seizures and has a better quality of life despite persisting psychosis.

It is unclear which patients are at risk of developing post-operative psychosis. Some patients may be vulnerable to having psychosis pre-operatively and may have developed psychotic symptoms in the future regardless of surgery (Inoue and Mihara, 2001). There is no clear relationship between the development of psychotic symptoms and post-operative seizure control (Mace and Trimble, 1991, Inoue and Mihara, 2001). There is conflicting evidence implicating the laterality of surgery resection (Nakarni et al., 2007). A family history of psychosis has also been implicated (Glosser et al., 2000).

The pathological mechanisms for the development of de novo post-operative psychosis are not known. Studies have associated the
development of de novo psychotic disorders with bilateral epileptiform activity, a smaller amygdala on the non-operated side and lesions other than mesial temporal sclerosis (MTS) such as gangliogiomas and DNETS (dysembryoplastic neuroepithelial tumours) (Leinonen et al., 1994, Andermann et al., 1999, Shaw et al., 2004). Another hypothesis is that de novo post-operative psychosis may result from aberrant re-innervation with axonal sprouting or synaptic reorganization in projection sites of the surgical area (Stevens, 1990). Despite the lack of clarity regarding risk factors and prevalence rates, identification of patients with psychosis both pre and post operatively is crucial in order to improve psychiatric outcome post-operatively.

1.11.4 Surgical treatment and anxiety

Following epilepsy surgery, many authors have reported increased anxiety symptoms with prevalence rates of between 17-54% which peaks at 1 month post-operatively and decreases from 3 months following surgery (Bladin, 1992, Ring et al., 1998, Wrench et al., 2004). Longer term studies have confirmed that anxiety significantly reduces after 1-2 years post-operatively and returns to its pre-operative rate (Malmgren et al., 2002, Devinsky et al., 2005). A number of studies exploring anxiety pre and post operatively demonstrated reduced prevalence of anxiety postoperatively (Spencer et al., 2003, Cankurtaran et al., 2005, Meldolesi et al., 2007, Pintor et al., 2007). Anxiety levels generally decrease if seizures remit (Mattsson et al., 2005). Another study reported a significant relationship between anxiety and seizure freedom (Reuber et al., 2004). Patients who had less than a 50% improvement in seizure frequency or an increase in seizures post-operatively demonstrated an increase in anxiety.

Patients with a past history of affective disorders including anxiety disorders are likely to be more susceptible to post-operative anxiety (Anhoury et al., 2000, Devinsky et al., 2005). In addition, TLE patients
with fear as a typical aura pre-surgically may be at greater risk of post-operative anxiety and panic attacks despite becoming seizure free (Kohler et al., 2001). New post-operative complications such as memory deficits may also impact on anxiety (Sawrie et al., 1999). As with depression and psychosis post-operatively, there is no convincing evidence with respect to lateralization of the surgical resection.

There is little in the literature on de novo anxiety rates post-operatively. Devinsky et al found a de novo rate of 6.9% of patients post-operatively whereas de Araujo Filho found a rate of 2.6% (Filho et al., 2012, Devinsky et al., 2005).

1.1.5 Surgical treatment and personality disorders
The literature on personality disorders following epilepsy surgery is very limited. Patients with pre-morbid personality disorders or prominent personality traits as well as organic personality symptoms are at risk of poor psychosocial outcome (Inoue and Mihara, 2001, Koch-Weser et al., 1988). The evidence to date suggests that patients with personality disorders are more likely to experience post-operative psychiatric complications if they have ongoing seizures (Inoue and Mihara, 2001) or right temporal lobe surgery (Koch-Weser et al., 1988). It has been suggested that this may be related to right hemispheric dysfunction resulting in misperception or misinterpretation of emotional cues and impaired coping mechanisms (Glosser et al., 2000). Guarnieri et al found that 12.4% of a sample of TLE post-operative patients had an Axis II diagnosis with a cluster B diagnosis being most common. They found that patients with personality disorder were more likely to have persisting auras post-operatively compared to patients with an Axis I disorder or without a psychiatric diagnosis (Guarnieri et al., 2009).

Patients with personality disorders and epilepsy are affected by organic factors and negative environmental influence. They have restricted ability to cope with stress. As a consequence, patients with personality disorders
are at risk of suffering from severe psychiatric complications post-operatively. In order to minimize the negative influence of personality disorders in the process of surgical intervention, psychosocial efforts are needed to reduce peri-surgical stress factors and to strengthen the self-efficacy and social skills of these patients (Koch-Weser et al., 1988).

1.11.6 Surgical treatment and quality of life outcomes
Health related quality of life is impaired by seizures and patients who become seizure free report significantly more positive change than those who do not (Birbeck et al., 2002). Psychosocial outcome concerning work, marital status and independent living is related to seizure outcome (Malmgren et al., 1997, Carran et al., 1999). A systematic review and meta-analysis on long-term non-seizure outcomes in epilepsy surgery found that non-controlled studies consistently reported improved long-term psychosocial outcomes but the effect was less clear in controlled studies (Tellez-Zenteno et al., 2007a). Intelligence was unchanged by surgery but long term memory outcomes were associated with seizure freedom and side of temporal lobe resection. Left sided temporal resections had a higher risk of additional post-operative memory impairment. Longer follow up studies were associated with lower rates of anticonvulsant discontinuation reflecting lower seizure free rates over time. All uncontrolled long-term studies reported improved psychosocial outcomes with epilepsy surgery including employment, education, driving status, satisfaction and quality of life but the results of the few existing controlled studies were less persuasive (Tellez-Zenteno and Wiebe, 2008).

However, it must be noted that successful surgical outcome can also produce problems of its own making. Bladin found that 35% of patients following temporal lobectomy reported post-operative problems stemming from the necessity to restructure family dynamics and familial hierarchic arrangements (Bladin, 1992). The relatively sudden removal of the
lifestyle limiting disability demands fundamental restructuring of the patient’s existence. Removal of the shield or excuse for personal shortcomings and mandatory rearrangement of dynamics of interpersonal interaction both inside and outside the family circle are all important factors in the patient’s rehabilitation period. The ‘burden of normality’ has been the term used to describe to patient’s difficulty adjusting to life without seizures (Wilson et al., 2001). Also following surgery, patients may expect dramatic positive changes in their lives as a result of being ‘healed’ by the intervention (Meldolesi et al., 2007). However following surgery, they usually need time to rebuild and organise their life and they find themselves facing the many difficulties that all other people meet when trying to achieve their aims in key life domains such as work, social and personal relationships. There may be a discrepancy between their pre-operative expectation and the actual reality of their lives post-operatively irrespective of seizure freedom.

Personality factors have also been implicated in psychosocial outcome following epilepsy surgery. Patients high in neuroticism and low in extraversion reported more depressive symptoms following surgery and high neuroticism was also associated with disrupted family dynamics early after surgery and psychological difficulties adjusting to being well (the burden of normality) by 12 months (Wilson et al., 2010).

A recent systematic review looking at measures of patient satisfaction following epilepsy surgery found that overall 71% of patients from 8 pooled studies reported that they were satisfied with surgery and 87% would repeat surgery (Macrodimitris et al., 2011b). Seizure freedom was the most common predictor of epilepsy surgery satisfaction whereas post-operative neurological deficit predicted dissatisfaction. Two studies explored employment following epilepsy surgery and found it to be significantly associated with satisfaction with epilepsy surgery (Chin et al., 2006, Guldvog, 1994).
In the only randomized controlled trial of temporal lobe surgery for epilepsy, the surgical group without seizures consistently scored higher on the QOLIE 89 than the medical group as early as 3 months after surgery and continuing to 12 months, but both groups reported improvements in Health Related Quality of Life (HRQOL) and the effect of seizure freedom was not reported (Wiebe et al., 2001). In a large prospective surgical series (396 patients) in which the QOLIE 89 was used before surgery and up to 5 years after surgery, the most substantial improvement in HRQOL was immediately after surgery in all patients but further improvements were seen in the seizure free group. This effect stabilized at 2 years after surgery and was related to duration of seizure freedom. In the group with best seizure outcome at 5 years after surgery, HRQOL was comparable to that in the general population in all domains of the SF-36 (a 36 item short form health survey that comprises the generic core of the QOLIE 89) except for social functioning (Spencer et al., 2007).

A pre-surgical assessment of the person’s psychosocial and vocational status is an essential step in planning for a better post-surgical adjustment. This assessment should consider the individual within the broader family and psychosocial context including patient and family expectations of surgery (Kerr et al., 2011).

Studies have also examined longer-term follow-ups of 5 and 12 years following surgery. Cunha et al carried out a 5 year prospective study about the effects of epilepsy surgery on patient’s quality of life (Cunha and Oliveira, 2010). Improvement in overall cognitive and social function scores was significant at 5 years. Seizure worry score ceased to be significant at 5 years. Previous psychopathology was a negative influence on seizure and social worry score. Neither years of disease or patient age at surgery affected quality of life. In a 12 year follow up of patients following surgery, there was no difference in terms of quality of life improvement after 12 years compared to 2 years (Tanriverdi et al., 2008). This appears logical as patients who are seizure free perceive
themselves as cured and improvements reach the level of the general population.

However, no study has been undertaken to examine the relationship between quality of life outcomes post-operatively and psychiatric disorders.

1.12 Summary
From review of the literature, it is clear that epilepsy is associated with changes in mental state but it is unclear who is at risk of deterioration in mental health and conversely who is likely to benefit from surgical intervention. The lack of clarity in the literature about the prevalence of mental illness in refractory epilepsy and the potential positive or negative effects of surgery led to the hypotheses of this study.

There are three aims to this thesis. The first aim of this thesis was to comprehensively investigate psychiatric and psychosocial characteristics of a sample of patients with epilepsy refractory to medical treatment.

1) Examination of the prevalence and severity of psychiatric disorders
2) Assessment of quality of life
3) Examination of possible associations between psychiatric disorders, epilepsy variables and quality of life.

The second aim of this thesis was to examine the impact of epilepsy surgery on psychiatric diagnosis, severity of psychiatric illness and on quality of life.

Two different samples were examined for each aim. The patients in aim 1 comprised of all patients with refractory epilepsy attending a specialist neurology centre between 2008 and 2012 who were potential candidates for surgery (i.e. 'the medically refractory sample') and the patients in aim 2 were all patients who underwent surgery and had psychiatric follow up one year later (i.e. 'the surgical cohort'). The findings of these two
samples are presented in separate results chapters, chapters 3 and 4. It is important to note that sample 2, 'the surgical cohort' is a subset of sample 1, the 'medically refractory sample'.

The third aim of this study was to conduct systematic reviews and meta-analyses on 1) the prevalence of psychosis in epilepsy and 2) the prevalence of psychosis in post-operative epilepsy surgery patients as this information is deficient and contradictory at times in the existing literature.

Hypotheses

The following hypotheses were formulated at the outset of the study for aim 1:

In a sample of medically refractory epilepsy patients there will be:

1) A high rate of psychopathology in particular mood, psychotic, anxiety and personality disorders
2) Seizure frequency will be correlated with the presence and severity of psychiatric symptoms and with quality of life
3) Quality of life scores are associated with presence and severity of psychiatric diagnosis.

The following hypotheses were formulated at the outset of the study for aim 2:

In a surgical cohort of patients:

1) The prevalence of psychiatric diagnoses will be higher in the pre-operative group compared to the post-operative group
2) The severity of psychiatric symptoms will be higher in the pre-operative compared to the post-operative group
3) Surgical treatment of refractory epilepsy is associated with an improvement in quality of life.
Chapter 2

The prevalence of psychosis in epilepsy: a systematic review and meta-analysis

2.1 Introduction

The nature of the relationship between psychosis and epilepsy has been of great interest to psychiatrists for over a century (Esquirol, 1838, Kraepelin, 1913, Gibbs et al., 1948, Slater et al., 1963, Flor-Henry, 1969, Scott, 1978, Trimble, 1991, Kanner and Barry, 2001, Krishnamoorthy, 2001, Marsh and Rao, 2002, Devinsky, 2003, Gaitatzis et al., 2004b). In one of the most epidemiologically complete studies involving direct patient interviews of all individuals with epilepsy in Iceland, Gudmundsson (1966) reported a rate of psychosis of 7.2% (Gudmundsson, 1966). In keeping with this the majority of studies (Gibbs et al., 1948, Slater et al., 1963, Lindsay et al., 1979, Schmitz, 1995b) have found a higher prevalence of psychosis in patients with epilepsy compared with the general population, but this finding is not consistent and reported rates varying from 0.48% (Swinkels et al., 2005) to 35.7% (Jensen and Larsen, 1979a). Methodological differences such as changing diagnostic classifications, clinical heterogeneity, different ascertainment methods, and lack of power likely account for much of the inconsistency. Previous qualitative reviews of this topic these reported an overall rate of psychosis in epilepsy of 7% and 7.6% respectively (McKenna et al., 1985, Trimble, 1992). More recently Gaitatzis et al looking at psychiatric morbidity overall in epilepsy estimated that the prevalence of psychosis in population based studies at between 2-7% and estimated a prevalence of psychosis at 10-19% in patients with TLE or refractory epilepsy (Gaitatzis et al., 2004b).
Improving our understanding of the basis to the relationship between psychosis and epilepsy is important as it may provide clues to the pathophysiology of psychosis generally (Slater et al., 1963, Toone, 2000, Adachi et al., 2010). In the current investigation we have undertaken the first systematic review of the prevalence of psychosis in epilepsy. Our main aim was to estimate the overall pooled prevalence of psychosis among patients with epilepsy. Secondary aims were 1) to examine the prevalence of psychosis associated specifically with temporal lobe epilepsy, 2) to estimate the prevalence of postictal and interictal psychosis, 3) to estimate prevalence of psychosis in specific subgroups of patients with intellectual disability, children and adolescents, and individuals with genetic vulnerability to psychosis and 4) to carry out separate analysis for studies with control groups to allow estimation of risk for psychosis among patients with epilepsy in terms of pooled odds ratios.

2.2 Methods

Study Selection

We conducted a systematic review of all published literature in English on the prevalence of psychosis in patients with epilepsy. We were guided by PRISMA criteria (Moher et al., 2009). A search was undertaken of the electronic databases PUBMED, OVID MEDLINE and EMBASE from their inception to September 2010 with the following terms: prevalence, incidence, rate, rates, psychosis, schizophrenia, schizophreniform illness, epilepsy, seizures and temporal lobe epilepsy. In addition to this search procedure, we used the reference lists of the identified publications to find further relevant articles.

Inclusion criteria

Papers were included if they gave prevalence rates of psychosis, schizophrenia, interictal psychosis (see definition below) or postictal
psychosis (see definition below) in persons with epilepsy. We included studies involving adults, children and patients with learning disability.

The definition of interictal psychosis (also known as the schizophrenia-like psychosis in epilepsy) is a psychotic disorder that would fulfill diagnostic criteria for schizophrenia if epilepsy was not present. The interictal psychotic disorders are of reasonably long duration and are not related to the occurrence of seizures (Slater et al., 1953, David, 2010).

The definition of postictal psychosis is a psychosis that manifests itself immediately upon a seizure or emerges with one week of return of apparently normal mental function. The psychosis has to last a minimum length of 24 hours and a maximum length of 3 months (David, 2010).

Exclusion criteria
Papers excluded were those that (a) did not have the full article published in English, (b) did not report prevalence rates or data from which rates could be calculated (c) involved case reports, letters, short reports, reviews or book chapters.

Data Extraction
Following initial searches, all titles of papers and abstracts were examined and assessed for relevance and appropriateness of the main question under review. Full texts of potentially relevant papers were obtained. Authors of papers were contacted where necessary. The methodological quality of studies was assessed.

For the purpose of the meta-analysis, we extracted the following domains or variables from the articles that were finally included:
1) prevalence rates for psychosis including interictal and postictal psychosis and schizophrenia. (where specified)
2) date of publication, country (developing or developed world), year of publication, proportion of children or individuals with learning disability within epilepsy sample.
3) sample size, gender composition, whether the study was carried out in a hospital or community setting, study design (cross-sectional or cohort),
4) diagnosis of epilepsy and whether International League Against Epilepsy (ILAE) classification was used
5) diagnostic tools used for psychosis and method of obtaining diagnosis- (unstructured interview, case note review, structured interview).

Data Analysis
Pooled estimates of the prevalence of psychosis in epilepsy patients were calculated using random-effects meta-analysis. This allows a more robust and true estimate of effect size and one that is weighted by the sample size of individual studies. A random effects model weights studies more equally and is considered more appropriate for meta-analyses with substantial heterogeneity (Egger, 2001, Fazel et al., 2010) and this meta-analytic approach has been used with data containing similar levels to those seen here (Fazel et al., 2010). In a random effects model, the true effect sizes are allowed to differ. It is possible that all studies share a common size but it is also possible that the effect size varies from study to study. For example, the effect size may be higher or lower in studies where the participants are older or more educated or healthier than in other studies or when a more intensive variant of an intervention is used. Because studies will differ in the mixes of participants and in the implementation of interventions among other reasons, there may be different effect sizes underlying different studies. If it were possible to perform an infinite number of studies, the true effect sizes for these studies would be distributed about some mean. In random effects meta-analysis model, the effect sizes in the studies that actually were performed are assumed to represent a random sample from a particular distribution of these effect sizes (hence the term random effects). The between-study variance or heterogeneity in estimates was modelled using Cochran Q and the I^2 statistic. The Q statistic is reported with χ^2 and p-values and the I^2 statistic is reported as a percentage with increasing
values indicating greater heterogeneity between estimates of individual studies ($I^2 < 25\%$ indicates low heterogeneity; $30-70\% = \text{moderate heterogeneity}$ and $>75\%$ indicates high heterogeneity (Fazel et al., 2010). Meta-regression was used to estimate the extent to which measured covariates (study design, study setting, assessment instrument used, types of epilepsy, year of study, family history of psychiatric illness, International League Against Epilepsy (ILAE) classification used, exclusion criteria applied, country in which study took place) could explain the observed heterogeneity in prevalence estimates across studies. The regression coefficients ($\beta$) reported indicate the average difference in prevalence proportion for one category compared to the other (eg assessment by clinical interview versus case notes). Effects of individual covariates were examined first in univariate models and then in a multivariate model constructed in a step-wise fashion. Multivariate model is the area of statistics that deals with observations made on many variables. The main objective is to study how the variables are related to one another, and how they work in combination to distinguish between the cases on which the observations are made. All analyses were carried out using STATA statistical software package, version 11.0.

2.3 Results

Literature search
Our preliminary search identified a total of 431 papers on EMBASE, 773 papers on PUBMED and 999 papers on MEDLINE via OVID. There was a substantial degree of overlap between the 3 databases. After these titles were screened, 215 papers were examined in detail. After applying inclusion and exclusion criteria, 58 papers (27%) were deemed to have data relevant to the systematic review and meta-analysis. See Figure 1.
Included studies and study design

Thirteen of the studies were from the UK, 11 from the US, 11 from Japan, 5 from Brazil, 2 from Denmark, 2 from the Netherlands, 2 from Canada, 2 from India, 2 from Iceland, 2 from Australia and 6 from other countries. Ten papers specified the gender of participants in the study. The number of patients with psychosis in the studies varied from 1 (Swinkels et al., 2005, Jones et al., 2005, McLellan et al., 2005, Siegel et al., 2008) to 795 (Qin et al., 2005).

The number of participants in studies varied from 50 (Blumer et al., 1998) to 34,494 (Qin et al., 2005). With regard to the prevalence rates, forty-eight studies were cross sectional studies, 9 were cohort and 1 was case control. The time periods over which the prevalence rates were calculated were as follows: 27 studies were for an unknown time period, 7 studies were lifetime prevalence studies, 21 studies were for more than 1 year and 3 studies were less than 1 year.

Only 6 of the studies had control groups. (de Araujo Filho et al., 2007, Deb and Hunter, 1991, Jalava and Sillanpaa, 1996, Mendez et al., 1993b, Stefansson et al., 1998, van der Feltz-Cornelis et al., 2008)

Seven studies were in a community setting, 3 were in a mixed hospital/community setting, 1 was unknown, 3 were from population databases and the remaining 44 were from hospital settings.

In 39 of the studies, patients were interviewed, in 19 studies the patients were not interviewed or it was not stated in the study.

The prevalence rates of psychosis varied from 0.02% (Mohammadi et al., 2006) to 27% (Jensen and Larsen, 1979a).

Forty of the studies used ICD criteria or DSM criteria for diagnosis. Of these studies, 17 used DSM IV criteria, 5 used DSM IIIR criteria, 1 used DSM III criteria, 1 used DSM II criteria, 6 used ICD 10 criteria, 4 used ICD 9 criteria and 1 used ICD 8 criteria. 5 studies used a mixture of these criteria.
Seven studies used a Structured Clinical Interview for DSM IV on patients in their studies (Jones et al., 2005, de Araujo Filho et al., 2007, Victoroff, 1994, Alper et al., 2001, Kanner et al., 2009, Filho et al., 2008, Sanchez-Gistau et al., 2010). Nine studies were conducted before 1990. Seventeen of the 58 studies gave the prevalence of schizophrenia.
Ten studies had prevalence rates for interictal psychosis.
Thirteen studies had prevalence rates for postictal psychosis.
Three studies used a sample group of patients with children/adolescents only (Lindsay et al., 1979, McLellan et al., 2005, Caplan et al., 1998).
Four studies studied patients with Learning Disability only (Deb and Hunter, 1991, Espie et al., 2003, Ring et al., 2007, Pawar, 2008).
Seventeen studies included patients with TLE only.
Seven of the studies mentioned a family psychiatric history, only 3 mentioned a family history of psychosis.
17 studies had TLE patients only, in 26 studies, the authors did not differentiate whether patients had TLE or not and in 15 studies, there was a mixture of patients with TLE and other forms of epilepsy but unfortunately it was not possible to extract the non TLE or TLE sample from each other. Therefore for the TLE prevalence sample, we only used studies where all the patients had TLE. We did not contact authors personally to access data as this was not possible in many of the studies as the contact details were not current and 22 of the studies were conducted before 2000.

