Surgical treatment of drug-resistant focal epilepsy: selection, economic considerations and long-term outcomes

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Declarations

Declaration of originality

I, Anthony Chong Kwan Khoo, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Statement of contributions

Professor John Duncan supervised the preparation of this thesis. Elements from Chapter 3 and Chapter 5 draw upon data from the UCLH Epilepsy Surgery database that has been updated for many years by Ms Jane de Tisi, Epilepsy Data Manager at The National Hospital for Neurology and Neurosurgery. Dr Ali Alim-Marvasti performed the preliminary analysis with the Semiology Visualisation Tool used in Chapter 6. Ms Lauren Martin assisted with the tariff interpretation in Chapter 7. All other work presented in this thesis is my own, and all sources of information derived from the work of others have been appropriately referenced.

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Publications

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Presentations

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Abstract

Epilepsy surgery can be an effective treatment for drug-resistant focal epilepsy, but requires careful selection of appropriate candidates to achieve optimal results and minimise the chance of adverse outcomes, including seizure recurrence. Long-term data on multimodal outcomes and a better appreciation of various factors influencing surgical suitability will help facilitate informed discussions between clinicians and prospective surgical candidates.

This thesis includes a comprehensive analysis of a cohort of individuals who had epilepsy surgery at a tertiary neurosciences centre over the last 30 years, supplemented by data on individuals who completed presurgical evaluation at the same centre but did not proceed to surgical resection.

An inability to localise the epileptogenic zone (EZ), multifocal epilepsy, or an individual choice not to have either intracranial electroencephalography or surgery were the most common reasons why people referred for presurgical evaluation did not proceed to a definitive resection. A predictive model based on demographic, imaging and electroclinical data was constructed to assist early discussions about surgical suitability. Those with normal MRI, extratemporal epilepsy and evidence of bilateral seizure onsets on video telemetry had an estimated 2.9% chance of proceeding to surgery, and people with a normal MRI brain invariably required intracranial EEG.

Frontal lobe epilepsy surgery was safe and effective, with a long-term (median seven years) seizure freedom rate of 27%, and another 11% having auras only. Psychiatric comorbidity frequently improved postoperatively and paralleled seizure freedom. Focal MRI abnormality and fewer anti-seizure medications at the time of surgery could help predict a good outcome. In contrast, the site of resection and intracranial monitoring were not independently significant. Localisation of the EZ should rely on clinical features and multimodal investigation, as in our cohort frontal lobe semiology alone could correctly lateralise the EZ in only 77% and localise to a sublobar level in 52%.

For those who completed presurgical evaluation but did not have surgery, under 5% had >12 months of seizure-freedom following the decision not to proceed, although a quarter had substantial improvement with further anti-seizure medication (ASM) or neurostimulation.

Evaluation for epilepsy surgery was lengthy for individuals and costly for the public health system. Both duration and cost depended on what investigations were required and varied according to different routes through the presurgical pathway, especially the need for intracranial EEG. The median duration of evaluation was 29.7 months (IQR 18.6-44.1 months), with a median cost per person of £9,138 (IQR £6,984-£14,868). Approximately £123,500 was spent per additional person seizure-free.

Impact Statement

Epilepsy is the fourth most common neurological disorder in the world. Approximately a third of people with epilepsy continue to have seizures despite medication, and are at increased risk of premature death, most commonly through direct accident and injury or Sudden Unexpected Death in Epilepsy (SUDEP).

Surgery to remove the part of the brain responsible for causing seizures can be an effective cure for certain people. There is increasing demand for this treatment, however it is a major undertaking that requires extensive evaluation that can span several years. Of those who complete evaluation, over half do not proceed to surgery.

This work has examined why people who complete presurgical evaluation do not have surgery, and helped to create a model that can help predict the chance of a person proceeding to surgery based on individual data. This will help guide early discussions with people with drug-resistant epilepsy and help them decide whether they want to pursue investigation, including the likelihood of needing invasive tests. We also report seizure outcomes seen in people who complete presurgical evaluation but do not have an operation.

Epilepsy surgery involving the frontal lobe of the brain is much less common than surgery involving the temporal lobes, and outcomes are less well described. We report seizure outcomes, changes in psychiatric function, and levels of

socioeconomic deprivation observed in people who have had frontal lobe epilepsy surgery at our centre over the last 30 years. This adds to global data that provides information to help guide decision-making on who should have frontal lobe epilepsy surgery and their likely outcomes. We also examine the value of observed and experienced seizure manifestations, or ‘semiology’, in this group of people and how well this can help predict where seizures may be originating from within the brain.

Lastly, we perform an economic evaluation using National Health Service tariffs in the UK to estimate the cost and time taken to evaluate people for epilepsy surgery at a tertiary hospital in London. This information helps provide valuable data to healthcare administrators who may be involved in developing or establishing epilepsy surgery programs, within the UK and worldwide.

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
aOR	Adjusted odds ratio
ASM	Anti-Seizure Medication
BMI	Body mass index
CI	Confidence interval
CSF	Cerebrospinal fluid
DBS	Deep brain stimulation
DNT	Dysembryoplastic neuroepithelial tumour
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalogram
ESGS	Epilepsy Surgery Grading Scale
ETLE	Extratemporal lobe epilepsy
EZ	Epileptogenic zone
FCD	Focal cortical dysplasia
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FLE	Frontal lobe epilepsy
FMRI	Functional magnetic resonance imaging
FTBTCS	Focal to bilateral tonic-clonic seizures
GABA	Gamma-aminobutyric acid
GEFS+	Genetic epilepsy with febrile seizures plus
GGE	Genetic generalised epilepsy
GTCS	Generalised tonic-clonic seizures
HRQOL	Health related quality of life
HS	Hippocampal sclerosis
icEEG	Intracranial electroencephalography
ILAE	International League Against Epilepsy
IMD	Index of multiple deprivation
IQR	Interquartile range

LITT	Laser interstitial thermotherapy
MDT	Multidisciplinary team
MEG	Magnetoencephalography
MRI	Magnetic Resonance Imaging
mTOR	Mammalian target of rapamycin
NHNN	National Hospital for Neurology and Neurosurgery
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NSQIP	National Surgical Quality Improvement Program
OR	Odds ratio
PET	Positron emission tomography
PGP	P-glycoprotein
PNES	Psychogenic non-epileptic seizure
RCT	Randomised controlled trial
SANAD	Standard and New Antiepileptic Drugs trial
SDE	Subdural electrodes
SEEG	Stereoelectroencephalography
SMA	Supplementary motor area
SMR	Standardised Mortality Ratio
SPECT	Single-photon-emission computed tomography
SUDEP	Sudden Unexpected Death in Epilepsy
SV2A	Synaptic vesicle 2A
SVT	Semiology Visualisation Tool
TLE	Temporal lobe epilepsy
UCLH	University College London Hospitals
UK	United Kingdom
VNS	Vagus nerve stimulation

Table of Contents

List of Figures

List of Tables

Chapter 1: General Introduction

1.1 What is epilepsy: a historical context

Epilepsy is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures (Fisher et al., 2005). It is a common neurological condition that affects people of all ages, races, social classes and geographical locations. These individuals frequently report decreased quality of life and suffer from increased rates of premature death, particularly in the absence of seizure freedom (Beghi et al., 2019, Mbizvo et al., 2019, Shorvon and Tomson, 2011).

Knowledge of epilepsy as a disease entity has existed for at least three millennia. Very early texts, such as Babylonian tablets from around 1067-1046 BC, depict different types of seizures, which were initially thought to be ailments due to the supernatural (Wolf, 2014). The understanding that epilepsy may be a natural condition driven by a disorder of the nervous system was first advocated by Hippocrates around 450 BC, but only in the last few centuries have advances in medical research effectively emancipated the condition from religious and spiritual superstition (Magiorkinis et al., 2014).

It is postulated that the prehistoric practice of trephination, whereby a hole was made in the skull, may have originated as a method of treating epilepsy. While this is difficult to prove, medical documents from the second century describe trephination as a possible treatment for seizures, among other neurological conditions (Wolf, 2014, Finger and Clower, 2001). Such early surgical

approaches suggest a search for rational explanations for symptoms and a scientific approach toward treatment. If trephination was indeed a procedure aimed at treating epilepsy, it is clear from examining partially healed skulls that at least some individuals survived this form of surgery (Magiorkinis et al., 2014). The success of these procedures is otherwise poorly described.

These historical aspects provide important context into the evolving nature of epilepsy classification and our understanding into why seizures occur. This is central to our ability to provide tailored treatment for individuals with epilepsy, and in selected cases epilepsy surgery. An underlying cause for epilepsy is only identified in approximately half of those with the condition. For the remainder, the reasons why seizures occur are unknown, although likely to result from a complex interaction between a number of susceptibility genes (Mulley et al., 2005, Perucca et al., 2020).

1.2 Classification of seizures and epilepsy

A seizure (from the Latin *sacire* – "to take possession of") is defined as a transient occurrence of signs and/or symptoms due to abnormal, excessive or synchronous neuronal activity in the brain (Fisher et al., 2005). Seizures can manifest with diverse symptoms, reflecting involvement of different brain areas. As our knowledge of the structure and function of different brain areas has developed, our ability to predict where seizures originate from in each individual case has improved (Chowdhury et al., 2021, Beniczky et al., 2022).

While all people with epilepsy experience seizures, not all who have seizures have epilepsy. This distinction is crucial in understanding which individuals require long-term treatment with medication or are potential candidates for epilepsy surgery. Seizures may occur in the context of an acute disturbance affecting the brain, including direct insults such as stroke, trauma or encephalitis, but can also occur as a consequence of systemic illness or metabolic derangements. These seizures, currently referred to as acute symptomatic or provoked seizures, are manifestations of the acute condition, and seizures will not necessarily recur once the underlying pathology has been treated. This is in contrast to those with a diagnosis of epilepsy, who remain at higher risk of seizures than the general population, and often require long-term and sometimes lifelong medication.

Multiple classifications of epilepsy have been proposed. Since 1964, the International League Against Epilepsy (ILAE) has published consensus statements to standardise the descriptions of seizures and various epilepsy categories, with the latest revision published in 2017 (Fisher et al., 2017). Currently, an individual is diagnosed with epilepsy if they satisfy at least one of the following conditions:

a) At least two unprovoked seizures occurring >24 hours apart, or
b) One unprovoked seizure where there is a >60% chance of seizure recurrence over the next 10 years, or
c) An epilepsy ‘syndrome’ can be identified, defined as a characteristic cluster of clinical and EEG features, often supported by specific

aetiological findings such as a pathogenic genetic abnormality (Wirrell et al., 2022).

An unprovoked seizure in this context refers to a seizure that occurs in the absence of precipitating factors such as drug or alcohol use, and does not refer to acute symptomatic seizures. Prediction on whether an individual's risk of seizures exceeds 60% revolves around identifying abnormalities in brain structure or function, achieved in most instances through the use of neuroimaging and electroencephalography (EEG). Epilepsy 'syndromes' are included in the classification and refer to distinctive electroclinical combinations of features that define a clinical disorder (Berg et al., 2010, Wirrell et al., 2022). These syndromes often have a genetic basis, for example sleep-related hypermotor epilepsy (previously termed autosomal dominant nocturnal frontal lobe epilepsy) or Dravet syndrome. While these individuals invariably experience seizures, there is much phenotypic variability, and penetrance of the genetically-determined epilepsies is often incomplete (Ding et al., 2021). The genetics behind epilepsy syndromes is discussed in further detail in Chapter 1.4.

Neuroimaging and EEG are often used in conjunction with semiology, which refers to the clinical signs of a seizure, in helping to classify what form of epilepsy an individual has. The ILAE has now provided an operational classification of seizures and epilepsy, which aims to be understandable to the public and applicable to all ages (Fisher et al., 2017, Scheffer et al., 2017).

This operational classification begins with determining if initial manifestations arise from a single region of the brain and are therefore of ‘focal’ onset, or if they are ‘generalised’, suggesting the seizure engages bilateral networks from seizure onset. Seizures are then further divided into those that affect a person’s awareness of self or environment and are termed ‘impaired awareness’ seizures, and those that do not (focal aware seizures). There can be motor components to seizures, for example tonic or clonic movements, loss of muscle tone (atonic seizures) or myoclonus, or a variety of non-motor manifestations such as behavioural arrest or perceptual abnormalities, including gustatory or olfactory hallucinations. The term ‘focal-to-bilateral tonic-clonic seizures’ (FTBTCS) refers to focal onset seizures that begin in one area but subsequently propagate to involve bilateral networks. The current ILAE classification of seizures is shown below in Figure 1.1.

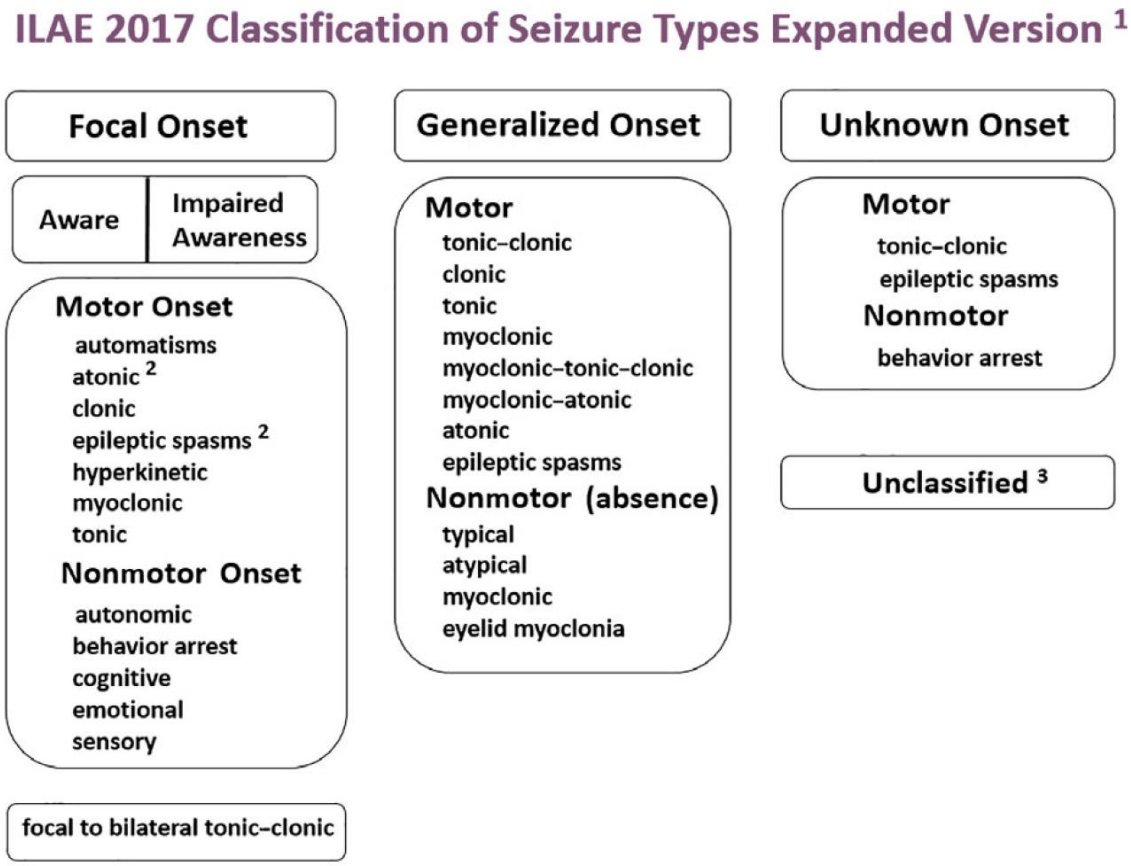

Figure 1.1: Classification of seizure types. *From:* Fisher et al. 2017. *Epilepsia.* Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Used with permission.

1.3 Focal Epilepsy

Focal epilepsy is the most common epilepsy syndrome in children and adults (Beghi et al., 2019). Seizures most commonly arise from the temporal lobe, with these individuals being described as having temporal lobe epilepsy (TLE). Seizures can also arise from extratemporal regions, including the frontal, parietal or occipital lobes. Depending on their origin, and which brain areas are activated during seizures – the so-called symptomatogenic zone – the observed characteristics of a seizure often differ.

The neurologist Hughlings Jackson (1835-1911) recognised these clinico-

anatomic correlations over 150 years ago, and described a variety of observations associated with temporal lobe seizures, which he originally termed ‘uncinate fits’. These attacks were characterised by ‘a crude sensation of smell’, fear, and what he labelled a ‘dreamy’ state, which one patient described as a sensation he ‘were saying, doing, and looking at things he had experienced before’, reminiscent of déjà vu (Jackson and Stewart, 1899). All these symptoms, which are now well recognised as focal aware seizures, have been mapped on intracranial EEG studies as originating from mesiotemporal structures within the brain (Maillard et al., 2004, Chauvel et al., 2019).

Focal epilepsy may arise from various genetic, structural, metabolic, immune or infectious causes (Scheffer et al., 2017). In approximately 70% of cases a structural abnormality can be visualised on neuroimaging with MRI at 1.5 or 3 Tesla field strength (Muhlhofer et al., 2017). These abnormalities are thought to give rise to seizure generation through a variety of neuronal mechanisms that lead to paroxysmal excitatory activity (Pitkänen et al., 2015). Animal studies, which have primarily focussed on hippocampal neurons, implicate a loss of inhibitory circuitry, such as may occur with loss of hilar mossy cells that excite inhibitory neurons in the dentate gyrus (Sloviter, 1991, Cronin et al., 1992). The role of other mechanisms such as pro-epileptogenic cytokine release (Siebenbrodt et al., 2022, Xu et al., 2013) and altered gene expression (Kumar et al., 2022, Perucca et al., 2020) are also being explored. It is likely that combinations of various factors result in paroxysmal changes in neuronal function that manifest as epileptic seizures.

Even with high definition 7 Tesla MRI, approximately 70% of those with 'MRI-negative' focal epilepsy do not have a visible abnormality to explain their seizures (De Ciantis et al., 2016). This suggests that abnormal molecular mechanisms leading to neuronal hyperexcitability can occur even in the absence of a macroscopic lesion. Increasingly, focal epilepsy is being conceptualised as a network disorder. These networks refer to interconnected brain areas that interact dynamically to produce seizure activity (Gil et al., 2020, Chauvel et al., 2019). This may explain why individuals who have abnormal areas of brain resected can still continue to experience seizures after epilepsy surgery.

1.4 Genetic determinants of epilepsy

In recent decades there has been a growing understanding of the genetics that underpin many epilepsy syndromes. In 2018, the ILAE Consortium on Complex Epilepsies published the most comprehensive genome-wide analysis to date, involving 15,212 individuals with epilepsy and 29,667 controls (International League Against Epilepsy, 2018). In this analysis, 16 risk loci for epilepsy were detected, the majority of which were associated with genetic generalised epilepsy (GGE). These syndromes, which are clinically characterised by combinations of myoclonic, absence or generalised tonic-clonic seizures, make up most of the generalised epilepsy syndromes (Figure 1.1). The genetic architecture of these conditions is complex, and most epilepsy syndromes result from the interplay of multiple susceptibility genes (Speed et al., 2014, Perucca et al., 2020, Mulley et al., 2005).

In contrast, monogenic forms of epilepsy are described in only a minority of cases, accounting for approximately 2% of idiopathic epilepsy (Nicita et al., 2012, Perucca et al., 2020). These can cause both generalised or focal epilepsy syndromes, and the first gene described was a missense variant in *CHRN4,* encoding the neuronal nicotinic acetylcholine receptor a4 subunit, which was found to cause autosomal dominant nocturnal frontal lobe epilepsy in an Australian pedigree in the mid-1990s (Steinlein et al., 1995). Many other genes have since been described with Mendelian forms of inheritance, most involving ion-channel genes (Perucca et al., 2020). The most common is *SCN1A,* which encodes voltage-gated sodium channel subunit 1A, however others involve voltage-gated potassium channels (eg. *KCNQ2* and *KCNQ3*), ligand-gated ion channels (eg. *CHRNA4* and *GABRG2*) or the mammalian target of rapamycin (mTOR) pathway (eg. *DEPDC5*) (Dibbens et al., 2013).

Notably, genotype-phenotype associations in many monogenic epilepsies remain broad and heterogenous (Nicita et al., 2012). Tuberous sclerosis, for example, is associated with mutations in *TSC1* or *TSC2,* which leads to hyperactivation of the mTOR pathway and is a condition characterised histopathologically by malformations of cortical development. *DEPDC5* mutations, which also influence the mTOR pathway, can be associated with malformations of cortical development, but also non-lesional focal epilepsy where no MRI abnormality is identified, and individuals within the same family can have epilepsy of different severity (Dibbens et al., 2013, Scheffer et al., 2014). Individuals with *SCN1A* can

manifest a range of phenotypes – for example Dravet syndrome, characterised by an intractable epileptic encephalopathy, to much milder cases of genetic epilepsy with febrile seizures plus (GEFS+) or even a variety of non-epilepsy related diseases such as hemiplegic migraine (Ding et al., 2021).

Genetic testing is not routinely performed as part of the presurgical evaluation of adults with drug-resistant epilepsy. There is nonetheless an emerging role for such testing in adult epilepsy, particularly for those with comorbid intellectual disability and childhood-onset seizures (Johannesen et al., 2020, McKnight et al., 2022). Uncovering a genetic diagnosis may lead to changes in management, for example avoidance of sodium channel blockers in *SCN1A* epilepsy, early consideration of clobazam in *PCDH19* epilepsy, and use of carbamazepine or oxcarbazepine in *PRRT2* associated epilepsy (McKnight et al., 2022, Li et al., 2022b). Curative surgery is rarely effective for individuals with epilepsy due to genes associated with channel function and synaptic transmission (Stevelink et al., 2018, Sanders et al., 2019). Outcomes are more favourable in those with mutations in the mTOR pathway, particularly if a lesion is present on MRI (Stevelink et al., 2018, Sanders et al., 2019). The range of surgical procedures performed for drug-resistant epilepsy are discussed in detail in Chapter 1.9.

1.5 Global burden of epilepsy

Neurological disorders are the leading cause of disability and second leading cause of death worldwide (Feigin et al., 2019). Approximately 50 million individuals worldwide have active epilepsy, with either uncontrolled seizures or the need to take ongoing treatment. Epilepsy is the fourth most common neurological condition after migraine, stroke and Alzheimer's disease (World Health Organization, 2021, Feigin et al., 2021, Stovner et al., 2018). Globally, five million people are diagnosed with epilepsy yearly (Beghi et al., 2019). Age-standardised mortality rates for epilepsy have been estimated to be 1.74 per 100,000, and death is more likely in those with uncontrolled seizures (Beghi et al., 2019, Shorvon and Tomson, 2011).

Mortality in those with epilepsy can occur for diverse reasons and is under-recognised (Devinsky et al., 2017, Harowitz et al., 2021). Seizures are unpredictable and can cause death from drowning, motor vehicle or bicycle accidents, falls, burns or other seizure-related accidents (Devinsky et al., 2016). Status epilepticus, which in clinical practice is defined as a seizure that lasts longer than 5 minutes, or having more than a single seizure without returning to a normal level of consciousness in between (Lowenstein et al., 1999), can lead to irreversible brain damage or death as a consequence of cerebral hypoxia (Betjemann et al., 2015, Chen and Wasterlain, 2006).

Sudden unexpected death in epilepsy (SUDEP) refers to deaths in people with epilepsy that are not caused by injury, drowning or other known causes. SUDEP

is the leading cause of premature death in epilepsy, accounting for 10-50% of cases (Shorvon and Tomson, 2011). It has an incidence of 1-2/1000 person-years in people with chronic epilepsy, but is substantially higher in those with severe, recurrent seizures (Shorvon and Tomson, 2011). Frequency of generalised tonic-clonic seizures (GTCS) is the most important risk factor for SUDEP, however other risk factors include multiple ASMs, duration of epilepsy and male gender (Hesdorffer et al., 2011, Shorvon and Tomson, 2011). Compared to those without GTCS on monotherapy, odds of SUDEP are increased five-fold in those having 1-2 GTCS/year, and 25-fold in those with >3 GTCS/year and polytherapy (Hesdorffer et al., 2011). This highlights the necessity of trying to render people seizure-free, particularly from convulsive seizures.

Standardised mortality ratios among people with epilepsy indicate individuals are approximately three times more likely to suffer from premature death, even in developed countries like the United States, Australia and the United Kingdom (Neligan et al., 2011, Puteikis and Mameniškienė, 2021, Chen et al., 2016, Foster et al., 2020). In less developed areas of the world, where epilepsy prevalence is highest, premature all-cause mortality in people with epilepsy can be five to ten times higher than in those without epilepsy (Mbizvo et al., 2019). This is likely due to a range of issues, but in particular limited access and availability to neurological services. The total number of neurologists and neurosurgeons is estimated at 9 per 100,000 in Europe, but only 0.3 per 100,000 in South-East

Asia and 0.1 per 100,000 in Africa, highlighting stark geographic disparities in the neurological workforce (World Health Organization, 2017).

In addition to mortality, epilepsy is associated with substantial morbidity, particularly for those with ongoing seizures. Approximately a third of individuals suffer from major depression, and other neuropsychiatric conditions like bipolar and attention-deficit/hyperactivity disorder are more than twice as prevalent compared to those without epilepsy (Ottman et al., 2011, Li et al., 2022a). Rates of suicide are approximately three times higher in people with epilepsy (Bell et al., 2009, Guo et al., 2021), and individuals are twice as likely to suffer from anxiety and panic disorders (Hermann et al., 2008, Christensen et al., 2007).

People with epilepsy consistently report higher unemployment rates, lower income, lower education and being single compared to those without epilepsy (Hermann et al., 2008). Those with uncontrolled seizures cannot safely drive and may experience a degree of social stigma. The economic burden of epilepsy stems from not only the direct costs associated with the disease, which includes hospital admission following seizures, cost of antiseizure medication, and investigation for causes of epilepsy, but also a huge range of indirect costs. These include downstream effects from loss of productivity or employment and consequences of physical and psychiatric comorbidity. The indirect costs of epilepsy (such as cost of unemployment) are challenging to quantify but likely dwarf the direct costs of the condition (Allers et al., 2015). The Global Cost of Epilepsy Task Force, established by the ILAE, have recently estimated the

annual cost of epilepsy worldwide at approximately 120 billion US dollars per year (Begley et al., 2022). Even in countries with ostensibly universal healthcare coverage like Australia and the UK, a variety of out-of-pocket costs, such as unpaid care and transportation to medical centres contribute to substantial economic burden. In resource-poor areas, where epilepsy prevalence is highest, the economic burden associated with epilepsy drives higher rates of poor medication adherence, hospital attendance and treatment abandonment, contributing to the higher mortality rates in these regions (Radhakrishnan, 2009).

Seizure freedom is considered the most important factor influencing morbidity, with seizure-free individuals having health-related quality of life (HRQOL) levels comparable to the general population (Leidy et al., 1999). The association between seizure reduction and quality of life is less robust, with some studies suggesting that seizure freedom (rather than just reduced seizure frequency) is imperative for significant improvements in HRQOL to occur (Birbeck et al., 2002). Others have shown that seizure severity and frequency are independently associated with poorer quality of life (Bautista and Tannahill Glen, 2009). Many anti-seizure medication drug trials use clinical endpoints of a >50% reduction in seizure frequency to determine efficacy. A recent population-based analysis in Australia using epilepsy prevalence, mortality and productivity data estimated substantial morbidity, mortality and economic benefits could be obtained with increasing seizure-freedom rates by as little as 5% (Foster et al., 2020).

1.6 Medical management of epilepsy

Antiseizure medication (ASM) is the mainstay of treatment for epilepsy, and results in seizure freedom in approximately 70% of individuals. These drugs suppress symptoms (seizures) rather than the underlying disease. The primary aim of ASM therapy is to maximise seizure control, and ideally produce seizure freedom, without significant side effects or drug toxicity.

Antiseizure medications are often required to be used long-term. As such, meticulous selection of the appropriate drug is necessary from the outset, based on the likely efficacy tailored to the epilepsy phenotype and the possible side effect profile. Initial selection is usually based on whether the individual is thought to suffer from focal or generalised epilepsy, highlighting the need to carefully examine seizure semiology in conjunction with investigations such as EEG and neuroimaging. An example of an EEG demonstrating a focal onset seizure originating in the left temporal lobe is demonstrated in Figure 1.2.

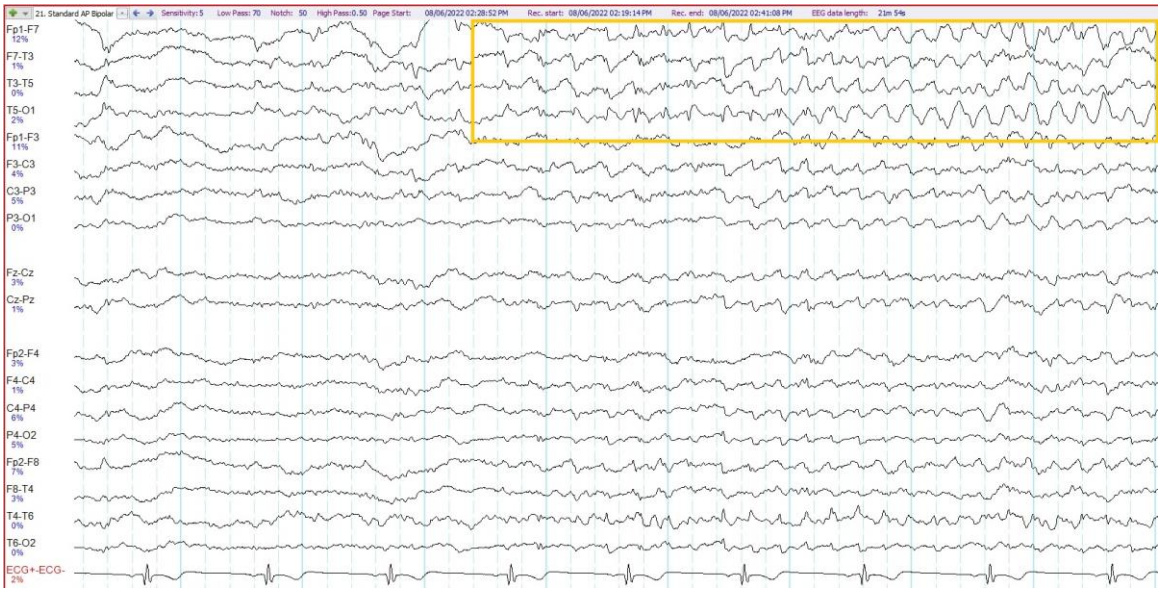

Figure 1.2: Scalp-EEG showing an electrographic seizure of left temporal onset (yellow box) in a 20-year-old man with a new diagnosis of epilepsy and normal MRI brain.

Before 2000, the medications used most frequently for treating epilepsy were barbiturates, phenytoin or sodium valproate for idiopathic generalised epilepsy and carbamazepine for focal epilepsy (Leach et al., 2001). These prescribing practices had been mainly influenced by early drug trials in the 1980s and 1990s, although no clear differences in efficacy between these medications had been established (Leach et al., 2001).

The standard and new antiepileptic drugs trial (SANAD-1) began in 1999, with results published in 2007 comparing the effectiveness and cost-effectiveness of different ASMs available. SANAD-1 established lamotrigine as an effective, non-inferior first-line alternative to carbamazepine for focal epilepsy (Marson et al., 2007a). It also suggested valproate should remain first-line for those with generalised or unclassified epilepsies (Marson et al., 2007b).

Subsequently, the SANAD-2 study was published in 2021, comparing lamotrigine, levetiracetam and topiramate for focal epilepsy and valproate with levetiracetam for generalised epilepsy. This trial now forms the basis of current practice, with lamotrigine considered first-line for focal epilepsy and valproate first-line for generalised epilepsy (Marson et al., 2021b, Marson et al., 2021a), although considerations such as teratogenic risk – which is substantially higher with valproate compared to other ASMs – influence drug choice. Medications are usually started at low doses, and subsequently titrated to effect or tolerability. Individuals who continue to have seizures despite being on a single adequately dosed ASM can be started on a second ASM, either replacing the first medication

or used in combination (if the initial ASM had been partially effective).

An important consideration when deciding ASM use relates to each drug's mechanism of action and pharmacodynamic properties. There are four main mechanisms of action for ASMs. Medications such as phenytoin or carbamazepine (and its derivatives oxcarbazepine and eslicarbazepine) act primarily by enhancing fast inactivation of sodium channels, which are responsible for the generation and propagation of action potentials in neurons (Macdonald and Kelly, 1995). Others, such as benzodiazepines and phenobarbital bind to gamma-aminobutyric acid (GABA) receptors and enhance binding of GABA, a neurotransmitter that exerts postsynaptic inhibition. Medications like topiramate and perampanel act through antagonism of the excitatory neurotransmitter glutamate (topiramate also increases GABA activity) (Hanada et al., 2011). Lastly, medications such as pregabalin, gabapentin or ethosuximide affect calcium channels and attenuate neurotransmitter release. Many medications act via several of these methods. Others have novel mechanisms of action, such as levetiracetam or brivaracetam, which bind to the synaptic vesical SV2A receptor, or lacosamide, which enhances slow inactivation of sodium channels (Beydoun et al., 2009).

Understanding these mechanisms of action can help appreciate potential side effects and is particularly important when considering combination therapy. Combining medications with the same mechanism of action may increase the risk of side effects (such as hyponatraemia); conversely, choosing medications with

complementary actions may increase the potential synergistic effect in suppressing seizures. It has been shown, for example, that combinations of valproate and lamotrigine may produce seizure control in those who do not respond to the highest tolerated dose of either drug given alone (Pisani et al., 1999).

Enzyme-inducing ASMs such as carbamazepine, phenytoin, phenobarbital and primidone stimulate cytochrome P450 enzymes, predominantly in the liver, which results in increased metabolism of these and a wide range of other commonly used medications. This is particularly important when these medications are ceased, as serum concentrations of concurrently administered drugs may increase to potentially toxic levels. In contrast, sodium valproate is an enzyme inhibitor, and can increase serum levels of medications metabolised by cytochrome P450 enzymes. This has been identified most strongly with lamotrigine, with lamotrigine metabolism maximally inhibited at dosages of approximately 500mg of valproate per day (Perucca, 2006). When lamotrigine is introduced to an individual already taking sodium valproate, a slower titration rate is recommended.

Potential side effects also guide ASM choice and dosing. Many ASMs are associated with teratogenic risks, with rates of major congenital malformations substantially higher than the background average in developed countries of 2-3% (Feldkamp et al., 2017, Tomson et al., 2018). Registry data involving pregnant women has shown the prevalence of major congenital malformations to be

approximately 10% for those exposed to valproate, 5-7% for those exposed to phenytoin or carbamazepine, and 2-3% for those exposed to lamotrigine or levetiracetam (Tomson et al., 2018). Prenatal exposure to valproate is also associated with an increased risk of other neurodevelopmental outcomes such as intellectual disability, autism spectrum disorder and ADHD (Meador et al., 2021, Boukhris et al., 2016). Other side effects include increased rates of osteoporosis in those taking sodium channel blockers long-term and cognitive or neuropsychiatric symptoms in those taking levetiracetam, topiramate or perampanel (Josephson et al., 2019, Mammì et al., 2022).

Antiseizure medication choice must thus be an individualised decision tailored to epilepsy classification and seizure type as well as patient-specific factors such as demographics, ASM tolerability and medical comorbidities.

1.7 Drug resistance

Despite the increasing availability of different ASMs for the symptomatic treatment of epileptic seizures, one-third of individuals with epilepsy continue to experience seizures (Kalilani et al., 2018). This phenomenon is known as drug-resistance, and is currently defined by the ILAE as failure of adequate trials of two tolerated, appropriately chosen and used ASM drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (Kwan et al., 2010a). This definition may incorrectly encompass the minority of people who subsequently become seizure-free on the third or successive medication trial although numbers of these decrease exponentially with each medication failure.

The dichotomy between ‘seizure free’ and ‘not seizure free’ reflects the current understanding that lifelong seizure freedom is the most clinically relevant outcome of any intervention for epilepsy (Duble et al., 2019, Wojewodka et al., 2021, Bauman and Devinsky, 2021). Sustained seizure freedom is generally considered to occur if no seizures have occurred for a duration at least three times greater than the longest interseizure interval prior to starting medication (Kwan et al., 2010a). Provoked and unprovoked seizures can, however, recur even in those who have experienced prolonged periods of remission (Chen et al., 2021, Contento et al., 2021).

A systematic review in 2018 suggested that younger age of seizure onset, symptomatic epilepsy (i.e. epilepsy due to some form of brain injury or dysfunction), abnormal neuroimaging, abnormal EEG, mental retardation, neuropsychiatric disorders, prolonged febrile seizures and previous status epilepticus were all associated with an increased risk of drug-resistant epilepsy (Kalilani et al., 2018). In most cases, however, it is difficult to know at the outset whether an individual will be drug-resistant, which highlights the need for careful follow-up once a diagnosis of epilepsy has been confirmed.

Various mechanisms have been proposed to underpin drug resistance (Löscher et al., 2020). One hypothesis is that acquired changes of brain structure in people with epilepsy result in altered targets for ASM binding. This ‘target hypothesis’ is primarily based on animal studies in which loss of sodium channel blockade with

medications such as phenytoin or carbamazepine has been demonstrated when studying hippocampal neurons derived from drug-resistant subjects (Remy et al., 2003). Another study examining hippocampal neurons showed that animal subjects with resistance to phenobarbital and diazepam had GABA receptors that exhibited an altered structure when compared with normal controls (Volk et al., 2006). The target hypothesis does not convincingly explain why most individuals with drug-resistant epilepsy are refractory to medications with different modes of action.

An alternative hypothesis is that of altered drug uptake in the brain. This 'transporter hypothesis' could explain why individuals resistant to two ASMs often resist other medications, regardless of the mode of action. The presence of efflux transporters such as p-glycoprotein (pgp) is readily accepted as being an important part of the 'blood-brain barrier' that plays an important role in keeping the brain an immunoprivileged site, as well as protecting the brain from the accumulation of potentially toxic substances (van Assema et al., 2012). Several studies have confirmed pgp overexpression in epileptogenic brain tissue of those with drug-resistant epilepsy (Sisodiya et al., 2002, Liu et al., 2012). This hypothesis is further strengthened by data suggesting that many ASMs such as phenytoin, valproate, lamotrigine and levetiracetam are pgp substrates (Zhang et al., 2012). Immunohistochemistry on temporal lobe brain tissue from those who have undergone temporal lobe resections for drug-resistant epilepsy have demonstrated overexpression of pgp (Kwan et al., 2010b). In addition, those who had seizure recurrence also had significantly more pgp overexpression than

those who were seizure free (Kwan et al., 2010b). To date, however, drugs such as verapamil that inhibit pgp have not had a significant impact in rendering drug-resistant individuals seizure-free (Borlot et al., 2016, Elkhayat et al., 2017, Narayanan et al., 2016).

There are several guiding principles in the clinical approach to drug-resistant epilepsy. The first step is ruling out ‘pseudoresistance’, which can occur in several situations, such as if the diagnosis is not actually epilepsy. Several epilepsy ‘mimics’ account for most misdiagnoses, such as vasovagal syncope, cardiac arrythmias, transient ischaemic attacks, migraine or psychogenic non-epileptic seizures (PNES) (Xu et al., 2016). It is estimated that at least 20-30% of people initially diagnosed with epilepsy may have an alternative diagnosis (Xu et al., 2016, Zaidi et al., 2000). This is often due to clinical overlap between these conditions. Cerebral hypoxia, which occurs in many forms of syncope, leads to loss of consciousness and many individuals also experience abnormal limb posturing.

In one video-EEG study of 65 individuals with tilt-induced syncope, abnormal posturing was seen in 42 (65%) cases and jerks in 33 (51%) (Shmuely et al., 2018). When comparing these findings with individuals with convulsive seizures, some differences in semiology were more frequently seen in syncope such as fewer jerks, loss of tone, and atonia (Shmuely et al., 2018). Nonetheless, all these findings were also seen in epileptic seizures. Furthermore, syncope and seizures may coexist in approximately a third of individuals with epilepsy (Ungar

et al., 2017).

Similarly, individuals who experience PNES, also termed dissociative seizures, are frequently misdiagnosed with epilepsy. A variety of psychogenic factors ranging from a history of trauma to personality disorders may underpin PNES (Bodde et al., 2009). While episodes may resemble epileptic seizures, there is no electrophysiologic correlate to these attacks (Bodde et al., 2009). Several semiologic features have been described that help to distinguish PNES from epileptic seizures. Pelvic thrusting, a waxing-and-waning tempo and asynchronous jerks are all seen more commonly in PNES, whereas postictal stertorous breathing and confusion are more commonly seen in epileptic seizures (Xiang et al., 2019).

Pseudoresistance to drug therapy may also occur in the setting of inadequate dosing or poor compliance with ASM therapy, which is a common cause for hospital presentation with breakthrough seizures (Khoo et al., 2020, Ernawati et al., 2018, Awan et al., 2022). Once pseudoresistance has been excluded, individuals with drug-resistant epilepsy often try further ASMs. Unfortunately, the proportion of people who respond to further medication trials having failed to respond to two previously chosen and dosed medications has remained low despite the exponential rise in new ASM. A study of 470 people between 1984 and 1997 in whom epilepsy was diagnosed and ASM initiated for the first time demonstrated that 301 (64%) were seizure-free at a median of 5 years later (Kwan and Brodie, 2000). This encompassed 47% of people who had become

seizure-free following the first ASM, an additional 13% after a second ASM and only 4% after a third or multiple other ASM (Kwan and Brodie, 2000). Individuals with a known structural cerebral abnormality were 1.5 times as likely to have a refractory disease, a finding which has been replicated elsewhere (Kwan and Brodie, 2000, Kalilani et al., 2018). Of note, newer ASMs such as levetiracetam, lacosamide, zonisamide and perampanel were not available at the time of early studies, however similar results have also been seen in a recent long-term longitudinal cohort with contemporary real-world prescribing practices (Chen et al., 2018).

A systematic review of 15 studies, including those where a wider range of 'newer' ASMs were used estimated that the prevalence of drug-resistant epilepsy was 25% (95% CI 17-32%) (Kalilani et al., 2018). The majority of epilepsy-related death and morbidity occurs in this group of people (Strzelczyk et al., 2017, Beghi et al., 2019), and therefore managing drug-resistant epilepsy continues to be a global healthcare challenge that must be further explored.

1.8 Ketogenic diet

The ketogenic diet, which consists of a high-fat (usually a minimum of 80% of total caloric intake), adequate-protein and low-carbohydrate diet, induces metabolic changes that can help reduce seizure frequency in those with drug-resistant epilepsy (Freeman et al., 2007, Green et al., 2020). Although the exact mechanism by which the ketogenic diet ameliorates seizures is not known, it has been proposed that a combination of ketone bodies generated by the starvation

state, cross the blood-brain barrier and exerts an anticonvulsant effect (Rho and Boison, 2022). It is likely, however, that more complex metabolic effects underpin the anti-seizure activity of the ketogenic diet (Rho and Boison, 2022). Ketosis increases GABA synthesis within the brain and may also upregulate energy metabolism genes in brain tissue (Bough and Rho, 2007, Rho and Boison, 2022).

Although first used in childhood epilepsy, there is also evidence that the ketogenic diet can benefit adults with drug-resistant epilepsy. In a meta-analysis of 16 studies including 338 adults with intractable epilepsy, it was estimated that 13% of individuals became seizure-free on the ketogenic diet, with a further 53% experiencing a seizure reduction of >50% (Liu et al., 2018).

Certain medical conditions may be aggravated by ketogenic diet, including renal stones, hypercholesterolaemia and liver disease. Abnormal lipid parameters are commonly seen, although long-term atherosclerotic consequences have not been extensively studied, and may be particularly relevant in adults. Side effects, including gastrointestinal symptoms (diarrhoea, constipation or gastro-oesophageal reflux) are common, and these, together with the relatively unpalatable nature of the diet, can affect long-term retention rates. In one prospective study of ketogenic diet initiation for adults with epilepsy, retention rates were 60% at three months, 43% at six months and 29% at 12 months, with side effects and the restrictive diet being common reasons for discontinuing therapy (Green et al., 2020).

1.9 Epilepsy surgery

A variety of surgical methods have been developed to treat drug-resistant focal epilepsy. Surgery encompasses potentially curative resections, which can lead to seizure freedom, and palliative techniques such as corpus callosotomy and neurostimulation, which aim to decrease the number and/or severity of seizures but rarely result in complete seizure remission. All these surgical procedures aim to reduce or eliminate the seizure burden while limiting any neurological complications or consequences of surgery.

1.9.1 Epilepsy surgery with curative intent

Anterior temporal lobe resection

Anterior temporal lobe resection is the most common resective surgery performed in specialist epilepsy centres (Rugg-Gunn et al., 2020, Rolston et al., 2016, Neligan et al., 2013). This involves resection of the anterior temporal pole, hippocampus and part of the amygdala. The first modern surgical intervention for epilepsy (discounting the ancient practice of trephination) is often attributed to Victor Horsley, who performed a cortical resection in 1886 at what is now the National Hospital for Neurology and Neurosurgery (NHNN) at Queen Square, London. Other surgeons later reported successful resections, and the advent of neuroimaging and EEG techniques have allowed more precise identification of the epileptogenic zone (EZ), which is surgically defined as “the area of cortex that is necessary and sufficient for initiating seizures and whose removal (or disconnection) is necessary for the complete abolition of seizures” (Luders et al., 1993).

Early surgeons aimed to spare the hippocampus to avoid memory disruption, however it was noted that failure to resect mesial temporal structures was often associated with poor epilepsy control. Therefore, standard anterior temporal lobe resection consists of resecting lateral and mesial temporal structures, either en bloc or separately. Removal of lateral temporal structures permits better visualisation of mesial structures such as the hippocampus. Contemporary techniques attempt to limit the size of neocortical resection, for example with the anteromedial temporal resection technique developed by Spencer et al, in which no more than 4.5 cm of the anterolateral temporal lobe is removed en bloc (Spencer et al., 1984). This has the benefit of preserving functional association areas of the lateral temporal cortex including speech and visuospatial networks.

Much of the data supporting the efficacy of anterior temporal lobe resection comes from observational studies, and these procedures are associated with long-term seizure freedom rates of approximately 50-60% (de Tisi et al., 2011). The first randomised controlled trial (RCT) of epilepsy surgery, published in 2001, enrolled 80 people with drug-resistant temporal lobe epilepsy divided equally into surgery or a medical group of ASM treatment alone (Wiebe et al., 2001). This was ethically approved as individuals at this institution typically had a one-year waiting list for epilepsy surgery, to which those allocated to the ‘medical group’ were placed. In comparison, those who were randomised for surgery underwent an expedited pre-operative evaluation and surgery within four weeks.

At one-year follow-up, individuals who had been allocated to surgery experienced significantly greater rates of complete seizure freedom than those with ASM treatment alone (38% vs 3%, p<0.001). Furthermore, significant benefits were seen in quality of life scores, and a trend toward better rates of employment and school attendance (56.4% vs 38.5%, p=0.11) was also demonstrated (Wiebe et al., 2001). There was one unexpected death in the medical group and none in the surgical group, although the small sample size makes mortality estimates unreliable. Surgical morbidity included one person who had a thalamic infarct after surgery, causing sensory abnormalities in the left thigh, one with a wound infection and two (5%) individuals with a decline in verbal memory. Asymptomatic superior sub-quadrantic visual-field defects were also seen in 22 (55%) people in the surgical group (Wiebe et al., 2001).

Following the first RCT of anterior temporal lobectomy in drug-resistant epilepsy, a second RCT (the Early Randomised Surgical Epilepsy Trial) was conducted across multiple centres in the US however recruited only 38 individuals of a planned 200 before the trial was terminated early (Engel et al., 2012). There was nonetheless a significant difference in seizure freedom demonstrated on intention-to-treat analysis, with 11/15 in the surgical group and 0/23 in the medical group seizure-free during year two of follow-up (Engel et al., 2012).

Frontal lobe resection

Frontal lobe epilepsy (FLE) surgery accounts for approximately 10-20% of epilepsy surgeries and is the second most common operation after those for TLE

(Neligan et al., 2013). Several neurosurgical techniques have been used depending on the site and extent of the planned resection. Wen et al. described low complication rates with an extensive frontal lobe decortication technique involving selective gray matter removal and preservation of the frontal horn (Wen et al., 2017). There have since been variations of this surgical technique, although the principles remain of maximising the resection of non-eloquent frontal lobe tissue while preserving eloquent cortex, including motor and speech areas (Hirata et al., 2020).

