Neuropsychological outcomes following paediatric temporal lobe surgery for epilepsy: Evidence from a systematic review

Alice Elizabeth Flint

Submitted in accordance with the requirements for the degree of
Doctor of Clinical Psychology (D. Clin. Psychol.)

The University of Leeds
School of Medicine
Academic Unit of Psychiatry and Behavioural Sciences

July, 2016

The candidate confirms that the work submitted is her own and that appropriate credit has been given where reference has been made to the work of others.

ACKNOWLEDGEMENTS

I would like to extend my sincere thanks to some people who have been instrumental in this thesis project. Thanks to my supervisors, Dr Mitch Waterman and Dr Matthew Morrall, for their help in developing the research idea, their methodological guidance, their patience and their enthusiasm. I would also like to thank Mr Paul Chumas, Consultant Neurosurgeon at The Leeds Teaching Hospitals NHS Trust for his input to the research protocol and to Ms Elizabeth Neilly, Scholarly Communications and Researcher Skills (SCoReS) Advisor, University of Leeds Library, for her assistance with the development of electronic database terms. I would also like to thank Dr Vicky Gray, Consultant Neuropsychologist at Northern Children's Epilepsy Surgery Service (NorCESS), Alder Hey's Children's Hospital NHS Trust, for taking the time to speak with me about current issues in clinical practice and national audit.

ABSTRACT

The objective of this thesis was to present evidence from a systematic review of the literature to assess wider neuropsychological outcomes for temporal lobe resections for epilepsy in children. Neuropsychological outcome domains included intellectual, memory, language, quality of life, psychological wellbeing, educational, vocational, social and behavioural outcome. A systematic literature search was conducted firstly for all studies reporting any outcomes of any resective paediatric epilepsy surgery, yielding 8189, of which 1259 met criteria. After a brief exploration of these broader epilepsy surgery studies, more focussed eligibility criteria were applied. The final review included only those 73 studies that reported neuropsychological outcome of paediatric temporal lobe surgery for epilepsy. Core findings of the review were that for each neuropsychological outcome domain, the majority of participants remained stable after surgery; some declined and some improved. There was some evidence for increased material-specific memory deficits after temporal lobe surgery based on resection side, and more positive cognitive outcome for those with lower pre-surgical ability level. No quantitative analysis of the factors predicting neuropsychological outcome could be performed due to limitations in methodological and reporting quality of the included studies. However, it is this appraisal of the evidence that is of most interest, as it highlights the need for changes in methodology and reporting. Appropriately designed prospective multicentre trials should be conducted, with adequate follow-up for long-term outcomes to be measured. Surgical centres should continue to publish routine clinical case series, but ensure that they report individual participant data, according to established reporting standards. Core outcome measures should be agreed between centres and researchers should collaborate by making their data available for open reviews, in order to build a higher quality evidence base, so that clinicians, young people and their families can make better informed decisions about whether or not to proceed with surgery.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABBREVIATIONS

AED	Antiepileptic drug
ASD	Autism spectrum disorder
ATL	Anterior temporal lobectomy
BNT	Boston Naming Test
CAVLT	Children's Auditory Verbal Learning Test
CBCL	Child Behavior Checklist
CD	Cortical Dysplasia
CESS	Children's Epilepsy Surgery Service
CMS	Children's Memory Scale
CNS	Central Nervous System
CPS	Complex partial seizures
CRD	Centre for Reviews and Dissemination
CVLT	California Verbal Learning Test
DBS	Deep brain stimulation
DCS-R	Diagnostikum für Cerebralschadigung-Revised
DQ	Developmental quotient
EBM	Evidence Based Medicine
EEG	Electroencephalogram
FSIQ	Full Scale Intelligence Quotient
GABA	gamma-Aminobutyric acid
HPA	Hypothalamic-pituitary-adrenal axis
ILAE	International League Against Epilepsy
ISAP	intracarotid sodium amytal procedure
LTLE	Lateral temporal lobe epilepsy
MACS	Memory Assessment Clinics Self-rating Scale
MEG	Magnetoencephalography
MRI	magnetic resonance imaging
MST	Multiple subpial transection
MTLE	Medial temporal lobe epilepsy
NEPSY	A Developmental NEuroPSYchological Assessment
OCEBM	Oxford Centre for Evidence Based Medicine
PET	Positron emission tomography
PIQ	Performance Intelligence Quotient
PRI	Perceptual Reasoning Index
PRISMA	Preferred Reporting Items for Systematic Reviews
PSI	Processing Speed Index
QoL	Quality of Life
RAKIT	Revised Amsterdam Kinder Intelligence Test
RAVLT	Rey Auditory-Verbal Learning Test
RBMT	Rivermead Behavioural Memory Test
RCT	Randomised Controlled Trial
ROCFT	Rey–Osterrieth Complex Figure Test

SAH	Selective amygdalohippocampectomy
SD	Standard deviation
SES	Socio-economic Status
SGTCS	Secondary generalised tonic-clonic seizures
SPECT	Single-photon emission computed tomography
SPS	Simple partial seizures
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SUDEP	Sudden unexpected death in epilepsy
T	Tesla
TLE	Temporal lobe epilepsy
TOMAL	Test Of Memory And Learning
VCI	Verbal Comprehension Index
VIQ	Verbal Intelligence Quotient
VNS	Vagus nerve stimulation
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children
WMI	Working Memory Index
WMS	Wechsler Memory Scale
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAML	Wide Range Achievement of Memory and Learning

CHAPTER ONE: INTRODUCTION

'Epilepsy' describes a group of different conditions characterised by the experience of recurrent epileptic seizures, which are “transient occurrences of signs or symptoms due to abnormal excessive or synchronous neuronal activity in the brain” (Fisher et al., 2005). Taken together, epilepsies represent one of the most common neurological conditions, with an estimated prevalence rate in the UK of 1 in 103 people of the population and an incidence of 51 per 100,000 annually (Joint Epilepsy Council, 2011). Epilepsies are rarer in children with a prevalence of 1 in 220, meaning that there are approximately 63400 children with an epilepsy in the UK (Joint Epilepsy Council, 2011). An epilepsy can be defined by any of three working criteria produced by the International League Against Epilepsy (ILAE; Fisher et al., 2014):

1. Two or more unprovoked seizures occurring more than 24 hours apart in a child over one month old, excluding seizures provoked by transitory factors such as fever;
2. One unprovoked seizure and a 60% or greater risk of further seizure;
3. Diagnosis of a known epilepsy syndrome.

Thus the definition of epilepsy is somewhat circular, as diagnosis of an epilepsy syndrome can be the reason for an epilepsy diagnosis, and the concept of epileptic seizures both defines and is defined by the concept of epilepsy. The neurophysiological mechanisms of seizures remain unclear but are characterised by abnormal synchronisation of excitatory neural activation, thought to be a result of a lowered threshold for activation of excitatory neurons at seizure onset (Quyen et al., 2003). There are a broad range of seizure presentations, epilepsy syndromes and potential aetiologies for epilepsy. A detailed discussion of these is beyond the scope of this thesis but they are described in Appendix A. This Chapter aims to introduce a broad overview of the relevant background literature before setting out the aims of the systematic review project. Section 1.1 will introduce the type of epilepsy that is the focus of this thesis; temporal lobe epilepsy (TLE). Section 1.2 introduces the impact of chronic TLE on the lives of children and their families, before Section 1.3 describes the available treatment options. Sections 1.4, 1.5 and 1.6 discuss the available surgical treatments and then Sections 1.7 and 1.8 introduce the rationale and aims for the thesis.

1.1 Temporal lobe epilepsy

Temporal lobe epilepsy (TLE) describes the experience of recurrent epileptic seizures that originate from the temporal lobe. It is the most common cause of partial seizures (Wiebe, 2000), which unlike generalised seizures only affect one brain hemisphere. Partial seizures may be either simple (SPS), where the person remains conscious throughout, or complex (CPS), where the person experiences impaired consciousness (McCandless, 2002). Seizures that spread from their initial

location to affect the whole brain are called secondary generalised tonic-clonic seizures (SGTCS). Common symptoms of these seizure types are displayed in Table 1.1.

Table 1.1 Common symptoms of seizure types in TLE (Berg et al., 2010)

SPS	**CPS**	**SGTCS**
Déjà vu (familiarity sense)	Impaired consciousness	Tonic phase: stiffening of the arms, trunk, and legs
Jamais vu (unfamiliarity sense)	Motionless staring	Clonic phase: bilateral jerking of limbs in rhythmic motion.
Amnesia	Automatic movements of hand/mouth	
Auditory (hearing unusual sounds)	Altered speech	
Gustatory (tasting unusual tastes)	Unusual behaviour	
Olfactory (unusual smell)	Impaired responsiveness	
Dysphoria		
Euphoria		
Fear		
Anger		
Visual		

Two main types of temporal lobe epilepsy have been described by the ILEA (Engel, 2001). Mesial temporal lobe epilepsy (MTLE) involves medial temporal lobe structures such as the hippocampus, amygdala and parahippocampal gyrus. Lateral temporal lobe epilepsy (LTLE) involves the lateral temporal lobe neocortex as the epileptogenic region. The clinical features of LTLE and MTLE are broad and varied, and seizure patterns observed in those with LTLE and MTLE can overlap. However, seizures of people with MTLE are more likely than LTLE to include affective and gustatory symptoms, automatic movements, dystonic posturing, epigastric sensations and longer seizure duration, whereas LTLE seizures are more likely to include auditory hallucinations and clonic movements (Bercovici et al., 2012).

1.2 Impact of TLE in childhood

Evidence suggests that children with chronic conditions that involve the brain or central nervous system (CNS) have lower quality of life (QoL) and greater psychological, social and educational difficulties than children with disorders without CNS involvement (Breslau, 1985; Rutter et al., 1970). In keeping with these findings, epilepsies are associated with a number of harmful outcomes for children, discussed in Sections 1.2.1 to 1.2.5.

1.2.1 Sudden unexplained death in epilepsy

Sudden unexplained death in epilepsy (SUDEP; Donner et al., 2001) describes any unanticipated death of a person with epilepsy where no anatomical or toxicological explanation can be found post-mortem. It accounts for between 7.5 and 17% of all deaths in epilepsy (Terra et al., 2013). There are few reports of SUDEP incidence in children, although a prospective cohort study found

11 cases of SUDEP out of 1012 patients (Terra et al., 2013) and a larger retrospective cohort study of children with epilepsies found 9 SUDEP cases out of 6190 patients (Ackers et al., 2011). TLE carries lower risk of SUDEP than other epilepsies but risk of death is still significantly higher than in the general population (Hennessy et al., 1999). There is some evidence that knowledge of SUDEP risk itself raises parental anxiety and reduces QoL (Brodie & Holmes, 2008). However, Gayatri et al. (2010) found that despite concern from neurologists, provision of information about SUDEP risk to parents did not have a significant impact on their wellbeing in the immediate or longer-term, and most parents believed that this information should be provided to families of children with epilepsies.

1.2.2 Cognitive problems

Cognitive problems are common in children with an epilepsy; between 26% and 57% have an IQ lower than 80 (Berg et al., 2008; Cormack et al., 2007; Rantanen et al., 2011). A high proportion of children with epilepsies have a learning disability, though this is often attributable to comorbid conditions with a higher prevalence in children with epilepsies than in the general population, including autism spectrum conditions (Clarke et al., 2005). Deficits in a number of specific cognitive domains have been reported, including memory and executive functioning, attention and information processing (Hermann et al., 2008; Jambaqué et al., 1993; MacAllister & Schaffer, 2007; Pulsipher et al., 2009). However, these studies often have small sample sizes (e.g. Pulsipher et al., 2009) and heterogeneous participants with a range of epilepsies and underlying pathologies (e.g. Jambaqué et al., 1993), making it difficult to know if results are representative of the wider population of children with epilepsy.

1.2.2.1 Cognitive difficulties reported in TLE

TLE is posited to have a large impact on cognition due to its effect on temporal lobe structures such as the hippocampus and amygdala (Zeman et al., 2012). TLE in adults is associated with deficits in memory, executive function, social deficits and language (Zhao et al., 2014). A distinctive memory profile has been described for a section of people with TLE, who have normal recall on episodic memory tasks over a short delay, but accelerated long-term forgetting (Blake et al., 2000). Studies of children with TLE have also reported memory problems (Fedio & Mirsky, 1969; Guimaraes, 2007; Jambaqué et al., 1993) as well as executive function, naming and construction difficulties (Nolan et al., 2003; Roeschl-Heils et al., 2002), however not all studies have found deficits (e.g. Camfield et al., 1984). The study of cognitive difficulties in epilepsies is complex because of the number of factors that may influence cognitive functioning, such as brain pathology, age of onset at

seizures, duration of seizures, seizure frequency comorbid conditions, antiepileptic drugs (AEDs) and epileptogenic region (Hermann & Seidenberg., 2008).

It would seem intuitive that seizures may affect the functions subserved by the brain areas where they occur, though this has not always been found (Kernan et al., 2012). Fedio and Mirsky (1969) and Jambaqué et al., (1993) found that impairment occurred in the memory domain subserved by the hemisphere that was ipsilateral to the memory domain lateralised there (i.e. generally children with right TLE had greater visual impairment and children with left TLE had greater verbal impairment). However, as Stefanatos (2015) notes, these studies were limited due to uneven group size and differences in participant characteristics and other studies found no such effect for children (Helmstaedter & Elger, 2009; Gonzalez et al., 2007; Nolan et al., 2004). Other research suggests that children with epilepsy may have less localisation-specific cognitive deficits than adults, and instead exhibit a broad pattern of cognitive deficits, beyond those subserved by the epileptogenic region. For example, Hermann et al (2006) noted that poorer cognitive functioning with early focal seizures appears to generalise to cognitive functions beyond those subserved by the localisation area of the epilepsy and Stefanatos (2015) found little difference between the neuropsychological profile of children with frontal and temporal epilepsies. However, the sample size of each group was also small so the study may have been underpowered to detect group differences. Gonzales et al. (2007) found higher levels of memory problem in children with MTLE than LTLE but no lateralisation of verbal and visual memory, suggesting that memory in children with TLE are localised but not lateralised (Stefanatos, 2015).

The relationship between seizure variables and cognitive functioning also remains unclear (Reynolds & Fletcher-Janzen, 2009). However, generalised seizures appear to be associated with lower memory scores and lower general cognitive functioning compared to focal seizures (Kernan et al., 2012; Reynolds & Fletcher-Janzen, 2009). Clearly, this may be related to differences in underlying pathology, which is responsible for both generalisation of seizures and poorer cognitive functioning. Early onset of seizures is associated with reduced cortical volume and reduced white matter and well as poorer cognitive functioning (Hermann et al., 2002; Hermann et al., 1997; Schoenfeld et al., 1999). Studies in both animals (Sayin, et al., 2004) and humans (Aicardi & Chevrie, 1970; Roy et al., 2011) suggest that seizure activity such as status epilepticus[1]can cause cognitive impairment in the developing brain. However, studies have found cognitive impairment in

[1] in which a seizure lasts for more than five minutes or where multiple seizures occur for more than five minutes without return to normal functioning in between (Al-Mufti & Claasson, 2014)

children prior to the start of their seizures or very early in their epilepsy (Hermann et al., 2006) before seizures could have impacted on function, suggesting that underlying pathology may account for both earlier seizure onset and cognitive deficits.

Anti-epileptic drugs (AEDs) also carry side effects including an impact on cognitive functioning (Eddy et al., 2011). Use of older AEDs, such as Phenobarbital, has reduced significantly in western countries due to findings of it negatively affecting IQ (Farwell et al., 1990), including when compared to other AEDs such as Valproate or Carbamazepine (Calandre et al., 1990; Vining et al., 1987). Phenytoin has been associated with deterioration in memory, attention and psychomotor speed (Andrewes et al., 1986; Pulliainen & Johelainen, 1995) and these effects reduce after discontinuation (May et al., 1992). Carbamazepine has been associated with declines in processing speed and attention (Wesnes et al., 2009). More recently developed AEDs such as Gabapentin, Oxcabazepine and Levetiracetam (Keppra) have not been found to be linked to cognitive impairment (Dodrill et al., 1999; Donati et al., 2007; Huang et al., 2008; Levisohn et al., 2009; Meador et al., 1999) and may lead to some improvement (Ciesielski et al., 2006; Donati et al., 2006; Neyens et al., 1995; Placidi et al., 2000), although some are linked to disturbances in affect and conduct, as presented in Section 1.2.3. It is also possible that cognitive deficits could be psychosocial in origin, as discussed in Section 1.2.5. Thus it is not always possible to disentangle the interrelated effects of underlying pathology, age of onset, seizure burden, AED use and psychosocial factors, as these factors are not independent of each other and effects of these factors may be cumulative.

1.2.3 Psychological Wellbeing

The experience of chronic illness in childhood is associated with increased risk of mental health problems (Cadman, 1987). This may be attributable to the many challenges that chronic illnesses present, such as disrupted attachment due to parental anxiety or separation for treatment (Ødegård, 2005). Chronic illness presents unexpected and uncontrollable stressors to the family and introduces a perception of threat (Christie & Khatun, 2012). Children with chronic illness have lower self-esteem than peers (Pinquart, 2013) and their social relationships and education are negatively affected, in part because illness or treatment may cause increased school absence and these different experiences can lead to feelings of isolation and difference (Yeo & Sawyer, 2005), which can affect mental health into adulthood (Christie & Khatun, 2012).

Children with an epilepsy face further challenges to their mental health in addition to those associated with other chronic illness. In an early epidemiological study Rutter (1970) found that 7%

of children in the general population and 12% of those with health problems not involving the CNS have a psychiatric disorder. This compares to a prevalence of psychiatric problems in 29% of children with idiopathic seizures, 38% of children with structural brain abnormalities and 58% of children with both structural brain abnormalities and seizures (Rutter, 1970). Children with an epilepsy have been reported to have over five times the rate of depression as healthy children, over 1.5 times the rate of anxiety and over 2.5 times the rate of attention deficit hyperactivity disorder (ADHD; Jones et al., 2007). There are a number of psychological theories for the development of mental health difficulties in children with epilepsies. Elliot et al. (2005) found that young people with epilepsies sensed a loss of control of their bodies which increased their sense of uncertainty and led to worry about seizures. They also reported frustration with having seizures, treatments and being monitored by their parents. The loss of control experienced by a child during seizures may cause embarrassment or shame when in public, particularly if they are incontinent (Nikcevic et al., 2009). Fear of experiencing this shame can lead to avoidance of social situations, and development of social anxiety. This pattern of avoidance can restrict development of confidence, independence and social skills, and lead to social isolation, which is a risk factor for developing depression (Heinrich & Gullone, 2006). Qualitative studies have found that teenagers with an epilepsy face struggles with identity formation, including developing their autonomy and being accepted by peers (McEwan et al., 2004).

Some studies suggest that young people with TLE are at greater risk of depression (Salpekar et al., 2013; Sanchez-Gistau et al., 2010) than other types of epilepsy. This may be related to findings that focal epilepsies appear more predictive of psychological difficulties than generalised epilepsies (Austin et al., 2001; Thome-Souza et al., 2004). However, Ott et al. (2001) found no difference in psychopathology between children with TLE and children with primarily generalised epilepsy. One potential mechanism for psychopathology in children with TLE is dysregulation of the hypothalamus-pituitary-adrenal (HPA) axis which mediates cortisol release in response to stress. The HPA axis is affected in mental health problems (Pariante, 2003; Spencer & Hutchinson, 1999) and it affects the activity of other neurotransmitter systems such as serotonin. Mesial temporal structures, the hippocampus and amygdala, play a key role in this neuroendocrine pathway as the amygdala stimulates the pathway on detection of threat, and the hippocampus regulates the system by inhibition (Smith & Vale, 2006). Aberrant development or damage in the temporal lobe may disrupt this system and play a role in mental health problems in TLE (Kandratavicius et al., 2012). In keeping with a neurodevelopmental contribution to psychological problems in children with epilepsy, Austin et al (2001) found that children with epilepsies had an increased risk of behaviour problems at the time of their first seizure. A strength of this study was the large sample size, its use

of a sibling comparison group and its consideration of socioeconomic status (SES) and parental education. However, like most studies it failed to adequately stratify the results for children with different epilepsy locations, and results were not presented separately for children with TLE. Some studies have linked TLE to regression, the slowing or reversal in the development of skills, in language, behaviour and social communication, similar to that seen in children with a diagnosis of Autism Spectrum Disorder (ASD) but mechanisms for this remain unclear (Bolton & Griffiths, 1997; Taylor et al., 1999).

Another potential contributor to mental ill health in children with an epilepsy is the effect of AEDs, which act as psychotropic agents and can influence behaviour (Nadkarni & Devinsky, 2005). For example, Felbamate and Lamotrigine can act as antidepressants but can also increase agitation, anxiety and insomnia (Ettinger et al., 1996). Levetiracetam can induce anxiety, depression and especially in children (Cramer et al., 2003) and Vigabatrin has been linked to behaviour change and psychosis (Thomas et al., 1996). Carbamazepine and Valproate can be used to treat mania for mood stabilisation but carry a side effect risk of depression (Nadkarni & Devinsky, 2005). Studies of psychological difficulties in children with epilepsy have failed to adequately measure the effects of AEDs individually, but Austin (2001) and Thome-Souza et al (2004) did not find any difference in the emergence of psychological difficulties between children on AED monotherapy or polytherapy. Similarly, observational studies that study the long-term outcomes of AED use, such as the emergence of psychological problems, have generally failed to stratify results by seizure and epilepsy variables, or to take into account all possible confounding variables that may influence the development of psychological difficulties, and systematic reviews of these studies have inappropriately pooled data (Maguire et al., 2008).
Factors predictive of mental health problems in TLE include earlier age at onset, longer duration, cognitive impairment (Camfield et al., 1984; Hermann et al., 1988), left temporal focus (Caplan et al., 1991; Pritchard et al., 1980) and AEDs (Harbord, 2000). Again, these factors are not independent and their effects are likely cumulative.

1.2.4 Family functioning and quality of life

Family environment clearly has a significant influence on child development for all children, and as all families are different, families may interact differently with the epilepsy, which may have differential impacts upon wellbeing and QoL (Ellis et al., 2000). Families of children with an epilepsy report increased feelings of guilt and stress and reduced self-esteem compared to other families (Ellis et al., 2000). Maternal attitudes have been found to be related to child coping (Austin & McDermott, 1988). For example, Nicholas and Pianta (1994) found that parent-child interactions

predicted behaviour problems independently from seizure activity. However, there is also evidence that these problems may be associated with underlying pathology rather than seizure activity or family reactions to the epilepsy, as behavioural problems have been identified in children, who went on to develop epilepsy, six months before their first seizure (Austin et al., 2001; Jones et al., 2007; Oostrom et al., 2003). Parental behaviour may alter following epilepsy diagnosis, for example more dependent sleeping arrangements were found in children with epilepsy compared to children with diabetes, which was associated with parental worry about nocturnal seizures (Williams et al., 2000). Children and their families may also understandably develop a fear of SUDEP or of injury during seizures, which may change parenting style and lead to further restrictions in the young person's life, which may further isolate the child from peers and reduce self-efficacy (Ellis et al., 2000). Families with a child diagnosed with an epilepsy also have higher levels of financial hardship than those without (Ellis et al., 2000), in part due to time taken of work. In a study, children with epilepsies were found to underperform academically relative to their IQ when tested (Mitchell et al., 1991), and this was related to contextual factors rather than epilepsy characteristics, suggesting that sociocultural disadvantage may mediate poor psychosocial outcomes in children with an epilepsy, as it does for children in the general population (McLoyd, 1998). Family functioning may also affect cognitive functioning as Oostrom et al. (2003) found that poorer cognitive performance in children with an epilepsy relative to controls at diagnosis was related to contextual factors, such as parenting style and marital distress, rather than to factors pertaining to the child's epilepsy. It may be that this relationship is bidirectional, as having a child with a learning disability is posited to increase stress within the home and affect family functioning (Dyson, 1996; Heiman & Berger, 2008).

1.2.5 Relationships between the different outcomes of epilepsy

The factors of epileptic seizure activity, underlying pathology, family environment and underlying child characteristics are interactive and difficult to disentangle when attempting to understand the cause of poorer cognitive development in children with temporal lobe epilepsy relative to the general population. Nevertheless, it appears that frequent seizures may interrupt the developmental tasks of childhood. There are likely to be complex and cyclical interactions between these variables. For example, risk of mental health difficulties is likely to be increased by cognitive impairment and low IQ, as these are risk factors, particularly for externalising disorders and behavioural problems (Berg et al., 2011). These difficulties are likely to reduce the child's ability to engage in education further, which may further reduce the opportunities for neurodevelopment and acquisition of skills. Furthermore, children with epilepsies may feel restricted in activities, which is associated with lower QoL (Carpay et al., 1997).

1.3 Treatments for TLE in childhood

Given the reported impact of seizures on children's lives, it appears crucial that their frequency is limited as much as possible. Generally pharmacological treatment using AEDs is the first treatment that is attempted in order to control seizures in children with epilepsies. They work to counteract the hyper-excitability of neurons that causes seizures by either acting on voltage-gated ion channels on neuronal membranes to limit neuronal firing, by stimulating activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), or by reducing activity of the excitatory neurotransmitter glutamate (Sills, 2011). AEDs are selected for use based on seizure type, although there is no definitive evidence to suggest which is the most efficacious (French et al., 2004). Choice of medication depends on side effect profiles and the types of seizures presented (Browne & Holmes, 2008). Older AEDs, including Carbamazepine are used in children with TLE and newer AEDs are also being introduced due to improvements in their side effect profile, for example, Oxcarbazepine, Levetiracetam, Lamotrigine and Topirimate (Beghi, 2004). However, as discussed above, many newer medications also carry risks of cognitive, behavioural and emotional difficulties (Nickels et al., 2011). Multiple AEDs may be prescribed to control seizures before surgery is considered, although there are increasing calls for more rapid referral of children for assessment for surgery (Cross et al., 2006). Kwan and Brodie (2000) found that patients who failed to respond to their first AED seldom gained seizure-freedom with their second, questioning the merit of repeated drug trials for a child. Deciding if an epilepsy is medically intractable is not a trivial process in children. Generally, medically refractory epilepsy is defined as trial of two or three AEDs, disabling side effects of AEDs, or disabling effect of seizures, however centres vary in how they reach this decision (Cataltepe & Jallo, 2010). Surgical treatment for epilepsy is discussed in Section 1.4.

For those children with refractory seizures that are not suitable candidates for resective epilepsy surgery, alternative treatments include vagus nerve stimulation (VNS), deep brain stimulation (DBS) and the ketogenic diet. In VNS, a device is inserted into the neck to deliver electrical impulses to the vagus nerve, which reduces the irregular electrical activity in the brain that causes seizures (Elliott, Morsi et al., 2011). Elliott, Rodgers et al. (2011) found that at least 50% of children experienced a reduction of at least 50% in seizure burden after VNS, although this case series lacked a control group so the reduction in seizures may be due to factors other than the VNS insertion. However, a review found that this finding was common amongst case series (Morris et al., 2013) and a case-control series (Terra et al., 2014) also found that 54% of children experienced at least 50% reduction in seizures after VNS, whereas the control group did not show any change in seizure frequency. Subjective improvement in mood and alertness has also been noted (Terra et al., 2014; Morris et al., 2013). The ketogenic diet involves children eating increased fat, and having

adequate protein but low carbohydrate intake; this increases the level of ketones in the blood, which replace glucose as the brain's source of energy, reducing seizures (Groesbeck et al., 2006). A meta-analysis found that between 55% and 60% of children given the ketogenic diet have at least 50% reduction in seizures after three to six months (Henderson et al., 2006). A randomised controlled trial (RCT; Neal et al., 2008) found that children on ketogenic diets experienced 38% fewer seizures compared to a 37% increase in seizures in the AED as usual group. In DBS, electrodes are inserted into specific brain regions to deliver electrical impulses to that area with the effect of reducing seizures (Miatton al., 2011). In a study of adults 54% of participants who received DBS had at least 50% reduction in seizures after two years (Fisher et al., 2010). Another adult study suggested that DBS had no major neuropsychological effects and was associated with improved emotional wellbeing, although this study lacked a control group. Higher quality data on the outcomes of DBS, and its efficacy for children, is awaited.

1.4 Surgical Treatment for Epilepsies in Childhood

Neurosurgery is a treatment option that usually involves removal, resection or disconnection of epileptogenic brain tissue (Harvey et al., 2008). There are a large number of different procedures, summarised in Table 1.2.