Prevalence of psychosis in epilepsy
Overall, the pooled prevalence rate for psychosis in epilepsy patients was 5.6% (95% CI = 4.8-6.4). (see Figure 2). The pooled prevalence rate when postictal psychosis was excluded was 5.4% (95% CI = 4.5-6.2).

The pooled prevalence rate for psychosis in patients with temporal lobe epilepsy was 7.0% (CI 4.9-9.1). (See Figure 3). The pooled prevalence
rate of interictal psychosis was 5.2% (95% CI 3.2-7.2) and the pooled prevalence rate for post ictal psychosis was 2.0% (95% CI 1.2-2.8).

Four papers studied an intellectual disability sample only (Deb and Hunter, 1991, Espie et al., 2003, Ring et al., 2007, Pawar, 2008). The prevalence of psychosis in patients with epilepsy and comorbid learning disability was 7.4% (95% CI 2.6-12.2).

Three studies used child and adolescent subjects only (Lindsay et al., 1979, McLellan et al., 2005, Caplan et al., 1998). The prevalence of psychosis in children and adolescents with epilepsy was 5.4%, (95% CI 0.6-10.2).

Three papers mentioned a family history of psychosis. The prevalence of psychosis in patients with epilepsy where a family history of psychosis was present was 5.4% (95% CI=1-9.8).

Six of the studies had control groups. However, only 4 studies (de Araujo Filho et al., 2007, Mendez et al., 1993b, Stefansson et al., 1998, van der Feltz-Cornelis et al., 2008) were used for analysis because two of them (Deb and Hunter, 1991, Jalava and Sillanpaa, 1996) had no psychosis outcome in the control group so an odds ratio could not be calculated. The pooled odds ratio for risk of psychosis among people with epilepsy was 7.83 (95% CI 2.8-21.8). (See Figure 4)

**Heterogeneity analyses**

There was substantial heterogeneity between the prevalence estimates of psychosis in epilepsy patients across individual studies ($I^2 > 70\%$). We examined the effect of nine factors on the prevalence of psychotic symptoms in epilepsy patients found across studies in a meta-regression analysis: (1) study design (2) study setting (3) instrument used to assess psychotic symptoms (4) types of epilepsy (5) year of study (6) family
history of psychosis noted (7) ILAE classification used (8) exclusion criteria applied (9) country in which the study took place.

Meta-regression Analyses

None of the following factors significantly explained any of the variance in the estimates on an individual basis. (1) Study Design: ($\beta = -1.1, SE(\beta = 1.9, p =0.58)$).
(2) Study setting: (whether recruiting patients from the community or from hospitals or from tertiary centres) = ($\beta = -0.11, SE(\beta) = 0.9, p =0.90)$.
(3) Instrument used to assess psychosis: (employing a clinical interview or using case notes) ($\beta = 0.31, SE(\beta) = 1.7, p =0.85)$.
4) Types of epilepsy reported: (all types of epilepsy patients or temporal lobe epilepsy patients only or other types of epilepsy) =($\beta = 0.74, SE(\beta) = 0.8, p =0.39)$.
5) Year of study: (whether studies carried out before 1990 or after 1990) ($\beta = -2.8, SE(\beta) = 2.1, p =0.17$).
6) Family history of psychosis: family of history of psychosis assessed or not assessed = ($\beta = 3.7, SE(\beta) = 2.1, p =0.09$).
7) ILAE classification used: studies reporting use of ILAE classification or not reporting this classification = ($\beta = 0.3, SE(\beta) = 1.7, p =0.85$).
8) Exclusion criteria applied: studies reporting the use of exclusion criteria or those not reporting exclusion criteria ($\beta = 1.1, SE(\beta) = 1.4, p =0.45$).
9) Country in which study took place: studies from countries classified as 'developed' or those classified as 'not developed' ($\beta = 2.0, SE(\beta) = 1.9, p =0.31$).

A multivariate model constructed in step-wise fashion showed that the specific combination of 5 factors explained the largest amount of heterogeneity in the prevalence estimates: study setting (p= 0.9), assessment instrument used (p=0.85), year of study (p=0.17), family history of psychosis (p=0.09), type of epilepsy (p=0.39). These 5
variables together explained 10% of the variance in estimates of the prevalence of psychotic symptoms in epilepsy patients across studies.

2.4 Discussion
This is the first systematic review and meta-analysis to examine the prevalence rate of psychosis in epilepsy. Our finding of 5.6% pooled prevalence of psychosis in epilepsy is lower than estimates of approximately 7% estimates from previous narrative reviews, (McKenna et al., 1985, Trimble, 1992) although our finding of 7% for the rate of psychosis in temporal lobe epilepsy is similar. Based on results from population based studies with control samples, (de Araujo Filho et al., 2007, Mendez et al., 1993b, Stefansson et al., 1998, van der Feltz-Cornelis et al., 2008) we found that the rate of psychosis among people with epilepsy is 7.8 times higher than in people without epilepsy. However there were very few studies fulfilling these criteria. Our findings are consistent with Gudmundsson who found that 7.2% of subjects with epilepsy were currently or had at some time suffered from psychotic illness (Gudmundsson, 1966).

We found a low prevalence of postictal psychosis in epilepsy-2%. This has traditionally been described as the most common form of psychosis in patients with epilepsy (David, 2010). Prevalence rates of around 6% from two telemetry series have been reported in the past (Alper et al., 2001, Kanner et al., 1996). The relatively low postictal rate found in this study may be explained by the transitory nature of PIP, its acute and short presentation and that it is often managed in non-specialised departments and may go undiagnosed. It may be mistaken for acute confusional states rather than postictal psychosis. However, postictal psychosis may be over or under represented depending on the availability of psychiatric assessment, the frequency of review and potentially the knowledge base of the treating neurologist and neuropsychiatry teams. The rate of interictal psychosis at 5.2% was over two and a half times the rate of
postictal psychosis, but similar to the rate for overall psychosis in epilepsy.

TLE is the most common of the anatomically defined syndromes accounting for around 60% of all patients with localisation related epilepsies (David, 2010). It is the most common type of epilepsy in adults who experience seizures poorly controlled by anticonvulsant medication. Our results found a slightly higher rate of psychosis in TLE as compared to all epilepsies (7% v 5.6%). There has been some debate in the past whether there is a higher rate of schizophrenia-like psychosis in patients with TLE compared to generalized epilepsies. In the original study by Slater et al, the high rates of psychosis may have been in part due to somewhat imprecise clinical diagnostic data as the terms schizophrenia and psychosis were relatively loosely defined by today’s standards (Slater et al., 1963). There is also the possibility of an ascertainment bias as the study drew its subjects from tertiary centres in two major London hospitals. More recently, Stevens argued that the proportion of TLE in epilepsy-psychosis patients is similar to the proportion rate of generalized epilepsy patients with epilepsy psychosis which is estimated to be about 60% (Stevens, 1991, Shorvon, 1990, Hauser et al., 1996). Furthermore, in the large epidemiological study by Qin et al, patients with localization related epilepsy were only slightly over-represented among those who were psychotic and this difference fell short of statistical significance (Qin et al., 2005). Several studies have failed to confirm the commonly held view that there is a specific association between temporal lobe epilepsy and psychopathology which is in contrast to commonly accepted clinical practice (Stevens, 1988, Manchanda et al., 1992, Swinkels et al., 2001).

Methodological issues
Most of the studies included in this review were cross sectional in design (77.6%) and based on samples from tertiary referral centres (71%) and these factors may limit the interpretation of the results with respect to the
general population. Only 10% of the studies were population-based. Prevalence measures derived from such unrepresentative samples may therefore overestimate psychiatric morbidity among epilepsy patients (Eden and Toone, 1987).

We were unable to draw conclusions about the influence of a genetic vulnerability to psychosis from this study as data was too limited. Family history of psychosis was only mentioned in 3 studies (Qin et al., 2005, Mendez et al., 1993b, Alper et al., 2001). Further family studies are needed to elucidate this association. Heterogeneity may also play a role.

It was not possible to identify a group of patients which did not have temporal lobe epilepsy to compare with the TLE group as some studies did not state whether the patients had TLE or not and also some studies has TLE and non TLE patients mixed together in their study samples, thus it was impossible to differentiate these 2 disparate groups out.

There was no relationship between what country that the study took place in and the effect sizes results. Smaller studies appear to have larger effect sizes than larger studies overall. Meta-analysis regression showed that the study setting (e.g. tertiary versus community) (p=0.9) and the country where the study took place (p=0.31) did not impact upon effect sizes.

**Temporality of the association between epilepsy and psychosis**

The question of whether epilepsy is a risk factor for psychosis and/or whether psychosis is a risk factor for epilepsy has repeatedly arisen in the literature, however, very few studies had the data necessary to adequately provide answers (Cascella et al., 2009). We have not addressed the temporality of the association in this study because the majority of studies included do not have temporal information. However, Clarke et al have recently found in a population based family study that patients with epilepsy have a 5.5 fold increase in the risk of having a broadly defined psychotic disorder and an 8.5 fold increase in the risk of
having schizophrenia (Clarke et al., 2012). Individuals with a parental history of epilepsy had a 2 fold increase in the risk of developing psychosis, compared to individuals without a parental history of epilepsy. Individuals with a parental history of psychosis had reciprocally a 2.7 fold increase in the risk of having a diagnosis of generalised epilepsy compared to individuals without a parental history of psychosis. Post hoc analyses showed that these analyses were not driven by the comorbidity of epilepsy and psychosis in the parents.

Classification of psychosis
A consensus on the classification of psychotic symptoms associated with epilepsy is lacking (Sachdev, 1998). Neither ICD 10 nor DSM V classifies seizure-related psychosis separately. It could be debated whether postictal psychosis for example should be classified as a brief psychotic disorder/psychotic disorder due to a general medical condition or a psychotic disorder not otherwise specified in DSM. Furthermore, the psychopathology of patients with epilepsy can be atypical and does not readily conform to these diagnostic manuals (Anhoury et al., 2000). A dedicated sub-commission of the International League Against Epilepsy commission on neuropsychiatric aspects has developed a proposal on the classification of neuropsychiatric disorders in epilepsy (Krishnamoorthy et al., 2007). Recent genetic studies reinforce the view that more attention should be given to the relationship between the functional psychoses and neurodevelopmental disorders such as autism (Craddock and Owen, 2010).

Possible mechanisms
It has been suggested that the neurotoxic effect of epilepsy explains the association between epilepsy and psychosis (Cascella et al., 2009). Various mechanisms through which this effect might be brought about have been proposed. These include firstly, a ‘kindling’ process whereby acute seizure discharges may cause changes in brain function perhaps through receptor-based changes and changes in cerebral blood flow (Lax
Pericall and Taylor, 2010); secondly, a ‘forced normalisation’ process whereby an inverse relationship exists between seizure control and psychotic symptoms (Sachdev, 1998, Jones et al., 2010) and thirdly, ongoing subictal activity in the limbic system that is undetectable on EEG but which leads to brain changes that result in psychosis (Cascella et al., 2009, Elliott et al., 2009b).

Antiepileptic medication may also play a role in the development of psychosis especially among patients with other risk factors such as family history or past psychiatric history. Psychoses have been noted as a potential adverse effect in many different antiepileptic medications suggesting that the phenomenon is not medication specific. Antiepileptic medications implicated include ethosuxamide, topiramate, vigabatrin, zonisamide and leviteracetam (Mula and Monaco, 2009). One study found a prevalence of psychosis of 3.7% in patients after they were commenced on topiramate (Mula et al., 2003a). High starting doses of medication and a rapid titration schedule in more vulnerable patients with past psychiatric history and with more severe epilepsy with high seizure frequency were associated with greater risk.

However, it is also possible that epilepsy and psychotic illness may represent different outcomes of a common aetiological process. Neuropathological, neuroimaging and genetics findings show that similar structural brain abnormalities and genetic abnormalities are present in patients with schizophrenia and patients with epilepsy (Cascella et al., 2009, Bruton et al., 1994, Barr et al., 1997, Helbig et al., 2009, Masurel-Paulet et al., 2010, Sundram et al., 2010, Vassos et al., 2010). For instance, enlarged ventricles have been found to be common to first episode psychosis and temporal lobe epilepsy patients without psychosis (Barr et al., 1997). Neuronal migration defects have been proposed as a mechanism related to enlarged ventricles and this defect could be common both to schizophrenia and epilepsy. From a neurobiological perspective, significant grey and white matter deficits occur in temporal
lobe epilepsy with psychosis. Some of these deficits overlap with those found in schizophrenia. These include the medial temporal structures but also extend to lateral temporal and extratemporal regions (Sundram et al., 2010).

Recent genetic work shows that a rare genetic mutation can lead to either epilepsy or schizophrenia. A micro-deletion in the genomic area 15q 13-14 containing the nicotine receptor was linked to development of either schizophrenia or juvenile epilepsy (Helbig et al., 2009, Masurel-Paulet et al., 2010, Vassos et al., 2010). The gene leucine-rich glioma-inactivated 1 gene (LGI1) in autosomal dominant partial epilepsy with auditory features, (Kalachikov et al., 2002, Morante-Redolat et al., 2002) may also play a role in regulating glutaminergic synaptic transmission, a process that is involved in the pathophysiology of schizophrenia (Fukata et al., 2006). Genes encoding ion channels may also be a source of interest. Ion channelopathies are known to underlie some epilepsies and it has been shown that variation within the gene CACNA1C (encoding a subunit of the L-type voltage dependent calcium channel) is associated with schizophrenia as well as depression and bipolar affective disorder (Ferreira et al., 2008). This study provides support for the possibility that some people might experience both psychosis and epilepsy at least in part because of an underlying vulnerability to both.

Summary
In summary, adequate recognition and treatment of psychosis in epilepsy is essential for patient management because of their considerable burden in morbidity and quality of life (Gaitatzis et al., 2004b, de Boer et al., 2008). We would recommend that future studies in this area should be used for defining psychotic presentations. Improved diagnostic classification would allow better characterisation of prevalence rates. Unfortunately standardized criteria for psychiatric disorders such as ICD 10 or DSM V do not allow this presently. Further investigations in
population-based studies are warranted for a more accurate prevalence rate at a population level and family-based studies are needed to investigate the possible clustering of psychosis and epilepsy within families. In conclusion, this study is the first meta-analysis and systematic review on the prevalence of psychosis in epilepsy. The methodological rigour of a systematic review adds clarity to the previous findings on this topic and confirms the results. We report an almost 8-fold increased risk of psychosis in epilepsy. An improved understanding of the mechanisms underlying this association would be a fruitful line of enquiry and may yield useful information on the aetiopathogenesis of both psychosis and epilepsy.

List of abbreviations
DSM: Diagnostic and Statistical Manual of mental disorders; ILAE: ICD: International Classification of Disease; International League Against Epilepsy; LGI1: Leucine-inactivated Glioma Inactivated one; TLE: Temporal Lobe Epilepsy

Competing interests
The authors declare that they have no competing interests.

Author’s contributions
MJC and DRC conceived the idea for the study. MJC and DJC were responsible for the data collection. MCC was responsible for all the statistical analysis. MJC wrote the first draft of the paper. MJC, MCC, MC and DRC all reviewed and edited the manuscript. MJC, MCC, MC and DRC revised it critically. All authors approved the final version of the manuscript.
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2.5 Tables and figures (a total of 4)
Figure 2.1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) flow diagram

- Studies from electronic databases and reference lists: N=215
- Excluded studies: N=157
- Included articles: N=58

- Review/commentary/other case reports: N=82
- Comparison study with other epilepsy types: N=6
- Papers not available in English: N=25
- No rates given: N=30
- Referred to same study: N=2
- Methodological problems: N=12
- Note-overlap reasons with some papers for excluded studies
Figure 2.2: Pooled prevalence of psychosis in individuals with epilepsy

<table>
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Pooled Rate: 6.63% (95%CI: 4.85%-6.41%)
Figure 2.3: Prevalence of psychosis in Temporal Lobe Epilepsy

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Pooled Rate: 7.04% (95% CI: 4.95% - 9.14%)
Figure 2.4: Pooled odds ratio for studies with controls

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Total: 100.00
Chapter 3

The prevalence of psychosis in post-operative epilepsy surgery patients: a systematic review and meta-analysis

3.1 Introduction

Epilepsy is associated with an increased risk of psychosis (Gibbs et al., 1948) (Slater et al., 1963) (Flor-Henry, 1969) (Schmitz, 1995a) and of psychiatric morbidity more generally (Torta and Keller, 1999) (Gaitatzis et al., 2004b) (Devinsky, 2003) (Swinkels et al., 2005) (Garcia-Morales et al., 2008). The findings of the largest population based study to examine the relationship between psychosis and epilepsy has shown that people with epilepsy are two and a half times more likely to develop schizophrenia and three times more likely to develop a schizophrenia-like psychosis than the general population (Qin et al., 2005). The factors that determine this increased risk of psychosis are unclear and likely include adverse side effects of antiepileptic drugs (Ettinger, 2006, Mula and Monaco, 2009, Schmitz, 1999) and shared genetic factors (Adachi et al., 2010, Craddock and Owen, 2010). In keeping with this, Clarke and colleagues have shown that a family history of either epilepsy or of psychosis independently confers increased risk of the other among offspring (Clarke et al., 2012).

Concern has also focussed on the issue of whether the surgical management of medically intractable epilepsy increases the risk of psychosis among subjects with epilepsy. It is well recognised that the surgical management of epilepsy reduces seizure frequency and improves quality of life (Wiebe et al., 2001) (Spencer et al., 2005) (Spencer and Huh, 2008) (Tanriverdi et al., 2008, Cunha and Oliveira, 2010), however the surgical treatment for epilepsy may be a risk factor for the development of de novo psychosis postoperatively or for the exacerbation
of existing psychosis (Stevens, 1990) (Mace and Trimble, 1991) (Jensen and Larsen, 1979a). Unfortunately, most recent studies vary considerably regarding the rates of developing psychosis post operatively (Blumer et al., 1998) (Ring et al., 1998) (Bladin, 1992) (Kanner et al., 2009) (Devinsky et al., 2005) (Anhoury et al., 2000), with the rates varying from as little as 0% (Ring et al., 1998) to 15% (Anhoury et al., 2000).

To help clarify the evidence, we conducted the first systematic review and meta-analysis of the literature on the prevalence rate of psychosis following surgery for any type of epilepsy and the prevalence rate of de novo psychosis, specifically following such surgery. As most surgical procedures involve temporal lobe resections (Engel et al., 2003) we also examined the prevalence of psychosis before and after temporal lobe resections specifically. We also looked at de novo onset psychosis following temporal lobectomy.

3.2 Methods
See methods for Section 2.2. The search terms used were prevalence, incidence, rate, rates, psychosis, schizophrenia, schizophreniform illness, epilepsy, seizures, temporal lobe epilepsy, surgery and post-operative. 'Surgery' and 'post-operative' were additional search terms in this study. The methods were otherwise identical to Section 2.2.

3.3 Results

Literature search
Our preliminary search identified 431 titles of papers or abstracts on EMBASE, 773 papers or abstracts on PUBMED and MEDLINE via OVID revealed 999 papers or abstracts. There was a substantial degree of overlap between the three search engines. After these titles were screened, 215 papers were examined in detail. After applying inclusion
and exclusion criteria, 15 papers (7%) were deemed to have data relevant to the systematic review and meta-analysis.

**Included studies and study design**

Four of the studies were from the UK (Anhoury et al., 2000) (Christodoulou et al., 2002) (McLellan et al., 2005) (Shaw et al., 2004), 4 were from the US, (Blumer et al., 1998) (Sherwin, 1981) (Siegel et al., 2008) 3 from Japan (Inoue and Mihara, 2001) (Kanemoto et al., 2001) (Mayanagi et al., 2001) and there was 1 from Canada (Manchanda et al., 1993), Denmark (Jensen and Larsen, 1979a) Australia (Bladin, 1992) and Spain (Pintor et al., 2007). The number of participants in studies varied from 50 (Blumer et al., 1998) to 320. (Shaw et al., 2004) The number of patients with postoperative psychosis in the studies varied from 1 (McLellan et al., 2005) (Siegel et al., 2008) to 28. (Inoue and Mihara, 2001) Eleven studies were cohort and four were cross sectional. None of the studies had a control group. The prevalence rates of psychosis post-operatively ranged from 1.06% (McLellan et al., 2005) to 27% (Jensen and Larsen, 1979a) Only one study followed up a child and adolescent sample. (McLellan et al., 2005)

**Prevalence of post-operative psychosis (all studies with this information)**

Overall, the pooled prevalence rate for psychosis in epilepsy patients post-operatively in all studies was 4% (95% CI 3.4-7.8) See figure 1. This figure was calculated from a total of 15 studies. One study had 0% rate of psychosis post-operatively and this was excluded (Kanner et al., 2009). The Stata statistics programme does not allow input of '0%' data. This was discussed with all of the authors of the paper and a joint decision was made to omit this study. This study had 2 patients with pre-operative psychosis and 0 patients with post-operative psychosis ie the patients with pre-operative psychosis had resolution of their psychosis following surgery. If this study was included, it might have contributed erroneously to an overall lower pooled rate of psychosis in patients post-operatively.
Prevalence of pre-operative vs post-operative psychosis (only studies with information on both)

Twelve studies reported both pre-operative and post-operative surgery rates. In studies which reported both pre-operative and post-operative rates, the mean pre-operative rate of psychosis was 4.2% (95% CI 2.0-6.4) and the mean post-operative rate of psychosis was 6.2% (95% CI 3.3-9.1). Of these twelve studies, five studies had higher psychosis rates postoperatively (Bladin, 1992, Blumer et al., 1998, Jensen and Larsen, 1979a, Mayanagi et al., 2001, McLellan et al., 2005), four had higher psychosis rates preoperatively (Devinsky et al., 2005, Inoue and Mihara, 2001, Kanemoto et al., 2001, Kanner et al., 2009), and three had the same rates both pre and post operatively (Anhoury et al., 2000, Pintor et al., 2007, Siegel et al., 2008). One of these studies was not included in our meta-analysis in calculating the post-operative psychosis rate as the number of patients who were psychotic post operatively was zero. (Kanner et al., 2009) These twelve studies comprised a total of 1301 patients.