Outcomes following FLE surgery are less well described compared to those having anterior temporal lobe resection. In one cohort of 70 people, the probability of complete seizure freedom was 55.7% after the first postoperative year, 45% at three years and 30% after five years (Jehi et al., 2007). Other centres have reported higher or lower long-term (>5 years) seizure-free outcomes of between 14-53% (Samuel P et al., 2019, Lazow et al., 2012), reflecting heterogeneity between cohorts and differences in study design.

Lesionectomy

Compared to lobar resections, which involve large volumes of brain resection, lesionectomies involve the resection of specific lesions. This is particularly suited for small cortically-based lesions such as cavernomas, focal cortical dysplasia and dysembryoplastic neuroepithelial tumours, which can be highly epileptogenic.

The development of more sensitive MRI imaging techniques have allowed better identification of these epileptogenic lesions, and lesionectomies have been associated with 5-year seizure freedom rates of 57% for temporal lesionectomy and 40% for extratemporal lesionectomy (de Tisi et al., 2011).

Although limited by small numbers, improvements in imaging and stereotactic techniques have also enabled minimally invasive surgery to be used to treat small epileptogenic lesions. This has the benefit of limiting perioperative morbidity associated with an open resection. Two physical mechanisms of action are commonly applied, radiosurgery (also known as gamma knife) and thermocoagulation (also known as thermoablation). Both these techniques utilise a tiny craniectomy for inserting a guiding catheter or laser applicator and therefore avoid the need for a craniotomy.

Outside epilepsy, laser interstitial thermotherapy (LITT) has been used safely in those with primary glioma and brain metastases (Hoppe et al., 2017). Over the last decade, LITT has subsequently been used to treat hypothalamic hamartomas, tuberous sclerosis and ablate epileptogenic foci involving the hippocampus and amygdala (LaRiviere and Gross, 2016, Hoppe et al., 2017). This minimally invasive option may be a good choice for those where there is a strong surgical hypothesis but who are either poor candidates for or resistant to the idea of open surgery (Culler and Jobst, 2022). At present, comparative studies with open resection have not been comprehensively explored, although seizure-freedom outcomes appear approximately 10-20% worse than with

resective surgery (Hoppe et al., 2017). These reports are likely influenced by a degree of publication bias, where positive outcomes are more likely to be reported.

1.9.2 Epilepsy surgery without curative intent

Various surgical techniques have been developed to reduce seizure frequency and severity for those not felt to be appropriate candidates for a potentially curative surgical resection.

Corpus callosotomy

Corpus callosotomy is a procedure that involves the division of the corpus callosum, which is a group of white matter tracts that span the left and right cerebral hemispheres. This procedure is based on the hypothesis that the corpus callosum is a primary pathway facilitating the interhemispheric spread of ictal discharges, and disconnection may therefore help to limit seizure spread throughout the brain. Callosotomy is most effective in reducing the number of drop attacks (tonic and atonic seizures), and has been particularly effective in managing childhood epilepsies such as Lennox Gastaut syndrome (Vaddiparti et al., 2021, Graham et al., 2016), although it can be performed in both children and adults. In addition to Lennox Gastaut syndrome, it has been used for individuals with recurrent episodes of status epilepticus or focal seizures with rapid generalisation without an apparent lesion (Vaddiparti et al., 2021, Stigsdotter-Broman et al., 2014). At long-term prospective follow-up, corpus callosotomy has been shown to significantly reduce drop attacks by at least 75% in three-quarters

of people, of whom half were no longer having this seizure type (Stigsdotter-Broman et al., 2014, Graham et al., 2016). There was also a modest reduction in tonic-clonic seizures (Stigsdotter-Broman et al., 2014).

One risk with corpus callosotomy is the chance of disconnection syndrome, which can occur in up to 12.5% of total corpus callosotomies and can present with a combination of alien limb, apraxia, agraphia and neglect (Graham et al., 2016). This is usually transient, although rare cases of persistent disconnection syndrome have been described. In one series, complications such as hemiparesis, disconnection syndrome, gait difficulty and decreased speech output were seen in 21% of individuals, although were permanent in only 3.8% (Nei et al., 2006).

Hemispherectomy

This procedure is usually performed only in children and involves either removing or disconnecting tissue from one side of the brain. It is reserved for those in whom seizures are felt to originate predominantly from one cerebral hemisphere, for example in cases of Rasmussen encephalitis, hemimegalencephaly or large perinatal hemispheric stroke (Joris et al., 2022, Fallah et al., 2021). The resected or disconnected hemisphere is typically functioning poorly so that removal does not cause significantly new neurocognitive deficits or worsened contralateral motor function (Joris et al., 2022).

Contemporary approaches include functional hemispherectomy which is

associated with fewer complications (such as blood loss, hydrocephalus or infection) than anatomic hemispherectomy. Recent endoscopic interhemispheric techniques have also been developed, which produce similar outcomes, with reports of durable seizure-freedom rates of approximately 60% at 10 years (Fallah et al., 2021).

Multiple subpial transections

Multiple subpial transections (MST) were first described by Morrell et al. in 1989 (Morrell et al., 1989) however are rarely performed in contemporary practice due to the higher risk of complications and increased availability of other palliative procedures such as vagus nerve stimulation (VNS). In MST, several shallow transections are made in the area of cerebral cortex where seizures are thought to originate. Usually, a more definite resection is unable to be performed because the epileptogenic lesion lies in eloquent cortex, where resection would cause substantial deficits. The shallow transections are thought to interrupt local connections between epileptogenic areas of brain to adjacent areas and therefore prevent the spread of epileptic discharges without altering normal cortical function (Krishnaiah et al., 2018, Morrell et al., 1989).

Multiple subpial transections (MST) can be performed in isolation or together with partial resection. Outcomes are often more favourable when performed together with resection than when MST is performed alone. In a meta-analysis from 2016 (Rolston et al., 2018), 16/68 (23.9%) of individuals who had MST alone were seizure-free, compared with 80/146 (55.2%) who had MST together with another

procedure, such as callosotomy. Complications were encountered relatively frequently, with transient hemi- or mono- paresis in 26.4%, which remained permanent in 14 (6.6%) people. Permanent language difficulties were also encountered in 4 people (1.9%) (Rolston et al., 2018). These complication rates are higher than those seen with resective surgery (hemiparesis in 1.8% and dysphasia in 0.8% on meta-analysis), and are likely a consequence of the direct manipulation of eloquent tissue during MST (Hader et al., 2013).

Vagus nerve stimulation

Vagus nerve stimulation involves the implantation of an electrode around the vagus nerve, which is attached to a pulse generator placed under the clavicle. The left vagus nerve is involved to avoid the risk of bradycardia or cardiac arrhythmias (the right vagus nerve innervates the sinoatrial node), although right-sided VNS has rarely been reported for individual cases (Galbarriatu et al., 2015). One of the key mechanisms by which VNS exerts an anticonvulsant effect is thought to be due to an increase in central noradrenergic release, which activates neuronal networks involving the thalamus and locus coeruleus in the brainstem (Krahl and Clark, 2012). Clinical and experimental models have highlighted the importance of noradrenaline in modulating epilepsy-induced neuronal changes, especially in the limbic system, and counteracting the development of epileptic circuits (Giorgi et al., 2004).

Vagus nerve stimulation is a broad-spectrum treatment of epilepsy, with benefits in drug-resistant focal epilepsy secondary to neuronal migration disorders,

tuberous sclerosis, traumatic brain injury, and various types of epilepsy, including those where epilepsy aetiology is unknown. Although initially approved only for adults with focal epilepsy, VNS has proven effective for children (Jain and Arya, 2021) and those with generalised epilepsy syndromes, including GGE (Englot et al., 2011, Suller Marti et al., 2020). The efficacy of VNS on seizure frequency and severity has been demonstrated in RCTs, and a meta-analysis conducted in 2011 reported that seizure frequency was reduced by 50% or more in approximately 50% of people >1 year after implantation (Englot et al., 2011). Long-term observational data suggests these benefits can be maintained up to 10-17 years after VNS insertion (Chrastina et al., 2018).

In addition to its anti-seizure effect, VNS has also been associated with improved rates of treatment-resistant depression and other mood disorders, which are frequent comorbidities in epilepsy (Conway et al., 2018, Morris et al., 2013). Application of VNS has also proven of benefit in other non-epilepsy related diseases, and it has been used in refractory depression, cluster headache and migraine (Aaronson et al., 2017, Silberstein et al., 2016, Tassorelli et al., 2018).

Deep Brain Stimulation

The SANTE trial was a prospective, randomised, double-blinded parallel-group study that demonstrated significant improvements in seizure control with bilateral deep brain stimulation (DBS) of the anterior nucleus of the thalamus over controls (Fisher et al., 2010). In this study, participants aged 18-65 with drug-resistant epilepsy underwent DBS followed by a 3-month blinded period where

they were randomised to stimulation or no stimulation. This was followed by a 9-month unblinded period where all participants underwent stimulation.

At the end of the blinded phase, the stimulation group experienced a median reduction of seizure frequency of 40.4%, compared with 14.5% in the control group. Seizure reduction rates were equivalent between those with temporal or frontal lobe epilepsy or those who had previously undergone VNS (Salanova et al., 2015). A subsequent report on the long-term follow-up of these individuals described a median seizure frequency reduction of 41% at 12 months and 69% at five years (Salanova et al., 2015). Of 57/110 individuals with at least ten years follow-up, there was a median per cent reduction in seizures from a baseline of 75% at seven years, suggesting a long-term benefit from DBS could be sustained (Salanova et al., 2021). Similar long-term outcomes following DBS have been reported in other case series, with a 70% reduction in seizure frequency rates at >24 months of follow-up (Lee et al., 2012, Kim et al., 2017).

As DBS involves the invasive implantation of stimulation electrodes into the brain, it can be associated with serious complications, including infection and haemorrhage. In Parkinson's Disease, where DBS has been used since the late 1980s, rates of infection range from 1.2-15.2% (Voges et al., 2006, Fenoy and Simpson, 2012), with intracranial haemorrhage risks associated with functional neurosurgery of approximately 5.0% (Zrinzo et al., 2012). In the SANTE trial, two individuals died from SUDEP however no deaths were encountered as a consequence of DBS lead implantation or stimulation. Five (4.5%) had evidence

of haemorrhage on neuroimaging, although this was not deemed clinically significant (Fisher et al., 2010).

Responsive Neurostimulation

The third neurostimulation device currently approved for selected individuals is the responsive neurostimulation (RNS) device. In this procedure, a neurostimulator is implanted through a craniotomy and lies under the scalp over the seizure focus. This neurostimulator continually senses electrocorticographic activity and is programmed to provide stimulation in response to previously identified patterns of abnormality that characterise each individual's seizures.

The only randomised controlled trial was published in 2011 and implanted 191 individuals with the RNS device (Morrell, 2011). During the 3-month blinded evaluation period, seizure frequency was reduced by 37.9% in the stimulation group compared to 17.3% in the control group. Seizure reduction was subsequently sustained during the 84-week open-label period where all individuals received active stimulation with median seizure reduction of 44% at 1 year and 53% at 2 years post-implantation (Morrell, 2011, Heck et al., 2014). The overall rate of intracranial haemorrhage was 4.7% (9/191 people), of which six were postoperative (Morrell, 2011). Implant or incision site infections occurred in 5.2% (10/191). No adverse effects were described on mood or neuropsychological function.

A recent systematic review of 17 studies, including a total 541 participants

reported a mean seizure reduction rate of 68%, with a complication rate of 18.9% (including 3.1% intracranial haemorrhages and 7.4% surgical-site infections) (Kusyk et al., 2022). However, there was a strong publication bias toward positive primary outcomes and a cautious interpretation of the current literature was advised.

Comparing neurostimulation techniques

No head-to-head trials have compared the three approved neurostimulation techniques (VNS, DBS and RNS). All devices are associated with seizure reduction, which was relatively higher in the DBS and RNS trials compared to the initial VNS trial. Recent improvements in VNS technology, however, with autostimulation algorithms based on cardiac-based seizure detection modes that were not used in the original trial, suggest current efficacy may be higher than previously published (Hamilton et al., 2018).

Unlike resective surgery, few individuals experience periods of sustained seizure freedom with neuromodulation, and expectations of outcome should be clearly outlined to candidates (Ryvlin et al., 2021). A recent ILAE Surgical Therapies Commission review concluded that seizure-reduction rates among the three therapies were similar (Touma et al., 2022). This suggests that the choice between different modalities should primarily be influenced by individual preference and levels of local expertise. At the time of writing, for example, RNS neuromodulation is not being routinely performed in the UK.

Both DBS and RNS require the implantation of subcranial leads or electrodes, which comes with a risk of intracranial haemorrhage, whereas VNS implantation does not enter the cranial cavity. In the pivotal DBS trial, there was a higher rate of postoperative depression and memory impairment after stimulation, although studies of DBS in Parkinson's disease have yielded conflicting results (Accolla and Pollo, 2019).

In summary, the choice between neurostimulation devices should be guided by individual preference and local availability. Based on the wider availability of broad efficacy data and a lower side effect profile, VNS may be a better choice for those with multifocal or poorly localised epilepsies, psychiatric comorbidity, or those less inclined or able to safely undergo intracranial procedures.

1.10 The risk-benefit ratio of epilepsy surgery

The decision to recommend any therapy must account for potential risks and the likelihood of the potential benefits. This is particularly relevant for epilepsy surgery, which is a major undertaking that carries a small but not insignificant perioperative mortality, estimated in systematic review at approximately 0.6% (Hader et al., 2013). Furthermore, surgery requires a comprehensive presurgical evaluation that involves a substantial investment in time, as individuals will require input and investigation from a multidisciplinary team.

The risk of complications must be juxtaposed against the risks inherent with continued medical management alone, which is associated with low rates of

seizure freedom. Although surgery carries a 0.1-0.6% risk of perioperative mortality, the chance of SUDEP in epilepsy surgery cohorts can be as high as 0.6-0.9% per year, which also does not include mortality risks from direct seizure-related accident or injury (Edwards et al., 2018).

1.10.1 Risks of epilepsy surgery

Surgical complications

Epilepsy surgery can be associated with a variety of medical and neurologic complications. In a systematic review conducted in 2013, which included 76 studies, minor medical complications were estimated at approximately five percent, and most commonly consisted of CSF leak, aseptic meningitis, bacterial infection and intracranial haematomas (Hader et al., 2013). Major medical complications were seen in <1% of cases, similar to other major elective surgeries, including risks of anaesthesia, extracranial infection, venous thrombosis, and embolism (Hader et al., 2013).

The rate of surgical complications varies according to the type of operation performed and surgical centre, in addition to how complications are defined. The National Surgical Quality Improvement Program (NSQIP), commenced by the American College of Surgeons in 2005, reported a 30-day complication rate of 17.9%, comprising of a return to surgery in 5.3%, bleeding requiring transfusion in 3.6%, mortality in 3.4% and stroke in 2.1% (Rolston et al., 2016). These complication rates are substantially higher than those reported in academic series from high-volume centres, and was attributed to the inclusion of low-

volume centres (where adverse events were more frequent) and inclusive criteria that also documented medical complications such as pneumonia (1.5%) and urinary tract infection (2.7%). Complications were seen more commonly in those of older age, male gender and individuals with a higher American Society of Anaesthesiologists (ASA) classification (Rolston et al., 2016). While other reports also describe older age as a risk factor for complications (Bjellvi et al., 2015, Kerezoudis et al., 2021), this has not always been a consistent finding (Punia et al., 2018). Age does not preclude favourable seizure outcomes after surgery (Patra et al., 2014, Bialek et al., 2014, Kerezoudis et al., 2021). While it should factor in presurgical counselling, older age should not be considered an absolute contraindication to epilepsy surgery.

In a large prospective study of 865 epilepsy surgery procedures in Sweden between 1996 and 2010, surgical complications were seen in approximately 5% of cases, comprising of infection (2.2%), haematoma (1.6%), thromboembolism (0.6%), CSF leakage (0.5%) and hydrocephalus (0.2%), with no cases of perioperative mortality (Bjellvi et al., 2015). Retrospective cohorts elsewhere have described surgical complication rates between 1.8-12%, most commonly comprising of intracranial haemorrhage and infection of the CNS (Vermeulen et al., 2016, Gooneratne et al., 2017, Mathon et al., 2017, Punia et al., 2018).

Neurological complications

Neurological complications can also be encountered postoperatively and can involve visual, motor, speech and memory systems. While many of these

complications are transient (<3 months), there is also the potential for long-term deficits which interfere with quality of life, and are highly associated with dissatisfaction following resective surgery. During presurgical counselling, a distinction should be made between predictable consequences of a planned surgery (for example hemianopia after occipital resection), and potential complications, which can occur even during the resection of what appears to be non-eloquent tissue.

In the systematic review by Hader et al., minor complications which resolved within three months occurred in approximately 13%, most commonly involving a visual field defect (one quadrant or less), which was frequently not evident to the individual concerned (Hader et al., 2013). Major complications, which persisted for longer than 3 months, included visual field defects in 2.1%, hemiparesis in 1.8% and dysphasia in 0.8% (Hader et al., 2013).

Complications after surgery are often closely associated with the location of resection, which emphasizes the importance of careful presurgical evaluation, planning of the proposed operation and discussion with each individual about potential risks. In the large prospective series from Bjellvi et al. reporting 523 temporal lobe resections, 15 (2.9%) major complications were seen, and these were more commonly encountered in those where resection included the hippocampus (Bjellvi et al., 2015). In other observational cohorts of temporal lobe resection, with variable methodologies and data collection methods, major complications have been reported in 1-8%, most commonly comprising

quadrantanopia, dysphasia and hemiparesis (Gooneratne et al., 2017, Heller et al., 2009, McClelland et al., 2011, Tanriverdi et al., 2009). Overall, the permanent visual field defect and hemiparesis rates were similar to those with temporal and extratemporal resections (Hader et al., 2013). However, proportionate risk should be considered on an individual level based upon the planned procedure and proximity to eloquent structures.

Neuropsychological consequences

A decline in memory scores on neuropsychological testing is commonly seen after temporal lobe resection. The average rate of verbal memory decline in left-operated individuals is approximately 44%, and 20% in right-sided operations (Sherman et al., 2011). For visual memory, the risk of loss is similar (23% and 21%) for right and left-sided surgery (Sherman et al., 2011). Rare improvements in memory have also been described and may relate to the positive effects of seizure reduction. Most information on neuropsychological outcomes following surgery relates to group-level findings, which in practice can be difficult to translate to clinically relevant risk and benefit estimates for individuals. The primary predictor of postsurgical verbal or visual memory loss is the presurgical functional status of the tissue to be resected (Dulay and Busch, 2012, Baxendale et al., 2006). This emphasises the importance of baseline neuropsychological tests, which can include multivariable risk models (Baxendale and Thompson, 2018) and assessment of postictal memory deficits (Sveikata et al., 2019) to estimate the potential for neuropsychological decline before surgery. The role of presurgical neuropsychological testing is described in more detail in Chapter

1.11.

Depending on the site of resection, the pattern of predicted neurocognitive decline differs (Dulay and Busch, 2012). Although it is the second most common epilepsy surgery performed, there is little information on neuropsychological outcomes following FLE surgery. A study of 30 consecutive individuals at a single centre showed cognitive stability at a group level two years after surgery but a decline in verbal reasoning ability (comprehension) in 4/7 of those with lateral and 4/7 of those with premotor/SMA resection patterns (Ljunggren et al., 2015). This result was independent of seizure outcome and side of surgery, and another study demonstrated no significant relationship between cognitive outcomes after surgery and the side or volume of resection (Busch et al., 2017). In contrast, a retrospective study of 36 adults who had FLE surgery reported 9/36 (25%) experienced significant decline in verbal fluency, which was more common in those with dominant resections or who had high presurgical test scores (Sarkis et al., 2013). Other centres report approximately half of the individuals having FLE surgery may experience a decline in one or two cognitive domains (Busch et al., 2017). However, further research, which utilises standardised, reliable change indices, is required to delineate better variables that can predict postoperative decline.

1.10.2 Presurgical evaluation

Given the benefits and potential risks of epilepsy surgery, a comprehensive presurgical evaluation is necessary to gauge suitability and guide informed

discussions around the risk-benefit ratio, individualised for each person (Duncan, 2011). The surgical, neurological and neuropsychological risks of a proposed procedure must be balanced with the morbidity and mortality associated with ongoing seizures, as well as the chance of surgical success in rendering the individual seizure-free. This evaluation of individualised risk-benefit involves synthesising multiple data sources and formulating this information in a form intelligible for individuals and their families (Duncan, 2011, Culler and Jobst, 2022).

The goals of any potential surgery must be explained to individuals, together with the likelihood of success and risk of complications. Overall, in carefully selected individuals with drug-resistant epilepsy, surgery may result in an up to 70% chance of seizure freedom (Jobst and Cascino, 2015). Prediction of these odds can, however, be further refined on the basis of the presurgical evaluation, for example through the use of Epilepsy Surgery Nomograms and other multivariable models (Jehi et al., 2015b, Gracia et al., 2019, Bell et al., 2017). In those where resective surgery is not an option, the neurostimulation techniques described in Chapter 1.9 should be considered as an alternative, as they have been shown to reduce seizure burden, risk of SUDEP and epilepsy comorbidities such as major depression (Aaronson et al., 2017, Morrell, 2011, Ryvlin et al., 2018, Touma et al., 2022).

Initial assessment

The clinical history must be elucidated, with particular emphasis on the start and

evolution of epilepsy and the current seizure pattern. Excluding those who require surgery for tumour control or future risks (such as bleeding into a cavernoma), resective surgery is only effective in those with focal epilepsy and is reserved for those with drug-resistance.

As described in Chapter 1.6, individuals who continue to experience seizures after two or three adequately dosed and chosen ASM have a <5% chance of achieving seizure freedom with further medication, including newer ASM choices (Chen et al., 2018). One exception may be those with previously well-controlled epilepsy who have a single seizure relapse with or without an identifiable trigger, of whom >50% can experience sustained seizure freedom (Chen et al., 2021). Prognostic factors for seizure recurrence in this group include the duration of initial seizure remission and the number of ASMs used during this period (Chen et al., 2021).

Resective surgery is not appropriate for generalised epilepsy syndromes, although individuals should still be considered for neurostimulation (Suller Marti et al., 2020). The semiology must therefore be scrutinised, and the diagnosis of focal epilepsy confirmed (Beniczky et al., 2022). Medicolegal cases have been described where epilepsy surgery has been performed on people who do not have epilepsy, including psychogenic non-epileptic seizures – in these cases, the apparent ‘seizures’ may continue postoperatively (Baxendale and Baker, 2022). Obtaining a thorough history of the nature of the individual’s seizures, including where possible witness accounts or home videos, can assist in confirming the

likely diagnosis of focal epilepsy, even before a video-EEG study (Muayqil et al., 2018). It is important to consider the validity of witness accounts, as these may inaccurately lateralise movements and more commonly associate seizures with generalised rather than focal semiologies (Mannan and Wieshmann, 2003, Muayqil et al., 2018). Epileptic seizures are stereotyped, and the stability and repertoire of semiological patterns, particularly for TLE, have been well described (Beniczky et al., 2022, Attard Navarro and Hamandi, 2022).

A neurological and physical examination may help identify an underlying cause of seizures (for example, those with peripheral stigmata of neurofibromatosis or tuberous sclerosis). It may also identify consequences of seizures such as physical injuries or evidence of tongue-biting. It is rare for an individual to have a seizure while in the consulting room. The general examination also helps determine if factors influence the decision to proceed with surgery. This includes medical comorbidities that may increase surgical or anaesthetic risk, most notably cardiorespiratory disease or elevated Body Mass Index (BMI). Although obesity has not been shown to be predictive of the duration of hospital stay or seizure outcome after epilepsy surgery, it has been associated with reduced long-term quality of life and mortality, which may undermine the benefits of surgery (Kang and Cascino, 2009). The American Society of Anaesthesiologists physical status (Mayhew et al., 2019) is commonly used to classify a person's fitness before surgery, and has been associated with morbidity following epilepsy surgery (Rolston et al., 2016). Features of the past medical history, in particular cardiorespiratory status, is also crucial in stratifying perioperative risk (Smilowitz

and Berger, 2020).

Baseline investigations such as an electrocardiogram, pulmonary function tests or echocardiogram will frequently have been performed before review but should not be neglected. In particular, arrhythmogenic syncope can be a common seizure mimic, and can also coexist with epilepsy (Ungar et al., 2017). Sinus tachycardia may occur in approximately 80% of seizures (Sevcencu and Struijk, 2010), and those with drug-resistant epilepsy may have ischaemic changes on the ECG which are closely related to seizures (Tigaran et al., 1997).

Neuropsychology assessment is routinely performed before surgery. This consultation serves several purposes, providing a baseline assessment of cognitive function, clues as to the likely localisation or lateralisation of seizure foci, and helping to provide evidence-based predictions of risk with surgery (Sherman et al., 2011). Neuropsychiatric assessments are also performed to optimise pre-existing psychiatric comorbidity, which are commonly encountered in people with drug-resistant epilepsy and can be under-recognised. Preoperative depression is a strong predictor of postoperative depression, and can also be associated with poor seizure control after surgery (Foong and Flugel, 2007). The strongest risk factor for postoperative psychiatric complications is previous history of psychiatric comorbidity (Fasano and Kanner, 2019). While these are not contraindications to surgery, behavioural disturbances and personality disorders can be exacerbated postoperatively, and adequate supports should be set up prior to surgery (Foong and Flugel, 2007).

Many people who are referred for consideration of epilepsy surgery will already have been investigated with MRI and EEG; however, it is essential for these investigations to be reviewed before embarking on more extensive or potentially invasive investigation. Imaging findings are strongly associated with postoperative outcome, and those with focal abnormalities are more likely to have a favourable outcome (de Tisi et al., 2011). Higher resolution 3T MRI scanners can improve the identification of structural lesions and may yield relevant new diagnoses in five percent of individuals that can impact management decisions (Winston et al., 2013). The likely pathology on imaging also influences the chance of predicted seizure freedom. The highest 5-year seizure freedom rates for anterior temporal resection, for example, are seen in hippocampal sclerosis (57% seizure-free) and dysembryoplastic neuronal epithelial tumours (63% seizure-free) (de Tisi et al., 2011). Functional MRI (fMRI) is performed to help determine language localisation and lateralisation, which can help guide resection margins and preserve eloquent cortex.

The interictal EEG may provide clues as to the lateralisation and localisation of the seizure onset zone, however ictal video-EEG telemetry is required to confirm the EZ. This typically involves admission for prolonged video telemetry. During this period, medication doses can be reduced, and provocative techniques such as hyperventilation or photic stimulation can be performed. For some individuals, alcohol can be a potent trigger (Heckmatt et al., 1990), and can be administered to inpatients within a controlled setting. Video telemetry aims to observe the

individual's habitual seizures in a safe environment while they are connected to EEG – this 'ictal' recording provides essential information in understanding which areas of the brain are involved in seizure onset and propagation.

In some centres, electric and magnetic source imaging methods are used in conjunction with routine video telemetry in helping to localise epileptiform discharges (Sharma et al., 2019, Mégevand and Seeck, 2020). However, these techniques have not been adopted worldwide (Mouthaan et al., 2016). Source imaging is limited by the need for dedicated software (and hardware in the case of magnetic source imaging), and expertise in their interpretation. Ictal source imaging relies on constructing voltage maps based on routine EEG data to model the location of electric (epileptiform) foci within the brain, rather than relying only upon regions of peak negativity on scalp EEG. There is emerging data that ictal source imaging can be a helpful adjunct in accurately localising the seizure onset zone, and can be performed with high inter-rater validity (Beniczky et al., 2016, Sharma et al., 2019).

For individuals in whom the onset of seizures is not clear, even on ictal video-EEG telemetry, additional investigations such as fluorodeoxyglucose position emission tomography (FDG-PET), ictal single-photon-emission computed tomography (SPECT) and intracranial EEG (icEEG) recordings are routinely used to help identify the EZ.

Utility of FDG-PET

Positron emission tomography can help localise epileptic foci by imaging the brain's topographic distribution of glucose uptake. The characteristic finding in epilepsy is regional hypometabolism (as indicated by reduced glucose uptake) during the interictal state, reflecting evidence of a dysfunctional neural network in that region (Willmann et al., 2007, Knowlton, 2006). In a recent multicentre real-world study of four epilepsy surgery centres, FDG-PET influenced decision-making in 47% of cases (Steinbrenner et al., 2022). This was similar to previous studies, where FDG-PET has been shown to influence presurgical decision-making in 53-71% of cases (Rathore et al., 2014, Uijl et al., 2007). FDG-PET can be sensitive in up to 80-90% cases of TLE (Salanova et al., 2001, Knowlton, 2006, Tomás et al., 2019), although there are mixed results in extratemporal epilepsy (ETLE). In selected populations, FDG-PET may be up to 80% sensitive in ETLE (Tomás et al., 2019), although others have reported lower sensitivities of 20-40% in those with ETLE or non-localisable epilepsy syndromes (Knowlton et al., 2008, Kim et al., 2001).

A meta-analysis that examined the utility of PET in epilepsy surgery found that this was concordant with ictal scalp EEG in 75.2% of cases; moreover, 84.2% of those with non-localising EEG findings had an area of regional hypometabolism on PET (Willmann et al., 2007). In clinical practice, findings on FDG-PET may lead directly to a recommendation for resection, help in tailoring electrode placement for intracranial EEG, the post-hoc discovery of an MRI lesion, lateralisation of the EZ, or a decision that surgery is infeasible, for example if

widespread or multifocal abnormalities are found (Steinbrenner et al., 2022). An example of an abnormal PET is shown in Figure 1.3.

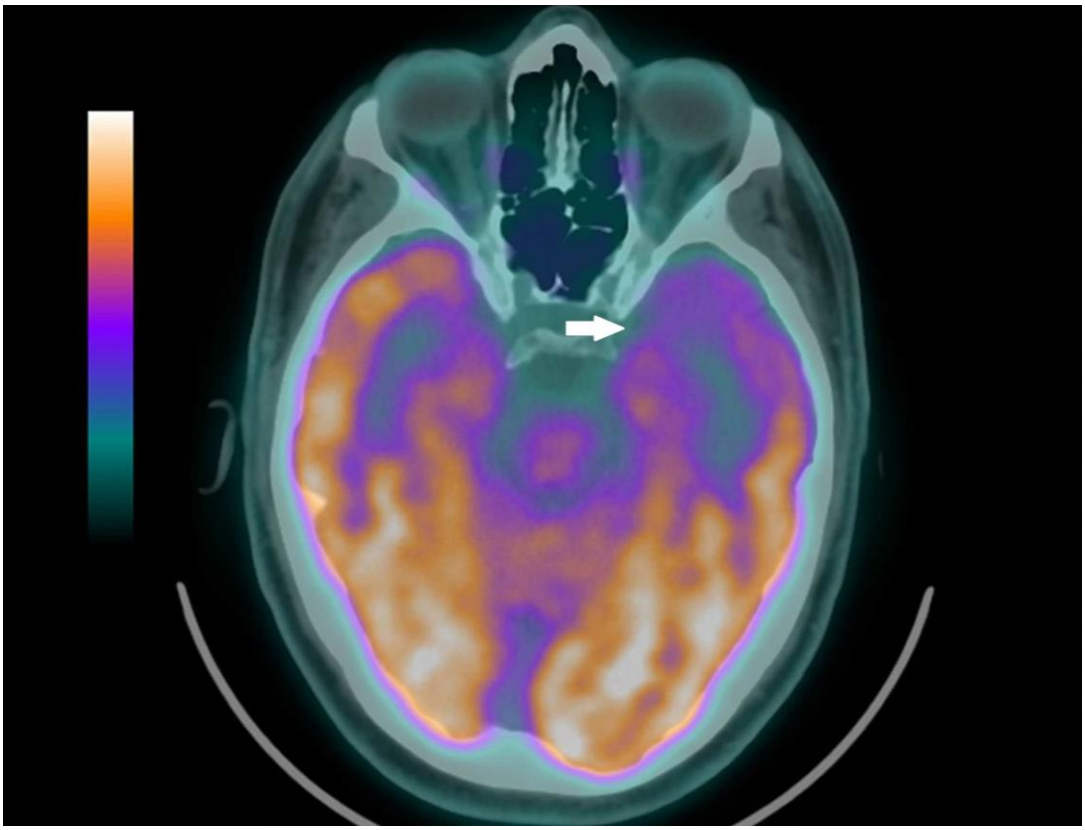

Figure 1.3: FDG-PET demonstrates hypometabolism (white arrow) in a man with a normal MRI brain in the left temporal lobe. He became seizure-free following a left anterior temporal lobectomy.

In mesial temporal lobe epilepsy, FDG-PET often reveals hypometabolism in mesial temporal, temporal polar and anterolateral temporal regions, i.e. to a greater extent than the actual seizure focus seen on MRI or electrical source imaging (Brodbeck et al., 2010, Tomás et al., 2019). As such, the precise localisation of the EZ may be confounded by relatively low spatial resolution. When findings are concordant with other investigations, FDG-PET nonetheless helps build a hypothesis for seizure onset and can help direct further

investigations such as intracranial EEG (Knowlton, 2006, Steinbrenner et al., 2022).

Having an abnormal PET may also help predict the outcome following epilepsy surgery. Concordance between PET temporal hypometabolism and hippocampal sclerosis on MRI correlated with better results in one study (Salanova et al., 1998), and qualitative or quantitative PET analysis could help predict outcome following temporal lobectomy (Manno et al., 1994). In a mixed cohort of individuals with both temporal and extratemporal resections, unilobar hypometabolism on FDG-PET was a strong predictor of complete seizure control (Tomás et al., 2019).

Use of ictal-SPECT in presurgical evaluation

Single-photon-emission computed tomography (SPECT) is another technique used to help delineate the EZ and has the advantage of being able to assess brain activity during an epileptic seizure. A meta-analysis of 11 studies including 320 individuals comparing ictal-SPECT results to the presumed EZ on the basis of resection site or multimodal electroclinical data reported correct localisation in 65.3% of cases, including both TLE and ETLE (Chen and Guo, 2016).

Two radiotracers are commonly used – Technetium-99m-hexamethyl-propyleneamine-oxime (99mTc-HMPAO) and technetium-99m-ethyl cysteinate diethyl ester (99mTc-ECD). Both these tracers have intravascular binding properties, and if injected intravenously after a clinical seizure are deposited

according to blood-flow within the brain (Masdeu and Arbizu, 2008, O'Brien et al., 1999). This allows a snapshot of ictal blood flow to be captured. A recent comparative study demonstrated no significant difference between both tracers, which correctly localised the seizure onset zone in approximately 60% of cases (Jaber et al., 2021). Both radiotracers cannot be prepared more than a day in advance, as 99mTc-HMPAO is stable for only 4 hours, and 99mTc-ECD is stable for 6-8 hours (Van Paesschen, 2004).

Early methods of analysing perfusion patterns in ictal brain perfusion SPECT included qualitative visual pattern classification and univariate voxel-based testing. (Masdeu and Arbizu, 2008). More recently, the SISCOM technique, which subtracts the interictal study from the ictal SPECT and co-registers the digitally subtracted image to an MRI scan has provided the most optimal results (Chen and Guo, 2016, Říha et al., 2022, Krishnan et al., 2021, Hlauschek et al., 2021).

The main drawback of ictal SPECT is the need to inject the radiotracer within seconds of seizure onset. An early study evaluating interictal, ictal and postictal perfusion patterns respectively showed correct lateralisation in 48% (i.e. no better than chance), 71% and 97%, highlighting the need to reliably inject during the clinical seizure (O'Brien et al., 1999). This often requires the involvement of an experienced clinician or epilepsy-trained nurse waiting by the bedside during video telemetry.

Similar to FDG-PET, the spatial resolution of ictal-SPECT is limited, and the hyperperfused region is often larger than the EZ, particularly for seizures that arise from deep brain regions like the insula (Sala-Padro et al., 2019, Aupy et al., 2018). Ictal-SPECT must therefore be used in conjunction with other clinical, electrophysiological and imaging findings in surgical planning. In many cases, particularly of MRI-negative epilepsy, ictal-SPECT results are crucial in helping to plan a subsequent intracranial study (Englot and Lagrange, 2022). In addition, concordance between clinical consensus and ictal SPECT is a good predictor of surgical outcome (Peedicail et al., 2020, Uribe San Martin et al., 2020).

Intracranial EEG recording

Despite the non-invasive investigations described previously, when results are discordant, the MRI scan is normal, or scalp EEG is non-localising, intracranial EEG may be required to identify the precise origin of seizures. In these cases, intracranial EEG is performed to record ictal and interictal data to support the hypothesis on localisation of the EZ, and determine the extent of eloquent cortex, which helps define safety margins for epilepsy surgery (Culler and Jobst, 2022). Approximately 25-50% epilepsy surgery in tertiary centres require intracranial EEG (Kovac et al., 2017, Cossu et al., 2008). Numerous observational studies have published seizure freedom rates of up to 50-70% with surgery following intracranial EEG, although these rates are inevitably influenced by case selection (Serletis et al., 2014, Yang et al., 2014, Jehi et al., 2021).

In current practice, intracranial EEG monitoring typically involves one of two main methods. In the first method, subdural electrodes (SDE) are implanted in the subdural space as strips or grids following a craniotomy (Englot, 2018). Several depth electrodes may also be inserted to allow sampling of deep brain structures and provide a more three-dimensional volumetric view of the seizure onset zone. The second method involves the stereotactic implantation of recording electrodes, or stereoencephalography (SEEG). This method, in which depth electrodes are implanted without the need for a craniotomy, was first described in Paris in the late 1960s, but advancements in neuroimaging and robotic guidance have led to increased utilisation of this technique worldwide (Morsi et al., 2022, Mullin et al., 2016, Englot, 2018). SEEG has the advantage of avoiding craniotomy, which is associated with greater surgical morbidity, and can better assess deep areas such as the insular cortex that cannot be readily assessed with subdural grids (Kovac et al., 2017, Jayakar et al., 2016).

These two methods have been compared in a recent propensity-matched retrospective observational study, which analysed data from 1,468 people from ten different study sites (Jehi et al., 2021). In comparison with SEEG, individuals who had SDE were more likely to have epilepsy surgery (78.6% vs 66.5%, $p<0.05$), however SDE was associated with more surgical complications (9.6% vs. 4.4%, $p<0.05$) and individuals had a lower probability of long-term seizure freedom (41.1% for SDE vs. 54.6% for SEEG) (Jehi et al., 2021). These results suggest SDE may not be as delineating of the EZ as compared to SEEG (Yan et al., 2019). These findings have been replicated in a systematic review, where

61% of those who had SEEG were seizure-free compared with 56.4% of those who underwent SDE (Yan et al., 2019). It is possible, however, that differences in seizure freedom between groups in these studies may have resulted from less-suited candidates proceeding to surgery following SDE, despite attempts at propensity matching.

The main advantage of both intracranial EEG techniques over scalp EEG stems from their greater spatial resolution. Recording electrodes are much closer to neurons, and signals do not have to be recorded through the skull. Approximately $10cm^2$ of cortex needs to be excited for spikes to be picked up on scalp EEG (Tao et al., 2005). Intracranial studies also have the advantage of minimising muscle artefact, which can often obscure scalp recordings. Depth electrodes allow sampling of deeper brain regions, such as the insular cortex, but only record the activity of a small area of surrounding brain tissue (von Ellenrieder et al., 2012). This underscores the need for a clear hypothesis based upon all the non-invasive data to guide the overall implantation strategy. The use of intracranial EEG as an exploratory procedure with extensive bilateral implantations has been discouraged, although it remains the method of choice in resolving the divergence of non-invasive data (Jayakar et al., 2016).

Subdural electrode placement allows wide coverage of the neocortical gyral surface and selected sampling of deep targets, and may therefore be better suited for cases where an extensive unilateral EZ requires coverage of both surface and deep targets. SDE also permits greater manoeuvrability of

electrodes along the cortical surface, mapping of eloquent cortex using direct cortical stimulation, and opens up the possibility of definitive surgery (explantation of electrodes, then resection) without the need for a separate craniotomy (Yan et al., 2019). Its ability to evaluate bilateral hemispheres is, however, more limited than SEEG, and it cannot readily sample gray matter within sulci (eg. depth of sulcus focal cortical dysplasia) (Katz and Abel, 2019, Chauvel et al., 2019, Culler and Jobst, 2022).

In comparison, SEEG allows better exploration of all deep targets including mesial temporal structures and the possibility of bilateral exploration when necessary. It may be suited to those with a deep-seated EZ or where non-invasive tests suggest multilobar or bilateral involvement (Chauvel et al., 2019, Katz and Abel, 2019). In one evaluation of 100 people with difficult-to-localise epilepsy, a third of whom had failed subdural grid evaluation, SEEG was able to successfully localise the EZ in 96%, and 75 individuals proceeded to a resection (Gonzalez-Martinez et al., 2013). Electrical stimulation mapping can also occur using SEEG electrodes, and the observation of stimulation-induced ictal patterns and clinical semiology can provide insights into epileptogenic and symptomatogenic zones (George et al., 2020).

The risk of complications with both intracranial EEG methods is small but must be closely discussed with individuals, given the elective nature of the procedure. The most common complications with SEEG include haemorrhage (subdural haematoma, epidural haematoma or intracerebral haemorrhage) in 1%, and

infection (cerebral abscess, meningitis or superficial infections) in 0.8% (Mullin et al., 2016). In comparison, the risk of haemorrhage with SDE is approximately 3-4%, with a 2-4% risk of infection (Tebo et al., 2014, Arya et al., 2013). Both intracranial EEG methods have an estimated mortality rate of approximately 0.3%, often as a consequence of intracranial haemorrhage (Mullin et al., 2016, Arya et al., 2013, Tebo et al., 2014).

Although practices differ among centres, intracranial EEG is not usually necessary in TLE when there is electroclinical concordance and an evident imaging lesion (Chauvel et al., 2019). In frontal or parietal epilepsies, intracranial EEG may help explore remote multilobar connectivity and help define regions of eloquent cortex, for example when the EZ is located in or near the motor cortex. In posterior epilepsies, bilateral exploration is often needed due to rapid contralateral spread and involvement of bilateral occipital, parietal or posterior temporal structures (Chauvel et al., 2019)

1.11 Synthesis of data

Robust methods are needed to identify the most appropriate candidates for epilepsy surgery through synthesis of all the above data, framed within an individual context. Recent consensus guidelines from the UK National Institute for Health and Care Excellence (NICE) and International League Against Epilepsy suggest that all individuals under 70 years of age with drug-resistant epilepsy should be considered for and referred for epilepsy surgery (National Institute for Health and Care Excellence, 2021, Jehi et al., 2022).

This guidance aims to maximise the chances of delivering appropriate therapy to selected individuals, with the highest chance of rendering them seizure-free. The need for a detailed presurgical evaluation does, however, result in long waiting times for both evaluation (particularly video-telemetry or intracranial EEG) and surgery. A considered approach to investigation may help identify appropriate candidates earlier, and conversely allow early discussions with those unlikely to proceed to surgery about what presurgical evaluation will entail.

This is particularly relevant given the largest proportion of people with drug-resistant epilepsy reside in developing nations, where epilepsy surgery (and presurgical evaluation) is a scarce resource. In addition, the uptake of epilepsy surgery among those of lower socioeconomic class in developed nations is also significantly lower. Addressing this disparity remains a public health challenge, particularly as the reasons that underpin this finding are likely to be heterogenous. Of 105 countries surveyed by the WHO across the globe, only 16% had an epilepsy surgery unit, with a disproportionate shortage in lower-income countries (World Health Organization, 2017).

In most tertiary centres, careful discussion on surgical suitability or the need for intracranial EEG take place at a multidisciplinary team meeting (Duncan, 2022). This group approach can help synthesise individual data, and a consensus decision on proceeding with evaluation or surgery can be made. A flowchart describing an approach to presurgical evaluation is illustrated in Figure 1.4.

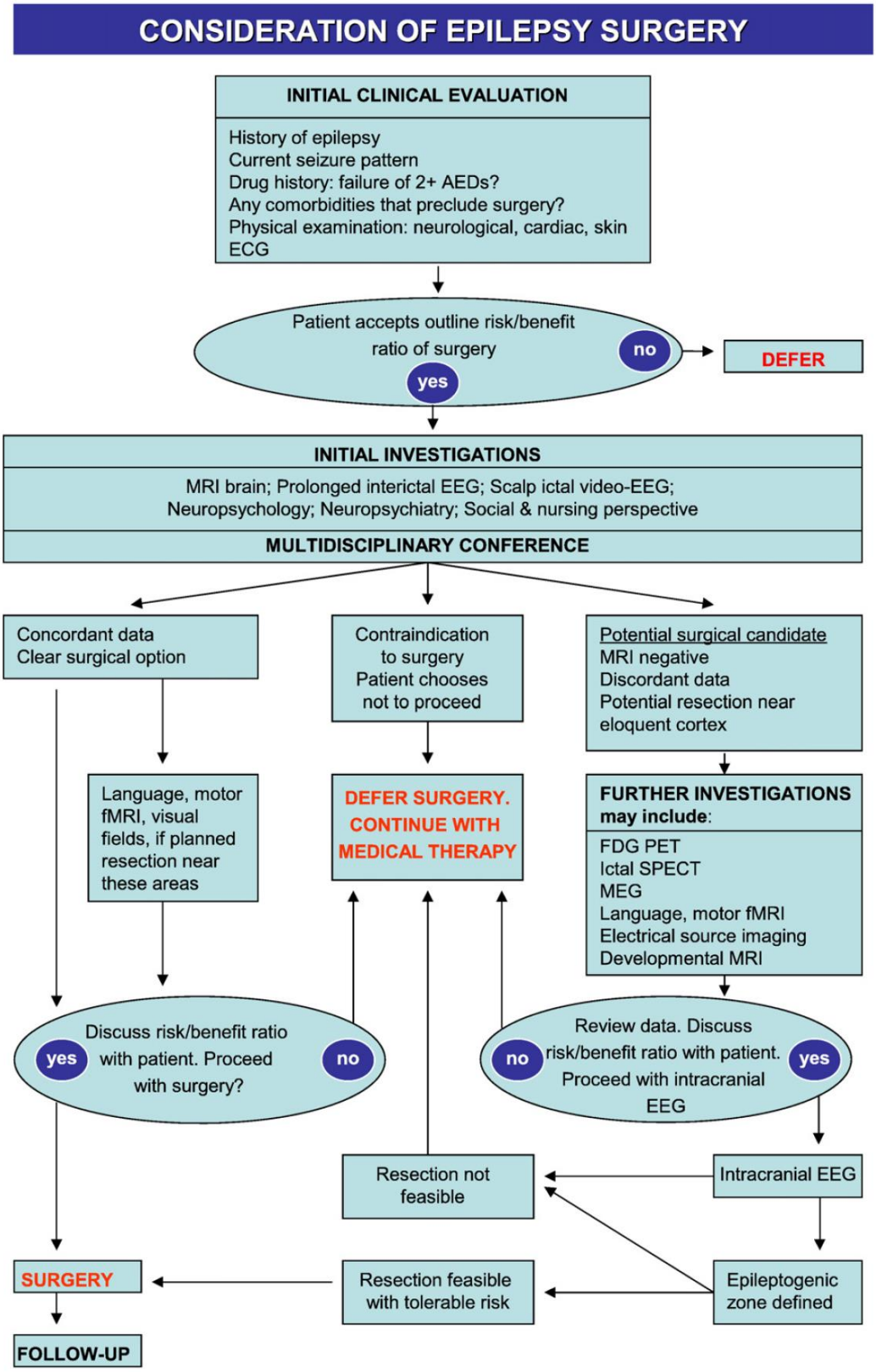

Figure 1.4: Common pathways for presurgical evaluation. From: Duncan J. Selecting patients for epilepsy surgery: synthesis of data. Epilepsy & Behaviour 2011 Feb;20(2):230-2. Used with permission.

In Chapters 3 and 4 of this thesis, we aim to identify why individuals referred for epilepsy surgery do not proceed to a definitive resection and use this data to construct a model that can assist discussions with individuals about the likelihood of being a surgical candidate. We also investigate and present seizure outcome data in people who complete presurgical evaluation but do not proceed to an operation.

There is more data worldwide supporting epilepsy surgery in those with TLE than other focal epilepsies. In Chapter 5, we report long-term seizure relapse and remission patterns, psychiatric and socioeconomic outcomes in a large cohort of individuals who had FLE surgery. In Chapter 6 we delve deeper into this cohort with particular scrutiny on individual semiology and how well this can relate to localising or lateralising the EZ. Lastly, in Chapter 7, we use a tariff-based approach to assess the overall cost and implications of an epilepsy surgery program in the UK.

Chapter 2: Outline of General Methods

2.1 The UCLH Epilepsy Surgery Database

The epilepsy surgery programme at the National Hospital for Neurology and Neurosurgery at Queen Square, which is part of the University College London Hospitals (UCLH) NHS Trust, has been running since 1990 and receives referrals from all over the UK and worldwide. General principles of presurgical assessment were established in 1990, although recent technological advances, as described in Chapter 1, have built upon this foundation and are routinely used in our clinical practice.