Table 1.2 Paediatric neurosurgeries for epilepsy, adapted from (Harvey et al., 2008)

Resection		
	Lesionectomies	
	Lobar	Frontal
		Temporal
		Parietal
		Occipital
		Hypothalamic
		Cerebellum
	Multilobar	
	Hemispherectomy	
Functional disconnection		
	Hemispherotomy	
	Corpus callosotomy	
	Multiple subpial transection	
Other		
	Vagal Nerve Stimulation	
	Deep Brain Stimulation	

The surgical technique chosen will depend on the underlying pathology, and the functions performed by the epileptogenic area. For example, focal lesions may be resected with lobar focal resection. Multiple subpial transection (MST) is indicated where the epileptogenic focus lies in the eloquent cortex. Eloquent cortex is the term used to describe regions of cortex that are necessary for defined cortical functions (Rosenow & Lüders, 2001), such as sensory processing, speech and motor functions. Damage to the eloquent cortex may therefore cause loss of these functions so efforts are made to preserve these regions as far as possible during resective surgery.
Hemispherectomies and hemispherotomies are performed on children who have a diffuse unilateral epileptogenic focus, including congenital disorders of neuronal development, such as Sturge-Weber syndrome, or acquired lesions such as Rasmussen's encephalitis (Cataltepe & Jallo, 2010).
For children with TLE, resective surgeries of the temporal lobe can range in the amount of tissue resected, and how much of the temporal lobe they preserve. Extensive temporal lobectomies that remove both lateral temporal lobe tissue and medial tissues, including the hippocampus and amygdala, can be performed, but more restricted surgeries are often performed in order to preserve as much of the eloquent cortex as possible (Engel, 1996). Anterior temporal lobectomies (ATL) involve removal of the anterior part of the temporal lobe and can be performed with or without

resection of the hippocampus and amygdala. Selective amygdalohippocampectomies (SAH) involve removal of only the hippocampus and amygdala (Engel, 1996). It should be noted that claims of success for a particular resection rest on the integrity of that surgical procedure. The precision of resecting the planned region without damaging neighbouring tissue is a considerable task for the surgeon, and regions resected are likely to differ slightly for each case of a given procedure, both due to the differences between children's brains and the slight differences in surgical approach in each operation. This is likely to be a factor that introduces variance in reported outcomes in research (Höller et al., 2015).

1.5 Pre-surgical assessment

Benefits and risks of surgery are weighed and pre-surgical assessments are conducted to determine candidacy. These tend to be focused on seizure outcome and medical risks of operation but also involve gaining an understanding of the cognitive and psychosocial risks and benefits (Cataltepe & Jallo, 2010). Pre-surgical assessment is required in order to lateralise and localise the epileptic focus, and determine the function of that brain tissue, before determining which procedure can most appropriately maximise clinical gains whilst minimising risk (Cataltepe & Jallo, 2010). Details of these localising and lateralising procedures are provided in Table 1.3. Interictal sleep electroencephalogram (EEG) recording, video EEG recoding of seizures, cranial Magnetic Resonance Imaging (MRI), functional imaging if required, neuropsychological assessment, diagnosis and advice on educational interventions and neuropsychiatry assessment and treatment are required as standard (NHS Commissioning Board, 2013), and guidelines specify that surgical centres should have access to 3 Tesla (3T) MRI, Single-photon emission computed tomography (SPECT), Positron Emission Tomography (PET), functional MRI (fMRI), magnetoencephalography (MEG) and stratigraphy in case they are needed depending on presentation and possible risks. Wada/intracarotid sodium amytal procedure (ISAP) may also be required (Cross et al., 2006).

Table 1.3 Description and purpose of pre-surgical imaging assessments

Pre-surgical assessment	Description and purpose
EEG and video EEG	EEG is non-invasive scalp surface recording of the electrical activity in the brain, used to initially diagnose epilepsy and to identify the epileptic focus prior to surgery and determine candidacy (Cataltepe & Jallo, 2010). Combining EEG recording with video of seizures is important for acurately recording the seizure semiology and to rule out non-epileptic seizures. EEGs should also be perfomed in the interictal (between seizures) period, to capture spontaneous seizures (Hauptman & Mathern, 2016), and during a period of sleep, as brain activity changes.
Subdural EEG	Electrodes are implanted onto the surface of the cortex by craniotomy. This carries risk of infection (3-12%) but the procedure is "highly contributory" in indenitfying epileptogenic regions and eloquent cortex (Guerrini et al., 2013, p.41).
MRI	Structural MRI uses magnetic fields and radio waves to produce images of body structure and it is used prior to paediatric epilepsy surgery to locate abnormalities, including both the epileptogenic lesion, and find any additional abnormalities present (Cataltepe & Jallo, 2010). The magnetic field of 3T MRI is stronger than the standard 1.5T MRI, which allows it to have a higher resolution, making detection of abnormalities e.g. focal corical dysplasia more likely (Prabhu & Mahomed, 2015).
SPECT	SPECT uses radioactive tracers to measure blood flow to a brain area. It is often used in combination with CT or MRI scans, to provide structural and metabolic information (Cataltepe & Jallo, 2010). Ictal (during seizures) and interictal SPECT are used both to detect the epileptogenic focus, and for mapping language, sensory and motor areas of cortex. The identified area from ictal SPECT is congruent with epileptogenic zone in 70-97% of cases (Guerrini et al., 2013). Krsek et al. (2013) found that ictal SPECT found the same epileptogenic focus as EEG in most cases and was predictive of positive surgical outcome. However, interictal SPECT can provide misleading results and should be interpreted with caution (Duchowny & Cross, 2012).
PET	PET uses radioactive tracers to measure brain glucose metabolism, often used in combination with CT or MRI scans, to provide structural and metabolic information (Cataltepe & Jallo, 2010). Ictal PET is used to localise the epileptogenic zone and functional PET can identify eloquent cortex. Tracers vary in sensitivity (Duchowny & Cross, 2012). Sensitivity of interictal PET at detecting the epileptogenic area is 40-100%, depending on the lesion (Guerrini et al., 2013).
fMRI	fMRI is a functional imaging method whereby the blood oxygenation level of brain areas is measured, to indicate the activity occurring in different brain regions. fMRI has higher temporal resolution than PET (Raybaud et al., 2006). This is helpful for assessing the cognitive and motor functions of cortex to assess the feasibility of resection and deciding how much of the area to resect (Cataltepe & Jallo, 2010).
MEG	MEG is a non-invasive imaging technique which has high spatiotemporal resolution and can be helpful for localisation of the epileptic focus, particularly where EEG and MRI data are discordant (Cataltepe & Jallo, 2010).
Wada/ISAP	Wada/ISAP assesses lateralisation of language and memory functions. A barbiturate is administered to one hemisphere of the brain via the femoral artery, which inhibits these functions in that hemisphere. The patient remains awake and memory and language tests are administered. The degree of impairment indicates whether these functions are subserved by the anaesthetised hemisphere (Cataltepe & Jallo, 2010). Language concordance with fMRI is reported in 90% of patients (Guerrini et al., 2013).

During this pre-surgical stage, the child and family are prepared and provided with information on possible risks and anticipated benefits of surgery. Locating a comprehensive list of risks and benefits of surgery was difficult to find in the peer-reviewed literature, however this may be an outcome of the proposed review. The risks and benefits presented by the charity Epilepsy Action are summarised in Table 1.4. This chapter will not review the literature around outcomes of surgical resection for epilepsy in childhood in detail, as this will be the focus of the systematic review contained in later chapters.

Table 1.4 Potential benefits and risks of epilepsy surgery, after Epilepsy Action (2013a)

Anticipated Benefits	**Potential Risks**
Reduced seizures or seizure cessation	**Non-anticipated** Stroke Death **Anticipated** Visual impairment e.g. hemianopia Increased seizures Re-operation Motor problems e.g. one-sided paralysis Behavioural problems Cognitive problems e.g. memory difficulties

1.6 Clinical context of epilepsy surgery

1.6.1 Reform and centralisation of paediatric epilepsy surgery services in the UK

Neurosurgery for paediatric epilepsy has recently fallen under the spotlight of the Safe and Sustainable review of neurosurgical services for children, which aims to address concerns about standards of clinical care, availability of specialists and the efficiency of the current organisational structure of child neurosurgery in the UK (Young, 2014). It is argued that the large number of centres performing such surgeries in the UK meant that some were performing only a few of each procedure each year, which risked the surgeons deskilling (Young, 2014). Therefore, it was proposed that there would be Children's Epilepsy Surgery Service (CESS) centres performing the majority of paediatric epilepsy surgeries, and consulting on those carried out at other hospitals (Epilepsy Action, 2013b). The Safe and Sustainable review of paediatric neurosurgical services has agreed national standards for best care (National Specialised Services, 2012) and aims to create hubs of excellence, staffed with an expert workforce of neurosurgeons and specialised support services, including neuropsychologists. Similar conclusions were made following the Safe and Sustainable review of children's congenital cardiac services, which led to a heated debate as families objected to increased travel times when local paediatric heart surgery services were lost (Ipsos MORI, 2011). The accuracy of the findings of the Safe and Sustainable review of children's

congenital cardiac services were called into question, leading to a period of uncertainty about organisational change, media speculation and judicial review (Gallagher, 2013). Despite the drive towards centralisation of surgical services, as yet, there is little high quality data to support the prediction that increasing volume via fewer centres is beneficial for outcome (Young, 2014). A report conducted for the National Specialised Commissioning Group failed to find a clear link between volume of surgeries conducted by an institution or surgeon and outcome (Ewart, 2009), although it seems intuitive that more experienced teams and centres would yield better outcomes. As Shastin et al. (2015) discuss, few of the CESS centres have routinely published their outcome data, which makes it difficult to compare outcomes between centres and to assess whether centralisation has led to improved outcomes. In this time of organisational change, therefore, the collection, publication and synthesis of a broad range of paediatric epilepsy surgery outcomes is highly important.

1.6.2 Ethical issues with control groups and the effects of prolonged seizure duration

Ethical and practical issues make it difficult to conduct controlled studies in this area of research. The best matched control participants for studies of epilepsy surgery outcomes would be children with similar epilepsy characteristics to surgical candidates, who do not have the surgery. However, these children are also likely to be eligible for surgery and there are ethical problems in withholding surgery from potential surgical candidates who may benefit from it. As discussed in Section 1.2, young people who continue to experience seizures are at risk of poor cognitive, developmental, social and quality of life outcomes, and these outcomes can worsen with increased seizure duration. Surgery may represent a chance to eliminate seizures and their effects. It is therefore important that all young people who are eligible for surgery are offered it as soon as possible, rather than being allocated to the control arm of a trial. Other possible control groups could be those who are on the waiting list to receive surgery, but these are unable to provide long-term follow up data for comparison, or children with chronic epilepsy who are not surgical candidates. These children are likely to differ from surgical candidates in terms of their epilepsy characteristics or underlying pathology, so may not fully control for confounding variables that may affect outcome. However, a study found no significant differences in cognitive functioning between children awaiting epilepsy and those who were not surgical candidates (Smith et al., 2002), suggesting that they could act as controls for cognitive outcomes of epilepsy surgery. Despite this finding, it may not always be possible to design appropriately controlled studies in this area and many studies may be uncontrolled. Therefore, outcomes of participants who have received epilepsy surgery should be interpreted in the context of existing knowledge about the life outcomes of young people with chronic epilepsy who do not undergo surgery.

1.7 Rationale for undertaking the systematic review of neuropsychological outcomes of temporal lobe epilepsy surgery in childhood.

Given the reform of paediatric epilepsy surgery services, it is important to ensure that clinical outcomes are being adequately measured, reported and synthesised. This is particularly important when research and services may be shaped by commissioning and financial pressures in addition to clinical considerations. Although there are a growing number of studies reporting outcome of paediatric epilepsy surgery (Cross et al., 2013), there are several unanswered questions that emerge from the literature (Section 1.7.1). There are strong claims for efficacy of surgery at an early age (Section 1.7.1.2) so it is necessary to examine the quality of evidence upon which these claims are made. Although there is growing research interest in outcomes broader than seizure frequency, claims for efficacy still focus on this measure of success (Section 1.7.1.3). A greater understanding of the effects of temporal lobe surgery on a child's neuropsychological and psychosocial functioning in addition to seizure frequency is required. An increased understanding of these broader outcomes of paediatric epilepsy surgery of the temporal lobe will have two main implications for clinical psychology and neuropsychology services. Firstly, we may gain an improved psychological understanding of the impact of undergoing temporal lobe surgery for young people and their families. Secondly, reported outcomes may highlight the need for neuropsychology and clinical psychology input. A third possibility may be that heterogeneity of the literature may not reveal enough comparable data to enable meaningful conclusions about outcomes of paediatric epilepsy surgery to be derived. However, this result would be an important finding that may motivate further study on the impact of surgery for epilepsy in childhood. Factors that are predictive of short- and long-term success from paediatric temporal lobe surgery for epilepsy remain unclear, yet these are of great relevance and importance to surgical teams, commissioning groups and children with TLE and their families. It is important to ensure that clinicians and families have the correct information about all surgical outcomes when deciding whether or not to proceed with surgery.

A number of reviews have already been conducted on paediatric epilepsy surgery (Sherman et al., 2011; Spencer & Huh, 2008; Tellez-Zenteno et al., 2005; Tellez-Zenteno et al., 2007; Tellez-Zenteno et al., 2010). However, each has methodological limitations, does not specify findings separately for temporal surgical site and/or fails to encompass the broad scope of the proposed review. A number have reported inadequate search strategies which search too few databases or contain only a narrow range of outcomes (Sherman et al., 2011; Spencer & Huh, 2008; Tellez-Zenteno et al., 2005; Tellez-Zenteno et al., 2007; Tellez-Zenteno et al., 2010). The search strategies fail to encompass sufficient redundancy of terms to enable a sensitive search; they do not appear

extensive enough to capture all descriptors that relevant papers could use to describe each concept. For example, Tellez-Zenteno et al. (2007) only included 'memory' in relation to neurocognitive outcomes, and did not include other similar terms such as 'cognitive', 'attention' or 'neuropsychological', despite specifically reviewing neuropsychological outcomes of surgery. No reviews have been found that review broad neuropsychological outcomes of temporal lobe surgery for epilepsy in childhood. Vaz (2004) systematically reviewed studies reporting verbal memory outcomes after anterior temporal lobectomy, and thus had a much narrower focus than this thesis. Hamiwka et al. (2011) reviewed social outcomes after temporal lobe surgery for epilepsy, but did not review other outcomes of interest, and did not review children and adults separately. Lah (2004) conducted a systematic review of focal cortical resections for epilepsy in children. However, the method and search strategy were not reported, and it focussed only on intellectual and memory outcomes. Schmidt et al. (2004) reviewed seizure outcomes of paediatric and adult temporal lobe surgery but no neuropsychological outcomes. Baldeweg and Skirrow (2015a) reviewed long-term cognitive outcomes of paediatric epilepsy surgery, but this was not restricted to temporal lobe surgery and their search criteria were not sensitive. They searched only one electronic database, PubMed, using the terms "epilepsy surgery in children" and "cognitive outcome" (Baldeweg & Skirrow, 2015a, p.88). This strategy would not be able to detect papers that use synonyms of these words or altered word order. Failing to build an expansive search strategy may lead to relevant papers being excluded from these reviews. In other chapters of the same book, Skirrow and Baldeweg (2015b), McLellan (2015) and Smith and Puka (2015) review the educational/employment, psychiatric, QoL and psychosocial outcomes of paediatric epilepsy surgery respectively. These reviews also failed to report a systematic process for study selection, assessment of study quality or data extraction, and with the exception of McLellan (2015), which did not present results for temporal lobe surgery separately. Therefore, the systematic review contained in this thesis can make a novel contribution.

Conclusions about neurosurgery for epilepsy in childhood are often based on data from multiple types of surgery. It is important to investigate separately the impact of epilepsy surgery in different brain areas, as they may be associated with different outcomes for young people.
It is possible to envisage a systematic review of all outcomes of all types of paediatric epilepsy surgery. However, this would yield a large array of results, which would be difficult to meaningfully synthesise, and beyond the scope of this thesis. This thesis will perform a more focussed review of outcomes in neuropsychological domains after temporal lobe surgery for epilepsy in childhood. Thus this systematic review will be performed in three stages. Firstly, in order to investigate the landscape of the paediatric epilepsy surgery literature as a whole, all studies

reporting outcome of paediatric epilepsy surgery will be identified. Secondly, studies reporting neuropsychological outcomes will be selected from these. Neuropsychological outcomes will be defined in the broadest sense, to include any outcomes that may concern the work of a paediatric neuropsychology service, including cognitive, educational, QoL, emotional, vocational, social outcomes, and satisfaction with surgery outcomes. These are the outcomes that are most relevant given the nature of this thesis, submitted as part of a doctorate in clinical psychology. Thirdly, studies reporting both temporal lobe resections and neuropsychological outcomes will be selected, in order that the review focusses on one surgical site. Temporal lobe resections will be the focus of the review because surgery at this location is of particular relevance for neuropsychologists, due to the effects on memory and emotional processing, and because it is the most common location for focal epilepsy (Wiebe, 2000). Progressively limiting the scope of the search in this way will allow a broad analysis of how many studies do not report neuropsychological outcomes, and how many report outcomes separately for different surgical locations.

1.7.1 Research questions

In considering the evidence from the literature on neuropsychological outcomes following temporal lobe surgery for epilepsy in childhood, this thesis will seek to answer the following questions:

1.7.1.1 What are the long-term neuropsychological outcomes after temporal lobe epilepsy surgery in childhood?

Literature from all disciplines will be reviewed to assess the long-term outcome of children who have undergone temporal lobe surgery for epilepsy in terms of their cognition, education, social life, work, mood, and any other neuropsychological domains that have been reported. Length of follow-up by each study will be recorded to illustrate the outcomes of children in the short-, medium- and long-term post-surgery.

1.7.1.2 Is earlier better?

Earlier surgical intervention is increasingly advocated (Cataltepe & Jallo, 2010). It has been estimated that only a quarter of the necessary surgeries are performed in the UK (Berg et al., 2009). This treatment gap has been highlighted by Cross (2011), who has called for a quicker referral pathway, in which more children are considered for surgery at an earlier stage. Earlier age at surgery has been associated with greater reduction in seizure frequency, better long term outcomes and reduced risk of SUDEP (Loddenkemper et al., 2007).

It is posited that earlier surgery may be beneficial because the greater plasticity of the infant brain is proposed to lower the developmental impact of removal of brain tissue by allowing greater

relocalisation of functions (Cross et al., 2006). However, there is some debate about this, because it has been reported that relocalisation of functions reported after epilepsy surgery can result in lower functioning levels, due to 'crowding' effects (Anderson et al., 2011) and Dennis et al. (2013 p.2761) suggest that 'the young age plasticity privilege has been overstated'.

It is suggested that early surgery reduces exposure to damaging seizures during sensitive periods for development (Cross, 2011). Therefore, harmful effects of seizures on neuropsychological, psychosocial and neurological functioning discussed in Section 1.2 can potentially be ameliorated earlier.

Loddenkemper et al. (2007) found that seizure freedom after surgery was associated with improved developmental trajectory, but this was not replicated by Wyllie et al. (1996) or Duchowny et al. (1998). Indeed, Wyllie et al. (1996) describe a subset of children who suffered reduced cognitive ability after surgery, which was not associated with seizure frequency. These studies all lacked a non-surgical chronic epilepsy control group, so were unable to control for the effect of factors other than surgery that may have affected outcome, such as maturation or the effect of continued seizures over the follow-up period. Furthermore, they each had small sample sizes and pooled data from participants with varied surgical sites, seizure patterns and pathologies, meaning that their results cannot be generalised and applied to determine the efficacy of surgery for a given child.

Another argument for earlier surgery is that young brains are vulnerable to the effects of remaining on AEDs (Cataltepe & Jallo, 2010). Many AEDs are neurotoxic and can induce cell death in the infant brain and cognitive impairment (Kaindl et al., 2006). Therefore, cessation of AEDs may in itself be beneficial for cognitive development and the timing of cessation is under review (Boshuisen et al., 2015).

However, the question is complicated because there are different rates of each type of surgical procedure, and of presenting epilepsies amongst surgical candidates of different age groups, which may also account for differences in outcome (Harvey et al., 2008), as displayed in Table 1.5. Therefore, the methodological quality of studies, and the extent to which they stratify these many variables in their analysis, needs to be factored into conclusions drawn from results. This review will assess whether the literature suggests that earlier surgery is better for temporal lobe epilepsy, and if so, better for which outcomes.

Table 1.5 Surgical procedures and aetiologies of age groups undergoing paediatric epilepsy surgery. Source: Harvey et al. (2008).

	Birth to 4 years	**Over 4 to 8 years**	**Over 8 to 12 years**	**Over 12 to 18 years**
Surgical procedure				
Hemispherectomy	32%	15%	10%	8%
Multilobar	20%	11%	12%	10%
Lobar/focal	35%	47%	49%	60%
Electrode only	4%	2%	6%	3%
Palliative	9%	25%	23%	20%
Aetiology				
Cortical dysplasia (CD)	60%	45%	32%	32%
Tumour	10%	20%	24%	25%
Stroke/atrophy	7%	8%	14%	12%
Hippocampal sclerosis	1%	5%	9%	12%
Gliosis	5%	5%	8%	8%
Tuberous Sclerosis	9%	4%	5%	3%
Hypothalamic	1%	6%	4%	5%
Sturge-Weber	5%	3%	2%	2%
Rasmussen	2%	5%	2%	2%

1.7.1.3 Are studies still focussing solely on seizure outcome and is it important to consider other outcomes?

In considering the basic question "Does paediatric epilepsy surgery work?" it is necessary to define what is meant by "work"; a definition of outcome is required. Claims for success of paediatric epilepsy surgery tend to be based on seizure outcome, i.e. change in severity and frequency of seizures after surgery (Cataltepe & Jallo, 2010; Cross, 2011). Hermann et al. (2002) noted that psychosocial outcome after epilepsy surgery is seldom measured, and when it is, it is poorly operationalised, standardised measures are not employed and studies are methodologically limited. This study will investigate how many paediatric epilepsy surgery studies measure and report broader neuropsychological and psychosocial outcomes.

However, there is a question of whether measurement of non-seizure-related outcomes is necessary, if seizure outcome can be used as a viable proxy for other outcomes of interest. For example, poor seizure control has been associated with the development of mental health problems, behavioural problems and cognitive impairment (Ott et al., 2003), higher family stress levels (Mims, 1997) and poor health related QoL (Ronen et al., 2003). If seizure outcome can reliably predict these other outcomes, it may not be necessary to measure them, given that seizure outcome is more easily measured. However, associations may be found between seizure outcome and neuropsychological

outcomes by virtue of their shared associations with additional unmeasured variables, rather than due to a causal link between seizure outcome and neuropsychological outcome. Developmental and social outcomes may be mediated by a complex interaction of factors operating within the child, family and the wider system, such as parental anxiety, genetic disposition, environmental stressors, time off school, risk of bullying, time taken off work by parents, and financial implications of having a child with an epilepsy (Ellis et al., 2000), as discussed in Section 1.2.5. Indeed, a number of studies suggest that changes in psychosocial and cognitive functioning do not always follow changes in seizure outcome (Duchowny et al., 1998; Hermann et al., 2008; Nicholas & Pianta, 1994; Oostrom et al., 2003; Reynolds & Fletcher-Janzen, 2009; Wyllie et al., 1996), suggesting that this is not a reliable proxy measure for other outcomes of interest.

The potential consequence of only reporting on seizure data may be that other outcomes, such as neuropsychological and psychosocial impact of undergoing surgery is neglected, and that the opportunity to investigate the relationships between these variables is missed. As a major reason for advocating surgery is amelioration of the psychosocial and neurodevelopmental effects of seizures (Cross et al., 2006), it follows that these outcomes themselves should be systematically measured, as surgery may have implications for these aspects of development independently from its effect on seizure frequency. Therefore, part of the remit of this review will be to ascertain the extent to which neuropsychological outcomes of epilepsy are now being reported and to synthesise data presented in the studies of temporal lobe surgeries to determine the efficacy of paediatric temporal lobe epilepsy surgeries for neurocognitive and psychosocial development, whilst assessing their quality.

1.7.1.4 Are limitations in reporting and study design biasing conclusions drawn about the efficacy of epilepsy surgery in children?

Reporting of epilepsy surgery outcomes for children is a complex undertaking as there are many potential confounding variables to consider, including potential differences between surgical candidates in their developmental level, use of AEDs, their duration of seizures, the type of resection performed and the influence of family and social factors. This review will investigate the methodological and reporting quality of studies reporting neuropsychological outcomes of temporal lobe surgery for epilepsy, and assess the risk of bias in their conclusions.

1.8 Research Aims

The aims of the research are as follows:

1. To find, evaluate and summarise all published research on neuropsychological outcomes of paediatric temporal lobe surgery for epilepsy, in order that evidence can better support decision-making for clinicians, the public and commissioners.
2. To investigate outcomes for a child's life that are reported in the literature, beyond the scope of seizure frequency, and highlight the need for these to be systematically measured and reported by developing a follow-up assessment protocol with a list of outcomes which should be routinely assessed.
3. To investigate factors that are predictive of better outcomes as far as is accessible from the literature. (e.g. age at surgery, surgical technique and side of surgery). This will include a consideration of psychosocial determinants of outcome, if these data are reported, e.g. family background, psychosocial status, behavioural difficulties and psychological problems. It is important to consider these factors as behavioural and emotional difficulties reported after surgery may be pre-existing, rather than a result of surgery.
4. To assess design quality and reporting quality of research conducted in the area and present recommendations for quality measurement and improvement.
5. To plan further work to determine the factors predictive of improved outcome after surgery, by outcome measure agreement.

CHAPTER TWO: METHOD

This chapter will describe the development of the method for this study, and outline how each stage of the systematic review was conducted. Section 2.1 introduces the study design chosen and explains the reasons for this choice. Section 2.2 outlines the inclusion and exclusion criteria for the review before Section 2.3 describes the development of the search strategies. Section 2.4 outlines the process of conducting literature searches and Section 2.5 outlines the process of study selection. Section 2.6 and 2.7 describe the methods used for data extraction and methodological appraisal of studies. Finally, Section 2.8 outlines the method of data synthesis used in the review.

2.1 Study design

Systematic reviews are literature reviews that answer research questions by using an exhaustive approach to survey all relevant studies and then critically analysing the findings to produce a synthesis of the literature. According to the Centre for Reviews and Dissemination (CRD), a strength of this design is that systematic reviews use established transparent and systematic methods to identify, select, evaluate and synthesise evidence from the literature to provide a summary of relevant material, thus reducing risk of bias (CRD, 2009). The review was conducted according to guidance from the Cochrane Handbook for systematic reviews of interventions (Higgins & Green, 2011) and the CRD (2009). This design was chosen in order to draw together outcomes from the literature of different disciplines and obtain a more comprehensive and critical view of neuropsychological outcome following temporal lobe surgery for epilepsy in children. Additionally, this method allowed for an appraisal of the current state of measurement and reporting of these outcomes in existing studies. These dual study aims could not be met through other research designs. The systematic review may offer an important contribution by deriving meaningful outcomes from existing published data and build on the current knowledge base rather than continually adding to the number of small, under powered, heterogeneous and often conflicting studies. Furthermore, analysis of methodological quality of published studies and providing a realistic view of standards of reporting in the field may moderate the weight with which their results are interpreted for clinical and commissioning decision making.

2.2 Search strategy: identifying the literature

2.2.1 Inclusion and exclusion criteria

Inclusion and exclusion criteria are required for systematic reviews as they form the operationalisation of the research questions in terms of the patients, interventions and outcomes of interest (Abrami et al., 1998). Setting criteria for including and excluding ensures that a systematic

and defensible approach is taken and that the same standards are applied to inclusion throughout the selection process (Meline, 2006).

Inclusion and exclusion criteria were determined through discussions with supervisors, and where further guidance was required, advice was sought from a member of the paediatric neurosurgical team. To capture a broad overview of the paediatric epilepsy surgery literature, inclusion criteria for the search were papers reporting any outcome from paediatric surgery for epilepsies. These criteria are now outlined in further detail below for the categories of participants, outcomes, interventions, study design, language and publication status (Sections 2.2.1.1-2.2.1.6).