Psychosis occurring de novo following surgery

Eleven papers gave rates for de novo post-operative psychosis, referring to psychosis which developed for the first time post-operatively. The rate of post-operative de novo psychosis was 2% (95% CI 1.1-2.9).

Prevalence of post-operative psychosis following TLE Surgery

The total pooled prevalence rate for psychosis following surgery for TLE was 7.3% (95% CI 3.0-11.6). Eight studies were used to calculate this figure. The prevalence of pre-operative psychosis in TLE patients was 4.1% (95% CI 1.3-6.8). The same eight studies were used for this figure. These 8 studies comprised a total of 622 patients. The prevalence of de novo psychosis in TLE patients following surgery was 2.5% (95% CI 1.1-4.0)
There was substantial heterogeneity between the prevalence estimates of psychosis pre and post-surgery in epilepsy patients across individual studies ($\chi^2_{10} = 78.34, p < 0.001; I^2 = 87.2\%$ for pre-operative rates, $\chi^2_{10} = 58.23, p < 0.001; I^2 = 82.8\%$ for post-operative rates and $\chi^2_{10} = 19.8, p < 0.05; I^2 = 49.5\%$ for new-onset rates). We examined the effect of the age of participants and the method of assessment used in each study on the prevalence of psychosis pre and post-surgery in epilepsy patients in a meta-regression analysis. The mean age of participants in each study did not explain variation in pre, post or new onset rates across studies to a significant extent ($\beta = -0.84, SE(\beta) = 0.56, p = 0.17; \beta = 0.05, SE(\beta) = 0.35, p = 0.87; \beta = 0.01, SE(\beta) = 0.12, p = 0.92$). However, the types of assessment used in the studies (interview versus case notes) explained 57.1\% of the variation in pre-operative rates found across studies ($\beta = 9.4, SE(\beta) = 2.9, p < 0.01$) and 69.9\% of variation in post-operative rate ($\beta = 12.56, SE(\beta) = 3.58, p < 0.01$). Method of assessment did not explain a significant amount of the variation in new-onset rates reported across studies ($\beta = 0.21, SE(\beta) = 1.0, p = 0.84$).

3.4 Discussion
A core concern for those involved in the care of patients with treatment refractory epilepsy is whether the surgical management of this disorder is a risk factor for the subsequent development of psychosis. In this study, the first systematic review to examine the rate of psychosis in post-operative epilepsy patients, we have observed that the rate of psychosis following surgery (4\%) appears to be lower than the rate of psychosis in all patients with epilepsy generally found in a recent systematic review (5.6\%) (Clancy et al., 2014). Our study thus provides reassuring support for the view that the surgical treatment of epilepsy does not lead to an increased risk of psychosis post-operatively.
Psychosis and its relationship with the site of resection
While the surgical management of epilepsy typically involves some form of temporal lobectomy, it also involves resection of other brain regions containing epileptic foci. It is therefore important to try to distinguish psychosis occurring in the context of temporal lobe surgery from that occurring in the context of non-temporal lobe surgery. Unfortunately, this is not possible as the published studies involving such extra temporal resections do not give psychiatric outcome data separately from their temporal lobe resection psychiatric outcome data (Siegel et al., 2008, Devinsky et al., 2005, Inoue and Mihara, 2001, Mayanagi et al., 2001). We could however look exclusively at the prevalence of psychosis in those studies involving temporal lobe resections only. In our systematic review we observed a rate of 7.3% among those who experienced temporal lobectomy, compared to an overall rate of 4% among those whose surgery involved both temporal and extra-temporal brain regions. These findings suggest that patients who have their temporal lobes operated on have a higher risk of psychiatric sequelae than patients who have non temporal areas operated upon. The only previous review of the prevalence of psychosis specifically following temporal lobectomy for the management of epilepsy found a prevalence rate of 7.6% (Trimble, 1992) but this review included studies with less stringent sampling and diagnostic criteria. However, our finding of 7.3% rate of psychosis following post TLE surgery is very similar. In our recent systematic review on the prevalence of psychosis in epilepsy, the rate of psychosis overall in epilepsy was 5.6% (95% CI 4.8-6.4) and the pooled prevalence rate of psychosis in patients with temporal lobe epilepsy was 7% (95% CI 4.9-9.1)(Clancy et al., 2014)

The value of pre and post-operative psychiatric assessment
Studies with longitudinal psychiatric data spanning the periods before and after surgical intervention provide a unique opportunity to assess the
psychiatric consequences of surgery. Twelve such studies exist. (figure 3.3) However, it was not possible to assess information in relation to individual patients’ cases and consequently we cannot determine if these rates refer to the same individuals or whether they reflect resolution of disorder in some subjects and the onset of new disorders in other subjects. Nine of these studies used interviews to assign diagnosis and three used only case notes (Inoue and Mihara, 2001, Jensen and Larsen, 1979a, Mayanagi et al., 2001). DSM or ICD criteria were used in eight of these twelve studies.

De-novo psychosis?
The possibility that psychosis can either develop, or indeed resolve, following surgical treatment makes it difficult to clarify the rates of new onset, or de novo psychosis following surgery. This can only be done in studies that have incorporated pre and post-operative structured diagnostic interviews in their study design, as discussed above. Two such studies have been undertaken. Firstly, Kanner and colleagues (Kanner et al., 2009) observed a pre-operative rate of 2%, with a postoperative rate of 0%, therefore there was no de novo psychosis. Similarly, Pintor and colleagues observed a pre-operative rate of 1.4%, and postoperative rate of 1.4%, based on the same single subject in their study remaining psychotic before and after surgery. Therefore Pintor and colleagues also observed a 0% de novo psychosis 0% (Pintor et al., 2007). Both of these studies used SCIDs as their diagnostic instruments. Other studies also obtained prospective clinical diagnostic information, but did not necessarily utilise structured diagnostic tools. These studies found de novo psychosis rates ranging from 1.1% (Devinsky et al., 2005, Christodoulou et al., 2002) to 3.8% (Kanemoto et al., 2001).

Interestingly, the lower rates of de novo psychosis are found in studies which use pre-operative and post-operative semi-structured interviews and the highest rates are found in studies which took their rates retrospectively from case notes.
The results of our systematic review found the prevalence of de novo psychosis following any type of surgical intervention for epilepsy generally to be 2% and following temporal resection specifically to be 2.5%. Other studies have estimated the incidence of de novo psychosis between 0.2-2.5% (Fenwich, 1994) and around 4% (Matsuura, 1997). With regard to all psychiatric illness postoperatively, a systematic review on psychiatric outcomes of epilepsy surgery found that de novo psychiatric issues are relatively rare post operatively and more likely to occur in the context of continued seizures, surgical complications and continued medical management (Macrodimitris et al., 2011a).

Limitations
There are a number of methodological limitations to our study. Firstly, there are few studies looking at psychiatric outcome following surgical management of epilepsy. Secondly, often no formal diagnosis has been made or diagnoses are taken from case notes (Inoue and Mihara, 2001, Mayanagi et al., 2001, Manchanda et al., 1993). Structured clinical diagnostic instruments for psychiatric diagnosis were applied in only two studies (Devinsky et al., 2005, Pintor et al., 2007). Thirdly, there are concerns regarding the small number of subjects involved in some of the studies. (Blumer et al., 1998) (McLellan et al., 2005) (Sherwin, 1981) (Kanemoto et al., 2001) and the potential for bias arising from the older literature involving case series (Stevens, 1990) (Mace and Trimble, 1991).

Several of the studies were based on potentially unrepresentative samples. For example, in one of the larger of the studies with 226 patients, (Inoue and Mihara, 2001) a preoperative psychosis rate of 16% is documented, but diagnosis was made retrospectively from case notes. Furthermore, another study was based on a very small sample and found
a preoperative psychosis rate of 23%, with diagnoses again made retrospectively from case notes (Kanemoto et al., 2001). These figures are atypical and unrepresentative of patients with epilepsy on waiting lists for neurosurgical treatment for medically intractable epilepsy.

Fourthly, as none of the studies had control groups, it is uncertain whether post-operative psychiatric outcome was exclusively due to surgery or whether it was a component of the natural time course of the disease process. For example, subjects with TLE who are candidates for surgery may be different from patients with TLE who are not pre-surgical candidates. Furthermore, candidates for surgery may have had more frequent or severe seizures and may have been exposed to greater numbers of anticonvulsant medications with the side effects that they bring. Consequently, care must be taken in extrapolating our results to non-surgical populations.

Several modifications have been made to surgical techniques and methods over the last 50 years. Modifications of temporal lobe respective surgery have been based on either resection of the epileptogenic zone assisted by the use of electrocorticography and cortical mapping to avoid functional deficits, or on resection of the seizure onset zone as with selective amygdalohippocampectomy. Transsylvian selective amygdalohippocampectomy, subtemporal selective amygdalohippocampectomy, stereotactic ablation and resection of the hippocampus, and stereotactic radiosurgery have all been newer techniques in the last 20 years used to treat TLE surgically, but consensus is lacking about which has the best outcomes. It is difficult to compare the success of various surgical techniques because of the lack of standardized outcome criteria. (Al-Otaibi et al., 2012)
Conclusion
In conclusion, our study provides reassuring evidence, for patients and clinicians alike, that there is no increased risk of psychosis postoperatively, relative to other epilepsy populations, regardless of whether the surgery involves only temporal lobe or extra-temporal resections. Future studies in this area should focus on obtaining formal neuropsychiatric assessment of subjects with epilepsy both pre and post operatively. Such studies will improve our knowledge of the risk factors and vulnerabilities relating to the development of postoperative psychiatric disorder following surgical treatment for the management of medically intractable epilepsy.

3.5 Figures (a total of 7)
Figure 1. Pooled prevalence rate from all studies reporting post-operative psychosis in epilepsy patients

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anheuser (2006)</td>
<td>2.73 (0.32, 5.82)</td>
<td>7.01</td>
</tr>
<tr>
<td>Baden (1992)</td>
<td>2.80 (0.32, 5.93)</td>
<td>7.61</td>
</tr>
<tr>
<td>Bruner (1966)</td>
<td>12.46 (3.45, 21.47)</td>
<td>2.52</td>
</tr>
<tr>
<td>Christodoulou (2002)</td>
<td>1.06 (0.13, 2.25)</td>
<td>9.97</td>
</tr>
<tr>
<td>Devinsky (2005)</td>
<td>1.07 (0.14, 2.28)</td>
<td>9.94</td>
</tr>
<tr>
<td>Inoue (2001)</td>
<td>12.38 (6.09, 16.67)</td>
<td>6.11</td>
</tr>
<tr>
<td>Jersn (1979)</td>
<td>27.03 (16.91, 37.15)</td>
<td>2.16</td>
</tr>
<tr>
<td>Kase (2006)</td>
<td>19.23 (8.53, 29.93)</td>
<td>1.92</td>
</tr>
<tr>
<td>Manchanda (1993)</td>
<td>1.34 (0.44, 2.65)</td>
<td>9.87</td>
</tr>
<tr>
<td>Mayenagi (2000)</td>
<td>5.00 (0.73, 9.27)</td>
<td>6.14</td>
</tr>
<tr>
<td>McLellan (2005)</td>
<td>1.57 (1.57, 4.51)</td>
<td>7.46</td>
</tr>
<tr>
<td>Punter (2007)</td>
<td>1.42 (1.34, 4.16)</td>
<td>8.16</td>
</tr>
<tr>
<td>Shaw (2004)</td>
<td>3.44 (1.44, 5.43)</td>
<td>9.11</td>
</tr>
<tr>
<td>Siegel (2008)</td>
<td>1.33 (1.26, 3.93)</td>
<td>8.32</td>
</tr>
</tbody>
</table>

*Pooled Rate: 4.09% (95% CI: 2.46% - 5.73%)

*Includes all studies that report post-operative rate
Figure 2. Pooled prevalence rate for pre-operative psychosis in epilepsy patients

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthony (2000)</td>
<td>0.76 (0.53, 0.99)</td>
<td>10.27</td>
</tr>
<tr>
<td>Blethu (1992)</td>
<td>0.93 (0.62, 2.18)</td>
<td>11.86</td>
</tr>
<tr>
<td>Blanes (1994)</td>
<td>4.00 (1.43, 9.43)</td>
<td>7.21</td>
</tr>
<tr>
<td>Devinsky (2005)</td>
<td>1.40 (0.90, 2.80)</td>
<td>12.20</td>
</tr>
<tr>
<td>Inoue (2001)</td>
<td>16.90 (11.13, 26.47)</td>
<td>2.51</td>
</tr>
<tr>
<td>Jensen (1979)</td>
<td>14.88 (8.71, 22.97)</td>
<td>4.88</td>
</tr>
<tr>
<td>Kenemott (2001)</td>
<td>25.08 (11.43, 34.50)</td>
<td>2.87</td>
</tr>
<tr>
<td>Kenner (2009)</td>
<td>3.00 (0.74, 4.74)</td>
<td>10.70</td>
</tr>
<tr>
<td>Meynager (2001)</td>
<td>2.00 (4.74, 4.74)</td>
<td>10.70</td>
</tr>
<tr>
<td>Pirnot (2007)</td>
<td>1.43 (0.38, 4.21)</td>
<td>10.44</td>
</tr>
<tr>
<td>Singh (2008)</td>
<td>1.33 (1.26, 3.93)</td>
<td>10.19</td>
</tr>
</tbody>
</table>

Pooled Rate: 4.21% (95% CI: 2.01% - 6.41%)
Figure 3. Pooled prevalence rate of post-operative psychosis in epilepsy patients

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthony (2010)</td>
<td>2.71 (0.32, 3.82)</td>
<td>10.79</td>
</tr>
<tr>
<td>Baudin (1993)</td>
<td>2.81 (0.32, 3.82)</td>
<td>10.74</td>
</tr>
<tr>
<td>Blumer (2000)</td>
<td>13.46 (3.66, 27.47)</td>
<td>5.61</td>
</tr>
<tr>
<td>Derry (2003)</td>
<td>1.04 (-0.14, 2.23)</td>
<td>12.02</td>
</tr>
<tr>
<td>Irout (2001)</td>
<td>15.5 (11.16, 20.76)</td>
<td>9.21</td>
</tr>
<tr>
<td>Jensen (1979)</td>
<td>27.03 (18.91, 37.15)</td>
<td>4.91</td>
</tr>
<tr>
<td>Kanhoto (2001)</td>
<td>23.08 (11.80, 34.85)</td>
<td>4.20</td>
</tr>
<tr>
<td>Mavanad (2001)</td>
<td>5.00 (0.73, 9.27)</td>
<td>9.69</td>
</tr>
<tr>
<td>McKeegan (2005)</td>
<td>1.87 (-1.57, 4.91)</td>
<td>10.64</td>
</tr>
<tr>
<td>Pieter (2007)</td>
<td>1.45 (-4.25, 7.14)</td>
<td>11.03</td>
</tr>
<tr>
<td>Jorgel (2000)</td>
<td>1.33 (-1.28, 3.93)</td>
<td>11.18</td>
</tr>
</tbody>
</table>

Pooled Rate: 6.18% (95% CI: 3.26 - 9.06%)
Figure 4. Pooled prevalence rate of new onset psychosis in epilepsy patients after surgery.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladin (1992)</td>
<td>1.87 (0.70, 4.64)</td>
<td>8.28</td>
</tr>
<tr>
<td>Bharer (1990)</td>
<td>12.09 (2.30, 61.01)</td>
<td>1.02</td>
</tr>
<tr>
<td>Christodoulou (2002)</td>
<td>1.08 (0.19, 5.26)</td>
<td>16.24</td>
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<tr>
<td>Davinson (2005)</td>
<td>1.08 (0.14, 7.60)</td>
<td>16.24</td>
</tr>
<tr>
<td>Inoue (2001)</td>
<td>2.85 (0.59, 14.78)</td>
<td>10.64</td>
</tr>
<tr>
<td>Jensen (1979)</td>
<td>12.16 (4.72, 32.11)</td>
<td>1.46</td>
</tr>
<tr>
<td>Karremolo (2001)</td>
<td>3.65 (1.78, 7.47)</td>
<td>2.77</td>
</tr>
<tr>
<td>Madhavada (1993)</td>
<td>1.34 (0.04, 4.65)</td>
<td>15.46</td>
</tr>
<tr>
<td>Mayanagi (2001)</td>
<td>1.00 (0.00, 2.96)</td>
<td>11.24</td>
</tr>
<tr>
<td>McLellan (2003)</td>
<td>3.87 (1.57, 9.94)</td>
<td>6.21</td>
</tr>
<tr>
<td>Shaw (2004)</td>
<td>3.44 (1.46, 8.43)</td>
<td>10.98</td>
</tr>
</tbody>
</table>

Pooled Rate: 1.98 (1.05, 2.91)
Figure 5. Pooled prevalence rate of post-operative psychosis in temporal lobe epilepsy patients

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthony (2000)</td>
<td>2.70 (4.32, 5.02)</td>
<td>17.94</td>
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<tr>
<td>Bijlo (1992)</td>
<td>2.00 (1.32, 3.30)</td>
<td>17.84</td>
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<tr>
<td>Jensen (1979)</td>
<td>37.03 (16.51, 77.65)</td>
<td>8.41</td>
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<td>Kenmochi (2001)</td>
<td>23.08 (11.43, 41.03)</td>
<td>5.21</td>
</tr>
<tr>
<td>McLeish (2005)</td>
<td>1.87 (1.57, 4.90)</td>
<td>17.76</td>
</tr>
<tr>
<td>Pistor (2007)</td>
<td>1.43 (1.36, 4.23)</td>
<td>18.24</td>
</tr>
</tbody>
</table>

Pooled Rate: 7.31% (95% CI: 3.01% - 11.60%)
Figure 6. Pooled prevalence rate of pre-operative psychosis in temporal lobe epilepsy patients

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anhuvry (1990)</td>
<td>2.76 (1.92, 3.60)</td>
<td>7.72</td>
</tr>
<tr>
<td>Bladin (1992)</td>
<td>0.18 (0.09, 2.78)</td>
<td>20.83</td>
</tr>
<tr>
<td>Blumer (1998)</td>
<td>4.00 (2.43, 6.53)</td>
<td>0.22</td>
</tr>
<tr>
<td>Jensen (1979)</td>
<td>14.06 (9.16, 22.17)</td>
<td>7.62</td>
</tr>
<tr>
<td>Kanner (2001)</td>
<td>23.08 (19.82, 26.33)</td>
<td>1.75</td>
</tr>
<tr>
<td>Kanner (2009)</td>
<td>2.90 (2.74, 4.74)</td>
<td>18.81</td>
</tr>
<tr>
<td>Pirkor (2007)</td>
<td>4.12 (3.35, 5.11)</td>
<td>18.43</td>
</tr>
</tbody>
</table>

Pooled Rate: 4.06% (95% CI: 1.25% - 6.87%)
Figure 7. Pooled prevalence rate of new-onset psychosis in temporal lobe epilepsy postsurgery.

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Rate (95% CI)</th>
<th>Weight %</th>
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</thead>
<tbody>
<tr>
<td>Bladin (1992)</td>
<td>1.97 (0.15, 4.44)</td>
<td>14.54</td>
</tr>
<tr>
<td>Rumer (1983)</td>
<td>12.25 (2.39, 12.09)</td>
<td>2.56</td>
</tr>
<tr>
<td>Christodoulou (2012)</td>
<td>1.04 (0.13, 3.36)</td>
<td>22.67</td>
</tr>
<tr>
<td>Jensen (1979)</td>
<td>12.16 (4.75, 15.88)</td>
<td>3.30</td>
</tr>
<tr>
<td>Kanemoto (2001)</td>
<td>3.65 (1.36, 3.97)</td>
<td>5.96</td>
</tr>
<tr>
<td>Manchanda (1993)</td>
<td>1.34 (0.54, 2.45)</td>
<td>22.02</td>
</tr>
<tr>
<td>McLellan (2005)</td>
<td>1.87 (1.57, 4.35)</td>
<td>11.42</td>
</tr>
<tr>
<td>Shaw (2004)</td>
<td>2.40 (1.46, 2.52)</td>
<td>17.71</td>
</tr>
</tbody>
</table>

Pooled Rate: 2.52% (95% CI: 1.08% - 3.97%)
Chapter 4

Methods for Experimental Chapters 5 and 6
The previous two chapters, chapters 2 and 3 are both systematic reviews and meta-analyses of the existing literature. Chapters 2 and 3 do not directly involve the patients recruited for this study.