Since its inception, information on individuals who have had epilepsy surgery at Queen Square has been prospectively recorded in an Epilepsy Surgery Database. This has included demographic information encompassing the age of epilepsy onset, age at time of surgery, frequency of seizures, history of febrile convulsions, and previous episodes of status epilepticus or significant head injuries. Details of the presurgical evaluation, including clinical historical data, seizure classifications, medications, comorbidities, EEG, video-EEG, MRI, FDG-PET, ictal-SPECT and intracranial EEG data, have also been recorded, in addition to general details on the type of surgery performed and postoperative histology. Lastly, annual postoperative seizure outcomes, determined by direct enquiry, supplemented by data from primary care teams and treating neurologists, are recorded in the database together with results of postoperative psychiatric and neuropsychology assessments.

A summary of selected components in the epilepsy surgery database utilised for the work in this thesis is presented in Table 2.1.

Table 2.1 Information extracted from the UCLH Epilepsy Surgery Database
Patient characteristics & demographics
Gender
Date of birth
Postcode
Handedness
Age of epilepsy onset
Complications with pregnancy/delivery
Medical History
Early childhood convulsions
Prior neurological insult
Significant head injury
Epilepsy-specific information
Focal aware seizures; frequency
Impaired awareness seizures; frequency
FTBTCS
Frequency of FTBTCS
Presurgical evaluation results
Abnormal MRI brain
Region of MRI brain abnormality
Radiological pathology
Language functional MRI lateralisation
Video EEG telemetry
Interictal background and localisation
Ictal discharge localisation
FDG-PET performed; localisation
Ictal SPECT performed; localisation
Intracranial EEG performed
Operative details
Previous vagus nerve stimulation
Date of surgery
Type of operation
Postoperative histology
ASM at time of operation
Postoperative outcomes
ASM at latest contact
Deceased; reason for death
Annual seizure outcomes
Psychiatric comorbidity
Neuropsychology scores
Abbreviations: FTBTCS – focal to bilateral tonic-clonic seizures; MRI – Magnetic resonance imaging; EEG – electroencephalography; FDG-PET – fluorodeoxyglucose positron emission tomography, SPECT – single photon electron computed tomography; ASM – anti-seizure medications

2.2 Extending the database to include those who do not proceed to surgery

To identify differences between those who do and do not proceed to surgery and factors of the presurgical assessment that could predict the likelihood of epilepsy surgery, we extended the Epilepsy Surgery Database to include the large number of people who were referred for and completed presurgical evaluation at our centre but did not ultimately proceed to a resection. To identify these individuals, we reviewed records of a multidisciplinary team (MDT) meeting held in our department weekly since 2012.

Almost all those at our centre who undergo epilepsy surgery are discussed in this MDT, as are the majority of those who complete presurgical evaluation but do not proceed. While in select cases individuals may be given a final decision on surgical candidacy by their individual consultant without going through this meeting, in the great majority of cases the MDT serves as the forum where clinical information is presented, data on the presurgical evaluation is reviewed, and a consensus decision to proceed (or not) to surgery is made.

2.2.1 Reasons for not having epilepsy surgery

We retrospectively reviewed data from all individuals discussed in the epilepsy MDT over five years, from January 2015 to December 2019. All individuals had been referred by neurologists for consideration of epilepsy surgery. Information on clinical history, examination, MRI brain, video-EEG telemetry, neuropsychological and neuropsychiatric evaluations, and in selected cases FDG-PET, ictal SPECT and intracranial EEG recordings for these individuals was

systematically recorded in the Epilepsy Surgery database to capture those that do not proceed to resection.

We analysed the reasons outlined in the MDT meeting for people not proceeding to surgery following presurgical evaluation. We also reviewed subsequent clinical encounters to identify reasons underpinning the reasons not to proceed.

After identifying those who had completed presurgical evaluation but who did not proceed to surgery, we populated the information in Table 2.1 for all these individuals. This involved reviewing imaging, video-telemetry data and outcomes of neurology, neurosurgery, neuropsychology and neuropsychiatry assessments for every individual. This information was then compared with that of the individuals within the Epilepsy Surgery database, and the results of this comparison are presented in depth in Chapter 3.

2.2.2 Seizure outcomes in those that complete presurgical evaluation but do not have epilepsy surgery

The chances of seizure freedom with medical management in the heterogenous group of individuals diagnosed with epilepsy is well-described and summarised in Chapter 1.6. There is, however, little data on seizure outcomes in the select cohort of individuals with drug-resistant focal epilepsy who complete presurgical evaluation but subsequently do not proceed to a resection, either as a consequence of being unsuitable for surgery, or declining an operation after it has been offered to them. Identifying outcomes in these individuals will better

direct the ability to have discussions regarding risk and benefit of surgery, which should include an informed conversation on the likely outcomes if surgery is not pursued.

We adapted a postsurgical outcome grading score (Table 2.2) to utilise among those who do not have surgery following evaluation and surveyed these individuals to obtain contemporaneous information on seizure outcomes. Information on seizure outcomes was supplemented through direct contact with treating general practitioners, neurologists and where available a review of hospital medical correspondence. A direct comparison of seizure outcomes was then undertaken between these individuals and others who had undergone epilepsy surgery following the epilepsy MDT over the same period. This work is presented in detail in Chapter 4.

Table 2.2: Classification of seizure outcomes

Modified* ILAE outcome score	Description
1	Completely seizure-free; no auras
2	Only auras; no other seizure
3	One to three seizure days per year; +/- auras
4	Four seizure days per year to 50% reduction of baseline seizure days; +/- auras
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +/- auras
6	More than 100% increase of baseline seizure days; +/- auras

*ILAE post-surgical outcome score in the last 12 months where surgery is replaced by 'decision not to have surgery'

2.3 Outcomes following frontal lobe epilepsy surgery

Data in the Epilepsy Surgery database were analysed to describe long-term outcomes in those who have FLE surgery. This included an analysis of various factors that could aid in predicting seizure-free outcomes. Factors associated with complete seizure freedom were identified, as well as factors associated with earlier time to a seizure relapse.

To improve the granularity of our analysis, information on specific sites of frontal lobe resection was added to the database. We reviewed all available pre- and post-operative imaging on individuals in the Epilepsy Surgery database who had undergone frontal lobe surgery and reclassified resections into those that involved orbitopolar, frontomedial, dorsolateral or frontocentral regions. We further subdivided resections into those that involved various gyri of the frontal lobe, as well as extrafrontal regions commonly involved in frontal resections such as the anterior cingulate gyrus.

We retrospectively reviewed psychiatric and neuropsychology assessments to describe multimodal outcomes in addition to rates of seizure freedom. Psychiatric diagnoses were categorised according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5th Edition criteria, and diagnostic trajectories were recorded. This information is essential to providing comprehensive information to clinicians involved in the decision to offer FLE surgery, particularly given the high rates of psychiatric comorbidity that are seen in this cohort.

2.4 Economic aspects of epilepsy surgery

2.4.1 Index of Multiple Deprivation

Since 2000, the Ministry of Housing, Communities & Local Government in the United Kingdom has published geographic measures of relative deprivation among 32,844 small areas of England, each containing approximately 1,500 residents (Ministry of Housing, 2019). These areas are ranked in order of deprivation, which is assessed on the basis of relative income, employment, education, health and disability, crime, housing and living environment. From these domains, an Index of Multiple Deprivation (IMD) is calculated, which has been used as a marker of socioeconomic status in several studies, including previous work investigating differences in epilepsy prevalence among different regions of England. (Steer et al., 2014).

We used the IMD as a surrogate measure of socioeconomic status in both Chapter 3 and Chapter 5. This allowed us to examine if IMD was a significant predictor of proceeding to epilepsy surgery and therefore investigate if uptake of this treatment were different among different socioeconomic areas of England. By tracking changes in the IMD over time, we also assessed whether significant differences in the trajectory of deprivation status could be seen between those who had epilepsy surgery and those who did not, as well as those who were or were not seizure-free.

2.4.2 National Health Service Tariffs

In Chapter 6 we estimated the costs of an epilepsy surgery program in the National Health Service (NHS), and in particular how this varies for each individual according to different paths through the epilepsy surgery program. Providing this information to hospital managers is vital in demonstrating that not only is epilepsy surgery effective, but that it presents a cost-effective solution to manage drug-resistant epilepsy within a public healthcare system.

Tariffs are reference costs collected from NHS health providers each year and reflect the average unit cost to the NHS of providing a defined service. By calculating the summed tariffs of presurgical encounters in each individual, we could estimate the overall cost per person of presurgical evaluation through different pathways of the epilepsy surgery program at Queen Square. We used these findings to estimate the total cost per additional person seizure-free with epilepsy surgery. These data are presented in detail in Chapter 7.

2.5 Ethics

All work in this thesis was conducted following the principles of Good Clinical Practice, and studies were registered and approved by an Institutional Review Board at the National Hospital for Neurology and Neurosurgery, London, UK. Work from Chapters 3, 4 and 7 was registered as service evaluations into epilepsy surgery at University College London Hospitals (registration number 45-202021-SE). The studies included in Chapters 5 and 6 were approved as a separate evaluation into frontal lobe epilepsy surgery at University College

London Hospitals (registration number 135-202021-SE). As this work was based on previously acquired data and posed no risk to patients, the need for individual informed consent was waived by the Institutional Review Board at our centre (reference number 22/SC/0016). All information was kept within Trust servers and de-identified before statistical analysis.

2.6 Statistical Analysis

Over the course of this thesis we used a mixed-methods approach to analyse retrospective and prospectively collected data on people with drug-resistant focal epilepsy evaluated for surgery at the National Hospital for Neurology and Neurosurgery (NHNN). This included reporting observational data on seizure outcomes, univariate and multivariable logistic regression to model predictors of proceeding to surgery or outcome after resection, and Kaplan Meier survival analysis to assess predictors of time to a seizure relapse. Detailed information on statistical analyses is presented separately in each chapter.

Chapter 3: Predicting poor suitability for epilepsy surgery

3.1 Objective

This study was undertaken to determine the reasons why adults with drug-resistant focal epilepsy who undergo presurgical evaluation do not proceed with surgery, and identify predictors of this outcome.

2.2 Epilepsy Surgery paradigm

Surgery for selected people with drug-resistant focal epilepsy gives a greater chance of seizure freedom than medical therapy (de Tisi et al., 2011, Wiebe et al., 2001). As detailed in Chapter 1.9 – 1.11, candidates for epilepsy surgery require a detailed presurgical evaluation to determine whether potentially curative surgery is feasible. This is extensive and time-consuming, requiring multimodal investigations and input from an experienced multidisciplinary team (Duncan, 2011). The whole process is costly, but cost-effective if the outcome is seizure freedom (Wiebe et al., 1995, Sheikh et al., 2020).

In people with concordant semiology, EEG data and a neuroimaging abnormality, the chance of postoperative seizure freedom can be accurately predicted (Vakharia et al., 2018). When this is not the case, additional information from FDG-PET, ictal-SPECT and intracranial EEG may be required, which entail additional time and healthcare costs. A recent report concluded presurgical evaluation was cost-effective even if the chance of proceeding to surgery was 5% (Sheikh et al., 2020). This did not, however, include individuals with

extratemporal epilepsy or the need for intracranial EEG studies, which are both factors associated with lower surgical suitability (Malmgren and Edelvik, 2017).

Guidelines suggest referring all people with drug-resistant focal epilepsy to an epilepsy surgery centre. Still, realistic expectations of a favourable outcome, the need for intracranial EEG, and the risks of surgery should be discussed at the outset. The average time between the initial review to surgery has been reported between 56 and 183 weeks, highlighting the lengthy evaluation and the need to streamline presurgical assessment (Martínez-Juárez et al., 2017, Mumford et al., 2019). While epilepsy surgery may be underutilized (Jehi et al., 2015a, Kaiboriboon et al., 2015), up to two-thirds of people referred with drug-resistant focal epilepsy do not ultimately proceed to surgical resection (Fois et al., 2016, Cloppenborg et al., 2016, Mansouri et al., 2013).

Providing individuals with an early indication of their surgical suitability may help to better focus the presurgical evaluation and guide informed discussions between clinicians and people referred for assessment. A previous review at our centre of 612 people admitted for presurgical video-telemetry between 2007 and 2012 found that most did not proceed to surgery (Fois et al., 2016). A third of those who were offered surgery decided against proceeding. We aimed to determine the current situation at our centre and characterize the demographics and clinical features of those who undergo presurgical evaluation but do not proceed to surgery. By comparing these characteristics with those of individuals

who underwent surgery, we sought to identify factors that could predict the decision not to proceed.

3.3 Study design and selection process

Data from consecutive individuals discussed at our weekly epilepsy MDT from 01 January 2015 to 31 December 2019 was collected. This included comprehensive information on the presurgical evaluation as described in Chapter 2. Following MDT discussion, one of three possible consensus decisions was made:

a) Recommendation for surgery
b) Recommendation for further investigation
c) Recommendation not to proceed with surgery

Individuals were classified into two groups. The first group consisted of those who did not have surgery, which included both those in whom the MDT decision was not to proceed with surgery as well as those who were initially recommended for surgery or further investigation, but where the individual subsequently decided not to proceed. The second group consisted of individuals who underwent definitive surgery over the same 5-year period at the same site. These two groups are illustrated in Figure 3.1.

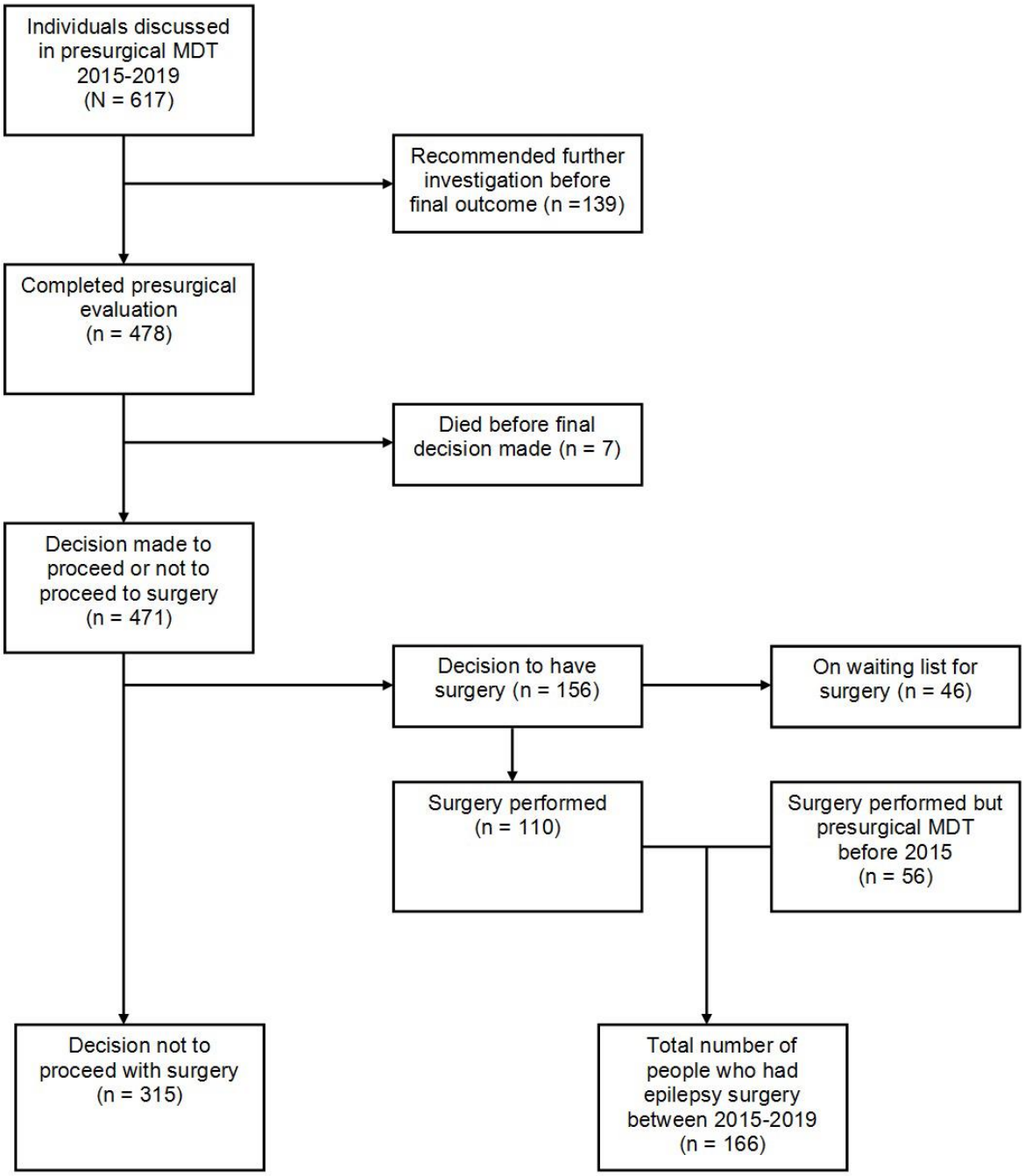

Figure 3.1: Flowchart of individuals included for analysis during the study period

We compared demographic and clinical features between those who did and did not have surgery, focusing on those characteristics often known before investigations with long waiting times, such as scalp video-EEG telemetry, ictal

SPECT and intracranial EEG recordings. The socioeconomic status of individuals, who mostly lived in England, was assessed through the Index of Multiple Deprivation (IMD), as described in Chapter 2, which estimates relative deprivation levels among discrete areas of England, known as Lower-layer Super Output Areas. The IMD is based on seven domains: income, employment, education/skills, health deprivation or disability, crime, barriers to housing and living environment deprivation (Ministry of Housing, 2019). A map of the distribution of IMDs in England in 2019 is shown in Figure 3.2.

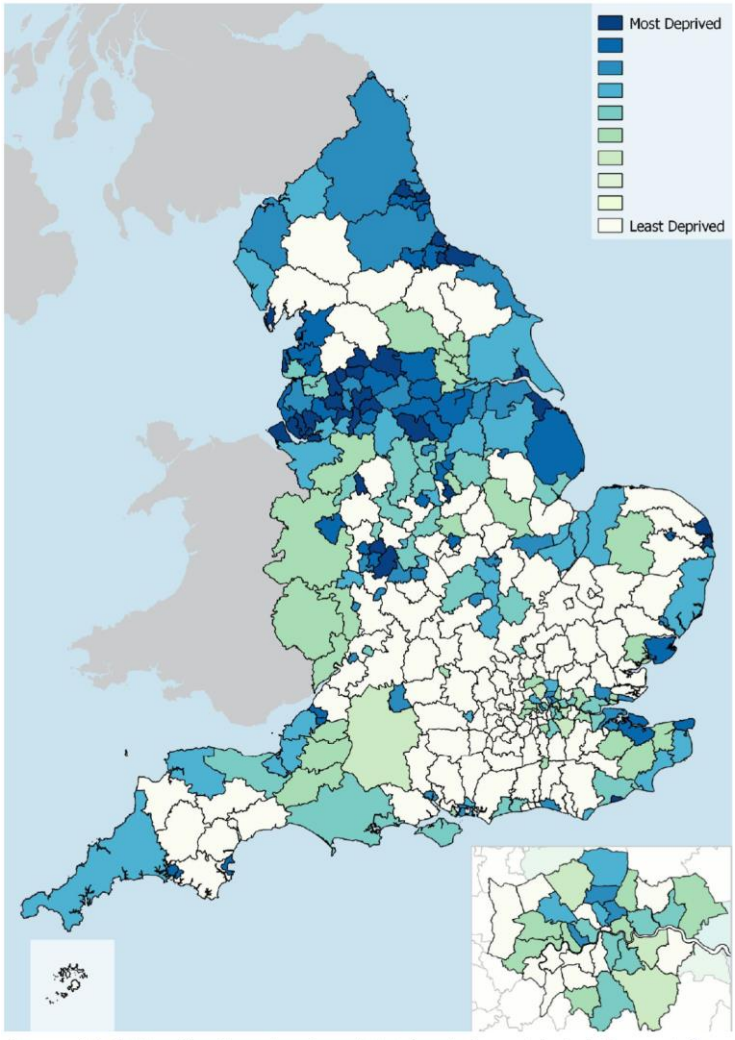

Figure 3.2: Distribution of the IMD based on the proportion of neighbourhoods in the most deprived decile nationally. Adapted from The English Indices of Deprivation 2019. Ministry of Housing, Communities & Local Government. Statistical Release 26 September 2019. Used with permission.

3.4 Data analysis

We compared demographic, clinical, imaging and EEG findings between individuals who did and did not proceed to surgery. We used a Pearson's Chi-Square test for dichotomous data and a Mann-Whitney U-test for continuous data, in each case to test the null hypothesis of no association between the outcome of interest and the decision whether or not to proceed with surgery. Odds ratios for binary outcomes were estimated using univariable logistic regression. Significant factors on univariable analysis were entered into a multivariable binary logistic regression to assess predictors of not proceeding to epilepsy surgery with a p-value <0.05 deemed statistically significant. We estimated odds ratios and associated 95% confidence intervals for individuals with combinations of demographic, imaging and electroclinical data not proceeding with surgery. Predicted probabilities of surgery were estimated from the fitted logistic regression model with associated 95% confidence intervals. We used IBM SPSS Statistics for Windows v20 (International Business Machines Corp, Armonk, NY) for data analysis.

3.5 Results

3.5.1 Characteristics of the cohort

A total of 617 individuals were discussed at the epilepsy surgery MDT meeting over the five years between 01 January 2015 and 31 December 2019. A definitive decision not to proceed with surgery, either at the MDT meeting or subsequently, was made in 315 (51%) people (Figure 3.1). Of the remainder, 139 (23%) were awaiting further investigation or intracranial EEG (as of January

2021), 110 (18%) had surgery, 46 (7%) were on the waiting list for surgery, and seven (1%) had died while still under evaluation, with five deaths deemed to be a direct consequence of seizures.

We compared baseline clinical characteristics and investigatory data between those in whom a decision not to have surgery was made (n=315), with individuals who underwent definitive epilepsy surgery at our centre over the same time period (n=166). This information is summarised in Table 3.1. A proportion of individuals in this surgical group had been discussed at the presurgical MDT prior to 2015 (Figure 3.1).

Table 3.1: Baseline characteristics of individuals discussed in the Queen Square presurgical MDT and did or did not have surgery from Jan 2015 - Dec 2019				
	Not for surgery (n=315)	**Had surgery (n=166)**	**Odds Ratio (95% CI)**	**P value**
Demographics				
Women, n/N (%)	157/315 (50)	80/166 (48)	1.07 (0.73-1.56)	0.73
Age of epilepsy onset, median (IQR), y	12 (7-18)	15 (7-23)	**0.98 (0.96-1.00)**	**0.014**
Age at final decision [a], median (IQR), y	36 (28-44)	38 (30-48)	0.99 (0.97-1.00)	0.06
Learning disability, n/N(%)	51/315 (16)	10/166 (6)	**3.01 (1.49-6.11)**	**<0.001**
History of febrile convulsions, n/N (%)	36/315 (11)	27/166 (16)	0.64 (0.37-1.09)	0.34
Prolonged early childhood convulsion, n/N (%)	17/315 (5)	16/166 (10)	0.54 (0.26-1.09)	0.08
Previous significant head trauma, n/N (%)	21/315 (7)	9/166 (5)	1.25 (0.56-2.79)	0.59
Psychiatric diagnosis, n/N (%)	110/315 (35)	72/166 (43)	0.69 (0.47-1.02)	0.10
Prior neurological insult Meningitis/encephalitis, n/N (%) Previous stroke, n/N (%) Previous brain surgery, n/N (%)	18/315 (5) 7/315 (2) 19/315 (6)	8/166 (5) 6/166 (2) 11/166 (7)	1.20 (0.51-2.81) 1.06 (0.26-4.27) 0.96 (0.45-2.05)	0.68 0.76 0.99
Epilepsy features				
Duration of epilepsy, median (IQR), y	21 (12-31)	22 (10-33)	1.01 (0.99-1.02)	0.62
History of generalised sz, n/N (%)	228/315 (72)	131/166 (79)	0.70 (0.45-1.10)	0.12
Focal unaware sz/month, median (IQR)	8 (2.5-23)	6 (2.0-20)	1.00 (0.99-1.01)	0.07
Generalised sz/month, median (IQR)	0 (0-1)	0 (0-0.56)	1.01 (0.98-1.05)	0.13
Imaging characteristics				
Abnormal MRI, n/N (%)	172/315 (55)	150/166 (90)	**0.13 (0.07-0.23)**	**<0.001**
Bilateral MRI abnormality, n/N (%)	30/315 (10)	8/166 (5)	0.48 (0.22-1.07)	0.14

Video telemetry data				
Bilateral [b] epileptiform abnormality (interictal), n/N (%)	114/315 (36)	47/166 (28)	1.44 (0.95-2.16)	0.08
Bilateral [b] epileptiform abnormality (ictal), n/N (%)	72/315 (23)	10/166 (6)	**4.62 (2.32-9.23)**	**<0.001**
Extratemporal epilepsy, n/N (%)	190/315 (60)	43/166 (26)	**4.35 (2.87-6.58)**	**<0.001**
[a] final decision not to have surgery or date of surgical procedure [b] Inclusive of both synchronous and independently bilateral epileptiform abnormalities				

3.5.2 Initial investigations

Of the 315 individuals in whom a decision not to proceed with surgery was made, MRI was available in 314 (one had metal fragments in his skull, precluding MRI). Imaging showed a significant pathology in 172 (55%), with 30 (10%) having bilateral pathology. Bilateral MRI pathology (OR: 0.50; 95% CI 0.21-1.20) was not significantly more common in those who did not have surgery. There were differences in radiological features between the operated and non-operated cohorts. Those with a normal MRI or imaging evidence of gliosis were less likely to proceed to surgery. Conversely, those who proceeded to surgery had greater odds of having hippocampal sclerosis, focal cortical dysplasia, a cavernoma or a dysembryoplastic neuroepithelial tumour (DNT) on MRI (Table 3.2).

Of 166 individuals who had surgery, 16 (10%) had a normal MRI and 43 (26%) had extratemporal epilepsy. All 16/16 of those with normal MRI and 20/43 with extratemporal epilepsy required intracranial EEG before surgery.

Table 3.2: MRI features in those with drug-resistant focal epilepsy who did and did not have epilepsy surgery following presurgical evaluation				
Finding	**Not for surgery (n=315, %)**	**Had surgery (n=166, %)**	**Adjusted [a] OR (95% CI)**	**P Value**
Normal	142 (45)	16 (10)	**4.48 (1.68-11.94)**	**<0.001**
Gliosis	28 (9)	4 (2)	**4.25 (1.38-13.11)**	**0.013**
Polymicrogyria	5 (2)	0 (0)		
Encephalomalacia	20 (6)	5 (3)	1.81 (0.63-5.24)	0.27
Atrophy	13 (4)	3 (2)	1.59 (0.41-6.20)	0.5
Focal cortical dysplasia	17 (5)	16 (10)	**0.21 (0.09-0.49)**	**<0.001**
Hippocampal sclerosis	37 (12)	48 (29)	**0.48 (0.28-0.84)**	**0.018**
Cavernoma	7 (2)	16 (10)	**0.17 (0.06-0.46)**	**<0.001**
DNT	5 (2)	37 (22)	**0.08 (0.03-0.21)**	**<0.001**
Heterotopia	8 (2)	2 (1)	0.98 (0.18-5.25)	0.98
Other [b]	32 (11)	19 (11)		
[a] Adjusted for baseline characteristics, video-telemetry findings and presence of bilateral pathology.				
[b] Including cases with mixed or indeterminate pathology				

Of 481 individuals included for analysis (166 who had surgery, 315 who did not proceed), all individuals had scalp video-EEG telemetry (n=478) or prolonged ambulatory EEG (n=3). Bilateral seizure onsets on ictal video telemetry were a strong predictor for not proceeding to surgery (OR: 3.05; 95% CI 1.41 to 6.61). In cases in whom surgery was performed despite this finding (n=10), this was because seizures from one hemisphere were thought to be subclinical (n=8) or subsequent intracranial EEG demonstrated unifocal seizure onset (n=2). Bilateral

interictal epileptiform discharges (OR 1.11; 95% CI 0.69-1.80) were not significantly more common in those who did not have surgery.

3.5.3 Stage Two investigations

Stage Two investigations, which include FDG-PET, ictal SPECT and intracranial EEG are often required when the electroclinical presentation is discordant with imaging or when scalp EEG is non-localising.

An FDG-PET scan was performed in 186 (59%) people within the group who did not proceed to surgery (Table 3.3). A higher proportion of those who did not proceed to have surgery had FDG-PET scans (OR: 2.78; 95% CI 1.48 to 5.19), likely reflecting the larger number of non-lesional cases in this cohort. Combining MRI and FDG-PET data showed that while 16/166 (10%) of those who had a resection had a normal MRI scan, and 13/166 (8%) had a normal FDG-PET scan, only 5/166 (3%) had normal MRI and FDG-PET scans, compared with 51/315 (16%) in the group who did not proceed to surgery (OR: 5.62; 95% CI 1.96 to 16.08). Individuals were less likely to be declined if they had an abnormal FDG-PET (OR: 1.89; 95% CI 1.25 to 2.85).

An ictal SPECT was performed in 17 (10%) surgical cases and in 51 (16%) of those who did not proceed to surgery. Individuals were less likely to be declined if they had focal changes on ictal SPECT (OR: 2.34; 95% CI 1.38 to 3.95).

Seventy-six individuals between both groups had intracranial EEG (65 SEEG, 11 SDE). Of these, 48 (63%) proceeded to resection and 28 (37%) did not proceed. In these cases, reasons for not offering a resection were evenly distributed between the ictal onset not being adequately localised following intracranial EEG (n=8; 29%), evidence of multifocality (n=7; 25%), the subject declining a resection (n=7; 25%) and seizure onset in or adjacent to an eloquent cortex area (n=6; 21%).

Table 3.3: Additional investigations performed during presurgical evaluation prior to a final decision not to proceed with epilepsy surgery

	Not for surgery (n=315)	**Had surgery (n=166)**
FDG-PET scan, n/N (%)	186/315 (59)	45/166 (27)
Abnormal scan, n (%)	119/186 (64)	32/45 (71)
Normal scan, n (%)	67/186 (36)	13/45 (29)
Normal MRI & normal PET, n/N (%)	51/315 (16)	5/166 (3)
Ictal SPECT, n/N (%)	51/315 (16)	17/166 (10)
Bilateral abnormality, n (%)	5/51 (10)	1/17 (6)
Dominant involvement, n (%)	15/51 (29)	4/17 (24)
Non-dominant involvement, n (%)	28/51 (55)	7/17 (41)
No abnormality found, n (%)	3/51 (6)	5/17 (29)
Intracranial EEG recording, n/N (%)	28/315 (9)	48/166 (29)
Subdural strips, grids +/- depth electrodes	3/28 (11)	12/48 (25)
Stereo-EEG	25/28 (89)	36/48 (75)

3.5.4 Predictors of not proceeding to surgery

We entered significant explanatory variables into a multivariable logistic regression model to further explore associations with proceeding to surgery and confirmed that those with a learning disability (OR: 2.35; 95% CI 1.07 to 5.16), extratemporal epilepsy (OR: 2.93; 95% CI 1.82-4.71), evidence of bilateral seizure onsets on an ictal recording (OR 3.05; 95% CI 1.41 to 6.61) and a normal MRI (OR: 4.48; 95% CI 1.68 to 11.94) were more likely not to proceed with surgery.

Different combinations of these four factors could help predict the likelihood of individuals proceeding to surgery (Table 3.4). Those with normal MRI and extratemporal epilepsy were much less likely to have surgery (OR: 8.71; 95% CI 3.89 to 19.53), as were those with a combination of extratemporal epilepsy and learning disability (OR: 3.76; 95% CI 1.56 to 9.66) or bilateral seizure onsets (OR: 4.25; 95% CI 1.68 to 10.72). The estimated probability of someone with none of these factors having surgery was 61.9% (95% CI 54.8% to 68.4%). Conversely, the likelihood of those with a normal MRI together with a learning disability, bilateral seizure onset or extratemporal epilepsy proceeding to surgery was under 10% (Table 3.5).

Table 3.4: Multivariable predictors of not proceeding to epilepsy surgery				
Characteristic	**No surgery (n=315)**	**Had surgery (n=166)**	**Adjusted [a] OR (95% CI)**	**P value**
Learning disability, n/N (%)	51/315 (16)	10/166 (6)	2.35 (1.07-5.16)	**<0.001**
Learning disability & extratemporal epilepsy, n/N (%)	39/315 (12)	6/166 (4)	3.76 (1.46-9.66)	**0.003**
Learning disability & normal MRI, n/N (%)	18/315 (6)	1/166 (1)	8.10 (1.02-64.18)	**<0.05**
Bilateral interictal epileptiform abnormalities, n/N (%)	114/315 (36)	46/166 (28)	1.11 (0.69-1.80)	0.23
Extratemporal origin, n/N (%)	190/315 (60)	43/166 (26)	2.93 (1.82-4.71)	**<0.001**
Bilateral seizure onsets, n/N (%)	72/315 (23)	10/166 (6)	3.05 (1.41-6.61)	**0.002**
Normal MRI scan, n/N (%)	142 (45)	16 (10)	4.48 (1.68-11.94)	**<0.001**
Extratemporal origin & bilateral seizure onsets, n/N	53/315 (17)	6/166 (4)	4.25 (1.68-10.72)	**<0.001**
Normal MRI & extratemporal epilepsy, n/N (%)	95/315 (30)	7/166 (4)	8.71 (3.89-19.53)	**<0.001**
Normal MRI, bilateral interictal abnormalities & extratemporal epilepsy, n/N (%)	42/315 (13)	2/166 (1)	9.65 (2.27-40.95)	**<0.001**
[a] Adjusted for age, psychiatric comorbidity and frequency of seizures/month				

Table 3.5: Estimated probabilities of surgery for combinations of predictive factors					
Learning Disability?	**Normal MRI?**	**Bilateral seizure onset?**	**Extratemporal epilepsy?**	**Estimated Pr(Surgery)**	**95% Confidence Interval**
No	No	No	No	0.619	(0.548, 0.684)
Yes	No	No	No	0.407	(0.241, 0.599)
No	Yes	No	No	0.204	(0.127, 0.311)
No	No	Yes	No	0.345	(0.199, 0.528)
No	No	No	Yes	0.364	(0.277, 0.462)
Yes	Yes	No	No	0.098	(0.041, 0.217)
Yes	No	Yes	No	0.183	(0.072, 0.392)
Yes	No	No	Yes	0.196	(0.103, 0.340)
No	Yes	Yes	No	0.077	(0.033, 0.169)
No	Yes	No	Yes	0.083	(0.047, 0.142)
No	No	Yes	Yes	0.157	(0.082, 0.281)
Yes	Yes	Yes	No	0.034	(0.011, 0.103)
Yes	Yes	No	Yes	0.037	(0.015, 0.086)
Yes	No	Yes	Yes	0.073	(0.028, 0.176)
No	Yes	Yes	Yes	0.029	(0.012, 0.065)
Yes	Yes	Yes	Yes	0.012	(0.004, 0.037)

3.5.5 Differences in socioeconomic status

We compared the Index of Multiple Deprivation when evaluating those who did not proceed to surgery to those who did. The median decile of deprivation was higher in those who did not proceed (median decile of deprivation 40-50% vs 50-60%, $p<0.05$), indicating that these people came from deprived areas (Figure 3.3).

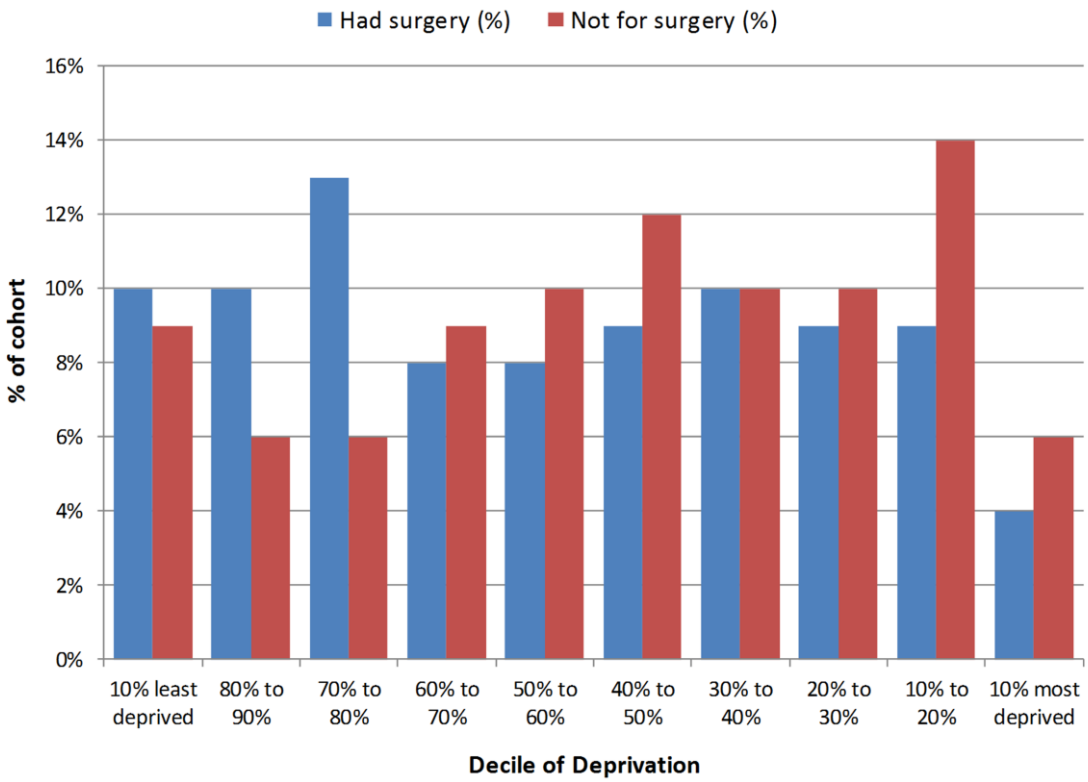

Figure 3.3 Distribution of deprivation deciles between those who do and do not have surgery

3.5.6 Duration of presurgical evaluation

Of the 166 individuals who had definitive epilepsy surgery between 01 January 2015 and 31 December 2019, the median time from the first presurgical clinic appointment to surgery was 135 weeks (IQR 94-213 weeks).

3.5.7 Reasons for not proceeding with surgery

There were several reasons why individuals did not proceed to surgery following presurgical evaluation (Figure 3.4).

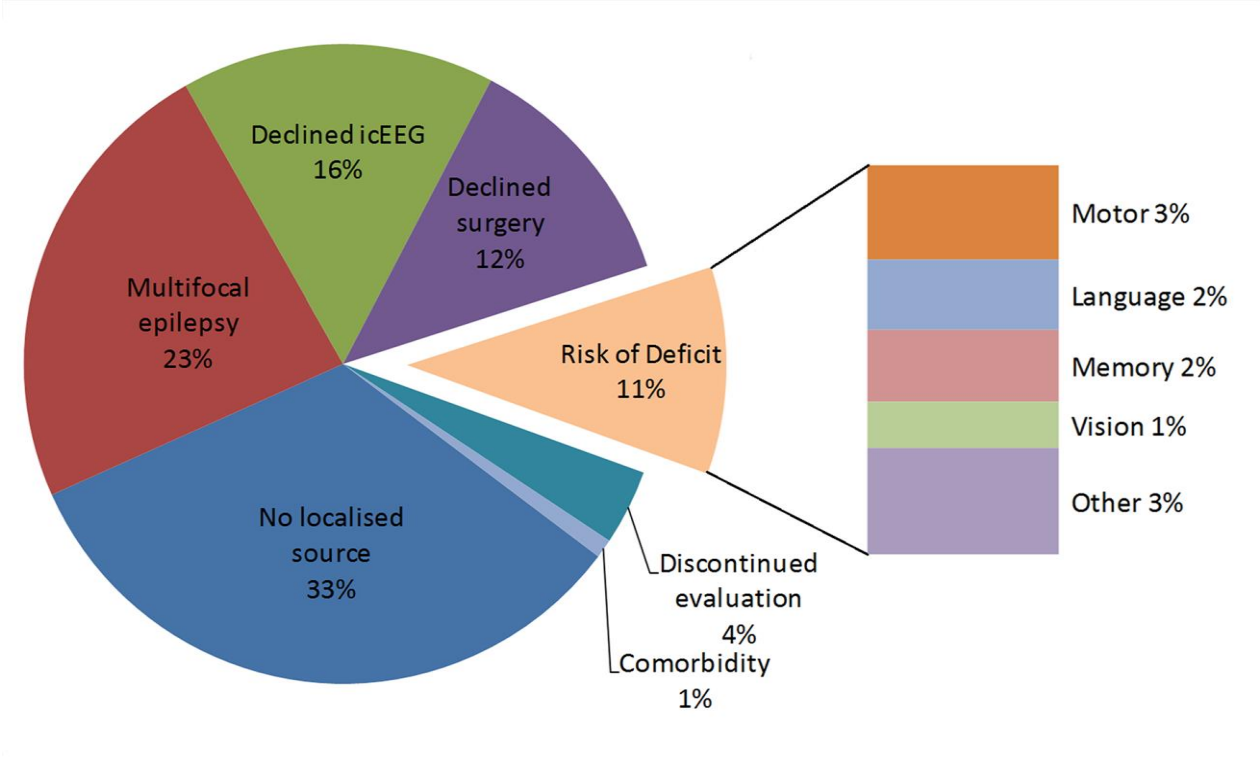

Figure 3.4: Reasons for not proceeding with epilepsy surgery

The most common reason for not proceeding was an inability to localise the epileptogenic zone (n=104; 33%). In 96 of these cases the non-invasive electroclinical data including ictal recordings on scalp EEG did not provide sufficient lateralising or localising information to generate a hypothesis for the seizure onset zone. In the remaining eight cases, individuals proceeded to intracranial EEG however ictal patterns had a widespread distribution implicating

extensive epileptic networks, and a single focus could not be adequately identified.

Other reasons for not proceeding to surgery included multifocal epilepsy (n=74; 23%), decision by the individuals not to proceed with intracranial EEG (n=50; 16%), declining surgery (n=39; 12%), risk of significant deficit (n=33; 11%), declining further non-invasive investigations (n=12; 4%), or coexisting neurological co-morbidity (n=3; 1%).

In the 33 individuals in whom surgery was not performed due to the risk of a postoperative deficit, the concern was of affecting motor function (n=8; 3%), language (n=6; 2%), memory (n=6; 2%), vision (n=4; 1%) or other neuropsychological domains (Figure 3.5).

The decision not to proceed with surgery was made at different time-points of the presurgical evaluation pathway (Figure 3.5). In most, this was made at the MDT meeting (n=185; 59%) following a review of initial investigations, 16% after offering intracranial EEG and 12% after offering surgery.

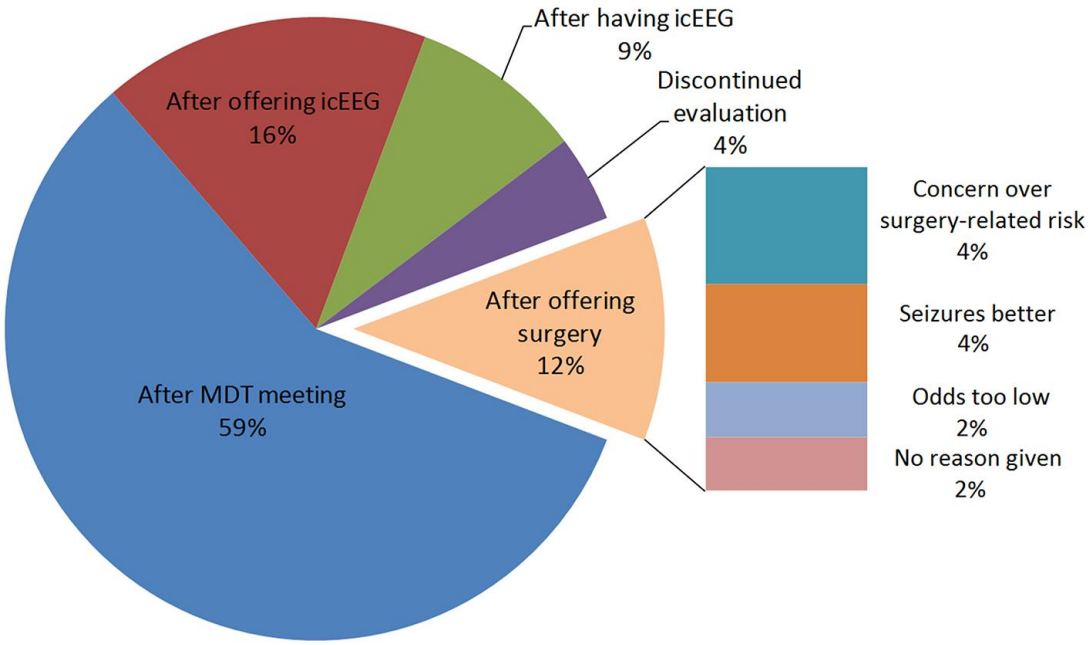

Figure 3.5: When was the decision not to proceed with surgery made?

Information on the time taken to decide whether to proceed to surgery is presented in detail in Chapter 7, and varied widely according to different routes through the presurgical pathway and whether individuals proceeded to intracranial EEG.

3.6 Discussion

There are several reasons why those who are evaluated for epilepsy surgery do not proceed. Some individuals are deemed unsuitable following presurgical evaluation, whereas others decline due to low odds of seizure freedom or concern over surgical risks. An early, realistic discussion surrounding the likelihood of surgery or the need for invasive intracranial EEG monitoring may help inform individuals in deciding whether to undergo presurgical evaluation.

We investigated the predictive value of basic demographic data and non-invasive investigations in assessing the likelihood of having epilepsy surgery. Learning disability, normal MRI scan, extratemporal epilepsy and bilateral seizure onset on video-EEG telemetry were all independent predictors of not proceeding to surgery on multivariable analysis. Combining demographic, imaging and EEG data improved the ability to predict the likelihood of not proceeding to surgery.

Our data add to several models designed to improve the selection of people for presurgical evaluation and ultimately resective surgery (Dugan et al., 2017, Jehi et al., 2015b). A recent Epilepsy Surgery Grading Scale (ESGS) based on expert consensus opinion used basic information to assess the likelihood of proceeding to surgery and having a favourable outcome (Dugan et al., 2017). Stratification into different grades of the ESGS could predict the likelihood of surgery between 61.5% and 14.7%. Our study gives concordant results in a different centre and adds weight to these findings. The estimated probability in our cohort of someone with a normal MRI together with a learning disability, bilateral seizure onset or extratemporal epilepsy proceeding to surgery was under 10%.

Individuals should be carefully advised on the probability of surgical feasibility, optimal chances of seizure remission, and inevitable risks of surgery at the outset. In many cases, this discussion can occur even before being referred for investigations with high demand and long waiting times such as video-EEG telemetry, ictal SPECT or intracranial EEG recordings. This will reduce the number of those who are thought suitable for intracranial EEG or surgery but who

decide not to proceed. At our centre, over 70% of those who proceeded to intracranial EEG were thought to be suitable surgical candidates, which is slightly higher than previously reported (Mansouri et al., 2013). This highlights the utility of invasive recordings in further defining the seizure onset zone following non-invasive video-EEG telemetry.

Those who did not proceed to surgery had a threefold higher chance of having bilateral seizure onset on video-EEG telemetry. In those who subsequently had surgery, seizures from one hemisphere were thought to be subclinical or electroclinical findings following scalp or intracranial EEG were consistent with unifocal epilepsy. Previous studies have suggested approximately a third of people with unilateral TLE have bitemporal interictal epileptiform abnormalities (Sadler and Desbiens, 2000). Most cases with bitemporal interictal changes on scalp EEG have seizures that originate from one temporal lobe (So et al., 1989a, So et al., 1989b). Surgery for selected individuals with bitemporal epileptiform abnormalities but unilateral seizure onset on intracranial EEG can still have good outcomes, with up to 40% seizure freedom. In people with bilateral seizure onset zones, surgery is not as favourable (12% seizure freedom) (So et al., 1989b, Hufnagel et al., 1994).

Concerning further investigations, an FDG-PET was performed in a more significant proportion of people who did not have surgery, reflecting the higher number of non-lesional cases and searching for a focus. One-third of individuals with a normal MRI scan had an abnormal PET scan. Those who did not have

surgery were over five times more likely to have had a normal MRI and normal FDG-PET, highlighting the utility of PET in determining surgical suitability for those with normal MRI. This is consistent with other reports that concordance between clinical consensus and FDG-PET can aid the decision to proceed with intracranial EEG monitoring and possible surgery (Peedicail et al., 2020, Steinbrenner et al., 2022).