2.2.1.1 Participants

Participants were children and young people aged less than 19 years old with an epilepsy who underwent surgery for an epilepsy. However, many studies report on outcomes of surgeries performed on both adults and children. In these cases, only studies that report disaggregated outcomes for children were included.

2.2.1.2 Outcome

One of the tasks of this study was to define "outcome". There are many potential outcomes of epilepsy surgery and many measures for each outcome domain. In many studies, the primary outcome of interest is seizure frequency, categorised according to Engel's classifications (Engel, 1987), as defined in Table 2.1. In the development of the search strategy, a broader perspective on outcome was taken and initially it was decided that studies that discussed any outcome of paediatric neurosurgery for epilepsy would be included. These included anticipated and non-anticipated, medical and non-medical, and short and long term outcomes, such as those shown in Table 2.1.

Table 2.1 Preliminary outcomes of interest from the literature

Anticipated Outcomes		
Medical Outcomes	Engel's categories	Class I: seizure free for one year Class II: almost seizure free Class III: worthwhile improvement in seizure frequency Class IV: no worthwhile improvement in seizure frequency
	Discontinuation of medication	
	Changes to vision	
Psychosocial Outcomes	Quality of Life	
	Educational attainment	
	Affect	
	Behavioural difficulties	
	Psychiatric diagnoses	
	Social and vocational functioning	
	Family Functioning	
Developmental Outcomes	IQ trajectory	
	Learning	
	Motor skills	
	Cognitive functioning	Memory Executive Functions Processing speed Attention Language Visuo-spatial
Structural Outcomes	Financial cost	
Unanticipated Outcomes		
	Mortality	
	Stroke	
	Infection	
	Complications	
	Increased seizures	

2.2.1.3 Interventions

During the search strategy development phase of the project, a broad inclusion criterion was adopted for interventions. This included any neurosurgical resective or disconnective procedure conducted for the purpose of epilepsy treatment. Procedures that were not resective or disconnective, such as insertion of vagal nerve stimulators, were excluded. Preliminary searches yielded some studies of questionable relevance and this contributed to the process of defining inclusion and exclusion criteria. For example, a number of papers where resective surgeries were performed for the primary purpose of removing risk of haemorrhage, but epilepsy outcomes were reported as an addition (e.g. Lopez-Ojeda et al., 2013). These papers were excluded and the criterion was strengthened to include only interventions with a primary aim of treating an epilepsy. Preliminary searches also found a number of papers that very briefly reported surgical outcomes

incidentally, whilst focussing on some other area of interest (e.g. Ochi et al., 2011; Pokharel et al., 2011). These papers were excluded from the review and it was decided that only studies that focussed, at least in part, on reporting outcome, or that had reporting of outcomes as one of their aims, would be included. These criteria were complicated by the frequent failure of authors to report either the primary aims of the surgical intervention, or the primary aims of the study.

2.2.1.4 Study design

No limits were placed on the study designs that could be included. Randomised and non-randomised controlled trials were both included, although it was not anticipated that many such studies would exist in this area. Most of the published studies in this area are case series emerging from routine clinical work. Therefore, case series and single case studies were included. Methodological quality was assessed as discussed in Section 2.7. However, papers with poor methodological quality were not discarded from the search, as it was deemed important to review all available literature, while weighting evidence according to methodological quality.

2.2.1.5 Publication status

Initially, study types to be reviewed included journal articles, conference proceedings, theses and unpublished works. It was not planned to exclude studies on the basis of publication status, to minimise publication bias.

2.2.1.6 Language

Research published in languages other than English were excluded, due to the financial demands of translation services.

2.2.2 Development of the search strategy

Designing search strategies is a complex undertaking and, given the initially broad scope of the review, the scale of this task proved greater than expected. The search strategies went through a number of refinements, in an iterative process towards the final search. Development of the search strategy had a reciprocal relationship with development of inclusion and exclusion criteria. This process required the sensitivity and specificity of search terms to be balanced. Advice was sought from Ms Elizabeth Neilly (Scholarly Communications and Researcher Skills (SCoReS) Advisor, University of Leeds Library) and members of the paediatric neuroscience team at The Leeds Teaching Hospitals NHS Trust, in order to check the accuracy of included terms.

Search strategies were initially designed in MEDLINE and then translated into search strategies that were appropriate for each of the other databases searched (outlined in Section 2.3). This involved changing subject headings where appropriate, as different databases use different subheadings to

categorise the same topics. As the search strategy advanced, further terms were added. Development of the search strategy required clarification of some conceptual issues and decision-making about balancing sensitivity and specificity of searches, as described in Sections 2.2.2.1 to 2.2.2.8. The final search strategy is displayed in Appendix B.

2.2.2.1 Development of the preliminary search strategy

The preliminary search strategy was developed by grouping synonyms for 'Epilepsy', synonyms for 'surgery', and terms describing initial outcomes of interest, including some of the outcomes displayed in Table 1. Search terms included truncation, to allow variants of words to be captured by the search, and both subheadings and keyword terms. These groups of terms were then linked with the AND operand, such that only papers with topics or keywords matching each of these three concept groups are included in the search results. At this stage a MEDLINE limit was used in order to limit the search to papers that included children. This search yielded 4258 results in MEDLINE, though a brief review of the results showed that many were not relevant to the review as they did not describe paediatric epilepsy surgery. Examples of studies found are case reports about a metabolic disease (e.g. Bais et al., 2003) and leg weakness (e.g. Banerjee & Crain, 2008).

2.2.2.2 Using a child search term instead of age limits

The next major step in developing the search was inclusion of a child search term, so as not to rely on the database's electronic age limit function. The use of limits risks excluding potentially relevant studies, as they rely on accurate classification of papers by database staff. An existing optimised child search strategy, described by Boluyt et al. (2008; Figure 2.1), was used to select child studies so this was combined into the developing search strategy. After inclusion of this child search term, the search provided 4549 results compared to 4438 results when using filters. Therefore, it was used in all subsequent versions of the search. However, some adaptations were made in order to improve sensitivity, for example adding the American spelling 'pediatric', both hyphenated and un-hyphenated versions of terms, and more child descriptor words such as 'young person', 'young people', 'infants school' and 'junior school'. It was also adapted for use in other databases by adaptation of the subject headings.

Infant[MeSH] OR Infant* OR infancy OR Newborn* OR Baby* OR Babies OR Neonat* OR Preterm* OR Prematur* OR Postmatur* OR Child[MeSH] OR Child* OR Schoolchild* OR School age* OR Preschool* OR Kid or kids OR Toddler* OR Adolescent[MeSH] OR Adoles* OR Teen* OR Boy* OR Girl* OR Minors[MeSH] OR Minors* OR Puberty[MeSH] OR Pubert* OR Pubescen* OR Prepubescen* OR Pediatrics[MeSH] OR Paediatric* OR Paediatric* OR Peadiatric* OR Schools[MeSH] OR Nursery school* OR Kindergar* OR Primary school* OR Secondary school* OR Elementary school* OR High school* OR Highschool*

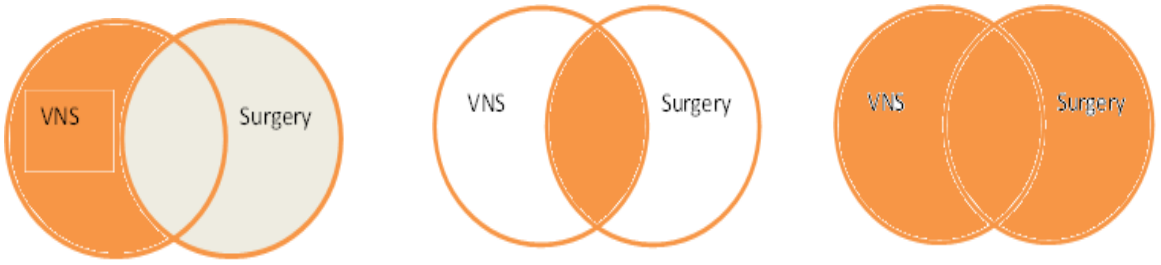
Figure 2.1 Recommended child search strategy, from Boluyt et al., (2008)

2.2.2.3 Use of adjacency terms

Adjacency terms were used for words that commonly occur near each other, but not necessarily in the same order every time. For example, the outcome seizure freedom could be described in some papers as 'seizure freedom' and in other papers as 'freedom from seizures'. MEDLINE allows the distance in words to be specified using an adj*n* term, where n is the number of major words allowed between words of the search term. For the seizure frequency and seizure freedom terms, the relative value of using adj2, adj3 and adj4 searches was investigated. Using adj 2 for these terms in the search strategy returned 4812 results, using adj3 returned 4818 and using adj4 returned 4822. In order to determine whether these extra papers found by increasing the adjacency n were relevant, firstly the whole search strategy was run with those seizure frequency/freedom terms using adj2. Next the whole search using adj4 terms was run. Finally, the NOT operand was used to combine the search results (i.e. (the results of the adj4 search) NOT (the results of the adj2 search)). Inspecting the ten results of this search revealed that none were relevant, so no value was added by increasing the adj term from adj2 to adj4. Therefore, adj2 was chosen as the adjacency n for seizure frequency and seizure freedom.

2.2.2.4 Use of the NOT operand

Use of the NOT operand in the search strategy was considered in order to increase specificity by removing excluded participant groups or interventions, such as VNS. However, using the NOT operand in this way is not recommended by the Cochrane Handbook (Higgins & Green, 2011). This is because it excludes papers that contain both terms searched-for terms and NOT-terms, as indicated in Figure 2.2.



NOT – finds just VNS (not VNS and surgery)

AND – finds studies that include both VNS and surgery

OR– finds studies that include VNS, studies that include surgery, and studies that include both VNS and surgery

Figure 2.2 Boolean logic of search operators

A NOT operand was included in a test version of the search in an attempt to minimise the many irrelevant results pertaining to adult studies, (exp Adult/ or Adult*.mp). This reduced the returns of this search from 3501 to 1245. However, to ensure that this search did not exclude relevant papers, the NOT operand was used to test the papers excluded by use of the term: (Original Search NOT (Original Search NOT (exp Adult/ or Adult*.mp)), which yielded 2256 results. Systematically screening every 20th of these papers revealed relevant papers, such as those covering long-term follow up from childhood epilepsy surgery into adulthood. Therefore, it was decided that excluding adults with the NOT operand was not possible, as the long-term follow-up papers are of considerable interest to the review.

2.2.2.5 Balancing sensitivity and specificity

As outcomes were often poorly specified in titles and keywords of papers, they were difficult to search for directly, and some advise not to include outcome terms in the search strategy (Higgins & Green, 2008). In line with this advice, terms to describe outcomes (such as emotion* and cogniti*; see Appendix B.1 for complete list) were at one stage removed from the search for a more inclusive approach. This added 2006 results to the MEDLINE search, which then totalled 7057 results. After transcribing the search terms into four other databases (EMBASE, PsycINFO, CINAHL and Global Health) and de-duplicating results in Endnote, a total of more than 13000 results were obtained. On initial brief screening, the majority did not meet inclusion criteria as they did not report paediatric epilepsy surgery outcomes. Therefore, there was a need to refine the search to capture only relevant papers. Two possible adaptations to the search strategy were considered, as outlined below:

1. Instead of searching for 'surgery' then 'epilepsy' concepts separately and then combining with an AND term, searching for the concept ‘epilepsy surgery’ using subheadings, "Epilepsy/su", adjacency terms, and specific surgeries e.g. hemispherectomy.
2. Including outcomes in the search strategy.

Using adaptations 1 and 2 above reduced studies returned by the MEDLINE search from 7057 to 3504 papers in MEDLINE. Using just adaptation 2 reduced returns from 7057 to 5728. In order to investigate the value added by maintaining surgery and epilepsy as separate concepts in the search, the NOT operand, explained above in Section 2.2.2.4, was used to test the different results of (search with adaptations 1 and 2) compared to (search with adaptation 2). An approach of screening every 20th result was taken to screen the 2224 results of this test search, in order to maximise time-efficiency but maintain a standardised approach. Of the papers screened, none were marked as relevant, suggesting that this could be a feasible approach for limiting the search returns. However, in discussion with project supervisors it was decided that it was preferable to conserve “epilepsy” and “surgery” as two separate concepts in the search. Therefore, it was decided to use adaptation 2 instead and include outcomes in the search strategy. After running this search in all databases & de-duplicating in EndNote Version X7, there were 13464 studies. As this number of studies would be unfeasible to screen, there was a need to apply further limits to the search.

2.2.2.6 Application of limits to the search

A date limit was applied to the database searches to find publications from 1995 to the present day. This cut-off was chosen to allow a twenty year range of publications to be included, and because 1995 also represents the time when magnetic resonance imaging became widely used in pre-surgical evaluation for epilepsy surgery (Fried, 1995). Applying this limit reduced the results of the MEDLINE search from 6092 studies to 5008 studies.

A number of other database limits were trialled. For example, pre-defined MEDLINE limits such as “prognosis”, “therapy” or “economics” was considered. Application of these limit functions to the search reduced the number of results considerably. However, these database-designed limits include study design criteria (such as limiting to RCTs) within their operating terms (BMA Library - MEDLINE Plus, 2012). Therefore, these limits were not used in the search strategy.

2.2.2.7 Refinement by exclusion of publication types

Perusal of the publications yielded by the search showed a number of editorial and comments sections had been found. Therefore, the NOT operand was used to exclude certain types of articles: letters, editorials, comments, historical articles and reviews. This reduced the number of studies returned from the MEDLINE search from 5008 to 4376.

2.2.2.8 Search Fields

At the beginning of search strategy development, the fields searched by the electronic databases were title, abstract and keyword. However, when further refinement of the search was required, the effect of altering search fields was investigated in MEDLINE with the following results:

- Searching title, abstract and keyword produced 6143 results
- Searching title only produced 2376 results
- Searching keyword only produced 2242 results
- Searching keyword and title produced 2693 results
- Searching abstract and title produced 4109 results

Although searching all three fields would clearly maximise sensitivity, a balance was required in order for screening of studies from all database searches to be feasible. Guidance suggests that systematic reviews should search titles and abstracts (EPPI-centre methods for conducting systematic reviews, 2010) and many reviews do only use title and abstract as their search fields (e.g. Bramer, Giustini, Kramer and Anderson, 2013).

2.3 Electronic searches

The search strategy was developed for seven databases (MEDLINE, HMIC, CINAHL, PsycINFO, EMBASE, Web of Science and Global Health), in order to capture the greatest number of relevant papers possible. Appendix B shows the search strategies used for each database. These databases were searched separately using specially adjusted search terms. Auto-alerts were set up to allow inclusion of papers published for 12 months after the initial search, during the course of the review.

2.4 Study Selection

The process of study selection was conducted according to guidance from the Preferred Reporting Items for Systematic Reviews (PRISMA) Statement (Liberati et al., 2009; Appendix C) and the CRD Handbook (CRD, 2009). Papers retrieved from the database searches were de-duplicated within EndNote X7. Then titles and abstracts of search results were screened to determine inclusion in the review according to the inclusion and exclusion criteria (studies were included if they reported outcomes of paediatric neurosurgery for epilepsy as their primary aim, and were written in English). However, this process was made significantly more difficult by poor reporting quality. Titles and abstracts frequently did not contain the necessary information and inspection of the full paper was required. In particular, there was poor specification of factors such as the age of participants and purpose of surgery in the abstracts. The purpose of the surgery was frequently not clearly specified, especially in studies of surgeries for tumours and arteriovenous malformations, in which surgery could have been for malignancy or haemorrhage rather than seizures (e.g. Young &

Johnston, 2004; Zeiler et al., 2011). Similarly, it was often necessary to inspect the full paper of studies with mixed age samples to find out if surgical outcomes for children and adults were presented separately (e.g. Davies et al., 2005).

Where a decision about inclusion of studies was in doubt, advice was sought from the supervisory team. It was decided that if doubt remained and the study authors had supplied insufficient information for the supervisory group to decide then the paper should be excluded. Reasons for exclusion were recorded and are available on request.

Where studies had the same author, title and year (for example where one was a conference abstract and one a published study), the published journal article was retained and the other excluded.

Where publications clearly described the same study (with the same sample of participants and the same results), the most recent publication was retained.

As discussed in Chapter One, following the first phase of study selection from the results of electronic database searches, inclusion and exclusion criteria were revised in order to narrow the focus of the review. These amendments led to another two phases of study selection. First the new criterion of studies reporting neuropsychological outcomes was applied to those studies that had met the original inclusion criteria then, as a second amendment, the criterion of temporal lobe resection was applied to the studies that had met the neuropsychological inclusion criterion. These amendments were made in order to enable a meaningful and focussed synthesis that would be useful to neuropsychologists and target the epileptogenic region most frequently operated on for focal epilepsies. The entire study selection process is summarised in Figure 2.3.

2.5 Hand searches

After the study selection phase from the electronic searches had been completed, reference lists of all finally included papers were hand searched. Key journals were hand searched for recently published articles meeting inclusion criteria. To identify which journals should be hand searched, the most commonly occurring journals within the included studies were identified. This led to hand-searching of the following journals: Child's Nervous System (Volume 32, issues 1-4), Pediatric Neurology (Volumes 54-57), Epilepsia (Volume 57, issues 1-4), Epilepsy and Behaviour (Volumes 54-58), and the Journal of Neurosurgery: Pediatrics (Volume 16, Issues 1-4). Grey literature (including conference proceedings, theses and records of ongoing research) was not included in the final results, due to the surprisingly large volume of published studies. This introduces a risk of publication bias affecting the results of the review. EndNote X7 was used to manage references and identify and de-duplicate results.

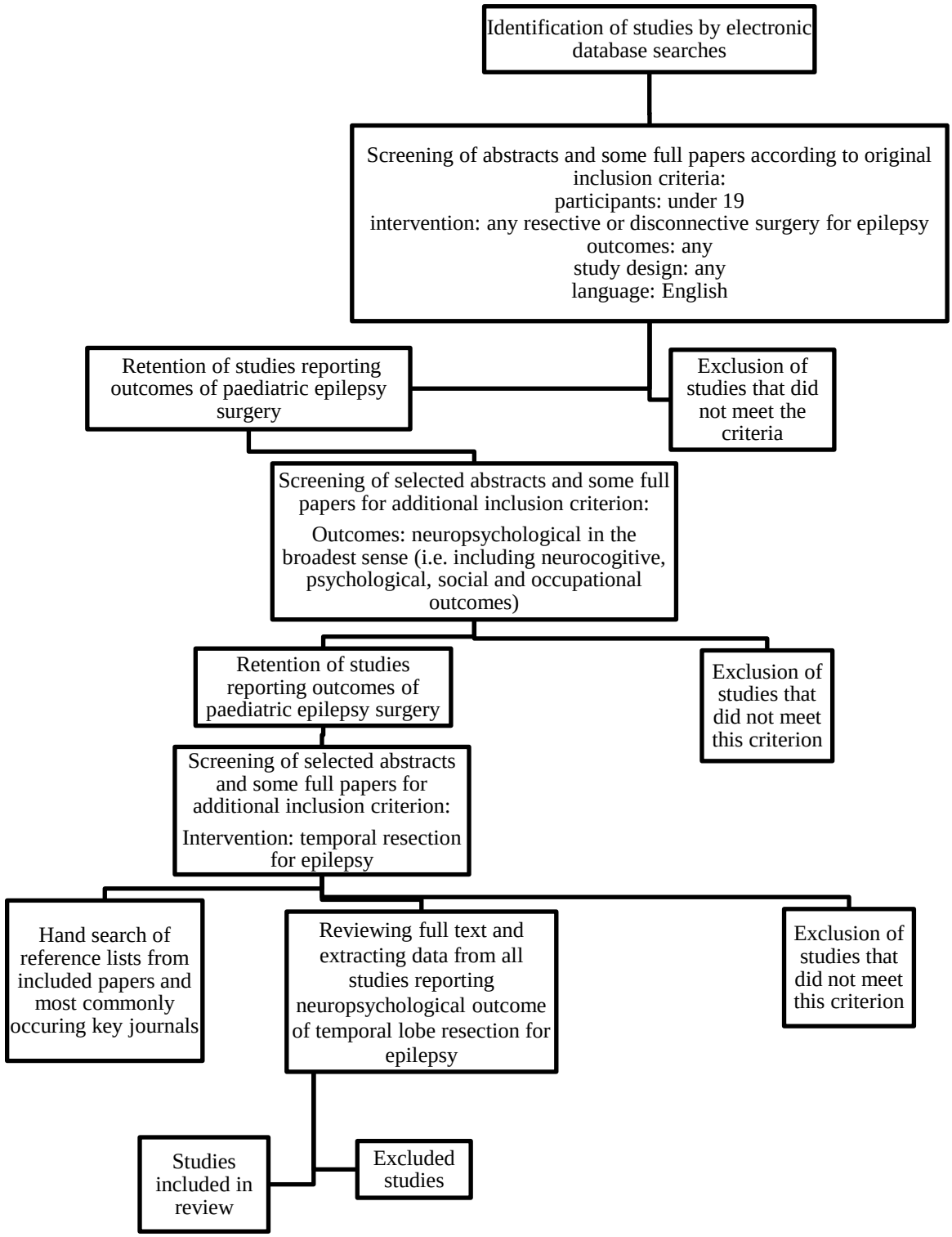


Figure 2.3 The Process of Study Selection

2.6 Data extraction

Once the final study selection phase was completed, all included studies that appeared to meet the final inclusion criteria were retrieved in full for data extraction. As the data extraction phase progressed, further inspection of the papers resulted in further exclusions.

A number of formats of data extraction form were piloted, based on guidance from the Cochrane Handbook (Higgins & Green, 2011). However, in discussion with project supervisors, these forms were decided to be too exhaustive to allow efficient extraction of the most relevant data from the large number of included studies. RevMan software (Cochrane Collaboration, 2014) was considered for data extraction. However, after trialling its functionality, it was too restrictive to allow sufficient adaptation to fit the format of the present review. The functions are designed for studies with control groups, and using this software would not enable data to be extracted in a meaningful way to allow narrative synthesis.

Finally, a spreadsheet was designed in Microsoft Excel to allow for data to be consistently extracted from all included studies in a way that presented the data in a simple way that aided synthesis. This spreadsheet was organised with fields to extract study characteristics (surgical centre, sample size, drop-out rate, age at surgery, type of surgery, side of surgery, epilepsy syndrome, aetiology of epilepsy, sex, comorbidities, length of follow up and outcomes measured), outcome data for each outcome and conclusions. Outcome categories were: QoL, cognitive development, behaviour, language, memory, psychiatric disorders, mood, educational functioning, vocational functioning, social functioning, disability status and satisfaction. These categories were developed based on the outcomes presented in the papers. For each outcome category there were fields for each study for outcome measures used, summaries of individual outcome data, group level outcome data, and results of predictors of that outcome.

2.7 Assessment of methodological quality

A systematic review must assess the methodological quality of studies included, in order that the evidence presented can be understood in the context of each study's risk of bias in its results or conclusions and the applicability of its findings (Higgins & Green, 2011). The CRD advises that, when evaluating studies, attention should be paid to risk of bias, appropriateness of the design for the research aims, quality of reporting, quality of the intervention, statistical methods used, choice of outcome measures, validity of conclusions and generalizability of results (CRD, 2009).

Most systematic reviews use quality assessment tools designed for evaluating controlled trials. Indeed, Cochrane reviews generally only use RCTs, which are considered the gold standard for evaluating the effectiveness of an intervention, as the design minimises the risk of bias (CRD,

2009). However, the majority of studies in this field are case series designs. Case series are observations of participants with no control group. This design is problematic as it does not allow the researcher to control for other factors that could account for outcome. The evidence-based medicine (EBM) movement was started with the aim of encouraging practitioners to base their clinical decision making on empirical evidence, whilst still using their clinical judgement based on the individual case (Sackett et al., 1996). This approach relies on using the strongest possible forms of evidence to aid decision making, from well-designed research. Therefore, EBM champions the use of evidence provided by systematic reviews and RCTs, over forms of evidence more prone to bias, such as case series. However, there have recently been criticisms of the EBM approach, including that the adoption of a priori assumptions can cause the benefits of observational studies to be ignored and there is a growing movement towards medicine-based evidence (MBE; Concato, 2013). MBE emphasises clinical relevance, such as "who and where were the patients, what and why were the treatments, and when and how were the outcomes assessed" (Concato, 2012, p.1642), whilst appraising validity and generalizability. Although generally, single case studies and case reports are considered low in the hierarchy of evidence, some well-designed case study designs, such as n-1 trials, are now recognised by the Oxford Centre for EBM (OCEBM) as some of the highest levels of evidence for certain research questions (OCEBM levels of evidence working group, 2011). Nevertheless, it was expected that most case reports in this area would be uncontrolled single case studies with low methodological quality. When considering evidence provided by studies in the results and discussion chapters, their contribution was considered with reference to the study design's place in the hierarchy of evidence, displayed in Figure 2.4. However, the appropriateness of the design for the research aims was considered on an individual basis for each paper. For example, single case reports are helpful for reporting rare side effects or unanticipated outcomes of interventions (OCEBM levels of evidence working group, 2011).

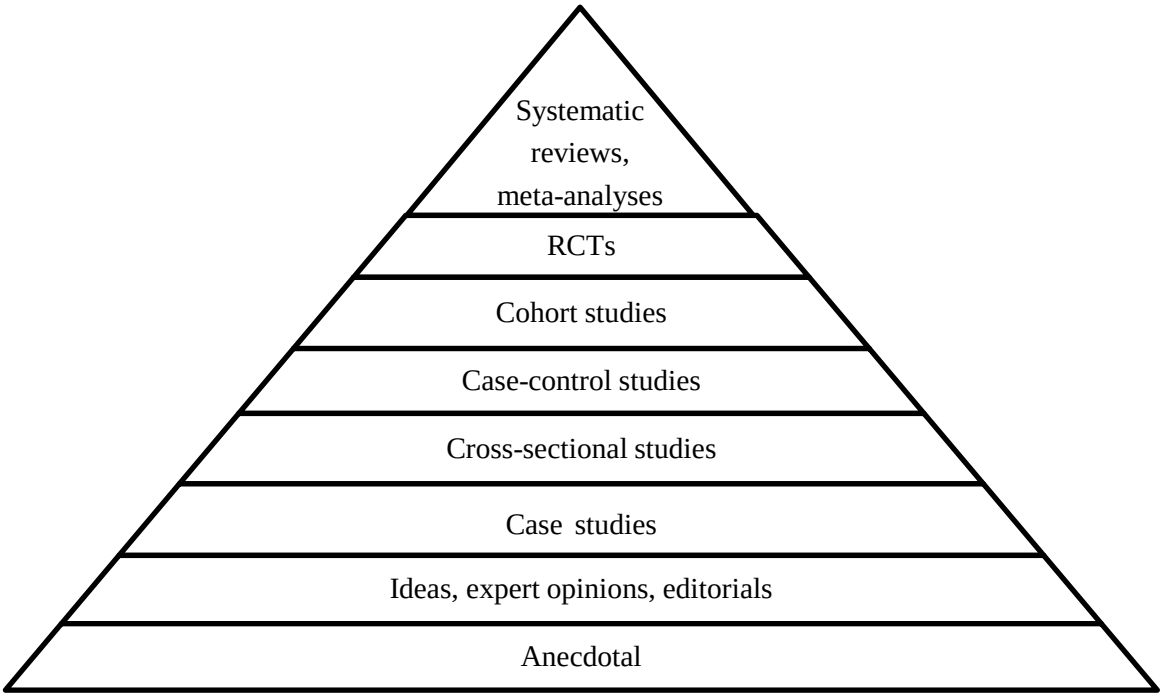


Figure 2.4 Hierarchy of evidence, after Mhaskar et al., (2009)

Guidance suggests that it may not be helpful to include biased studies even when there is no better evidence (Higgins & Green, 2008). The Cochrane Handbook's chapter on inclusion of non-randomised studies suggests two alternative approaches; either to only include reliable studies or to include the best available evidence (Higgins & Green, 2008). However, it acknowledges that study designs are complex and not easily assimilated into existing hierarchies (Higgins & Green, 2008). Given the wide range of the literature, heterogeneity of study samples and outcomes, and the lack of RCTs retrieved, it was deemed important to include all study designs in order to include all relevant data in the review. This decision is further justified as these studies are already used to inform clinical decision making, and thus it is important to gain a broad perspective of the existing literature. Indeed, Pagliaro et al. (2010) suggest that the Cochrane reviews may emphasise methodology over clinical relevance which lessens their utility for clinical decision making.