Study sample

4.1 Study setting
The study was carried out in Beaumont Hospital, a large 820 bed academic teaching hospital in Dublin, Ireland. It is the Irish national referral centre for neurology, neurosurgery and neuropsychiatry; it can be seen as the Irish equivalent of the National Hospital for Neurology and Neurosurgery in Queens Square, London. It covers a catchment area of the entire Irish Republic population which stood at 4.6 million in 2012. It was the only hospital in the Irish Republic that carried out adult neurosurgical operations for medically refractory epilepsy during the period of this study from 2008 to 2012. The hospital has a dedicated neurology ward which includes a 2 bedded Epilepsy Monitoring Unit (EMU) where patients with complex and severe epilepsy are admitted and monitored in order to record seizures using 24 hour video EEG (electroencephalogram) recordings. Patients who are found to have localisation related epilepsy, (ie epilepsy that can be pinpointed to a discrete area of the brain) can sometimes be treated surgically for their epilepsy. The principle behind this is the removal of the aberrant piece of brain tissue that is responsible for the seizures. Such patients are highly selected for surgery and need detailed video EEG monitoring (average length of stay in the unit is eight days) to capture seizures, they also need high resolution MRI scanning and neuropsychological involvement
including a WADA (a procedure to establish language and memory dominance) of each hemisphere.

4.2 Recruitment of the cohort sample
All in-patients aged 16 or over admitted to the Epilepsy Monitoring Unit (EMU) who had a diagnosis of medically refractory epilepsy between July 2008 and July 2012 were included in the study. All had an ILAE diagnosis of localisation related epilepsy which had proven resistant to treatment. Their written consent was sought before they were included in the study if there were no factors that prevented their participation. Patients were excluded if they had a diagnosis of PNES without a diagnosis of Localization Related Epilepsy or if they had a moderate or severe learning disability which prevented them from providing informed consent. Intractable epilepsy was defined as epilepsy with a failed trial of at least 2 appropriate and tolerated different anticonvulsant medications at sufficient dosage for an adequate period of time.

The study was undertaken between July 2008 and July 2012 during which a total of 152 patients were admitted to the Epilepsy Monitoring Unit (EMU) for evaluation for their potential suitability for surgery for medically refractory epilepsy. Of these, one hundred and thirty eight patients were eligible and agreed to participate in the study. The other 90 patients either did not proceed to surgery due to a reduction in their seizure frequency on medication, they were on the waiting list for surgery, they had decided against having surgery or one year had not elapsed since they had surgery (see figure 4.1 flow diagram, recruitment of participants). Six patients were confirmed as having PNES on video EEG without a diagnosis of epilepsy and therefore did not proceed to surgery. During the timeframe of the study, forty-eight patients proceeded to surgery and were therefore evaluated post-operatively at one year; this sample of patients is described as the 'surgical cohort'. It is a subset of the 138 patients who agreed to participate in the study.
This research study was undertaken as part of a larger prospective study which aims to perform 3 month, 1 year and 2 year psychiatric assessments and follow up of medically refractory patients who proceed to surgery. The focus of my thesis was on the one year follow up patients.
Between 2008 and 2012, a total of 152 patients were admitted to the epilepsy monitoring unit for surgical evaluation.

8 patients declined to participate in the study.

138 patients agreed to participate in the study.

90 patients were not considered candidates for surgery, are currently awaiting surgery or 1 year had not elapsed since they had surgery.

48 patients proceeded to surgery and had one year follow up within the timeframe of the study.

*Psychogenic Non Epileptic Seizures*
4.3 Ethical approval
The study received ethical approval for all aspects of the study from Beaumont Hospital Research and Education Committee. The ethical protocol code was 07/66. If patients were diagnosed with mental illness, they were referred to the Department of Psychiatry for treatment. Patients were free to withdraw from the study whenever they desired without implications for their further treatment.

4.4 Study design
The study comprised initially a cross sectional sample of medically refractory epilepsy patients and within this was a nested prospective cohort study of the patients who proceeded to surgery and who had one year follow up. The study aims involved 1) baseline pre-operative assessment of a sample of medically refractory epilepsy patients and 2) follow-up of patients who proceeded to surgery at one year post-operatively to determine impact of epilepsy surgery on psychiatric diagnosis and subjective quality of life outcomes.

Outcome measures

4.5 Baseline Assessments
All consenting patients underwent baseline assessments pre-operatively while they were in-patients on the Epilepsy Monitoring Unit. The following 4 items/scales were used which will be described in more detail below;
   a) A proforma with patient demographic and epilepsy details
   b) SCID I and SCID II (SCID Structured Clinical Interview for DSM IV)
   c) HADS (Hospital Anxiety and Depression Scale)
   d) QOLIE-89 (Quality of Life in Epilepsy 89)
4.6 Proforma
A proforma document was used to collect demographic and clinical data comprising age, gender, marital status, education, employment status, living circumstances, age of seizure onset, hand dominance, family history of epilepsy, family history of psychiatric illness, any self-reported past psychiatric history, a history of febrile convulsions, any history of birth injuries or developmental delay and anticonvulsant medication. This information was obtained from the patient and the patient's medical notes. Collateral history for this information was often obtained from the patient's family or next of kin after consent was obtained. Seizure frequency information was classified according to the mean seizure frequency per month and presence of generalized tonic-clonic seizures as indicators of severity of illness.
Patients' epilepsy diagnoses were confirmed by video EEG (electroencephalogram), neurological assessment and neuro-imaging which usually involves high resolution MRI scans. Seizures were classified using the revised International League Against Epilepsy (ILAE) commission on classification and terminology. This commission has recently revised the old 1989 concepts, terminology and approaches for classifying seizures and forms of epilepsy (Berg et al., 2010). Generalized and focal seizures are redefined as occurring in and rapidly engaging bilaterally distributed networks limited to one hemisphere and either discretely localized or more widely distributed (focal). Classification of generalized seizures is simplified. No natural classification for seizures exists; focal seizures should be described according to their manifestations (e.g. dys-cognitive, focal, motor,) (Berg and Scheffer, 2011).
4.7 Structured Clinical Interview for DSM IV (SCID I)

All Psychiatric diagnoses are categorized by the Diagnostic and Statistical Manual of Mental disorders 5th Edition (APA, 2013). This manual is published by the American Psychiatric Association and covers all mental health disorders in adults and children. The most recent update, DSM V was published in May 2013. In my study, I used the DSM IV criteria as these were the criteria used during the time period of the study (APA, 2000).

The Structured Clinical Interview for DSM-IV Axis I disorders (SCID I) is a semi-structured interview for making the major DSM-IV Axis I diagnoses. The semi structured interview covers all major psychiatric diagnoses which meet diagnostic criteria as specified in DSM IV. Within each section, the diagnosis is assessed for the presence of the symptoms currently (ie within the last month) or in the patient’s past. Patients were assessed using the computerised Structured Clinical Interview for DSM IV Axis I clinician administered version which is designed to be administered by a clinician or a trained mental health professional(First, 1996). I administered this instrument for 64 of the 138 pre-operative assessments and all 48 post-operative assessments. I viewed SCID training videos prior to commencing my assessment of patients using the SCID.

The SCID I assessment is a well-established assessment tool with a reliability of between 0.6 and 0.93 for diagnosis of major depressive disorder (i.e. the internal consistency ranged between acceptable and excellent), 0.64 and 0.95 for a diagnosis of schizophrenia and 0.56 and 0.95 for generalized anxiety disorder(Ventura et al., 1998) (Skre et al., 1991). Superior validity of the SCID I in comparison to standard clinical interviews has also been demonstrated (Lowe et al., 2004).
The administration time of the SCID I is quite variable and can range from about 45 minutes on the short end (i.e., a patient with virtually no psychopathology or psychiatric history) up to several hours (i.e. a patient with extensive psychiatric comorbidity with a circumstantial style of speech). The administration time of the full SCID I for a psychiatric patient likely averages around 90 minutes whereas the administration time for a non-psychiatric patient is closer to one hour. Patients were also asked subjectively whether they had ever been given a psychiatric diagnosis in the past.

4.8 Structured Clinical Interview for DSM IV Personality disorder (SCID II)

Diagnosis of personality disorder was assessed using the Computerised Structured Clinical Interview for DSM Personality Disorder (SCID II) (Gaitatzis and Sander, 2004). In addition to evaluating full criteria for personality disorder, the presence of personality disorder traits was also elicited. Inter-rater reliability coefficients of this assessment tool range from .48 to .98 for categorical diagnosis (Cohen K) and from .90 to .98 for dimensional judgements (Intra-class correlation coefficient). Internal consistency coefficients were satisfactory (0.71-0.94). The results suggest that SCID II has adequate inter-rater and internal consistency (Maffei et al., 1997). One study comparing results of a personality assessment using the SCID II with a longitudinal clinician observation diagnosis found that the diagnostic power of the SCID II (ratio of true test results to total number of tests administered) to vary by diagnosis (from 0.45 for Narcissistic to 0.95 for antisocial), with the diagnostic power being 0.85 or greater for five types of personality disorders (Skodol et al., 1988).

Several studies comparing the SCID II to other measures of personality (Millon Clinical Multiaxial Inventory and Personality Disorder Examination) have shown rather poor agreement between the instruments although no conclusion could be reached about which instrument was more valid (O’Boyle and Self, 1990, Oldham et al., 1992).
4.9 Hospital Anxiety and Depression Scale (HADS)
(see Appendix III for copy)

The Hospital Anxiety and Depression Scale (HADS) has been found to be a reliable instrument for detecting states of depression and anxiety in a general hospital setting. It was developed by Zigmond and Snaith in 1983 to identify caseness of anxiety disorders and depression among patients in non-psychiatric hospital clinics (Zigmond and Snaith, 1983). It is divided into an Anxiety subscale (HAD-A) and a depression subscale (HADS-D) both containing 7 intermingled items. To prevent 'noise' from somatic disorders on all scores, all symptoms of anxiety and depression relating also to physical disorder such as dizziness, headaches, insomnia and fatigue were excluded.

More than 700 published studies from medical settings worldwide have reported experiences with the HADS. A review of validation data (Bjelland et al., 2002) identified that in terms of reliability, the results show satisfactory or good item-total correlations within the 2 subscales. Cronbach's alpha for HADS-A varied from .68 to .93 (mean .83) and for HADS-D from .67 to .90. (mean .82) In most studies, an optimal balance between sensitivity and specificity was achieved when caseness was defined by a score of 8 or above on both subscales. For anxiety (HADS-A) this gave a specificity of 0.78 and a sensitivity of 0.9. For depression (HADS-D) this gave a specificity of 0.79 and a sensitivity of 0.83. There is no single generally accepted cut-off score for HADS. In their original study, Zigmond and Snaith recommended two cut off scores for both subscales, 7/8 for possible and 10/11 for probable anxiety or depression (with possible ranges of 0-21 for each subscale). There has been some discussion of whether the anxiety and depression subscales really measure different aspects of mood but subscale scores are clearly correlated in most patient groups. Nevertheless, there is sufficient evidence that both subscales differ in a clinically meaningful way.
4.10 Quality of Life in Epilepsy 89 scale
(see appendix IV for copy)
The Quality of Life in Epilepsy 89 item (QOLIE-89) is a health related quality of life self-report instrument that is specific for adults 17 years and older with epilepsy and covers 17 domains (Devinsky et al., 1995b). These are overall quality of life (2 items), emotional well-being (5 items), role limitations due to emotional problems (5 items), social support (2 items), social isolation (2 items), energy/fatigue (4 items), seizure worry (5 items), medication effects (3 items), health discouragement (2 items), work/driving/social function (11 items), attention/concentration (9 items), language (5 items), memory (6 items), physical function (10 items), pain (2 items), role limitations due to physical problems (5 items), and health perceptions (6 items). A QOLIE 89 overall score is obtained using a weighted average of the multi-item scale scores. QOLIE 89 also includes one item on change of health over the preceding year. The time frame for some questions is the previous 4 week time period and is unspecified for others.
The QOLIE 89 is scored from 0 to 100 points with lower scores reflecting a worse quality of life and higher scores reflecting a better quality of life. In terms of reliability, Cronbach's alpha was 0.97 for the overall score and 0.78-0.92 for the subscales. Test re-test reliability was 0.88 for the overall score and 0.64-0.68 for the subscales.

4.11 Follow up assessments
As mentioned above the proforma, SCID I and II, HADS and QOLIE-89 were conducted on all patients at baseline. The SCID I and II information was recorded on a password protected laptop computer and hard copies were then printed out and stored in locked cabinets in the research department.
SCIDs I and II, HADS, QOLIE 89 and the proforma were repeated at the one year post-operative follow up assessment in patients who proceeded to surgery.

4.12 Post-operative seizure outcome
Many classification systems to define surgical outcome are used by epilepsy surgery centres. The Engel classification system devised in 1987 is the most commonly used scale (Engel et al., 1992). All seizure-outcome scales now used contain subjective components such as 'worthwhile improvement' or 'significant reduction'. The Engel classification for example requires these subjective assessments to distinguish a class 3 outcome from a class 4 outcome even though each centre may have a different definition of improvement. The Engel classification system is as follows:

**Class I**-free of disabling seizures (completely seizure free; non-disabling, simple partial only, some disabling seizures, but free of disabling seizures for at least 2 years; generalized convulsion with antiepileptic drug withdrawal only)

**Class II**- rare disabling seizures (initially free of disabling seizures, but rare seizures now; rare disabling seizures since surgery; more than rare disabling seizures, but rare seizures for at least 2 years; nocturnal seizures only)

**Class III**- Worthwhile improvement (worthwhile seizure reduction; prolonged seizure-free intervals amounting to more than half the follow up period, but not less than 2 years

**Class IV**- No worthwhile improvement (no significant seizure reduction; no appreciable changes; seizures worse)

Class I includes patients with residual auras. Usually, auras do not bother the patient if they are infrequent. However, depending on the frequency and the nature of the auras, (e.g. intense anxiety) they can affect
postoperative quality of life (QOL) even though they do not affect driving ability or independence.

In order to examine the impact of epilepsy surgery on psychiatric diagnosis, severity of psychiatric illness and on quality of life, I evaluated these post-operative outcomes in relation to the success of surgery as measured by the Engel score which was previously described above. The Engel score was grouped from 1-3 where benefit was displayed and 4 or above where no benefit was seen. A variable was then calculated for change in the HADS or QOLIE score and these 2 were correlated while controlling for the presence of a SCID diagnosis.

4.13 Data Analysis
The primary outcome measures were the presence or absence of a SCID diagnosis, and the actual diagnosis if present (grouped into a mood, psychotic, anxiety disorder and other diagnosis). Seizure frequency following surgery was measured and Engel surgical criteria which look at outcomes following epilepsy surgery were measured. Seizure type was recorded. In terms of rating scales, HADS overall scores, the depression and anxiety sub-scales and the QOLIE 89 overall score was recorded. Secondary outcomes included other QOLIE 89 rating scores and SCID II diagnoses where present.

4.14 Statistical Methodology
Data was analysed using SPSS version 18 for Windows (SPSS Inc. Chicago, IL). Data are presented as means (standard deviation) and tests were 2 sided with p values of less than 0.05 judged as significant. Effect sizes were calculated between groups based on the standard pooled deviation.

Baseline demographic and clinical characteristics of the 2 groups were analysed using Student’s t test, chi squared test, McNemar test and ANOVA analysis.
A Bonferroni correction is an adjustment made to p values when several
dependent or independent statistical tests are being performed
simultaneously on a single data set. The Bonferroni correction is used to
reduce the chances of obtaining a false positive results (Type I errors)
when multiple pair wise tests are performed on a single set of data. The
probability of identifying at least one significant result due to chance
increases as more hypotheses are tested. However, although the
Bonferroni correction controls for false positives, it can become very
conservative if there are a large number of tests and/or the test statistics
are positively correlated. This in turn increases the risk of generating false
negatives (Type II errors).

Patient data was analysed in 2 separate groups. The first aim of the study
was to investigate psychiatric and psychosocial characteristics of patients
with epilepsy refractory to medical treatment i.e. 'the medically refractory
sample'. The following hypotheses were tested:

- Patients with increased seizure frequency are more likely to have a
  psychiatric disorder than patients with lower seizure frequency
- Patients with a psychiatric diagnosis are more likely to have a
  higher HADS score and a lower QOLIE 89 score
- The HADS score will be higher in patients with more frequent
  seizures
- The QOLIE 89 score will be lower in patients with more frequent
  seizures

T tests, chi squared tests and logistic regression were used to test the
above hypotheses.

The second aim of the study was to compare the outcomes of the pre-
operative and post-operative group at 12 months i.e. the 'surgical cohort'.
The following hypotheses were tested:

- Patients are more likely to have a psychiatric diagnosis pre-
  operatively than post-operatively
• There will be lower HADS score and higher QOLIE 89 scores post-operatively.
• Patients with a poor surgical outcome will be more likely to have a psychiatric diagnosis post-operatively.

T tests, McNemar tests and ANOVA (analysis of variance) were used to test the above hypotheses. The third aim of the study was to conduct systematic reviews and meta-analyses on 1) the prevalence of psychosis in epilepsy and 2) the prevalence of psychosis in post-operative epilepsy surgery patients. The statistical methods utilized in the meta-analyses are described in chapters 2 and 3 under the methods sections.

4.15 ANOVA
In order to take into account various interactions, a repeated measures ANOVA was used because the same group was tested at two points in time, pre and post-operatively. As there were two within subject variables, HADS score and QOLIE-89 score which changed over time, the Engel outcome is the between subjects factor as this is the aspect of the group that was manipulated or changed. A significant result here means that Engel outcome (or surgical success) is shown to have an effect driving the changes seen in HADS and QOLIE-89 scores so it can be said that surgery is an effective intervention.
Chapter 5

Medical refractory epilepsy sample results

Introduction

This chapter presents the results of the study examining the medical refractory epilepsy sample of patients, i.e. all the patients who had a pre-operative assessment. Demographic data, epilepsy data, psychiatric diagnosis and quality of life assessment results are presented for the entire sample of 138 patients diagnosed with medically refractory epilepsy who participated in the study.

The following hypotheses were tested as mentioned in chapter 4:

Patients with increased seizure frequency are more likely to have a psychiatric disorder than patients with lower seizure frequency.

Patients with a psychiatric diagnosis are more likely to have a higher HADS score and a lower QOLIE 89 score.

The HADS score will be higher in patients with more frequent seizures.

The QOLIE 89 score will be lower in patients with more frequent seizures.

5.1 Demographic data

Table 5.1 shows the total sample of 138 patients’ age at the time of assessment and gender. Demographics also include relationship status, employment, residential circumstance and level of education. Data was found to be normally distributed. The increased number of females in the sample is a reflection of the admission policy to the 2 bedded epilepsy monitoring unit where males and females are admitted in separate blocks for different periods. The gender of patients was not found to be a
statistically significant factor influencing results; also the gender difference of those who proceeded to surgery was not significant.

Table 5.1 Patient demographic data

<table>
<thead>
<tr>
<th>Patient</th>
<th>N=138</th>
<th>Male 59</th>
<th>42.7%</th>
<th>Female 79</th>
<th>57.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean age 36.7</td>
<td></td>
<td></td>
<td>Median age 34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median age 34</td>
<td></td>
<td></td>
<td>Age range 17-65</td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>Full time 38 (27.5%)</td>
<td></td>
<td></td>
<td>Part time 26 (18.8%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Disability 43 (31.2%)</td>
<td></td>
<td></td>
<td>Student 12 (8.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other 19 (13.8%)</td>
<td></td>
<td></td>
<td>Other 5 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Relationship status</td>
<td>Married 40 (29%)</td>
<td></td>
<td></td>
<td>Single 91 (65.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Widowed 2 (1.4%)</td>
<td></td>
<td></td>
<td>Other 5 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td>Primary 13 (9.4%)</td>
<td></td>
<td></td>
<td>Secondary 73 (52.9%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tertiary 52 (37.7%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td>Family 116 (84.1%)</td>
<td></td>
<td></td>
<td>Alone 16 (11.6%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Supported 1 (0.7%)</td>
<td></td>
<td></td>
<td>Other 5 (3.6%)</td>
<td></td>
</tr>
</tbody>
</table>

5.2 Psychiatric history

Sixty patients (43.5%) reported that they had contact with mental health services or treatment of a psychiatric illness by a general practitioner prior to assessment while 78 (56.5%) had no past psychiatric history. The past psychiatric history was obtained by the patient’s history and by review of their medical chart.
Table 5.2
Psychiatric history

<table>
<thead>
<tr>
<th>Psychiatric History</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>78</td>
<td>56.5%</td>
</tr>
<tr>
<td>Mild learning disability</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>17</td>
<td>12.3%</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>25</td>
<td>18.1%</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>6</td>
<td>4.4%</td>
</tr>
<tr>
<td>Alcohol/substance abuse</td>
<td>4</td>
<td>2.9%</td>
</tr>
<tr>
<td>Unclear diagnosis</td>
<td>6</td>
<td>4.4%</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.3 Family history of mental health problems

Ninety one (66%) of the 138 patients had no family history of psychiatric illness. Eight patients (5.8%) were not aware of a family psychiatric history. Twenty two (15.9%) had a family history of depression. Five (3.6%) had a family history of schizophreniform illness and five (3.6%) had a family history of alcohol or substance abuse. Four patients (2.9%) had a family history of delirium, dementia and other cognitive disorders and one (0.7%) had a family history of an eating disorder. Two patients (1.4%) had a family member who committed suicide.
Table 5.3 Family History of mental health problems

<table>
<thead>
<tr>
<th>Psychiatric Family History</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>91</td>
<td>66%</td>
</tr>
<tr>
<td>Unclear</td>
<td>8</td>
<td>5.8%</td>
</tr>
<tr>
<td>Yes depressive disorder</td>
<td>22</td>
<td>15.9%</td>
</tr>
<tr>
<td>Yes schizophreniform disorder</td>
<td>5</td>
<td>3.6%</td>
</tr>
<tr>
<td>Yes alcohol/substance abuse</td>
<td>5</td>
<td>3.6%</td>
</tr>
<tr>
<td>Yes other</td>
<td>5</td>
<td>3.6%</td>
</tr>
<tr>
<td>Yes Family history of suicide</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

5.4 Family history of epilepsy

Eighty nine (64.5%) patients of the 138 patients had no family history of epilepsy. Fifteen (10.9%) had a first degree relative with epilepsy, twelve (8.7%) had a second degree relative with epilepsy, fourteen (10%) had a third degree relation affected and three (2.1%) had a relative with trauma related epilepsy. Five participants (3.6%) were unsure of their family history of epilepsy. One patient with a family history of schizophreniform illness also had a first degree relation with epilepsy and one patient with a family history of schizophreniform illness had a third degree relation with epilepsy. Three patients with a family history of schizophreniform illness had no family history of epilepsy.
5.5 Birth complications, developmental delay and childhood illness
One hundred and six patients (76.8%) had a normal birth and no relevant childhood illnesses. Thirteen (9.4%) had birth complications and fourteen (10.1%) had developmental delay. Four (2.9%) had a relevant childhood illness of head trauma. Information was unknown in one patient.
Twenty-seven (19.6%) patients reported a history of febrile convulsions, 102 (73.9%) had no history of febrile convulsions and nine (6.5%) patients did not know whether they had febrile convulsions.