As described in Chapter 1.10, ictal SPECT is generally carried out as a prelude to intracranial EEG to refine the strategy for placing intracranial electrodes. In our cohort, less than half of those with an ictal SPECT proceeded to intracranial recording, as many individuals subsequently declined intracranial EEG once it was offered. This underlines the importance of informing individuals adequately on the purpose of ictal SPECT before it is undertaken. Ictal SPECT is a time and resource-intensive investigation with radiation exposure.

3.6.1 Reasons not to have surgery

Consistent with previous reports, the main reasons for not proceeding to surgery in our cohort were an inability to define the EZ, presence of multiple foci or the individual/caregiver declining an operation (Weber et al., 2019, Mansouri et al., 2013). This decision was often made at the MDT meeting following a review of initial investigations. Ictal video telemetry was a critical factor in deciding not to proceed. It was also a major determinant in guiding referral for Stage Two investigations such as FDG-PET, ictal SPECT or intracranial monitoring. Risk of a postsurgical deficit accounted for only a small proportion of people being

unsuitable for surgery. Functional MRI to determine language dominance and baseline neuropsychology and neuropsychiatry assessments were all factors that influenced this reason not to proceed. Only 1% of people were rejected based on concurrent comorbidity at our centre, reflecting referral selection at initial review in outpatient clinics.

3.6.2 Individuals who decline evaluation or surgery

Many people decided not to proceed after being offered intracranial EEG or surgical resection. This is comparable to reports from other centres, where up to a third of people or caregivers declined a resection (Weber et al., 2019, Mansouri et al., 2013, Cloppenborg et al., 2016). In a minority of cases, this was because seizure control had improved. Compared to a previous audit of 2007-2012 at our centre in which a third of those offered surgery declined to proceed, in the current study, this was 12%, suggesting that selection for presurgical evaluation and advice given has improved (Fois et al., 2016). Nonetheless, this finding emphasizes the critical importance of clearly describing the risks and benefits of surgery at the outset before embarking on investigations. This would also help avoid situations wherein, at the end of a complex process, the individual declines to proceed when the risk/benefit ratio may have been evident at the start of the process.

For example, in an individual with hippocampal sclerosis and concordant clinical and EEG data, there is an 80% chance of remission greater than one year, a 40% chance of long-lasting seizure freedom and 70% of individuals choose to

remain on anti-seizure medication (Bell et al., 2017, Vakharia et al., 2018). There is a 30-50% chance of a significant decline in verbal memory and word-finding ability in a speech-dominant hemisphere, a 5-10% risk of a visual field defect that precludes driving and a 1% risk of severe morbidity from surgery such as hemiparesis (Bell et al., 2017). This needs to be weighed against a 1% annual risk of fatality with continued seizures and 2% chance of remission with anti-seizure medication, if four have already been tried (Bell et al., 2017, Vakharia et al., 2018). For those with normal MRI and a history of FTBTCS in addition to a learning disability or extratemporal epilepsy, the chance of seizure freedom five years after surgery is less than 10% (Bell et al., 2017).

Realistic odds of a good outcome should be conveyed to individuals throughout the entire process. Advising people of the likely chance of seizure remission and the inevitable risks of surgery is appropriate at the outset. If they do not find these acceptable, there is little merit in subjecting them to a full evaluation.

Notably, approximately half of those who had surgery for extratemporal epilepsy and all those with a normal MRI brain scan had required intracranial EEG before resection. Informing those with normal MRI or extratemporal epilepsy of this likely investigation early in the evaluation is crucial, as if they do not wish to proceed to intracranial EEG there is likely to be little benefit to arranging other investigations such as inpatient video telemetry, FDG-PET or ictal SPECT, which all have long wait times. Compared to a previous audit at our centre, rates of people declining intracranial recording or surgery once it is offered have dropped substantially,

likely due to our efforts at improved counselling throughout the presurgical evaluation.

3.6.3 Socioeconomic deprivation and epilepsy surgery

We also investigated whether socioeconomic deprivation was more severe among those with drug-resistant epilepsy who do not end up having epilepsy surgery compared to those that do. This could highlight groups in society where further efforts should be made to help facilitate access to epilepsy surgery. There was a significant difference in the distribution of deprivation deciles, with people who did not have epilepsy surgery residing in more deprived areas. Whether socioeconomic deprivation is a cause or consequence of not proceeding to epilepsy surgery is unclear, though the impact that poor seizure control has on work capability, driving status and employment has been well established (Jennum et al., 2011, Khoo et al., 2020, Djibuti and Shakarishvili, 2003). Accessing appropriate services can be challenging for those without private health insurance, and many adults with epilepsy struggle to afford important elements of health care, including medication (Thurman et al., 2016). Even with free at the point of delivery healthcare provision, presurgical evaluation is demanding in terms of repeated visits to the centre, with associated costs and a need for support that may not be readily available for those living with a degree of deprivation. While the UK National Health Service aspires to provide equal access to healthcare, our findings suggest it does not fully compensate for social deprivation, as deprived people may be less likely to stay the course. It also

raises the possibility that the low uptake of surgery in socially deprived areas may be a mechanism by which health inequality is maintained.

The cost-effectiveness of surgery, particularly for those who achieve seizure freedom with anterior temporal lobectomy has been well established (Wijnen et al., 2017, Langfitt, 1997). Data on the cost-effectiveness of the presurgical evaluation itself, however, particularly when over 50% of individuals assessed do not have surgery, is much less clear. Intracranial monitoring requires expertise in the implantation of electrodes and interpretation of these results but comes with associated costs related to the antecedent non-invasive investigation, the need for the additional operating room, nursing and neurophysiology staff, and admission to a video-EEG telemetry unit. The costs involved in working up individuals through different routes of the presurgical pathway, including intracranial EEG are described in further detail in Chapter 7.

We support guidelines recommending early referral for consideration of epilepsy surgery in those with drug-resistant focal epilepsy. This should, however, be tempered by realistic expectations of surgical suitability, which must be conveyed to individuals and their families early in the process.

3.6.4 Study Limitations

There were several limitations to our study. This was a retrospective analysis of a prospectively followed cohort of adults investigated at a single tertiary referral centre. As our cohort consisted only of people who had been discussed in a

presurgical MDT meeting, there was also a selection bias with those thought unsuitable for surgery following initial clinic consultation not included in the analysis. Presurgical advice to people at our centre routinely includes discussing the likelihood of seizure freedom, as assessed by current literature. Inevitably, this could reduce the possibility of individuals with specific characteristics, such as normal MRI, proceeding to surgery and introduce a bias to our findings. Nonetheless, our results reflect real-world experience of an epilepsy surgery centre in a developed country with free at the point of delivery healthcare and describe the likelihood of these individuals proceeding with evaluation or surgery following counselling. It would be of great interest to obtain comparative data from other Epilepsy Surgery Centres.

In keeping with the intention to treat methodology, we included the minority of people who were offered surgery but declined an operation in our multivariate analysis. This could have reduced the impact of significant findings, as it is likely some of these individuals had a more favourable presurgical evaluation. Our assessment of socioeconomic status was also limited to the Index of Multiple Deprivation. While this is frequently used to approximate socioeconomic status in England, it does not consider individual variations or those who reside in other areas of the UK or overseas.

3.7 Conclusions

We have identified how demographic, clinical, and investigatory data combinations can help predict whether people with drug-resistant focal epilepsy are likely to proceed to surgery. Learning disability, a normal MRI or FDG-PET scan, extratemporal origin and bilateral seizure onset zones on scalp-EEG are associated with lower surgical suitability. Discussing these results and their implications may help clinicians and individuals decide whether to undergo the expensive, time-consuming and sometimes invasive presurgical evaluation.

Chapter 4: Seizure outcomes without surgery

4.1 Introduction

It is clear that neurosurgery leads to the highest chance of seizure freedom for suitable people with drug-resistant focal epilepsy who fulfil feasibility criteria. (Wiebe et al., 2001, de Tisi et al., 2011, Malmgren and Edelvik, 2017). The results of Chapter 3 suggested, however, that most of those who complete presurgical evaluation do not proceed to surgery. Common reasons for this in our cohort included an inability to adequately localise the epileptogenic zone, multifocal epilepsy, or the risk of developing a post-surgical neurological deficit, consistent with reports from other centres elsewhere (Weber et al., 2019, Cloppenborg et al., 2016). Many candidates suitable for surgery also decided not to proceed, considering the risks involved to outweigh potential benefits.

There are limited data reporting follow-up outcomes in those who have undergone multidisciplinary presurgical evaluation but not proceeded to surgery. Often, these individuals will subsequently try different ASM, neurostimulation or ketogenic diet to reduce seizure frequency. Over the last three decades, there has been a considerable increase in the number of available ASM. Their ability to impart seizure freedom in people with drug-resistant epilepsy, however, remains low (Chen et al., 2018, Luciano and Shorvon, 2007, Kalilani et al., 2018). Similarly, while vagus nerve stimulation may improve seizure frequency, seizure freedom rarely occurs (Chavel et al., 2003).

Identifying outcomes in the select cohort of people with drug-resistant epilepsy who complete presurgical evaluation but do not proceed to surgery will improve our ability to have informed discussions of seizure outcomes with this group of people.

4.2 Objective

In this chapter we will describe seizure outcomes in people with drug-resistant epilepsy who completed presurgical evaluation but did not proceed to surgery.

4.3 Study design

We recorded reported seizure outcomes in the previous year for individuals identified in Chapter 3 who had completed presurgical evaluation but not proceeded to a definitive operation. This included those in whom a clinical decision was made not to proceed, as well as those who declined an operation after it had been offered. Information on seizure outcomes were obtained in each case through direct contact with these individuals, primary care physicians and their consultant neurologists. Where applicable, cause of death was identified from correspondence from treating physicians and/or individual death certificates.

Seizure outcomes in all cases were directly self-reported by individuals or family members, who were asked to maintain prospective seizure records. Electronic records of seizure frequency at time of presurgical evaluation and contemporary follow-up were reviewed in all cases to classify subjects into the ILAE outcome scale. Those who had less than 12-month follow-up were not included. For

comparison, seizure outcomes in people who had surgery at our centre during the study period were also recorded from the UCLH Epilepsy Surgery Database.

4.4 Results

Of the 617 individuals discussed in presurgical epilepsy MDT meetings from 01 January 2015 to 31 December 2019, 471 completed presurgical evaluation, and 156 had or were on the waiting list for surgery. A definitive decision not to have surgery was made in the remaining 315 individuals, including 39 who were considered suitable candidates but who declined resective surgery. The reasons why these people did not have surgery are summarized in Table 1 and have been reported in detail in Chapter 3. Nine (3%) of these 315 people had died in the years following the MDT meeting, and data were not available for 25 (8%), leaving 281 (89%) included for analysis. The median duration of follow-up was 2.4 (IQR 1.5-4) years.

Table 4.1: Reasons for not having epilepsy surgery in people who underwent presurgical evaluation at Queen Square from 2015 to 2019

Reason	**N=315 (%)**
No localised source found	104 (33)
Multifocal epilepsy	74 (23)
Declined further investigation	62 (20)
Declined resective surgery	39 (12)
Risk of significant post-surgical deficit	33 (10)
Neurological comorbidity	3 (1)

The median age at the time of the decision not to have surgery was 36 (IQR 28-45) years old, with a median duration of epilepsy of 21 (IQR 13-31) years. Individuals took a median of 3 (IQR 2-4) ASM at the time of the presurgical MDT meeting and had tried a median of 7 (IQR 5-9) ASM. The seizure frequency reported by these individuals over the last 12 months at their most recent follow-up is listed in table 4.2:

Table 4.2: Seizure frequency over the last 12 months at most recent follow-up in people who underwent presurgical evaluation from 2015 to 2019 but did not proceed to a resection (N = 281)

Modified* ILAE outcome score	Description	N (%)
1	Completely seizure-free; no auras	13 (5)
2	Only auras; no other seizure	2 (0)
3	One to three seizure days per year; +/- auras	7 (3)
4	Four seizure days per year to 50% reduction of baseline seizure days; +/- auras	61 (22)
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +/- auras	180 (64)
6	More than 100% increase of baseline seizure days; +/- auras	18 (6)

*ILAE post-surgical outcome score in the last 12 months with surgery replaced by 'decision not to have surgery'

Thirteen (5%) people were seizure-free over the preceding twelve months at the most recent follow-up. In nine, this followed additional drug therapy (one each with the addition of carbamazepine, lamotrigine, oxcarbazepine, lacosamide, zonisamide and topiramate and in two following starting clobazam). In each case, individuals had been previously taking 2-7 ASM before the MDT discussion. Three people became seizure-free following an increase in the dose of a current ASM.

Fifty-three people (19%) had a VNS implanted. One was seizure-free for three years following VNS insertion, and another only reported auras, having previously experienced frequent focal seizures with impaired awareness. A further 17/53 (32%) reported a >50% reduction of seizures (ILAE outcome class 3 or 4), while 29/53 (55%) experienced no change in seizure frequency (ILAE outcome class 5). Five people (10%) experienced a >100% increase in seizure frequency (ILAE outcome class 6).

Four (1%) people were started on a ketogenic diet. Of these, three reported no change in seizure frequency (ILAE outcome class 5) and one person experienced a modest improvement in seizure control (ILAE outcome class 4).

Thirty-nine people were offered resective surgery but declined an operation. In this subset, 33/39 (85%) had an abnormal MRI scan, and 27/39 (69%) had temporal lobe epilepsy. Outcomes over the last 12 months in this group are shown in Table 4.3. For comparison, the latest 12-month outcomes in 166

individuals who had epilepsy surgery at our centre within the same 5-year period is also presented. Individuals in this surgical group may have been discussed in the MDT before 2015. They included 150/166 (90%) with an abnormal MRI and 123/166 (74%) people with temporal lobe epilepsy.

Table 4.3: Seizure frequency over 12 months in people who declined epilepsy surgery following presurgical evaluation compared to those who had surgery over the same 5-year period from 2015 to 2019

Modified ILAE outcome score		Declined surgery, n=39 (%)	Had surgery, n=166 (%)
1	Completely seizure-free; no auras	5 (13)	85 (51)
2	Only auras; no other seizure	0 (0)	16 (10)
3	One to three seizure days per year; +/- auras	3 (8)	15 (9)
4	Four seizure days per year to 50% reduction of baseline seizure days; +/- auras	9 (23)	30 (18)
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +/- auras	17 (44)	10 (6)
6	More than 100% increase of baseline seizure days; +/- auras	2 (5)	0 (0)
7	Deceased	1 (3)	0 (0)
8	No follow-up available	2 (5)	10 (6)

Of the 9 (3%) individuals who died following the decision not to have surgery, death was epilepsy-related in six, giving an epilepsy-related death rate of 1/116 per patient/year. Causes of death included Sudden Unexpected Death in Epilepsy (SUDEP) in four people, and one death each due to suicide by drug overdose, status epilepticus and drowning following a seizure. We could not obtain documentation of the cause of death in the remaining two cases.

4.5 Discussion

4.5.1 Seizure outcomes in drug-resistant focal epilepsy without surgery

The chance of achieving seizure remission with ASM after having tried three ASM is slight (Chen et al., 2018), but it does happen. In those who are evaluated for surgery but do not proceed, further ASM and VNS may be associated with seizure remission in 5% and >50% reduction of seizure frequency in a further quarter. This is consistent with previous reports that individuals with previously refractory epilepsy may improve and rarely enter remission with ASM changes (Luciano and Shorvon, 2007, Kwan and Brodie, 2000, Elsharkawy et al., 2012). A previous study that also focused on those who are considered for epilepsy surgery but do not proceed found that approximately 10% were seizure-free over the preceding 12-month period four years after evaluation (Elsharkawy et al., 2012). While this does not consider relapse and remission patterns, seizure freedom over 12 months is often predictive of more prolonged remission. (Cockerell et al., 1997).

Surgery is an effective treatment for selected individuals with drug-resistant temporal lobe epilepsy, and long-term benefits can also be seen in those with extratemporal epilepsy (de Tisi et al., 2011, Wiebe et al., 2001, Lamberink et al., 2020). At our centre, approximately half of people having epilepsy surgery are seizure-free five years after surgery, consistent with reports of long-term outcomes elsewhere (Mohan et al., 2018, de Tisi et al., 2011, Téllez-Zenteno et al., 2005, Lamberink et al., 2020). Many people with focal epilepsy are not suitable for surgery, and up to a third of those who are offered an operation subsequently decline (Cloppenborg et al., 2016, Fois et al., 2016).

Although surgery leads to prolonged periods of seizure remission, many people experience relapses after surgery (Kwan and Sperling, 2009). This should be considered when discussing the risks and potential benefits in prospective surgical candidates. Our findings suggest that in those who do not proceed to surgery, a worthwhile improvement in seizure control may still be achieved with nonsurgical treatments. Rates of seizure freedom are lower without surgery, and this should be discussed with those who choose not to proceed when an operation is deemed feasible. The epilepsy-related death rate in our cohort was consistent with previous reports of SUDEP, which has been estimated at 9 per 1000 patient-years in epilepsy surgery cohorts (Tomson et al., 2008). Discussing this finding with potential surgical candidates may also help inform the decision of whether to proceed to surgery.

Consistent with previous reports, vagus nerve stimulation in our cohort was associated with a >50% reduction in seizure frequency in approximately one-third of people (Chavel et al., 2003, Morris et al., 2013). VNS was not curative, and only one individual became seizure-free. VNS remains a reasonable palliative procedure in those who are not eligible for a definitive resection, particularly while different ASMs are being trialled.

4.5.2 Strengths and limitations

Our data has provided important information on seizure outcomes in a highly pharmacoresistant cohort who had already tried a median of seven ASM. Given the large number of available ASMs with different mechanisms of action described in Chapter 1, it is nearly impossible to try all these medications in every combination. Our real-world data provides a snapshot of 12-month seizure outcomes in people with focal epilepsy who do not have surgery. One limitation is, however, that we did not obtain detailed documentation on the various different medication trials (if any) that were performed in those with ongoing seizures.

It is widely established that medical treatment in unselected cohorts of newly diagnosed epilepsy demonstrates progressively lower numbers of seizure-free individuals with successive medication trials. In one of the first studies examining response rates in these people, 47% became seizure-free after the first ASM, 13% after the second, and 4% on a third or successive medication (Kwan and Brodie, 2000). These data, however, draw upon a median follow-up of five years

and may not necessarily reflect long-term outcomes in those with established epilepsy having further drug trials. In an observational trial of 155 people with drug-resistant epilepsy, 23% achieved 12 months of seizure freedom with drug manipulation. However, this took up to 6 medication trials in some, and rates of sustained (>12 months) seizure remission were not reported (Luciano and Shorvon, 2007).

Our data are observational, with no control group, and individuals were not randomized to receive additional drug therapy or neurostimulation. Nonetheless, all individuals had focal epilepsy, had been referred for surgical assessment and completed initial presurgical evaluation, including neuroimaging and ictal video telemetry. Outcome data within our cohort was limited to seizure frequency and death, with other adverse events, such as medication side effects not being systematically recorded. Despite these limitations, our data reflect real-world conditions for treating individuals with drug-resistant focal epilepsy and may help inform discussions with those not suitable for surgery.

Future studies looking beyond single snapshots of seizure outcome would greatly enhance our ability to discuss patterns of relapse and remission with these individuals.

4.6 Conclusions

Additional ASM and neurostimulation rarely result in seizure freedom for those with drug-resistant epilepsy who are evaluated for surgery and do not proceed.

Nonetheless, these treatments can be associated with a reduction in seizure frequency and should be considered for those not suitable for resection. In those who are offered a resection but subsequently decline, rates of seizure freedom are substantially lower than those who proceed to surgery.

Chapter 5: Outcomes after frontal lobe epilepsy surgery

5.1 Context

We identified in Chapter 3 that extratemporal epilepsy – of which FLE is the most common type – was a significant predictor of not proceeding to epilepsy surgery. There were many reasons for this, including greater difficulty localising the EZ on scalp-EEG and more varied clinical semiology, reflecting the diverse connectivity of frontal lobe networks. Furthermore, 31% of those who were offered an operation but declined had FLE. This may relate to a perception of poorer odds of seizure freedom compared to TLE surgery. To date, the only completed randomised trial of epilepsy surgery in adults excluded those with frontal lobe seizures (Wiebe et al., 2001).

5.2 Objective

In this study we report long-term multimodal outcomes following FLE surgery.

5.3 Multimodal outcomes following FLE surgery

Most long-term outcome data for epilepsy surgery relates to anterior temporal lobe resection, for which surgery is associated with 5-year seizure freedom rates of approximately 50% (Wiebe et al., 2001). Studies of FLE surgery are usually in smaller cohorts and typically report seizure outcomes at individual time-points using single outcome measures, which may not capture postoperative seizure remission and relapse patterns (Jehi et al., 2007, Samuel et al., 2019, Alsumaili et al., 2021, Elsharkawy et al., 2008, Lazow et al., 2012).

Seizure freedom is considered the most critical factor affecting the quality of life and employment following epilepsy surgery (Chapter 1.5 – 1.7), but analysis of long-term socioeconomic outcomes has been constrained by a lack of standardised composite quality of life scores (Elsharkawy et al., 2008, Birbeck et al., 2002). Several factors, including physical and psychiatric comorbidities following surgery, are likely to influence socioeconomic outcomes and quality of life, as well as seizure freedom (Lendt et al., 1997, Sadr et al., 2018, Jennum et al., 2016).

A better understanding of long-term seizure, psychiatric and socioeconomic outcomes will help inform discussions with individuals considering FLE surgery. Previous studies identified several factors associated with favourable outcomes after surgery, such as a focal abnormality on MRI, shorter duration of epilepsy and younger age at the time of surgery (Alsumaili et al., 2021, Elsharkawy et al., 2008, Jehi et al., 2007, Lazow et al., 2012, Samuel et al., 2019). Some results are conflicting, with equally good outcomes between those with normal and abnormal MRI scans reported (Elsharkawy et al., 2008, O'Brien et al., 2004, de Tisi et al., 2011), and variable associations between duration of epilepsy and postoperative seizure freedom (Samuel et al., 2019). Further, the significance of factors such as needing intracranial EEG and extent of resection are less well defined in frontal lobe, as opposed to temporal lobe, epilepsy surgery (Samuel et al., 2019).

We describe long-term seizure outcome patterns, rates of psychiatric comorbidity and socioeconomic outcomes in a large cohort of individuals who underwent frontal lobe surgery for drug-resistant focal epilepsy at our centre.

5.4 Study design

We reviewed data from all individuals who had FLE surgery at our centre between February 1990 and December 2020. Data included prospectively collected preoperative data and annual updates on seizure type and frequency as detailed previously in Chapter 2. Preoperative and contemporary records of each individual's current residential postcode are available in the database and were double-checked against those held in the National Health Service (NHS) Digital Spine, a collaborative IT infrastructure that links summary and demographic records across the country.

Type and location of surgery was identified from operation records and postoperative MRI scans. Frontal resections were stratified into those that involved orbitopolar, frontomedial, dorsolateral and frontocentral regions. An example of each resection location is demonstrated in Figure 5.1. Operations were deemed extensive if they involved two or more of these regions. Resections were further stratified by gyral involvement, including adjacent regions such as the anterior cingulate cortex and insula. We only included data for the first procedure for those who had more than one surgical procedure.

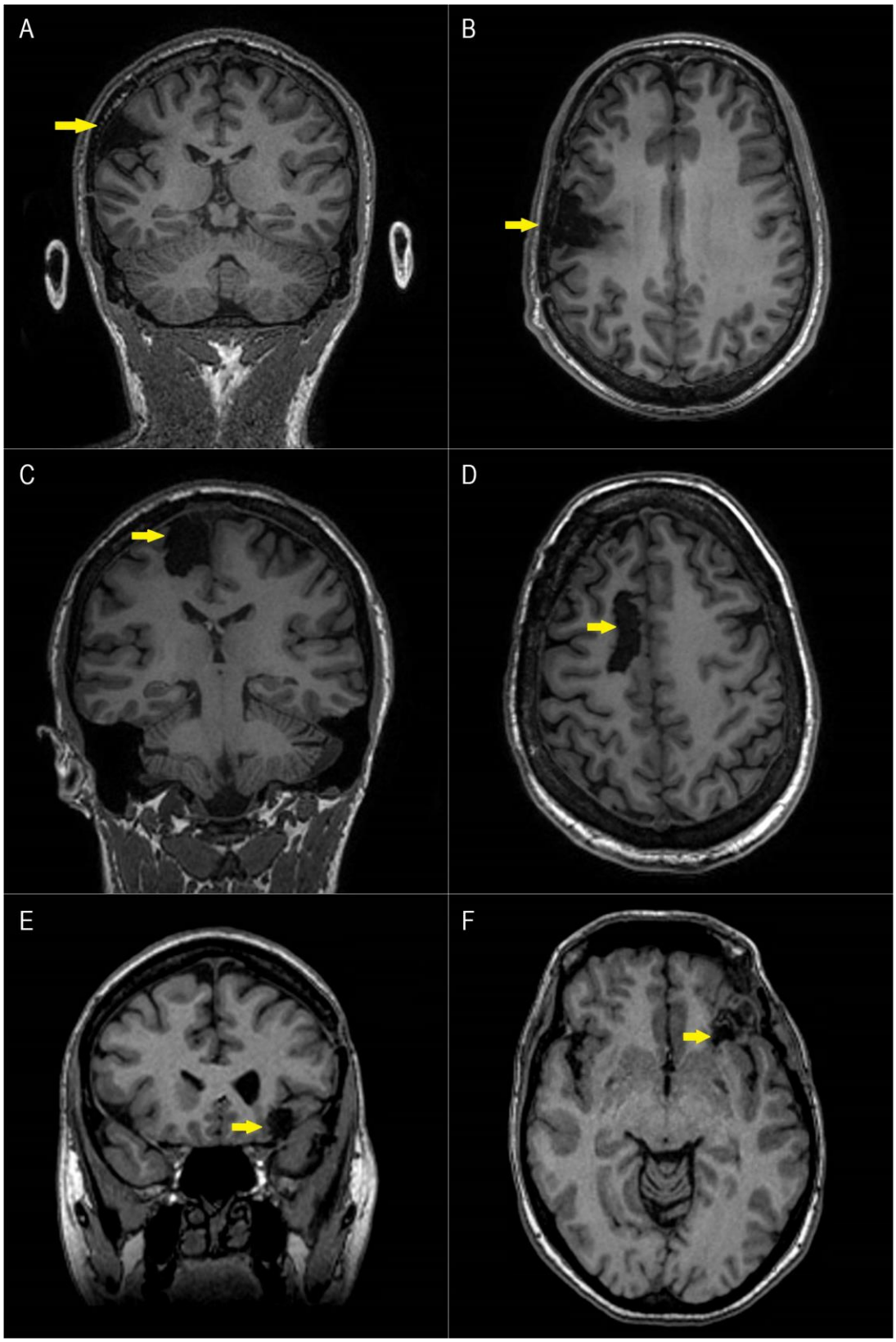

Figure 5.1: Dorsolateral resection for right focal cortical dysplasia in coronal (A) and axial (B) views. Frontomedial resection of right supplementary motor area in non-lesional epilepsy in coronal (C) and axial (D) views. Orbitopolar resection of left cavernoma in coronal (E) and axial (F) views. All images are T1-weighted 3T MRI sequences; yellow arrows indicate site of resection.

5.4.1 Seizure outcome

Seizure outcomes for each postoperative year were classified according to the ILAE surgery outcome scale. Patterns of seizure remission and relapse following surgery were recorded to assess longitudinal seizure outcomes (de Tisi et al., 2011). Those who discontinued ASMs were recorded, as were the numbers and causes of death of those who died in the years following epilepsy surgery.

5.4.2 Psychiatric comorbidity

All individuals had structured preoperative interviews with a consultant neuropsychiatrist as part of the presurgical evaluation. At this interview, psychiatric diagnoses were recorded in accordance to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. At our centre, individuals also routinely undergo standardised postoperative neuropsychology and neuropsychiatry review at 6, 12 and 24 months. We reviewed electronic records of these encounters to identify rates of psychiatric comorbidity before and after surgery. Only active diagnoses, for which individuals were taking psychoactive medication (such as selective serotonin reuptake inhibitors) or had ongoing symptoms, were included for analysis.

5.4.3 Socioeconomic status

The use of Lower Super Output Areas to approximate socioeconomic status has been described previously in Chapter 2 and Chapter 3.

We matched postcode at time of surgery and last follow-up to Lower Super Output Areas within England. We referred to publicly available statistical releases to obtain decile ranks for each individual based on their residential postcode. Socioeconomic deciles were matched to demographic data from 2004, 2007, 2010, 2015 and 2019 to measure changes in socioeconomic status over time. We hypothesized that those who were seizure-free following surgery were more likely to experience IMD improvement than those with ongoing seizures.

To investigate whether those who had surgery had a different socioeconomic status from those who did not, we also compared deprivation deciles at the latest follow-up to an age, sex and duration of epilepsy matched cohort of individuals who completed presurgical evaluation for FLE but did not proceed to an operation. This comparison group was derived from the work in Chapters 3 and 4, in which we collected data on 617 consecutive individuals evaluated for epilepsy surgery at our centre between January 2015 and December 2019, followed up for a median of 2.2 (IQR 1.3-3.2) years.

5.5 Statistical analysis

We compared the baseline characteristics of those with complete seizure freedom following surgery (outcome group pattern A1) with those who were not completely seizure-free. We used the Kaplan-Meier method to estimate the probability of remaining seizure-free for the entire postoperative duration. Exploratory univariate analysis was performed using Fisher exact, chi-square and Mann-Whitney U tests, for categorical and continuous outcomes, with a p-value

<0.05 deemed statistically significant. Significant covariates on univariate analyses were entered into a multivariable logistic regression model to assess predictors of favourable seizure outcome following surgery, with estimated odds ratios and associated 95% Confidence Intervals produced. A Bonferroni correction was performed to account for multiple comparisons when assessing levels of association between covariates and seizure freedom. We examined variables with a p<0.05 in the multivariable model as this was an exploratory analysis with a small number of significant covariates. The multivariable model was also adjusted for the duration of follow-up to account for differing follow-up lengths between individuals. IBM SPSS Statistics for Windows v20 (International Business Machines Corp, Armonk, NY) was used for data analysis, with Kaplan-Meier curves created with MedCalc Statistical Software v20 (MedCalc Software Ltd, Ostend, Belgium; 2021).

5.6 Results

5.6.1 Baseline characteristics

One hundred and twenty-two individuals had FLE surgery during the period. At the time of surgery, the median age was 33 (IQR 27-41) years, with a median duration of epilepsy of 20 (IQR 12-28) years. An abnormal MRI was seen preoperatively in 98 (80%) operated individuals. This included 75 (61%) with a focal abnormality such as focal cortical dysplasia (n=38), DNT (n=23) and cavernomas (n=14), and 23 (19%) with more diffuse abnormalities such as gliosis and encephalomalacia. Intracranial EEG recordings were undertaken in 70 (57%). Demographic and baseline preoperative characteristics of these

individuals alongside a comparison group who completed evaluation but did not have surgery are provided in Table 5.1.

Table 5.1: Baseline preoperative characteristics of people who had frontal lobe epilepsy surgery at Queen Square from 1990 to 2020

Characteristic	Surgical cases (n=122) (%)	Comparison group* (n=100) (%)
Age of epilepsy onset, yr, median (IQR)	12 (6-18)	12 (6-17)
Age at surgery**, yr median (IQR)	33 (27-41)	33 (28-39)
Duration of epilepsy, yr, median (IQR)	20 (12-28)	21 (12-28)
Learning disability, n(%)	12 (10)	14 (14)
Prolonged early childhood convulsions, n (%)	5 (4)	4 (4)
Previous significant head injury, n (%)	9 (7)	4 (4)
History of focal to bilateral tonic clonic seizures, n (%)	94 (77)	74 (74)
History of status epilepticus, n (%)	17 (14)	14 (14)
Number of anti-seizure medications, median (IQR)	3 (2-3)	3 (2-4)
Psychiatric comorbidity, n (%)	50 (41)	38 (38)
Abnormal MRI, n (%) Focal abnormality Diffuse abnormality	98 (80) 75 (61) 23 (19)	35 (35) 25 (25) 10 (10)
FDG-PET performed, n (%) Focal abnormality	37 (30) 15/37	76 (76) 44/76
Intracranial EEG performed, % with focal abnormality on MRI	70, 57%	11, 64%
Previous VNS, n (%)	8 (7)	16 (16)

*Individuals with FLE who entered the presurgical pathway but did not proceed to an operation

**In the comparison group this referred to age at the decision not to have surgery

Reasons for people in the comparison group not proceeding to surgery included an inability to localise the epileptogenic zone (n=43), multifocal seizure onset (n=28), declining intracranial EEG (n=11), declining surgery (n=9), risk of a post-surgical deficit (n=8) and co-existing neurological comorbidity (n=1).

5.6.2 Operation details

Of 122 surgeries performed, 37 (30%) were lesionectomies, and 85 (70%) were more extensive resections. There was an even distribution between left and right hemispheric resections. Frontomedial and dorsolateral resections were most common, followed by extensive lobectomies and orbitopolar resections. We could not access postoperative imaging in 15 (12%) people for detailed classification. Extrafrontal regions included with frontal resections were the anterior cingulate cortex in 31 (29%) and insular cortex in 8 (7%). The prefrontal cortex was the most common site of resection, with superior frontal gyrus resections in 34 (32%), middle frontal gyrus in 4 (4%), inferior frontal gyrus in 16 (15%) and combinations of the above in 52 (49%) cases. Focal cortical dysplasia (FCD) was the most common pathology identified, followed by dysembryoplastic neuroepithelial tumours (DNT) and cavernomas. Details are summarized in Table 5.2.

Table 5.2: Operation details of frontal lobe epilepsy surgeries performed at Queen Square from 1990 to 2020	
Side of resection	**Number (%)**
Right	60 (49)
Left	62 (51)
Location of resection	
Orbitopolar	8 (7)
Frontomedial	35 (29)
Dorsolateral	42 (34)
Frontocentral	1 (1)
Extensive	21 (17)
Unknown	15 (12)
Postoperative complications	
Mono/Hemiparesis Transient (<3months) Persistent (>3months)	 11 (9) 6 (5)
Dysphasia Transient (<3months) Persistent (>3months)	 9 (7) 3 (2)
Infection (requiring antibiotics)	9 (7)
CSF leak	1 (1)
Pathology	
Focal cortical dysplasia Type 2a Type 2b Unspecified	38 (31) 5/38 30/38 3/38
Dysembryoplastic neuroepithelial tumor	23 (19)
Cavernoma	14 (12)
Gliosis	14 (12)
Glioma**	13 (11)
No abnormality	8 (7)
Dual pathology	2 (2)
Other*	10 (8)
*Including Rasmussen's encephalitis (n=2), nonspecific abnormality (n=7) and gangliocytoma (n=1) **Individuals referred with drug-resistant epilepsy with a lesion subsequently found on MRI	

Surgical complications were seen in 34 (28%) individuals, including hemiparesis (14%), dysphasia (9%) and infection requiring antibiotics (7%). These operations included three extensive lobectomies and five dorsolateral resections. In most cases, neurological deficits resolved by three months; however, 6 (5%) had persistent weakness and 3 (2%) dysphasia. All instances of dysphasia were after left hemisphere resections.

5.6.3 Seizure outcomes

All included individuals had annual updates of seizure outcome for a minimum of 12 months. Twelve months after surgery, 61 (50%) people were seizure-free (ILAE outcome group 1 or 2). This dropped to 53 (44%) at the end of the second year and 47 (39%) at the end of the third postoperative year. Patterns of seizure relapse and remission, at last follow-up, are recorded in Table 5.3.

Table 5.3: Seizure outcome group patterns following frontal lobe epilepsy surgeries at Queen Square from 1990 to 2020

OGP	Description	N (%)
A1	Completely seizure free since surgery	33 (27)
A2	Auras only since surgery	13 (11)
B	Seizures initially, then terminal remission	9 (7)
C	Initial seizure-freedom (>12 months) then relapse	10 (8)
D	Initial seizure-freedom, transient relapse, then terminal remission	3 (2)
E	Never seizure-free	46 (38)
F	Complex pattern of remissions and relapses	7 (6)
G	Information <1 yr or not enough information to categorize	1 (1)

The median length of follow-up was seven years (range 1-23 years). Of the entire cohort, 60 (49%) were seizure-free in the last 12 months of follow-up, of whom 33 (27%) had been seizure-free for the entire duration of follow-up (outcome group pattern A1). A further 13 (11%) had only experienced auras postoperatively. At last follow-up, 14/122 (11%) people were no longer taking ASMs, and all these individuals were seizure-free.

Over a cumulative 1066 years of follow-up among the 122 individuals who had FLE surgery, 367/1066 (34%) years were spent seizure-free (ILAE outcome group 1), represented pictorially in Figure 5.2.

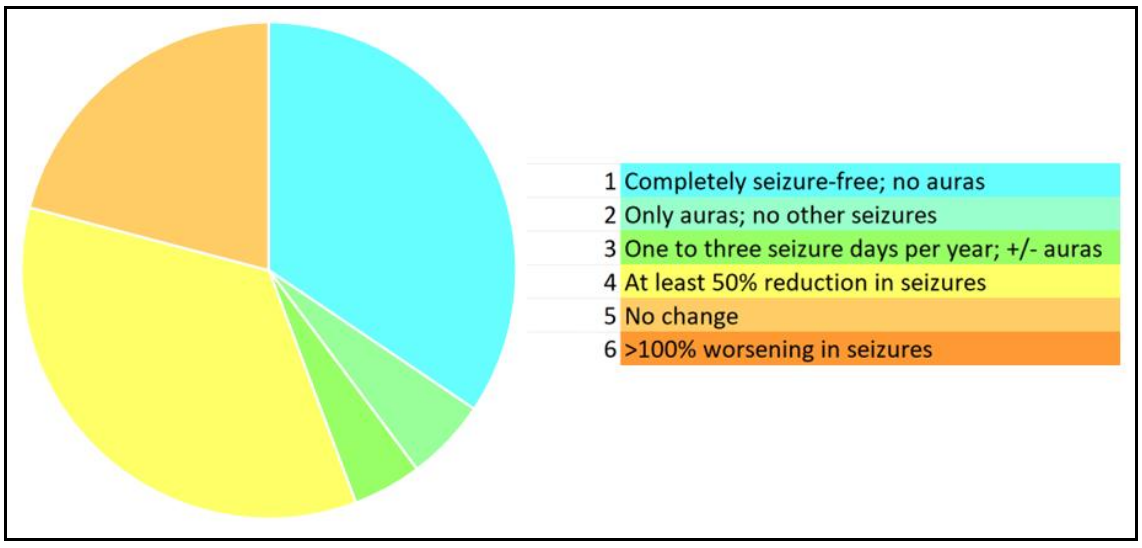

Figure 5.2: Pictorial representation of total years spent in each ILAE outcome group over 1066 cumulative years of follow-up among 122 people who had frontal lobe epilepsy surgery

Rates of long-term seizure freedom for different pathologies are listed in Table 5.4. The highest rate of seizure-freedom was seen in those with focal cortical dysplasia (47% seizure-free). In contrast, none of the eight individuals with no histopathological abnormality in the resected specimen experienced long-term seizure freedom.

Table 5.4: Rates of seizure freedom for different pathologies identified in post-surgical specimens after frontal lobe epilepsy surgery

Pathology	**Number of cases, N (%)**	**Percentage seizure free for entire duration of follow-up (outcome group pattern A1)**
Focal cortical dysplasia	38 (31)	47%
Cavernoma	14 (11)	43%
Dysembryoplastic neuroepithelial tumor	23 (19)	39%
Low-grade glioma** Astrocytoma Oligodendroglioma	 8 (7) 5 (4)	 33% 20%
Gliosis	14 (11)	14%
Dual pathology	2 (2)	0%
No abnormality in resected specimen	8 (7)	0%
Other*	10 (8)	10%

*Including Rasmussen's encephalitis (n=2), nonspecific abnormality (n=7), gangliocytoma (n=1)

**Individuals were referred with drug-resistant epilepsy with a lesion subsequently found on MRI

In the comparison group of people who completed presurgical evaluation for FLE but did not proceed to surgery, none of the individuals were seizure-free at a median follow-up of 2.2 (IQR 1.3-3.2) years. A pictorial representation of the distribution of ILAE outcome groups over the last 12 months in this group is shown in Figure 5.3.

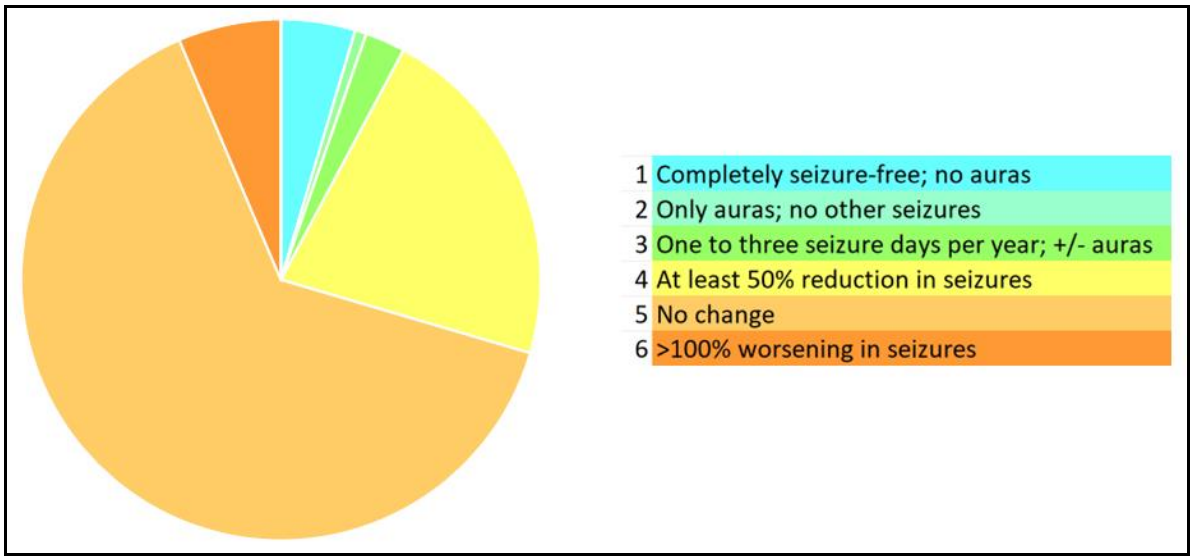

Figure 5.3: Distribution of ILAE outcome groups at a median of 2.2 years follow-up among 100 individuals with frontal lobe epilepsy who completed presurgical evaluation but did not have resective surgery

We compared the preoperative findings, surgical resections and 12-month seizure outcomes between those who were completely seizure-free postoperatively (outcome group pattern A1) and those who were not (Table 5.5).

Table 5.5: Differences between those who did and did not have complete seizure freedom following frontal lobe epilepsy surgery				
Characteristic	**Seizure free (OGP A1), n=40**	**Not seizure free*, n=82**	**OR (95% CI)**	**p**
Preoperative				
Age of epilepsy onset, yr, median (IQR)	12 (5-18)	12 (6-18)	0.97-1.05	0.65
Age at surgery, yr median (IQR)	30 (24-40)	36 (28-43)	0.99-1.07	0.08
Duration of epilepsy, yr, median (IQR)	19 (14-24)	21 (12-30)	0.99-1.06	0.22
Learning disability, n(%)	2 (5)	8 (10)	0.42-10.15	0.37
Prolonged early childhood convulsions, n (%)	1 (3)	4 (5)	0.22-18.50	0.53
History of focal to bilateral tonic clonic seizures, n (%)	28 (70)	66 (81)	0.74-4.22	0.2
History of status epilepticus, n (%)	3 (8)	14 (17)	0.69-9.41	0.15
More than 3 ASM, n (%)	4 (10)	22 (27)	0.10-0.95	**0.03**
Abnormal MRI, n (%)	35 (88)	63 (77)	0.16-1.38	0.16
Focal abnormality on MRI, n (%)	34 (85)	42 (51)	2.04-14.29	**<0.001**
icEEG performed, n (%)	19 (48)	51 (62)	0.85-3.90	0.12
Previous VNS, n (%)	0 (0)	8 (10)		

Index of Multiple Deprivation, median decile (IQR)	6 (4-9)	5 (3-8)	0.76-1.03	0.11
Psychiatric comorbidity	12 (30)	38 (46)	0.90-4.50	0.09
Operative				
Right sided resection, n (%)	19 (48)	41 (50)	0.43-1.93	0.8
Extensive resection, n (%)	7 (18)	14 (17)	0.36-2.63	0.95
Dorsolateral, n (%)	16 (40)	26 (32)	0.32-1.53	0.37
Frontomedial, n (%)	11 (28)	24 (29)	0.47-2.53	0.84
Orbitopolar, n (%)	1 (3)	7 (9)	0.43-30.65	0.24
Postoperative				
Seizure free in first 12 months after surgery	33 (83)	16 (20)	-	-
Focal cortical dysplasia	18 (45)	20 (24)	0.18-0.88	**.02**
Cavernoma	6 (15)	8 (10)	0.20-1.90	0.39
Dysembryoplastic neuroepithelial tumor	9 (23)	14 (17)	0.28-1.81	0.47
Low-grade glioma	4 (10)	9 (11)	0.32-3.85	0.87
Gliosis	2 (5)	12 (15)	0.69-15.31	0.12
No abnormality in resected specimen	0 (0)	8 (10)		0.05
*Includes individuals who experienced any postoperative seizures, including auras				

On univariable analysis, taking less than four regular ASMs at time of surgery, a focal abnormality on MRI, and having focal cortical dysplasia on postoperative histology were associated with seizure freedom. On adjustment for multiple comparisons, only focal abnormality on MRI was statistically significant. Seizure freedom in the first 12 months was also a strong predictor of long-term outcome. Of 49 people seizure-free in the first 12 months postoperatively, 33/49 (67%) had sustained seizure freedom.

We included both focal abnormalities on MRI and taking four or more ASMs into the multivariable logistic regression model, adjusted for the duration of follow-up. Focal cortical dysplasia was not included in the fitted model as this was highly correlated with focal abnormality on MRI. Compared to those taking less than four regular ASMs (n=96) at the time of surgery, those taking four or more regular ASMs (n= 26) were more likely to experience a seizure relapse (OR 4.71, 95% CI: 1.37-16.20) on multivariable analysis. Those with a focal abnormality on MRI had a significantly higher chance of achieving sustained seizure freedom than those with diffuse pathologies or normal scans (OR 7.61, 95% CI: 2.66-21.74).

Four factors were associated with a significant difference in time to seizure relapse on log-rank testing of Kaplan-Meier plots (Figure 5.4). These were age at the time of surgery<30 years, taking less than four ASMs, presence of a focal MRI abnormality and the nature of the pathology. At the latest follow-up, ten (8%) had died, with four epilepsy-related deaths (two due to Sudden Unexpected Death in Epilepsy and two due to seizure-related injuries).