Therefore, a methodological quality assessment tool was developed, that was suitable for all research designs. A number of extant quality measures for observational studies exist (Downs & Black, 1998; Slim et al., 2003; Sterne et al., 2014; Wells et al., 2000) but these were too lengthy to complete for each paper, and generally contained items that were considered to be inapplicable for uncontrolled studies, such as allocation concealment. Slim and colleagues' (2003) tool for use with surgical studies, including case series designs was the most appropriate. The quality criteria specified include: a clearly stated aim, consecutive inclusion of patients, adequate reporting of raw

data, follow-up duration appropriate for the outcome measured, validated outcome measures, and loss to follow-up less than 5% (Slim et al., 2003). However, this tool was only appropriate for uncontrolled studies. After piloting various combinations of these scales, it was found that including all potentially relevant items for all study designs yielded a scale that was too exhaustive to allow for efficient appraisal of methodological quality of included studies. The Study Quality Guide produced by the Cochrane Consumers and Communication Review Group (2013) acknowledges that quality assessment methods will vary according to the literature being assessed. In the absence of specific guidance around the assessment and reporting of quality for uncontrolled case series, the decision was taken to rate each study's risk of bias according to main categories of bias recommended by Cochrane (2013): sample bias (representativeness of cohort, selection bias), attrition bias (loss to follow-up), confounding (or performance bias e.g. comorbidities, concurrent treatments, poorly defined predictive factors), measurement bias (detection bias, validity of outcome measurement) and validity of reporting/ claims made, as well as recording notable biases or threats to validity. This allowed a large number of papers to be efficiently assessed for methodological quality in a consistent and structured manner.

Only one researcher undertook methodological quality appraisal and data extraction. Guidance from the CRD (2009) recommends that more than one researcher appraises methodological quality, to increase reliability of the assessment. However, the Cochrane handbook suggests that it is appropriate for a single researcher to appraise quality, to avoid disagreements over decisions (Higgins & Green, 2008). There was no blinding for author and journal details, however the researcher had no conflicts of interest so this was unlikely to bias the review.

2.8 Data Synthesis

The wide range of methodological variability, in terms of design and quality, included in the review meant that extracted data could not be pooled statistically or investigated using meta-analysis due to the risk of introducing bias and producing spurious results (CRD, 2009). Furthermore, given the wide range of resection types and participant characteristics included in each study, it was inappropriate to pool the data, as this could provide misleading results. Therefore, a narrative approach was used to synthesise data. An advantage of a narrative synthesis is the possibility of offering an analysis of relationships between outcomes of interest (CRD, 2009). Narrative synthesis was conducted in accordance with the guidance produced by Economic and Social Research Council (ESRC; Popay et al., 2006).

CHAPTER THREE: RESULTS

This chapter describes the findings of the search process as a whole, before focussing in to review the studies that reported neuropsychological outcomes after temporal lobe surgery for epilepsies in children. Firstly, an overview of the search results will be presented in Section 3.1. Secondly, Section 3.2 systematically reviews the neuropsychological outcomes of temporal lobe resections for intractable epilepsy in children, considering each outcome reported in turn. Section 3.3 discusses the methodological quality of included studies. Based on this appraisal, Section 3.4 selects the studies that present the highest quality evidence and synthesises the findings about neuropsychological outcomes following temporal resection for epilepsy. Throughout the chapter, percentages are presented alongside numerical values, in order to provide a common frame of reference between studies. However, it should be noted that for small values percentages have the potential to overstate the effect.

3.1 Overview of search results

The final search strategies were performed in all databases on 2nd April 2015 and they yielded 4109 papers in MEDLINE, 6080 in Embase, 639 in PsycINFO, 86 in Global Health and 3798 in Web of Science and 248 in CINAHL. Only two results were returned from the HMIC and neither met inclusion criteria for the review. After a lengthy de-duplication process, 8189 publications remained. Auto-alerts retrieved all papers from these database searches for a period of one year. However, no further studies obtained after the original search date met the final criteria for inclusion in qualitative synthesis. The results from each phase of study selection are displayed in a modified PRISMA flow chart in Figure 3.1. Study selection was performed in three stages: first, all studies reporting outcome of paediatric epilepsy surgery were identified, second, studies reporting neuropsychological outcomes were selected from these and third, studies including temporal lobe resections were selected from these.

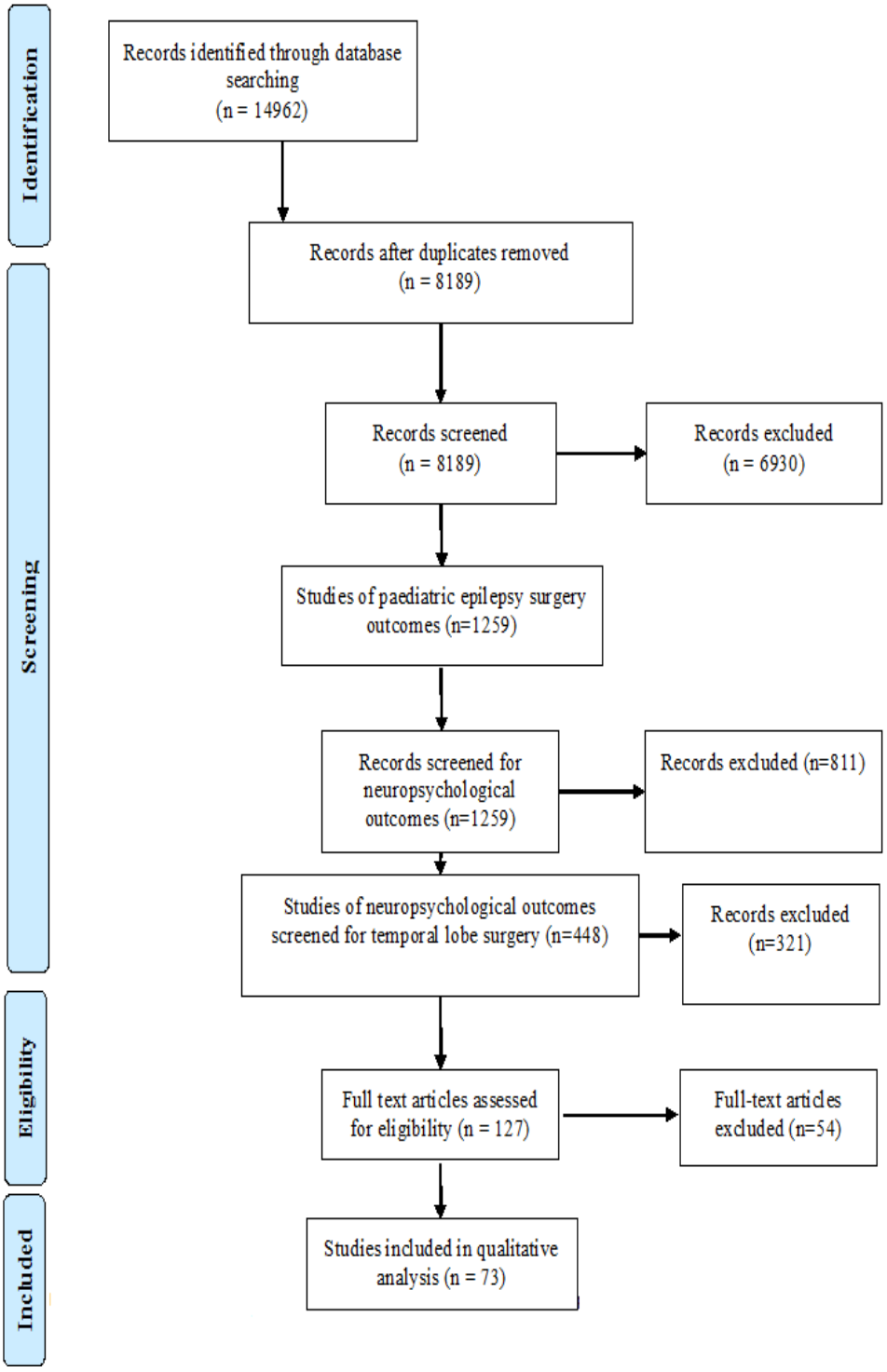


Figure 3.1 PRISMA diagram of study selection process

The first phase of screening led to 1259 studies meeting initial inclusion criteria. The most common locations of surgery that could be identified from the abstracts are displayed in Figure 3.2. Many of these papers included results from different resection locations and mixed age groups of adults and children and combined the results of these groups so that it was not possible to discern only the outcomes of one surgical location or for children.

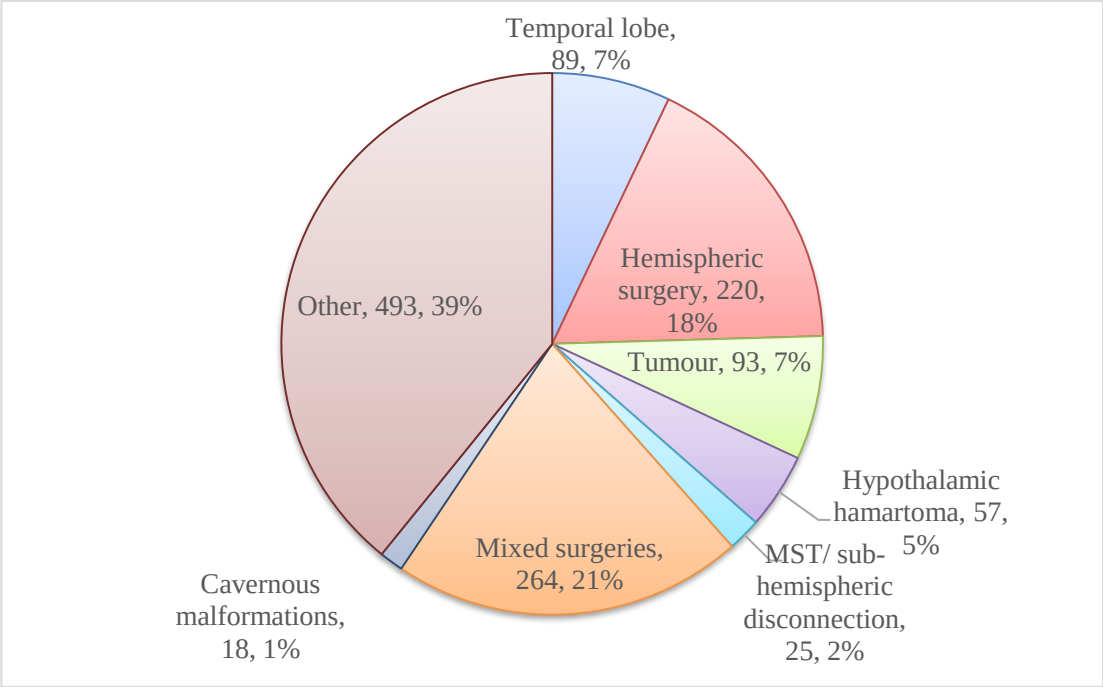


Figure 3.2 Most common types of epilepsy surgery from studies reporting outcomes of paediatric epilepsy surgery

Inspection of the abstracts of these studies showed that 811 (64%) papers did not report any psychological, neurocognitive or social outcomes, with most reporting only seizure outcome. The number of papers that did report at least one neuropsychological outcome was 448 (35%). These 448 papers included many different types and locations of surgery. The most common were studies reporting surgeries of mixed locations, hemispheric surgery and temporal surgeries. The relative proportions of each surgery type in papers reporting neuropsychological outcomes are displayed in Figure 3.3.

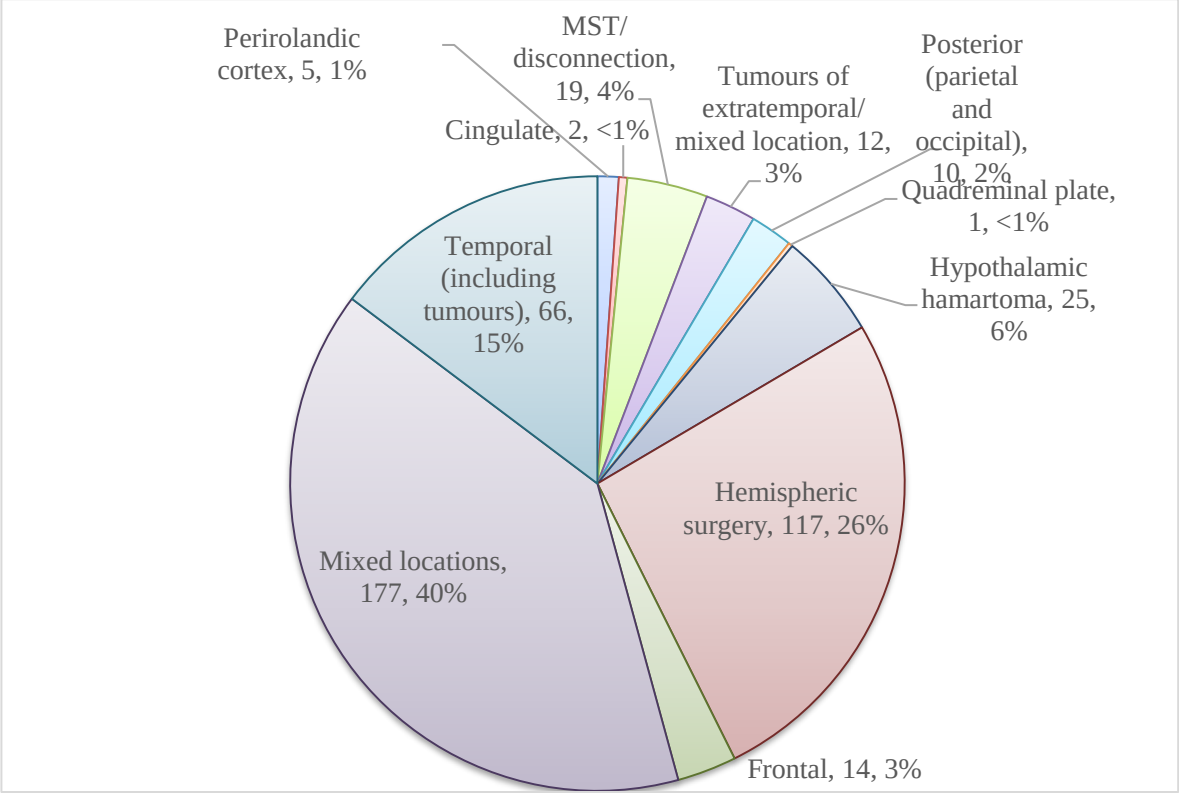


Figure 3.3 Type/Location of surgeries from papers reporting neuropsychological outcomes of epilepsy surgery

As discussed in Chapter One, temporal lobe resections were chosen as the focus of the review because surgery at this location is of particular relevance for neuropsychologists, due to the effects on memory and emotional processing. A further screening of the 448 included abstracts resulted in 127 (28.3%) papers meeting this new criterion. This included both studies that exclusively reported temporal lobe surgery and studies that reported a mix of surgeries and provided separable outcomes for temporal lobe resection cases. Following final screening and inspection of the full text of these studies, a final 73 studies met inclusion criteria and were included in the review.

3.2 Characteristics of studies included in the final review of neuropsychological outcomes following temporal lobe resection for epilepsy

The 73 included studies presented the neuropsychological outcomes of 1379 children following temporal lobe surgery for epilepsy. Sample sizes within each study varied from case studies with a sample of 1 to the largest study that had a sample size of 89.

3.2.1 Study designs and settings

Included studies had a number of designs. Forty five (62%) were uncontrolled retrospective case series and twenty (27%) studies presented case reports. These study designs are ranked as Level 4

according to the OCEBM Levels of Evidence Working Group (2011) as they are at risk of bias, as discussed above in Section 2.7. Three (4%) studies presented mixed longitudinal data from a case series and cross-sectional data from comparison with a chronic epilepsy control group (Meekes et al., 2013; Skirrow et al., 2011; Skirrow et al., 2015). Two (3%) studies presented longitudinal case series data with cross-sectional data from a comparison group of healthy young people (Lendt et al.,.1999; Leunen et al., 2009). One (1%) study was a single case study with a healthy control group (Grosmaitre et al., 2014) and one (1%) was a single case study with the child's twin as a control participant (Cronel-Ohayson et al., 2006). These studies, despite attempting to use a control group to minimise the influence of bias, would also be ranked as Level 4 by the Oxford CEBM, due to a number of methodological problems, such as groups not being fully matched on participant characteristics, there being no randomisation or blinding, retrospective study design or use of historical controls. One (1%) study that may have been ranked at Level 3 by OCEBM was a prospective cohort study with a chronic epilepsy control group (Micallef et al., 2010). These designs may have been influenced by the aims of each study; some aimed only to report unusual case studies (e.g. Adami et al., 2006; Romanelli et al., 2001; Wouters et al., 2006), some aimed to explore the neuropsychological basis of skills by comparing temporal lobe operated participants with other participants (e.g. Grosmaitre et al 2014), and others sought to report the impact of undergoing temporal lobe epilepsy surgery for their outcomes of interest (e.g. Lewis et al 1996; Meekes et al, 2013; Micallef et al 2010; Skirrow et al 2011; Westerveld et al, 2000).

Length of follow up for participants within the included studies ranged from 6 months to 27 years. Across the 60 studies that reported mean follow-up duration, the mean duration overall was 3.21 years. Follow-up duration varied between individual participants in the majority of studies. The included studies originated mostly from developed countries, with the majority of studies reporting outcomes from surgical centres in North America and Europe, as displayed in Table 3.1.

Table 3.1 Location of Surgical Centres in Included Studies

Location of Surgical centre	**Number of studies**
USA	22
Canada	10
UK	7
Germany	4
Netherlands	3
Switzerland	3
Korea	3
France	3
Austria	2
Australia and New Zealand	2
Lebanon, Belgium, Turkey, Italy, Sweden, Finland, Japan, Brazil, Spain, Israel, China and Poland	1 each

3.2.2 Participant characteristics

Participants ranged in age from 3 months to 18 years and the mean age at surgery was 11.9 years. The mean age of seizure onset was 4.7 years (range 0-17) and 51% of participants were male. All were suffering from medically intractable temporal lobe epilepsy.

Seizure type was not consistently reported among studies, but the seizure types reported were complex partial seizures, partial seizures, partial seizures with secondary generalisation, infantile spasms, generalised tonic-clonic seizures, absences/ unresponsiveness, episodic aggressive behaviour, focal seizures associated with migraine and aura. Many participants had multiple seizure types, and most studies reported outcomes for patients with a variety of seizure presentations. The majority of studies reported the epilepsy-associated pathology. Figure 3.4 displays the total number of children with the most commonly reported pathologies from included studies.

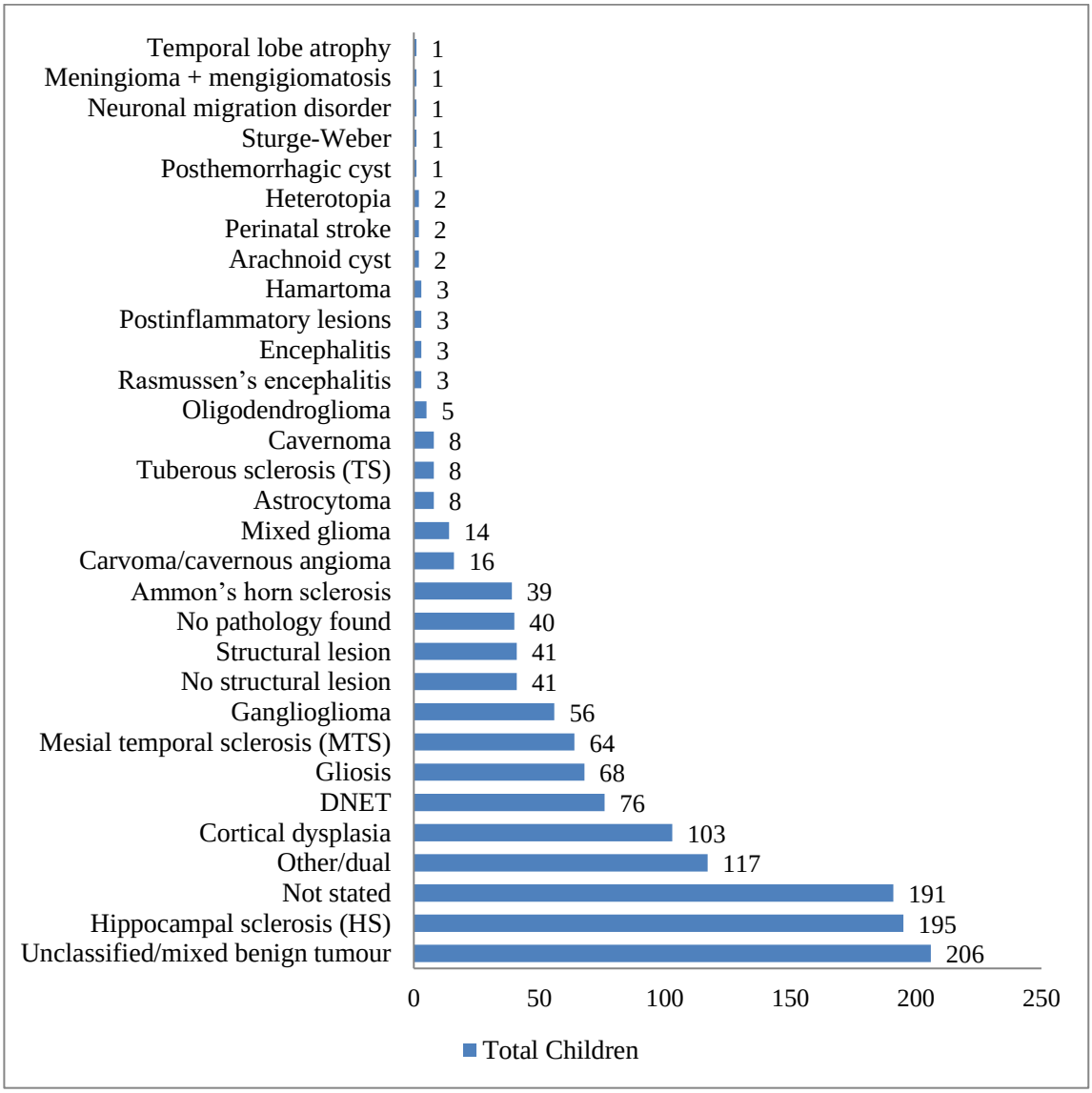


Figure 3.4 Surgically confirmed pathology for each participant

It should be noted that the underlying pathology has implications for pre-surgical neuropsychological functioning and developmental trajectory, and thus may influence neuropsychological performance at both pre- and post-surgical assessments and neuropsychological outcome of surgery (Arzimanoglou et al., 2005, p.252). Most studies did not note whether comorbid conditions were present. Within the 30 that did, comorbidities included: globally delayed development, learning disability, microcephaly, hemianopia, hemiparesis, hyperactivity, reading disorders, behavioural problems, autism spectrum conditions, hydrocephalus, memory problems, anxiety disorder, family difficulties, poor educational attainment, sleep disturbance, irritability, a diagnosis of schizophrenia, precocious puberty, hypertension, fragile X syndrome, aphasia and auditory verbal agnosia. Two studies reported that a participant had experienced previous sexual abuse as a child.

3.2.3 Interventions

Type of surgery was more fully specified in some papers than others. All included resection of the temporal lobe for the purpose of epilepsy control. The reported surgeries for all participants across included studies are presented in Figure 3.5.

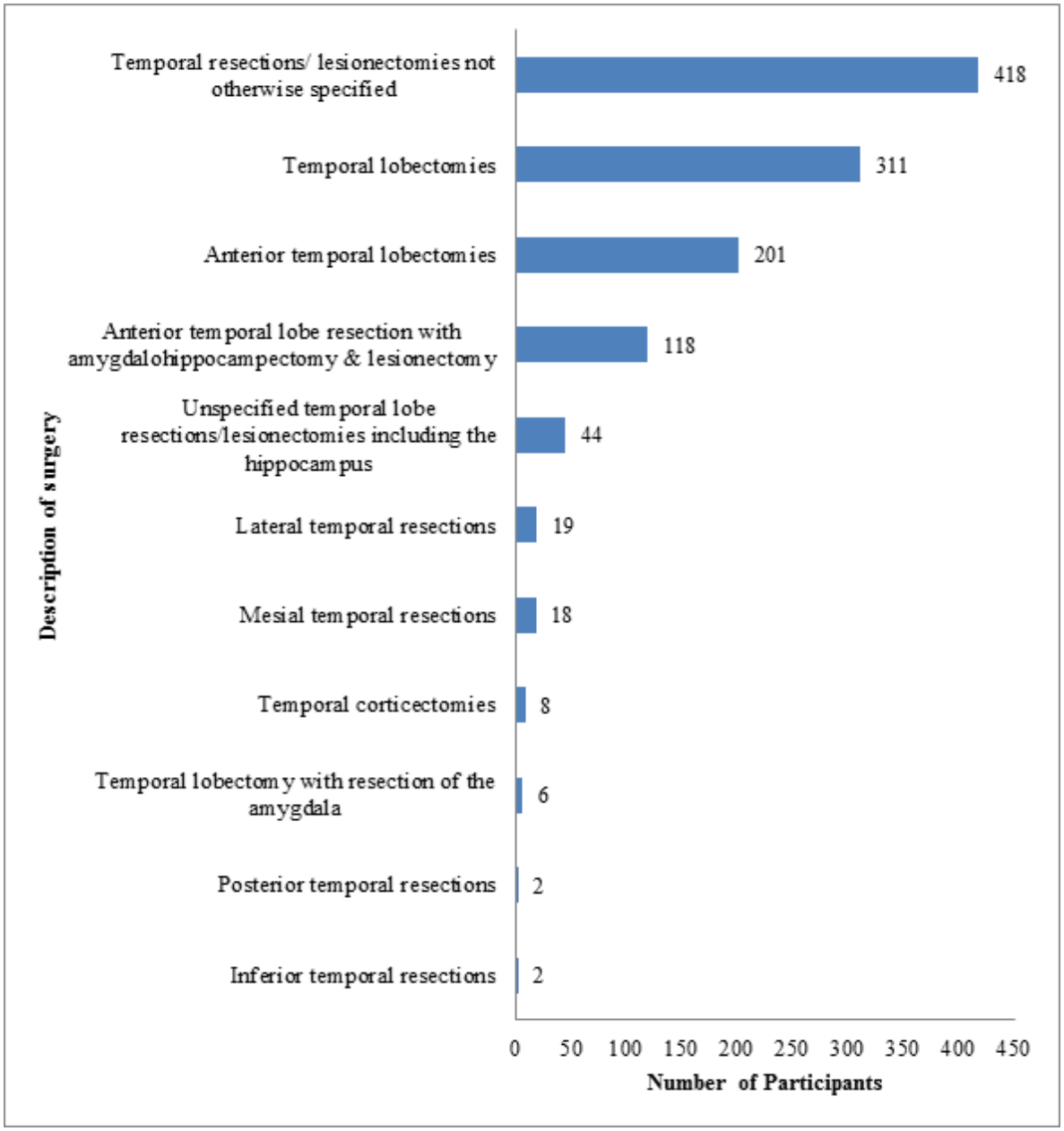


Figure 3.5 Type of temporal lobe surgery described for each participant

It should be noted that the implications of including structures of the amygdala and hippocampus may be great in terms of the neuropsychological outcomes, due to the role of these structures in mediating fear response (LeDoux, 2003; Yates, 2015) and memory (Bannerman et al., 2008). Therefore, failure to report whether or not these structures are included in resections is problematic, as is combining the results of many different resection types, as reported outcomes of such papers do not provide information that can aid clinical decisions about a specific surgery. Across the studies, 35 (48%) children underwent left hemisphere resections, 33 (45%) underwent right sided resections and for 5 (7%) the laterality was not reported. Authors reported conducting a range of

pre-surgical assessments for localisation of seizure focus and determination of eloquent cortex before surgery, including: EEG/video EEG in 66 (90%) studies, MRI in 54 (74%) studies, PET in 23 (32%) studies, SPECT in 17 (23%) studies, intracranial EEG in 11 (15%), Wada in 11 (15%) studies, CT in 10 (14%) studies, fMRI in 7 (10%) studies, and MEG and TMS, reported by one (1%) study each. Pre-surgical imaging was not reported in 16 (22%) studies.