5.6 Epilepsy diagnosis according to site of origin
Epilepsy type was classified as either localization related epilepsy or generalized epilepsy. Localisation related epilepsy is also known as partial epilepsy or focal epilepsy i.e. arising from a specific focus. Of the patients with localisation related epilepsies, 100 (72.5%) had a temporal lobe focus, 18 (13%) had a frontal lobe focus, 5 (3.6%) had a parietal lobe focus and 5 (3.6%) had an occipital lobe focus. One patient (0.7%) had non lesional right fronto-central epilepsy and one patient (0.7%) had fronto-temporal epilepsy.
Of the participants diagnosed with generalised epilepsy, two (1.4%) had generalised post traumatic epilepsy, one had Juvenile Myoclonic epilepsy, one had tuberous sclerosis, one had localisation related non lesional, one had an oligodendrogloma, one had generalised idiopathic and one had LRE (Localization related epilepsy) cause unknown.
5.7 Seizure classification
The most common type of seizure was complex partial and generalised tonic-clonic seizures followed by complex partial and secondary generalisation seizures. See table 5.4 below for the breakdown of the type of seizures.
Table 5.4 Seizure classification according to ILAE 1989 guidelines

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex partial</td>
<td>21</td>
<td>15.2%</td>
</tr>
<tr>
<td>Complex partial and secondary generalisation</td>
<td>30</td>
<td>21.7%</td>
</tr>
<tr>
<td>Simple partial</td>
<td>9</td>
<td>6.5%</td>
</tr>
<tr>
<td>Simple partial and secondary generalisation</td>
<td>6</td>
<td>4.3%</td>
</tr>
<tr>
<td>Simple and complex partial</td>
<td>13</td>
<td>9.4%</td>
</tr>
<tr>
<td>Simple partial and complex partial and secondary generalisation</td>
<td>20</td>
<td>14.5%</td>
</tr>
<tr>
<td>Complex partial and generalised tonic-clonic seizure</td>
<td>33</td>
<td>23.9%</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Generalised tonic-clonic seizure</td>
<td>3</td>
<td>2.2%</td>
</tr>
<tr>
<td>Complex partial and aura</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.8 Seizure frequency

Data on the number of seizures of any type per month was gathered. The mean number of seizures a month was 24.5 and the standard deviation was 44.6. The median seizure frequency was eight. This includes seizures of all types from simple partial to generalised tonic-clonic seizures. Data was missing on two patients.

The frequency of seizures per month was also sub-divided as a measure of both the severity of epilepsy and the presumed impact on the quality of
life into groups: one or less seizure a month, between 2 and 4 seizures a month, between 5-15 seizures a month and greater than 30 seizures a month.

Table 5.5 Frequency of seizures grouped

<table>
<thead>
<tr>
<th>Number of seizures per month</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or less</td>
<td>17</td>
<td>12.3%</td>
</tr>
<tr>
<td>2-4</td>
<td>38</td>
<td>27.5%</td>
</tr>
<tr>
<td>5-15</td>
<td>35</td>
<td>25.4%</td>
</tr>
<tr>
<td>16-30</td>
<td>23</td>
<td>16.7%</td>
</tr>
<tr>
<td>30+</td>
<td>23</td>
<td>16.7%</td>
</tr>
<tr>
<td>Missing</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.9 Handedness and hemisphere of origin
Twenty seven (19.6%) patients were left handed, 110 (79.7%) were right handed and data was missing for one patient. (0.7%) Sixty nine (50%) patients had seizures originating in the right hemisphere, 50 (36.3%) patients had seizures originating in the left hemisphere. Fifteen (10.9%) patients had bilateral points of origin and hemisphere affected was unknown in four (2.9%) patients.

5.10 Age of seizure onset
The mean age of seizure onset was 14.9 years of age (range 0-59 years, standard deviation 12.4 years). The median age of onset was 12. Data was missing on seven patients.
5.11 Psychiatric diagnosis

Of the total sample of 138 patients, 75 (54.4%) patients had an Axis I SCID diagnosis, 59 (42.7%) had no Axis I SCID diagnosis and data was missing on four patients.

Table 5.6 Psychiatric diagnosis of medically refractory epilepsy sample

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>75</td>
<td>54.4%</td>
</tr>
<tr>
<td>No</td>
<td>59</td>
<td>42.7%</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2.9%</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.11.1 Mood disorders

Of these patients, 30 (21.7%) had a diagnosis of a mood disorder. Eleven had a major depressive disorder in full remission, 8 had a depressive disorder due to a general medical condition, 6 had a diagnosis of depressive disorder not otherwise specified, 3 patients had a diagnosis of major depressive disorder, recurrent ongoing, 1 had a diagnosis of dysthymia and 1 had a diagnosis of major depressive disorder single episode.
Table 5.7 Mood disorder in medical refractory epilepsy sample (NOS-not otherwise specified) (GMC-general medical condition)

<table>
<thead>
<tr>
<th>Mood disorder</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No mood disorder</td>
<td>104</td>
<td>75.4%</td>
</tr>
<tr>
<td>Major depressive disorder recurrent in full remission</td>
<td>11</td>
<td>8%</td>
</tr>
<tr>
<td>Major depressive disorder recurrent ongoing</td>
<td>3</td>
<td>2.2%</td>
</tr>
<tr>
<td>Depressive disorder due to a GMC</td>
<td>8</td>
<td>5.8%</td>
</tr>
<tr>
<td>Depressive disorder NOS</td>
<td>6</td>
<td>4.3%</td>
</tr>
<tr>
<td>Dysthymia</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Major depressive disorder single episode</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Missing data</td>
<td>4</td>
<td>2.9%</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.11.2 Anxiety disorders

Eighteen patients (13%) had a diagnosis of an anxiety disorder. Of these, 7 patients had a diagnosis of panic disorder without agoraphobia, 3 had a diagnosis of agoraphobia without panic disorder, 2 patients each had a diagnosis of social phobia, and conversion disorder and 1 patient each had a diagnosis of a specific phobia, obsessive compulsive disorder, Post-Traumatic Stress Disorder (PTSD) and generalised anxiety disorder.
Table 5.8 Anxiety disorder in medically refractory epilepsy sample

<table>
<thead>
<tr>
<th>Anxiety Disorder</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anxiety disorder</td>
<td>116</td>
<td>84.1%</td>
</tr>
<tr>
<td>Panic disorder without agoraphobia</td>
<td>7</td>
<td>5.1%</td>
</tr>
<tr>
<td>Agoraphobia without panic disorder</td>
<td>3</td>
<td>2.2%</td>
</tr>
<tr>
<td>Social phobia</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Conversion disorder</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Specific phobia</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Obsessive Compulsive Disorder</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>PTSD</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Generalised Anxiety Disorder</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Missing data</td>
<td>4</td>
<td>2.9%</td>
</tr>
<tr>
<td>Total</td>
<td>138</td>
<td>100%</td>
</tr>
</tbody>
</table>

5.11.3 Psychotic disorders

Forty-nine patients (28.9%) were diagnosed with a psychotic disorder according to DSM IV criteria. Data was missing on four patients. Thirty one patients had a psychotic disorder due to a general medical condition with hallucinations and 5 patients had a psychotic disorder due to a general medical condition with delusions. Nine patients has a diagnosis of psychosis not otherwise specified (NOS). The definitions of and implications of psychosis due to a general medical condition and psychosis not otherwise specified will be elaborated upon in the discussion.
### Table 5.9 Psychotic disorder in medically refractory epilepsy sample (NOS) not otherwise specified, GMC (general medical condition)

<table>
<thead>
<tr>
<th>Psychotic disorder</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>No psychotic disorder</td>
<td>85</td>
<td>61.6%</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Brief Psychotic Disorder</td>
<td>2</td>
<td>1.4%</td>
</tr>
<tr>
<td>Psychotic disorder due to GMC with delusions</td>
<td>5</td>
<td>3.6%</td>
</tr>
<tr>
<td>Psychotic disorder due to GMC with hallucinations</td>
<td>31</td>
<td>22.5%</td>
</tr>
<tr>
<td>Psychotic disorder NOS</td>
<td>9</td>
<td>6.5%</td>
</tr>
<tr>
<td>Missing</td>
<td>4</td>
<td>2.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>138</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

#### 5.11.4 Other diagnoses

Nine patients (6.5%) had a history of either alcohol abuse/dependence; one each respectively had a diagnosis of benzodiazepine dependence, opiate dependence and cannabis abuse. Thirty-one patients (22.8%) of the cohort had more than one Axis one DSM IV diagnosis.

#### 5.11.5 Personality disorders

One hundred and five patients completed the Structured Clinical Assessment of DSM IV criteria for personality disorder. Data was missing or incomplete for 33 patients. Seven patients fulfilled criteria for avoidant personality disorder, 3 met the criteria for obsessive compulsive personality disorder, and one patient each had a dependent and a passive aggressive personality disorder.
Table 5.10 Personality disorder in medically refractory epilepsy sample

<table>
<thead>
<tr>
<th>Personality disorder</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>93</td>
<td>67.4%</td>
</tr>
<tr>
<td>Avoidant personality disorder</td>
<td>7</td>
<td>5.1%</td>
</tr>
<tr>
<td>Obsessive compulsive personality disorder</td>
<td>3</td>
<td>2.2%</td>
</tr>
<tr>
<td>Dependent personality disorder</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Passive aggressive personality disorder</td>
<td>1</td>
<td>0.7%</td>
</tr>
<tr>
<td>Missing</td>
<td>33</td>
<td>23.9%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>138</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

5.12 Hospital Anxiety and Depression Scale

One hundred and five patients completed a Hospital Anxiety and Depression Scale (83.3% of the sample). The mean Hospital Anxiety and Depression Scale (HADS) score for the cohort was 13.5 (standard deviation 11.6). The median was 11.

The mean anxiety subscale score was 6.2 (standard deviation 3.8). The median was 6. A score of 0-7 is normal; a score of 8 to 10 is suggestive of a disorder: a score of greater than 11 indicates probable presence of a disorder.

The mean depression subscale score was 4.5 (standard deviation 3.7). The median was 4. A score of 0 to 7 is normal; a score of 8 to 10 is suggestive of a disorder. A score of greater than 11 indicates probable presence of a disorder.
5.13 Quality of life in Epilepsy-89 (QOLIE-89)
Eighty nine patients out of 138 completed the QOLIE-89 questionnaire (64.4% of the sample). The average overall total score was 63.2 (standard deviation 15.5). The median was 64. This score is calculated using a weighted average of the multi-item scale score. Scores range from 0-100 where 100 indicate best possible quality of life. QOLIE-89 subtotal scores for health perceptions and overall quality of life were also measured. The mean health perception score was 62.5 (standard deviation was 19.7). The mean overall quality of life score was 59.4 (standard deviation was 20).

5.14 Correlations between HADS, QOLIE-89, seizure frequency and SCID diagnoses in medically refractory epilepsy sample
In order to test whether seizure frequency was related to QOLIE-89 or HADS score, the correlations between these factors was tested. I found no relationship between seizure frequency and HADS score. Pearson correlation testing was conducted which gave a correlation coefficient of -0.08 implying no relationship between the 2 variables. The p value was 0.94.
There was also no relationship between seizure frequency and overall QOLIE-89 score. Pearson correlation testing was conducted. The correlation coefficient of 0.009 and the p value of 0.934 confirm that there is no relationship between seizure frequency and QOLIE-89 total score.
Patients with a SCID diagnosis had on average higher HADS scores and lower QOLIE-89 scores than in patients without a SCID diagnosis. Mean HADS scores in patients with a SCID diagnosis (15.31) was higher than in patients without a SCID diagnosis (10.84). This result was statistically significant (p=0.043).

Patients with a SCID diagnosis had a lower overall QOLIE-89 score (57.44) compared to patients without a SCID diagnosis who had a higher QOLIE-89 score (68.86). This result was statistically significant (p=0.0001)

The correlation between HADS score and QOLIE-89 scores was examined. There was also a strong correlation between HADS and QOLIE-
89 scores in that patients with higher HADS scores had lower QOLIE-89 scores. (2 tailed Pearson correlation coefficient -.658, p value =0.0001). The medications which patients were on pre-operatively and post-operatively were examined. Thirteen patients (27%) were on the same medications pre-operatively and post-operatively. Seventeen patients (35.4%) had their medications regimen reduced at 1 year post-operatively. The most common medications to be stopped were clobazam (4 patients), carbamazepine and phenytoin (3 patients each). Clobazam which is a benzodiazepine may have an effect upon reducing anxiety symptoms. Carbamazepine is often used by psychiatrists as a mood stabilizer. Ten patients (20.8%) had their medications increased at 1 year post-operatively. The most common medication to be increased post-operatively was lamotrigine (4 patients). Lamotrigine is prescribed by psychiatrists as a mood stabilizer or as an adjunct in treatment –resistant depression. Eight patients (16.7%) had medications changed ie one medication stopped and a different medication commenced instead, it was not possible to clearly discern whether there had been an overall increase or reduction in total medication with these patients. The iatrogenic effects of medication related to psychiatric co-morbidity have already been outlined in Section 1.3.2 Mood disorders: aetiology in epilepsy: medication factors, Section 1.3.3 Mood disorders: treatment in epilepsy, Section 1.5.3 Anxiety disorders: treatment in epilepsy, Section 1.6.2 Psychosis: aetiology in epilepsy: medication factors and 1.6.3 psychosis: treatment in epilepsy.
There is a strong negative relationship here.

It was hypothesised that patients were more likely to have a SCID diagnosis if they had an increased number of seizures. Increased seizure frequency did not increase the risk of a SCID diagnosis \((p=0.246)\). See figure 5.5 for a graphical representation of this. This \(p\) value was generated using a Wald chi squared test and logistic regression.
Patients with a mood disorder were more likely to have a lower QOLIE-89 score. This was examined using a t test and was statistically significant ($p<0.0001$). Patients without a mood disorder had a mean QOLIE-89 score of 66.2 whereas those with a mood disorder had a mean QOLIE-89 score of 52.4.
Figure 5.6 Boxplot to show the distribution of QOLIE-89 scores in patients with and without a mood disorder (1=mood disorder absent, 2 mood disorder present)
Chapter 6

Surgical cohort results

Overview
This chapter presents the results of the study examining the cohort of patients who underwent surgery for epilepsy. Demographic data, epilepsy data, psychiatric diagnosis and quality of life assessment results are presented for the cohort of 48 patients who had pre-operative and post-operative assessments. The main interesting finding of the whole study is the change in psychiatric diagnosis before and after surgical treatment for refractory epilepsy.

6.1 Demographic data
Forty eight of the baseline sample of participants with medically refractory epilepsy proceeded to surgery within the timeframe of the study. The demographic information on the patients who proceeded to surgery is presented in this section.

Twenty male (41.7%) and 28 (58.3%) female patients had surgery. The average age of the patients participating was 34.95 (standard deviation 10.67) and the median age was 33. The range was 17 to 65.

The most common employment status was “working”. Seventeen patients (35.4%) were in full time employment, 11 (22.9%) were in part time employment, 8 (16.7%) were on disability allowance, 6 (10.4%) were students, and it was not known what 6 (12.5%) patients were doing. Thirty three patients were single (68.8%) and 13 (27%) were married. One patient each was widowed and separated respectively. Twenty three patients (47.9%) had completed a third level educational level educational course, 21 patients (43.8%) had attended second level
education and 4 had primary level education. A large majority of patients, 40 (83.3%) lived with their family and 6 (12.5%) lived on their own.

Table 6.1 Surgical cohort demographic data

<table>
<thead>
<tr>
<th>Patient</th>
<th>N = 48</th>
<th>Male 20</th>
<th>41.7%</th>
<th>Female 28</th>
<th>56.3%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean age 35</td>
<td></td>
<td></td>
<td>Median age 33</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age range 17-65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment</td>
<td>Full time 17</td>
<td></td>
<td></td>
<td>Part time 11</td>
<td>(22.9%)</td>
</tr>
<tr>
<td></td>
<td>(35.4%)</td>
<td></td>
<td></td>
<td>Disability 8</td>
<td>(15.7%)</td>
</tr>
<tr>
<td></td>
<td>Student 5</td>
<td>(12.5%)</td>
<td></td>
<td>Other 6</td>
<td>(12.5%)</td>
</tr>
<tr>
<td></td>
<td>Married 13</td>
<td>(27%)</td>
<td></td>
<td>Single 33</td>
<td>(68.8%)</td>
</tr>
<tr>
<td>Relationship status</td>
<td>Widowed 1</td>
<td>(2.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Separated 1</td>
<td>(2.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational level</td>
<td>Primary 4</td>
<td>(8.3%)</td>
<td></td>
<td>Secondary 21</td>
<td>(43.8%)</td>
</tr>
<tr>
<td></td>
<td>Tertiary 23</td>
<td>(47.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residence</td>
<td>Family 40</td>
<td>(83.3%)</td>
<td></td>
<td>Alone 6</td>
<td>(12.5%)</td>
</tr>
<tr>
<td></td>
<td>Other 2</td>
<td>(4.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6.2 Psychiatric History

Thirty six patients (75%) subjectively reported no previous contact with mental health services or treatment of a psychiatric illness by their GP, 12 patients (25%) reported a prior diagnosis of a psychiatric illness. The results are outlined in table 6.2. The psychiatric history was obtained by self-report and by review of the patient's medical chart. This self-reported view by the patient was much lower than the objective findings on SCID. (See 6.11.1 of this chapter). One patient had two separate diagnoses having both a depressive episode and generalized anxiety disorder.
Table 6.2 Psychiatric history of surgical cohort

<table>
<thead>
<tr>
<th>Psychiatric history</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>36</td>
<td>75%</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>4</td>
<td>8.3%</td>
</tr>
<tr>
<td>Depressive disorder</td>
<td>4</td>
<td>8.3%</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>1</td>
<td>2.1%</td>
</tr>
<tr>
<td>Deliberate self-harm</td>
<td>2</td>
<td>4.2%</td>
</tr>
<tr>
<td>Mild learning disability</td>
<td>1</td>
<td>2.1%</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>100%</td>
</tr>
</tbody>
</table>

6.3 Psychiatric family history

Thirty-one patients (64.6%) of patients reported no family history of psychiatric disorders. Nine patients (18.8%) had a family history of mood disorders, four (8.3%) had a family history of substance abuse related disorders, one had a family history of a schizophrenia or other psychotic disorder, one patient had a family history of suicide and family psychiatric history was unknown in two patients. Of note, this information was obtained by history from the participants and not confirmed by medical records.
6.4 Birth complications and developmental delay
Thirty-nine patients (81.25%) had a normal delivery and no history of illness in childhood or developmental delay. Three patients (6.25%) had a history of developmental delay, two had a forceps delivery, two had neonatal encephalopathy or encephalitis as a baby, one had apnoea episodes in infancy and one had a resection of a temporal lobe tumour as an infant.

6.5 Febrile convulsions
Thirty-six patients (75%) in the surgical group had no history of febrile convulsions, 10 (20.8%) had a history of febrile convulsions and there was no data for two patients.

6.6 Handedness and hemisphere of seizure origin
Of the surgical cohort, 7 patients (14.6%) were left handed and 41 (85.4%) were right handed. Twenty-six patients (54.2%) had seizures originating in the right hemisphere, 19 (39.56%) had a left sided seizure origin and 3 had bilaterally originating seizures.