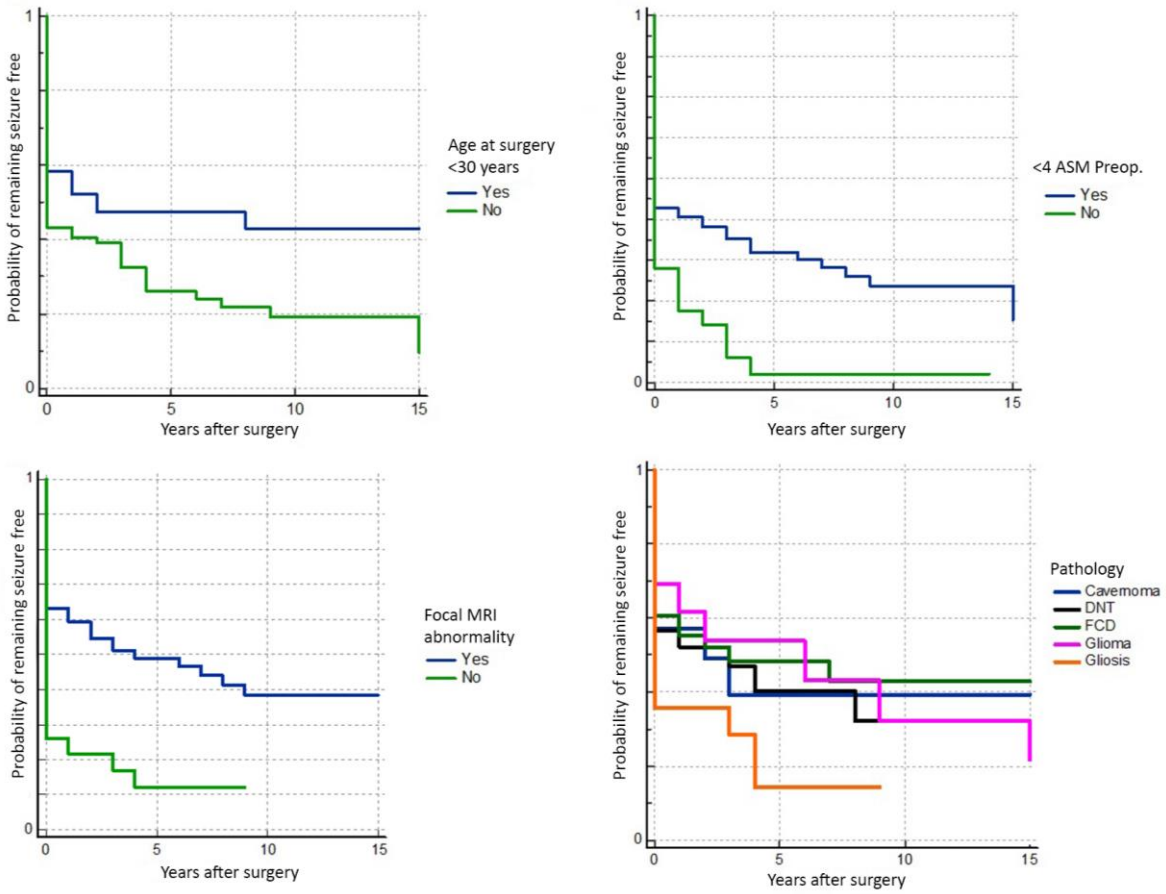

Figure 5.4: Kaplan Meier curves for time to seizure relapse following frontal lobe epilepsy surgery

The monthly seizure frequency, presence of FBTCS or psychiatric pathology, and site or extent of resection did not significantly affect seizure outcome.

5.6.4 Neuropsychiatric outcomes

Before surgery, 50 (41%) individuals were being treated for psychiatric comorbidity. Diagnoses included major depression in 27 (22%), anxiety in 10 (8%), schizophrenia spectrum disorders in five (4%), behavioural disturbances in four (3%) and other diagnoses such as obsessive-compulsive disorder or post-traumatic stress disorder in the remaining four (3%). Four (3%) individuals had a

history of PNES, and one person had been diagnosed with a dissociative disorder.

After surgery, 31/50 (62%) had remission of psychiatric symptoms at two years of follow-up. This group was significantly more likely to have experienced an improvement in seizure control, with seizures reduced by more than 50% baseline, within the first two years postoperatively (87% vs 63%, $p<0.05$).

Two-year follow-up data was available for 109 individuals. New psychiatric comorbidity was diagnosed, using contemporary DSM criteria, in 10 (8%) at 2-years follow-up (six new diagnoses of depression, three of anxiety and one of pathological aggression/behavioural disorder). Of these, 80% had ongoing seizures following surgery. There was no clear association between site or extent of resection and incidence of new psychiatric comorbidity after surgery. Rates of psychiatric diagnosis, including new diagnoses following surgery, are illustrated in Figure 5.5.

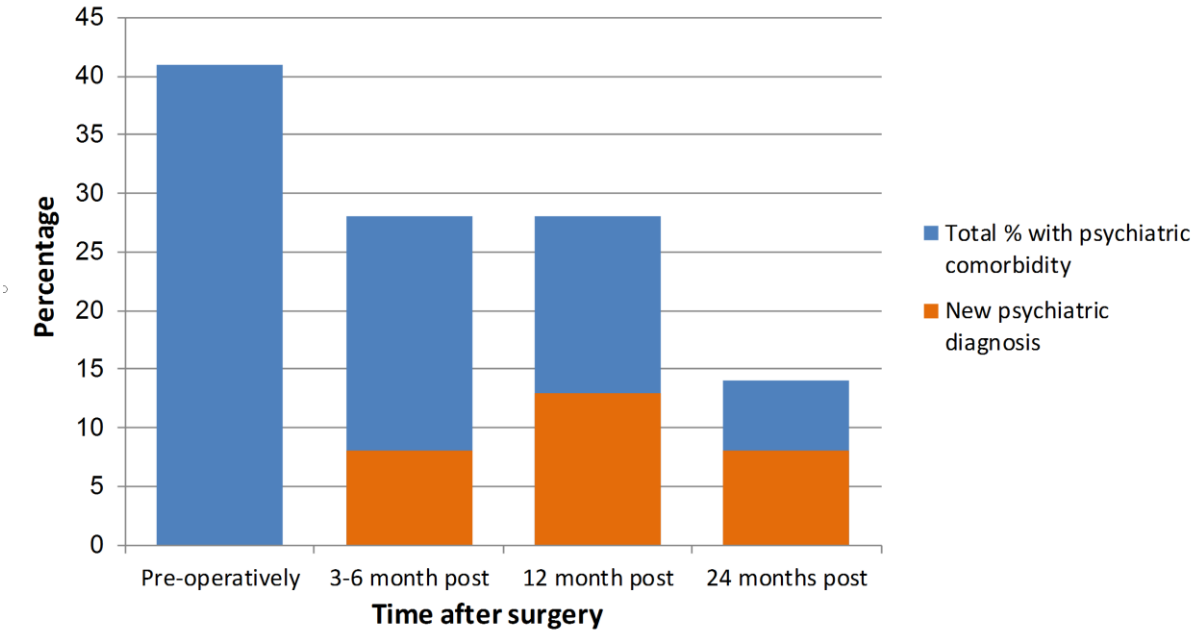

Figure 5.5: Rates of psychiatric comorbidity after surgery

5.6.5 Socioeconomic outcomes

Nineteen (16%) of the cohort resided outside England and were excluded from the socioeconomic analysis. Four (3%) individuals were excluded as there was only 12 months of postsurgical follow-up information.

Consequently, 99 (81%) individuals were included in the socioeconomic analysis. The median Index of Multiple Deprivation (IMD) before surgery and at the latest follow-up was in the 5th decile (i.e. residing in the 40-50% most deprived regions of England). The distribution of deprivation deciles before and after surgery is listed in Figure 5.6.

There was no association between having a seizure free outcome postoperatively and the preoperative IMD (Figure 5.6). Of those seizure-free, 20/40 (50%) did not move residence during the follow-up period. There was no

significant difference in IMD at the latest follow-up between those who had epilepsy surgery and a matched cohort of individuals who completed presurgical evaluation but did not proceed to surgery. There was also no significant change in IMD from preoperatively to the latest follow-up comparing those who were seizure-free to those who were not.

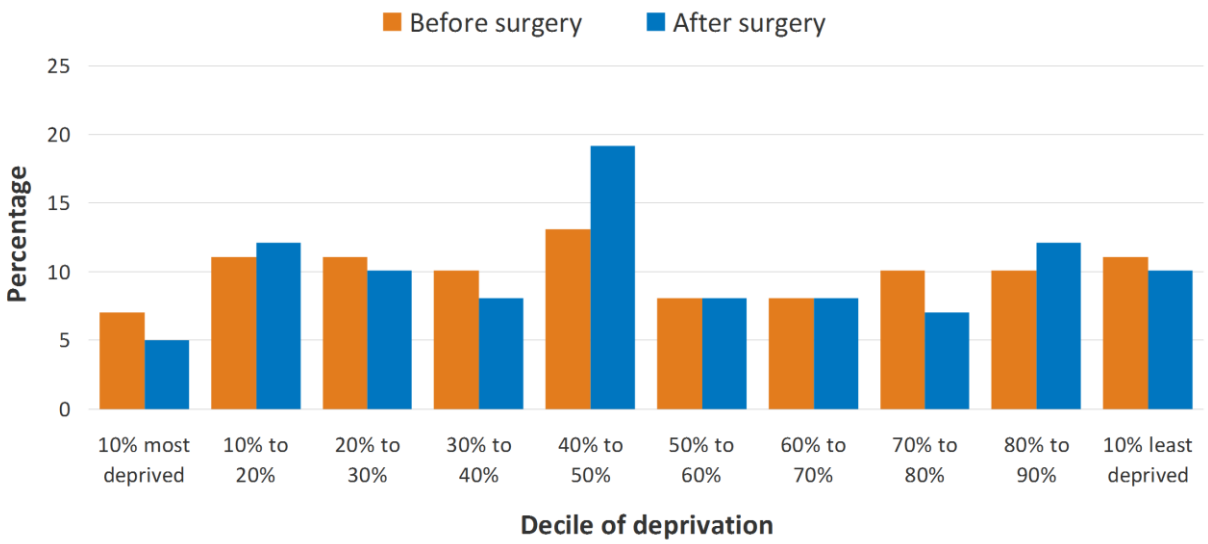

Figure 5.6: Distribution of deprivation deciles before and after surgery

5.7 Discussion

Long-term follow-up of individuals who underwent FLE surgery showed that approximately a third were seizure-free after surgery, and more than half experienced at least one seizure-free year. These rates are consistent with previous reports and highlight the benefits of FLE surgery (Jehi et al., 2007, Lazow et al., 2012, Elsharkawy et al., 2008).

5.6.1 Predictors of seizure outcome

We identified several predictors of complete seizure freedom postoperatively. The finding that those taking four or more ASM at the time of surgery were less likely to have prolonged seizure freedom has not been extensively explored and may be helpful to discuss with prospective surgical candidates. This does not infer that reducing the number of ASMs before surgery would improve outcomes. These individuals may have more widespread epileptic networks necessitating combination ASM, making them less likely to become seizure-free with surgery. In a study that considered the chance of people with drug-resistant epilepsy being offered surgery, a lower lifetime number of ASMs was associated with an increased likelihood of physicians recommending resection (Davids et al., 2021). A higher lifetime number of ASMs has previously been reported to be associated with a reduced chance of postoperative seizure freedom (Bell et al., 2017), although this was in a mixed cohort of people who had temporal and extratemporal epilepsy surgeries. No significant relationship was identified between the average monthly number of seizures, the occurrence of FBTCS, site or extent of resection and the rate of postoperative seizure freedom, in contrast to other studies in which temporal lobe epilepsy predominates (Bell et al., 2017).

Younger age at the time of surgery was associated with a more extended period of seizure remission, emphasizing the importance of offering surgery to suitable individuals earlier in life. This is consistent with data that suggest those with shorter epilepsy durations are more likely to be seizure-free at follow-up and

underscores the importance of early referral to a surgical centre (Bjellvi et al., 2019).

Having a focal abnormality on preoperative MRI was a favourable predictor for seizure freedom. In contrast to previous reports, intracranial EEG was not predictive of poor seizure outcome (Samuel et al., 2019, Malmgren and Edelvik, 2017). This may reflect the selection of appropriate surgical candidates for and after intracranial EEG, and demonstrates the utility of detailed preoperative investigation in those in whom the EZ is unclear on imaging and scalp-EEG. Those who proceeded to surgery after accurate localisation of the EZ on intracranial EEG had similar seizure freedom rates to those who did not need intracranial EEG. This supports the concept that surgical outcome is more closely related to our ability to identify the EZ rather than the specific investigations required for this identification.

Although numbers were small, none of the individuals who had undergone previous VNS experienced complete seizure freedom after subsequent resective surgery. These people had often been considered for epilepsy surgery at earlier stages of presurgical evaluation before embarking on VNS while awaiting further multidisciplinary discussion or investigation. All these people had proceeded to intracranial EEG prior to resective surgery. It is likely that these individuals were less optimal candidates for epilepsy surgery, for example due to difficulty identifying the EZ, rather than VNS itself being a negative prognostic factor.

The underlying pathology was a strong predictor of favourable seizure outcomes. Those with focal pathologies, particularly focal cortical dysplasia, had the highest rates of complete seizure freedom after surgery. Those with more diffuse pathologies such as gliosis, or who had no pathology identified in the resected specimen had the lowest rates of prolonged seizure freedom. There was no association between the size or extent of resection with seizure freedom. No association between resection site and incidence of psychiatric comorbidity was demonstrated.

5.7.2 Risks of frontal lobe epilepsy surgery

One of the main factors limiting uptake of epilepsy surgery is the perceived risk of potential complications. The persistent postoperative weakness or dysphasia rate was slightly higher than previous reports of approximately 2% significant complications with extratemporal epilepsy surgery (Joudi Mashhad et al., 2020). This likely reflects the nature of our design in which even mild symptoms were actively sought and included, even if there was no significant functional impairment. Dysphasia was recorded if noted by treating physicians, and the use of aphasia grading scales was not routinely recorded. The supplementary motor area (SMA) syndrome is a well-recognized transient disturbance of the ability to initiate voluntary motor and speech actions that may occur after dorsal superior frontal gyrus resections that usually resolve by 3 months (Potgieser et al., 2014).

Epilepsy has long been associated with psychiatric comorbidity, considerably impacting quality of life (LaFrance et al., 2008). Psychiatric diagnoses are up to

three times as common in people with epilepsy when compared to the general population (Jansen et al., 2019, Ottman et al., 2011). Our cohort rates of depression and anxiety were slightly lower than reported elsewhere (Lu et al., 2021), likely because we only included those on treatment or having active, ongoing symptoms. Most individuals experienced an improvement in psychiatric symptoms following surgery, with a smaller proportion developing new psychopathology. These new cases were usually linked to an absence of seizure freedom and likely reflected disappointment over a lack of benefit with surgery. Only one individual was diagnosed with a new behavioural disorder, with most new psychiatric diagnoses being depression or anxiety.

We have not reported upon changes in the neuropsychological profiles of our cohort. A previous study reported cognitive stability at a group level in thirty individuals two years after frontal lobe resection (Ljunggren et al., 2015). A decline in verbal reasoning ability was, however, commonly seen in those who had lateral and premotor/supplementary motor area resections. Further research delineating cognitive phenotypes and trajectories in people who have frontal lobe epilepsy surgery is required.

5.7.3 Socioeconomic status

We did not find a significant difference in rates of seizure freedom between people of different preoperative socioeconomic status. This is consistent with other literature demonstrating no clear association between socioeconomic status and likelihood of a seizure-free surgical outcome (Rubinger et al., 2016).

Uptake of epilepsy surgery is, however, consistently less in people with lower socioeconomic status and these individuals often spend longer in presurgical evaluation (Rubinger et al., 2016). This was also consistent with the results of Chapter 3, where people from more deprived backgrounds were more likely to go through presurgical evaluation and not proceed to a resection. This highlights the need to address social and economic barriers to accessing epilepsy surgery in the UK.

There was no significant improvement in IMD after surgery, even for those who became seizure-free. This could relate to the IMD being based on residential status, and half of those who became seizure-free postoperatively did not move during the follow-up period. Literature elsewhere investigating socioeconomic outcomes after surgery have yielded mixed results. It has been suggested that epilepsy surgery reduces hospital utilization rates but does not clearly correlate with better employment rates or higher educational attainment (Jennum et al., 2016, Dupont et al., 2006). Other studies have shown epilepsy surgery is associated with higher employment levels and positive psychosocial outcomes, particularly for those with seizure freedom (Andersson-Roswall et al., 2013, Eliashiv et al., 1997, Paglioli et al., 2004, Dupont et al., 2006). There is marked heterogeneity between these studies, which are usually observational in nature, and with markers of socioeconomic status being variably defined.

5.7.4 Study limitations

There were several limitations to our study, which was confined to the experience of a single tertiary referral centre, lacked controls and was retrospective. Three neurosurgeons carried out more than 90% of surgeries. The determination of seizure freedom was based upon self-reported outcomes, which may under- or overestimate seizure relapse rates, but is a real-life measure used in clinical practice. While residential postcodes can be used to approximate socioeconomic status in England, individual variations undoubtedly exist. The length of our follow-up nonetheless allowed us to evaluate long-term patterns of seizure remission in addition to a variety of other outcome measures which reflect real-world clinical data.

5.8 Conclusion

Frontal lobe epilepsy surgery is safe and effective. It should be offered to suitable individuals early, and having intracranial EEG does not predict a poorer outcome. Approximately a third who have surgery will experience long-lasting seizure freedom, with another tenth only having auras. Rates of psychiatric comorbidity are lower following surgery and often resolve in those seizure-free.

Chapter 6: Predicting the epileptogenic zone in frontal lobe epilepsy from semiology

6.1 Context of study

In Chapter 5 we described several predictors of long-term seizure outcome after FLE surgery. There was no significant relationship between the sites or extent of surgery and outcome. This strongly suggests that postsurgical outcome intrinsically depends on adequately identifying the epileptogenic zone, consistent with findings in TLE surgery (Harroud et al., 2012).

6.2 Objective

As described in Chapter 1.3, links between semiology and the symptomatogenic zone have been recognised for over a hundred years. We sought to evaluate how well semiology performed in lateralising and localising EZ in people with FLE who underwent resective surgery. In these individuals, the site of resection following multimodal investigation and multidisciplinary team discussion was used as a surrogate for the presumed EZ, with subgroup analysis based on 12-month postsurgical seizure freedom.

6.3 Frontal lobe semiology

Seizure semiology helps identify areas of the brain involved in the onset and propagation of epileptic seizures (Foldvary-Schaefer and Unnwongse, 2011, Beniczky et al., 2022). This aids in determining the EZ, which is a critical step in evaluating the feasibility of epilepsy surgery (Tufenkjian and Lüders, 2012). The

lateralising and localising value of semiology varies according to which features are seen. Many of these observations, however, relate to temporal lobe seizures, where semiological patterns are often more stable than in FLE (Beniczky et al., 2022).

Frontal lobe epilepsy can be associated with a wide variety of clinical manifestations, reflecting the rich and diverse connectivity of frontal lobe networks (Chowdhury et al., 2021, Chauvel et al., 2019). Furthermore, frontal seizures are frequently brief and may manifest complex behaviours that can be difficult to accurately describe (Bonini et al., 2014). In these cases, semiology often arises from interaction of many brain regions, which may not be intimately related to the EZ (McGonigal et al., 2021). Although characteristic seizure patterns have been described, there is only modest correlation with anatomical origin, particularly at the sublobar level. (O'Muircheartaigh and Richardson, 2012, Jobst et al., 2000). This may relate to rapid propagation of epileptic discharges within widely connected frontal networks, which lead to activation of areas distinct from the seizure onset zone (Unnwongse et al., 2012).

Recent advances in correlating semiology with sublobar regions have come primarily from SEEG studies. Different patterns of ictal aphasia such as impaired speech comprehension or reduced verbal fluency can implicate involvement of posterolateral or mediobasal temporal structures respectively (Trebuchon et al., 2018). In FLE, different electroclinical subgroups have also been described. For example, seizures involving precentral or premotor regions are characterised by

elementary motor signs, whereas those involving lateral prefrontal cortex or the frontal pole are associated with gestural motor behaviour with distal stereotypies (Bonini et al., 2014). By their nature these observations are, however, limited to the areas that have been sampled.

Prediction of the EZ should consider multiple data sources, including clinical, neuroimaging and electroencephalography (EEG) data. The lateralising and localising value of semiology has been estimated to be approximately 60-90%, equivalent to scalp EEG and MRI. (Elwan et al., 2018, Hur et al., 2017, Rathke et al., 2011) These studies again, however, tend to focus on TLE, and the relative contribution of semiology in identifying the EZ in FLE has not been well established.

6.4 Methods

6.4.1 Participants and Setting

We reviewed electronic records of all individuals who had FLE surgery at the National Hospital for Neurology & Neurosurgery, London, UK, over the 10-year period between January 01, 2011 and December 31, 2020. Although Chapter 5 evaluated individuals from February 01, 1990 to December 31, 2020, only since 2011 have comprehensive documentations of ictal semiology been recorded in an electronically-stored standardised proforma (Duncan, 2022). All individuals had been discussed in presurgical multidisciplinary meetings having undergone scalp video-EEG telemetry, neuropsychology and neuropsychiatry assessments, MRI imaging, and in selected cases FDG-PET, ictal SPECT or intracranial EEG

monitoring before proceeding to resective surgery. We excluded those in whom surgery was primarily performed for reasons other than epilepsy.

Seizure outcomes 12 months after surgery were obtained from the Epilepsy surgery database, as described in Chapter 5. Outcomes were classified according to the International League Against Epilepsy (ILAE) surgery outcome scale.

6.4.2 Data: Semiology

Detailed descriptions of ictal semiology and their evolution were obtained from video telemetry reports and summaries of multidisciplinary meetings. Semiologies were categorised using the descriptions listed in Appendix 1, based on previously described semiological seizure classification (Lüders et al., 1998), and subsequently categorised according to the latest ILAE classification of seizure types (Fisher et al., 2017). Using the semiology-to-brain visualisation tool described below, initial and combined set-of-semiology were correlated with the site of resection, which indicated the final presumed EZ following multidisciplinary discussion and review of all investigations. Initial semiology was defined as the first seizure manifestation described by the patient or witnessed on video telemetry. Combined set-of-semiology included all ictal manifestations, devoid of chronological sequence, as witnessed on video-EEG telemetry. The most frequently encountered chronological sequence for included semiologies was recorded but chronology was not included for analysis as this was not reliably

available in the literature review that underpinned the semiology visualisation tool (Alim-Marvasti et al., 2022a).

6.4.3 Data: Localisation and Lateralisation

Surgical records and post-operative MRI imaging were reviewed to identify the site and extent of resective surgery as described in Chapter 5. Resections were visually categorised into those that involved orbitofrontal, frontomedial, dorsolateral, and/or frontocentral regions, as has been previously described. Surgical operations were deemed extensive if they involved two or more of these regions. Localisation was then further categorised at the gyral level, with resections involving the precentral gyrus, superior, middle or inferior frontal gyri as well as those that extended into the anterior cingulate and insula. Although these are distinct brain areas, frontal lobe resection for non-lesional frontal lobe epilepsy may involve part of the anterior cingulate gyrus (Wen et al., 2017, Hirata et al., 2020). Only data for the first surgical resection were included for the one individual who had more than one procedure.

6.4.4 Predictions: Semiology-to-Brain Visualisation Tool

We assessed how well initial and combined set-of-semiologies anatomically correlated with surgical resections, using Semiology Visualisation Tool (SVT v1.8.1) to generate probabilistic cortical heatmaps of involvement in seizures. This software uses the Semio2Brain database which links descriptions of semiologies to brain regions using data from 4,643 people with epilepsy across 309 peer-reviewed articles, and generates probabilities of brain regions being

involved in the generation of the semiology. We used default SVT settings including the normalisation and high-resolution options, and analysed non-topological data to mitigate publication bias that favours temporal lobe epilepsies.

Predictions of the epileptogenic zone from SVT were visually assessed using the probabilistic colour bar. Any brain region highlighted in bright yellow on the viridis colourmap spectrum signified a high probability of being involved in that semiological feature. SVT predictions were categorised using seven top level brain regions (frontal lobe, cingulate cortex, insula, hypothalamus, temporal, occipital, and parietal lobes). Inevitably, if SVT predicts a large area of involvement there is more likely to be a stronger correlation with the resection volume.

6.4.5 Comparison of Predicted and Resected Localisations and Lateralisation

Predictions from SVT were scored in comparison with resections at three levels: 1) frontal lobe (all frontal lobe regions, including extension into cingulate cortex and insula); 2) frontal lobe regions (orbitofrontal, frontomedial, dorsolateral, or frontocentral); 3) at the level of the gyri (precentral gyrus, superior, middle or inferior frontal gyri, anterior cingulate, and insula).

For all three levels, if the top predicted region(s) (“bright yellow”) on SVT overlapped with the resection, it was regarded as a correct/congruent prediction. Conversely, if the top predicted brain region(s) in SVT did not overlap with the resection, an incongruent prediction was recorded.

Lateralisation was scored correctly if SVT's top predicted region was on the same side as the resection. If lateralisation was bilateral or toward the opposite side of the resection it was scored as incorrect.

The proportion lateralising and localising correctly at all three levels were compared between initial and set-of-semiologies using two-sided Fisher's exact tests with a p-value of <0.05 considered significant.

An example of SVT is shown in Figure 6.1.

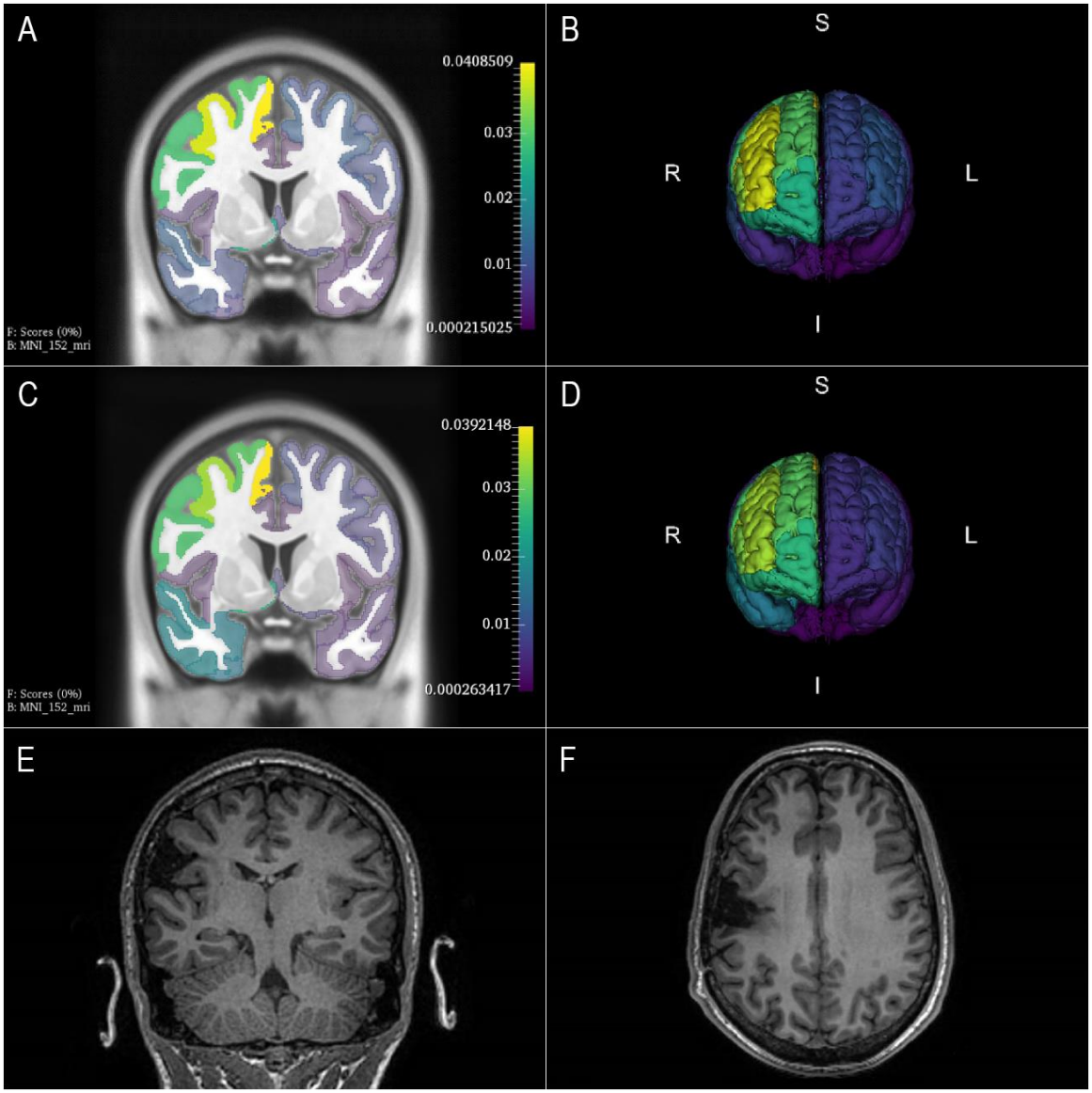

Figure 6.1: Example of Semiology Visualisation Tool. The top row demonstrates epileptogenic zone prediction using initial semiology in coronal (A) and 3D (B) views. The middle row demonstrates epileptogenic zone prediction using combined set-of-semiology in coronal (C) and 3D (D) views. The bottom row demonstrates the postoperative MRI in T1 coronal (E) and axial (F) views.

In this example, initial semiology and combined set-of-semiology correctly lateralised the seizure focus to the right hemisphere and localised to the frontal lobe, however neither correctly localised to the inferior frontal gyrus.

6.4.6 Subgroup Analysis: Predicting Seizure Freedom

Subgroup analysis was performed to determine if the correlation between predicted and actual resections were different between those who were completely seizure free (ILAE outcome score 1) and those who were not (ILAE outcome score 2-6). This would help identify individuals in whom discordance between semiology and site of resection was a consequence of an inadequately localised epileptogenic zone, as implied by ongoing seizures following surgery. Additionally, we evaluated the univariate association between the presence of any semiology in predicting seizure freedom.

Subgroup analysis for both individual semiologies and set-of-semiology were compared between seizure-free and not seizure-free groups using two-sided Fisher's exact test with a p-value <0.05 considered significant.

6.5 Results

6.5.1 Baseline characteristics

Sixty-one individuals had frontal lobe epilepsy surgery at our centre during the 10-year study period. The median age at surgery was 33.9 (IQR 28.1-43.1) years, with a median duration of epilepsy of 21.9 (IQE 21.3-25.1) years. An abnormal MRI was present in 43 (70%) individuals, with a focal abnormality in 35 (57%). Operations comprised 52 (85%) cortical resections and 9 (15%) lesionectomies. In 23/61 (38%) people, frontal lobe resections also included regions of anterior cingulate cortex, and one individual had a resection that also

involved the insula. Baseline characteristics of all individuals and site of resections are summarised in Table 6.1.

Table 6.1: Characteristics of 61 consecutive individuals who had frontal lobe epilepsy surgery at Queen Square from 2011 to 2020	
Characteristic	
Age of epilepsy onset, yr, median (IQR)	12.0 (6.8-18.0)
Age at time of surgery, yr, median (IQR)	33.9 (28.1-43.1)
Duration of epilepsy, yr, median (IQR)	21.9 (21.3-25.1)
Abnormal MRI, n (%)	
Focal abnormality	35 (57)
Diffuse abnormality	8 (13)
Intracranial EEG performed, n (%)	41 (67)
Side of resection, n (%)	
Left	32 (53)
Right	29 (47)
Location of resection, n (%)	
Orbitofrontal	4 (7)
Frontomedial	22 (36)
Dorsolateral	20 (33)
Frontocentral	1 (2)
Extensive	
OF+FM+DL	9 (15)
OF+FM	2 (3)
FM+DL	3 (5)
Pathology in surgical specimen, n (%)	
Focal cortical dysplasia	26 (43)
Cavernoma	6 (10)
Dysembryoplastic neuronal tumour	6 (10)
Low grade glioma	3 (5)
Gliosis	7 (12)
No abnormality / non-specific changes	13 (22)
Abbreviations – MRI: Magnetic Resonance Imaging, EEG: electroencephalography, OF: orbitofrontal, FM: frontomedial, DL: dorsolateral, IQR: interquartile range	

6.5.2 Semiology

A variety of seizure manifestations were noted on ictal video telemetry. The frequency of initial and subsequent semiologic features are noted in Table 6.2. The most common initial semiology was loss of awareness, seen in 12 (20%) individuals, focal aware seizures (non-specific auras) in 9 (15%), cognitive seizures (such as Deja vu) in 6 (10%) and focal sensory (somatosensory) seizures in 6 (10%). The most frequently observed chronological semiologic features in these 61 individuals are displayed in Table 6.3.

Table 6.2: Frequency of semiologies identified on ictal video telemetry in 61 individuals who had frontal lobe epilepsy surgery from 2011 to 2020

	Initial semiology	**Combined (set of) semiology**
Semiology	**Frequency, N = 61 (%)**	**Frequency, N = 61 (%)**
Focal cognitive (aphasia)	1 (2)	3 (5)
Focal motor (unilateral tonic)	0 (0)	11 (18)
Focal motor (atonic)	0 (0)	2 (3)
Focal sensory (auditory)	1 (2)	1 (2)
Focal motor (automatisms)	2 (3)	13 (21)
Autonomic	2 (3)	9 (15)
Focal motor (clonic)	2 (3)	7 (11)
Complex behaviour	3 (5)	12 (20)

Impaired awareness	12 (20)	25 (41)
Focal motor (dystonic)	0 (0)	2 (3)
Eye movements	1 (2)	2 (3)
Eye version	0 (0)	4 (7)
Focal non-motor (emotional)	2 (3)	3 (5)
Focal sensory (gustatory)	2 (3)	2 (3)
Head/Body turn	3 (5)	6 (10)
Head version	1 (2)	12 (20)
Hypermotor	0 (0)	6 (10)
Ictal speech	0 (0)	2 (3)
Focal motor (myoclonic)	0 (0)	5 (8)
Focal aware (non-specific aura)	9 (15)	10 (16)
Focal cognitive (deja vu/jamais vu)	6 (10)	6 (10)
Focal sensory (somatosensory)	6 (10)	9 (15)
Focal motor (tonic – bilateral)	3 (5)	23 (38)
Focal sensory (vestibular)	1 (2)	1 (2)
Vocalisation	4 (7)	7 (11)

Table 6.3: Sequential* semiologic features identified in 61 individuals who had frontal lobe epilepsy surgery at Queen Square between 2011 and 2020								
Individual	**First seizure manifestation**	**Subsequent set of semiology in order of occurrence**						
1	Clonic (L)	Asymmetric tonic (L)						
2	Vocalisation	Hypermotor						
3	Somatosensory (L)	Autonomic						
4	Non-specific aura	Asymmetric tonic (L)	Tonic (Bil)	Dialeptic				
5	Vocalisation	Automatisms - oral & manual						
6	Eye movements (R)	Aphasia						
7	Autonomic	Head turn (L)						
8	Tonic (L)	Clonic						
9	Tonic (Axial)	Tonic (L)	Hyperkinetic	Behavioural				
10	Automotor (R)	Tonic (R)	Clonic (R)					
11	Dialeptic	Custom (utilisation)						
12	Psychic aura	Dialeptic	Head turn (R)	Tonic (R)				
13	Asymmetric tonic (R)	Dialeptic	Clonic (R)					
14	Head turn (L)	Tonic						
15	Psychic aura	Dialeptic	Eye movement (L)	Head version (L)	Asymmetric tonic (R)			
16	Non-specific aura	Somatosensory (R)	Myoclonic (R)					
17	Psychic aura	Aphasia	Head version (R)	Asymmetric tonic (R)				
18	Fear-Anxiety	Hyperkinetic						
19	Clonic (R)	Somatosensory (R)						
20	Tonic (Bil)	Dialeptic						

21	Dialeptic	Automatisms - manual (L)						
22	Vestibular	Dialeptic	Head version (L)	Tonic (L)				
23	Fear-Anxiety	Head version (L)	Eye version (L)	Dialeptic				
24	Head turn (R)	Tonic (R)	Automotor (R)					
25	Dialeptic	Myoclonic (L)	Astatic					
26	Non-specific aura	Fear-Anxiety	Autonomic					
27	Gustatory aura	Dialeptic	Somatosensory aura					
28	Psychic aura	Head version (R)	Tonic (R)	Eye version (R)				
29	Automotor	Dystonic (L)						
30	Body turn (L)	Complex behavioural	Autonomic					
31	Non-specific aura	Head version (L)	Tonic (L)	Hypermotor				
32	Gustatory aura	Dialeptic						
33	Somatosensory aura	Body turn (R)	Complex behavioural	Hypermotor				
34	Complex behavioural	Body turn						
35	Dialeptic	Automotor						
36	Automotor (mimetic)	Automotor (L)	Dialeptic	Autonomic				
37	Autonomic	Clonic (L)	Asymmetric tonic (L)					
38	Somatosensory (R)	Aphasia	Atonic (R)					
39	Somatosensory (R)	Tonic (R)						
40	Vocalisation	Tonic (Bil)						
41	Non-specific aura	Tonic (Bil)						

42	Psychic aura							
43	Non-specific aura	Automotor						
44	Dialeptic	Head version (R)						
45	Dialeptic	Head turn (R)	Clonic (R)					
46	Dialeptic	Asymmetric tonic (R)						
47	Vocalisation	Hyperkinetic						
48	Vocalisation	Complex behavioural						
49	Complex behavioural							
50	Dialeptic	Complex behavioural	Hyperkinetic					
51	Somatosensory	Tonic (L)	Head version (L)					
52	Aphasic	Complex behavioural	Head turn (L)					
53	Vocalisation							
54	Non-specific aura	Myoclonic	Automotor					
55	Dialeptic	Ictal speech						
56	Automotor	Complex behavioural						
57	Somatosensory (R)	Tonic (R)	Myoclonic (R)					
58	Dialeptic							
59	Non-specific aura	Asymmetric tonic (L)						
60	Head version (R)	Tonic (L)						
61	Fear-Anxiety	Autonomic	Clonic (L)	Tonic (Bil)				

Abbreviations – R: right, L: left, Bil: bilateral
*For individuals with several seizure types only the most frequently observed seizure chronology is listed

6.5.3 Seizure outcomes

Following surgery, 28 (46%) people were completely seizure free at 12 months, with a further eight (13%) experiencing only focal aware seizures. Eight (13%) had experienced only one to three seizure days in the preceding year (ILAE outcome class 3), thirteen (21%) experienced a >50% reduction in seizure frequency (ILAE outcome class 4), and three (5%) people noted no change in seizure frequency following surgery (ILAE outcome class 5).

Seizure outcomes for all individuals are listed in Table 6.4.

Table 6.4: Self-reported seizure frequency 12 months after surgery in 61 individuals who had frontal lobe epilepsy surgery between 2011 and 2020

Postsurgical ILAE outcome score	Description	Number of individuals, n = 61 (%)
1	Completely seizure-free; no auras	28 (46)
2	Only auras; no other seizures	8 (13)
3	One to three seizure days per year; +/- auras	8 (13)
4	Four seizure days per year to 50% reduction of baseline seizure days; +/- auras	13 (21)
5	Less than 50% reduction of baseline seizure days to 100% increase of baseline seizure days; +/- auras	3 (5)
6	More than 100% increase of baseline seizure days; +/- auras	0 (0)
Other	Lost to follow-up	1 (2)

6.5.4 Localisation and lateralisation

We compared how well the first reported semiology and set of combined semiologies performed in localisation and lateralisation of the presumed EZ. Analysis was divided into those individuals who were completely seizure free following surgery (ILAE outcome group 1) and those who had ongoing seizures (ILAE outcome group 2-6).

Initial semiology alone was able to correctly lateralise the epileptogenic zone in 26%, localise to the frontal lobe in 18%, localise to subregions of the frontal lobe in 15% and localise to frontal lobe gyri in 8%. Combined set-of-semiology lateralised correctly using SVT in 47/61 (77%), lateralised to the opposite hemisphere in 8/61 (13%) and was non-lateralising in 6/61 (10%). Of the eight people with mis-lateralised predictions, 3/8 (38%) were seizure-free at one year, compared to 1/6 (17%) of those with non-lateralising predictions, and 24/47 (51%) who had congruent predictions. The combined set-of-semiology was able to correctly localise to the frontal lobe in 57%, localise to frontal lobe subregions in 52% and localise to frontal gyri in 25% (Table 6.5). The combined set-of-semiologies were superior to initial semiology alone for lateralisation and localisation at all levels ($p<0.05$).

Table 6.5 Retrospective lateralisation and localisation of seizure onset focus by semiology in people who had frontal lobe epilepsy surgery*		
	Initial semiology alone	**Combined set-of-semiology**
Lateralisation correct Lateralisation incorrect Unable to lateralise	26% (95% CI: 18%-35%) - -	77% (95% CI: 69%-85%) 13% (95% CI: 10%-16%) 10% (95% CI: 7%-13%)
Localise to frontal lobe	18% (95% CI: 10%-26%)	57% (95% CI: 48%-67%)
Localise to frontal sub-region	15% (95% CI: 8%-22%)	52% (95% CI: 43%-62%)
Localise to frontal gyri	8% (95% CI: 3-14%)	25% (95% CI: 16%-33%)
*No significant difference was identified comparing those who were completely seizure-free (ILAE outcome group 1) with those who had ongoing seizure (ILAE group 2-6)		

No significant differences were found in SVT semiology prediction scores comparing those who were seizure-free (ILAE outcome group 1) to those who were not seizure free (ILAE outcome group 2-6) for either the initial or set-of-semiologies. No significant differences in prediction scores were seen among those with focal MRI abnormalities compared with diffuse MRI abnormalities or normal imaging. Similarly, no differences in correct lateralisation or localisation rates to any of the levels was seen among those with lobar resections compared with those with lesionectomies.

6.6 Discussion

Several semiologic features, such as adopting a ‘fencing posture’ and duration of postictal confusion, have been demonstrated to distinguish between frontal and temporal lobe epilepsy (O'Brien et al., 2008, Chauvel et al., 2019, McGonigal et al., 2021). Sub-lobar identification of ictal foci within the frontal lobe on the basis of semiology alone is, however, more challenging. Certain clinical features such as focal clonic activity can be characteristic of frontal lobe involvement and may have lateralising value however do not always localise to specific frontal lobe regions (Jobst et al., 2000, Chauvel et al., 2019).

Intracranial studies have suggested that certain semiologic features can be correlated with specific frontal lobe areas, organised along a rostrocaudal axis (Bonini et al., 2014). Seizures originating from rostral prefrontal regions have been associated with integrated behaviours that resemble natural activities, whereas those from more posterior regions produce elementary motor manifestations. In practice, however, accurate localisation can be challenging due to rapid propagation through shared networks (Bonini et al., 2014, Chauvel et al., 2019). Semiologic features of mesial frontal lobe seizures have not been consistently elicited during electrocortical stimulation (Unnwongse et al., 2012). A key point in the correlation of semiology and anatomy is that the inferred localisation of a semiology was based on seizure freedom following resection, intracranial ictal onset and congruent structural imaging lesions. The network sustaining semiology may of course be distant from the site of seizure onset.

Although clinical teaching emphasises the identification of initial semiology as helping to identify the epileptogenic zone (Noachtar and Peters, 2009, Kotagal et al., 2003), this feature alone performed poorly in localising the presumed epileptogenic zone. This is likely to be the result of many of these first manifestations involving consciousness or sensorial spheres, and in our cohort loss of awareness and a variety of auras were the most common initial semiologic features. This is consistent with a previous report where over two-thirds of those with FLE reported some type of subjective sensation before their seizures (Jobst et al., 2000). These auras, which are classified in the latest ILAE seizure classification as focal aware, or focal sensory seizures, can be seen in seizures arising from both temporal or extratemporal regions.

Combined semiology performed better than initial semiology, and could successfully lateralise seizure foci in 77% of cases. These results are consistent with previous studies looking at the lateralizing value of seizure semiology (Alim-Marvasti et al., 2021, Elwan et al., 2018). There was no significant difference in semiology prediction rates between those with focal MRI abnormalities and those with diffuse MRI changes or normal imaging. This emphasises the important distinction between imaging abnormalities and the symptomatogenic zone, both of which may not always correspond to the epileptogenic zone. Notably, 13% of the whole cohort had combined semiology which SVT lateralised to the opposite hemisphere, highlighting the need for caution when lateralising seizure foci based on semiology alone.

Localisation to sublobar frontomedial, dorsolateral, orbitofrontal and frontocentral regions by semiology alone remained relatively poor, and was correct in only half of all cases. This is lower than estimates in TLE, in which lobar localisation by semiology can be up to 90% (Elwan et al., 2018). It is likely that even in dorsolateral or ventrolateral prefrontal seizures, projection to medial structures plays an important role in observed motor semiology (Bonini et al., 2014). This also highlights how semiology needs to be coupled with other components of the presurgical evaluation, such as neuroimaging, scalp video-EEG telemetry and, in selected cases, intracranial recording to adequately identify the seizure onset zone (Duncan, 2011). Over two-thirds of individuals who had FLE surgery during the 10-year study period had undergone intracranial EEG recordings prior to resection.

No significant association was found between seizure freedom outcome and accuracy of SVT predictions, and no relationship was identified between outcome and specific site of resection. These results are consistent with previous reports in epilepsy surgery cohorts that suggest that focal semiology is an uncertain prognostic feature (Alim-Marvasti et al., 2021, Alim-Marvasti et al., 2022b). Postsurgical outcome is influenced by a variety of other factors such as presence and location of focal MRI and EEG abnormalities, and the nature of the underlying pathology (de Tisi et al., 2011).

Over 90% of those who had epilepsy surgery in our cohort experienced an improvement in seizure frequency at 12 months, and approximately half were

seizure free. This shows the value of surgery in drug-resistant frontal lobe epilepsy, with seizure freedom rates considerably higher than those who complete presurgical evaluation but do not have a resection (Chapter 4). Our present study nonetheless highlights the complex relationship between symptomatogenic and epileptogenic zones in the workup for epilepsy surgery suitability, and suggests relatively few frontal lobe seizures can be reliably localised to sublobar regions on clinical grounds alone (Rosenow and Lüders, 2001, Manford et al., 1996).

There were limitations to our study, which was retrospective, so details of semiological features could not be probed, and limited to a single tertiary hospital in the UK. We used site of resection as a surrogate for the seizure onset zone. SVT predictions extending across many gyri may have led to bias favouring those with larger resections. The cohort was selected from individuals who had completed presurgical evaluation and subsequently proceeded to surgery, which may also lead to bias, as this group is likely to have more lateralising and localising semiology than those who are not deemed to be surgical candidates. Resections often involved combinations of the orbitofrontal, frontomedial, dorsolateral and precentral regions, reducing the granularity of our analysis. Lastly, seizure outcomes in all cases were self-reported, which is susceptible to reporting bias, but reflects real world conditions.

6.7 Conclusion

Semiology alone could correctly localise the seizure focus to a sublobar level in approximately half of individuals who had frontal lobe epilepsy surgery, and correctly lateralised the focus in 77%. Semiology must be combined with other aspects of the multimodal presurgical evaluation to accurately predict the epileptogenic zone.

Chapter 7: Cost of epilepsy surgery

7.1 Introduction

The cost-effectiveness of surgery, mainly if it results in seizure freedom, has been shown in longitudinal studies of TLE (Langfitt et al., 2007, Wiebe et al., 1995, Platt and Sperling, 2002). In these cases, reduced health expenditures offset the cost of surgery, with cost-time curves intersecting at approximately 8.5 years postoperatively (Wiebe et al., 1995). There are limited data on the cost-effectiveness of surgery in extratemporal epilepsy, although as described in Chapter 5 approximately 40% of these individuals also experience favourable long-term outcomes (ILAE outcome group 1 or 2).

With the advent of better neuroimaging and surgical techniques, FLE surgery is becoming more common, and this is an effective therapy that should be offered to selected individuals early (Chapter 5). The majority of those in our cohort, however, required intracranial EEG and other advanced investigations, and the overall cost of requiring these Stage Two investigations in the context of an epilepsy surgery program has not been thoroughly investigated.

In Chapter 3 we demonstrated that presurgical evaluation in a heterogenous cohort with drug-resistant epilepsy was a lengthy undertaking. This was particularly so for those with extratemporal epilepsy, normal brain MRI or when imaging and electrophysiological data were discordant. Probing how duration is affected by traversing different routes through the presurgical pathway will help

provide advice to patients and healthcare administrators about the estimated time from review in the clinic to epilepsy surgery. At our centre and elsewhere, the average time overall between initial assessment in an epilepsy service to surgery is between 14 and 46 months, reflecting the requirement for multiple stages of the investigation, reflection and input from a multidisciplinary team (Martínez-Juárez et al., 2017, Mumford et al., 2019).

It has been suggested that presurgical evaluation is cost-effective if the chance of proceeding to surgery is 5% (Sheikh et al., 2020). This study did not, however, include those with extratemporal epilepsy, which is associated with lower surgical suitability, and of whom approximately half will need intracranial EEG (Chapter 4). Intracranial EEG monitoring is a costly procedure requiring highly specialised input in the implantation and interpretation of intracranial electrodes, in addition to increased nursing and neurophysiological support on a video-EEG telemetry unit. Planning intracranial EEG often requires additional non-invasive investigations such as FDG-PET and ictal SPECT.

7.2 Objective

We evaluated the costs of presurgical evaluation and surgery in a cohort of people at our centre, including those requiring intracranial EEG, and the cost of various routes through the presurgical pathway.

7.3 Methods

We reviewed data on 100 consecutive individuals considered for epilepsy surgery at our centre in 2017. Individuals were all adults referred by treating neurologists for consideration of epilepsy surgery. Healthcare records were reviewed to document the total time spent within the surgical pathway. Time of entry into the pathway was defined as the date individuals and treating clinicians discussed surgical treatment and agreed to perform a presurgical evaluation. Time of exit was defined as the date of surgery or the date a definitive decision not to proceed to surgery was made.