3.2.4 Outcomes

Sixty five (89%) studies reported seizure outcome and eight (11%) studies did not. Of the 65 (89%) studies that reported seizure outcome, most used Engel's criteria (described in Table 2.1) and the others described seizure outcome in a way that allowed conversion into Engel's classifications. Unfortunately, some studies (e.g. Van Oijen et al., 2006) grouped Engel's Class III and IV outcomes, potentially losing important information about whether or not seizure frequency improved in those who continued to have persistent seizures after surgery. These 65 studies reported seizure outcome for a total of 1184 participants, of whom 878 (74%) achieved Engel's Class I outcome (seizure free for at least one year), 64 (5.4%) achieved Class II outcome (almost seizure free) and 242 (20.4%) achieved Class III (worthwhile improvement in seizure frequency) or Class IV outcome (no worthwhile improvement). As the focus of this thesis is on neuropsychological outcomes, the remainder of this section will focus on the reported neuropsychological outcomes of temporal lobe surgery for epilepsy.

Studies reported a range of neuropsychological outcomes. The most commonly reported was cognitive development as measured by IQ or developmental quotient, reported by 38 (52%) studies. However, other broader outcomes were also considered by many papers. Figure 3.6 displays how many papers reported each outcome.

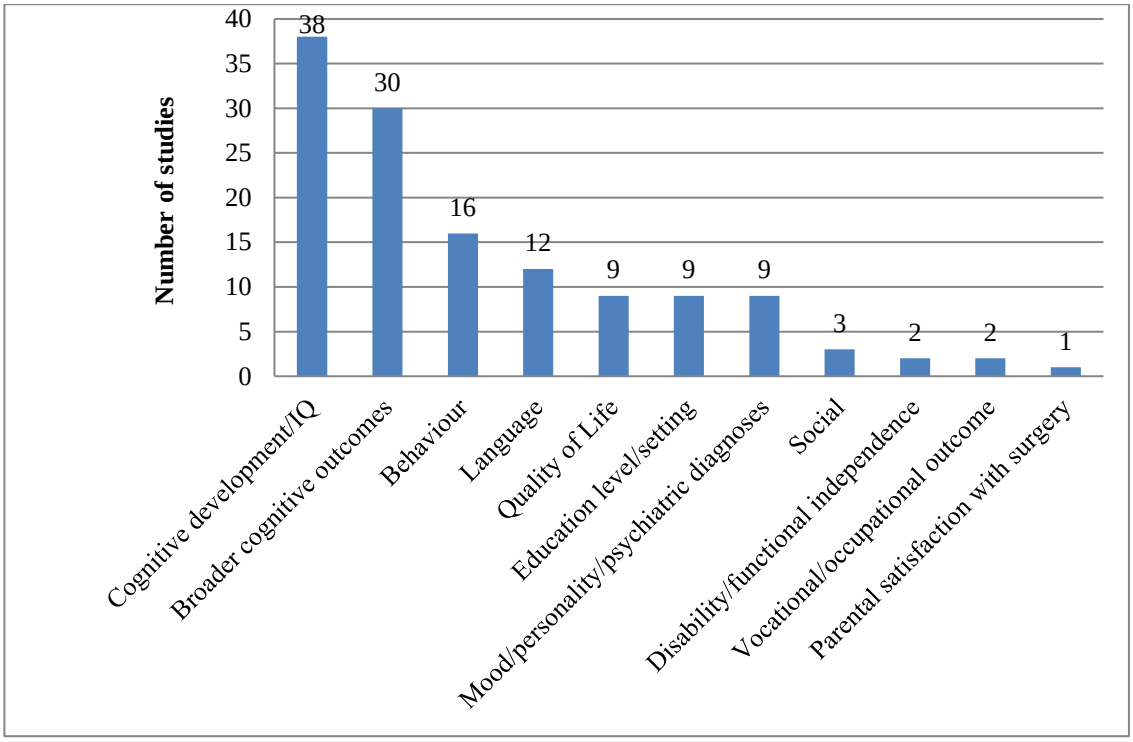


Figure 3.6 Neuropsychological outcomes reported by included studies

The assessment methods and outcome measures frequently differed between studies, making assimilation of the data across studies difficult, as studies may not be measuring exactly the same abilities with their assessments. This complexity is particularly evident in studies reporting cognitive outcomes, as neurocognitive domains are intrinsically interconnected so assessments are unable to assess purely one domain. As assessments place demands on a number of skills simultaneously, it is impossible to obtain a pure measure of the outcomes in each cognitive domain. As such a change in scores in one domain, such as memory, may be indicative of a change in skills in another domain, such as attention, which is required for memory tasks. Similarly, IQ tests frequently assess semantic knowledge, which taps into memory and language systems, and so a change in IQ could reflect a change in memory. Although acknowledging these complexities, this chapter presents outcomes in each domain separately in order to organise the many reported data in a manner that may be clinically useful, whilst attempting to minimise duplication of results. The next sections review the findings for each of these outcome categories in turn.

3.2.4.1 Cognitive outcome

There is a developing consensus that continued uncontrolled seizures are severely detrimental to intellectual and functional development of children and this is frequently cited as a reason to pursue early surgery (e.g. Cross et al., 2006). However, resective brain surgery also poses a risk to cognitive functioning so these risks must both be weighed in the decision to pursue surgery. Thirty seven studies reported either IQ or developmental quotient (DQ). The characteristics and results of these studies are displayed in Table 3.2. Simple inspection of individual IQ change scores after surgery is insufficient to determine the effect of surgical intervention on cognitive development. As IQ tests determine scores relative to population norms for healthy age-matched children, scores reflect a child's functioning compared to peers. Therefore, as noted by Baldeweg and Skirrow (2015), a decrease in a child's IQ may represent either a loss of their skills, a plateau in their skills relative to the cognitive development of other children at that age, or an improvement in their skills but not at the same rate as the age-matched normative group. Furthermore, any change in DQ or IQ may be related to other factors besides the surgery, such as a change in antiepileptic drugs use, seizure recurrence, missing out on education or the psychosocial challenges of going through rigorous treatment, or the widening gap between their social experiences and those of peers. Unfortunately, the lack of non-surgical control groups makes it impossible to tease apart these factors when considering the cognitive outcome of paediatric temporal lobe resection.

These 37 studies presented the intellectual development outcomes of 588 patients who had temporal lobe epilepsy surgery (mean 15.89 participants per study). Ten studies were single case studies, fourteen included participants with mixed surgeries (though data was presented individually and only the participants undergoing temporal resection were included in this review) and twenty-five contained only temporal lobe resections. Only one study included a non-surgical control group (Skirrow et al., 2011). Follow-up time ranged from 11 weeks to 9 years. Age at surgery ranged from 4 months to 18 years (mean 12.58). Seizure outcome was reported by 33 studies, for a total of 480 participants, and of these 366 (76%) achieved seizure freedom/Engel's Class I outcome. Figure 3.7 displays the intellectual outcome measures used and shows that outcome measures were varied but the most common were various editions of the Wechsler scales of intelligence: Wechsler Intelligence Scale for Children (WISC; Wechsler, 2003), Wechsler Preschool and Primary Scale of Intelligence (WPPSI; Wechsler, 2002) and Wechsler Adult Intelligence Scale for ages 16 and above (WAIS; Wechsler, 2014). Several outcome measures were only used by one study, bringing into question whether studies are measuring the same skills, and suggesting that surgical centres publishing their intellectual functioning outcome data have not all agreed on outcome measures.

Table 3.2 Characteristics and results of studies reporting cognitive/intellectual outcome following paediatric temporal resection for epilepsy

Study Author, year	Design	N[a]	Age at surgery mean (range) in years	Age at epilepsy onset mean (range) in years	Mean neuro-psychological follow up mean, (range) in years	Seizure outcomes (Engel Class where reported)	Outcome measures	Results
Lee et al., 2015	Case series (U, R)[b]	20	12.8 (6.5-18.1)	7.26 (1-11)	3.6 (2.5-4.83)	14 (70%) Class I; 6 (30%) Class II	Korean WAIS or WISC	Individual: 7 (35%) children improved FSIQ[c] (more than 5 points) and 6 (30%) worsened. Group: median values of the difference between pre-op and post op IQ were not significant. There was no significant difference between IQ outcome for patients who had right and left surgery.
Ghatan et al., 2014	Case series (U, R)	9	12 (1-17)	3.44 (0-10)	4.22 (0.5-6.17)	6 (67%) Class 1A, 1 (11%) Class 1B, 1 (11%) Class 1C, 1 (11%) Class IVA.	"neuro-psychological tests, not stated"	Individual: all improved in cognition, but not separately given or quantified.
Grosmaitre et al., 2014	Single case study with healthy control group	1	16.17	11	not stated	Class III	WISC IV	Individual: intellectual profile remained stable.
Berl et al., 2013	Single case report	1	7	3	1	No seizure outcome reported	WISC-IV	Individual: change <10 points (i.e. not significant) on VCI[d] and PRI[e] but improved by 13 on WMI[f] and by 11 on PSI[g]
Meekes et al., 2013	Prospective case series with healthy control group	10	14.83 (10.42 - 17.12)	7.38 (0.75-13.9)	24 months	10 (100%) Class I	WISC (Verbal Comprehension index only)	Individual: no results reported. Group: no significant change in VIQ[h] for whole group (temporal group not reported separately).

Beaton et al., 2012	Case series (U, R)	10	15.4 (3.58-18)	2.88 (0.67-8.6)	1.58 (0.67-2.42)	7 (87.5%) Class 1; 1 (12.5%) Class 2	WPSSI, WAIS-III, WISC III and IV	Individual: Processing speed: 8 (8%) no change/improved, 3 (30%) improved by more than 1 SD, 1 (10%) deteriorated, WMI: 7 (7%) no change, 2 (2%) declined. VCI: 100% improved or remained within 1 SD of pre-op scores. Perceptual reasoning: 100% no change.
Vadera et al, 2012	Case series (U, R)	45	11.5 (1.5-18)	3.8 (0-15)	5.02 (0.33-12.25)	31 (69%) Class I; 7 (16%) Class II; 4 (9%) Class III; 3 (7%) Class IV	WISC-IV	Individual: not reported. Group: no significant change.
Garcia-Fernandez et al., 2011	Case series (U, R)	13	11.5 (2-16.3)	7.2 (0.2-14)	5.4 (1.5-7.75)	12 (92%) Class I; 1 (8%) Class II	not described, reference to a paper in Spanish	Individual: no results. Group: For group overall (including extra-temporal) no significant deterioration in any cognitive domains, pre-post, significant improvement in visual attention, perceptive-auditory skills, line orientation, grammatical comprehension, semantic verbal fluency, verbal learning and recall selective attention, non-verbal fluency.

Skirrow et al., 2011	Long-itudinal + Cross-sectional with chronic epilepsy control group (N=11)	42	13.3 (no range[i], sd 3.1)	4.01 (no range)	>5 years	36 (86%) seizure free	WAIS-III	Individual: FSIQ improved at least 10 points in 17 surgery patients (41%) and in one control participant (9%). Only one surgical patient lost at least 13 points (lost 22 points on first procedure then gained 9 after second). Group: Mean FSIQ improved in surgical patients but unchanged for non-surgical epilepsy group [$F_{(1,47)}$=4.8, p=0.033]. Changes in VIQ[j] and PIQ were dependent on side of surgery (interaction of task by side, [$F_{(2,46)}$=5.1, p=0.01]. PIQ improved in both left and right surgery but VIQ only in left. Significant partial correlations (controlled for age at scan and sex) between total grey matter volume and FSIQ. Current AEDs were negative predictors of FSIQ change. Age at onset, duration, number of prior IQ assessments, surgery and time since last seizure were not significant.
Lee et al., 2010	Case series (U, R)	19	14.6 (no range, SD 2.8)	8.3 (2-17)	2.3 (1.2-3.5)	12 (63.2%) Class I; 5 (26.3%) Class II; 2 (10.5%) Class III	Korean WAIS or WISC	Individual: 3 (16%) children showed decrease more than 10 points in IQ. Increases not reported. Group: IQ values remained nearly steady without significant decline.
Muehlebner et al., 2010	single case report	1	15	15	1	seizure free on AEDs	not stated	Individual: significant improvement of general intellectual performance
Roulet-Perez et al., 2010	Case series (U, R)	6	No mean[k] (0.33-4.25)	1.37 (0.33-2.75)	2-6 years	3 (60%) seizure free; 2 (40%) transient relapses	Bayley Scale of Infant development (BSID II), WPPSI-R; WISC III) - calculated DQ	Individual: 2 (33%) improved, 3 (50%) worsened and 1 (17% was not evaluable at baseline, but was at follow-up).

Cunningham et al., 2007	Single case report	1	7	not stated	1	Class III	"neuro-psychological tests" not specified	Individual: pre-surgical IQ in low average range and remained in this range, mild improvement in visuo-perceptual, academic skills unchanged except for mild deterioration in reading. Attention improved.
Hori et al., 2007	Case series (U, R)	2	18 and 9	2 (2-2)	7.83 (5.7-10)	1 (50%) Class 1a, 1 (50%) Class 1b	WAIS-R and WISC	Individual: 18 year-old: VIQ stable, PIQ and FSIQ improved >10 points at 2 years follow-up. 9 year-old: not assessed at 2 years but at 2 months showed improvement but less than 10 points.
Jambaqué et al., 2007	Case series (U, R)	20	12 (7.2-14.6)	5.3 (0.7-12)	1.04 (no range given)	20 (100%) Engel's 1	WISC-III	Individual: results not reported. Group: No significant change (p=0.11 for FSIQ; p=0.10 for PIQ). Younger age at surgery associated with higher improvement of FSIQ (p=0.02), VIQ(p=0.01) and information (p=0.01).
Liu et al., 2007	Case series (U, R)	11	11 (6-15)	7.2 (3.1-12.60	9-23 months (mean 14.2 months) for whole sample	8 (73%) Class I; 2 (18%) Class II; 1 (9%) Class III	WISC-R (age 6-13), WPPSI (age 4-6)	Individual: 8 (73%) improved >10 IQ points, 3 (27%) improved <10 IQ points. Shorter drug resistance and seizure history were correlated to increase in IQ (whole sample).
Cronel-Ohayon et al., 2006	Single case study with twin control	1	10	8	8	Class I	WISC-III	Individual: Normal range for VCI, PRI and FSIQ[h], deteriorated at age 18 compared to pre-surgery at age 9.
Moser et al., 2006	Single case report	1	7	5	0.03	seizure free	Raven's coloured progressive matrices	Individual: IQ unchanged.

Van Oijen et al., 2006	Case series (U, R)	34	No mean (3-17) for all surgeries, not just temporal	3.8 for all surgeries, not just temporal	4-13 years (mean 7.5 years)	37 (73%) Class I; 9 (18%) Class II; 5 (9.8%) Class III or IV	WISC-R (Dutch), Revised Amsterdam Kinder Intelligence Test (RAKIT), McCarthy Development Scales, Intelligence Scale for Pre-schoolers (Stutsman, 1948; it was unclear whether this or the more recent version, Merill-Palmer Revised Scales of Development, was used), Bayley Scales of Infant Development (Dutch)	Individual: 26/30 (86%) no significant (i.e. >10 points) change in IQ, 2 (7%) deteriorated, 2 (7%) improved.
Korkman et al., 2005	Case series (U, R)	23	12.25 (3.5-17.42)	not stated	2 years	19 (82%) Class I; 2 (9%) Class II; 2 (9%) Class III.	WISC-R, WISC III, WPPSI-R, WAIS-R (in Finnish)	Individual: 4 (17.4%) significant increase in VIQ/ PIQ, 2 (8.7%) significant decrease in VIQ/ PIQ, 16 (69.6%) no change. Group: No significant change. No significant effect of side of surgery on IQ change.
Sinclair et al., 2003	Case series (U, R)	25	9 (1.5-16)	2.71 (0-13)	1	33 (79%) Class I;0 Class II; 5 (11.9%) Class III; 4 (9.5%) Class IV	WPPSI, WISC-III	Individual: results not reported. Group: no significant changes in IQ pre- post in either older or younger children (ANOVA).

Bittar et al 2002	Case series (U, R)	3	1 (0.58 - 1.67)	0.56 (0.25-1.08)	3 (1.5-4.67) for whole sample, not given for temporal only	3 (100%) seizure free	not stated: review of medical notes and telephone interview with parents.	Individual: 2 (67%) normal at pre-surgery also normal expected development post-surgery. One (33%) regressed after initial surgery and then accelerated following reoperation. Now has mild language and cognitive delay.
Kuehn et al., 2002	Case series (U, R)	20	12.9 (SD 3.2, no range)	not stated	mixed, mean not stated; 5-15 months	Not stated. No seizure outcome reported	WPPSI-R, WISC III, WAIS-R or WAIS III	Individual: no results reported. Group: no significant change in verbal, performance or full scale IQ in L or R temporal groups. No significant correlation with size of resection and difference between pre- and post-surgery scores. No significant difference in those with hippocampal resection and those without.
Bigel et al., 2001	Case series (U, R)	29	13.27 (6-18)	6.88 (no range)	1.38 (no range)	Not stated. No seizure outcome reported	WISC-III	Individual: results not reported. Group: No significant change. No effect of side of surgery on FSIQ change ($p>0.05$).
Romanelli et al., 2001	single case report	1	2.5	0	24 months	CPS and generalised seizures stopped; SPS reduced by 80%: Class III	Not stated	Individual: improved, not quantified.

Miranda & Smith, 2001	Case series (U, R)	50	Left: 13.36 (6.43-18.25) Right: 13.37 (6.58-17.91)	6.06 (0.5-14.5)	1.82 (0.04-6.58)	34 (58%) seizure free; 16 (42%) not seizure free	WISC-R/ WISC-III or WAIS-R	Individual: significant defined by diff of more than 2xSEM. VIQ: 36 (72%) had no significant change, 7 (14%) improved and 7 (14%) deteriorated. PIQ: (available for N=49): 33 (67%) showed no change, 12 (24%) improved and 4 (8%) deteriorated. Group: Mean VIQ and FSIQ did not change. Small positive change in PIQ [$F_{(1, 47)}$=8.24, P=0.006]. Stepwise multiple regression analysis: VIQ: increases were associated with older age at surgery and lower VIQ at pre-operative assessment. Seizure free candidates were more likely to have increased VIQ. PIQ: dual pathology and length of follow up were inversely related to change in PIQ There was no significant effect of side of surgery on IQ.
Robinson et al., 2000	Case series (U, R)	21	not stated	5.2 (0.67-12.4)	0.5	11 (65%) Class I; 1 (6%) Class II; 3 (18%) Class III; 2 (12%) Class IV.	WISC-III or WAIS-R.	Individual: Defined significant change as greater than 8 points. 19 (90%) were stable or significantly improved in all cognitive tests. 1 (5%) significantly declined in VIQ, 1 (5%) significantly declined in PIQ and FSIQ Group level: no statistically significant changes (pre-post), paired t tests. Longer duration of seizures was associated with lower cog IQ at both pre- and post-surgery. No difference in IQ change between right and left surgical candidates.

Westerveld et al., 2000	Case series (U, R)	82	14.38 (no range)	5.4 (no range given)	1.17 (0.42-5)	not stated	WISC-R/ WISC-III	Individual: Significant change defined as 2xSE of test. 67 (82%) did not significantly change in VIQ, 8 (10%) declined, 7 (9%) improved. PIQ: 67 (82%) no change, 2 deteriorated, 3 improved. Group: Repeated-measures ANOVA showed L temporal lobectomy attained higher PIQ after surgery than at baseline, p=0.014. However, no significant change in VIQ or FSIQ or any IQ for R temporal lobectomy. Stepwise multiple regression to determine predictors from variables: speech dominance, baseline IQ, age at seizure onset, presence/absence of structural lesion, side of surgery, seizure outcome, follow-up interval, hand dominance, gender and age at surgery. Younger patient age at surgery, male sex and lower pre-surgical VIQ was associated with greater positive change in VIQ [R^2=0.198; p<0.005]. Higher baseline VIQ and longer duration of follow up together account for 12% of PIQ outcome [R^2=0.121; p=0.03]. No other predictors were significant.
Dlugos et al., 1999	Case series (U, R)	5	13.92 (8.83-18.83)	8.48 (4.5-12.75)	No mean (0.67-3)	4 (80%) Class I; 1 (20%) Class III	WISC-III or WAIS-R, Woodcock Johnson Test of Cognitive ability	Individual: 1 (20%) deteriorated more than 1 SD on VIQ, one (20%) improved more than 1SD on PIQ. 3 (60%) did not change. No significant change in FSIQ. Group: No significant change on any measures.

Szabó et al., 1999	Case series (U, R)	4	4.75 (2-8)	0.92 (0-1.75)	1.68 (0.5-3.25)	4 (80%) seizure free; 1 (20%) persistent seizures	Developmental Profile II, Kaufman Assessment Battery for Children, Bayley Scales of Infant development, Stanford-Binet Intelligence Scale-IV, parental report	Individual: 2 (50%) improved, 1 (25%) unchanged, 1 (25%) deteriorated.
Manford et al., 1998	single case report	1	13	10	4	seizure free	not stated	Individual: PIQ slightly decreased to 125 (so still high).
Szabó et al., 1998	Case series (U, R)	14	9.4 (7-12)	3.6 (2-8)	2.83 (1.92-4)	10 (71%) seizure free; 3 (21%) significantly improved; 1 (7%) worsened	WISC-R or WISC-III	Individual: no results. Group: FSIQ, VIQ and PIQ all within low average range ad did not change significantly after surgery.
Williams et al., 1998	Case series (U, R)	9	13 (8-15)	3 (0.67-8)	2.58 (1.33-4.17)	6 (66.7%) Class I; 2 (22.2%) Class II; 1 (11.1%) Class III	WISC-R/ WISC-III	Individual: no results. Group: none significant increases in FSIQ, PIQ, VIQ. No significant changes in reading, spelling, maths from WRAT-R. No significant effect of side of surgery on IQ change.
Gilliam et al., 1997	Case series (U, R)	18	9.2 (6-12)	2.44 (0.25-5)	7 months-6 years (mean 2.7 years) for whole sample, not reported for temporal	13 (72%) seizure free; 2 (11%) no worthwhile improvement (Class IV), 3 (17%) some improvement.	WISC, WPPSI	Individual: VIQ: 1 participant (6%) significantly declined (>10 points), 1 (6%) improved significantly (>10 points). PIQ: 3 (17%) improved >10 in performance and 1 in verbal. All other differences were not significant. Group: mean difference across all group (not just temporal) not significant. There were no significant differences in IQ scores between resection location groups or pathology.

Neville et al., 1997	Single case reports (2)	1	0.83	0	1 year	2 (100%) seizure free	not stated	Individual: developmental progress postoperatively was encouraging, frequency and quality of eye contact improved, began to anticipate in action songs, babble became inflected, vocalised for her bottle, using referential eye gaze in support. Raised arms to be picked up, imitative skills observed at 5 months had returned, developing more appropriate use of toys, more eye contact, communication remained largely motoric and understanding remained situational.
Lewis et al., 1996	case series (U, R)	23	14.5 (up to 17, no range)	4.8 (SD 2.5, no range)	4.24 (1-8)	17 (74%) seizure free; 4 (17%) significantly improved; 2 (9%) no significant improvement	WISC or WAIS	Individual: no results. Group: Significant increase in FSIQ post op (mean 82.78 vs. 86.30, $[F_{(1,22)}=6.99, p<0.05]$. VIQ and PIQ not significantly different but trend towards improvement.
DeVos et al., 1995	Case series (U, R)	8	11.9 (5-16)	4.01 (0.1-6)	3.1 (0.33-10.2)	7 (87.5%) seizure free, 1 (12.5%) persistent seizures.	WISC-R or WISC-III	Individual: 4 (50%) unchanged IQ, 2 (25%) not tested post-op, 1 (12.5%) deteriorated VIQ (>10), 1 (12.5%) improved (>10) PIQ & FSIQ.

a: N= number of participants who underwent temporal resection and neuropsychological follow-up.
b: U= uncontrolled study, R=retrospective study
c: FSIQ=full scale IQ
d: VCI= verbal comprehension index
e: PRI= perceptual reasoning index
f: WMI= working memory index
g: PSI= processing speed index
h: PIQ= performance intelligence quotient
i: no range= no range provided by the study authors, and not calculable as individual participant data not provided.
j: VIQ= verbal intelligence quotient;
k: no mean = no mean provided by the study authors, and not calculable as individual participant data not provided.

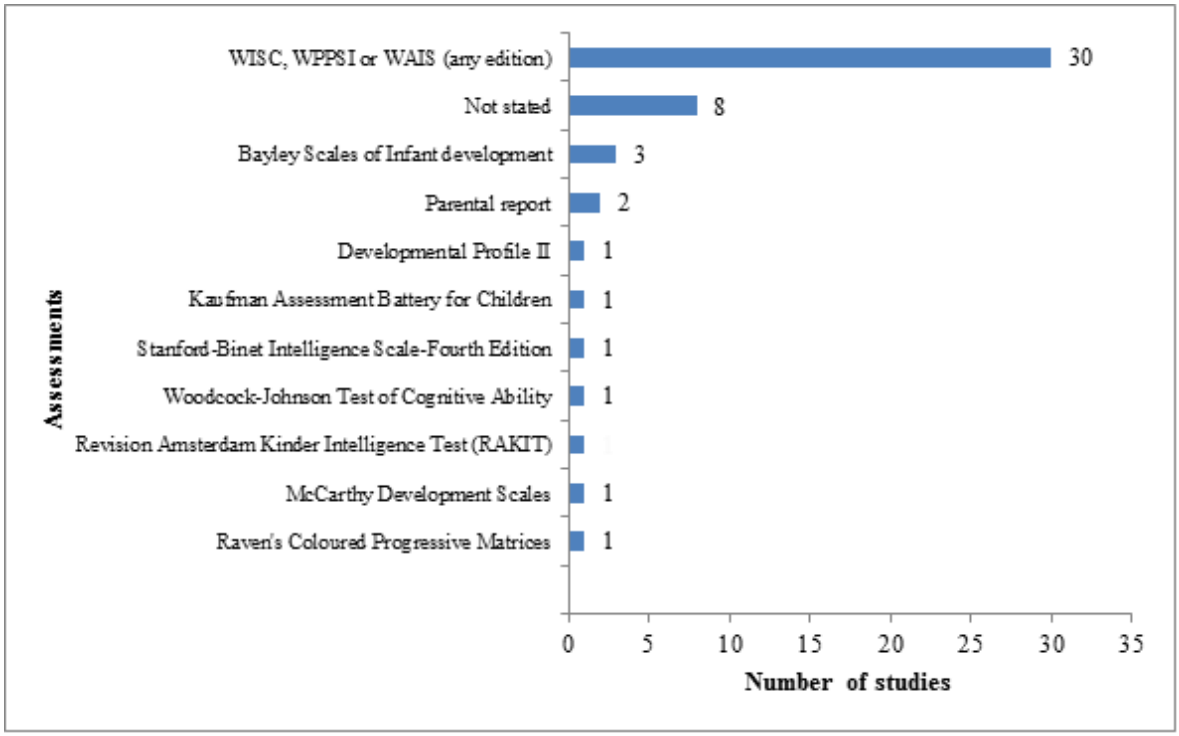


Figure 3.7 Outcome measures for intellectual functioning used by studies

Twenty seven studies presented IQ change data at the level of individual participants (i.e. reporting the number of participants who improved to a statistically significantly degree, remained stable or deteriorated in score), ten studies presented IQ change data only at group level, and nine studies presented IQ change at both the individual and group level.

At the individual level, studies differed in their definition of significant change. Many defined significant change as a change in 10 points or more in Full-Scale IQ (FSIQ). Others reported significant changes as 15 points or greater change, or as change twice greater than the standard error of the mean (SEM) or by 1 standard deviation (SD). Some studies reported changes in VIQ or DQ rather than FSIQ. One case report (Wouters et al., 2006) presented verbal and performance age equivalents rather than IQ score at follow-up. Across the 27 studies reporting individual data (for a total of 365 patients) the number of participants who had significantly improved, declined or remained stable in FSIQ was calculated. Where FSIQ was not reported, VIQ, PIQ or DQ was used instead. For this calculation, each study's definition of significant change was used. Across these 27 studies, 70 (19%) participants improved, 259 (72%) were stable and 33 (9%) deteriorated. Three (1%) participants did not have results for both pre-surgical and follow-up assessments.