6.7 Age of seizure onset
The mean age of seizure onset in the surgical cohort was 14.45, standard deviation 11.4.

6.8 Epilepsy diagnosis according to site of origin
Epilepsy type was classified as either localization related epilepsy or generalized epilepsy. Localisation related epilepsy is also known as partial or focal epilepsy ie arising from a specific focus. As would be expected in a cohort assessed as suitable for surgical intervention, the entire group had localisation related surgery. Of these, 42 (87.5%) had temporal lobe localisation epilepsy, 5 patients (10.4%) had a frontal focus and 1 patient had an occipital focus.
6.9 Seizure classification

The most common seizure type was complex partial and generalised tonic-clonic seizures followed by complex partial and secondary generalised seizures. See table 6.3 for details.
Table 6.3 Surgical cohort: seizure classification according to the International League Against Epilepsy guidelines 1989. Table refers to the number and type of seizures per month experienced pre-operatively in the cohort who proceeded to surgery

<table>
<thead>
<tr>
<th>ILAE 1989 classification type</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex partial</td>
<td>2</td>
<td>4.2%</td>
</tr>
<tr>
<td>Complex partial and secondary generalisation</td>
<td>13</td>
<td>27.1%</td>
</tr>
<tr>
<td>Simple partial</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Simple partial and secondary generalisation</td>
<td>2</td>
<td>4.2%</td>
</tr>
<tr>
<td>Simple and complex partial</td>
<td>8</td>
<td>16.7%</td>
</tr>
<tr>
<td>Simple Partial and Complex partial and secondary</td>
<td>5</td>
<td>10.4%</td>
</tr>
<tr>
<td>generalisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex partial and generalised tonic-clonic</td>
<td>17</td>
<td>35.4%</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>100%</td>
</tr>
</tbody>
</table>

6.10 Seizure Frequency

Data on the number of seizures of any type per month was gathered. The mean number of seizures per month in the surgical group was measured pre-operatively and post-operatively. Pre-operative seizure frequency per month was not always necessarily the immediate month prior to surgery. Some patients had their pre-operative assessments up to 1 year before surgery as there was a waiting length for surgery which varied in terms of time duration. Some of the post-operative seizure frequencies may have been more than one year after surgery, e.g. up to 15-18 months in cases. It depended upon when they returned to Beaumont Hospital for post-operative neurological, neurosurgical or neuropsychiatric follow up clinic appointments. The frequency of seizure episodes per month was also subdivided as a measure of both the severity of epilepsy and improved impact on quality of life into groups: one or less seizures per month,
between 2-4 seizures a month, between 5-15 seizures a month, between 15 to 30 seizures a month and greater than 30 seizures per month. Table 6.4 shows the number of seizures pre-operatively and post-operatively in the 48 patient cohort who proceeded to surgery.

Table 6.4 Surgical cohort: Change in number of seizures experienced pre-operatively versus post-operatively

<table>
<thead>
<tr>
<th>Number of seizures per month</th>
<th>Frequency pre-operatively</th>
<th>Percentage pre-operatively</th>
<th>Frequency post-operatively</th>
<th>Percentage Post-operatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or less</td>
<td>10</td>
<td>20.8%</td>
<td>34</td>
<td>70.8%</td>
</tr>
<tr>
<td>2-4</td>
<td>13</td>
<td>27.1%</td>
<td>9</td>
<td>18.8%</td>
</tr>
<tr>
<td>5-15</td>
<td>12</td>
<td>25%</td>
<td>3</td>
<td>6.3%</td>
</tr>
<tr>
<td>15-30</td>
<td>7</td>
<td>14.6%</td>
<td>2</td>
<td>4.1%</td>
</tr>
<tr>
<td>30+</td>
<td>6</td>
<td>12.5%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>100%</td>
<td>48</td>
<td>100%</td>
</tr>
</tbody>
</table>
Comparing seizure frequency groups pre-operatively and post-operatively.

Ten patients had the same frequency of seizures pre-operatively and post-operatively (relatively rare, except for patients who were already in the lowest frequency group).

Thirty-five patients had a lower number of seizures post-operatively. Three patients had an increase in seizure frequency post-operatively.
6.11 Psychiatric diagnosis

Table 6.5 Surgical cohort: psychiatric diagnosis

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>Pre-operative assessment</th>
<th>Post-operative assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric diagnosis</td>
<td>24 (50%)</td>
<td>14 (29.2%)</td>
</tr>
<tr>
<td>No psychiatric diagnosis</td>
<td>24 (50%)</td>
<td>34 (70.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>48 (100%)</td>
<td>48 (100%)</td>
</tr>
</tbody>
</table>

6.11.1 All Psychiatric diagnoses

Pre-operatively 24 patients (50%) of patients were objectively diagnosed with a psychiatric disorder, 24 (50%) had no psychiatric diagnosis. This was much higher than patients' subjective accounts (See Section 6.2 Psychiatric History). Post operatively, 14 patients (29.2%) were diagnosed with a SCID I disorder. Thirty four patients (70.8%) did not meet criteria for a psychiatric disorder. This result was statistically significant ($p < 0.021$).

Table 6.6 Psychiatric diagnoses pre and post-operatively

<table>
<thead>
<tr>
<th>Psychiatric diagnosis</th>
<th>Pre-operatively N (%)</th>
<th>Post-operatively N (%)</th>
<th>Exact Significance(2 sided) McNemar test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood diagnosis</td>
<td>8 (16.7%)</td>
<td>5 (10.4%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Psychosis diagnosis</td>
<td>18 (37.5%)</td>
<td>9 (18.8%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Anxiety diagnosis</td>
<td>4 (8.3%)</td>
<td>4 (8.3%)</td>
<td>0.625</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>24 (50%)</td>
<td>24 (70.1%)</td>
<td>0.021</td>
</tr>
</tbody>
</table>
6.11.2 Pre and post-operative changes in mood disorder status
Pre-operatively eight patients were diagnosed with a depressive illness using the objective SCID I assessment tool. This was much higher than the number of 4 patients subjectively reporting a pre-operative history of depression. Four patients had major depressive disorders, two patients had depressive episodes due to a General Medical Condition (i.e. epilepsy) and two patients had a diagnosis of depression not otherwise specified. Post operatively, five of the patients with a mood disorder had a remission of their illness and three had ongoing depression. One new patient was diagnosed with a major depressive episode and one patient had a new onset diagnosis of adjustment disorder. This adjustment disorder was not related to the patient’s epilepsy.

6.11.3 Pre and post-operative changes in psychotic disorders status
Pre-operatively 18 patients were diagnosed with a psychotic illness of some type. Sixteen patients were diagnosed with psychosis due to a general medical condition (GMC), one was diagnosed with psychosis not otherwise specified (NOS) and one was diagnosed with a brief psychotic disorder. Eight patients post operatively had a diagnosis of psychosis due to a GMC and one had diagnosis of psychosis NOS. Eight patients with psychosis due to a GMC saw their symptoms remit and one patient with brief psychotic disorder had their symptoms remit.

6.11.4 Pre and post-op changes in anxiety disorders status
Pre-operatively, one patient each had generalised anxiety disorder (GAD), panic disorder, social phobia and agoraphobia. Post operatively the patients with GAD and panic disorder had their illness remit and the patient with agoraphobia continued to have their illness, they also had had a new diagnosis of panic disorder post operatively. The patient with pre-operative social phobia continued to have social phobia
postoperatively. However, two new patients were diagnosed with generalised anxiety disorder postoperatively.

6.11.5 Other disorders
One patient met the criteria for alcohol dependence syndrome pre-operatively but no longer met the criteria post operatively.

6.11.6 Personality disorders
Three patients were diagnosed with Obsessive Compulsive personality disorder pre-operatively. However, data was missing for 15 patients (31.25% of sample). Seven of the missing pre-operative patients were assessed by my colleague Helen Barry. The other 8 patients reviewed by me declined consent to have an Axis II assessment pre-operatively as they felt that they had had enough questions answered after SCID I assessment. Five patients were diagnosed with personality disorders post operatively, 2 had the pre-operative assessments missing so it is not possible to say whether surgery had an influence on their personality. The three patients who had a pre-operative and post-operative SCID II assessment were diagnosed with Obsessive Compulsive personality disorder. Of the 2 patients who had missing pre-operative SCID assessments, one patient was diagnosed with having both avoidant and dependent personality disorder and the second patient was diagnosed with Obsessive Compulsive Personality Disorder.
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalised anxiety disorder</td>
<td>2 (4.2%)</td>
</tr>
<tr>
<td>Major depressive disorder</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Adjustment disorder</td>
<td>1 (2.1%)</td>
</tr>
<tr>
<td>Psychosis (any type)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4 (8.3%)</td>
</tr>
</tbody>
</table>

### 6.11.7 De novo psychiatric diagnosis post-operatively

In order to clarify what changes had occurred, i.e. whether SCID diagnosis had resolved post-operatively or whether a de novo (new onset) diagnosis had developed, the cases were examined in more detail. A total of 4 patients (8.3%) developed a de novo psychiatric illness post-operatively. With regard to affective disorders, one patient developed a new onset major depressive episode post-operatively. Two patients with pre-operative SCID diagnoses had changes in their SCID diagnoses post-operatively. One patient with a diagnosis of psychosis NOS had this resolve post-operatively but had a diagnosis of an adjustment disorder post-operatively which was unrelated to epilepsy or physical illness. The second patient who had a diagnosis of a major depressive episode with agoraphobia continued to have a major depressive illness post-operatively and they also developed panic attacks as well as agoraphobia.

There were no new cases of de novo (new onset) psychosis post-operatively. Two patients developed de novo anxiety disorders post-operatively; both patients were diagnosed with generalised anxiety disorder. Of the 24 patients who met the criteria for a SCID diagnosis pre-operatively, 8 continued to meet the criteria for the same SCID diagnosis post-operatively. Twelve patients (25%) no longer met the criteria for SCID diagnosis post-operatively i.e. the psychiatric disorder with which they were diagnosed pre-operatively was no longer evident following surgery. Of these patients who had remission post-operatively, they included seven patients who pre-operatively were diagnosed with psychosis due to a GMC, one patient with a brief psychotic disorder, one
with alcohol dependence, two patients with depressive episodes and one patient with a SCID diagnosis of both depressive disorder due to a General Medical Condition and psychosis not otherwise specified.

6.12 Hospital Anxiety and Depression Scale (HADS)

Table 6.8 Surgical cohort Hospital Anxiety and Depression Scale pre-and post-operative assessment (SD standard deviation, CI confidence interval)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Preoperative</th>
<th>95% CI of the mean</th>
<th>Postoperative</th>
<th>95% CI of the mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>HADS overall mean score</td>
<td>34</td>
<td>8.1 (6.7)</td>
<td>5.76-10.41</td>
<td>8.7 (7.3)</td>
<td>6.18-11.28</td>
</tr>
<tr>
<td>(SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS anxiety mean score</td>
<td>34</td>
<td>5.3 (4.1)</td>
<td>3.79-6.78</td>
<td>5.6 (4.5)</td>
<td>4.07-7.22</td>
</tr>
<tr>
<td>(SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS depression mean</td>
<td>34</td>
<td>3.6 (3.2)</td>
<td>2.40-4.76</td>
<td>3.1 (3.4)</td>
<td>1.86-4.25</td>
</tr>
<tr>
<td>score (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The pre and post-operative HADS scores were analysed using paired t tests. Thirty four patients (71%) completed a pre-operative and a post-operative HADS questionnaire. There were no significant differences pre-operatively versus post-operatively in the overall HADS score or for the anxiety or depression subscales. Pre-operatively, the mean overall Hospital Anxiety and Depression Scale (HADS) score of the surgical cohort was 8.1 (standard deviation 6.67). The pre-operative mean anxiety score was 5.3 (standard deviation 4.1) and the pre-operative mean depression score was 3.6 (standard deviation 3.2). A score of 0-7 is normal, a score of 8-10 is suggestive of a disorder and a score of greater than 11 indicates probable presence of a disorder.

Post-operatively, the mean HADS total was 8.7 (standard deviation 7.3). The mean anxiety score was 5.6 (standard deviation 4.5) and the mean depression score was 3.1 (standard deviation 3.4).
6.13 Quality of life in Epilepsy 89 (QOLIE-89)

Table 6.9 Surgical cohort QOLIE-89 scores pre and post operatively

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>QOLIE-89 total score pre-op</td>
<td>30</td>
<td>46.52</td>
<td>96.59</td>
<td>69.88</td>
<td>12.23</td>
</tr>
<tr>
<td>QOLIE-89 total score post-op</td>
<td>33</td>
<td>30.78</td>
<td>95.33</td>
<td>74.38</td>
<td>21.62</td>
</tr>
</tbody>
</table>

A paired t test was used to examine the change between the pre-operative and post-operative group in the Quality of Life in Epilepsy 89 score (QOLIE-89). Thirty patients (62.5%) completed a pre-operative QOLIE-89 and 33 patients (68.8%) completed a post-operative QOLIE-89. In the surgical cohort, the preoperative overall mean QOLIE-89 score was 69.9 (standard deviation 12.2). Post operatively the overall mean QOLIE-89 score was 74.8 (standard deviation 14.1). This result was statistically significant (p<0.002). This score is calculated using a weighted average of the multi-item scale score. Scores range from 0-100 where 100 indicate the best quality of life. The QOLIE-89 scales are subjective scales filled in by the individual patients. It was not possible to do inter-rater reliability measures.

6.14 Surgical Outcome

In relation to Engel surgery criteria outcome, (see methods section 4.12) forty two (87.5%) patients scored between class 1 and class 3, which captures a range of outcomes from complete seizure freedom to a worthwhile improvement. Six patient fulfilled criteria for class four which describes either no improvement or worsening of seizures. Twenty three
patients (41.7%) had a class I outcome (the best possible), 11 patients (22.9%) had a class II outcome, 8 patients (16.7%) had a class III and 6 patients (12.5%) had a class IV outcome.

Of the six patients who had a class IV outcome, three had no post-operative SCID diagnosis, and one each had generalised anxiety disorder, psychosis due to a GMC and a major depressive disorder.

6.15 Surgical Cohort Correlations

Examining the surgical group for the relationship between Structured Clinical Interview of DSM IV diagnosis, HADS score and Quality of Life in Epilepsy 89 scale, the following correlations were identified. The scores and diagnosis refer to assessments carried out on the surgical cohort post-operatively. 2 sample t tests were used to compare mean HADS and QOLIE scores in patients with and without a SCID diagnosis.

Effects of SCID diagnosis on QOLIE and HADS score

A two sample t test was conducted in order to examine whether there was an association between the HADS total score and presence of SCID I diagnosis, the p value was 0.057. The p value is not quite small enough to say that the two groups with and without a SCID diagnosis have different HADS scores, but it is very close and approaching significance. Thirty-four (70.8%) of the 48 patients had postoperative HADS questionnaires completed.

There was no association between QOLIE 89 scores and the presence of a SCID diagnosis, (p=0.21) There is no evidence for different QOLIE scores in patients with and without a SCID diagnosis. Thirty three (68.8%) of the 48 patients completed post-operative QOLIE questionnaires. A Pearson correlation test was used to examine the correlation between HADS score and QOLIE 89 score. As expected, there was a strong correlation between HADS and QOLIE scores in that patients with higher
HADS score had lower QOLIE scores (2 tailed Pearson correlation coefficient -0.645 p<0.0001)

Patients with a depressive diagnosis post-operatively were found to have a lower QOLIE 89 score (58) than patients without depression post-operatively (77). Despite only 4 patients being diagnosed with depression post-operatively, this result was found to be statistically significant (p=0.01 using an independent sample t test).

6.16 ANOVA
In order to examine interactions in greater detail, repeated measures of ANOVA (analysis of variance) was used as the same group was tested in two points in time. Two within subject variables changed over time, HADS score and QOLIE score, while the Engel classification of surgical outcome score is the 'between subjects' factor as this is the aspect of the group which was manipulated, i.e. by surgical intervention. A significant result implies that success in surgery is shown to have been the driving force for HADS and QOLIE. However the results of analysis show that ANOVA does not give significant results for change. The change is not relating to the actual Engel outcome, therefore it cannot be stated that the surgical outcome was the factor driving the changes in test scores. It is worth noting that only 6 patients (12.5%) had an Engel score of 4 or above and so 'not beneficial'. Therefore the majority of participants had a successful Engel score with surgical intervention and it could be interpreted that statistically there were not enough people with an unsuccessful result for it to be used as a measure. Conversely, the small number of unsuccessful surgical outcomes meant that the influence of the presence or absence of psychiatric disorder pre-operatively could be assessed in terms of its influence in affecting the outcome of surgery.

Two way ANOVA was used to examine the effect of Engel (Surgical) outcome and SCID diagnosis on the HADS score. The mean HADS score
was higher in the group with poorer surgical outcome than with a good surgical outcome but this was not statistically significant (p=0.136).

ANOVA was also used to examine the effect of Engel outcome and SCID diagnosis on the QOLIE 89 score. QOLIE 89 score was not found to be dependent on the Engel score when the SCID diagnosis is controlled for. This result was not statistically significant (p=0.87).
Chapter 7

Discussion

Overview
The principle aim of this study were to assess in detail and describe the psychiatric and psychosocial phenotype of a cohort of patients with medically refractory epilepsy (medically refractory epilepsy is defined in Introduction 1.1) by examining the prevalence and severity of psychiatric illness, assessing patients' quality of life and also to examine possible associations between psychiatric disorders, epilepsy variables and quality of life. The second main aim was to examine the impact of epilepsy surgery on psychiatric diagnosis, severity of illness and quality of life and to examine associations between psychiatric diagnosis, quality of life and surgical outcome. The results of the study are examined and considered in relation to the hypotheses formulated at the beginning of the study.

7.1 Summary of findings
This study is a prospective cohort study using structured clinical instruments which examines the relationship between psychopathology, medically refractory epilepsy and quality of life. Previous older studies in the literature examining the relationship between epilepsy and psychopathology have been cross sectional in nature, have had limited follow up periods and have lacked structured clinical instruments. The main findings of the examination of the medically refractory epilepsy sample show that:

1) Patients with medically refractory epilepsy have high rates of psychopathology-54.4%
2) Seizure frequency is not correlated with the presence or severity of psychiatric symptoms. Seizure frequency is not correlated with quality of life.

3) The presence of a psychiatric disorder and its severity is strongly correlated with quality of life.

4) Patients who are depressed have a worse quality of life irrespective of seizure frequency.

The main findings of the assessment of the surgical cohort show that

1) There was a significant reduction in psychopathology following surgery from 50% to 29.2%

2) There was a statistically significant improvement in quality of life scores following surgery

3) There was a statistically significant reduction in the number of patients who had a diagnosis of a psychotic disorder post-operatively (p < 0.004)

4) There was a slight increase in the severity of psychiatric symptoms experienced post-operatively (8.8-overall HADS score) compared to pre-operatively (8.1-overall HADS score). This result was not statistically significant.

5) Surgery was associated with an improvement in quality of life and psychopathology but this improvement was not associated with the degree of success in surgery.
7.2 Medically refractory epilepsy sample

7.2.1 Medically refractory epilepsy sample: psychiatric diagnosis
In this study, 54.4% of participants with medically refractory had a psychiatric diagnosis. Population based studies of epilepsy patients estimating the rates of overall psychiatric morbidity are few, with studies estimating rates between 11% and 35% (Jalava and Sillanpaa, 1996, Stefansson et al., 1998). Smaller studies consistently show higher rates of psychopathology in epilepsy although there is also evidence indicating that psychiatric illness continues to remain under-diagnosed and undertreated in patients with epilepsy (Kanner and Palac, 2000, Wiegartz et al., 1999). Studies examining the relationship between psychopathology and epilepsy to date have tended to be small, use a non-representative sample and have failed to use standardised instruments (Swinkels et al., 2005). The high rate of psychiatric diagnosis in this study therefore may be due to the use of the standardised diagnostic instrument therefore identifying more cases. My findings are very similar to Bragatti et al who found that 54.1% of patients in a tertiary referral centre had a SCID I diagnosis (Bragatti et al., 2010). Other studies which also used the SCID I and examined a chronic epilepsy populations in tertiary referral centres found a similar rates of 45.7%, 49% and 70% of Axis I psychiatric disorders (Pintor et al., 2007, Jones et al., 2005, Victoroff, 1994). Also the population that I studied were those with severe medically refractory epilepsy, therefore it could be said that these patients are more likely to have psychopathology than the general epilepsy population. I found no evidence that higher seizure frequency predicted an increased likelihood of a SCID diagnosis being made. However, the relatively small number of patients involved in the study may have influenced this. The powering of the study is discussed further in the limitations section.
Forty three percent of patients reported some contact with mental health services or treatment of a psychiatric illness by a GP prior to the assessment for the purpose of this study. However, only 17.4% of participants were undergoing treatment for an identified psychiatric disorder. It must be noted though that some patient’s illnesses may have been in remission. This study supports previous findings that not only may psychiatric illness be under-diagnosed; disorders identified may also be potentially undertreated.

7.2.2 Medically refractory epilepsy sample: mood disorders
Twenty two per cent of participants with medically refractory epilepsy were diagnosed with a mood disorder. This figure is very similar to a recent systematic review and meta-analysis which found a 23.1% (95%CI 20.6%-28.3%) prevalence of depression in epilepsy (Fiest et al., 2013). In one of the few multicentre studies which used operational diagnostic criteria, Jones et al reported an almost identical figure (21%) for depressive disorder in patients with epilepsy (Jones et al., 2005). Other smaller studies using SCIDs found rates of depression of 42.9% (Bragatti et al., 2010) and 58.3% (Victoroff, 1994). Thirty-seven percent of patients who had been diagnosed with a mood disorder had received treatment. The use of anti-depressant therapy in epilepsy is well established and shown to be effective with no major impact on seizure threshold with SSRIs, paroxetine and fluoxetine excepted. It has also been demonstrated that treatment of depression can have a positive effect on the frequency of seizures. The need for comprehensive psychiatric evaluation and initiation of treatment of comorbid mood disorders in patients with epilepsy is therefore well established.
7.2.3 Medically refractory epilepsy sample: anxiety disorders
Thirteen per cent of patients were diagnosed with an anxiety disorder, the most common diagnosis being panic disorder without agoraphobia (5.1%). Only one patient was found to have OCD which goes against the now discredited theory of the association between epilepsy and obsessionality as outlined in the introduction. The overall anxiety findings are lower compared with previous published rates of anxiety disorders in this population using SCIDs 18.4% (Bragatti et al., 2010), 21.5% (Pintor et al., 2007) and 30.4% (Jones et al., 2005). The unpredictability and uncontroliability of seizures have been likened to the 'learned helplessness' model of Seligman thus predisposing potentially to the development of anxiety and panic symptoms (Hermann et al., 1996).