7.3.1 Routes through the presurgical pathway

We identified four principal routes through the presurgical pathway (Figure 7.1). Individuals who had not received a final decision by May 2021 were excluded from the analysis. We classified the remaining individuals to each route through the pathway and reviewed the frequency of different components of the presurgical evaluation. Components included neurology and neurosurgical outpatient appointments and Stage One investigations, including MRI brain, language functional MRI, EEG video telemetry, elective day-case admission for neuropsychology, neuropsychiatry, and nursing assessments. Stage Two investigations included FDG-PET, ictal SPECT, additional functional or structural MRI scans, magnetoencephalography (MEG) and intracranial EEG.

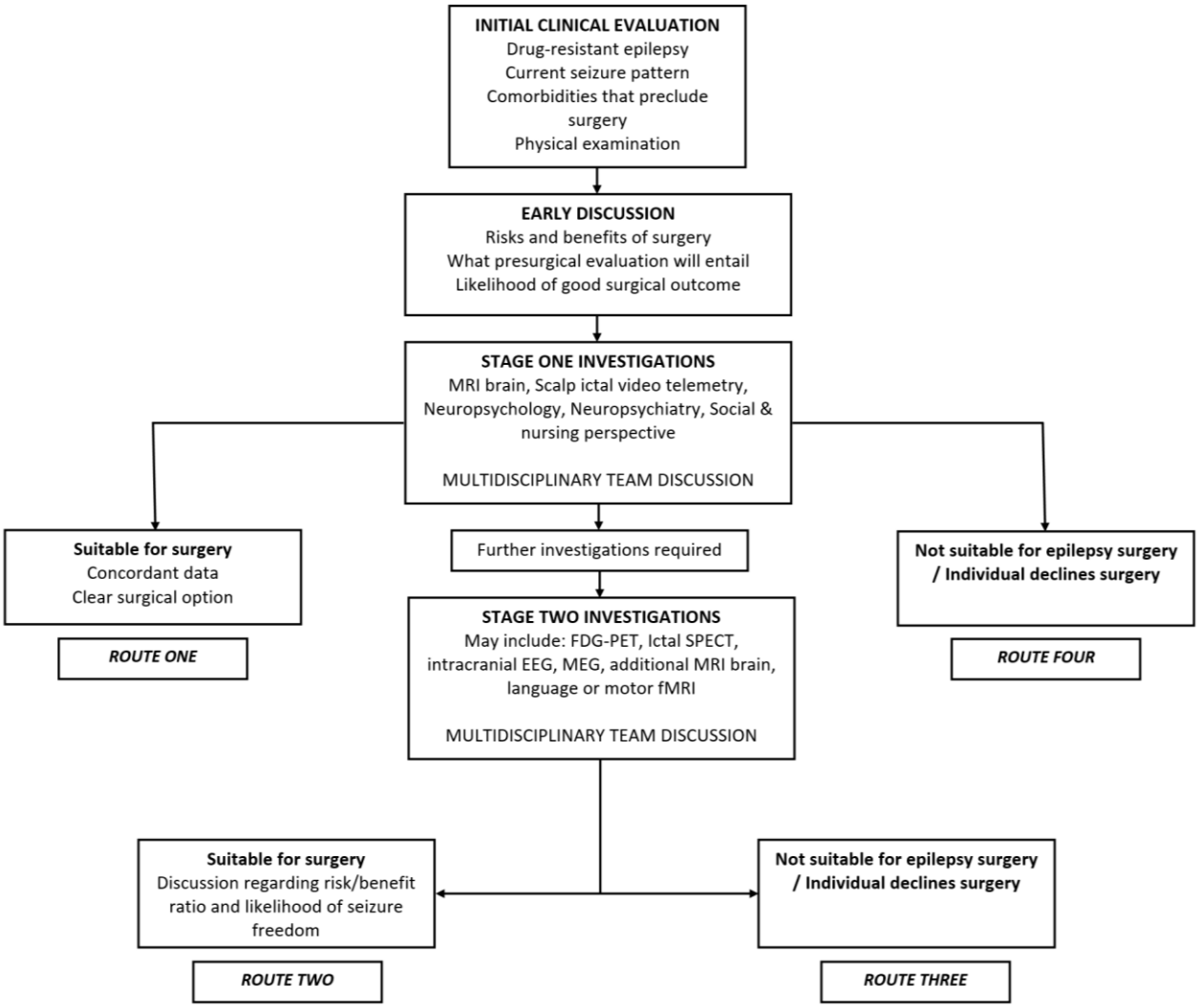

Figure 7.1: Routes through the presurgical evaluation pathway

7.3.2 Using tariffs to approximate cost

National Health Service tariffs applicable at our centre for each of these components were used to estimate the total cost of presurgical evaluation for individuals through each route of the presurgical evaluation. Tariffs are not actual costs but reference costs collected from NHS health providers in England each year for finished consultant episodes (FCEs). The NHS defines these FCEs as a continuous period of admitted care under one consultant within one healthcare

provider. They reflect the average unit cost to the NHS of providing a defined service in a given financial year. The providers' costings include direct costs such as drugs and clinical staff, indirect expenses such as laundry, and overhead costs such as buildings and staff working in corporate functions. The consideration of all charges in this manner is known as Full Absorption Costing. A list of individual tariffs for components of the presurgical evaluation are displayed in Table 7.1.

Table 7.1: National Health Service (UK) tariffs for components of presurgical evaluation at our centre

Item	**Tariff**
Neurology clinic appointment: New	£341
Neurosurgery clinic appointment: New	£587
Neurology/Neurosurgery clinic appointment: Follow-up	£198
MRI brain, fMRI	£138
2-3xMRI sequences in the same session	£172
4xMRI sequences in the same session	£207
Day-case admission for psychology and psychiatry	£919
One week of scalp video EEG telemetry	£3,879
FDG-PET scan	£471
2x ictal SPECT scans (ictal+interictal)	£236
MEG	£600
Admission for intracranial EEG	£40,274
MDT (30min)	£289

The cost of surgical resection, including admission tariffs to the Intensive Care Unit and Neurosurgical ward, was obtained for each individual who had surgery from the Trust charge allocation server. This processes individual hospital activity data according to the National Health Service National Tariff Payment System rules.

7.3.3 Seizure outcomes

We obtained information regarding seizure outcomes for individuals who had surgery from our Epilepsy Surgery Database, including annual updates on seizure occurrence obtained through direct correspondence with individuals, GPs and treating neurologists. Seizure outcomes over the last 12 months in those who did not proceed to surgery were obtained from electronic health records and direct correspondence with individuals and treating clinicians as detailed previously in Chapter 4.

7.3.4 Statistical analysis

We assessed the duration and cost of presurgical evaluation for each individual and estimated cost per additional person seizure-free. Associations between these factors and different routes through the presurgical pathway were evaluated using Fisher's exact test for dichotomous data and two-sample t-tests of log-transformed data for continuous data with a p-value <0.05 deemed statistically significant. We used SPSS (IBM SPSS Statistics for Windows v20, Armonk, NY) for data analysis.

7.4 Results

Of 100 people discussed in 2017, 27 had surgery (Figure 7.2), comprising 13 lobar resections and 14 lesionectomies. Eighteen individuals proceeded to surgery after Stage One investigations and MDT discussion (Route 1). Nine required Stage Two investigations before surgery (Route 2), with 4 having intracranial EEG. Sixty-three individuals had a definitive decision not to proceed to surgery, of whom 18 had Stage One investigations only (Route 4) and 45 also had Stage Two investigations (Route 3), with 10 having intracranial EEG. Table 7.2 shows the baseline characteristics of these individuals. We excluded ten individuals who had not received a final decision regarding surgery from further analysis.

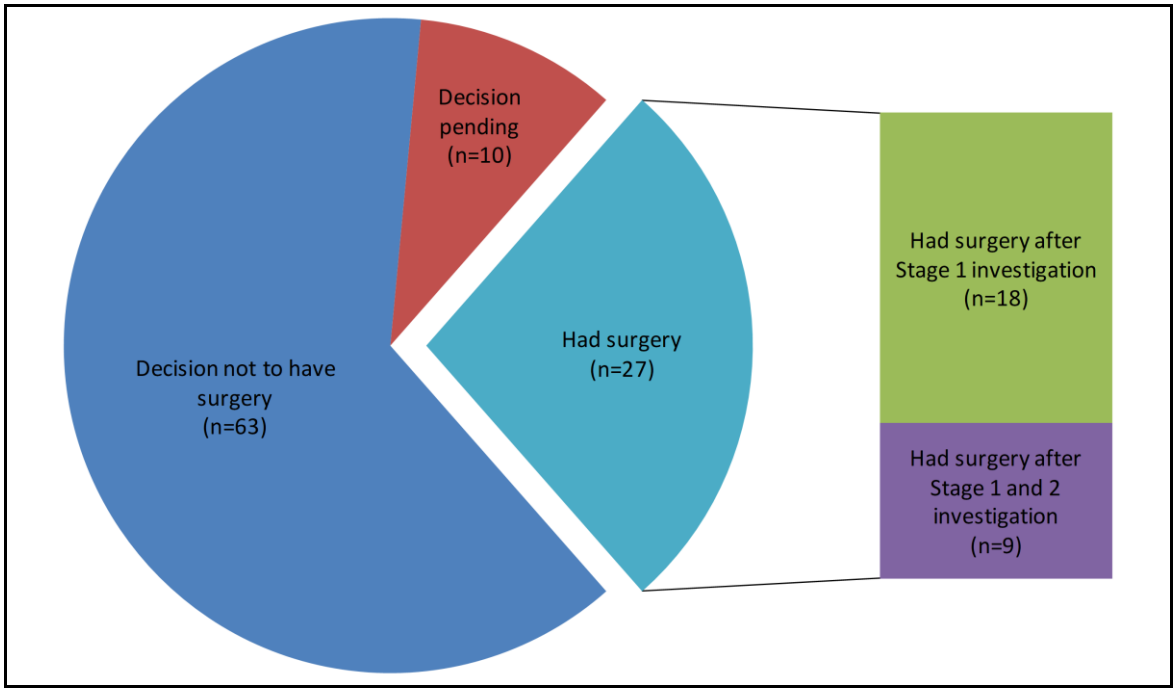

Figure 7.2: Status as of May 2021 of 100 consecutive people evaluated for surgery in 2017

Table 7.2: Baseline characteristics of 90 consecutive individuals who completed presurgical evaluation at Queen Square between 2017 and 2021				
Characteristic	**Had surgery**		**Did not have surgery**	
	Route 1 (n=18)	**Route 2 (n=9)**	**Route 3 (n=45)**	**Route 4 (n=18)**
Female, n (%)	7 (39)	4 (44)	23 (51)	9 (50)
Age of epilepsy onset, yr, median (IQR)	12.5 (7.4-24.5)	17.0 (8.3-24.0)	11.0 (5.0-17.0)	12.5 (4.8-16.3)
Duration of epilepsy*, yr, median (IQR)	20.2 (10.1-26.8)	10.6 (7.3-27.3)	25.4 (14.6-30.0)	26.6 (12.9-40.8)
Learning disability, n(%)	2 (11)	0 (0)	11 (24)	4 (22)
History of focal to bilateral tonic clonic seizures, n (%)	13 (72)	5 (56)	28 (62)	10 (56)
Extratemporal epilepsy, n (%)	5 (28)	3 (33)	35 (78)	7 (39)
Number of anti-seizure medications, median (IQR)	2 (2-3)	3 (1.5-3.5)	3 (2-4)	3 (2-4)
Abnormal MRI, n (%)	18 (100)	7 (78)	26 (58)	17 (94)
icEEG performed, n (%)	0 (0)	4 (44)	10 (22)	0 (0)
*At the time of surgery or decision not to have surgery				

People who had Stage Two investigations (Routes 2 and 3) were more likely to have normal neuroimaging (39% vs 4%, $p<0.001$) and extratemporal epilepsy (70% vs 33%, $p<0.001$) compared to those who did not proceed with these investigations (Routes 1 and 4). All individuals who had surgery without requiring Stage Two investigations had a lesion on MRI, and 13/18 (72%) had temporal lobe epilepsy (Table 2).

The total estimated cost of evaluating 90 people for surgery was £1,554,015, with a median individual cost of £9,138 (IQR £6,984-£14,868). This included a total of 44 FDG-PET scans, 21 ictal-SPECT scans, 1 MEG and 14 intracranial EEG procedures. The median duration of the presurgical evaluation was 30 months (IQR 19-44 months). Those who proceeded to Stage Two investigations (Routes 2 and 3) spent longer under assessment than those who did not (median duration 32.5 vs 28.4 months, p=0.03). This was most evident in those with intracranial EEG as part of their evaluation (median duration 59.9 vs 28.6 months, p<0.001). The total cost of the 27 neurosurgical resections, including admission tariffs, was £299,011, with a median cost of £10,200 (range £8,200-£21,200).

Differences in the duration of evaluation and median cost per individual for different routes through the presurgical pathway, including costs of resections, are shown in Table 7.3.

Table 7.3: Cost of different routes through the presurgical pathway for 90 individuals evaluated for epilepsy surgery between 2017 and 2021

	Route 1	**Route 2**	**Route 3**	**Route 4**
Number of individuals (N=90)	18	9	45	18
Duration of presurgical pathway, median (IQR), months	28.6 (24.1-32.3)	31.0 (21.6-46.0)	33.2 (18.6-59.4)	26.1 (18.0-32.4)
Cost of presurgical evaluation / individual, median (IQR), £	7,740 (7,050-10,500)	9,140 (8,640-47,700)	11,860 (7,980-47,400)	6,720 (6,190-10,000)
Cost of surgery / individual, median (range), £	10,200 (8,200 -21,200)		n/a	
% Seizure free at last follow-up	72%	22%	0%	11%

There was no significant difference in the evaluation cost between those who had surgery and those who did not proceed. The median cost of having only Stage One investigations was £7,210 (IQR £6,420-£9,940). Stage Two investigations without intracranial EEG added £1,930 (IQR £816-£1,943). The median evaluation cost for the 14 people with intracranial EEG was £49,881 (£47,505-£56,188). Of these, 4/14 went on to have surgery, with one person being seizure-free at last follow-up and two others having a >50% reduction in seizure frequency. The remaining ten individuals who had intracranial EEG did not proceed. This was because the seizure onset zone was not adequately localised (n=4), multifocal seizure onset (n=3), declining surgery (n=2), and involvement of eloquent cortex (n=1). The median cost of evaluation and surgery for those who were seizure-free without having intracranial EEG was £17,960 (IQR £17,240 – £20,890) and £57,970 for the single seizure-free person who had intracranial EEG.

After a median duration of 3.1 (IQR 2.3-3.7) years, 15/27 (56%) individuals who had surgery and 2/63 (3%) of those who did not have surgery reported being seizure-free in the preceding 12 months. The total cost of evaluating 90 people and performing surgery in 27 was £1,853,026. This equated to an approximate cost of £123,500 spent per additional person seizure-free.

7.5 Discussion

The evaluation to determine suitability for epilepsy surgery is lengthy, even for those with concordant clinical, imaging and neurophysiological data. This

highlights the need to streamline referral for epilepsy surgery and improve access to Stage One investigations such as video EEG telemetry. The presurgical evaluation is more extended for those who require Stage Two investigations. At our centre, people who required intracranial EEG spent over two years longer in the surgical pathway on average. This emphasizes the need to expand capacity to perform intracranial EEG, which is particularly useful for those with normal neuroimaging, extratemporal epilepsy, or a lack of concordance between MRI and scalp EEG (Pondal-Sordo et al., 2007).

In this sample, there was relatively low yield from intracranial EEG, with less than a third of people proceeding to surgery. This was likely a result of the relatively small sample size and did not reflect the typical utility of this investigation. The more comprehensive dataset developed in Chapter 3 demonstrated that over the five years from 2015 to 2019, 63% of individuals having intracranial EEG proceeded to resection, with 52% being seizure-free (ILAE Outcome Score 1 or 2) at the last follow-up, which is in keeping with data from other centres (Bulacio et al., 2012, Thorsteinsdottir et al., 2019).

The long duration and cost of presurgical evaluation underscore the need to consider the suitability and risk-benefit ratio of surgical treatment with individuals at each step of the pathway. This may help direct the need for investigations more efficiently. We demonstrated in Chapter 4 that for suitable individuals, surgery was much more likely to result in seizure freedom than continued medical treatment. Over half of those referred for surgery, however, do not

proceed, and a fifth of those eligible for resection subsequently decline the option. Strategies to identify these people earlier and direct them to alternative treatments such as vagus nerve stimulation and a ketogenic diet may help reduce long waiting times for more suitable individuals.

We have used tariffs as a proxy for cost and have not evaluated the annual healthcare expenditure for individuals with and without surgery. This means that our exercise is not a cost-effectiveness study. Still, it provides a comparative assessment of surgical pathways for people with epilepsy at a specialist tertiary neurosciences centre in London.

Instead of estimating direct costs (for example of a procedure) and indirect costs (for example of nursing staff, hospital staff and ASMs) we have used tariffs, which are based on full absorption reference costs, and take all these factors into account. As tariffs are averaged costs across all NHS providers in England, they also increase the applicability of our findings to other centres nationally. Tariffs better represent the cost to the NHS instead of each individual provider and consider the average costs of a particular care pathway nationally.

Higher total costs were seen in those undergoing Stage Two investigations, with a substantial additional tariff for intracranial EEG. Unsurprisingly, these individuals were more likely to have normal neuroimaging and extratemporal epilepsy. Stage Two investigations are often required in this setting to localise the epileptogenic zone accurately. For those with FLE, the need for intracranial EEG

does not always predict poorer outcomes and is often an essential step for assessing surgical suitability. The highest costs were in those with Stage One and Two investigations, with intracranial EEG, before proceeding to an operation. Non-invasive Stage Two investigations added approximately £2,000 to the evaluation cost, with the need for intracranial EEG adding approximately £40,000. This finding reinforces the need to carefully select the most suitable candidates for intracranial EEG.

Seizure freedom is the most critical determinant of the quality of life in epilepsy (Birbeck et al., 2002). It is also a significant determinant of healthcare utilization costs (Pillas and Selai, 2005). Complete seizure freedom after surgery substantially reduces the annual healthcare costs two years after surgery (Langfitt et al., 2007). This is mainly due to progressively reducing anti-seizure medication (ASM) costs and removing the cost of epilepsy-related hospitalizations.

Approximately £120,000 was spent per additional seizure-free individual. Our design does not permit a direct assessment of the cost-effectiveness of epilepsy surgery; however, these figures can be viewed alongside the estimated cost of care for those who are seizure-free (£443/annum) compared with those having at least monthly seizures (£3,508/annum) (Jacoby et al., 1998). These annual costs were derived from 1998 data, and current costs are likely much higher. A recent systematic review and extrapolation estimated direct costs per person at approximately $US 4,500 per year in high-income countries, with indirect costs

estimated at $US 6,000 per person per year (Begley et al., 2022). Cost varies substantially across countries, however, and in countries like Sweden and Denmark, estimated indirect costs were 3-6x higher than direct costs (Begley et al., 2022)

Drug-resistant epilepsy is a common cause of presentation to hospitals, with associated investigation and admission costs (Dixon et al., 2015). In the United States, epilepsy-attributable direct cost estimates per individual range from US$8,592 to US$19,749 each year (Begley and Durgin, 2015). Again, this does not consider indirect costs, such as lost productivity, which account for up to three-quarters of the total epilepsy cost (Begley and Beghi, 2002, Jędrzejczak et al., 2021, Platt and Sperling, 2002).

There are limitations to our study, which was retrospective and confined to a single tertiary centre. Data were observational and did not analyse the actual cost-effectiveness of surgery in the cohort. We only included costs of investigations performed during the contemporary presurgical evaluation and did not consider the cost or time spent at other centres for previous presurgical workup. Our centre has local agreements for some of the tariffs we used. For instance, Telemetry unit admissions earn in addition to the regular tariff a locally agreed rate of £944. As a result, the reimbursement we receive for some procedures is likely higher than those obtained by other providers. The proportional cost differences we identified should still be applicable nationally, despite variance in the actual costs compared to other centres.

During Covid-19, most providers were switched to a ‘block contract’ payment system, in which a fixed sum was paid to deliver all care, rather than being reimbursed for each treatment, appointment or procedure. We moved to a ‘block contract’ system before Covid-19 in April 2019. We continued to use tariff as a proxy for cost throughout for consistency as it still provided the best representation of system cost.

Day case evaluation for MRI, neuropsychology and neuropsychiatry is a standard part of our presurgical evaluation that may not be available at other centres. Seizure freedom rates were prospectively recorded and self-reported by individuals who may under- or overestimate seizure occurrence. Our findings constitute real-world experience in a tertiary referral centre with intracranial EEG availability that evaluates people with epilepsy for surgical suitability.

7.6 Conclusion

Evaluation for epilepsy surgery is lengthy and costly, particularly for those who require intracranial EEG. For those with drug-resistant focal epilepsy, surgery is, however, associated with a greater chance of seizure freedom. The suitability and the risk-benefit ratio of surgery should be considered at each step of the presurgical pathway.

Chapter 8: Conclusions

8.1 Key findings from this thesis

Managing epilepsy remains a global health challenge, with substantial rates of premature mortality and reduced quality of life, geographic and socioeconomic disparities in care, and limited options for those who prove to be drug-resistant.

In this thesis we have demonstrated that:

1. Many people with drug-resistant epilepsy who are referred for surgery do not proceed to an operation despite a lengthy presurgical evaluation.
2. The main reasons why people do not have surgery are an inability to localise the epileptogenic zone, multifocal epilepsy, and declining intracranial EEG.
3. A combination of clinical and investigatory data can help predict the likelihood of having surgery and should be used to inform discussions with individuals early in the referral process.
4. Approximately half of individuals with extratemporal epilepsy and all those with a normal MRI brain who had epilepsy surgery at our centre from 2015 to 2019 required intracranial EEG as part of the evaluation.
5. Individuals with a learning disability were significantly more likely not to proceed to epilepsy surgery following evaluation.
6. People who did not proceed to epilepsy surgery following presurgical evaluation were more likely to reside in more deprived areas of England.

7. A worthwhile improvement can be seen with further ASM trials and neurostimulation for those with drug-resistant focal epilepsy considered for surgery but who do not proceed. Up to a quarter can experience >50% reduction in seizures for at least 12 months, and one in twenty may eventually become seizure free (for periods >12 months).
8. Frontal lobe epilepsy surgery is safe and effective. Approximately a third will have long-lasting seizure freedom postoperatively, with a tenth having only auras.
9. Semiology can help localise the epileptogenic zone in FLE but has limitations. In a cohort of people who proceeded to FLE surgery, semiology could correctly lateralise the putative EZ in 77% and localise to a sublobar level in 52%. Semiology must therefore be combined with other components of the presurgical evaluation to establish the EZ.
10. Evaluation for epilepsy surgery is lengthy and costly, particularly for those requiring intracranial EEG, but varies substantially depending on route through the presurgical pathway. It is, however, more likely to lead to seizure freedom and may lead to long-term savings.

8.2 Implications for clinical practice

This thesis strengthens the current view that resective surgery can lead to more favourable outcomes than medical management alone for selected individuals with drug-resistant focal epilepsy, including those with FLE. The high demand for epilepsy surgery and necessity for specialised presurgical evaluation, however, mean most individuals spend years before a final decision on surgical suitability

is reached. It is imperative, therefore, to manage patient expectations throughout the entire journey, from initial consultation to referral to an epilepsy surgery centre, throughout the presurgical evaluation, and either following surgery or a decision not to proceed with a resection. The results of this thesis will aid early discussions between healthcare professionals and people with drug-resistant epilepsy, and these conversations can occur – tailored to each individual – even before they are seen in an epilepsy surgery centre. Managing patient expectations will help refine the selection of individuals for presurgical evaluation and reduce the number of people who undergo unnecessary investigation or decline surgery.

The findings that individuals with a learning disability were less likely to proceed to epilepsy surgery and that people who did not proceed to surgery were more likely to reside in areas of greater socioeconomic deprivation require further exploration. Importantly, it underscores potential disparities in the availability and access to epilepsy surgery, even in developed countries like the UK with free at the point of delivery healthcare.

8.3 Future Directions: Non-surgical Treatments

Despite exponential growth in the armamentarium of ASM over the last few decades, the proportion of people with drug resistance has remained largely unchanged. In most cases, drug development in epilepsy is based upon acutely provoked seizure models that do not necessarily replicate the pathophysiology of chronic, pharmacoresistant epilepsy. The burden of disease, however, is

disproportionately felt by those with drug-resistant epilepsy, with individuals with seizure freedom experiencing relatively normal lives.

Currently, very few options are available for the 30% of people who become drug-resistant. The ketogenic diet is partially effective but unpalatable and comes with its own potential long-term complications. Resective surgery is the treatment of choice with the highest chance of seizure freedom, but is a scarce resource that requires careful selection of appropriate candidates and a significant investment in time and resources from both the individuals concerned and healthcare system.

While surgery is a solution for some, it is not an option for everyone with drug-resistant epilepsy. It also has limited availability, particularly in lower-income countries (World Health Organization, 2017). Neuromodulation is beneficial but rarely leads to seizure freedom. There is, therefore, an ongoing need for drug research and development, focusing on those who have been unsuccessfully controlled on previous ASMs, and utilising multimodal long-term outcome measures. This must be driven by an understanding of the pathophysiologic mechanisms which underpin drug-resistant epilepsy, some of which have been outlined in Chapter 1.7.

8.4 Future Directions: Epilepsy Surgery

There is growing awareness that epilepsy surgery is effective, and the work in this thesis adds to a growing body of literature that supports offering surgery to

people early, including those with FLE. A substantial minority, however, do not achieve seizure freedom after surgery. Despite current and emerging predictive models, our ability to consistently identify this minority prior to surgery remains suboptimal. In some settings, this may reflect a selection bias with individuals known to have lower odds of seizure-freedom proceeding to an operation due to the lack of alternatives. More commonly though, individuals who are predicted to have a favourable outcome may still experience seizure recurrence, sometimes years after a seizure-free outcome.

This suggests a need to continually build upon our understanding of focal epilepsy and the changes in brain function following resective surgery. Widespread acceptance of focal epilepsy as involving dysfunctional networks (Gil et al., 2020) may explain the failure of surgery in selected cases and the distinction between symptomatogenic and epileptogenic zones. This has translated to ongoing improvements in the effective planning of intracranial procedures and tailoring of each resection specific to the individual.

There is growing expertise in minimally-invasive methods for epilepsy surgery, such as MRI-guided focussed ultrasound and laser interstitial thermotherapy as described in Chapter 1.9. At the current time these methods are not intended as a replacement to open resection, however individuals are likely to be receptive to the idea of minimally invasive surgery. Long-term multicentre research on outcomes following these therapies are yet to be comprehensively explored. The published seizure-freedom rates of these techniques (which are approximately

10-20% worse than resective surgery) are likely limited by a degree of positive-outcome bias (Hoppe et al., 2017).

With the increased recognition of epilepsy surgery as an effective therapy there is growing demand for the service and a heightened need to develop robust models that can help inform discussions with individuals about surgical suitability. The data presented in Chapter 3 provides an evidence-based model to better inform these early discussions, however remains constrained by the need for neuroimaging and video telemetry, for which there are often long delays. Occasionally, when people are informed of the likely need for intracranial EEG (for example if they have a normal MRI scan), or that there is a low likelihood of a surgical option, they decide not to continue with presurgical evaluation. Identifying these people early in the presurgical pathway and having informed discussions about the likely trajectory may help direct them to alternative treatment strategies and prioritise investigations for others who are more likely to proceed. It is nonetheless important that even those who appear to be unlikely surgical candidates are not discouraged from considering evaluation, and it remains appropriate to refer such individuals to a surgical centre for informed discussions around potential surgical options.

For individuals who are not surgical candidates or who decline surgery, new treatment approaches must be developed that continue to aim for seizure freedom, which is the ideal outcome for people with epilepsy. Our findings are consistent with real-world studies that show benefits can still be seen with further

ASM trials and/or vagus nerve stimulation, although only a minority experience seizure-freedom (Luciano and Shorvon, 2007, Choi et al., 2016, Moloney and Costello, 2021). A surgical algorithm for drug-resistant epilepsy is illustrated in Figure 8.1.

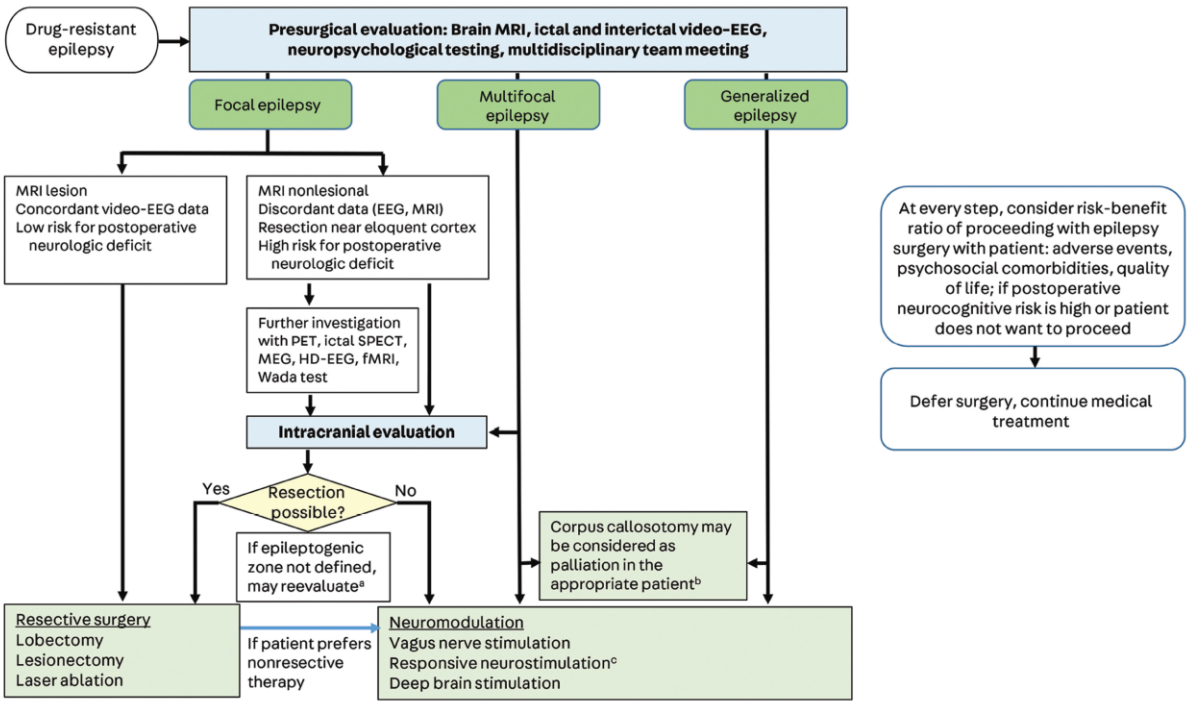

Figure 8.1: Surgical algorithm for drug-resistant epilepsy. From: Culler G, Jobst B. Surgical Treatments for epilepsy. Continuum (Minneap Minn) 2022;28(2). Used with permission.

Frontal lobe epilepsy is the second most common focal epilepsy after TLE. Despite this, rates of FLE surgery are substantially lower than surgery for TLE, accounting for approximately 10% of epilepsy surgeries at our centre. One of the challenges in evaluating these individuals for surgery is greater heterogeneity in frontal lobe semiology, which makes identifying the presumptive EZ more challenging without intracranial EEG. We describe use of a semiology visualisation tool to interrogate how well frontal lobe semiology can lateralise and

localise the presumed site of seizure onset in a cohort of individuals who subsequently had FLE surgery. Our findings suggest that although our appreciation of the correlation between semiological patterns and sublobar regions has grown over the last few decades, semiology must continue to be framed within the context of other elements of the multimodal presurgical evaluation in those with FLE.

In Chapter 5 we explored long-term outcomes in a large cohort of people having FLE surgery and identified favourable long-term outcomes (ILAE outcome score 1 or 2) in approximately 40%. It is important to recognise, however, that while the remainder may not be seizure-free, the majority have a sustained reduction in seizure frequency and over half have at least one seizure-free year. Nonetheless, an important area of further research is interrogating why individuals with a clear surgical hypothesis and favourable presurgical evaluation may not be seizure-free after surgery. The impact of additional presurgical investigations such as electric or magnetic source imaging, 7-Tesla MRI and scrutiny of high frequency oscillations on EEG in delineating the EZ is increasingly recognised, however whether this translates into achieving better seizure-freedom rates in epilepsy surgery cohorts has not been comprehensively explored. Notably, further presurgical investigations will inevitably lead to additional delays to surgery.

In our cohort of people who had FLE surgery, perioperative complication rates were low, and psychiatric comorbidities – which were present in >40% of the cohort – improved substantially, particularly for those who were seizure free.

There is, however, still limited information on the long-term changes in cognitive profiles after FLE surgery and how this should relate to individualised discussions about risk in the outpatient clinic.

Lastly, our findings that younger age at the time of surgery was associated with better outcomes on survival analysis highlights the need to offer surgery to suitable individuals early and is consistent with current ILAE guidelines. This emphasises the need to explore strategies to continue advocating for epilepsy surgery, exploring methods to reduce waiting times and continuing to refine the delivery of surgery treatment in suitable individuals.

8.5 Economic considerations

To be adopted widely, detailed information on the economic considerations inherent with any new intervention must be collated. Temporal lobe epilepsy surgery has been shown to be both effective and cost-effective, particularly if the result is seizure freedom, however there is limited information on the costs involved with an epilepsy surgery program that includes those with extratemporal epilepsy, and the added costs of crucial investigations such as FDG-PET, ictal SPECT or intracranial EEG. These investigations are often required to identify the EZ in people with normal MRI and/or extratemporal epilepsy. We used a tariff-based approach to estimate the costs involved in working individuals up for surgery through different routes of a presurgical pathway that includes those who go on to have Stage Two investigations, including intracranial EEG. Although this is based on NHS reference costs within the UK, findings can be replicated in

developed countries elsewhere (such as Australia) that utilise similar care models.

Significant costs were encountered in people having intracranial EEG, emphasising the need to carefully select individuals for this investigation. When viewed alongside the estimated direct and especially indirect costs associated with drug-resistant epilepsy, the increased upfront costs with epilepsy surgery are likely outweighed by reduced healthcare utilisation costs, particularly if surgery leads to seizure freedom. Further prospective studies, which compare the costs involved in people who have surgery following intracranial EEG and those who do not, are required to better determine the cost-effectiveness of epilepsy surgery in this cohort.

Although we could not demonstrate an improvement in socioeconomic status as measured by the IMD with epilepsy surgery, this is constrained by numerous factors. The IMD is estimated from an individual's residential postcode, and most people did not change residence following epilepsy surgery for the duration of our follow-up, which had a median duration of seven years. The IMD is also a composite measure of seven different domains (relative income, employment, education, health and disability, crime, housing and living environment), and further granularity examining changes in each of these factors could provide a more detailed measure of socioeconomic outcomes. It is nonetheless reassuring that there was no deterioration in IMD demonstrated in our cohort following epilepsy surgery.

We demonstrated that those who resided in more deprived areas of England were less likely to have epilepsy surgery. Further studies are required to determine the reasons that underpin this finding. It is possible that these people are less able to complete the lengthy presurgical evaluation, which requires numerous visits to tertiary centres. This finding also raises the possibility that low uptake of surgery in socially deprived areas may be a mechanism by which health inequality is maintained.

There are many causes of health inequality in epilepsy, and a conceptual framework is illustrated in Figure 8.2 (World Health Organization, 2010). Structural determinants of socioeconomic status and health relating to epilepsy include varying levels of epilepsy advocacy, epilepsy treatment regulations such as driving, cultural values within groups of society and societal/employment restrictions such as being unable to operate heavy machinery safely. Intermediary determinants of health, also known as mediating factors, include psychosocial mechanisms such as treatment adherence, support groups and access to healthcare (Szaflarski, 2014). Both these structural and intermediary factors contribute to and influence the socioeconomic health gradient and treatment gap in epilepsy.

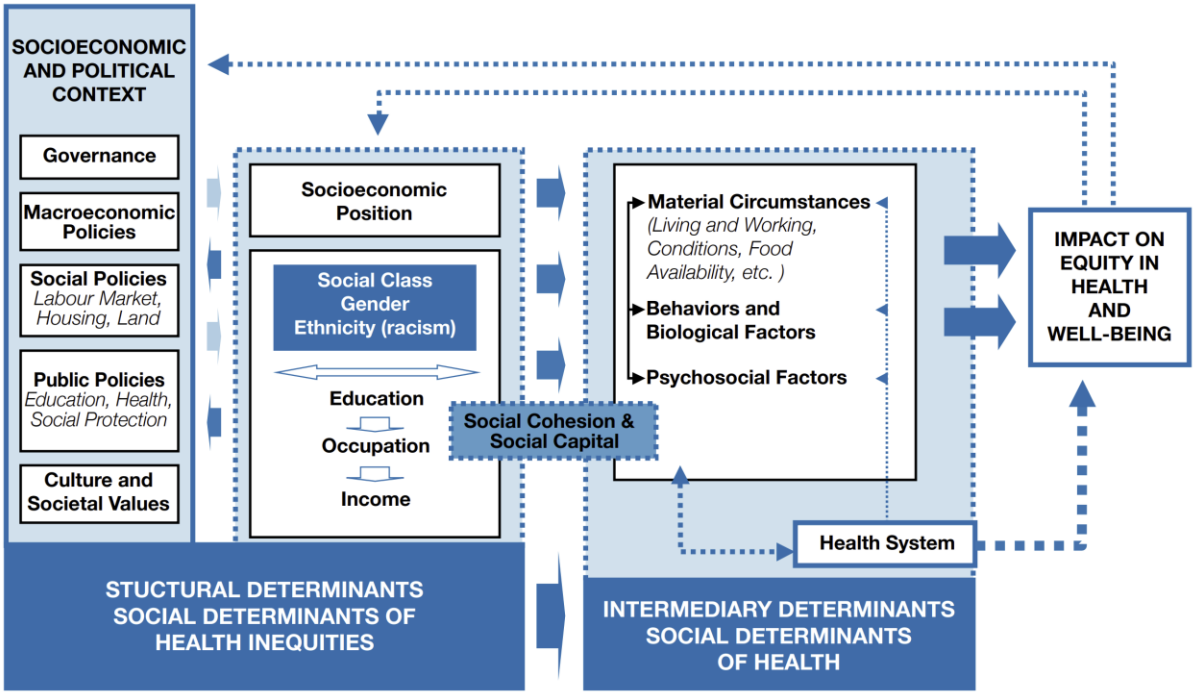

Figure 8.2: Conceptual framework for health inequality. From: Solar O, Irwin A. 2010. A conceptual framework for action on the social determinants of health. Social Determinants of Health Discussion Paper 2 (Policy and Practice). Used with permission.

Epilepsy is more prevalent in those with lower socioeconomic status, however individuals with epilepsy also have lower levels of education, income and employment, perpetuating a cycle that maintains health inequality (Banerjee et al., 2009, Beghi and Hesdorffer, 2014, Sadr et al., 2018). Socioeconomic deprivation has implications for education level and health literacy, which may in turn explain lower rates of ASM adherence and the early abandonment of presurgical evaluation. Poor adherence to ASM has broad implications, as it raises issues over the actual diagnosis of drug-resistance, leads to reluctance from medical staff to commit to extensive investigation (or surgery) which require a strong doctor-patient therapeutic alliance, and ultimately lower rates of seizure freedom. Poor ASM adherence is consistently more prevalent in people with

lower socioeconomic status (Elliott et al., 2009, Faught et al., 2008, Govil et al., 2021, Huber and Weber, 2022).

Closing these gaps in epilepsy care is a public health challenge that requires input and advocacy at an individual level and involvement from professional societies, governmental bodies and the international community. By increasing awareness of the challenges facing those who live with socioeconomic deprivation, we can better engage these stakeholders. While epilepsy is not the only chronic condition associated with health inequality, its burden is disproportionate to its prevalence.

From a global perspective, addressing healthcare inequalities must also emphasise treatment approaches in lower-income countries, where epilepsy prevalence is highest. A dedicated neurological workforce is required to care for the growing numbers of people with acute and chronic neurological disorders like epilepsy. Although this thesis has focussed on the 30% of people who are drug-resistant with an emphasis on care in a high-income country like the UK, epilepsy is a condition with global geographic inequalities that mean many individuals, particularly those in developing countries, are unable to reliably access effective medical therapy. Strategies to improve access to and availability of ASM therapy will likely lead to the greatest reduction in epilepsy-related morbidity worldwide.

Workforce disparities between high and low-income countries is stark, with the total number of neurologists and neurosurgeons estimated at 9 per 100,000

population in Europe, but only 0.3 per 100,000 in South-East Asia and 0.1 per 100,000 in Africa (World Health Organization, 2017). Of 105 countries surveyed by the WHO, only 16% had an epilepsy surgery unit (World Health Organization, 2017).

Given these numbers, it is unlikely that primary care physicians in low-income countries can always indulge in the luxury of referring everyone with drug-resistant epilepsy to a specialist epilepsy surgical centre, as is now recommended. In these areas, the findings of this thesis, together with the use of other epilepsy surgery nomograms and predictive tools, may help refine the selection of candidates for presurgical evaluation or surgery.

8.6 Conclusion

Our understanding of epilepsy continues to grow, although much remains unknown. More comprehensive diagnostic and treatment paradigms are being developed and validated, with clinical practice becoming increasingly individualised. We must integrate advancements in medical science to refine our therapeutic strategies, address disparities in healthcare delivery, and work to reduce the enormous burden that continues to be associated with drug-resistant epilepsy worldwide.

References

Aaronson, S. T., Sears, P., Ruvuna, F., Bunker, M., Conway, C. R., Dougherty, D. D., Reimherr, F. W., Schwartz, T. L. & Zajecka, J. M. 2017. A 5-Year Observational Study of Patients With Treatment-Resistant Depression Treated With Vagus Nerve Stimulation or Treatment as Usual: Comparison of Response, Remission, and Suicidality. *Am J Psychiatry,* 174**,** 640-648.

Accolla, E. A. & Pollo, C. 2019. Mood Effects After Deep Brain Stimulation for Parkinson's Disease: An Update. *Front Neurol,* 10**,** 617.

Alim-Marvasti, A., Pérez-García, F., Dahele, K., Romagnoli, G., Diehl, B., Sparks, R., Ourselin, S., Clarkson, M. J. & Duncan, J. S. 2021. Machine Learning for Localizing Epileptogenic-Zone in the Temporal Lobe: Quantifying the Value of Multimodal Clinical-Semiology and Imaging Concordance. *Frontiers in Digital Health,* 3.

Alim-Marvasti, A., Romagnoli, G., Dahele, K., Modarres, H., Pérez-García, F., Sparks, R., Ourselin, S., Clarkson, M. J., Chowdhury, F., Diehl, B. & Duncan, J. S. 2022a. Probabilistic landscape of seizure semiology localizing values. *Brain Communications,* 4**,** fcac130.

Alim-Marvasti, A., Vakharia, V. N. & Duncan, J. S. 2022b. Multimodal prognostic features of seizure freedom in epilepsy surgery. *Journal of Neurology, Neurosurgery & Psychiatry,* 93**,** 499.

Allers, K., Essue, B. M., Hackett, M. L., Muhunthan, J., Anderson, C. S., Pickles, K., Scheibe, F. & Jan, S. 2015. The economic impact of epilepsy: a systematic review. *BMC Neurology,* 15**,** 245.

Alsumaili, M., Alkhateeb, M., Khoja, A., Alkhaja, M., Alsulami, A., Alqadi, K., Baz, S., Abalkhail, T., Babtain, F., Althubaiti, I., Abu-Ata, M. & Alotaibi, F. 2021. Seizure outcome after epilepsy surgery for patients with normal MRI: A Single center experience. *Epilepsy Res,* 173**,** 23.

Andersson-Roswall, L., Engman, E., Samuelsson, H. & Malmgren, K. 2013. Psychosocial status 10years after temporal lobe resection for epilepsy, a longitudinal controlled study. *Epilepsy & Behavior,* 28**,** 127-131.

Arya, R., Mangano, F. T., Horn, P. S., Holland, K. D., Rose, D. F. & Glauser, T. A. 2013. Adverse events related to extraoperative invasive EEG monitoring with subdural grid electrodes: a systematic review and meta-analysis. *Epilepsia,* 54**,** 828-39.

Attard Navarro, G. & Hamandi, K. 2022. Lessons from the video-EEG telemetry unit. *Practical Neurology,* 22**,** 301.

Aupy, J., Wongwiangjunt, S., Wang, Z. I., Wu, G. & Alexopoulos, A. 2018. Subcortical SISCOM hyperperfusion: Should we pay more attention to it? *Seizure,* 62**,** 43-48.

Awan, S. A., Khawaja, I., Babar, M. & Khan, F. 2022. Prevalence of Non-adherence to Antiepileptic Drugs in Patients With Epilepsy Presenting to Emergency With Fits. *Cureus,* 14**,** e27072.

Banerjee, P. N., Filippi, D. & Allen Hauser, W. 2009. The descriptive epidemiology of epilepsy-a review. *Epilepsy Res,* 85**,** 31-45.

Bauman, K. & Devinsky, O. 2021. Seizure Clusters: Morbidity and Mortality. *Frontiers in Neurology,* 12.

Bautista, R. E. D. & Tannahill Glen, E. 2009. Seizure severity is associated with quality of life independent of seizure frequency. *Epilepsy & Behavior,* 16**,** 325-329.
Baxendale, S. & Baker, G. A. 2022. Uses and abuses of the neuropsychological assessment in the presurgical evaluation of epilepsy surgery candidates. *Epilepsy Behav Rep,* 18**,** 100507.
Baxendale, S. & Thompson, P. 2018. Red flags in epilepsy surgery: Identifying the patients who pay a high cognitive price for an unsuccessful surgical outcome. *Epilepsy Behav,* 78**,** 269-272.
Baxendale, S., Thompson, P., Harkness, W. & Duncan, J. 2006. Predicting Memory Decline Following Epilepsy Surgery: A Multivariate Approach. *Epilepsia,* 47**,** 1887-1894.
Beghi, E., Giussani, G., Nichols, E., Abd-Allah, F., Abdela, J., Abdelalim, A., Abraha, H. N., Adib, M. G., Agrawal, S., Alahdab, F., Awasthi, A., Ayele, Y., Barboza, M. A., Belachew, A. B., Biadgo, B., Bijani, A., Bitew, H., Carvalho, F., Chaiah, Y., Daryani, A., Do, H. P., Dubey, M., Endries, A. Y. Y., Eskandarieh, S., Faro, A., Farzadfar, F., Fereshtehnejad, S.-M., Fernandes, E., Fijabi, D. O., Filip, I., Fischer, F., Gebre, A. K., Tsadik, A. G., Gebremichael, T. G., Gezae, K. E., Ghasemi-Kasman, M., Weldegwergs, K. G., Degefa, M. G., Gnedovskaya, E. V., Hagos, T. B., Haj-Mirzaian, A., Haj-Mirzaian, A., Hassen, H. Y., Hay, S. I., Jakovljevic, M., Kasaeian, A., Kassa, T. D., Khader, Y. S., Khalil, I., Khan, E. A., Khubchandani, J., Kisa, A., Krohn, K. J., Kulkarni, C., Nirayo, Y. L., Mackay, M. T., Majdan, M., Majeed, A., Manhertz, T., Mehndiratta, M. M., Mekonen, T., Meles, H. G., Mengistu, G., Mohammed, S., Naghavi, M., Mokdad, A. H., Mustafa, G., Irvani, S. S. N., Nguyen, L. H., Nixon, M. R., Ogbo, F. A., Olagunju, A. T., Olagunju, T. O., Owolabi, M. O., Phillips, M. R., Pinilla-Monsalve, G. D., Qorbani, M., Radfar, A., Rafay, A., Rahimi-Movaghar, V., Reinig, N., Sachdev, P. S., Safari, H., Safari, S., Safiri, S., Sahraian, M. A., Samy, A. M., Sarvi, S., Sawhney, M., Shaikh, M. A., Sharif, M., Singh, G., Smith, M., Szoeke, C. E. I., Tabarés-Seisdedos, R., Temsah, M.-H., Temsah, O., Tortajada-Girbés, M., Tran, B. X., Tsegay, A. a. T., et al. 2019. Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology,* 18**,** 357-375.
Beghi, E. & Hesdorffer, D. 2014. Prevalence of epilepsy—An unknown quantity. *Epilepsia,* 55**,** 963-967.
Begley, C., Wagner, R. G., Abraham, A., Beghi, E., Newton, C., Kwon, C. S., Labiner, D. & Winkler, A. S. 2022. The global cost of epilepsy: A systematic review and extrapolation. *Epilepsia,* 63**,** 892-903.
Begley, C. E. & Beghi, E. 2002. The economic cost of epilepsy: a review of the literature. *Epilepsia,* 4**,** 3-9.
Begley, C. E. & Durgin, T. L. 2015. The direct cost of epilepsy in the United States: A systematic review of estimates. *Epilepsia,* 56**,** 1376-87.
Bell, G. S., De Tisi, J., Gonzalez-Fraile, J. C., Peacock, J. L., Mcevoy, A. W., Harkness, W. F. J., Foong, J., Pope, R. A., Diehl, B., Sander, J. W. & Duncan, J. S. 2017. Factors affecting seizure outcome after epilepsy surgery: an observational series. *J Neurol Neurosurg Psychiatry,* 88**,** 933-940.
Bell, G. S., Gaitatzis, A., Bell, C. L., Johnson, A. L. & Sander, J. W. 2009. Suicide in people with epilepsy: how great is the risk? *Epilepsia,* 50**,** 1933-42.