Of those 19 studies that reported group level intellectual outcome, 15 found no significant change in intellectual functioning between baseline and follow-up assessment. No studies reported a significant deterioration in IQ at the group level. Three studies reported improvements. Skirrow et

al. (2011) found that FSIQ improved in surgical patients but not matched-surgical controls with epilepsy [$F_{(1, 47)}$=4.8, p=0.033]. Westerveld et al. (2000) showed by repeated-measures ANOVA that for patients with left temporal lobe resections, PIQ improved significantly after surgery (p=0.014) but there was no significant change in VIQ or FSIQ and there was no significant change in participants who received right temporal lobe resection. Lewis et al. (1996) reported significantly increased FSIQ [$F_{(1,22)}$=6.99, p<0.05].

3.2.4.1.1 Factors affecting cognitive development outcome

Ten studies investigated the association of other factors on cognitive outcome. The predictive factors studied are displayed in Table 3.3.

Table 3.3 Studies reporting factors predicting intellectual outcome following temporal resection for childhood epilepsy

Predictor	Number of studies	Study Authors
Developmental level pre-surgery	5	Lee et al 2015 Skirrow et al 2011 Roulet-Perez et al., 2010 Miranda et al., 2001 Westerveld et al., 2000
Age at surgery	5	Lee et al 2015 Skirrow et al 2011 Jambaqué et al 2007 Miranda et al., 2001 Westerveld et al 2000
Seizure status	3	Lee et al 2015 Skirrow et all 2011 Miranda et al 2001
Seizure duration	3	Lee et al 2015 Skirrow et al 2011 Liu et al., 2007
Resection size/type	2	Lee et al 2015 Kuehn et al., 2002
AED use	1	Skirrow et al., 2011
Side of surgery	9	Lee et al 2015 Vadera et al 2012 Skirrow et al 2011 Korkman et al 2005 Bigel et al 2001 Miranda & Smith 2001 Robinson et al 2000 Westerveld et al 2000 Williams et al 1998

The association between developmental level before surgery with change in IQ after surgery was explored by five studies. The study by Roulet-Perez and colleagues (2010), which included only children with delayed development (all had DQ<72 at pre-surgical assessment), found that the

participants with a lower pre-surgical DQ experienced greater cognitive gains than those with a higher pre-surgical developmental level. Similarly, Miranda and Smith (2001) found that increases in VIQ were predicted by lower pre-surgical VIQ [ß=-0.379, t=3.342, p=0.002], but no significant association was found between pre-surgical PIQ and PIQ change. Skirrow et al. (2011) also found that higher preoperative FSIQ negatively predicted positive FSIQ change [$F_{2,46}$=8.0, p=0.001, R^2=0.26, ß=-0.47]. These results are further supported by Westerveld et al. (2000) who found that higher VIQ at baseline was associated with a negative change score in VIQ and PIQ. However Lee et al (2015) found that preoperative IQ level was not significantly associated with post-operative IQ.

The association between age at surgery and intellectual outcome was investigated by five studies. Miranda and Smith (2001) found that older age at surgery was associated with improved VIQ after surgery [ß =0.384, t=3.342, p=0.002]. Seizure duration was accounted for separately in the regression model. However, it is necessary to note that this study only included participants who were seizure free post-surgery and so it is not representative of the general population of children who undergo temporal lobe resection for epilepsy. By contrast Jambaqué et al. (2007) found that younger age at surgery was associated with improved FSIQ (p=0.02) and VIQ (p=0.01) following temporal lobe resection. However, there was no attempt in this analysis to control for disease duration. Westerveld et al. (2000) also found that younger age at surgery was associated with greater positive change in VIQ [R^2=0.198, p<0.005] and in this study age at onset was also entered into the predictive equation. However, these studies lack control groups of non-surgical aged-matched children with epilepsy, and as such, do not control for the effect of development over the follow-up period, which might be expected to be greater in younger children than older children, when cognitive development is less rapid. Both Skirrow and colleagues (2011) and Lee et al (2015) found that age at surgery was not a significant predictor of post-surgical FSIQ.

Three papers investigated the effect of current seizure status. Skirrow et al. (2011) found that seizure status was not a significant predictor of post-operative cognitive change. Miranda and Smith (2001) however, found that seizure freedom positively predicted increases in VIQ score. Lee et al (2015) found that participants with improved PIQ had a greater proportion of Engel's class 1 seizure outcomes compared to patients with worsened PIQ but reported no such effect for VIQ.

Three papers investigated the association between postoperative IQ change and seizure duration. Skirrow et al (2011) found no significant effect of seizure duration; however, Liu et al (2007) found that shorter seizure drug resistance history predicted improved IQ. Lee et al (2015) reported that patients with improved FSIQ had a significantly shorter epilepsy duration than those with worsened FSIQ. Kuehn et al (2001) reported that they found no association between change in IQ and resection of the hippocampus, or size of resection. Only one paper reported the association between

current AED use and cognitive outcome. Skirrow et al (2011) found that current AED use was a negative predictor of FSIQ change [$F_{2,46}$ =8.0, p=0.0001, R^2=0.26, ß= -0.47] and specifically Topirimate was a single negative predictor of IQ change (ß=-0.43, p=0.002).
Eight studies reported the effect of side of surgery on cognitive development. Skirrow et al (2011) reported that changes in VIQ and PIQ were associated with side of surgery [$F_{2,46}$=5.1, p=0.01]; PIQ improved after both left and right surgeries but VIQ improved only after left surgeries. Eight studies reported that there was no significant difference in the change in IQ scores between left and right temporal lobe resections (Bigel et al 2001; Korkman et al., 2005; Lee et al 2015; Miranda & Smith, 2001; Robinson et al 2000; Westerveld et al 2000; Williams et al 1998; Vadera et al 2012).

3.2.4.1.2 Summary of results from review of studies reporting cognitive development outcome

From the literature reviewed, the general pattern that emerges is of the majority of children showing no change in their cognitive functioning after surgery, a minority of children showing improvement and a smaller minority showing a decline in cognitive functioning at follow-up. The literature suggests that lower pre-surgical IQ predicts positive IQ change post-surgery. However, no clear predictive effects of age at surgery, seizure outcome or side of surgery were found, as studies had mixed results. These findings will be considered in the light of the methodological quality of studies in Section 3.4.

3.2.4.2 Broader neurocognitive outcomes: memory, attention, visuospatial and executive skills
Broader neurocognitive outcomes were reported for temporal lobe surgery by 28 studies. All of these reported memory outcome following temporal lobe surgery, six reported attention/processing speed, one reported visuospatial functioning and two reported executive functioning. A wide range of assessments were used, displayed in Table 3.4, and significant change for an individual was defined in a number of different ways across studies (for example 1.5 standard deviations, 2 standard deviations or more than ten points change in memory quotient). Some of the variety in measures used is necessitated by the wide age range of the children undergoing temporal lobe surgery, as children of different ages and developmental stages require different assessments which are appropriate to their developmental level. For example, the Children's Memory Scale (CMS) is designed for use with children between the ages of five and sixteen, so children younger or older than this range would require another assessment.

Table 3.4 Assessments used for assessment of wider neuropsychological outcomes following paediatric temporal lobe resection for epilepsy

Assessment method/measure	**Number of studies**	**Domain assessed**
Rey Auditory-Verbal Learning Test (RAVLT) or German version, VLMT)	5	Memory
The Rey–Osterrieth complex figure test (ROCFT)	5	
Wide Range Achievement of Memory and Learning (WRAML)	5	
Wechsler Memory Scale – 3rd Edition (WMS-III)	4	
Children's Memory Scale (CMS)	4	
Corsi spatial span	4	
Sentence, story and list learning, spatial memory and/or faces (not specified)	5	
Diagnostikum fur Cerebralschadigung-Revised (DCS-R): a visual learning and memory test for neuropsychological assessment	3	
Boston Naming Test (BNT)	3	
Children's Auditory Verbal Learning Test (CAVLT)	3	
California Verbal Learning Test (CVLT)	2	
Batterie d'Efficience Mnesique	2	
Rey-Kim Memory Battery	2	
Signoret Memory Battery, Rivermead Behavioural Memory Test (RBMT), Everyday Memory Questionnaire, Test of Memory and Learning-second edition (TOMAL-2), Questionnaire for Autobiographical Past Events & Public Events, Memory Assessment Clinics Self-rating Scale (MACS-S), drawing family tree, Pyramids and Palm Trees, Selective Reminding Procedure.	1 each	
NEPSY (A Developmental NEuroPSYchological Assessment)	2	Memory, attention, executive function, visuospatial skills
"Measures of attention" - not stated	2	Attention/processing speed
D2 test	2	
Letter Cancelation, Coding, Digit Span backwards	1 each	
Trails task	2	Executive function
Visuo-construction and mental rotation	1	Visuospatial skills

Twenty-four of the studies reporting broader neuropsychological outcomes also reported seizure outcome, for 506 participants, of which 391 (77%) were seizure free. One study (Leunen et al., 1999) did not complete neuropsychological assessments pre- and post-surgery, assessing memory post-surgery only and instead comparing scores to a healthy control group. This design was unable to isolate the effect of surgery from the effect of epilepsy on memory. Fifteen of twenty-eight studies reported outcomes at the individual participant level and eighteen presented group level data. Seven studies presented both individual and group data, eight presented only individual data and eleven presented only group data. Study findings and characteristics are displayed in Table 3.5.

Table 3.5 Characteristics and results of studies reporting broader neuropsychological outcomes following temporal resection for epilepsy in childhood

Study Author, year	Design	N[a]	Age at surgery mean (range) in years	Age at epilepsy onset mean (range) in years	Mean neuro-psychological follow-up mean, (range) in years	Seizure outcomes (Engel Class where reported)	Outcome measure	Results
Lah et al., 2015	Case series (U, R)	40	14.23 (no range, SD 3.36)	8.17 (SD 4.32, no range)	1.08 (no range)	24 (60%) seizure free; 16 (40%) not seizure free	CAVLT, CVLT, BNT	Group level: Naming: Left surgery candidates declined in naming score [$t_{(17)}$=-2.51, p=0.02, d=0.44] but there was no change for the right sided group. Episodic: no significant change, and no effect of group (p=0.07).
Lee et al., 2015	Case series (U, R)	20	12.8 (6.5-18.1)	7.26 (1-11)	3.6 (2.5-4.83)	14 (70%) Class I; 6 (30%) Class II	Rey-Kim Memory Battery	Individual level: 6 (30%) children improved, 7 (35%) remained stable and 7 (35%) decreased on Memory Quotient. Group level: no significant change in MQ from pre- to post- surgery assessment.
Skirrow et al., 2015	Long-itudinal and cross-sectional design (with non-surgical control group of N=11)	42	13.8 (SD 2.7, no range)	4 (no range)	9 (5-15)	6 (14%) regular seizures, 18 (43%) remained on medication, 36 (86%) seizure free (seizure freedom lasting 1-13 years)	WMS (pre- and post-surgery) CAVLT (pre- and post-surgery) Doors and people (post-surgery only)	Semantic memory: significant interaction of group and time [$F_{(2,44)}$=3.63, p=0.04] i.e. left surgical group significantly improved and right surgical group and non-surgical chronic epilepsy controls did not. WMS- Story recall: interaction between time and group [$F_{(2, 38)}$=3.38, p=0.04], right surgical group significantly improved and other groups remained stable. Design recall: left surgical group significantly improved relative to other groups [$F_{(2, 37)}$=4.64, p=0.02] CAVLT: No significant effects of group or interactions (minimum P=0.18). Doors and People: significant group x task interaction with left side surgery participants having significantly better visual than verbal scores.

Grosmaitre et al., 2014	single case study with healthy control group	1	16.17	11	not stated	Class III	Batterie d'Efficience Mnesique	Visual memory: immediate and delayed figure recall remained stable No verbal memory measures assessed pre- and post-surgery
Berl et al., 2013	Single case report	1	7	3	1	No seizure outcome reported	Sentence, story and list learning, spatial memory and faces, attention: "simple measures of attention" and parent questionnaires	Generally, stable but some improvement in verbal learning (not specified). Attention: greater difficulty on simple and complex attention tasks after surgery. Parents reported increased difficulty with attention, executive functions and self-regulation.
Meekes et al., 2013	Prospe-ctive Case series with healthy control group	10	14.83 (10.42 - 17.12)	7.38 (0.75-13.9)	24 months	10 (100%) Class I	Test of Memory and learning- second edition (TOMAL-2), Picture naming and controlled oral word production	Individual level: Verbal memory index: after correcting for practice effects, relative to predicted score: 4 (67%) left temporal patients significantly decreased on verbal memory index, 2 (33%) left temporal showed non-significant decreases, 3 (75%) right temporal showed non-significant increases, 1(25%) right temporal patient showed non-significant decline. No group level results for temporal participants only.
Miserocchi et al., 2013	Case series (U, R)	68	8.9 (1-15)	3.6 (0-14)	>3	58 (85%) Class I; 2 (3%) Class II; 5 (7.5%) Class III; 3 (4.4%) Class IV	Rey-Osterrieth figure, Corsi span, digit span, list learning, story recall. Executive Functions: attentional matrices trail making, digit span backward, frontal assessment battery, Raven's CPM	The percentage of participants with pathological scores reduced for verbal memory, visuospatial memory and executive functions. No individual data provided.

Beaton et al., 2012	Case series (U, R)[b]	10	15.4 (3.58-18)	2.88 (0.67-8.6)	1.58 (0.67-2.42)	7 (87.5%) Class 1; 1 (12.5%) Class 2	WMS, Children's memory scale (CMS), Rey Complex Figure, NEPSY and TEA	Individual level: 6/8 (75%) stable or improved visual memory, (2 (25%) declined. 7 (88%) showed stability/improvement in visual delayed memory. One (12.5%) patient declined more than 2 SDs. 7 (88%) showed stability/improvement in verbal immediate memory, one (12.5%) declined nearly 1.5 SDs, one (12.5%) improved by 1.5 SDs, 6 (88%) stable, 1 (12.5%) improved in verbal delayed memory, one (12.5%) declined by more than 1.5 SDs. One (12.5%) improved by nearly 2SDs. All patients stable or improved on facial memory.
Moseley et al., 2012	single case report	1	11	0	0.25	seizure free	Attention, not stated	"improved attention and focussing in school"- no formal testing
Vadera et al., 2012	Case series (U, R)	45	11.5 (1.5-18)	3.8 (0-15)	5.02 (0.33-12.25)	31 (69%) Class I; 7 (16%) Class II; 4 (9%) Class III; 3 (7%) Class IV	Children's Memory Scale	Group level: no statistically significant changes were reported. Non-significant changes: Visual immediate memory: right side operated participants mean improved by 2.3 index score points; left no change Visual delayed memory: right side operated participants mean reduced by 5 index points; left improved by 13.6. Verbal immediate memory: right side operated participants mean improved by 4.8 index points; left reduced by 0.1. Verbal delayed memory: right side operated participants mean improved by 6.2 index points; left increased by 10.4 Verbal delayed recognition: right side operated participants mean improved by 4.4 index points; left by 1.4. There was no significant difference between left and right groups on visual or verbal memory change.

Lee et al., 2010	Case series (U, R)	19	14.6 (no range, SD 2.8)	8.3 (2-17)	2.3 (1.2-3.5)	12 (63.2%) Class I; 5 (26.3%) Class II; 2 (10.5%) Class III	Rey-Kim Memory Battery	Individual level: 1 child (5%) declined more than 10 points in MQ, the others (95%) remained stable or improved.
Busch et al., 2008	Case series (U, R)	3	17	5.33 (1-10)	0.9 (0.58-1.83) for whole sample including adults, not just children	2 (67%) Class Ia, 1 (33%) Class IV	WMS-III and Memory Assessment Clinics Self-Rating Scale (MACS-S)	Individual level: 2 (67%) patients stable in Auditory Delayed memory but patient 1 significantly improved on Auditory Delayed memory. Visual delayed memory: 2 (67%) significantly improved and 1 (33%) significantly declined. MACS-S: 2 (67%) patients had no change, 1 (33%) patient significantly decreased on Ability and Frequency scores, indicating a decline in subjective memory and more frequent memory problems
Hori et al., 2007	Case series (U, R)	2	18 and 9	2 (2-2)	0.17	1 (50%) Class 1a, 1 (50%) Class 1b	selective reminding procedure (Japanese version)	Group level: No significant changes in scores on verbal paired associates before and after surgery. No significant effect of side of surgery.
Jambaqué et al., 2007	Case series (U, R)	20	12 (7.2-14.6)	5.3 (0.7-12)	1.04 (no range)	20 (100%) Engel's 1	Signoret memory battery, Rey complex figure, The Rivermead Behavioural Memory Test, Coding subtest (attention/working memory tests)	Individual level: Verbal: 9 children significantly improved, 9 stable, 2 deteriorated. Visual: 8 significantly improved, 10 stable, 2 declined. Group level: Significant improvement for immediate story recall (p=0.03), immediate word list recall (p=0.03), sentence recognition (p=0.02), Verbal Memory Score (p=0.03). There were no significant changes in delayed story recall, delayed word list recall, associated word pairs, or any measures of visual memory. All attention/working memory scores showed significant improvement on coding (p=0.007), digit span (p=0.005) and Corsi blocks test(p=0.01) Left side operated participants showed more positive change on visual memory and Right side operated shoed more positive change on verbal memory. This material specific deficit pattern existed pre-surgery but was enhanced post-surgery.

Cronel-Ohayon et al., 2006	single case study with twin com-parison	1	10	8	8	Class I	Age 9 pre-surgery: Batterie d'efficience mnesique. Follow-up: everyday memory questionnaire, digit span, Corsi visuo-spatial span, Rey's 15 words list, Story recall (CMS), Paired words (CMS), 15 drawings string, Rey's complex figure test, Questionnaire for auto-biographical past events, questionnaire for public events, vocabulary (WAIS), information (WAIS), Pyramids & Palm trees test, Boston naming test, Questionnaire about personal information, family tree	Pre-surgery had normal memory. Post-surgery: STM upper range and similar to twin. Reported difficulty learning new facts, interfering with training. Vocab and information and verbal fluency lower than normal. Did worse than twin brother on memory for past events. Normal range on CMS, but much greater forgetting rate than twin over longer delays: impaired long term consolidation. Reduced semantic memory compared to twin and below normal range. Memory for autobiographical and public past events below twin brother
Moser et al., 2006	single case report	1	7	5	0.03	seizure free	VLMT and figural learning and memory test: Diagnostikum Fur Cerebralschadigung	Normalised verbal learning and improved figural memory (not quantified)

Wouters et al., 2006	Single case	1	12.42	4	1	Seizure free	AVLT, CMS, Memory for faces from NEPSY	Learning scores improved but delayed memory scores reduced [z=-1.33], working memory deficit intensified postoperatively [z=-3.00] and impairment on verbal task also evident [z=-1.67].
Clussman et al., 2004	Case series (U, R)	89	12.7 (1.7-17.9)	5.9 (1-16)	1	73 (82%) Class I, 4 (4.5%) Class II, 7 (7.9%) Class III, 5 (5.6%) Class IV.	Memory: digit span, Corsi block design, DCS-R, VLMT. Attention: D2 test, C.1. test, coding, reaction time, Visuospatial visuo-construction & mental rotation	Group level: Verbal memory: Left sided candidates declined [χ^2=9.2, p=0.002] Visuospatial: Right sided candidates had lower scores 1 year after surgery [χ^2 =5.2, p=0.022]. Left sided candidates significantly improved [z=-2.4, p=0.015]. Attention: Left sided candidates improved in attention functions [z=-2.2, p=0.031] and so did right sided candidates [z=-2.1, p=0.038]. For left sided candidates, resection including hippocampectomy had a significant effect on verbal memory (p=0.026) but this was not seen for right side candidates.
Mabbott & Smith 2003	Case series (U, R)	35	age at pre-op assessment, R: 12.2 (5.5-16.7) L: 12.9 (7.6-1.0)	6.8 (no range)	Right: 1.34 (no range) Left: 1.24 (no range)	No seizure outcome reported	CAVLT, Rey-Osterrieth Complex figure, face recognition task	No significant difference between pre-and post- or between temporal and extra-temporal or right and left temporal for immediate and delayed recall of stories [$F_{(1,40)}$=1.60, p=0.22], list learning [$F_{(1,22)}$=2.86, p=0.10]. Mean memory performance in normal range pre- and post- operatively, but variance within group. Visual memory: no change on Rey complex figure and no effect of group, [$F_{(2,37)}$=1.66, p=0.21]. For recognition of unfamiliar faces all groups improved after surgery [$F_{(1,30)}$=25.11, p<0.001]. Right side patients were significantly worse on face recognition than left side, both before and after surgery but there was no interaction between group and side.

Gleissner et al., 2002	Case series (U, R)	55	13.3 (6-17)	7.27 (1-16)	1 (1-1)	38 (69%) seizure free (Class 1); 17 (31%) not seizure free (not specified)	Attention: letter cancellation test (psychomotor speed). Verbal memory: Verbal Learning and Memory Test, German AVLT	Group level: Psychomotor speed improved for R and L surgery candidates. Verbal memory: Left group significantly declined in learning (42.5 to 36.0) and loss after delay (45.7 to 39.2) 3 months after surgery (no change in recognition) but these had significantly recovered by one year (to 41.6 and 42.2). Right patients: no significant change in learning or loss after a delay ($p>0.05$) but significant decline in recognition (from 50.1 to 43.0) by 3 months, with significant recovery by 1 year (to 45.6). Side of surgery was a significant predictor of learning, loss after a delay ($p<0.01$) and recognition ($p<0.05$), with left side showing more negative change.
Kuehn et al., 2002	Case series (U, R)	20	12.9 (SD 3.2, no range)	not stated	mixed, mean not stated; 5-15 months	No seizure outcome reported	Wide Range Assessment of Memory and Learning (WRAML)	Group level: For left surgical candidates, there was no significant difference between pre- and post- mean scores for verbal and visual memory. Statistical analysis could not be used on the Right group as it was too small so these results were not reported.
Sinclair et al., 2003	Case series (U, R)	25	9 (1.5-16)	2.71 (0-13)	1	33 (79%) Class I;0 Class II; 5 (11.9%) Class III; 4 (9.5%) Class IV	Rey AVLT, WRAML	Both left and right sided participants improved on WRAML Sound Symbol Associative Learning ($p=0.016$). No significant change for picture memory, design memory or story memory). AVLT learning was worse for left than right candidates both pre- and post- surgery but there was no significant interaction between side of surgery and time of assessment.
Bigel et al., 2001	Case series (U, R)	29	13.27 (6-18)	6.88 (no range)[c]	1.38 (no range)	No seizure outcome reported	ROCFT, Peabody Picture Vocabulary Test, Story Recall, Trails A	Group level: No differences between pre- and postsurgical performance on verbal learning (list and story), figure learning, facial recognition, executive functions (WCST, trail-making or self-ordered pointing) or visual perception. No effect of side of surgery on ROCFT, story recall or trails.

Robinson et al., 2000	Case series (U, R)	21	not stated	5.2 (0.67-12.4)	0.5	11 (65%) Class I; 1 (6%) Class II; 3 (18%) Class III; 2 (12%) Class IV.	Boston Naming, WRAML, WMS-R logical memory-delayed recall, CVLT, Rey Complex Figure	Individual level: Naming: 6 (29%) improved, 10 (48%) stable, 3 (14%) declined. Rote verbal memory: 5 (24%) improved, 7 (33%) stable, 4 (5%) declined. Story memory: 9 (43%) improved; 6 29%) stable, 5 (24%) declined. Design: 4 (19%) improved, 9 (44%) stable, 3 (14%) declined. Group level: no significant change in naming, rote memory, story memory or design memory Right side operated participants improved more in rote verbal memory than left side (p=0.01) but no group differences in naming, story memory or design memory.
Lendt et al., 1999	Case series (R, with healthy control group)	20	Right: 15.1 Left: 12.5 (10-16)	8.3 (1-15)	1 (1-1)	14 (70%) seizure free	VLMT (German AVLT), DCS-R, d2 test for attention, block design test from WAIS	Individual level: Verbal learning: 3 (15%) significantly improved, 17 (85%) remained stable Verbal retention: 1 (5%) significantly improved, 2 (10%) significantly declined, 17 (85%) remained stable Verbal recognition: 1 (5%) improved, 1 (5%) declined, 18 (90%) stable. Figural learning: 5 (25%) improved, 1 (5%) declined, 14 (70%) stable Group level: No significant change on measures of verbal memory or figural memory. Attention (d2 test): significant improvement for both left and right groups ($p<0.05$).

Szabó et al., 1998	Case series (U, R)	14	9.4 (7-12)	3.6 (2-8)	2.83 (1.92-4)	10 (71%) seizure free; 3 (21%) significantly improved; 1 (7%) worsened	CAVLT	CAVLT: non-significant decline in immediate memory [$F_{(1,9)}$=3.49, p=0.09]. There was no interaction between side of surgery and delayed recall performance
Williams et al., 1998	Case series (U, R)	9	13 (8-15)	3 (0.67-8)	2.58 (1.33-4.17)	6 (66.7%) Class I; 2 (22.2%) Class II; 1 (11.1%) Class III	WRAML	Individual level: verbal memory 6 (67%) participants decreased; 3 (33%) increased/remained stable Visual memory: 3 (33%) decreased; 6 (67%) increased/remained stable. Group level: delayed verbal memory (list learning) decreased significantly from 95.2 to 84.8) [t=2.68, p<0.03]. Story learning decreased from 98.3 to 92. There was no significant change in immediate memory or visual memory. There was no effect of side of surgery on memory outcome.
Lewis et al., 1996	case series (U, R)	23	14.5 (up to 17, no range)	4.8 (SD 2.5, no range)	4.24 (1-8)	17 (74%) seizure free; 4 (17%) significantly improved; 2 (9%) no significant improvement	WMS	No significant change in mean WMS scores between pre- and post-surgical assessment. No individual results reported. Left operated participants had better figural memory than right operated participants at pre- and post-surgery but there was no significant interaction of group and time.

Key: **a: N= Number of participants who underwent temporal resection and neuropsychological follow-up.**
b: U= uncontrolled study, R= retrospective study
c: no range= no range provided by the study authors and not calculable as individual participant data not provided

3.2.4.2.1 Memory outcome

Fifteen studies presented verbal memory outcome at the individual level for 137 children who underwent temporal lobe resection. The characteristics and outcomes of these studies are displayed in Table 3.5. Across these studies, 23 (17%) improved, 78 (57%) remained stable, 34 (25%) deteriorated and 2 (1%) of assessments were not completed at both pre-surgical assessment and follow-up.

At the group level, ten studies reported no significant overall change in memory scores (Bigel & Smith, 2001; Kuehn et al., 2002; Lah & Smith, 2015; Lee et al., 2015; Lee et al., 2010; Lendt et al., 1999; Mabbott & Smith, 2003; Robinson et al., 2000; Vadera et al., 2012; Williams et al., 1998). Miserocchi et al. (2013) reported that the percentage of patients with pathological memory scores reduced after surgery, suggesting improved memory function. Mosely et al. (2012) reported a significant improvement in verbal memory but no change in visual memory. However, Szabó et al. (1998) presented a significant decline for delayed verbal memory and a non-significant decline on immediate verbal memory. Sinclair et al. (2003) reported no significant change in list learning score but a significant increase in sound symbol associative learning score.

Jambaqué et al. (2007) noted that story recall tasks most sensitively detected verbal episodic memory impairment and posited that this may be a result of the increased memory load and complexity of story tasks, which require elaboration around the context in addition to simple memorisation of words. However, this distinction was not investigated by other studies.