Whereas many patients with epilepsy experience anxiety or panic type symptoms pre-ictally or as part of an aura, the use of the SCID identifies those with true panic disorder i.e. panic symptoms occurring unexpectedly and not due to the direct physiological effect of a general medical condition. The use of a SCID I diagnostic interview therefore most likely accounts for this study identifying a percentage of participants with anxiety disorders being at the lower range of the published figures.

7.2.4 Medically refractory epilepsy sample: psychotic disorders
Thirty seven per cent of participants were diagnosed with a psychotic disorder according to DSM IV criteria. This compares to the results of the systematic review and meta-analysis which I conducted in chapter five which found a prevalence of psychosis in epilepsy of 5.6%. However, this is the figure which is applicable to the general epilepsy population rather than the medically refractory population evaluated in the study. Earlier population based studies found psychosis rates between 0.7% and 7% (Jalava and Sillanpaa, 1996, Gudmundsson, 1966).
In studies which focused specifically on temporal lobe or medical refractory epilepsy populations, the prevalence of psychosis has been shown to be higher ranging from 11%-16% (Jensen and Larsen, 1979b, Umbricht et al., 1995). Of the patients in this study diagnosed with a psychotic disorder, 1.4% were diagnosed with schizophrenia and 1.4% were diagnosed with a brief psychotic disorder. Six and a half per cent had a diagnosis of a psychotic disorder that was not brief but which could not directly be attributed to a general medical condition i.e. epilepsy. These patients instead met the criteria of psychotic disorder not otherwise specified (NOS). In general, a diagnosis of psychosis NOS was reached when patients experienced psychotic symptoms, e.g. hallucinations around the time of the seizures but either temporal relationship to seizures could not definitely be established or the duration of symptoms was not of sufficient length to make the diagnosis of psychotic disorder due to a general medical condition. This phenomenon has also been described as interictal or postictal psychosis. Twenty six per cent of patients had a psychotic disorder due to a general medical condition (GMC) i.e. epilepsy and the majority of these had hallucinatory (22.5%) rather than delusionary experiences (3.6%) which were predominately aura related. The most frequent presentations of these auras were olfactory, gustatory, somatic and tactile hallucinations.

There has been some confusion about the definition of psychotic disorders in epilepsy as the application of a DSM IV criteria can lead to a diagnosis of psychotic symptoms as 'psychosis secondary to a general medical condition' depending on a subjective judgement of epilepsy as a causative factor for psychotic symptoms.

The studies which showed lower rates of psychosis (including articles used in my systematic review and meta-analysis) did not use SCID I diagnostic interview which rigorously identifies all psychotic symptoms and codes them according to DSM IV criteria. It is possible therefore that the studies which identified lower numbers of psychotic diagnoses disregarded
psychotic symptoms directly related to seizures and focused on non-
epilepsy related psychotic symptoms.

If this study excluded psychosis due to a general medical condition (i.e. auras) then the rate of psychotic disorders was 9.3% which is more similar to rates published to date in similar populations but still higher than the rate of 5.6% that I found in my systematic review and meta-
analysis. This may be because of the diagnostic rigorousness of the SCID in detailing symptoms, SCID I diagnostic interview rigorously identifies all psychotic symptoms directly related to seizures and does not differentiate between epilepsy related and non-epilepsy related psychotic symptoms. In my systematic review and meta-analysis, only 7 of 58 studies used the SCID I as the diagnostic instrument utilized.

7.2.5 Medically refractory epilepsy sample: severity of mood and anxiety symptoms

There is general acceptance that a score of 8 or higher on both the anxiety and depression subscales of the HADS is indicative of probable 'caseness' i.e. the probable presence of an anxiety or depressive disorder.

In examination of the HADS anxiety subscales, the mean score was 6.2. While the mean score fell within the normal range, 34 of the 92 participants who completed the assessment met the criteria suggestive of disorder or probable presence of disorder i.e. 37% of participants had a score of 8 or higher on the anxiety subscale.

Similarly on the depression subscale, the mean score was 4.5 but 21% (19/91) of patients met the criteria for possible or probable presence of a depressive disorder. Research examining Hospital Anxiety and Depression Scale scores in the epilepsy population generally find 'caseness' numbers in the range of one third to a half (O'Donoghue et al., 1999).

It could be hypothesised that the severity of epilepsy or seizure frequency may impact upon anxiety symptoms. However, I found no significant co-
relation between HADS score and seizure frequency suggesting that there is no direct relationship between the frequency of seizure episodes and the severity of anxiety or depressive symptoms.

Conversely the presence of a psychiatric diagnosis using SCIDs strongly correlated with the HADS score. The same was true of SCID psychiatric diagnosis and lower QOLIE-89 scores—see below. Therefore the findings of this study can be shown to demonstrate that psychiatric symptoms and diagnosis impact significantly on quality of life in medically refractory epilepsy seizures but frequency of seizures does not. These findings in addition to the published literature on the under diagnosis and treatment of psychiatric disorder further support the need for comprehensive psychiatric assessment and care for these patients with epilepsy with important implications for potential improvements on quality of life.

7.2.5 Medically refractory epilepsy sample: quality of life measures
The average total QOLIE-89 score was 63. One study looking at epilepsy out-patients quality of life found a mean of 67.5 (Hecimovic et al., 2012). A sample of pre-operative patients’ QOLIE-89 scores were lower at 47.3 (Markand et al., 2000). As mentioned above, I found no relationship between quality of life score and seizure frequency although the presence of a psychiatric diagnosis and impaired quality of life (i.e. a lower QOLIE-89 score) were significantly correlated. The severity of psychiatric symptoms (i.e. higher HADS scores) were also significantly correlated with quality of life scores. There was also a significant correlation between a diagnosis of a mood disorder and lower QOLIE-89 scores compared to higher QOLIE-89 scores in any patient without a mood disorder diagnosis who may nevertheless still had another Axis I disorder. In recent years, other studies have shown that the presence of a psychiatric comorbidity has a detrimental effect on quality of life. Psychiatric status has been shown to be a strong predictor of quality of life in previous studies and my findings are consistent with these results (Pulsipher et al., 2006,
Johnson et al., 2004). Other studies have also found that psychiatric illness especially depression influence quality of life more than seizure frequency (Boylan et al., 2004, Tracy et al., 2007). From a clinical management point of view, these findings suggest that the recognition of comorbid psychiatric conditions is important in the assessment of quality of life. It would be of considerable importance to determine if successful management of these psychiatric conditions was shown to improve the reported quality of life. A greater emphasis on the evaluation and treatment of comorbid psychiatric conditions has important implications for improvement of quality of life.

7.3 Surgical cohort

7.3.1 Surgical cohort: Psychiatric diagnosis

There was a statistically significant reduction in the rate of psychiatric diagnosis following surgery for epilepsy compared to the pre-operative psychiatric diagnosis rate. Of the 48 participants who proceeded to surgery, pre-operatively 50% were diagnosed with a psychiatric disorder while one year post-operatively, 29% were diagnosed with a disorder (p<0.021). Therefore one of the key hypotheses of this study, that the prevalence of psychiatric diagnosis will be higher in the preoperative group compared to the post-operative group is proven. The change in rates of psychiatric illness pre-operatively to post-operatively were changes in group rates of illness as a whole.

This finding contributes to the literature which contradicts older studies which linked surgery to serious psychiatric sequelae including increased rates of suicide, psychosis and depressive disorders (Jensen and Larsen, 1979a, Taylor, 1972, Trimble, 1992, Blumer et al., 1995). More recent studies have found conflicting results, some found an increase in rates of depressive and anxiety symptoms but no change in rates of suicide or psychosis (Anhouri et al., 2000, Bladin, 1992) whereas other studies with
greater numbers or using structured clinical instruments found reductions in rates of depression and anxiety (Macrodimitris et al., 2011a, Devinsky et al., 2005, Pintor et al., 2007).

There was a very significant reduction in the number of patients who pre-operatively had a diagnosis of a psychotic disorder. This was due to auras which commonly comprise mainly hallucinatory phenomenon ceasing post-operatively. Auras lend credence clinically to the association between schizophrenia and epilepsy which has already been confirmed from neuropathological, neuroimaging and genetic perspectives as I elaborated upon in my introduction.

De novo psychiatric disorders have been reported as occurring post-operatively at rates of 1.1% to 18.1% with a predominance of milder psychiatric disorders (Macrodimitris et al., 2011a). This study identified 4 new cases of de novo psychiatric disorder (8.3% of the epilepsy surgery sample), 2 cases of generalized anxiety disorder and one patient each developed a major depressive disorder and a new onset adjustment disorder. There were no new cases of psychosis. This is in keeping with the literature which suggests that de novo psychiatric disorders post-operatively tend to be of lesser severity. The largest study to date in the literature looking at de novo post-operative depression and anxiety found de novo rates of 6.1% and 6.9% rates for depression and anxiety respectively, these numbers are very similar to my de novo findings. Another study looking at a post-operative sample using SCIDs found a higher de novo post-operative rate of psychiatric illness of 17.3% (Pintor et al., 2007). Overall, the literature suggests that de novo psychiatric issues are relatively rare post-operatively and are more likely to occur in the context of continued seizures, surgical complications or continued medical rather than surgical management (Macrodimitris et al., 2011a).

It has been hypothesised in the older literature that studies which show a decrease in the number of patients with post-operative psychopathology
are complicated by the presumed rejection for surgery of patients with pre-operative psychopathology. However, no patients in this study were rejected for surgery based upon the presence of psychiatric pathology. This was the case despite the pre-operative cohort demonstrating high levels of psychopathology (54.4%). This study therefore lends weight to the body of research establishing the potential benefit of surgery for patients with a comorbid psychiatric disorder (Fenwich, 1994, Reutens et al., 1997).

My results confirm the decrease in the frequency and severity of psychiatric disorders after epilepsy surgery observed in 1 or 2 year follow up studies performed in the last decade in contrast with the results of studies conducted in the 1960s and 1970s. This can be explained by the improvement of the accuracy of surgery, improved and longer follow up of psychiatric treatment for patients before and after surgery and the progress in anticonvulsant and psychotropic pharmacotherapy.

Nevertheless, the mechanism whereby psychiatric illness improves post operatively is not fully understood. Removal of dysfunctional brain tissue, reduced fear of seizures, the perception of improved locus of control and reduced anticonvulsant medication may all possibly be factors.

7.3.2 Surgical cohort: mood disorders
The most commonly reported psychiatric changes with surgery are mood changes and depression which have been reported to occur in the first 6 months to a year following surgery. Pre-operatively 17% of participants were diagnosed with a depressive disorder. Although 10.4% met criteria for a depressive disorder post-operatively, this reduction did not reach statistical significance. In one of the few other prospective studies which used a SCID, Pintor et al reported a decrease in depression from 17.2% pre-operatively to 4.3% at 12 month follow up post-operatively. My findings are also consistent with studies which demonstrated that patients
with a pre-existing history of depression were more likely to experience depression post-operatively (Pintor et al., 2007, Devinsky et al., 2005).

7.3.3 Surgical cohort: Anxiety disorders
Pre-operatively 8.3% of participants were diagnosed with an anxiety disorder and the same numbers were diagnosed with a post-operative anxiety disorder. However, these were not the same patients pre and post-operatively with one patient each having remission of generalized anxiety disorder (GAD) and panic disorder and two patients having a de novo GAD diagnosis. Previous studies have demonstrated contradictory findings. Several studies have demonstrated no changes in anxiety rates as I have found post-operatively (Hermann et al., 1989, Reuber et al., 2004, Mattsson et al., 2005). Others have demonstrated a decrease in anxiety disorders (Meldolesi et al., 2007, Spencer et al., 2003, Cankurtaran et al., 2005). Interestingly, while the majority of studies demonstrated a decrease in anxiety there have been studies which report worsening anxiety symptoms post-operatively and one study reported a significant relationship between anxiety and ongoing seizures (Reuber et al., 2004).

7.3.4 Surgical cohort: Psychotic disorders
This study found that 37.5% of the surgical cohort had a psychotic disorder pre-operatively while 18.75% had a diagnosis at post-operative evaluation. This result was very statistically significant (p<0.004). This finding is in marked contrast to older studies which found a higher rate of de novo psychotic disorders in the post-operative population. I found no cases of de novo psychosis in my study.

The findings of this study support the view that epilepsy surgery does not increase the risk of developing a de novo psychotic illness in contrast to older studies in the literature (Roberts et al., 1990, Jensen and Larsen, 1979b, Trimble, 1992). As mentioned in the section earlier on medically
refractory epilepsy: psychotic disorder, section 7.2.4, the majority of patients with a psychotic disorder had a diagnosis of psychosis due to a general medical condition (GMC) i.e. epilepsy and the majority of these had hallucinations which were predominately aura related. If the patients had auras excluded, i.e. cases of psychosis due to a GMC (i.e. epilepsy), then the rates of pre-operative psychosis would have been 2.4% and the rate of post-operative psychosis would have been 1.2%. Thus, whichever classification of psychosis in epilepsy is used, my study has shown a reduction in psychosis rates post-operatively.

7.3.5 Surgical cohort: severity of anxiety and depression symptoms
Pre-operatively the mean overall HADS score was 8.1 with a mean anxiety sub score of 5.3 and a mean depression sub score of 3.6. Post-operatively, there was an increase in the anxiety subscale score to 5.6 and a reduction in the depression sub scale score to 3.1. Both of these results were not statistically significant. The increase in anxiety scores post-operatively was surprising and counter-intuitive. One of my hypotheses was that the severity of anxiety symptoms would be higher in the pre-operative than the post-operative group but this was not the case. Reasons for this may include that the anxiety scores were low at baseline initially pre-operatively, they were lower than the medically refractory cohort (HADS anxiety score 6.2). There was the same frequency of seizures or worsening of seizures in 6 patients (12.5%) and these patients may have had higher subjective anxiety leading to an overall increased mean. The 2 patients with de novo anxiety disorders post-operatively may have also contributed to the overall higher anxiety subscale score. Increased anxiety may also have been due to increased expectation in relation to normal stressors of daily living and the problems of increased independence and responsibilities which patients were shielded from while they had a diagnosis of active epilepsy.

163
The HADS score was not statistically correlated with a SCID I diagnosis but it was very close to it and approaching significance (0.057). This fits with the hypothesis that self-reported anxiety and depression is associated with the presence of a psychiatric diagnosis.

7.3.6 Surgical cohort: Quality of life
The quality of life in epilepsy 89 (QOLIE 89) assessment pre and post operatively was shown to demonstrate significant improvement (p<0.002). The hypothesis that surgical treatment of refractory epilepsy is associated with an improvement of quality of life is demonstrated. However, there was no evidence for higher QOLIE-89 scores in patients without a SCID diagnosis (p<0.21) Again, as with the increase in the severity of anxiety on the HADS anxiety subscale post-operatively described above, the concept of the burden of normality and the loss of a familiar chronic sick role must be considered. Patients who continued to have or were diagnosed with a mood disorder post-operatively had significantly lower QOLIE 89 than patients who did not have depression post-operatively. It appears that impaired quality of life is more likely in depressed patients post-operatively than patients with any other psychiatric comorbidity post-operatively.

7.3.7 Surgical cohort: Surgical outcome
A secondary aim of this study was that surgical outcome (Engel score) was a significant factor impacting on psychiatric diagnosis, severity of psychiatric symptoms (as assessed by the HADS) and on quality of life outcomes. I found that when the effects of a SCID diagnosis were controlled for, there was no difference in HADS score in patients with positive or negative Engel outcome. There was also evidence that controlling for the effect of SCID diagnosis, there is no difference between the mean QOLIE-89 scores of patients in the positive and negative Engel group outcomes.
It could not be shown that surgical outcome was the factor driving the change in QOLIE-89 and HADS scores. In other words patients having surgery, irrespective of the post-operative seizure frequency was shown to improve QOLIE-89 scores but whether surgery was successful or not did not impact on QOLIE-89 and HADS scores. It must be noted that the majority of patients had a successful surgical outcome with Engel scores of less than 4 (88% of patients) so therefore there were too few unsuccessful outcomes for it to be used as a measure. These findings are in keeping with the literature that there is lack of clarity in relation to the link between success of surgery and psychopathology (Anhoury et al., 2000, Pintor et al., 2007). Undergoing surgery may also have a placebo impact improving the self-report of psychiatric symptoms and also resulting in higher quality of life scores.

7.4 Critique of study design methods, sample and limitations

7.4.1 Was sample representative?
The Epilepsy Monitoring Unit (EMU) in Beaumont Hospital from which the study participants were recruited accepts referrals nationally of all patients deemed to be medically refractory and potentially candidates for surgery. As a result, it can be assumed to be representative of the medically refractory epilepsy population in Ireland.

Previous similar studies have considered that selection bias may arise as patients with severe psychiatric comorbidities may not be considered surgical candidates and therefore not referred for surgical evaluation. However, in addition to the role of surgical evaluation, the EMU in Beaumont also considers patients with medically refractory epilepsy for evaluation of seizures, Vagus Nerve Stimulator work up and clarification of diagnosis if patients are not deemed suitable for surgical intervention. These are all situations where the presence of a psychiatric disorder does not exclude referral for consideration for epilepsy surgery. It is therefore
highly unlikely that the recruitment sample was biased in favour of those with less psychiatric comorbidities.

The findings of the study are somewhat limited by the relatively small sample that proceeded to surgery within the timeframe of the study. However, of a potential 152 patients who were admitted to the EMU within the timeframe of the study, 138 agreed to participate. The high proportion of potential candidates who agreed to participate further reduces potential selection bias.

The absence of a control group is another potential limitation of the study. However, the surgical group were comprehensively assessed at two points in time pre and post operatively thus effectively functioning as their own control group. Having a control group would have increased the reliability of the results. It would have helped to eliminate potential confounding variables and bias. In the literature on this subject, there are no studies which have surgical control groups. The control groups described are medical (pharmacotherapy) treatment as usual (Wiebe et al., 2001).

The subjective self-report questionnaires the HADS and QOLIE 89 together require approximately 40-50 minutes to complete. As the pre-operative patients were given the assessments to complete while admitted to the epilepsy monitoring unit, the response rate of these questionnaires was relatively high -71% for the HADS and 69% for the QOLIE 89 reducing the risk of a sampling bias.

7.4.2 Critique of evaluation and measures implemented in study

The SCID was used to assess for psychiatric illness in this study. This is a well validated diagnostic interview. As noted previously noted earlier, this diagnostic interview does not specifically consider the occurrence of psychotic phenomena in the context of seizures. As a result, some diagnostic lack of clarity arose depending on duration and temporal relationship to seizures; some of these psychotic symptoms were
designated as psychosis due to a GMC or psychosis NOS. There is some confusion as DSM IV criteria can lead to a diagnosis of psychotic symptoms as 'psychosis due to a GMC' or 'psychotic disorder NOS' depending on a subjective judgement of epilepsy as a causative factor of psychotic symptoms. SCID I diagnostic interview rigorously identifies all psychotic symptoms directly related to seizures and focuses on both epilepsy and non-epilepsy related psychotic symptoms.

Another limitation is that the SCID I diagnostic assessment does not identify some disorders that are specific to epilepsy such as interictal dysphoric disorder (IDD) as mentioned in the introductory chapter. This may have potentially led to under diagnosis of depressive symptoms.

The HADS is well validated and has been extensively used in patients with epilepsy. In contrast to most other mood or anxiety self-assessment scales, it focuses on the cognitive rather than the physical features of psychiatric symptoms and is therefore reliable in patients with comorbid physical illness.

The classification of epilepsy and seizure type was complicated by several factors. Firstly the gold standard international guidelines for diagnosis of epilepsy are currently unclear as there are two separate guidelines. These are the older ILAE guidelines published in 1989 and the more recently published revised ILAE version in 2010. Contemporary epilepsy studies in journals use a mixture of both of these classifications; therefore the description of the types of epilepsy can vary in research published since 2010.

In addition, I had access to medical notes and therefore could classify as per the treating neurologists classification and self-report, at times the neurology notes were unclear as to the exact diagnosis according to ILAE standards and required me to make a judgement as to epilepsy or seizure classification.
Several patients reported that they found the QOLIE 89 questionnaire to be quite long and detailed as it takes approximately 40 minutes to complete. A shorter version, the QOLIE 31 has also been shown to be valid with equal sensitivity and specificity and this could be an option for future studies.

7.4.3 Other limitations of the study

The study participants were selected due to their medically refractory epilepsy diagnosis. However, while the majority (88%) had temporal lobe epilepsy, there was a large degree of heterogeneity in organic diagnosis within this group making it difficult to extrapolate the findings to any specific epilepsy diagnosis.

While the participants were assessed at two time periods thus functioning as their own control group controlling for confounders such as family history of psychiatric illness, drug or alcohol use, it may have been useful to reassess those who did not proceed to surgery at the same time points in order to assess the course of psychiatric illness in those who did not have surgery. However, this would have been difficult from a logistical, financial and resource perspective. The relatively short period of one year follow up post-operatively is another potential limitation which may bias the prevalence rates of psychopathology in patients who underwent surgery in view of the relatively low prevalence and long latency of some psychiatric disorders.