Beniczky, S., Rosenzweig, I., Scherg, M., Jordanov, T., Lanfer, B., Lantz, G. & Larsson, P. G. 2016. Ictal EEG source imaging in presurgical evaluation: High agreement between analysis methods. *Seizure,* 43**,** 1-5.

Beniczky, S., Tatum, W. O., Blumenfeld, H., Stefan, H., Mani, J., Maillard, L., Fahoum, F., Vinayan, K. P., Mayor, L. C., Vlachou, M., Margitta, S., Ryvlin, P. & Philippe, K. 2022. Seizure semiology: ILAE glossary of terms and their significance. *Epileptic Disord,* 24**,** 447-495.

Berg, A. T., Berkovic, S. F., Brodie, M. J., Buchhalter, J., Cross, J. H., Van Emde Boas, W., Engel, J., French, J., Glauser, T. A., Mathern, G. W., Moshé, S. L., Nordli, D., Plouin, P. & Scheffer, I. E. 2010. Revised terminology and concepts for organization of seizures and epilepsies: Report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia,* 51**,** 676-685.

Betjemann, J. P., Josephson, S. A., Lowenstein, D. H. & Burke, J. F. 2015. Trends in Status Epilepticus—Related Hospitalizations and Mortality: Redefined in US Practice Over Time. *JAMA Neurology,* 72**,** 650-655.

Beydoun, A., D'souza, J., Hebert, D. & Doty, P. 2009. Lacosamide: pharmacology, mechanisms of action and pooled efficacy and safety data in partial-onset seizures. *Expert Rev Neurother,* 9**,** 33-42.

Bialek, F., Rydenhag, B., Flink, R. & Malmgren, K. 2014. Outcomes after resective epilepsy surgery in patients over 50 years of age in Sweden 1990-2009--a prospective longitudinal study. *Seizure,* 23**,** 641-5.

Birbeck, G. L., Hays, R. D., Cui, X. & Vickrey, B. G. 2002. Seizure reduction and quality of life improvements in people with epilepsy. *Epilepsia,* 43**,** 535-8.

Bjellvi, J., Flink, R., Rydenhag, B. & Malmgren, K. 2015. Complications of epilepsy surgery in Sweden 1996-2010: a prospective, population-based study. *J Neurosurg,* 122**,** 519-25.

Bjellvi, J., Olsson, I., Malmgren, K. & Wilbe Ramsay, K. 2019. Epilepsy duration and seizure outcome in epilepsy surgery. *Neurology,* 93**,** e159.

Bodde, N. M. G., Brooks, J. L., Baker, G. A., Boon, P. a. J. M., Hendriksen, J. G. M., Mulder, O. G. & Aldenkamp, A. P. 2009. Psychogenic non-epileptic seizures—Definition, etiology, treatment and prognostic issues: A critical review. *Seizure,* 18**,** 543-553.

Bonini, F., Mcgonigal, A., Trébuchon, A., Gavaret, M., Bartolomei, F., Giusiano, B. & Chauvel, P. 2014. Frontal lobe seizures: from clinical semiology to localization. *Epilepsia,* 55**,** 264-77.

Borlot, F., Wither, R., Ali, A., Wu, N., Verocai, F. & Andrade, D. 2016. A Pilot Double-Blind Trial Using Verapamil as Adjuvant Therapy for Refractory Seizures (P6.357). *Neurology,* 86**,** P6.357.

Bough, K. J. & Rho, J. M. 2007. Anticonvulsant mechanisms of the ketogenic diet. *Epilepsia,* 48**,** 43-58.

Boukhris, T., Sheehy, O., Mottron, L. & Bérard, A. 2016. Antidepressant Use During Pregnancy and the Risk of Autism Spectrum Disorder in Children. *JAMA Pediatr,* 170**,** 117-24.

Brodbeck, V., Spinelli, L., Lascano, A. M., Pollo, C., Schaller, K., Vargas, M. I., Wissmeyer, M., Michel, C. M. & Seeck, M. 2010. Electrical source imaging for presurgical focus localization in epilepsy patients with normal MRI. *Epilepsia,* 51**,** 583-591.

Bulacio, J. C., Jehi, L., Wong, C., Gonzalez-Martinez, J., Kotagal, P., Nair, D., Najm, I. & Bingaman, W. 2012. Long-term seizure outcome after resective surgery in patients evaluated with intracranial electrodes. *Epilepsia,* 53**,** 1722-30.

Busch, R. M., Floden, D. P., Ferguson, L., Mahmoud, S., Mullane, A., Jones, S., Jehi, L., Bingaman, W. & Najm, I. M. 2017. Neuropsychological outcome following frontal lobectomy for pharmacoresistant epilepsy in adults. *Neurology,* 88**,** 692-700.

Chauvel, P., Gonzalez-Martinez, J. & Bulacio, J. 2019. Presurgical intracranial investigations in epilepsy surgery. *Handb Clin Neurol,* 161**,** 45-71.

Chavel, S. M., Westerveld, M. & Spencer, S. 2003. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy & Behavior,* 4**,** 302-309.

Chen, H., Amdur, R., Pauldurai, J. & Koubeissi, M. 2021. Seizure recurrence after prolonged seizure control: Patterns and risk factors. *Epilepsy Behav,* 124**,** 108330.

Chen, J. W. & Wasterlain, C. G. 2006. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol,* 5**,** 246-56.

Chen, T. & Guo, L. 2016. The role of SISCOM in preoperative evaluation for patients with epilepsy surgery: A meta-analysis. *Seizure,* 41**,** 43-50.

Chen, Z., Brodie, M. J., Liew, D. & Kwan, P. 2018. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol,* 75**,** 279-286.

Chen, Z., Liew, D. & Kwan, P. 2016. Excess mortality and hospitalized morbidity in newly treated epilepsy patients. *Neurology,* 87**,** 718-25.

Choi, H., Hayat, M. J., Zhang, R., Hirsch, L. J., Bazil, C. W., Mendiratta, A., Kato, K., Javed, A., Legge, A. W., Buchsbaum, R., Resor, S. & Heiman, G. A. 2016. Drug-resistant epilepsy in adults: Outcome trajectories after failure of two medications. *Epilepsia,* 57**,** 1152-1160.

Chowdhury, F. A., Silva, R., Whatley, B. & Walker, M. C. 2021. Localisation in focal epilepsy: a practical guide. *Pract Neurol,* 21**,** 481-491.

Chrastina, J., Novák, Z., Zeman, T., Kočvarová, J., Pail, M., Doležalová, I., Jarkovský, J. & Brázdil, M. 2018. Single-center long-term results of vagus nerve stimulation for epilepsy: A 10–17 year follow-up study. *Seizure,* 59**,** 41-47.

Christensen, J., Vestergaard, M., Mortensen, P. B., Sidenius, P. & Agerbo, E. 2007. Epilepsy and risk of suicide: a population-based case-control study. *Lancet Neurol,* 6**,** 693-8.

Cloppenborg, T., May, T. W., Blümcke, I., Grewe, P., Hopf, L. J., Kalbhenn, T., Pfäfflin, M., Polster, T., Schulz, R., Woermann, F. G. & Bien, C. G. 2016. Trends in epilepsy surgery: stable surgical numbers despite increasing presurgical volumes. *J Neurol Neurosurg Psychiatry,* 87**,** 1322-1329.

Cockerell, O. C., Johnson, A. L., Sander, J. W. a. S. & Shorvon, S. D. 1997. Prognosis of Epilepsy: A Review and Further Analysis of the First Nine Years of the British National General Practice Study of Epilepsy, a Prospective Population-Based Study. *Epilepsia,* 38**,** 31-46.

Contento, M., Bertaccini, B., Biggi, M., Magliani, M., Failli, Y., Rosati, E., Massacesi, L. & Paganini, M. 2021. Prediction of seizure recurrence risk following discontinuation of antiepileptic drugs. *Epilepsia,* 62**,** 2159-2170.

Conway, C. R., Kumar, A., Xiong, W., Bunker, M., Aaronson, S. T. & Rush, A. J. 2018. Chronic Vagus Nerve Stimulation Significantly Improves Quality of Life in Treatment-Resistant Major Depression. *J Clin Psychiatry,* 79.

Cossu, M., Lo Russo, G., Francione, S., Mai, R., Nobili, L., Sartori, I., Tassi, L., Citterio, A., Colombo, N., Bramerio, M., Galli, C., Castana, L. & Cardinale, F. 2008. Epilepsy Surgery in Children: Results and Predictors of Outcome on Seizures. *Epilepsia,* 49**,** 65-72.

Cronin, J., Obenaus, A., Houser, C. R. & Dudek, F. E. 1992. Electrophysiology of dentate granule cells after kainate-induced synaptic reorganization of the mossy fibers. *Brain Res,* 573**,** 305-10.

Culler, G. W. T. & Jobst, B. C. 2022. Surgical Treatments for Epilepsy. *Continuum (Minneap Minn),* 28**,** 536-558.

Davids, R., Kowski, A. B., Meencke, H.-J., Oltmanns, F., Dehnicke, C., Schneider, U. C. & Holtkamp, M. 2021. Surgery in intractable epilepsy—physicians' recommendations and patients' decisions. *Acta Neurologica Scandinavica,* 143**,** 421-429.

De Ciantis, A., Barba, C., Tassi, L., Cosottini, M., Tosetti, M., Costagli, M., Bramerio, M., Bartolini, E., Biagi, L., Cossu, M., Pelliccia, V., Symms, M. R. & Guerrini, R. 2016. 7T MRI in focal epilepsy with unrevealing conventional field strength imaging. *Epilepsia,* 57**,** 445-454.

De Tisi, J., Bell, G. S., Peacock, J. L., Mcevoy, A. W., Harkness, W. F., Sander, J. W. & Duncan, J. S. 2011. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet,* 378**,** 1388-95.

Devinsky, O., Friedman, D., Cheng, J. Y., Moffatt, E., Kim, A. & Tseng, Z. H. 2017. Underestimation of sudden deaths among patients with seizures and epilepsy. *Neurology,* 89**,** 886-892.

Devinsky, O., Spruill, T., Thurman, D. & Friedman, D. 2016. Recognizing and preventing epilepsy-related mortality: A call for action. *Neurology,* 86**,** 779-86.

Dibbens, L. M., De Vries, B., Donatello, S., Heron, S. E., Hodgson, B. L., Chintawar, S., Crompton, D. E., Hughes, J. N., Bellows, S. T., Klein, K. M., Callenbach, P. M., Corbett, M. A., Gardner, A. E., Kivity, S., Iona, X., Regan, B. M., Weller, C. M., Crimmins, D., O'brien, T. J., Guerrero-López, R., Mulley, J. C., Dubeau, F., Licchetta, L., Bisulli, F., Cossette, P., Thomas, P. Q., Gecz, J., Serratosa, J., Brouwer, O. F., Andermann, F., Andermann, E., Van Den Maagdenberg, A. M., Pandolfo, M., Berkovic, S. F. & Scheffer, I. E. 2013. Mutations in DEPDC5 cause familial focal epilepsy with variable foci. *Nat Genet,* 45**,** 546-51.

Ding, J., Li, X., Tian, H., Wang, L., Guo, B., Wang, Y., Li, W., Wang, F. & Sun, T. 2021. SCN1A Mutation-Beyond Dravet Syndrome: A Systematic Review and Narrative Synthesis. *Front Neurol,* 12**,** 743726.

Dixon, P. A., Kirkham, J. J., Marson, A. G. & Pearson, M. G. 2015. National Audit of Seizure management in Hospitals (NASH): results of the national audit of adult epilepsy in the UK. *BMJ Open,* 5**,** 2014-007325.

Djibuti, M. & Shakarishvili, R. 2003. Influence of clinical, demographic, and socioeconomic variables on quality of life in patients with epilepsy: findings from Georgian study. *J Neurol Neurosurg Psychiatry,* 74**,** 570-3.

Duble, S. N., Nandini, V. S., Radhakrishnan, A., Menon, R., Cherian, A., Sarma, P. S. & Thomas, S. V. 2019. Long-Term Mortality Risk of People with Epilepsy Who Underwent Seizure Monitoring. *Ann Indian Acad Neurol,* 22**,** 453-457.

Dugan, P., Carlson, C., Jetté, N., Wiebe, S., Bunch, M., Kuzniecky, R. & French, J. 2017. Derivation and initial validation of a surgical grading scale for the preliminary

evaluation of adult patients with drug-resistant focal epilepsy. *Epilepsia,* 58**,** 792-800.
Dulay, M. F. & Busch, R. M. 2012. Prediction of neuropsychological outcome after resection of temporal and extratemporal seizure foci. *Neurosurgical Focus FOC,* 32**,** E4.
Duncan, J. S. 2011. Selecting patients for epilepsy surgery: synthesis of data. *Epilepsy Behav,* 20**,** 230-2.
Duncan, J. S. 2022. Multidisciplinary team meetings: the epilepsy experience. *Pract Neurol*.
Dupont, S., Tanguy, M. L., Clemenceau, S., Adam, C., Hazemann, P. & Baulac, M. 2006. Long-term prognosis and psychosocial outcomes after surgery for MTLE. *Epilepsia,* 47**,** 2115-24.
Edwards, J. C., Sobel, R. S. & Bonilha, L. 2018. Marginal decision-making in the treatment of refractory epilepsy. *J Med Econ,* 21**,** 438-442.
Eliashiv, S. D., Dewar, S., Wainwright, I., Engel, J., Jr. & Fried, I. 1997. Long-term follow-up after temporal lobe resection for lesions associated with chronic seizures. *Neurology,* 48**,** 621-6.
Elkhayat, H. A., Aly, R. H., Elagouza, I. A., El-Kabarity, R. H. & Galal, Y. I. 2017. Role of P-glycoprotein inhibitors in children with drug-resistant epilepsy. *Acta Neurol Scand,* 136**,** 639-644.
Elliott, J. O., Lu, B., Shneker, B. F., Moore, J. L. & Mcauley, J. W. 2009. The impact of 'social determinants of health' on epilepsy prevalence and reported medication use. *Epilepsy Res,* 84**,** 135-45.
Elsharkawy, A. E., Alabbasi, A. H., Pannek, H., Schulz, R., Hoppe, M., Pahs, G., Nayel, M., Issa, A. & Ebner, A. 2008. Outcome of frontal lobe epilepsy surgery in adults. *Epilepsy Res,* 81**,** 97-106.
Elsharkawy, A. E., Thorbecke, R., Ebner, A. & May, T. W. 2012. Determinants of quality of life in patients with refractory focal epilepsy who were not eligible for surgery or who rejected surgery. *Epilepsy Behav,* 24**,** 249-55.
Elwan, S., Alexopoulos, A., Silveira, D. C. & Kotagal, P. 2018. Lateralizing and localizing value of seizure semiology: Comparison with scalp EEG, MRI and PET in patients successfully treated with resective epilepsy surgery. *Seizure,* 61**,** 203-208.
Engel, J., Mcdermott, M. P., Wiebe, S., Langfitt, J. T., Stern, J. M., Dewar, S., Sperling, M. R., Gardiner, I., Erba, G., Fried, I., Jacobs, M., Vinters, H. V., Mintzer, S., Kieburtz, K. & Early Randomized Surgical Epilepsy Trial Study Group, F. T. 2012. Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy: A Randomized Trial. *JAMA,* 307**,** 922-930.
Englot, D. J. 2018. A modern epilepsy surgery treatment algorithm: Incorporating traditional and emerging technologies. *Epilepsy Behav,* 80**,** 68-74.
Englot, D. J., Chang, E. F. & Auguste, K. I. 2011. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J Neurosurg,* 115**,** 1248-55.
Englot, D. J. & Lagrange, A. H. 2022. Of Blobs and Buzzes: Does SISCOM Imaging Actually Help SEEG Planning? *Epilepsy Curr,* 22**,** 22-24.
Ernawati, I., Islamiyah, W. R. & Sumarno 2018. How to Improve Clinical Outcome of Epileptic Seizure Control Based on Medication Adherence? A Literature Review. *Open Access Maced J Med Sci,* 6**,** 1174-1179.

Fallah, A., Lewis, E., Ibrahim, G. M., Kola, O., Tseng, C.-H., Harris, W. B., Chen, J.-S., Lin, K.-M., Cai, L.-X., Liu, Q.-Z., Lin, J.-L., Zhou, W.-J., Mathern, G. W., Smyth, M. D., O'neill, B. R., Dudley, R. W. R., Ragheb, J., Bhatia, S., Delev, D., Ramantani, G., Zentner, J., Wang, A. C., Dorfer, C., Feucht, M., Czech, T., Bollo, R. J., Issabekov, G., Zhu, H., Connolly, M., Steinbok, P., Zhang, J.-G., Zhang, K., Hidalgo, E. T., Weiner, H. L., Wong-Kisiel, L., Lapalme-Remis, S., Tripathi, M., Sarat Chandra, P., Hader, W., Wang, F.-P., Yao, Y., Champagne, P.-O., Brunette-Clément, T., Guo, Q., Li, S.-C., Budke, M., Pérez-Jiménez, M. A., Raftopoulos, C., Finet, P., Michel, P., Schaller, K., Stienen, M. N., Baro, V., Cantillano Malone, C., Pociecha, J., Chamorro, N., Muro, V. L., Von Lehe, M., Vieker, S., Oluigbo, C., Gaillard, W. D., Al-Khateeb, M., Al Otaibi, F., Krayenbühl, N., Bolton, J., Pearl, P. L. & Weil, A. G. 2021. Comparison of the real-world effectiveness of vertical versus lateral functional hemispherotomy techniques for pediatric drug-resistant epilepsy: A post hoc analysis of the HOPS study. *Epilepsia,* 62**,** 2707-2718.

Fasano, R. E. & Kanner, A. M. 2019. Psychiatric complications after epilepsy surgery… but where are the psychiatrists? *Epilepsy Behav,* 98**,** 318-321.

Faught, E., Duh, M. S., Weiner, J. R., Guérin, A. & Cunnington, M. C. 2008. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology,* 71**,** 1572-8.

Feigin, V. L., Nichols, E., Alam, T., Bannick, M. S., Beghi, E., Blake, N., Culpepper, W. J., Dorsey, E. R., Elbaz, A., Ellenbogen, R. G., Fisher, J. L., Fitzmaurice, C., Giussani, G., Glennie, L., James, S. L., Johnson, C. O., Kassebaum, N. J., Logroscino, G., Marin, B., Mountjoy-Venning, W. C., Nguyen, M., Ofori-Asenso, R., Patel, A. P., Piccininni, M., Roth, G. A., Steiner, T. J., Stovner, L. J., Szoeke, C. E. I., Theadom, A., Vollset, S. E., Wallin, M. T., Wright, C., Zunt, J. R., Abbasi, N., Abd-Allah, F., Abdelalim, A., Abdollahpour, I., Aboyans, V., Abraha, H. N., Acharya, D., Adamu, A. A., Adebayo, O. M., Adeoye, A. M., Adsuar, J. C., Afarideh, M., Agrawal, S., Ahmadi, A., Ahmed, M. B., Aichour, A. N., Aichour, I., Aichour, M. T. E., Akinyemi, R. O., Akseer, N., Al-Eyadhy, A., Al-Shahi Salman, R., Alahdab, F., Alene, K. A., Aljunid, S. M., Altirkawi, K., Alvis-Guzman, N., Anber, N. H., Antonio, C. a. T., Arabloo, J., Aremu, O., Ärnlöv, J., Asayesh, H., Asghar, R. J., Atalay, H. T., Awasthi, A., Ayala Quintanilla, B. P., Ayuk, T. B., Badawi, A., Banach, M., Banoub, J. a. M., Barboza, M. A., Barker-Collo, S. L., Bärnighausen, T. W., Baune, B. T., Bedi, N., Behzadifar, M., Behzadifar, M., Béjot, Y., Bekele, B. B., Belachew, A. B., Bennett, D. A., Bensenor, I. M., Berhane, A., Beuran, M., Bhattacharyya, K., Bhutta, Z. A., Biadgo, B., Bijani, A., Bililign, N., Bin Sayeed, M. S., Blazes, C. K., Brayne, C., Butt, Z. A., Campos-Nonato, I. R., Cantu-Brito, C., Car, M., et al. 2019. Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology,* 18**,** 459-480.

Feigin, V. L., Stark, B., Johnson, C. O., Roth, G. A., Bisignano, C., Abady, G., Abbasifard, M., Abbasi-Kangevari, M., Murray, C. J. L. & Gbd 2019 Stroke Collaborators 2021. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol,* 20**,** 795-820.

Feldkamp, M. L., Carey, J. C., Byrne, J. L. B., Krikov, S. & Botto, L. D. 2017. Etiology and clinical presentation of birth defects: population based study. *Bmj,* 357**,** j2249.
Fenoy, A. J. & Simpson, R. K., Jr. 2012. Management of device-related wound complications in deep brain stimulation surgery. *J Neurosurg,* 116**,** 1324-32.
Finger, S. & Clower, W. T. 2001. Victor Horsley on "trephining in pre-historic times". *Neurosurgery,* 48**,** 911-7; discussion 917-8.
Fisher, R., Salanova, V., Witt, T., Worth, R., Henry, T., Gross, R., Oommen, K., Osorio, I., Nazzaro, J., Labar, D., Kaplitt, M., Sperling, M., Sandok, E., Neal, J., Handforth, A., Stern, J., Desalles, A., Chung, S., Shetter, A., Bergen, D., Bakay, R., Henderson, J., French, J., Baltuch, G., Rosenfeld, W., Youkilis, A., Marks, W., Garcia, P., Barbaro, N., Fountain, N., Bazil, C., Goodman, R., Mckhann, G., Babu Krishnamurthy, K., Papavassiliou, S., Epstein, C., Pollard, J., Tonder, L., Grebin, J., Coffey, R. & Graves, N. 2010. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia,* 51**,** 899-908.
Fisher, R. S., Cross, J. H., French, J. A., Higurashi, N., Hirsch, E., Jansen, F. E., Lagae, L., Moshe, S. L., Peltola, J., Roulet Perez, E., Scheffer, I. E. & Zuberi, S. M. 2017. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia,* 58**,** 522-530.
Fisher, R. S., Van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P. & Engel, J., Jr. 2005. Epileptic seizures and epilepsy: definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE). *Epilepsia,* 46**,** 470-2.
Fois, C., Kovac, S., Khalil, A., Uzuner, G. T., Diehl, B., Wehner, T., Duncan, J. S. & Walker, M. C. 2016. Predictors for being offered epilepsy surgery: 5-year experience of a tertiary referral centre. *J Neurol Neurosurg Psychiatry,* 87**,** 209-11.
Foldvary-Schaefer, N. & Unnwongse, K. 2011. Localizing and lateralizing features of auras and seizures. *Epilepsy Behav,* 20**,** 160-6.
Foong, J. & Flugel, D. 2007. Psychiatric outcome of surgery for temporal lobe epilepsy and presurgical considerations. *Epilepsy Research,* 75**,** 84-96.
Foster, E., Chen, Z., Zomer, E., Rychkova, M., Carney, P., Brien, T. J., Liew, D., Jackson, G. D., Kwan, P. & Ademi, Z. 2020. The costs of epilepsy in Australia. *Neurology,* 95**,** e3221.
Freeman, J. M., Kossoff, E. H. & Hartman, A. L. 2007. The ketogenic diet: one decade later. *Pediatrics,* 119**,** 535-43.
Galbarriatu, L., Pomposo, I., Aurrecoechea, J., Marinas, A., Agúndez, M., Gómez, J. C., Acera, M. A., Martínez, M. J., Valle, E., Maestro, I., Mateos, B., Cabrera, A., Fernández, J., Iturri, F. & Garamendi, I. 2015. Vagus nerve stimulation therapy for treatment-resistant epilepsy: a 15-year experience at a single institution. *Clin Neurol Neurosurg,* 137**,** 89-93.
George, D. D., Ojemann, S. G., Drees, C. & Thompson, J. A. 2020. Stimulation Mapping Using Stereoelectroencephalography: Current and Future Directions. *Front Neurol,* 11**,** 320.
Gil, F., Padilla, N., Soria-Pastor, S., Setoain, X., Boget, T., Rumiá, J., Roldán, P., Reyes, D., Bargalló, N., Conde, E., Pintor, L., Vernet, O., Manzanares, I., Ådén, U., Carreño, M. & Donaire, A. 2020. Beyond the Epileptic Focus: Functional Epileptic Networks in Focal Epilepsy. *Cereb Cortex,* 30**,** 2338-2357.

Giorgi, F. S., Pizzanelli, C., Biagioni, F., Murri, L. & Fornai, F. 2004. The role of norepinephrine in epilepsy: from the bench to the bedside. *Neurosci Biobehav Rev,* 28**,** 507-24.

Gonzalez-Martinez, J., Bulacio, J., Alexopoulos, A., Jehi, L., Bingaman, W. & Najm, I. 2013. Stereoelectroencephalography in the "difficult to localize" refractory focal epilepsy: Early experience from a North American epilepsy center. *Epilepsia,* 54**,** 323-330.

Gooneratne, I. K., Mannan, S., De Tisi, J., Gonzalez, J. C., Mcevoy, A. W., Miserocchi, A., Diehl, B., Wehner, T., Bell, G. S., Sander, J. W. & Duncan, J. S. 2017. Somatic complications of epilepsy surgery over 25 years at a single center. *Epilepsy Res,* 132**,** 70-77.

Govil, N., Chahal, S., Gupta, N., Kaloti, A. S., Nadda, A. & Singh, P. 2021. Factors Associated with Poor Antiepileptic Drugs Adherence in Below Poverty Line Persons with Epilepsy: A Cross-Sectional Study. *J Neurosci Rural Pract,* 12**,** 95-101.

Gracia, C. G., Chagin, K., Kattan, M. W., Ji, X., Kattan, M. G., Crotty, L., Najm, I., Gonzalez-Martinez, J., Bingaman, W. & Jehi, L. 2019. Predicting seizure freedom after epilepsy surgery, a challenge in clinical practice. *Epilepsy Behav,* 95**,** 124-130.

Graham, D., Tisdall, M. M. & Gill, D. 2016. Corpus callosotomy outcomes in pediatric patients: A systematic review. *Epilepsia,* 57**,** 1053-68.

Green, S. F., Nguyen, P., Kaalund-Hansen, K., Rajakulendran, S. & Murphy, E. 2020. Effectiveness, retention, and safety of modified ketogenic diet in adults with epilepsy at a tertiary-care centre in the UK. *J Neurol,* 267**,** 1171-1178.

Guo, Y., Xu, Z. Y., Cai, M. T., Gong, W. X. & Shen, C. H. 2021. Epilepsy With Suicide: A Bibliometrics Study and Visualization Analysis via CiteSpace. *Front Neurol,* 12**,** 823474.

Hader, W. J., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., Wiebe, S., Kwon, C. S. & Jette, N. 2013. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia,* 54**,** 840-7.

Hamilton, P., Soryal, I., Dhahri, P., Wimalachandra, W., Leat, A., Hughes, D., Toghill, N., Hodson, J., Sawlani, V., Hayton, T., Samarasekera, S., Bagary, M., Mccorry, D. & Chelvarajah, R. 2018. Clinical outcomes of VNS therapy with AspireSR(®) (including cardiac-based seizure detection) at a large complex epilepsy and surgery centre. *Seizure,* 58**,** 120-126.

Hanada, T., Hashizume, Y., Tokuhara, N., Takenaka, O., Kohmura, N., Ogasawara, A., Hatakeyama, S., Ohgoh, M., Ueno, M. & Nishizawa, Y. 2011. Perampanel: a novel, orally active, noncompetitive AMPA-receptor antagonist that reduces seizure activity in rodent models of epilepsy. *Epilepsia,* 52**,** 1331-40.

Harowitz, J., Crandall, L., Mcguone, D. & Devinsky, O. 2021. Seizure-related deaths in children: The expanding spectrum. *Epilepsia,* 62**,** 570-582.

Harroud, A., Bouthillier, A., Weil, A. G. & Nguyen, D. K. 2012. Temporal lobe epilepsy surgery failures: a review. *Epilepsy Res Treat,* 2012**,** 201651.

Heck, C. N., King-Stephens, D., Massey, A. D., Nair, D. R., Jobst, B. C., Barkley, G. L., Salanova, V., Cole, A. J., Smith, M. C., Gwinn, R. P., Skidmore, C., Van Ness, P. C., Bergey, G. K., Park, Y. D., Miller, I., Geller, E., Rutecki, P. A., Zimmerman, R., Spencer, D. C., Goldman, A., Edwards, J. C., Leiphart, J. W., Wharen, R. E.,

Fessler, J., Fountain, N. B., Worrell, G. A., Gross, R. E., Eisenschenk, S., Duckrow, R. B., Hirsch, L. J., Bazil, C., O'donovan, C. A., Sun, F. T., Courtney, T. A., Seale, C. G. & Morrell, M. J. 2014. Two-year seizure reduction in adults with medically intractable partial onset epilepsy treated with responsive neurostimulation: final results of the RNS System Pivotal trial. *Epilepsia,* 55**,** 432-41.

Heckmatt, J., Shaikh, A. A., Swash, M. & Scott, D. F. 1990. Seizure induction by alcohol in patients with epilepsy experience in two hospital clinics. *J R Soc Med,* 83**,** 6-9.

Heller, A. C., Padilla, R. V. & Mamelak, A. N. 2009. Complications of epilepsy surgery in the first 8 years after neurosurgical training. *Surg Neurol,* 71**,** 631-7, discussion 637.

Hermann, B., Seidenberg, M. & Jones, J. 2008. The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *Lancet Neurol,* 7**,** 151-60.

Hesdorffer, D. C., Tomson, T., Benn, E., Sander, J. W., Nilsson, L., Langan, Y., Walczak, T. S., Beghi, E., Brodie, M. J. & Hauser, A. 2011. Combined analysis of risk factors for SUDEP. *Epilepsia,* 52**,** 1150-9.

Hirata, S., Morino, M., Nakae, S. & Matsumoto, T. 2020. Surgical Technique and Outcome of Extensive Frontal Lobectomy for Treatment of Intracable Non-lesional Frontal Lobe Epilepsy. *Neurol Med Chir (Tokyo),* 60**,** 17-25.

Hlauschek, G., Sinclair, B., Brinkmann, B., Fuge, J., Kwan, P., O'brien, T. J. & Vivash, L. 2021. The effect of injection time on rates of epileptogenic zone localization using SISCOM and STATISCOM. *Epilepsy Behav,* 118**,** 107945.

Hoppe, C., Witt, J.-A., Helmstaedter, C., Gasser, T., Vatter, H. & Elger, C. E. 2017. Laser interstitial thermotherapy (LiTT) in epilepsy surgery. *Seizure,* 48**,** 45-52.

Huber, R. & Weber, P. 2022. Is there a relationship between socioeconomic factors and prevalence, adherence and outcome in childhood epilepsy? A systematic scoping review. *Eur J Paediatr Neurol,* 38**,** 1-6.

Hufnagel, A., Elger, C. E., Pels, H., Zentner, J., Wolf, H. K., Schramm, J. & Wiestler, O. D. 1994. Prognostic significance of ictal and interictal epileptiform activity in temporal lobe epilepsy. *Epilepsia,* 35**,** 1146-53.

Hur, Y. J., Kim, A. J. & Nordli, D. R., Jr. 2017. MRI supersedes ictal EEG when other presurgical data are concordant. *Seizure,* 53**,** 18-22.

International League against Epilepsy 2018. Genome-wide mega-analysis identifies 16 loci and highlights diverse biological mechanisms in the common epilepsies. *Nat Commun,* 9**,** 5269.

Jaber, M., Taherpour, J., Voges, B., Apostolova, I., Sauvigny, T., House, P. M., Lanz, M., Lindenau, M., Klutmann, S., Martens, T., Stodieck, S. & Buchert, R. 2021. No Evidence to Favor 99mTc-HMPAO or 99mTc-ECD for Ictal Brain Perfusion SPECT for Identification of the Seizure Onset Zone. *Clin Nucl Med,* 46**,** 890-895.

Jackson, J. H. & Stewart, P. 1899. EPILEPTIC ATTACKS WITH A WARNING OF A CRUDE SENSATION OF SMELL AND WITH THE INTELLECTUAL AURA (DREAMY STATE) IN A PATIENT WHO HAD SYMPTOMS POINTING TO GROSS ORGANIC DISEASE OF THE RIGHT TEMPORO-SPHENOIDAL LOBE. *Brain,* 22**,** 534-549.

Jacoby, A., Buck, D., Baker, G., Mcnamee, P., Graham-Jones, S. & Chadwick, D. 1998. Uptake and costs of care for epilepsy: findings from a U.K. regional study. *Epilepsia,* 39**,** 776-86.

Jain, P. & Arya, R. 2021. Vagus Nerve Stimulation and Seizure Outcomes in Pediatric Refractory Epilepsy. *Neurology,* 96**,** 1041.

Jansen, C., Francomme, L., Vignal, J. P., Jacquot, C., Schwan, R., Tyvaert, L., Maillard, L. & Hingray, C. 2019. Interictal psychiatric comorbidities of drug-resistant focal epilepsy: Prevalence and influence of the localization of the epilepsy. *Epilepsy Behav,* 94**,** 288-296.

Jayakar, P., Gotman, J., Harvey, A. S., Palmini, A., Tassi, L., Schomer, D., Dubeau, F., Bartolomei, F., Yu, A., Kršek, P., Velis, D. & Kahane, P. 2016. Diagnostic utility of invasive EEG for epilepsy surgery: Indications, modalities, and techniques. *Epilepsia,* 57**,** 1735-1747.

Jędrzejczak, J., Majkowska-Zwolińska, B., Chudzicka-Bator, A., Żerda, I., Władysiuk, M. & Godman, B. 2021. Economic and social cost of epilepsy in Poland: 5-year analysis. *Eur J Health Econ,* 22**,** 485-497.

Jehi, L., Friedman, D., Carlson, C., Cascino, G., Dewar, S., Elger, C., Engel Jr, J., Knowlton, R., Kuzniecky, R., Mcintosh, A., O'brien, T. J., Spencer, D., Sperling, M. R., Worrell, G., Bingaman, B., Gonzalez-Martinez, J., Doyle, W. & French, J. 2015a. The evolution of epilepsy surgery between 1991 and 2011 in nine major epilepsy centers across the United States, Germany, and Australia. *Epilepsia,* 56**,** 1526-1533.

Jehi, L., Jette, N., Kwon, C. S., Josephson, C. B., Burneo, J. G., Cendes, F., Sperling, M. R., Baxendale, S., Busch, R. M., Triki, C. C., Cross, J. H., Ekstein, D., Englot, D. J., Luan, G., Palmini, A., Rios, L., Wang, X., Roessler, K., Rydenhag, B., Ramantani, G., Schuele, S., Wilmshurst, J. M., Wilson, S. & Wiebe, S. 2022. Timing of referral to evaluate for epilepsy surgery: Expert Consensus Recommendations from the Surgical Therapies Commission of the International League Against Epilepsy. *Epilepsia*.

Jehi, L., Morita-Sherman, M., Love, T. E., Bartolomei, F., Bingaman, W., Braun, K., Busch, R. M., Duncan, J., Hader, W. J., Luan, G., Rolston, J. D., Schuele, S., Tassi, L., Vadera, S., Sheikh, S., Najm, I., Arain, A., Bingaman, J., Diehl, B., De Tisi, J., Rados, M., Van Eijsden, P., Wahby, S., Wang, X. & Wiebe, S. 2021. Comparative Effectiveness of Stereotactic Electroencephalography Versus Subdural Grids in Epilepsy Surgery. *Ann Neurol,* 90**,** 927-939.

Jehi, L., Yardi, R., Chagin, K., Tassi, L., Russo, G. L., Worrell, G., Hu, W., Cendes, F., Morita, M., Bartolomei, F., Chauvel, P., Najm, I., Gonzalez-Martinez, J., Bingaman, W. & Kattan, M. W. 2015b. Development and validation of nomograms to provide individualised predictions of seizure outcomes after epilepsy surgery: a retrospective analysis. *Lancet Neurol,* 14**,** 283-90.

Jehi, L. E., Najm, I., Bingaman, W., Dinner, D., Widdess-Walsh, P. & Lüders, H. 2007. Surgical outcome and prognostic factors of frontal lobe epilepsy surgery. *Brain,* 130**,** 574-84.

Jennum, P., Gyllenborg, J. & Kjellberg, J. 2011. The social and economic consequences of epilepsy: a controlled national study. *Epilepsia,* 52**,** 949-56.

Jennum, P., Sabers, A., Christensen, J., Ibsen, R. & Kjellberg, J. 2016. Socioeconomic outcome of epilepsy surgery: A controlled national study. *Seizure,* 42**,** 52-56.

Jobst, B. C. & Cascino, G. D. 2015. Resective epilepsy surgery for drug-resistant focal epilepsy: a review. *Jama,* 313**,** 285-93.

Jobst, B. C., Siegel, A. M., Thadani, V. M., Roberts, D. W., Rhodes, H. C. & Williamson, P. D. 2000. Intractable seizures of frontal lobe origin: clinical characteristics, localizing signs, and results of surgery. *Epilepsia,* 41**,** 1139-52.

Johannesen, K. M., Nikanorova, N., Marjanovic, D., Pavbro, A., Larsen, L. H. G., Rubboli, G. & Møller, R. S. 2020. Utility of genetic testing for therapeutic decision-making in adults with epilepsy. *Epilepsia,* 61**,** 1234-1239.

Joris, V., Weil, A. G. & Fallah, A. 2022. Brain Surgery for Medically Intractable Epilepsy. *Adv Pediatr,* 69**,** 59-74.

Josephson, C. B., Engbers, J. D. T., Jette, N., Patten, S. B., Singh, S., Sajobi, T. T., Marshall, D., Agha-Khani, Y., Federico, P., Mackie, A., Macrodimitris, S., Mclane, B., Pillay, N., Sharma, R. & Wiebe, S. 2019. Prediction Tools for Psychiatric Adverse Effects After Levetiracetam Prescription. *JAMA Neurology,* 76**,** 440-446.

Joudi Mashhad, M., Harati, H., Parooie, F. & Salarzaei, M. 2020. Epilepsy surgery for refractory seizures: a systematic review and meta-analysis in different complications. *The Egyptian Journal of Neurology, Psychiatry and Neurosurgery,* 56**,** 35.

Kaiboriboon, K., Malkhachroum, A. M., Zrik, A., Daif, A., Schiltz, N. M., Labiner, D. M. & Lhatoo, S. D. 2015. Epilepsy surgery in the United States: Analysis of data from the National Association of Epilepsy Centers. *Epilepsy Research,* 116**,** 105-109.

Kalilani, L., Sun, X., Pelgrims, B., Noack-Rink, M. & Villanueva, V. 2018. The epidemiology of drug-resistant epilepsy: A systematic review and meta-analysis. *Epilepsia,* 59**,** 2179-2193.

Kang, C. & Cascino, G. D. 2009. The effect of preoperative body mass index on outcome after temporal lobe epilepsy surgery. *Epilepsy Res,* 87**,** 272-6.

Katz, J. S. & Abel, T. J. 2019. Stereoelectroencephalography Versus Subdural Electrodes for Localization of the Epileptogenic Zone: What Is the Evidence? *Neurotherapeutics,* 16**,** 59-66.

Kerezoudis, P., Singh, R., Parisi, V., Worrell, G. A., Miller, K. J., Marsh, W. R. & Van Gompel, J. J. 2021. Outcomes of epilepsy surgery in the older population: not too old, not too late. *J Neurosurg***,** 1-10.

Khoo, A., Frasca, J. & Whitham, E. 2020. Epilepsy and Seizure-Related Hospital Admissions to an Australian Neurology Unit: A Prospective Observational Study. *Hosp Top,* 6**,** 1-8.

Kim, S. H., Lim, S. C., Kim, J., Son, B.-C., Lee, K. J. & Shon, Y.-M. 2017. Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: a 11-year, single center experience. *Seizure,* 52**,** 154-161.

Kim, S. K., Lee, D. S., Lee, S. K., Kim, Y. K., Kang, K. W., Chung, C. K., Chung, J. K. & Lee, M. C. 2001. Diagnostic performance of [18F]FDG-PET and ictal [99mTc]-HMPAO SPECT in occipital lobe epilepsy. *Epilepsia,* 42**,** 1531-40.

Knowlton, R. C. 2006. The role of FDG-PET, ictal SPECT, and MEG in the epilepsy surgery evaluation. *Epilepsy Behav,* 8**,** 91-101.

Knowlton, R. C., Elgavish, R. A., Limdi, N., Bartolucci, A., Ojha, B., Blount, J., Burneo, J. G., Ver Hoef, L., Paige, L., Faught, E., Kankirawatana, P., Riley, K. & Kuzniecky, R. 2008. Functional imaging: I. Relative predictive value of intracranial electroencephalography. *Ann Neurol,* 64**,** 25-34.

Kotagal, P., Arunkumar, G., Hammel, J. & Mascha, E. 2003. Complex partial seizures of frontal lobe onset statistical analysis of ictal semiology. *Seizure,* 12**,** 268-81.
Kovac, S., Vakharia, V. N., Scott, C. & Diehl, B. 2017. Invasive epilepsy surgery evaluation. *Seizure,* 44**,** 125-136.
Krahl, S. E. & Clark, K. B. 2012. Vagus nerve stimulation for epilepsy: A review of central mechanisms. *Surg Neurol Int,* 3**,** S255-9.
Krishnaiah, B., Ramaratnam, S. & Ranganathan, L. N. 2018. Subpial transection surgery for epilepsy. *Cochrane Database Syst Rev,* 11**,** Cd008153.
Krishnan, B., Tousseyn, S., Nayak, C. S., Aung, T., Kheder, A., Wang, Z. I., Wu, G., Gonzalez-Martinez, J., Nair, D., Burgess, R., Iasemidis, L., Najm, I., Bulacio, J. & Alexopoulos, A. V. 2021. Neurovascular networks in epilepsy: Correlating ictal blood perfusion with intracranial electrophysiology. *NeuroImage,* 231**,** 117838.
Kumar, K., Banerjee Dixit, A., Tripathi, M., Dubey, V., Siraj, F., Sharma, M. C., Lalwani, S., Chandra, P. S. & Banerjee, J. 2022. Transcriptomic profiling of nonneoplastic cortical tissues reveals epileptogenic mechanisms in dysembryoplastic neuroepithelial tumors. *Funct Integr Genomics*.
Kusyk, D. M., Meinert, J., Stabingas, K. C., Yin, Y. & Whiting, A. C. 2022. Systematic Review and Meta-Analysis of Responsive Neurostimulation in Epilepsy. *World Neurosurg*.
Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Allen Hauser, W., Mathern, G., Moshé, S. L., Perucca, E., Wiebe, S. & French, J. 2010a. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia,* 51**,** 1069-1077.
Kwan, P. & Brodie, M. J. 2000. Early Identification of Refractory Epilepsy. *New England Journal of Medicine,* 342**,** 314-319.
Kwan, P., Li, H. M., Al-Jufairi, E., Abdulla, R., Gonzales, M., Kaye, A. H., Szoeke, C., Ng, H. K., Wong, K. S. & O'brien, T. J. 2010b. Association between temporal lobe P-glycoprotein expression and seizure recurrence after surgery for pharmacoresistant temporal lobe epilepsy. *Neurobiol Dis,* 39**,** 192-7.
Kwan, P. & Sperling, M. R. 2009. Refractory seizures: Try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation? *Epilepsia,* 50**,** 57-62.
Lafrance, W. C., Jr., Kanner, A. M. & Hermann, B. 2008. Psychiatric comorbidities in epilepsy. *Int Rev Neurobiol,* 83**,** 347-83.
Lamberink, H. J., Otte, W. M., Blümcke, I. & Braun, K. P. J. 2020. Seizure outcome and use of antiepileptic drugs after epilepsy surgery according to histopathological diagnosis: a retrospective multicentre cohort study. *Lancet Neurol,* 19**,** 748-757.
Langfitt, J. T. 1997. Cost-effectiveness of anterotemporal lobectomy in medically intractable complex partial epilepsy. *Epilepsia,* 38**,** 154-63.
Langfitt, J. T., Holloway, R. G., Mcdermott, M. P., Messing, S., Sarosky, K., Berg, A. T., Spencer, S. S., Vickrey, B. G., Sperling, M. R., Bazil, C. W. & Shinnar, S. 2007. Health care costs decline after successful epilepsy surgery. *Neurology,* 68**,** 1290-8.
Lariviere, M. J. & Gross, R. E. 2016. Stereotactic Laser Ablation for Medically Intractable Epilepsy: The Next Generation of Minimally Invasive Epilepsy Surgery. *Frontiers in Surgery,* 3.
Lazow, S. P., Thadani, V. M., Gilbert, K. L., Morse, R. P., Bujarski, K. A., Kulandaivel, K., Roth, R. M., Scott, R. C., Roberts, D. W. & Jobst, B. C. 2012. Outcome of frontal lobe epilepsy surgery. *Epilepsia,* 53**,** 1746-55.

Leach, J. P., Marson, T. & Chadwick, D. 2001. New Antiepileptic Drugs Revolution or Marketing Spin? *Practical Neurology,* 1**,** 70.
Lee, K. J., Shon, Y. M. & Cho, C. B. 2012. Long-Term Outcome of Anterior Thalamic Nucleus Stimulation for Intractable Epilepsy. *Stereotactic and Functional Neurosurgery,* 90**,** 379-385.
Leidy, N. K., Elixhauser, A., Vickrey, B., Means, E. & Willian, M. K. 1999. Seizure frequency and the health-related quality of life of adults with epilepsy. *Neurology,* 53**,** 162-6.
Lendt, M., Helmstaedter, C. & Elger, C. E. 1997. Pre- and postoperative socioeconomic development of 151 patients with focal epilepsies. *Epilepsia,* 38**,** 1330-7.
Li, J., Ledoux-Hutchinson, L. & Toffa, D. H. 2022a. Prevalence of Bipolar Symptoms or Disorder in Epilepsy: A Systematic Review and Meta-analysis. *Neurology,* 98**,** e1913-e1922.
Li, J., Toffa, D. H., Lefèbvre, M., Tétreault, M., Cossette, P., Samarut, É. & Nguyen, D. K. 2022b. Usage of Genetic Panels in an Adult Epilepsy Clinic. *Can J Neurol Sci***,** 1-7.
Liu, H., Yang, Y., Wang, Y., Tang, H., Zhang, F., Zhang, Y. & Zhao, Y. 2018. Ketogenic diet for treatment of intractable epilepsy in adults: A meta-analysis of observational studies. *Epilepsia Open,* 3**,** 9-17.
Liu, J. Y., Thom, M., Catarino, C. B., Martinian, L., Figarella-Branger, D., Bartolomei, F., Koepp, M. & Sisodiya, S. M. 2012. Neuropathology of the blood-brain barrier and pharmaco-resistance in human epilepsy. *Brain,* 135**,** 3115-33.
Ljunggren, S., Andersson-Roswall, L., Rydenhag, B., Samuelsson, H. & Malmgren, K. 2015. Cognitive outcome two years after frontal lobe resection for epilepsy – A prospective longitudinal study. *Seizure,* 30**,** 50-56.
Löscher, W., Potschka, H., Sisodiya, S. M. & Vezzani, A. 2020. Drug Resistance in Epilepsy: Clinical Impact, Potential Mechanisms, and New Innovative Treatment Options. *Pharmacol Rev,* 72**,** 606-638.
Lowenstein, D. H., Bleck, T. & Macdonald, R. L. 1999. It's Time to Revise the Definition of Status Epilepticus. *Epilepsia,* 40**,** 120-122.
Lu, E., Pyatka, N., Burant, C. J. & Sajatovic, M. 2021. Systematic Literature Review of Psychiatric Comorbidities in Adults with Epilepsy. *Journal of clinical neurology (Seoul, Korea),* 17**,** 176-186.
Luciano, A. L. & Shorvon, S. D. 2007. Results of treatment changes in patients with apparently drug-resistant chronic epilepsy. *Ann Neurol,* 62**,** 375-81.
Lüders, H., Acharya, J., Baumgartner, C., Benbadis, S., Bleasel, A., Burgess, R., Dinner, D. S., Ebner, A., Foldvary, N., Geller, E., Hamer, H., Holthausen, H., Kotagal, P., Morris, H., Meencke, H. J., Noachtar, S., Rosenow, F., Sakamoto, A., Steinhoff, B. J., Tuxhorn, I. & Wyllie, E. 1998. Semiological Seizure Classification*. *Epilepsia,* 39**,** 1006-1013.
Luders, H., Engel, J. & Munari, C. 1993. *Surgical Treatment of the Epilepsies (2nd ed.),* New York: Raven Press.
Macdonald, R. L. & Kelly, K. M. 1995. Antiepileptic drug mechanisms of action. *Epilepsia,* 36 Suppl 2**,** S2-12.
Magiorkinis, E., Diamantis, A., Sidiropoulou, K. & Panteliadis, C. 2014. Highights in the history of epilepsy: the last 200 years. *Epilepsy Res Treat,* 2014**,** 582039.