3.2.4.2.1.1 Factors affecting memory outcome

Fourteen studies investigated the effect of side of surgery on memory outcome. Gleissner et al. (2002) reported that on a verbal memory measure, participants with left sided resections experienced significantly worsened learning and loss after a delay scores but improved recognition but the converse was observed in right side operated participants, who experienced a significant deterioration in recognition score but improved learning and loss scores. Overall there was no significant effect of side. Dlugos et al. (1999) reported a significant deterioration in verbal memory for left sided resections but no change in visual memory and no significant change in memory measures for right sided resections. Similarly, Robinson et al. (2000) reported that right side operated participants had more positive rote verbal memory change than left side resections, although there was no difference in naming, story memory or design memory. These findings point to material specific deficits after surgery on the left and right temporal lobes. However, Lewis et al. (1996) found that left side operated participants had better short-term figural memory than right side operated patients at pre- and post- surgical assessment but the interaction of side of surgery and

time of assessment was not investigated. Similarly, Sinclair et al. (2003) found that verbal learning was worse for left side candidates both before and after surgery but that there was no interaction between side of surgery and time of assessment. Therefore, these differences may be related to the epileptogenic focus and pre-date the surgery. Jambaqué et al. (2007) found that left side candidates improved more on visual memory and right candidates improved more on verbal memory post-surgery, and they concluded that existing material specific deficits are enhanced post-surgery. Meekes et al. (2013) reported that left sided surgery candidates had significantly worse verbal memory outcome than those who underwent right sided surgery, an effect which remained after preverbal IQ, age at surgery and AED use were accounted for. There may be an interaction between the effects of side of surgery and the nature of the resection on memory outcome. These results suggest that left temporal lobe resection is more likely to result in verbal memory deterioration. There is, however, some evidence to support recovery of memory function at longer follow-up (Lewis et al., 1996; Skirrow et al., 2015). Skirrow et al (2015) reported a significant interaction of time and group for story recall; right sided surgery candidates improved significantly on verbal memory whereas left side surgery candidates did not. Similarly left sided surgery candidates significantly improved on visual episodic memory. On the doors and people test that was administered post-surgery, they found that left operated participants had significantly better visual than verbal scores, and no such discrepancy was found for right operated participants. This study had a non-surgical control group, which allowed some comparison to development over the five-year follow-up period by un-operated children with epilepsy. Skirrow et al (2015) suggest that this result may represent enhanced development of the functions of the un-operated temporal lobe (thus when the right hemisphere is operated the left hemisphere-subserved verbal memory improves). They posit that this may represent the detrimental effects of epileptic activity and seizures; early reorganisation due to seizures means that the right hemisphere contributes to memory function, and when the left hemisphere is operated, the right hemisphere is released and allowed to resume visual memory activity. This finding has not been recorded by other studies, but they may have lacked adequate follow-up for the effect of reduced seizure activity to emerge over time. By contrast, Bigel and Smith (2001), Hori et al. (2007), Lah and Smith (2015), Mabbot and Smith (2013), Vadera et al (2002), Williams et al (1998), and Szabo et al (1998) found no significant effect of side of resection on change in memory scores after surgery.

Four studies also investigated the effect of surgical resection volume and anatomical structures on memory outcome. Clusmann et al. (2004) found that patients undergoing left sided surgery significantly differed by surgical group, with amygdalohippocampectomies resulting in more deterioration to below average verbal memory scores than anterior temporal lobectomies or lateral lesionectomies, but right sided surgeries did not show this effect. Gleissner et al. (2002) found that

amygdalohippocampectomy was associated with reduced learning capacity and greater loss after delay at follow-up compared to anterior temporal lobe resections, lesionectomies including part of the hippocampus or pure lesionectomies. The effect remained when age of onset and surgery and seizure outcome were accounted for, however, epilepsy duration was longer in the amygdalohippocampectomy group and this was not controlled for in the model. Similarly, Skirrow et al. (2015) found that post-surgical hippocampal volume was associated with higher verbal memory score (both semantic and episodic measures), particularly after left sided surgery. They also reported correlations between receptive vocabulary and category fluency (which rely on semantic system functioning) scores with post-surgical temporal pole integrity. However, Lah and Smith (2015) found no significant changes in memory test scores related to hippocampal resection.
Four studies investigated the impact of pre-surgical memory scores on memory change after surgery. Three studies found that lower pre-surgical memory scores were associated with more positive post-surgical change (Sinclair et al., 2003; Skirrow et al., 2015; Szabo et al., 1998) whereas one found that higher pre-surgical verbal scores was associated with stable scores after surgery (Robinson et al., 2000).
Skirrow et al. (2015) investigated the effect of age at onset and seizure duration, finding that better verbal memory outcome on one measure (the Doors and People) was associated with shortened seizure duration (<0.03), but age of onset was not significantly related to any memory outcome.

3.2.4.2.2 Attention and processing speed

Gleissner et al. (2002), Jambaqué et al. (2007), Lendt et al. (1999), Moseley et al. (2012) found that participants significantly improved on measures of attention and processing speed at the group level and Miserocchi et al. (2013) found that the percentage of participants obtaining pathological scores decreased after surgery. Clusmann et al. (2004) reported improvement in attention function for left surgery candidates but not right surgeries. The single case report from Berl et al. (2001) found increased difficulties with simple and complex attentional tasks following a left temporal lobe resection. These results provide insufficient evidence to determine the effect of surgery on attention, however, they suggest a general trend of increased attentional function.

3.2.4.2.3 Visuospatial skills

Only one paper reported change in visuospatial function: Clusmann et al. (2004) reported deteriorated post-surgery visuospatial scores in right sided patients but improved scores in left sided patients.

3.2.4.2.4 Executive functions

The two papers that reported executive function results found different results; Miserocchi et al. (2013) observed a reduction in pathological executive function scores after surgery whereas Williams et al. (1998) found no significant change in executive function scores at the group level after surgery.

3.2.4.2.5 Summary of findings on broader neuropsychological outcomes

The general pattern emerging from the extracted data for memory was that the majority of participants remained stable, a minority declined, and a smaller minority improved in memory functioning after surgery. Overall findings at the group level were generally of no significant change in memory performance. By contrast, attentional functioning was generally found to be improved at follow-up, and results were mixed for executive functions. There were few results for visuospatial skills but these indicated an effect of laterality, with right-side surgical patients improving and left-side surgical patients declining. The factors predicting outcomes were only explored for memory and there was an emerging trend from the results to suggest that left sided surgery and greater extent of hippocampal resection predicts deterioration in verbal memory, and lower pre-surgical memory scores predict more positive post-surgical change.

3.2.4.3 Language outcome

Language and semantic function is thought to be less dependent on the mesiotemporal system and hippocampus than episodic memory (Binder et al., 2009). Sixteen studies reported language outcomes following paediatric temporal lobe epilepsy surgery. The characteristics and findings of these 16 studies are displayed in Table 3.6, which also displays the wide variety of language assessments used. Studies measured a number of different aspects of language including semantic and phonetic fluency, reading skills and spelling, receptive and expressive language skills. Moreover, the variety of developmental levels and ages of children included in the studies meant that the type of language assessments undertaken necessarily varied greatly. Fifteen of the studies reported seizure outcome, for a total of 337 young people, of whom 273 (81%) achieved seizure freedom/Engel's Class I outcome. The language results are very mixed and the wide variety of assessments used and language skills assessed make it difficult to discern any clear pattern from the results.

Six studies reported pre- and post-surgical assessment results at the individual level for oral language. Of these, 23% improved, 42% remained stable and 35% worsened. Five studies reported group level expressive language outcomes: one showed no significant change, one showed significant improvement, one showed significant improvement for right sided surgeries but stable score for left surgeries and one (De Koning et al., 2009) showed significantly worsened scores after

surgery. Specifically, De Koning et al. (2009) showed worsened productive lexicon and syntax over the first year of follow-up, followed by stabilisation. Three studies reported group level outcomes of receptive language. One study showed significantly worsened performance, one showed no significant change and one showed stable receptive syntax score but worsened receptive lexicon score. Two studies assessed the effect of temporal lobectomy on reading. Grosmaitre et al. (2004) found that their participant worsened significantly in reading ability by one year of reading age. By contrast Lah and Smith (2015) found no significant effect of time in their analysis of reading score change from pre-surgical to post-surgical assessment.

3.2.4.3.1 Factors associated with language outcome

Seven studies investigated the effect of resection side on language outcome after temporal surgery. Four studies found no significant difference between left and right sided surgeries in predicting change in language scores after surgery (Blanchette and Smith, 2002; Clusmann et al., 2004; Jambaqué et al., 2007; Williams et al., 1998), although they generally reported that left hemisphere surgery candidates generally scored lower than right side candidates at both pre- and post- surgical assessment. Lah and Smith (2015) found a significant interaction of hemisphere and time [$F_{1,27}$=4.42, p=0.05] due to significant deterioration in naming score for the left but not the right surgical group. However, there was no significant interaction of time and side for vocabulary, reading or spelling. By contrast, Skirrow et al. (2015) also found a significant main effect of group [$F_{2, 44}$=3.63, p=0.004] on IQ-derived semantic score, but with left temporal lobe resection patients showing significant improvement, and no significant improvement for right side resected patients or non-surgical controls. De Koning et al. (2009) investigated language development through multiple assessment points before and after resection, which allowed a more nuanced assessment of the effect of surgery on children's language development trajectory. They reported language lateralisation of children, and considered the effect of surgery in the language-mediating hemisphere, rather than using the simple division of left and right like other studies. They found that delayed development of productive lexicon was increased more by surgery in the language-mediating hemisphere (for most children, the left). They found that children with more delayed syntax at pre-surgical assessment had better language development outcome after surgery.

Two studies reported the impact of resection characteristics on language development outcome. Lah and Smith (2015) found no significant effect of hippocampal involvement in the resection on literacy results. Skirrow et al. (2015) found significant correlations between category fluency and receptive vocabulary and temporal pole integrity, however semantic assessments from IQ tests did not show this relationship.

3.2.4.3.2 Summary of findings on language outcome

The results were mixed and the variety of assessments used and language skills assessed make it difficult to discern patterns from the results. As with the findings on cognitive outcomes, the most children had stable language from pre-surgical assessment to follow-up, a sizable minority declined and a smaller minority improved. There was no overall change in language scores at the group level. Results suggest that left side operated participants tend to do worse on language than right-operated patients and, although these differences tend to pre-date the surgery, surgery may be associated with further delay in development. However, many studies lacked control groups so their changes cannot be attributed to the surgery and may have resulted from confounding factors.

Table 3.6 Characteristics and results of studies reporting language outcome following temporal resection for epilepsy in childhood

Author, year	Design	N[a]	Mean age at surgery (range) in years	Age at epilepsy onset mean (range) in years	Mean language follow up (range) in years	Surgery side	Seizure outcome (Engel's Class if reported)	Outcome measures	Results
Lah & Smith, 2015	Case series (U, R)[b]	40	14.23 (SD 3.36, no range[c])	8.17 (SD 4.32, no range)	1.08 (no range)	22L, 18R[d]	24 (60%) seizure free; 16 (40%) not seizure free	Reading accuracy test, reading comprehension, spelling accuracy, EVT, EOWPT	Significant main effect of time on reading accuracy: lower scores post-surgery. No significant main effects for reading comprehension or spelling accuracy Significant interaction of side of surgery and time on naming (p=0.05), in which left operated participants deteriorated more than right side participants post-surgery. There was no significant effect of side of surgery on vocabulary outcome (p=0.70).

Skirrow et al., 2015	Longitudinal & cross-sectional design	42	3.8 (SD 2.7, no range given)	4 (no range)	>5 years	25L, 17R	6 (14%) regular seizures, 18 (43%) remained on medication. 36 (86%) seizure free (seizure freedom lasting 1-13 years)	Pre- and Post-surgery: vocabulary, comprehension and information from WAIS/WISC. British Picture Vocabulary scale, category fluency	Individual: No results Group: ANCOVA showed significant main interaction of time and group on IQ-derived semantic memory [$F_{(2,44)}$=3.63, p=0.04]. Left-operated patients significantly improved, and right-operated patients and non-surgical controls did not p=0.04). No group differences (between left operated, right operated, and non-surgical participants) in change in category fluency or receptive vocabulary scores.
Grosmaitre et al., 2014	single case study with healthy control group comparison	1	16.18	11	Not reported	L	Class III	Oral-BILO, phonemic & categorical verbal fluency, Depistage des Dyslexies (ODEDYS), L'Alouette, experimental reading task, spelling task	Oral language preserved from pre-post-, reading ability started below school level but regressed markedly by a year's reading age post-surgery Reading of irregular frequent words and irregular infrequent words decreased by post-surgery. Spelling was maintained in the main but reduced for irregular frequent words. Bayesian Monte Carlo methods used to compare patient's scores to control group.

Miserocchi et al., 2013	Case series (U, R)	68	8.9 (1-15)	3.6 (0-14)	>3	34L 34R	58 (85%) Class I; 2 (3%) Class II; 5 (7.5%) Class III; 3 (4.4%) Class IV	phonemic fluency, semantic fluency, naming token test, phonetic fusion, phonetic segmentation, reading, writing.	Percentage of patients with "pathological scores" decreased on all assessments
De Koning et al., 2009	Case series (U, C)	24	11 (5.8-15.7)	4.49 (0.1-13)	2	20% R, 15% bilateral, 46%L	22 (92%) Class I; 1 (4%) Class II; 1 (4%) Class IV	Language Tests for Dutch Children, Verbal comprehension Scale A from Dutch Reynell Developmental Language Scales, Vocabulary and Sentence Production from Schlichting Test of Language Production ad Dutch Peabody Picture vocabulary test.	Some children had large deteriorations followed by improvements however others had identical language scores (representing increasing delay). Receptive syntax did not change significantly, however, receptive lexicon, productive lexicon and productive syntax all worsened significantly after surgery in the first year and then stabilised
Mikati et al., 2009	Single case report	1	7	1.33	0.75	R	Seizure free	aphasia assessment	At latest follow-up had mild improvement in sleep, could use two words and understood some instructions. Pre-op mental age of 12-14 months. At follow up Expressive speech still at 1 year level whereas receptive speech was at 3.5 years.

Jambaqué et al., 2007	Case series (U, R)	20	12 (7.2-14.6)	5.3 (0.7-12)	1	12L 8R	20 (100%) Engel's 1	Vocabulary from WAIS, naming test, category verbal fluency	only naming showed significant improvement (p=0.03), higher in children with no previous hippocampal damage (p=0.03).
Clussman et al., 2004	Case series (R, U)	89	12.7 (1.7-17.9)	5.9 (1-16)	1	50R 39L	73 (82%) Class I, 4 (4.5%) Class II, 7 (7.9%) Class III, 5 (5.6%) Class IV.	Phonemic fluency, semantic fluency, token test, naming, vocab	One year after right sided surgery children had significant improvement in language [z=-2.3, p=0.02]. Patients with left surgery showed no change.
Blanchette & Smith, 2002	case series (R) with frontal lobe resection comparison group	10	11.5 (7.5-15.8)	4.4 (1.1-7.25)	not reported	5L 5R	Not stated. No seizure outcome reported	vocabulary and verbal IQ from WISC, reading and spelling from WRAT, FAS and categories word fluency, Peabody Picture vocabulary test, token test, test for the reception of grammar	5 (50%) children declined on phonetic fluency, 3 (30%) children declined on category fluency. no significant between frontal and temporal groups before and after surgery Laterality effect on category fluency (p=0.01), where left side candidates deteriorated more than right side candidates, although this calculation included both frontal and temporal participants.
Romanelli et al., 2001	Single case report	1	2.5	0	2	L	CPS and generalised seizures stopped; SPS reduced by 80%: Class III	Not stated measure of speech	Improved, not quantified.
Lendt et al., 1999	Case series (R) with healthy control group	20	13.8 (10-16)	8.3 (1-15)	1	10R, 10L	14 (70%) seizure free	Token test and written word fluency test	Token test score significantly decreased.

Szabó et al., 1999	Case series (U, R)	4	4.75 (2-8)	0.92 (0-1.75)	0.5-4.33	R	4 (80%) seizure free; 1 (20%) improved but persistent seizures	Parent report, Peabody picture vocabulary test	2 (50%) improved, 1 (25%) unchanged, 1 (25%) worsened.
Williams et al., 1998	Case series (U, R)	9	13 (8-15)	3 (0.67-8)	1.33-4.17	5L 4R	6 (66.7%) Class I; 2 (22.2%) Class II; 1 (11.1%) Class III	Peabody Picture Vocabulary test-revised	non-significant increase in scores. There was no significant effect of side of surgery on naming outcome.
Duncan et al., 1997	Case series (U, C)	8	12.6 (8-16)	not reported	0.08-2	4L 4R	8 (100%) seizure free (Class 1)	Not specified, medical notes	No child sustained post-operative speech or language deficit.
Aylett et al., 1996	Single case report	1	8.33	6.83	1.08	L	Not stated; seizures continued post-operatively but controlled via medication	Not specified; records of speech	13 months after surgery vacant episodes of hyperventilation, lacking in spontaneous communication, able to respond to some commands and could only speak name, not responsive to painful stimuli, occurring at any time of day and lasting up to 2 hours.

DeVos et al., 1995	Case series (U, C)	8	11 (5-16)	4.01 (0.1-6)	0.33-10.2	8L	7 (87.5%) seizure free, 1 (12.5%) persistent seizures.	VIQ (WISC), Controlled oral word association test, visual naming test, reading decoding test (WRAT), Peabody individual achievement test, Token test	2 (25%) improved, 4 (50%) unchanged, 2 (25%) temporarily worsened but resolved. Left side surgical candidates scored worse than right before surgery (p=0.05) and after surgery the delay in productive lexicon increased further if surgery was on the language dominant hemisphere. Overall "there was no remarkable differences in language development between children with left and right epilepsy surgery".

Key:
.a: N= Number of participants who underwent temporal resection and neuropsychological follow-up.
.b: U= uncontrolled study, R= retrospective study
.c: no range= no range provided by the study authors and not calculable as individual participant data not provided.
d: L= surgery on the left temporal lobe; R= surgery on the right temporal lobe

3.2.4.4 Quality of life

Children with an epilepsy who experience chronic seizures have reduced health-related QoL (Austin et al., 1994; Taylor et al., 2011) so this is a key outcome of interest after epilepsy surgery. Ten studies reported QoL outcomes following temporal lobe resection for epilepsy in childhood. The characteristics and findings of these studies are displayed in Table 3.7. Eight of the ten studies reported seizure outcome, for a total of 130 young people, and of these 94 (72%) were seizure free. Three of these studies (Gilliam et al., 1997; Keene et al., 1997; Zupanc et al., 2013) reported the quality of life outcomes for children who underwent temporal surgeries mixed in with children who underwent different surgeries, despite reporting other surgical outcomes separately for each group. This made it impossible to assess the specific effect of temporal lobe surgery and QoL, therefore their findings are not considered further. Three studies (Bittar et al., 2002; Romanelli et al., 2001; and Taylor et al., 2013) briefly reported quality of life outcome but did not specify the method of assessment. Romanelli et al (2001) reported in their case report that parents reported that the child's QoL improved but this was not quantified or qualified with further detail, making it difficult to know whether this QoL reported by the parents is the same construct that is measured by health-related QoL measures. Bittar et al (2002) failed to report the assessment method for parent-reported QoL, but did qualify the areas of reported improvement, as displayed in Table 3.7. Taylor et al (2013), however, mention QoL only in the abstract and conclusion, stating that "as evidenced by the lack of seizure activity following resection, the patient's quality of life greatly improved after neurological surgery" (pg. 21), whilst reporting no assessment of QoL. The authors appear to be using the concept of QoL in an informal manner and drawing the inference that successful seizure reduction necessarily results in improved QoL. However, as they present no evidence for this assertion, this conclusion is misleading, and an example of the conflation of concepts that seems apparent in this epilepsy surgery literature. As this study did not assess QoL it will not be considered further in this section.

The remaining four papers used structured parent- or self- report measures of QoL. Three assessed QoL longitudinally at pre-and post- surgery (Gagliardi et al., 2011; Guimarães et al., 2004; Larysz et al., 2007) but Skirrow et al. (2011) used a cross-sectional design and assessed QoL only after surgery, comparing scores to a non-surgical chronic epilepsy control group. Both of these designs introduce risk of bias. Without a control group, the longitudinal studies are unable to control for the effects of factors other than surgery that may account for change in quality of life, for example maturation or increased knowledge of their condition. The cross-sectional design, whilst having a control group for comparison, also cannot isolate the effect of surgery on quality of life, as the difference in QoL between groups before the surgery is unknown.

A further threat to the validity of these studies reporting QoL is that self- and parent- report measures are vulnerable to expectancy effects, and parent- report measures may reflect parental satisfaction with outcome and may not be able to accurately represent the experience of the child.

3.2.4.4.1 Factors associated with QoL outcome

Only one study (Skirrow et al., 2011) reported an analysis of factors associated with QoL, reporting that QoL was mainly predicted by seizure freedom [ß=0.44, p=0.001]. This fits with the findings of Zupanc et al. (2010) who found that the seizure free group had significantly higher post-surgical QoL than the non-seizure free group. However, neither study had pre-surgical assessment of QoL so these differences may have been pre-existing and not attributable to the surgery.

3.2.4.4.2 Summary of findings on quality of life outcome

Although the studies generally concluded that surgery is associated with favourable QoL outcome, none of the study designs can be used to assess the impact of surgery on QoL, so no conclusions can be drawn from these findings about whether paediatric temporal lobe resection for epilepsy is beneficial for QoL. Higher QoL was predicted by seizure freedom.

Table 3.7 Characteristics and results of studies reporting quality of life outcome following temporal resection for epilepsy in childhood

Author, year	Design	N[a]	Mean age at surgery (range) in years	Mean age at epilepsy onset (range) in years	Mean QOL follow-up (range) in years	Seizure outcome (Engel's class if reported)	Quality of life measures	Results
Taylor et al., 2013	Single case report	1	14	0.33	2	Seizure free	Not reported	Stated in abstract: patient's quality of life greatly improved, but not mentioned elsewhere.
Gagliardi et al., 2011	Case series (U, R)[b]	13	Not reported	Not reported	0.6-7.9	Not reported	Questionnaire given pre and post-surgery including health, physical, medication, emotional, behaviour, cognitive, social, schooling & environment aspects	12 (92%) participants significantly improved. One (8%) participant decreased. All aspects of QOL improved after surgery (significantly at $p<0.05$) for health, medication effects and behaviour of parents)
Skirrow et al., 2011	Longitudinal and cross-sectional design with non-surgical chronic epilepsy control group of N=11	42	13.3 years (SD 3.1; no range)[c]	4.01 (no range)	>5	36 (86%) seizure free	QOLIE-36-U, given post-surgery only	Total QoL scores higher in surgery group than in non-surgical group, but no longitudinal follow-up of QoL from pre- to post-surgery
Zupanc et al., 2010	Case series (U, R)	17	10 (0.75-21) for all participants (TLE not given separately)	3.7 (0-16) for all groups, TLE not reported alone	not reported	16 (84.2%) Class I; 2 (10.5%) Class II; 1 (5.3%) Class III	Quality of life in Childhood epilepsy; Quality of Life in Epilepsy for Adolescents	No Pre-post QoL results reported. At post-op assessment, seizure free group had significantly higher QoL than non-seizure free (but this was calculated across surgery types, not just TLE)

Larysz et al., 2007	Case series (U, R)	1	13	3	0.5	1 (100%) Class II	Newly developed Polish language QOL questionnaire, pre- and post- surgery	child improved
Guimarães et al., 2004	single case reports (2)	2	2 years and 6 years	2.79 (0.58-5)	0.5	Not reported	Questionnaire including perception of seizures, general health, limitations in daily activities, adverse events of antiepileptic drugs, emotional aspects, cognition, memory, language, motor skills and social relationships	All areas improved or stayed the same except for worsening on "behaviour/emotional, "school" and "environment" or one child and" behaviour/emotional" and "cognitive" for the second
Bittar et al., 2002	Case series (U, R)	3	1 (0.58-1.67)	0.56 (0.25-1.08)	1.5-4.7	3 (100%) seizure free	Parent report: not specified. Assessment appears to be post-surgery only but this is not explicitly stated	"Improved in all cases". Improvements reported in cognition, language, communication, level of care, parental anxiety or reduction in seizure frequency or severity
Romanelli et al., 2001	Single case report	1	2.5	0	2	Class III	not stated, parent report	child improved
Gilliam et al., 1997	Case series (cross-sectional comparison of QoL with healthy control group)	18	9.2 (6-12)	2.44 (0.25-5)	0.6-6	13 (72%) seizure free; 2 (11%) no worthwhile improvement (Class IV), 3 (17%) some improvement	Child health questionnaire completed by parents (only post-surgery)	Overall surgery group (not just temporal) significantly lower than controls on physical function, behaviour, general health, self-esteem, emotion impact on parent and time impact on parent

Keene et al., 1997	Case series (U, R)	44	13 (SD 4.5; no range)	6 (SD 4.6; no range)	1-14	24 (55%) Class I; 5 (11%) Class II; 7 (16%) Class III; 8 (18%) Class IV.	QOLIE-31	No Pre-post QoL results reported. At post-op assessment, seizure free group had significantly higher QoL than non-seizure free (but this was calculated across surgery types, not just TLE)

a: N= Number of participants who underwent temporal resection and neuropsychological follow-up.
b: U= uncontrolled study, R= retrospective study
c: no range= no range provided by the study authors and not calculable as individual participant data not provided.

3.2.4.5 Psychological wellbeing outcomes

Nine studies reported mood and mental health outcomes following temporal lobe surgery for epilepsy in childhood. The studies reported seizure outcome for a total of 228 young people, 148 (65%) of whom achieved Engel's Class I outcome/seizure freedom at last follow-up. The mental health outcomes measured varied between these studies, as displayed in Table 3.8, from self-report measures and interviews about mood to records of psychiatric diagnoses so the results are highly heterogeneous. Five studies reported mood or emotional disorder diagnosis outcome at the individual level, for a total of 161 children. Across these studies 33 (20%) children were reported to have worsened in mood or gained an emotional disorder diagnosis, and not all studies reported whether the remaining participants were stable or had improved. Individual studies also reported change in diagnoses such as eating disorders, psychosis and Autism Spectrum Disorders (ASD) following surgery. However, the data presented by studies was too heterogeneous to pool and these results are displayed for each study in Table 3.8.

Four studies reported mood and psychiatric outcomes at the group level. Two of these studies reported that there was no mean change from pre-surgery to post-surgical assessment on measures of anxiety and depression (Andresen et al., 2014; Williams et al., 1998). One study (Micallef et al., 2010) compared the psychological outcomes of seizure free participants, non-seizure free participants and non-surgical controls with epilepsy using an interview format. Participants who achieved seizure freedom following surgery did not have significantly different scores in depression, self-esteem or anxiety compared to chronic epilepsy non-surgical controls. This study detected improvements in self-esteem, identity and sense of a "cure" for those who achieved seizure freedom following surgery. This added a feeling of pressure for some participants to increase their activity levels, which was linked to worsening mood. The study found significantly reduced self-esteem and increased depression in those who were not seizure free after surgery compared to the chronic epilepsy control group. Lewis et al (1996) used the Minnesota Multiphasic Personality Inventory (MMPI) and found that after surgery participants demonstrated more hypochondriasis, psychaesthesia, schizophrenia and hypomania but also showed improved personal satisfaction on a social function interview.

3.2.4.5.1 Factors associated with mental health outcomes

Two studies (Mclellan et al., 2005; Micallef et al., 2010) investigated the relationship between mental health and seizure outcome following temporal lobe surgery. Micallef et al (2010), as outlined above, found significantly higher self-esteem and lower depression in seizure-free than non-seizure free participants following surgery. McLellan et al (2005) found "no clear relationship" (p.669) between seizure freedom and psychopathology. They noted that seizure free participants

were more likely to lose a diagnosis after surgery (24%) than non-seizure free participants (5%) though more seizure-free participants gained a diagnosis when they did not have one before (15%) than non-seizure free participants (9%). Two studies investigated the effect of side of surgery (Andresen, 2014; McLellan et al, 2005), and both found no significant effect on mood, but McLellan et al (2005) found that more those with right sided resections than left sided resections went on to gain a diagnosis of pervasive developmental disorder. One study (McLellan et al., 2005) investigated the effect of AEDs on mental health outcome and found no significant relationship between AED use and post-surgical psychiatric outcome, with the exception of one child who developed psychosis with Topirimate. McLellan et al. (2005) was also the only study to investigate the effect of resection type on mental health outcome; they found no significant association between type of temporal surgery and psychiatric outcome. No studies reported the predictive effect of age at surgery or epilepsy duration on mental health outcome.

3.2.4.5.2 Summary of findings on psychological wellbeing outcome

The results for this outcome domain were highly heterogeneous, making it difficult to draw any conclusions from the data. A sizeable minority of participants develop new psychiatric diagnoses after surgery. However, there was limited reporting of pre-surgical psychiatric assessment of candidates and little consideration of the base-rate of developing psychiatric conditions for children with chronic epilepsy. In the study that did perform pre- and post- operative assessment of psychiatric diagnoses (McLellan et al., 2005) the majority of participants who previously had a diagnosis improved or lost their diagnosis at follow-up, although a minority worsened, and some developed new diagnoses. Only one study had a control group so most could not attribute observed changes to the surgery. No overall change in mood after surgery was clear from the data and no significant predictors were found with the exception of seizure freedom, which appeared to be associated with more positive mental health outcome.