There was no blinding of the interviewing doctor to the psychiatric diagnosis of those who underwent surgery. This may have led to interviewer bias at the follow up assessment with an attempt to detect changes coinciding with expectations. This bias may have led to a decrease in the identification of psychiatric symptoms post-operatively. However, the use of a structured assessment tool in addition to self-administered questionnaires reduced this interview bias. Improvements post-operatively were demonstrated by both the SCID and QOLIE-89 but
not by the HADS, the results in relation to this which were different to what I had initially had hypothesised thus again providing evidence against interviewer bias.

Patients may also overestimate the occurrence of symptoms pre-operatively and underestimate post-operatively due to an inherent expectation of the positive impact of surgery leading to a recall bias. Again, the use of a structured interview reduces this risk. Also the HADS and QOLIE self-report specifically refer to symptoms experienced in the last 2 weeks or month respectively again reducing the risk of recall bias.

Another potential bias of the prospective cohort design is loss to follow up. However, all 48 participants who proceeded to surgery within the timeframe of the study were followed up therefore eliminating loss to follow up bias.

The only risk factor that appeared to impact on having a post-operative SCID diagnosis was having a pre-operative SCID diagnosis. I was unable to identify any other predictive risk factor for post-operative psychiatric illness. This is still a question which has been left unanswered in the literature on post-operative psychiatric illness.

Unfortunately the surgical cohort study was slightly underpowered. 55 patients would have been needed to detect a change with power of 80% whereas only 48 patients participated in the study.

There were obvious constraints with sample size as they were only two Epilepsy Monitoring Unit (EMU) beds in which patients could be assessed and following this, patients were on a long waiting list for surgery with a two year waiting time being not uncommon. There were cutbacks in neurosurgical theatre operating slots during the four year duration of this study due to financial and budgetary constraints and this obviously impacted heavily on the number of patients it was possible to recruit and assess at pre-operative baseline and at 1 year follow up post-operatively.
This was an unfortunate factor which I could not have anticipated in advance, nor could I have controlled for. The study used the data elicited from the patients that could be enrolled within the existing time frame, a principle described by Haynes et al as using 'the patients that I can get'(Haynes, 2006).

7.5 Implications for clinical practice

Patients with epilepsy have significantly higher rates of psychiatric disorder than the general population. The presence of psychiatric comorbidities has been shown to have more significant impact on quality of life than seizure frequency. Therefore identification and treatment of psychiatric illness especially depression is needed to improve quality of life in patients with epilepsy. There is a high level of need for specialist neuropsychiatry services in order to screen for psychosis and depression in epilepsy.

This study demonstrated a positive effect of surgery on medically refractory epilepsy in terms of mental health. The presence of a psychiatric disorder should not be considered a contraindication for surgical treatment for epilepsy when surgery is warranted. This is in contrast to the view in the older literature that mental illness is a contradiction for surgery.

Careful attention to the provision of effective psychiatric treatment of presurgical psychiatric comorbidities can help reduce the risk of postsurgical psychiatric complications. Eleven of the fourteen patients with a post-operative SCID diagnosis had a pre-operative SCID diagnosis. It has been argued that a detailed psychiatric assessment of patients should be as integral to the epilepsy surgery work-up as neuropsychological testing or the recording of seizures by video EEG. Close supervision and regular review for postoperative psychiatric complications and psychosocial adjustment difficulties are necessary and best provided through a formal follow up programme.
7.6 Implications for future clinical research
This study demonstrates that surgical intervention for refractory epilepsy is associated with an overall improvement in the presence of psychiatric diagnosis as well as an improvement in quality of life. This study demonstrates the need for more prospective, ideally larger multicentre studies using structured clinical instruments, to better delineate the prevalence and severity of psychiatric conditions occurring in the context of epilepsy surgery. Future studies over a longer time frame would establish the natural course of improvements in quality of life. Larger cohort studies may clarify the relationship between positive mental health outcomes and the success of surgery if such a relationship exists. The current study findings were limited by the small number of patients who had a negative surgical outcome. The impact of psychiatric treatment on depression, anxiety and psychosis post-operatively and its effect on seizures also needs to be examined. Finally, the concept of epileptic auras as psychotic symptoms leads to interesting questions about the overlap between schizophrenia and epilepsy on a clinical level as well as the common neuroimaging, neuropathological and genetic findings which have been demonstrated to date.

7.7 Conclusions
In this study, I have shown a high prevalence of psychiatric morbidity in patients with refractory epilepsy. In addition, I have demonstrated that the presence of a psychiatric disorder and the severity of psychiatric symptoms are strongly correlated with quality of life pre-operatively. Psychiatric morbidity appears to have more impact on quality of life than seizure frequency.

Overall, this study has demonstrated that undergoing surgery for medically refractory epilepsy has an overall positive impact on mental
health with a significant reduction in the prevalence of psychiatric symptoms in particular psychosis and there is an improved quality of life following epilepsy surgery.
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Appendix I
Patient Information Leaflet

Protocol Title:

Treating refractory epilepsy: Psychiatric and psychosocial morbidity before and after surgical treatment.

You are being invited to take part in a clinical research study carried out at Beaumont Hospital. Before you decide whether or not you wish to take part, you should read the information provided below carefully and if you wish discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as Informed Consent.

You may change your mind at any time (before the start of the study or even after you have commenced the study) for whatever reason without having to justify your decision and without any negative impact on the care you will receive from the medical staff.

WHY IS THIS STUDY BEING DONE?

Epilepsy is associated with an increased risk of mental health problems (such as low mood), in addition to psychological and social problems related to the condition (e.g. employment and driving restrictions). People with epilepsy that is poorly controlled by medication have an increased risk of these problems. Unfortunately doctors have little knowledge of the extent of these problems and the characteristics of those at increased risk. Many patients with epilepsy that responds poorly to medication are referred for surgery - to either remove any lesions causing the seizures or insert a device called a vagal nerve stimulator. These treatments can help to reduce the number and severity of seizures and need for medication. In addition they can also improve psychological and social functioning. Unfortunately some patients can experience problems after treatment related to mental health and social functioning.
This study aims to find out the frequency and severity of any difficulties before and after surgery.

WHO IS ORGANISING AND FUNDING THIS STUDY?

This study is being organised by the Department of Psychiatry in Beaumont Hospital. The study is not being funded by a pharmaceutical company.

HOW WILL IT BE CARRIED OUT?

This study is due to commence in August. Approximately one hundred patients will be involved in the study. All patients who have been admitted to the epilepsy monitoring unit or Beaumont Hospital for surgery will be asked to participate in the study.

This is a follow up study, which means that patients who agree to participate will be reviewed by a neuropsychiatrist after surgery when they attend the clinic for follow-up. The rates of mental health and social problems will be compared to results before treatment.

WHAT WILL HAPPEN TO ME IF I AGREE TO TAKE PART?

This study will involve two assessments, one before and one after surgery. You may withdraw from this study at any time including prior to the second assessment should you wish. A neuro-psychiatrist (Dr Maurice Clancy) assesses all patients admitted to the Epilepsy Monitoring Unit during their stay. If you are willing to participate in this study you will also meet with Dr Clancy when you attend outpatients 6 months after surgery. In outpatients you will be interviewed for approximately sixty minutes and be given some questionnaires to complete.

WHAT ALTERNATIVE TREATMENTS ARE AVAILABLE TO ME?

It is up to you whether to take part or not. Even if you do decide to take part you are free to withdraw at any time and without giving a reason. This will not affect the standard of care that you receive.
BENEFITS:

The aim of this study is to gather more information on mental health of people with epilepsy, which may be of benefit in future treatment/assessment of patients. You will receive a comprehensive psychiatric assessment prior to surgery whether you participate in the study or not.

CONFIDENTIALITY ISSUES:

As part of the study the investigators will review your medical notes. Your general practitioner will be informed that you are participating in the study although the contents of assessments will be confidential. Further information may be elicited from a family member by interview but only with your permission. All information that is collected about you during the study will be kept strictly confidential and restricted to the researchers. This information may be used in future studies subject to ethics committee approval. Statistical results of the study may be presented in medical journal but no identifiable information about you will be given to any outside party.

IF YOU REQUIRE FURTHER INFORMATION

If you have any further questions about the study, or if you wish to withdraw from the study you may do so without justifying your decision and your future treatment will not be effected.

For additional information now or any future time please contact:

Dr Maurice Clancy, Clinical Research Fellow in Neuropsychiatry, Beaumont Hospital

Phone No. 018093740
Appendix II

CONSENT FORM FOR STUDY

Treating refractory epilepsy: Psychiatric and psychosocial morbidity before and after surgical treatment.

Participant Name

Name of Doctor and Telephone Number: Dr Maurice Clancy
(Co-Investigator); 8093740

Please tick the appropriate answer.

I confirm that I have read and understood the Information Leaflet dated _____ attached, and that I have had ample opportunity to ask questions all of which have been satisfactorily answered.  □Yes □No

I understand that my participation in this study is entirely voluntary and that I may withdraw at any time, without giving reason, and without this decision affecting my future treatment or medical care.  □Yes □No

I understand that records may be viewed by members of the research team for this study only.  □Yes □No

I understand that my spouse/family members' identity will remain confidential at all times.  □Yes □No

I have been given a copy of the Information Leaflet and this Consent form for my records.  □Yes □No

FUTURE USE OF ANONYMOUS DATA:
I agree that I will not restrict the use to which the results of this study may be put. I give my approval that coded data concerning my person may be stored or electronically processed for the purpose of scientific research and may be used in related or other studies in the future. (This would be subject to approval by an independent body, which safeguards the welfare and rights of people in biomedical research studies - the Beaumont Hospital Ethics (Medical Research) Committee.)  □Yes □No

Patient ____________________________
Signature and dated ____________________________

Name in block capitals ____________________________

210
To be completed by the Principal Investigator or his nominee.

I the undersigned, have taken the time to fully explained to the above patient the nature and purpose of this study in a manner that he/she could understand. I have explained the risks involved, the experimental nature of the treatment, as well as the possible benefits and have invited him/her to ask questions on any aspect of the study that concerned them.

__________________________  ____________________________  __________________________
Signature:  Name in Block Capitals:  Qualification:  Date:

3 copies to be made: 1 for patient, 1 for PI and 1 for hospital records.
Appendix III

Hospital Anxiety and Depression Scale (HADS)

Patients are asked to choose one response from the four given for each interview. They should give an immediate response and be dissuaded from thinking too long about their answers. The questions relating to anxiety are marked "A", and to depression "D". The score for each answer is given in the right column. Instruct the patient to answer how it currently describes their feelings.

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

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

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

D I can laugh and see the funny side of things: As much as I always could 0
Not quite so much now 1
Definitely not so much now 2
Not at all 3
A  Worrying thoughts go through my mind a great deal of the time 3
    A lot of the time 2
    From time to time, but not too often 1
    Only occasionally 0

D  I feel cheerful:
    Not at all 3
    Not often 2
    Sometimes 1
    Most of the time 0

A  I can sit at ease and feel relaxed:
    Definitely 0
    Usually 1
    Not Often 2
    Not at all 3

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

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

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

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

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

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

D I can enjoy a good book or radio or TV program:
    Often 0
    Sometimes 1
    Not often 2
    Very seldom 3

Scoring (add the As = Anxiety. Add the Ds = Depression). Zigmond and Snaith (1983)
QUALITY OF LIFE IN EPILEPSY
QOLIE-31 (Version 1.0)

Patient Inventory

Today's Date ___/___/___

Patient's Name ____________________________

Patient's ID # ____________________________

Gender: □ Male □ Female Birthdate ___/___/___

INSTRUCTIONS

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3 ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is: (Circle one number)
   - Excellent 1
   - Very good 2
   - Good 3
   - Fair 4
   - Poor 5

2. Overall, how would you rate your quality of life? (Circle one number on the scale below)
   - Best Possible Quality of Life
   - Worst Possible Quality of Life (as bad as or worse than being dead)

   ![Scale with numbers from 0 to 10]

   10 0 6 7 5 4 3 2 1 0

   216
5. Compared to 1 year ago, how would you rate your health in general now? (Circle one number)

- Much better now than 1 year ago: 1
- Somewhat better now than 1 year ago: 2
- About the same as 1 year ago: 3
- Somewhat worse now than 1 year ago: 4
- Much worse now than 1 year ago: 5

4-15. The following questions are about activities you might do during a typical day. Does your health limit you in these activities? If so, how much? (Circle 1, 2, or 3 on each line)

<table>
<thead>
<tr>
<th>Activity</th>
<th>Yes, limited a lot</th>
<th>Yes, limited a little</th>
<th>No, not limited at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Lifting or carrying groceries</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Climbing several flights of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Climbing one flight of stairs</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Bending, kneeling, or stooping</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. Walking more than one mile</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>11. Walking several blocks</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>12. Walking one block</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>13. Bathing or dressing yourself</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
The following questions are about your regular daily activities, such as working at a job, keeping house, taking care of children, attending school, volunteer work, or taking part in community services.

14-18. During the **past 4 weeks**, have you had any of the following difficulties with your regular daily activities or work as a result of any **physical** problems? (Please answer **YES** or **NO** for each question by circling 1 or 2 on each line)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.</td>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
</tr>
<tr>
<td>15.</td>
<td>Accomplished less than you would like</td>
<td>1</td>
</tr>
<tr>
<td>16.</td>
<td>Were limited in the kind of work or other activities you do</td>
<td>1</td>
</tr>
<tr>
<td>17.</td>
<td>Had difficulty performing the work or other activities you do (for example, it took extra effort)</td>
<td>1</td>
</tr>
<tr>
<td>18.</td>
<td>Did your work or other activities less carefully than usual</td>
<td>1</td>
</tr>
</tbody>
</table>

15-23. During the **past 4 weeks**, have you had any of the following difficulties with your regular daily activities or work as a result of any **emotional** problems (such as feeling depressed or anxious)? (Please answer **YES** or **NO** for each question by circling 1 or 2 on each line)

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.</td>
<td>Cut down on the amount of time you spent on work or other activities</td>
<td>1</td>
</tr>
<tr>
<td>20.</td>
<td>Accomplished less than you would like</td>
<td>1</td>
</tr>
<tr>
<td>21.</td>
<td>Were limited in the kind of work or other activities you do</td>
<td>1</td>
</tr>
<tr>
<td>22.</td>
<td>Had difficulty performing the work or other activities you do (for example, it took extra effort)</td>
<td>1</td>
</tr>
<tr>
<td>23.</td>
<td>Did your work or other activities less carefully than usual</td>
<td>1</td>
</tr>
</tbody>
</table>
24. How much *bodily pain* have you had during the **past 4 weeks**?

<table>
<thead>
<tr>
<th>(Circle one number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
</tr>
<tr>
<td>Very mild</td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Very severe</td>
</tr>
</tbody>
</table>

25. During the **past 4 weeks**, how much did *bodily pain* interfere with your normal work (including both work outside the home and housework)?

<table>
<thead>
<tr>
<th>(Circle one number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
</tr>
<tr>
<td>A little bit</td>
</tr>
<tr>
<td>Moderately</td>
</tr>
<tr>
<td>Quite a bit</td>
</tr>
<tr>
<td>Extremely</td>
</tr>
</tbody>
</table>

26. During the **past 4 weeks**, to what extent have your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

<table>
<thead>
<tr>
<th>(Circle one number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not at all</td>
</tr>
<tr>
<td>Slightly</td>
</tr>
<tr>
<td>Moderately</td>
</tr>
<tr>
<td>Quite a bit</td>
</tr>
<tr>
<td>Extremely</td>
</tr>
</tbody>
</table>
These questions are about how you feel and how things have been for you during the past 4 weeks. For each question, please indicate the one answer that comes closest to the way you have been feeling.

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>27. Did you feel 'full of pep'?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>28. Have you been a very nervous person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>29. Have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>30. Have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>31. Did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>32. Have you felt downhearted and blue?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>33. Did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>34. Have you been a happy person?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>35. Did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
### Questionnaire Data

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>36. Has your epilepsy limited your social activities (such as visiting with friends or close relatives)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>37. Have you had difficulty concentrating and thinking?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>38. Did you have trouble keeping your attention on an activity for long?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>39. Were you discouraged by problems related to your health?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>40. Have you worried about having another seizure?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>41. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>42. Were you discouraged by your epilepsy-related problems?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>43. Have your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
44–48. Please choose the answer that best describes how **TRUE** or **FALSE** each of the following statements is for you. (Circle one number on each line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely true</th>
<th>Mostly true</th>
<th>Not sure</th>
<th>Mostly false</th>
<th>Definitely false</th>
</tr>
</thead>
<tbody>
<tr>
<td>44. I seem to get sick (any kind of sickness) a little easier than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>45. I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>46. I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>47. My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>48. When there is an illness going around, I usually catch it</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
49. How has the QUALITY OF YOUR LIFE been during the past 4 weeks (that is, how have things been going for you)?

(Circle one number)

1. Very well: could hardly be better

2. Pretty good

3. Good & bad parts about equal

4. Pretty bad

5. Very bad: could hardly be worse
The following question is about **MEMORY** (Circle one number)

<table>
<thead>
<tr>
<th></th>
<th>Yes, a great deal</th>
<th>Yes, somewhat</th>
<th>Only a little</th>
<th>No, not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>50. In the past 4 weeks, have you had any trouble with your memory?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

51–54: Circle one number for **how often** in the **past 4 weeks** you have had trouble remembering or **how often** these memory problems have interfered with your normal work or living.

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>51. Names of people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>52. Where you put things</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>53. Things people tell you</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>54. Things you read hours or days before</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

55–59: The following questions are about **LANGUAGE** problems you may have. Circle one number for **how often** you have trouble speaking or **how often** these problems have interfered with your normal work or living.

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>55. Finding the correct word</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>56. Understanding what others are saying in conversation</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>57. Understanding directions</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>58. Understanding what you read</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>59. Writing</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
60-64: The following questions are about **concentration** problems you may have. Circle one number for **how often in the past 4 weeks** you had trouble concentrating or how often these problems interfered with your normal work or living.

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>Concentrating on conversations</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>61</td>
<td>Concentrating on a task or job</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>62</td>
<td>Concentrating on reading</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>63</td>
<td>Concentrating on doing one thing at a time</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>64</td>
<td>How often do you feel you react slowly to things that are sad or done?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

65-68: The following questions are about problems you may have with certain **activities**. Circle one number for **how much** during the past 4 weeks your epilepsy or antiepileptic medication has caused trouble with...

<table>
<thead>
<tr>
<th>Activity</th>
<th>A great deal</th>
<th>A lot</th>
<th>Somewhat</th>
<th>Only a little</th>
<th>Not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>65       Working</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>66       Friendships and relationships (romantic)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>67       Leisure time (such as hobbies, going out)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>68       Driving</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
69-73: The following questions relate to the way you feel about your seizures. (Circle one number on each line)

<table>
<thead>
<tr>
<th>Question</th>
<th>Very fearful</th>
<th>Somewhat fearful</th>
<th>Not very fearful</th>
<th>Not fearful at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>69. How fearful are you of having a seizure during the next month?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>70. Do you worry about hurting yourself during a seizure?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>71. How worried are you about embarrassment or other social problems resulting from having a seizure during the next month?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>72. How worried are you that medications you are taking will be bad for you if taken for a long time?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>73. How well do you do with complicated projects that require organization or planning?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
74-80. For each of these PROBLEMS, circle one number for how much they bother you on a scale of 1 to 5, where 1 = Not at all bothersome, and 5 = Extremely bothersome.

<table>
<thead>
<tr>
<th>74.</th>
<th>Seizures</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>75.</td>
<td>Memory difficulties</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>76.</td>
<td>Driving limitations</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>77.</td>
<td>Work limitations</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>78.</td>
<td>Social limitations</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>79.</td>
<td>Physical effects of antiepileptic medication</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>80.</td>
<td>Mental effects of antiepileptic medication</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

81-83. In terms of your satisfaction with your family and social life, circle one number to indicate the following:

<table>
<thead>
<tr>
<th>81.</th>
<th>The amount of togetherness you have with your family and/or friends</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very good</th>
<th>Excellent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>82.</td>
<td>The support and understanding your family and/or friends give each other</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>83.</td>
<td>The amount you talk things over with your family and/or friends</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
84–88: In terms of your satisfaction with your family and social life, circle one number to indicate the following:

<table>
<thead>
<tr>
<th>Very satisfied</th>
<th>Somewhat satisfied</th>
<th>Neither satisfied nor dissatisfied</th>
<th>Somewhat dissatisfied</th>
<th>Very dissatisfied</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

85. How limited are your social activities compared with others your age because of your epilepsy or epilepsy-related problems?

<table>
<thead>
<tr>
<th>Much more limited</th>
<th>Somewhat more limited</th>
<th>About the same</th>
<th>Somewhat less limited</th>
<th>Much less limited</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

86. During the past 4 weeks, was someone available to help you if you needed and wanted help?

<table>
<thead>
<tr>
<th>Yes, as much as wanted</th>
<th>Yes, quite a bit</th>
<th>Yes, some</th>
<th>Yes, a little</th>
<th>No, not at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

87. How much of the time during the past 4 weeks did you feel left out?

<table>
<thead>
<tr>
<th>All of the time</th>
<th>Most of the time</th>
<th>A good bit of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>

88. During the past 4 weeks, how often did you feel isolated from others?

<table>
<thead>
<tr>
<th>Always</th>
<th>Very often</th>
<th>Fairly often</th>
<th>Sometimes</th>
<th>Almost never</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
How good or bad do you think your health is? On the thermometer scale below, the best imaginable state of health is 100 and the worst imaginable state is 0. Please indicate how you feel about your health by circling one number on the scale. Please consider your epilepsy as part of your health when you answer this question.

100 = Best imaginable health state
90
80
70
60
50
40
30
20
10
0 = Worst imaginable health state (as bad as or worse than being dead)
Comments (if any)

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