Maillard, L., Vignal, J. P., Gavaret, M., Guye, M., Biraben, A., Mcgonigal, A., Chauvel, P. & Bartolomei, F. 2004. Semiologic and electrophysiologic correlations in temporal lobe seizure subtypes. *Epilepsia,* 45**,** 1590-9.

Malmgren, K. & Edelvik, A. 2017. Long-term outcomes of surgical treatment for epilepsy in adults with regard to seizures, antiepileptic drug treatment and employment. *Seizure,* 44**,** 217-224.

Mammì, A., Ferlazzo, E., Gasparini, S., Bova, V., Neri, S., Labate, A., Mastroianni, G., Bianco, C. L., Cianci, V. & Aguglia, U. 2022. Psychiatric and Behavioural Side Effects Associated With Perampanel in Patients With Temporal Lobe Epilepsy. A Real-World Experience. *Front Neurol,* 13**,** 839985.

Manford, M., Fish, D. R. & Shorvon, S. D. 1996. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. *Brain,* 119 (Pt 1)**,** 17-40.

Mannan, J. B. & Wieshmann, U. C. 2003. How accurate are witness descriptions of epileptic seizures? *Seizure,* 12**,** 444-447.

Manno, E. M., Sperling, M. R., Ding, X., Jaggi, J., Alavi, A., O'connor, M. J. & Reivich, M. 1994. Predictors of outcome after anterior temporal lobectomy: positron emission tomography. *Neurology,* 44**,** 2331-6.

Mansouri, A., Fallah, A., Ibrahim, G. M. & Valiante, T. A. 2013. Predictors of Surgical Candidacy in 414 Epilepsy Patients Admitted to the EMU. *Canadian Journal of Neurological Sciences / Journal Canadien des Sciences Neurologiques,* 40**,** 372-377.

Marson, A., Burnside, G., Appleton, R., Smith, D., Leach, J. P., Sills, G., Tudur-Smith, C., Plumpton, C., Hughes, D. A., Williamson, P., Baker, G. A., Balabanova, S., Taylor, C., Brown, R., Hindley, D., Howell, S., Maguire, M., Mohanraj, R. & Smith, P. E. 2021a. The SANAD II study of the effectiveness and cost-effectiveness of valproate versus levetiracetam for newly diagnosed generalised and unclassifiable epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. *Lancet,* 397**,** 1375-1386.

Marson, A., Burnside, G., Appleton, R., Smith, D., Leach, J. P., Sills, G., Tudur-Smith, C., Plumpton, C., Hughes, D. A., Williamson, P., Baker, G. A., Balabanova, S., Taylor, C., Brown, R., Hindley, D., Howell, S., Maguire, M., Mohanraj, R., Smith, P. E., Lanyon, K., Manford, M., Chitre, M., Parker, A., Swiderska, N., Appleton, R., Pauling, J., Hughes, A., Gupta, R., Hanif, S., Awadh, M., Ragunathan, S., Cable, N., Cooper, P., Hindley, D., Rakshi, K., Molloy, S., Reuber, M., Ayonrinde, K., Wilson, M., Saladi, S., Gibb, J., Funston, L.-A., Cassidy, D., Boyd, J., Ratnayaka, M., Faza, H., Sadler, M., Al-Moasseb, H., Galtrey, C., Wren, D., Olabi, A., Fuller, G., Khan, M., Kallappa, C., Chinthapalli, R., Aji, B., Davies, R., Foster, K., Hitiris, N., Maguire, M., Hussain, N., Dowson, S., Ellison, J., Sharrack, B., Gandhi, V., Powell, R., Tittensor, P., Summers, B., Shashikiran, S., Dison, P. J., Samarasekera, S., Mccorry, D., White, K., Nithi, K., Richardson, M., Brown, R., Page, R., Deekollu, D., Slaght, S., Warriner, S., Ahmed, M., Chaudhuri, A., Chow, G., Artal, J., Kucinskiene, D., Sreenivasa, H., Velmurugan, Singara, Zipitis, C. S., Mclean, B., Lal, V., Gregoriou, A., Maddison, P., Pickersgill, T., Anderson, J., Lawthom, C., Howell, S., Whitlingum, G., Rakowicz, W., Kinton, L., et al. 2021b. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or

lamotrigine for newly diagnosed focal epilepsy: an open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. *The Lancet,* 397**,** 1363-1374.
Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., Appleton, R., Baker, G. A., Chadwick, D. W., Cramp, C., Cockerell, O. C., Cooper, P. N., Doughty, J., Eaton, B., Gamble, C., Goulding, P. J., Howell, S. J., Hughes, A., Jackson, M., Jacoby, A., Kellett, M., Lawson, G. R., Leach, J. P., Nicolaides, P., Roberts, R., Shackley, P., Shen, J., Smith, D. F., Smith, P. E., Smith, C. T., Vanoli, A. & Williamson, P. R. 2007a. The SANAD study of effectiveness of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, or topiramate for treatment of partial epilepsy: an unblinded randomised controlled trial. *Lancet,* 369**,** 1000-15.
Marson, A. G., Al-Kharusi, A. M., Alwaidh, M., Appleton, R., Baker, G. A., Chadwick, D. W., Cramp, C., Cockerell, O. C., Cooper, P. N., Doughty, J., Eaton, B., Gamble, C., Goulding, P. J., Howell, S. J., Hughes, A., Jackson, M., Jacoby, A., Kellett, M., Lawson, G. R., Leach, J. P., Nicolaides, P., Roberts, R., Shackley, P., Shen, J., Smith, D. F., Smith, P. E., Smith, C. T., Vanoli, A. & Williamson, P. R. 2007b. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. *Lancet,* 369**,** 1016-26.
Martínez-Juárez, I. E., Funes, B., Moreno-Castellanos, J. C., Bribiesca-Contreras, E., Martínez-Bustos, V., Zertuche-Ortuño, L., Hernández-Vanegas, L. E., Ronquillo, L. H., Rizvi, S., Adam, W. & Tellez-Zenteno, J. F. 2017. A comparison of waiting times for assessment and epilepsy surgery between a Canadian and a Mexican referral center. *Epilepsia Open,* 2**,** 453-458.
Masdeu, J. C. & Arbizu, J. 2008. Brain single photon emission computed tomography: technological aspects and clinical applications. *Semin Neurol,* 28**,** 423-34.
Mathon, B., Navarro, V., Bielle, F., Nguyen-Michel, V. H., Carpentier, A., Baulac, M., Cornu, P., Adam, C., Dupont, S. & Clemenceau, S. 2017. Complications After Surgery for Mesial Temporal Lobe Epilepsy Associated with Hippocampal Sclerosis. *World Neurosurg,* 102**,** 639-650.e2.
Mayhew, D., Mendonca, V. & Murthy, B. V. S. 2019. A review of ASA physical status - historical perspectives and modern developments. *Anaesthesia,* 74**,** 373-379.
Mbizvo, G. K., Bennett, K., Simpson, C. R., Duncan, S. E. & Chin, R. F. M. 2019. Epilepsy-related and other causes of mortality in people with epilepsy: A systematic review of systematic reviews. *Epilepsy Res,* 157**,** 106192.
Mcclelland, S., Iii, Guo, H. & Okuyemi, K. S. 2011. Population-Based Analysis of Morbidity and Mortality Following Surgery for Intractable Temporal Lobe Epilepsy in the United States. *Archives of Neurology,* 68**,** 725-729.
Mcgonigal, A., Bartolomei, F. & Chauvel, P. 2021. On seizure semiology. *Epilepsia,* 62**,** 2019-2035.
Mcknight, D., Bristow, S. L., Truty, R. M., Morales, A., Stetler, M., Westbrook, M. J., Robinson, K., Riethmaier, D., Borlot, F., Kellogg, M., Hwang, S. T., Berg, A. & Aradhya, S. 2022. Multigene Panel Testing in a Large Cohort of Adults With Epilepsy: Diagnostic Yield and Clinically Actionable Genetic Findings. *Neurol Genet,* 8**,** e650.
Meador, K. J., Cohen, M. J., Loring, D. W., May, R. C., Brown, C., Robalino, C. P., Matthews, A. G., Kalayjian, L. A., Gerard, E. E., Gedzelman, E. R., Penovich, P. E., Cavitt, J., Hwang, S., Sam, M., Pack, A. M., French, J., Tsai, J. J. & Pennell, P. B. 2021. Two-Year-Old Cognitive Outcomes in Children of Pregnant Women

With Epilepsy in the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs Study. *JAMA Neurol,* 78**,** 927-936.
Mégevand, P. & Seeck, M. 2020. Electric source imaging for presurgical epilepsy evaluation: current status and future prospects. *Expert Rev Med Devices,* 17**,** 405-412.
Ministry of Housing, C. L. G. 2019. The English Indices of Deprivation 2019 - Statistical Release.
Mohan, M., Keller, S., Nicolson, A., Biswas, S., Smith, D., Osman Farah, J., Eldridge, P. & Wieshmann, U. 2018. The long-term outcomes of epilepsy surgery. *PLoS One,* 13.
Moloney, P. B. & Costello, D. J. 2021. Unanticipated improvement in seizure control in drug-resistant epilepsy- real world observations. *Seizure,* 84**,** 60-65.
Morrell, F., Whisler, W. W. & Bleck, T. P. 1989. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. *J Neurosurg,* 70**,** 231-9.
Morrell, M. J. 2011. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology,* 77**,** 1295-304.
Morris, G. L., 3rd, Gloss, D., Buchhalter, J., Mack, K. J., Nickels, K. & Harden, C. 2013. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology,* 81**,** 1453-9.
Morsi, A., Sharma, A., Golubovsky, J., Bulacio, J., Mcgovern, R., Jehi, L. & Bingaman, W. 2022. Does Stereoelectroencephalography Add Value in Patients with Lesional Epilepsy? *World Neurosurgery*.
Mouthaan, B. E., Rados, M., Barsi, P., Boon, P., Carmichael, D. W., Carrette, E., Craiu, D., Cross, J. H., Diehl, B., Dimova, P., Fabo, D., Francione, S., Gaskin, V., Gil-Nagel, A., Grigoreva, E., Guekht, A., Hirsch, E., Hecimovic, H., Helmstaedter, C., Jung, J., Kalviainen, R., Kelemen, A., Kimiskidis, V., Kobulashvili, T., Krsek, P., Kuchukhidze, G., Larsson, P. G., Leitinger, M., Lossius, M. I., Luzin, R., Malmgren, K., Mameniskiene, R., Marusic, P., Metin, B., Özkara, C., Pecina, H., Quesada, C. M., Rugg-Gunn, F., Rydenhag, B., Ryvlin, P., Scholly, J., Seeck, M., Staack, A. M., Steinhoff, B. J., Stepanov, V., Tarta-Arsene, O., Trinka, E., Uzan, M., Vogt, V. L., Vos, S. B., Vulliémoz, S., Huiskamp, G., Leijten, F. S., Van Eijsden, P. & Braun, K. P. 2016. Current use of imaging and electromagnetic source localization procedures in epilepsy surgery centers across Europe. *Epilepsia,* 57**,** 770-6.
Muayqil, T. A., Alanazy, M. H., Almalak, H. M., Alsalman, H. K., Abdulfattah, F. W., Aldraihem, A. I., Al-Hussain, F. & Aljafen, B. N. 2018. Accuracy of seizure semiology obtained from first-time seizure witnesses. *BMC Neurol,* 18**,** 135.
Muhlhofer, W., Tan, Y.-L., Mueller, S. G. & Knowlton, R. 2017. MRI-negative temporal lobe epilepsy—What do we know? *Epilepsia,* 58**,** 727-742.
Mulley, J. C., Scheffer, I. E., Harkin, L. A., Berkovic, S. F. & Dibbens, L. M. 2005. Susceptibility genes for complex epilepsy. *Human Molecular Genetics,* 14**,** R243-R249.
Mullin, J. P., Shriver, M., Alomar, S., Najm, I., Bulacio, J., Chauvel, P. & Gonzalez-Martinez, J. 2016. Is SEEG safe? A systematic review and meta-analysis of stereo-electroencephalography-related complications. *Epilepsia,* 57**,** 386-401.
Mumford, V., Rapport, F., Shih, P., Mitchell, R., Bleasel, A., Nikpour, A., Herkes, G., Macrae, A., Bartley, M., Vagholkar, S. & Braithwaite, J. 2019. Promoting faster

pathways to surgery: a clinical audit of patients with refractory epilepsy. *BMC Neurology,* 19**,** 29.
Narayanan, J., Frech, R., Walters, S., Patel, V., Frigerio, R. & Maraganore, D. M. 2016. Low dose verapamil as an adjunct therapy for medically refractory epilepsy - An open label pilot study. *Epilepsy Res,* 126**,** 197-200.
National Institute for Health and Care Excellence. 2021. *Epilepsies: diagnosis and management.* [Online]. London: National Institute for Health and Care Excellence (NICE). Available: https://www.ncbi.nlm.nih.gov/books/NBK553536/ [Accessed 1 Aug 2022].
Nei, M., O'connor, M., Liporace, J. & Sperling, M. R. 2006. Refractory Generalized Seizures: Response to Corpus Callosotomy and Vagal Nerve Stimulation. *Epilepsia,* 47**,** 115-122.
Neligan, A., Bell, G. S., Johnson, A. L., Goodridge, D. M., Shorvon, S. D. & Sander, J. W. 2011. The long-term risk of premature mortality in people with epilepsy. *Brain,* 134**,** 388-395.
Neligan, A., Haliasos, N., Pettorini, B., Harkness, W. F. J. & Solomon, J. K. 2013. A survey of adult and pediatric epilepsy surgery in the United Kingdom. *Epilepsia,* 54**,** e62-e65.
Nicita, F., De Liso, P., Danti, F. R., Papetti, L., Ursitti, F., Castronovo, A., Allemand, F., Gennaro, E., Zara, F., Striano, P. & Spalice, A. 2012. The genetics of monogenic idiopathic epilepsies and epileptic encephalopathies. *Seizure,* 21**,** 3-11.
Noachtar, S. & Peters, A. S. 2009. Semiology of epileptic seizures: a critical review. *Epilepsy Behav,* 15**,** 2-9.
O'brien, T. J., Brinkmann, B. H., Mullan, B. P., So, E. L., Hauser, M. F., O'connor, M. K., Hung, J. & Jack, C. R. 1999. Comparative study of 99mTc-ECD and 99mTc-HMPAO for peri-ictal SPECT: qualitative and quantitative analysis. *J Neurol Neurosurg Psychiatry,* 66**,** 331-9.
O'brien, T. J., Mosewich, R. K., Britton, J. W., Cascino, G. D. & So, E. L. 2008. History and seizure semiology in distinguishing frontal lobe seizures and temporal lobe seizures. *Epilepsy Res,* 82**,** 177-82.
O'brien, T. J., So, E. L., Cascino, G. D., Hauser, M. F., Marsh, W. R., Meyer, F. B., Sharbrough, F. W. & Mullan, B. P. 2004. Subtraction SPECT coregistered to MRI in focal malformations of cortical development: localization of the epileptogenic zone in epilepsy surgery candidates. *Epilepsia,* 45**,** 367-76.
O'muircheartaigh, J. & Richardson, M. P. 2012. Epilepsy and the frontal lobes. *Cortex,* 48**,** 144-55.
Ottman, R., Lipton, R. B., Ettinger, A. B., Cramer, J. A., Reed, M. L., Morrison, A. & Wan, G. J. 2011. Comorbidities of epilepsy: Results from the Epilepsy Comorbidities and Health (EPIC) survey. *Epilepsia,* 52**,** 308-315.
Paglioli, E., Palmini, A., Paglioli, E., Da Costa, J. C., Portuguez, M., Martinez, J. V., Calcagnotto, M. E., Hoefel, J. R., Raupp, S. & Barbosa-Coutinho, L. 2004. Survival Analysis of the Surgical Outcome of Temporal Lobe Epilepsy Due to Hippocampal Sclerosis. *Epilepsia,* 45**,** 1383-1391.
Patra, S., Elisevich, K., Podell, K., Schultz, L., Gaddam, S., Smith, B. & Spanaki-Varelas, M. 2014. Influence of age and location of ictal onset on postoperative outcome in patients with localization-related epilepsy. *Br J Neurosurg,* 28**,** 61-7.
Peedicail, J. S., Singh, S., Molnar, C. P., Numerow, L. M., Gnanakumar, R., Josephson, C. B., Scott, J., Federico, P., Wiebe, S. & Pillay, N. 2020. Impact of ictal

subtraction SPECT and PET in presurgical evaluation. *Acta Neurol Scand,* 14**,** 13362.
Perucca, E. 2006. Clinically relevant drug interactions with antiepileptic drugs. *British journal of clinical pharmacology,* 61**,** 246-255.
Perucca, P., Bahlo, M. & Berkovic, S. F. 2020. The Genetics of Epilepsy. *Annu Rev Genomics Hum Genet,* 21**,** 205-230.
Pillas, D. & Selai, C. 2005. Economic aspects of epilepsy and antiepileptic treatment: a review of the literature. *Expert Rev Pharmacoecon Outcomes Res,* 5**,** 327-38.
Pisani, F., Oteri, G., Russo, M. F., Di Perri, R., Perucca, E. & Richens, A. 1999. The efficacy of valproate-lamotrigine comedication in refractory complex partial seizures: evidence for a pharmacodynamic interaction. *Epilepsia,* 40**,** 1141-6.
Pitkänen, A., Lukasiuk, K., Dudek, F. E. & Staley, K. J. 2015. Epileptogenesis. *Cold Spring Harb Perspect Med,* 5.
Platt, M. & Sperling, M. R. 2002. A comparison of surgical and medical costs for refractory epilepsy. *Epilepsia,* 4**,** 25-31.
Pondal-Sordo, M., Diosy, D., Téllez-Zenteno, J. F., Sahjpaul, R. & Wiebe, S. 2007. Usefulness of intracranial EEG in the decision process for epilepsy surgery. *Epilepsy Res,* 74**,** 176-82.
Potgieser, A. R., De Jong, B. M., Wagemakers, M., Hoving, E. W. & Groen, R. J. 2014. Insights from the supplementary motor area syndrome in balancing movement initiation and inhibition. *Front Hum Neurosci,* 8**,** 960.
Punia, V., Abdelkader, A., Busch, R. M., Gonzalez-Martinez, J., Bingaman, W., Najm, I. & Stojic, A. 2018. Time to push the age limit: Epilepsy surgery in patients 60 years or older. *Epilepsia Open,* 3**,** 73-80.
Puteikis, K. & Mameniškienė, R. 2021. Mortality among People with Epilepsy: A Retrospective Nationwide Analysis from 2016 to 2019. *Int J Environ Res Public Health,* 18.
Radhakrishnan, K. 2009. Challenges in the management of epilepsy in resource-poor countries. *Nature Reviews Neurology,* 5**,** 323-330.
Rathke, K. M., Schäuble, B., Fessler, A. J. & So, E. L. 2011. Reliability of Seizure Semiology in Patients With 2 Seizure Foci. *Archives of Neurology,* 68**,** 775-778.
Rathore, C., Dickson, J. C., Teotónio, R., Ell, P. & Duncan, J. S. 2014. The utility of 18F-fluorodeoxyglucose PET (FDG PET) in epilepsy surgery. *Epilepsy Res,* 108**,** 1306-14.
Remy, S., Urban, B. W., Elger, C. E. & Beck, H. 2003. Anticonvulsant pharmacology of voltage-gated Na+ channels in hippocampal neurons of control and chronically epileptic rats. *Eur J Neurosci,* 17**,** 2648-58.
Rho, J. M. & Boison, D. 2022. The metabolic basis of epilepsy. *Nature Reviews Neurology,* 18**,** 333-347.
Říha, P., Doležalová, I., Mareček, R., Lamoš, M., Bartoňová, M., Kojan, M., Mikl, M., Gajdoš, M., Vojtíšek, L., Bartoň, M., Strýček, O., Pail, M., Brázdil, M. & Rektor, I. 2022. Multimodal combination of neuroimaging methods for localizing the epileptogenic zone in MR-negative epilepsy. *Sci Rep,* 12**,** 15158.
Rolston, J. D., Deng, H., Wang, D. D., Englot, D. J. & Chang, E. F. 2018. Multiple Subpial Transections for Medically Refractory Epilepsy: A Disaggregated Review of Patient-Level Data. *Neurosurgery,* 82**,** 613-620.

Rolston, J. D., Englot, D. J., Knowlton, R. C. & Chang, E. F. 2016. Rate and complications of adult epilepsy surgery in North America: Analysis of multiple databases. *Epilepsy Res,* 124**,** 55-62.

Rosenow, F. & Lüders, H. 2001. Presurgical evaluation of epilepsy. *Brain,* 124**,** 1683-1700.

Rubinger, L., Chan, C., Andrade, D., Go, C., Smith, M. L., Snead, O. C., Rutka, J. T. & Widjaja, E. 2016. Socioeconomic status influences time to surgery and surgical outcome in pediatric epilepsy surgery. *Epilepsy Behav,* 55**,** 133-8.

Rugg-Gunn, F., Miserocchi, A. & Mcevoy, A. 2020. Epilepsy surgery. *Practical Neurology,* 20**,** 4.

Ryvlin, P., Rheims, S., Hirsch, L. J., Sokolov, A. & Jehi, L. 2021. Neuromodulation in epilepsy: state-of-the-art approved therapies. *Lancet Neurol,* 20**,** 1038-1047.

Ryvlin, P., So, E. L., Gordon, C. M., Hesdorffer, D. C., Sperling, M. R., Devinsky, O., Bunker, M. T., Olin, B. & Friedman, D. 2018. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. *Epilepsia,* 59**,** 562-572.

Sadler, M. & Desbiens, R. 2000. Scalp EEG in temporal lobe epilepsy surgery. *Can J Neurol Sci,* 27.

Sadr, S. S., Javanbakht, J., Javidan, A. N., Ghaffarpour, M., Khamse, S. & Naghshband, Z. 2018. Descriptive epidemiology: prevalence, incidence, sociodemographic factors, socioeconomic domains, and quality of life of epilepsy: an update and systematic review. *Arch Med Sci,* 14**,** 717-724.

Sala-Padro, J., Fong, M., Rahman, Z., Bartley, M., Gill, D., Dexter, M., Bleasel, A. & Wong, C. 2019. A study of perfusion changes with Insula Epilepsy using SPECT. *Seizure,* 69**,** 44-50.

Salanova, V., Markand, O. & Worth, R. 2001. Focal functional deficits in temporal lobe epilepsy on PET scans and the intracarotid amobarbital procedure: comparison of patients with unitemporal epilepsy with those requiring intracranial recordings. *Epilepsia,* 42**,** 198-203.

Salanova, V., Markand, O., Worth, R., Smith, R., Wellman, H., Hutchins, G., Park, H., Ghetti, B. & Azzarelli, B. 1998. FDG-PET and MRI in temporal lobe epilepsy: relationship to febrile seizures, hippocampal sclerosis and outcome. *Acta Neurol Scand,* 97**,** 146-53.

Salanova, V., Sperling, M. R., Gross, R. E., Irwin, C. P., Vollhaber, J. A., Giftakis, J. E. & Fisher, R. S. 2021. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. *Epilepsia,* 62**,** 1306-1317.

Salanova, V., Witt, T., Worth, R., Henry, T. R., Gross, R. E., Nazzaro, J. M., Labar, D., Sperling, M. R., Sharan, A., Sandok, E., Handforth, A., Stern, J. M., Chung, S., Henderson, J. M., French, J., Baltuch, G., Rosenfeld, W. E., Garcia, P., Barbaro, N. M., Fountain, N. B., Elias, W. J., Goodman, R. R., Pollard, J. R., Tröster, A. I., Irwin, C. P., Lambrecht, K., Graves, N. & Fisher, R. 2015. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. *Neurology,* 84**,** 1017-25.

Samuel P, J., Menon, R. N., Chandran, A., Thomas, S. V., Vilanilam, G., Abraham, M. & Radhakrishnan, A. 2019. Seizure outcome and its predictors after frontal lobe epilepsy surgery. *Acta Neurologica Scandinavica,* 140**,** 259-267.

Samuel, P. J., Menon, R. N., Chandran, A., Thomas, S. V., Vilanilam, G., Abraham, M. & Radhakrishnan, A. 2019. Seizure outcome and its predictors after frontal lobe epilepsy surgery. *Acta Neurol Scand,* 140**,** 259-267.

Sanders, M., Lemmens, C. M. C., Jansen, F. E., Brilstra, E. H., Koeleman, B. P. C. & Braun, K. P. J. 2019. Implications of genetic diagnostics in epilepsy surgery candidates: A single-center cohort study. *Epilepsia Open,* 4**,** 609-617.

Sarkis, R. A., Busch, R. M., Floden, D., Chapin, J. S., Kalman Kenney, C., Jehi, L., Ruggieri, P. & Najm, I. 2013. Predictors of decline in verbal fluency after frontal lobe epilepsy surgery. *Epilepsy Behav,* 27**,** 326-9.

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., French, J., Guilhoto, L., Hirsch, E., Jain, S., Mathern, G. W., Moshé, S. L., Nordli, D. R., Perucca, E., Tomson, T., Wiebe, S., Zhang, Y. H. & Zuberi, S. M. 2017. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia,* 58**,** 512-521.

Scheffer, I. E., Heron, S. E., Regan, B. M., Mandelstam, S., Crompton, D. E., Hodgson, B. L., Licchetta, L., Provini, F., Bisulli, F., Vadlamudi, L., Gecz, J., Connelly, A., Tinuper, P., Ricos, M. G., Berkovic, S. F. & Dibbens, L. M. 2014. Mutations in mammalian target of rapamycin regulator DEPDC5 cause focal epilepsy with brain malformations. *Ann Neurol,* 75**,** 782-7.

Serletis, D., Bulacio, J., Bingaman, W., Najm, I. & González-Martínez, J. 2014. The stereotactic approach for mapping epileptic networks: a prospective study of 200 patients. *J Neurosurg,* 121**,** 1239-46.

Sevcencu, C. & Struijk, J. J. 2010. Autonomic alterations and cardiac changes in epilepsy. *Epilepsia,* 51**,** 725-737.

Sharma, P., Seeck, M. & Beniczky, S. 2019. Accuracy of Interictal and Ictal Electric and Magnetic Source Imaging: A Systematic Review and Meta-Analysis. *Front Neurol,* 10**,** 1250.

Sheikh, S. R., Kattan, M. W., Steinmetz, M., Singer, M. E., Udeh, B. L. & Jehi, L. 2020. Cost-effectiveness of surgery for drug-resistant temporal lobe epilepsy in the US. *Neurology,* 95**,** e1404-e1416.

Sherman, E. M., Wiebe, S., Fay-Mcclymont, T. B., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., Hader, W. J. & Jetté, N. 2011. Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia,* 52**,** 857-69.

Shmuely, S., Bauer, P. R., Van Zwet, E. W., Van Dijk, J. G. & Thijs, R. D. 2018. Differentiating motor phenomena in tilt-induced syncope and convulsive seizures. *Neurology,* 90**,** e1339.

Shorvon, S. & Tomson, T. 2011. Sudden unexpected death in epilepsy. *The Lancet,* 378**,** 2028-2038.

Siebenbrodt, K., Schütz, V., Costard, L. S., Neubert, V., Alvarez-Fischer, D., Seidel, K., Schmeck, B., Meuth, S. G., Rosenow, F. & Bauer, S. 2022. Hippocampal Cytokine Release in Experimental Epileptogenesis-A Longitudinal In Vivo Microdialysis Study. *Brain Sci,* 12.

Silberstein, S. D., Mechtler, L. L., Kudrow, D. B., Calhoun, A. H., Mcclure, C., Saper, J. R., Liebler, E. J., Rubenstein Engel, E., Tepper, S. J. & Group, O. B. O. T. a. S. 2016. Non–Invasive Vagus Nerve Stimulation for the ACute Treatment of Cluster Headache: Findings From the Randomized, Double-Blind, Sham-Controlled ACT1 Study. *Headache: The Journal of Head and Face Pain,* 56**,** 1317-1332.

Sisodiya, S. M., Lin, W. R., Harding, B. N., Squier, M. V. & Thom, M. 2002. Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy. *Brain,* 125**,** 22-31.

Sloviter, R. S. 1991. Permanently altered hippocampal structure, excitability, and inhibition after experimental status epilepticus in the rat: the "dormant basket cell" hypothesis and its possible relevance to temporal lobe epilepsy. *Hippocampus,* 1**,** 41-66.

Smilowitz, N. R. & Berger, J. S. 2020. Perioperative Cardiovascular Risk Assessment and Management for Noncardiac Surgery: A Review. *JAMA,* 324**,** 279-290.

So, N., Gloor, P., Quesney, L. F., Jones-Gotman, M., Olivier, A. & Andermann, F. 1989a. Depth electrode investigations in patients with bitemporal epileptiform abnormalities. *Ann Neurol,* 25**,** 423-31.

So, N., Olivier, A., Andermann, F., Gloor, P. & Quesney, L. F. 1989b. Results of surgical treatment in patients with bitemporal epileptiform abnormalities. *Ann Neurol,* 25**,** 432-9.

Speed, D., O'brien, T. J., Palotie, A., Shkura, K., Marson, A. G., Balding, D. J. & Johnson, M. R. 2014. Describing the genetic architecture of epilepsy through heritability analysis. *Brain,* 137**,** 2680-9.

Spencer, D. D., Spencer, S. S., Mattson, R. H., Williamson, P. D. & Novelly, R. A. 1984. Access to the posterior medial temporal lobe structures in the surgical treatment of temporal lobe epilepsy. *Neurosurgery,* 15**,** 667-71.

Steer, S., Pickrell, W. O., Kerr, M. P. & Thomas, R. H. 2014. Epilepsy prevalence and socioeconomic deprivation in England. *Epilepsia,* 55**,** 1634-41.

Steinbrenner, M., Duncan, J. S., Dickson, J., Rathore, C., Wächter, B., Aygun, N., Menon, R. N., Radhakrishnan, A., Holtkamp, M. & Ilyas-Feldmann, M. 2022. Utility of 18F-fluorodeoxyglucose positron emission tomography in presurgical evaluation of patients with epilepsy: A multicenter study. *Epilepsia,* 63**,** 1238-1252.

Steinlein, O. K., Mulley, J. C., Propping, P., Wallace, R. H., Phillips, H. A., Sutherland, G. R., Scheffer, I. E. & Berkovic, S. F. 1995. A missense mutation in the neuronal nicotinic acetylcholine receptor alpha 4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy. *Nat Genet,* 11**,** 201-3.

Stevelink, R., Sanders, M. W., Tuinman, M. P., Brilstra, E. H., Koeleman, B. P., Jansen, F. E. & Braun, K. P. 2018. Epilepsy surgery for patients with genetic refractory epilepsy: a systematic review. *Epileptic Disord,* 20**,** 99-115.

Stigsdotter-Broman, L., Olsson, I., Flink, R., Rydenhag, B. & Malmgren, K. 2014. Long-term follow-up after callosotomy--a prospective, population based, observational study. *Epilepsia,* 55**,** 316-21.

Stovner, L. J., Nichols, E., Steiner, T. J., Abd-Allah, F., Abdelalim, A., Al-Raddadi, R., Geleto Ansha, M., Feigin, V. L., Vos, T., Murray, C. J. L. & Gbd 2016 Headache Collaborators 2018. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol,* 17**,** 954-976.

Strzelczyk, A., Griebel, C., Lux, W., Rosenow, F. & Reese, J.-P. 2017. The Burden of Severely Drug-Refractory Epilepsy: A Comparative Longitudinal Evaluation of Mortality, Morbidity, Resource Use, and Cost Using German Health Insurance Data. *Frontiers in neurology,* 8**,** 712-712.

Suller Marti, A., Mirsattari, S. M., Macdougall, K., Steven, D. A., Parrent, A., De Ribaupierre, S., Andrade, A., Diosy, D., Mclachlan, R. S. & Burneo, J. G. 2020. Vagus nerve stimulation in patients with therapy-resistant generalized epilepsy. *Epilepsy Behav,* 111**,** 107253.

Sveikata, L., Kavan, N., Pegna, A. J., Seeck, M., Assal, F., Momjian, S., Schaller, K. & Vulliemoz, S. 2019. Postoperative memory prognosis in temporal lobe epilepsy surgery: The contribution of postictal memory. *Epilepsia,* 60**,** 1639-1649.

Szaflarski, M. 2014. Social determinants of health in epilepsy. *Epilepsy Behav,* 41**,** 283-9.

Tanriverdi, T., Ajlan, A., Poulin, N. & Olivier, A. 2009. Morbidity in epilepsy surgery: an experience based on 2449 epilepsy surgery procedures from a single institution. *J Neurosurg,* 110**,** 1111-23.

Tao, J. X., Ray, A., Hawes-Ebersole, S. & Ebersole, J. S. 2005. Intracranial EEG substrates of scalp EEG interictal spikes. *Epilepsia,* 46**,** 669-76.

Tassorelli, C., Grazzi, L., De Tommaso, M., Pierangeli, G., Martelletti, P., Rainero, I., Dorlas, S., Geppetti, P., Ambrosini, A., Sarchielli, P., Liebler, E. & Barbanti, P. 2018. Noninvasive vagus nerve stimulation as acute therapy for migraine. *The randomized PRESTO study,* 91**,** e364-e373.

Tebo, C. C., Evins, A. I., Christos, P. J., Kwon, J. & Schwartz, T. H. 2014. Evolution of cranial epilepsy surgery complication rates: a 32-year systematic review and meta-analysis. *J Neurosurg,* 120**,** 1415-27.

Téllez-Zenteno, J. F., Dhar, R. & Wiebe, S. 2005. Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain,* 128**,** 1188-98.

Thorsteinsdottir, J., Vollmar, C., Tonn, J. C., Kreth, F. W., Noachtar, S. & Peraud, A. 2019. Outcome after individualized stereoelectroencephalography (sEEG) implantation and navigated resection in patients with lesional and non-lesional focal epilepsy. *J Neurol,* 266**,** 910-920.

Thurman, D. J., Kobau, R., Luo, Y.-H., Helmers, S. L. & Zack, M. M. 2016. Health-care access among adults with epilepsy: The U.S. National Health Interview Survey, 2010 and 2013. *Epilepsy & behavior : E&B,* 55**,** 184-188.

Tigaran, S., Rasmussen, V., Dam, M., Pedersen, S., Hegenhaven, H. & Friberg, B. 1997. ECG changes in epilepsy patients. *Acta Neurologica Scandinavica,* 96**,** 72-75.

Tomás, J., Pittau, F., Hammers, A., Bouvard, S., Picard, F., Vargas, M. I., Sales, F., Seeck, M. & Garibotto, V. 2019. The predictive value of hypometabolism in focal epilepsy: a prospective study in surgical candidates. *Eur J Nucl Med Mol Imaging,* 46**,** 1806-1816.

Tomson, T., Battino, D., Bonizzoni, E., Craig, J., Lindhout, D., Perucca, E., Sabers, A., Thomas, S. V. & Vajda, F. 2018. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. *Lancet Neurol,* 17**,** 530-538.

Tomson, T., Nashef, L. & Ryvlin, P. 2008. Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol,* 7**,** 1021-31.

Touma, L., Dansereau, B., Chan, A. Y., Jetté, N., Kwon, C. S., Braun, K. P. J., Friedman, D., Jehi, L., Rolston, J. D., Vadera, S., Wong-Kisiel, L. C., Englot, D. J. & Keezer, M. R. 2022. Neurostimulation in people with drug-resistant epilepsy: Systematic review and meta-analysis from the ILAE Surgical Therapies Commission. *Epilepsia,* 63**,** 1314-1329.

Trebuchon, A., Lambert, I., Guisiano, B., Mcgonigal, A., Perot, C., Bonini, F., Carron, R., Liegeois-Chauvel, C., Chauvel, P. & Bartolomei, F. 2018. The different

patterns of seizure-induced aphasia in temporal lobe epilepsies. *Epilepsy Behav,* 78**,** 256-264.
Tufenkjian, K. & Lüders, H. O. 2012. Seizure semiology: its value and limitations in localizing the epileptogenic zone. *J Clin Neurol,* 8**,** 243-50.
Uijl, S. G., Leijten, F. S., Arends, J. B., Parra, J., Van Huffelen, A. C. & Moons, K. G. 2007. The added value of [18F]-fluoro-D-deoxyglucose positron emission tomography in screening for temporal lobe epilepsy surgery. *Epilepsia,* 48**,** 2121-9.
Ungar, A., Ceccofiglio, A., Pescini, F., Mussi, C., Tava, G., Rafanelli, M., Langellotto, A., Marchionni, N., Van Dijk, J. G., Galizia, G., Bonaduce, D. & Abete, P. 2017. Syncope and Epilepsy coexist in 'possible' and 'drug-resistant' epilepsy (Overlap between Epilepsy and Syncope Study - OESYS). *BMC Neurology,* 17**,** 45.
Unnwongse, K., Wehner, T. & Foldvary-Schaefer, N. 2012. Mesial Frontal Lobe Epilepsy. *Journal of Clinical Neurophysiology,* 29**,** 371-378.
Uribe San Martin, R., Di Giacomo, R., Mai, R., Gozzo, F., Pelliccia, V., Mariani, V., Cardinale, F., Ciampi, E., Onofrj, M. & Tassi, L. 2020. Forecasting Seizure Freedom After Epilepsy Surgery Assessing Concordance Between Noninvasive and StereoEEG Findings. *Neurosurgery,* 88**,** 113-121.
Vaddiparti, A., Huang, R., Blihar, D., Du Plessis, M., Montalbano, M. J., Tubbs, R. S. & Loukas, M. 2021. The Evolution of Corpus Callosotomy for Epilepsy Management. *World Neurosurgery,* 145**,** 455-461.
Vakharia, V. N., Duncan, J. S., Witt, J. A., Elger, C. E., Staba, R. & Engel, J., Jr. 2018. Getting the best outcomes from epilepsy surgery. *Ann Neurol,* 83**,** 676-690.
Van Assema, D. M. E., Lubberink, M., Boellaard, R., Schuit, R. C., Windhorst, A. D., Scheltens, P., Lammertsma, A. A. & Van Berckel, B. N. M. 2012. P-glycoprotein function at the blood-brain barrier: effects of age and gender. *Molecular imaging and biology,* 14**,** 771-776.
Van Paesschen, W. 2004. Ictal SPECT. *Epilepsia,* 45**,** 35-40.
Vermeulen, L., Van Loon, J., Theys, T., Goffin, J., Porke, K., Van Laere, K., Goffin, K., Vandenbulcke, M., Thijs, V. & Van Paesschen, W. 2016. Outcome after epilepsy surgery at the University Hospitals Leuven 1998-2012. *Acta Neurol Belg,* 116**,** 271-8.
Voges, J., Waerzeggers, Y., Maarouf, M., Lehrke, R., Koulousakis, A., Lenartz, D. & Sturm, V. 2006. Deep-brain stimulation: long-term analysis of complications caused by hardware and surgery--experiences from a single centre. *J Neurol Neurosurg Psychiatry,* 77**,** 868-72.
Volk, H. A., Arabadzisz, D., Fritschy, J. M., Brandt, C., Bethmann, K. & Löscher, W. 2006. Antiepileptic drug-resistant rats differ from drug-responsive rats in hippocampal neurodegeneration and GABA(A) receptor ligand binding in a model of temporal lobe epilepsy. *Neurobiol Dis,* 21**,** 633-46.
Von Ellenrieder, N., Beltrachini, L. & Muravchik, C. H. 2012. Electrode and brain modeling in stereo-EEG. *Clin Neurophysiol,* 123**,** 1745-54.
Weber, J., Gustafsson, C., Malmgren, K., Strandberg, M., Can, Û., Compagno Strandberg, M. & Kumlien, E. 2019. Evaluation for epilepsy surgery - Why do patients not proceed to operation? *Seizure,* 69**,** 241-244.
Wen, H. T., Da Róz, L. M., Rhoton, A. L., Castro, L. H. M. & Teixeira, M. J. 2017. Frontal Lobe Decortication (Frontal Lobectomy with Ventricular Preservation) in

Epilepsy—Part 1: Anatomic Landmarks and Surgical Technique. *World Neurosurgery,* 98**,** 347-364.
Wiebe, S., Blume, W. T., Girvin, J. P. & Eliasziw, M. 2001. A Randomized, Controlled Trial of Surgery for Temporal-Lobe Epilepsy. *New England Journal of Medicine,* 345**,** 311-318.
Wiebe, S., Gafni, A., Blume, W. T. & Girvin, J. P. 1995. An economic evaluation of surgery for temporal lobe epilepsy. *Journal of Epilepsy,* 8**,** 227-235.
Wijnen, B. F. M., Van Mastrigt, G., Evers, S., Gershuni, O., Lambrechts, D., Majoie, M., Postulart, D., Aldenkamp, B. a. P. & De Kinderen, R. J. A. 2017. A systematic review of economic evaluations of treatments for patients with epilepsy. *Epilepsia,* 58**,** 706-726.
Willmann, O., Wennberg, R., May, T., Woermann, F. G. & Pohlmann-Eden, B. 2007. The contribution of 18F-FDG PET in preoperative epilepsy surgery evaluation for patients with temporal lobe epilepsy A meta-analysis. *Seizure,* 16**,** 509-20.
Winston, G. P., Micallef, C., Kendell, B. E., Bartlett, P. A., Williams, E. J., Burdett, J. L. & Duncan, J. S. 2013. The value of repeat neuroimaging for epilepsy at a tertiary referral centre: 16 years of experience. *Epilepsy Research,* 105**,** 349-355.
Wirrell, E. C., Nabbout, R., Scheffer, I. E., Alsaadi, T., Bogacz, A., French, J. A., Hirsch, E., Jain, S., Kaneko, S., Riney, K., Samia, P., Snead, O. C., Somerville, E., Specchio, N., Trinka, E., Zuberi, S. M., Balestrini, S., Wiebe, S., Cross, J. H., Perucca, E., Moshé, S. L. & Tinuper, P. 2022. Methodology for classification and definition of epilepsy syndromes with list of syndromes: Report of the ILAE Task Force on Nosology and Definitions. *Epilepsia,* 63**,** 1333-1348.
Wojewodka, G., Gulliford, M. C., Ashworth, M., Richardson, M. P. & Ridsdale, L. 2021. Epilepsy and mortality: a retrospective cohort analysis with a nested case–control study identifying causes and risk factors from primary care and linkage-derived data. *BMJ Open,* 11**,** e052841.
Wolf, P. 2014. History of epilepsy: nosological concepts and classification. *Epileptic Disord,* 16**,** 261-9.
World Health Organization 2010. A conceptual framework for action on the social determinants of health. Geneva: World Health Organization.
World Health Organization 2017. *Atlas: country resources for neurological disorders,* Geneva, World Health Organization.
World Health Organization 2021. Global status report on the public health response to dementia.
Xiang, X., Fang, J. & Guo, Y. 2019. Differential diagnosis between epileptic seizures and psychogenic nonepileptic seizures based on semiology. *Acta Epileptologica,* 1**,** 6.
Xu, D., Miller, S. & Koh, S. 2013. Immune mechanisms in epileptogenesis. *Frontiers in Cellular Neuroscience,* 7.
Xu, Y., Nguyen, D., Mohamed, A., Carcel, C., Li, Q., Kutlubaev, M. A., Anderson, C. S. & Hackett, M. L. 2016. Frequency of a false positive diagnosis of epilepsy: A systematic review of observational studies. *Seizure,* 41**,** 167-74.
Yan, H., Katz, J. S., Anderson, M., Mansouri, A., Remick, M., Ibrahim, G. M. & Abel, T. J. 2019. Method of invasive monitoring in epilepsy surgery and seizure freedom and morbidity: A systematic review. *Epilepsia,* 60**,** 1960-1972.
Yang, P. F., Zhang, H. J., Pei, J. S., Tian, J., Lin, Q., Mei, Z., Zhong, Z. H., Jia, Y. Z., Chen, Z. Q. & Zheng, Z. Y. 2014. Intracranial electroencephalography with

subdural and/or depth electrodes in children with epilepsy: techniques, complications, and outcomes. *Epilepsy Res,* 108**,** 1662-70.
Zaidi, A., Clough, P., Cooper, P., Scheepers, B. & Fitzpatrick, A. P. 2000. Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol,* 36**,** 181-4.
Zhang, C., Kwan, P., Zuo, Z. & Baum, L. 2012. The transport of antiepileptic drugs by P-glycoprotein. *Advanced Drug Delivery Reviews,* 64**,** 930-942.
Zrinzo, L., Foltynie, T., Limousin, P. & Hariz, M. I. 2012. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. *J Neurosurg,* 116**,** 84-94.

Appendix

Appendix 1: Semiology descriptions*		
Semiology	**ILAE Seizure Classification**	**Subset Examples**
Aphasia	Focal cognitive (aphasia)	Mutism, speech arrest
Asymmetric Tonic	Focal motor tonic (asymmetric)	Fencing, 'figure of 4'
Atonic	Focal motor (atonic)	Flaccid, head drop
Auditory	Sensory (auditory)	Hearing sounds, auditory hallucination
Automatism - Manual & Oral	Automatisms	Fiddling, lip smacking, chewing,
Automatisms - Other	Automatisms	Ictal spitting, ictal nose wiping, ictal face rub
Autonomic	Autonomic	Ictal bradycardia/tachycardia, sweating
Clonic	Focal motor (clonic)	Repetitive or rhythmical jerks
Complex Behavioural	Emotional or Behavioural arrest	Behavioural change, fearful behaviour, wandering, awakening or arousal, compulsive checking
Dialeptic	Loss of awareness	Blank, unaware, dreamy state, dyscognitive, not with it psychomotor arrest, loss of consciousness
Dysphasia	Focal cognitive (aphasia)	Difficulty speaking or incoherent speech, expressive dysphasia, incomprehensible speech
Dystonic	Dystonic	Twisted posture
Epigastric Aura	Focal sensory	Abdominal aura, butterfly sensation, rising sensation
Eye Movements		Nystagmus (fast phase direction), ocular flutter, complex ocular movements, gaze deviation and versive eye movements
Fear-Anxiety	Emotional	Sense of impending doom, fear, anxiety
Gustatory	Sensory	Taste aura
Head or Body Turn		Head turn, gyroscopic or body turn
Head Version		Forced head deviation over shoulder, extreme head turn

Hypermotor	Hyperkinetic	Large proximal limb or axial movements, hyperkinetic, head banging, pedalling, kicking, pelvic thrust
Ictal Pout		Chapeau de gendarme
Ictal Speech - Formed Words	Vocalisation	Ictal speech, palilalia, coprolalia
Mimetic Automatisms	Automatisms	Grimace, raising of eyebrows, mimetic, facial expression, fearful expression
Myoclonic	Focal motor (myoclonic)	Jerk
Non-Specific Aura	Focal sensory	Vague, unspecified aura, indefinable feeling, cephalic sensation
Olfactory	Focal sensory (olfactory)	Smell
Psychic	Focal Cognitive	Déjà vu, jamais vu, derealisation, depersonalisation
Somatosensory	Focal sensory (somatosensory)	Tingling, touch sensation
Spasms	Spasms	Infantile spasm and epileptic spasms
Tonic	Focal motor (tonic)	Stiff, tonic posturing
Vestibular	Focal sensory (vestibular)	Vertigo, spinning sensation
Visual	Focal cognitive (hallucinations)	Formed visual hallucinations e.g. people or objects, movement of objects
Vocalisation - Unintelligible Noises	Vocalisation	Grunt, mumble, hum
*Adapted from ILAE and semiological seizure classifications (Fisher et al., 2017, Tufenkjian and Lüders, 2012)		