Table 3.8 Characteristics and results of studies reporting mood and psychiatric outcomes of temporal resection for epilepsy in childhood

Study (Author, year)	Design	N[a]	Age at surgery mean (range) in years	Age at epilepsy onset mean (range) in years	Mean mental health follow-up (range) in years	Seizure outcome (Engel's Class if reported)	Outcome measure	Results
Andresen et al., 2014	Case series (U, R)[b]	64	11.3 (no range)[c]	5.81 (SD 3.93, no range given)	0.71 (SD 1.06),	37 (62%) Class I, 0 Class II, 21 (35%) Class III, 2 (3%) Class IV	Children's Depression Inventory CDI, Revised Children's Manifest Anxiety Scale-First or Second Edition (RCMAS)	Individual level: left temporal surgeries (N=38): Anhedonia: 12% declined, 80% stable, 8% improved. Social concerns: 19% declined, 58% stable, 23% improved. No data was presented for right surgeries. Group level: Both left and right patients remained stable on RCMAS and CDI as a group. There was no significant difference in mood outcome between mood outcome for right and left candidates.
Lee et al., 2011	Case series (U, R)	40	ATL: 8 (1-15) Lesion-ectomy: 6.2 (1-12)	4.8 (0.25-14)	not reported	37 (92.5%) Class I; 2 (5%) Class II; 0 Class III; 1 (2.5%) Class IV.	Not reported	Two patients developed mood disorder after ATL – no further detail provided

Micallef et al., 2010	Pro-spective cohort study with chronic epilepsy control group	20	No mean[d] (13.4-21; 75% before 15)	7.04 (1.5-13)	8.2 (0.25-14)	9 (45%) seizure free; 11 (55%) not seizure free	All measures at follow up, not pre-surgery. Psychological interview, using open-ended questions to explore all aspects of patient's psychosocial functioning and adjustment to epilepsy and treatment. BDI-II, Coopersmith Self-Esteem Inventory-Adult form, State-trait anxiety inventory. Patients with low IQ not administered self-report questionnaires	Those who were seizure free after surgery reported a sense of a "cure" and 50% reported change in perceived identity, which co-occurred with increased overall activity, and a sense of overdoing it. Depression score in this group was low, although one patient developed depression. Self-esteem was in normal limits as was anxiety. No significant difference in depression, self-esteem, or QoL compared to non-surgical controls with chronic epilepsy ($p<0.05$). Surgery-not seizure free group had poorest outcomes (compared to surgery seizure free, spontaneous remission and chronic epilepsy). They reported higher depression than chronic epilepsy [$t=2.99$, d.f.=16, $p<0.01$]. Two had severe depression. Two surgery non-seizure free developed new depression after surgery. 54% reported increased depression after surgery (compared to 16% increased depression in chronic epilepsy). More than 50% reported "new me" ad associated increase in activity levels, 33% reported feeling "cured", 67% reported feeling "sick". Non-seizure-free post-surgery group reported lower self-esteem than other groups [$F_{2,29}=4.21$, $p<0.05$].
Adami et al., 2006	Single case report		18	6	2	Class IV	Clinical diagnosis post-surgery (no pre-surgical assessment)	The participant was diagnosed with PTSD post-surgery (she had experienced childhood sexual abuse between ages 8 and 12 but did not develop PTSD until after amygdalohippocampectomy.

McLellan et al., 2005	Case series (U, R)	60	10.6 (0.6-17.9)	3.4 (no range)	5.16 (2-10)	34 (60%) Class 1; 3 (5%) Class 2; 9 (16%) Class 3; 11 (19%) Class IV.	DSM-IV	PDD: 23 (60%) had pre-op. Post-op: 11 (48%) improved, 7 (30%) stable, 3 (13%) deteriorated, 2 (8%) lost diagnosis at follow-up. ADHD: N=14, 3 (21%) lost diagnosis at follow-up, 5 (36%) improved, 5(36%) stable, 1 (7%) deteriorated, 2 developed post op. ODD/CD: N=14: 3(21%) lost diagnosis at follow-up, 2 (14%) improved, 4 (29%) stable, 5 (36%) deteriorated, 2 developed post-op. DBD (NOS): N=25: 5(20%) lost diagnosis at follow up, 8 (32%) improved, 8 (32%) stable, 16% deteriorated, 5 developed post op. Emotional Disorder: N=5: 3 (60%) lost diagnosis at follow-up, none improved, 1 (20%) stable, 1(20%) deteriorated, 10 developed post-op. Eating disorder: N=1: 1 lost diagnosis at post-op, 1 developed post-op. Conversion disorder: N=1: 1 lost diagnosis at follow-up, 1 developed diagnosis post-op. No participants had psychosis at pre-op assessment but one had developed at follow up. No significant difference between left and right sided surgeries in mood, but higher post-operative developmental disorder diagnoses in right than left surgical candidates ($p<0.05$).

Danielsson et al., 2002	Case series (U, R)	16	11 (3.5-19)	2.6 (0.08-10)	2	7 (44%) Class 1, 3 (19%) Class 2; 2 (12.5%) Class III, 3 (19%) Class IV; 3 (19%) re-operated and not followed up for 2 years afterward	Conner's parent/teacher rating scale. DSM-IV, parent report, neurologist observation.	5 children with ASD remained autistic but a positive change in behaviour was noted in 3, 1 autistic girl showed no change and a boy with ASD showed more signs of autism. 3 children with inattention improved in concentration and were less hyperactive. A girl with depressive disorder lost the diagnosis after surgery. A boy was less impulsive and aggressive. 2 of 3 children with no psychiatric disorder showed no change and the other gained post-operative depression.
Andermann et al., 1999	Single case reports	2	8 and 18	4.75 (2.5-7)	not reported	1 (50%) Class I; 1 (50%) "seizure frequency reduced by 90%".	DSM-IV diagnosis, suicidality assessment post-operatively. No pre-operative assessment	8year-old: Received diagnosis of psychotic disorder due to brain disease with hallucinations and depressive symptoms. 18 year-old: DSM-IV diagnosis of delusional disorder due to brain disease with paranoid and depressive features.
Williams et al., 1998	Case series (U, R)	9	8-15 years (Mean 13 years)	3 (0.67-8)	2.58 (1.33-4.17)	6 (66.7%) Class I; 2 (22.2%) Class II; 1 (11.1%) Class III	Depression Inventory Scale and Manifest Anxiety Scale	No significant change in mean scores for depression or anxiety. No individual results provided.
Lewis et al., 1996	Case series (U, R)	23	14.5 (no range; up to 17 years)	4.8 (SD 2.5; no range)	4.24 (1-8)	17 (74%) seizure free; 4 (17%) significantly improved; 2 (9%) no significant improvement	MMPI Social function scale	Significant post-operative increases on hypochondriasis [$F_{1,8}$=9.23, p<0.05], psychasthenia [$F_{1,8}$=9.02, p<0.05], schizophrenia [$F_{1,8}$=11.53, p<0.01] and hypomania [$F_{1,8}$=20.74, p<0.01]. Significant improvement in personal satisfaction [$F_{1,22}$=67.23, p<0.0001].

a: N= Number of participants who underwent temporal resection and neuropsychological follow-up.
b: U= uncontrolled study, R= retrospective study
c: no range= no range provided by the study authors and not calculable as individual participant data not provided
d: no mean= no mean provided by the study authors and not calculable as individual participant data not provided

3.2.4.6 Educational and vocational outcomes

Seven studies reported educational and vocational outcomes following temporal surgery for epilepsy in childhood. Study characteristics, follow-up durations and findings are displayed in Table 3.9. Six of the studies reported seizure outcome, for a total of 112 participants, of whom 72 (64%) achieved Engel's Class 1 outcome/seizure freedom at last follow-up. Three studies with shorter follow-up (3 years or less; Berl et al., 2013; Dlugos et al., 1999; Williams et al., 1998) reported that participants generally had poor educational outcomes after surgery and required extra support in schooling at follow-up. The four studies with longer follow-up duration (greater than 3 years; Benifla et al., 2008; Bird-Lieberman et al., 2011; Jarrar et al., 2002; Lewis et al., 1996) reported the employment and educational status of participants at last follow-up for a total of 98 participants. Across these studies, one (1%) was in residential special school, 76 (78%) were employed or in education, 18 (18%) were unemployed and three (3%) were homemakers. Two studies (Benifla et al., 2008; Jarrar et al., 2002) reported driving outcome for a total of 62 participants. At last follow-up, 38 (61%) of participants currently had a driving license, 17 (27%) had never had a license and 7 (11%) had had a licence when seizure free but no longer did due to seizure recurrence. These results are likely to be impacted by age of participants, and duration of follow-up for each participant.

3.2.4.6 Factors affecting educational and vocational outcome

Benifla et al (2008) found that more participants with Engel Class 1 outcome (86%) were employed or in education than Engel Class III/IV outcome (57%) and this difference was almost significant ($p=0.05$). There was no attempt to control for confounding factors such as pathology or pre-surgical IQ. No other predictors of employment were investigated by this or any other study.

3.2.4.6.2 Summary of findings for educational and vocational outcomes

To summarise, the majority of participants are found at long term follow-up to be doing well in terms of participation in education and the workplace. However, none of these studies have control groups, meaning that no conclusions can be drawn about the impact of surgery on educational and occupational functioning.

Table 3.9 Characteristics and results of studies reporting educational and vocational outcomes following temporal resection for epilepsy in childhood.

Study Author, year	Design	N[a]	Age at surgery mean (range) in years	Age at epilepsy onset mean (range) in years	Mean educational or vocational follow-up mean, (range) in years	Seizure outcome (Engel Class where reported)	Outcome measures	Results
Berl et al., 2013	Single case report	1	7	3	1	Not reported	teacher and parent report	After surgery, not keeping pace with peers and requiring simplification of instructions and more assistance
Bird Lieberman et al., 2011	Single case report	1	3	1.42	12	1 (100%) Class IV	Schooling type	In residential special school
Benifla et al., 2008	Case series (U, R)[b]	42	12.5 (0.67-18.8)	3.5 (0.16-15.8)	12 (10-22)	28 (67%) Class 1; 0 Class 2, 14 (33) Class III/IV (not stated which)	telephone interviews with patients or parents: Employment and driving	Engel class 1: 24 86% employed or in school. 4 14% not employed (2 with autism and 2 on disability pension). Engel class III/IV: 8 (57%) were employed or in school, 6 (43%) patients were not employed. Driver's licenses: 12/19 eligible Engel 1 (63%) gained driving licenses. Remaining 7 patients did not relate lack of a driver's license to their history of epileptic seizures. 3 (27%) of 11 eligible Engel III/IV had obtained licenses during seizure free periods
Jarrar et al., 2002	Case series (U, R)	32	14.4 (7-18)	7.2 (1-16)	19 (4-27)	Traditional Engel's criteria: 17 (53%) Class 1. Modified criteria: 19 (59.2%) seizure frequency score 0-4 (excellent), 13 (29.5) score 5-12.	Employment and driving outcome from scripted phone interview or chart review	Employment: 3/32 (9%) unemployed, 3 (9%) homemakers, 1 (3%) part time job, 25 (78% gainfully employed). Driving: 4 (13%) lost driving license, 2 (6%) never had driving license, 26 (81%) have driving license.

Dlugos et al., 1999	Case series (U, R)	5	13.92 (8.83-18.83)	8.48 (4.5-12.75)	No mean[c] (0.67-3)	4 (80%) Class I; 1 (20%) Class III	Schooling type	4 of 5 TLE group required educational adaptations after surgery, 1 did not and is attending community college. No data for R TL.
Williams et al., 1998	Case series (U, R)	9	13 (8-15)	3 (0.67-8)	2.58 (1.33-4.17)	6 (66.7%) Class I; 2 (22.2%) Class II; 1 (11.1%) Class III	Parent report	School performance declined (not quantified)
Lewis et al., 1996	Case series (U, R)	23	14.5 (up to 17, no range)[d]	4.8 (SD 2.5, no range)	4.24 (1-8)	17 (74%) seizure free; 4 (17%) significantly improved; 2 (9%) no significant improvement	Employment and educational status at follow-up Social function scale	10 were still in high school (6 employed part time), 9 graduated from high school (5 full-time employed, 1 employed part-time, 3 unemployed), 2 had attended only grade school, 2 were in college Social function scale: significant improvement in job/school performance [$F_{(1,22)}$=23.15, p<0.0001]

a: N= Number of participants who underwent temporal resection and neuropsychological follow-up.
b: U= uncontrolled study, R= retrospective study
c: no mean= no mean provided by the study authors and not calculable as individual participant data not provided
d: no range= no range provided by the study authors and not calculable as individual participant data not provided

3.2.4.7 Social and behavioural outcomes

Fifteen studies reported social and behavioural outcomes, using a range of assessment measures, displayed in Table 3.10. Fourteen studies reported seizure outcome, for 192 children, of whom 143 (74%) achieved seizure freedom/ Engel's Class I outcome at last follow-up. Twelve studies reported individual level behavioural outcomes, for 98 children; 13 (13%) children showed improved behaviour following surgery, 73 (74%) did not change in behaviour, 9 (9%) deteriorated and 3 (3%) showed behaviours that were qualitatively different. Three studies reported behavioural outcomes at the group level, all using the Child Behaviour Checklist (CBCL) as an outcome measure. Two of these reported no significant difference in mean behaviour scores from pre-surgical assessment to follow-up (Andresen et al., 2013; Sinclair et al., 2002). Williams et al. (1998) reported improved internalising, thought problems and aggression CBCL subscale scores, but improvements in the other subscales were not significant and change in total behaviour score was not reported. Four studies (Lewis et al., 1996; Manford et al., 1998; Mikati et al., 2009; Williams et al., 1998) reported social outcomes and all reported improved socialisation, family and peer relationships post-surgery.

3.2.4.7.1 Factors associated with behavioural and social outcome

No study investigated the factors associated with behavioural outcomes and just one study reported the predictors of social outcome (Lewis et al., 1998), finding that poor social adjustment at pre-surgical assessment predicted poor adjustment at follow-up. Additionally, a higher proportion (90%) of the participants who were socially well-adjusted at follow-up were seizure free compared to poorly adjusted participants (58%). The group that were poorly adjusted at follow-up had significantly lower IQs than the well-adjusted group both pre-operatively (80 versus 92, [$F_{1,21}$=8.65, $p<0.008$]) and post-operatively (81.5 versus 91.54 [$F_{1,21}$=4.57, $p<0.05$]). As this study did not have a non-surgical control group, results cannot be attributed to surgery and the predictive effects on social outcomes observed for variables such as seizure frequency may be a product of relationships with other associated variables that are pre-existing differences between the young people, such as underlying pathology. However, the well-adjusted and poorly adjusted groups did not differ in epilepsy duration.

3.2.4.7.2 Summary of findings on behavioural and social outcome

The majority of participants showed no change in the behaviour, a minority improved and a smaller minority showed worsening. There was no overall pattern of significant change in behaviour at the group level. By contrast, all studies that reported on social outcomes reported improvement after surgery. The literature does not support the drawing of any conclusions about factors that are predictive of behavioural and social outcomes after surgery.

Table 3.10 Characteristics and findings of studies reporting social and behavioural outcomes following temporal lobe resection for epilepsy in childhood

Study Author, year	Design	N[a]	Age at surgery mean (range) in years	Age at epilepsy onset mean (range) in years	Mean social or behavioural follow-up (range) in years	Seizure outcomes (Engel Class where reported)	Outcome measures	Results
Andresen et al., 2014	Case series (U, R)[b]	64	11.3 (no range[c])	5.81 (SD 3.93; no range)	0.71 (SD 1.06; no range)	37 (62%) Class I, 0 Class II, 21 (35%) Class III, 2 (3%) Class IV	CBCL	Individual level: Left sided surgeries (N=38): 9% aggressive behaviour declined, 88% aggressive behaviour was stable, 3% aggressive behaviour improved. Right sided surgeries not reported. Group level: no significant overall change
Boronat et al., 2013	Single case report	1	2.67	2	1	Class IV	Assessment method not reported	After surgery, developed hyper-orality, non-aggressive biting of new objects and people, worsened hyperactivity, constant motion, difficulty sustaining attention. Hyper-sexuality (present pre-op but much increased), polydipsia, mutism. Klüver-Bucy diagnosis was made.
Lee et al., 2011	Case series (U, R)	40	ATL: 8 (1-15), lesion-ectomy: 6.2 (1-12)	4.8 (0.25-14)	Not reported	37 (92.5%) Class I; 2 (5%) Class II; 0 Class III; 1 (2.5%) Class IV.	Assessment method not reported	2 ATL patients developed aggressive behaviour after operation
Roulet-Perez., et al 2010	Case series (U, R)	6	No mean[d] (0.33-4.25)	1.37 (0.33-2.75)	2-6 years	3 (60%) seizure free; 2 (40%) transient relapses	Assessment of behaviour: method not reported	1 improved, 2 unchanged, 3 qualitatively different

Mikati et al., 2009	Single case report	1	7	1.33	0.75	Seizure free	Assessment method not reported	Participant was observed to be more interactive and more joyful, calm and not as agitated, and played imaginatively with toys, beginning to have relationships with peers and constantly imitating housework
Cunningham et al., 2007	Single case report	1	7	Not reported	1	Class III	Parent report	Increase in non-compliant behaviour an emotional lability noted
Moser et al., 2006	Single case report	1	7	5	0.03	Seizure free	Assessment method not reported	verbalisation and behavioural deficits normalised
Guimarães et al., 2004	Single case reports (2)	2	2 and 6	2.79 (0.58-5)	0.5	Not reported	Parent report	Parents reported that behaviour worsened for both children.
Ozmen et al., 2004	Single case report	1	12	0.92	1	Seizure free	Parent report	Parents reported: one year after surgery developed excessive masturbation in inappropriate places, several times per day, causing parental anger, treated successfully with psychoeducation. Also social withdrawal, aggression
Nakaji et al., 2003	Single case reports (2)	2	5.5 and 13.5	4.3 (3.7-5)	1.5	2 (100%) seizure free	Assessment method not reported	Behaviour of both improved dramatically (not quantified, no further detail)
Sinclair et al., 2003	Case series (U, R)	25	9 (1.5-16)	2.71 (0-13)	1	33 (79%) Class I;0 Class II; 5 (11.9%) Class III; 4 (9.5%) Class IV	Child Behaviour Checklist	Individual level: results not reported. Group level: no significant changes no change pre- to post- surgery on Child Behaviour Checklist scores (ANOVA)
Szabó et al., 1999	Case series (U, R)	4	4.75 (2-8)	0.92 (0-1.75)	1.68 (0.5-3.25)	4 (80%) seizure free; 1 (20%) persistent seizures	Vineland adaptive behaviour scales-revised; parental report	3 improved, 1 worsened

Manford et al., 1998	Single case report	1	13	10	4	Seizure free	Parent report	Parents reported: school work much improved, now has friends and plays hockey. Relations with family markedly better, became very responsible at home including caring for sister. No serious family disharmony.
Williams et al., 1998	Case series (U, R)	9	13 (8-15)	3 (0.67-8)	2.58 (1.33-4.17)	6 (66.7%) Class I; 2 (22.2%) Class II; 1 (11.1%) Class III	Child Behaviour Checklist	Following surgery there was significant improvement for internalising [$t=2.33$, $p<0.05$], Thought problems [$t=4.36$, $p<0.002$] and Aggression [$t=2.31$, $p<0.05$]. Scores were lower i.e. improved on all subscales but the others were not significantly different. Parents observed improvements in social relationships and activities.
Lewis et al., 1996	Case series (U, R)	23	14.5 (up to 17, no range)	4.8 (SD 2.5, no range)	4.24 (1-8)	17 (74%) seizure free; 4 (17%) significantly improved; 2 (9%) no significant improvement	Social function interviews	Individual level: All participants improved in social function scores after surgery. Group level: Significant improvements in family relations [$F_{1,22}=10.03$, $p<0.01$], peer relations [$F_{1,22}=31.12$, $p<0.0001$], leisure activities [$F_{1,22}=67.23$, $p<0.0001$], job/school performance [$F_{1,22}=23.15$, $p<0.0001$], personal satisfaction [$F_{1,22}=26.19$, $p<0.0001$], and adaption to illness [$F_{1,22}=15.00$, $p<0.001$].

a: N= Number of participants who underwent temporal resection and neuropsychological follow-up.
b: U= uncontrolled study, R= retrospective study
c: no range= no range provided by the study authors and not calculable as individual participant data not provided
d: no mean= no mean provided by the study authors and not calculable as individual participant data not provided

3.2.4.8 Disability and functional independence

One study (Ghatan et al., 2014) reported disability status as an outcome of surgery, using the modified Rankin scale of disability (Banks & Marotta, 2007), which is a six-point scale of disability that ranges from a score of zero which denotes no symptoms at all to a score of six, which represents death. Ghatan et al. (2014) found that five out of nine participants (56%) improved on the modified Rankin Scale of disability (Banks & Marotta, 2007), each by one point from pre- to post-surgery, and four participants (46%) did not change. Study characteristics are displayed in Table 3.2 (Section 3.2.4.1). In conclusion, impact of temporal resection on disability level is an area for further study and, although this study appears positive, there were no control participants to control for confounding variables and there are too few results to allow meaningful conclusions to be drawn.

3.2.4.9 Satisfaction with surgery

Two studies reported parental satisfaction with surgery. Manford et al. (1998) stated that the parents of the child in their single case report very happy with surgical results. Benifla et al. (2008) used a five-point scale to rate parental satisfaction (from 1=very unsatisfied to 5=very satisfied) and found a mean satisfaction rating of 4.5 (SD 1.8). More specifically, parents of all participants with Engel's Class I seizure outcome reported at least grade 4 (mean 4.7 SD 0.4). Of the parents of the 14 children with Engel III/IV outcome, 3 were satisfied (grade 4) and 11 very unsatisfied to neutral (mean 2.2 SD 1.3). There was a significant difference between the groups ($p<0.001$). In conclusion, there were few studies reporting satisfaction after surgery. From the limited data available, better seizure outcome appears to predict parental satisfaction with surgery.

3.3 Methodological Quality

As discussed in Section 2.7, in the absence of precise guidance on quality assessment for uncontrolled case series, studies were rated for the following broad categories of bias, in accordance with Cochrane (2013): sample bias, attrition bias, confounding bias, measurement bias and validity of reporting and claims made based on the results. It is important too to note that the aims of the authors varied; many studies simply aimed to present the findings from their recent case series of epilepsy surgery patients, rather than to assess the efficacy of surgery. Therefore, the quality ratings in this section are not intended as criticism of researchers, but as a way of assessing the quality of evidence provided by each study for the purpose of answering the research questions of this thesis. Where possible, a distinction is made between methodological quality and reporting quality, however, in some cases it was not possible to assess whether potential biases arise from methodological or reporting problems. These issues are discussed further in Chapter Four. All

studies contained major sources of bias and no study was rated as "low" for risk of bias in all categories. The ratings for risk of bias for each of the 73 included studies are provided in Table 3.11. This section discusses methodological quality by addressing each of the risk of bias categories in turn.

3.3.1 Sample Bias

The majority of studies were retrospective uncontrolled observational case series, with participants drawn from a small population and selection method often not specified. The majority of studies had very small sample sizes and lacked power for the statistical analyses used. These factors are threats to the external validity of the study and reduce generalisability of findings to the wider population. Therefore, the results of these studies cannot with any certainty be used to support claims about the outcomes of temporal lobe surgery for children with epilepsy.

3.3.2 Attrition bias

As most studies were retrospective, the majority, 63 (86%) out of the 73 studies, did not report participants lost-to-follow-up. Nearly all studies described a range of follow-up durations; some participants were followed up for a few months, whilst others were followed for years. Furthermore, retrospective studies may be biased by only including participants who have been assessed at follow-up and never counting operated patients without follow-up data. This may threaten the representativeness of the cohort, as participants who did not take part in follow-up assessment may significantly differ from the rest of the sample in relevant attributes and affect the results obtained. For example, it could be hypothesised that participants with severe cognitive impairment following surgery may be less likely than those with higher cognitive functioning to undergo cognitive assessment at follow-up. It could also be hypothesised that those who agree to the longest follow-ups may be those who have achieved the most favourable outcomes or are more satisfied with the care they have received, which could introduce more bias to conclusions about longer-term outcomes. These factors underscore the importance of prospectively planned studies, to reduce this source of bias. In studies with variable follow-up, results should be presented in a stratified manner so that it is possible to inspect the results of children with different follow-up durations, and results of children with large differences in follow-up duration should not be statistically combined without any attempt to control for the effect of follow-up time.

3.3.3 Confounding bias

A particularly problematic aspect of the studies' measurement of developing skills in children is that very few studies measured the change in developmental trajectory before and after surgery; rather they simply measured the change in score at two or three time points, once before surgery

and once or twice afterwards. Reported increase or decrease in a particular skill following surgery may be unrelated to surgery and fit with an existing pattern of regression or development of that skill, particularly with variable follow-up durations. Establishing the developmental trajectory of children before surgery by measuring the skill at multiple time-points before surgery would enable firmer conclusions to be drawn on the effect of the surgery on development. The internal validity of the studies is threatened by combining the results of children with a range of surgery types (for example, combining results of resections including and excluding the hippocampal region), ages (infants and older adolescents) and pre-surgical developmental levels. This pooling of results limits the conclusions that can be drawn about the efficacy of surgery for a given child. Hrabok et al. (2013) noted a similar problem with quality in their review of reporting of neuropsychological outcomes of epilepsy surgery. Furthermore, confounding variables, such as length-of-follow-up, duration of seizures, pre-surgical level, age at onset, and age at surgery, were inadequately controlled for. Some studies did use statistical methods to control for these factors (e.g. Korkman et al., 2005; Lah & Smith, 2015; Miranda & Smith, 2001) however, these were often underpowered. Furthermore, increasing the number of comparisons can lead to increased risk of Type 1 errors, as with more comparisons, statistically significant results are likely to be found by chance (Ioannidis, 2005). In studies that did include a non-surgical control group (e.g. Meekes et al., 2013; Micallef et al.., 2010; Skirrow et al., 2011), there was no randomisation or blinding to group.

3.3.4 Measurement bias

Many of the studies reported psychosocial outcomes in one or two lines of text without quantifying or operationalising the outcome, based on clinical observation or parent report, for example stating that speech "improved" (Romanelli et al., 2001) or "behaviour improved dramatically" (Nakaji et al., 2003) and studies sometimes did not mention where this information came from. Where quantitative measures were used, for example for IQ, some were well known and validated measures such as the WISC-III, whereas other studies used briefer assessments, such as Raven's Coloured Progressive Matrices, and thus studies may have measured different skills. A large number of assessments were used for each outcome domain, each with their own validity, reliability and risks of bias. Some studies did not account for practice effects on neuropsychological assessments, which may also have introduced measurement bias (Chelune et al., 1993).

3.3.5 Reporting bias

Many studies did not report individual participant characteristics (e.g. Jarrar et al., 2002). Where individual results were presented it allowed the reader to disaggregate results for children who varied by important clinical factors, such as age at surgery, pathology, resection type and seizure duration. Where such results were only presented in combined form, reported outcomes are of

limited clinical utility. Unfortunately, two papers did not even report the age range or mean age at surgery for children undergoing temporal resection (Gagliardi et al., 2011; Robinson et al., 2000). Many studies did not report the nature of the temporal resection, and whether it included the hippocampus or amygdala. Furthermore, despite commenting on cognitive skills and psychosocial outcomes, very few studies reported factors of key importance to these domains, such as family functioning and socio-economic status of the children. Importantly, few studies reported whether or not children are currently using AEDs at follow-up, which could have a significant confounding effect on cognitive outcome. As noted by Ioannidis (2011), the calculation of multiple comparisons between pre-surgery and post-surgery outcome measure scores may increase the risk of publication bias at the level of outcome reporting (Ioannidis, 2011), in which only significant effects are reported. Ioannidis (2011) also notes that small research studies that use statistical methods to control for confounding variables are susceptible to selective analysis reporting bias, if researchers perform different analyses to adjust for different confounding variables and then selectively report only the analyses in which a significant effect of intervention remains. The poor reporting standards in cohort studies prompted the publication of a set of standards called Strengthening the Reporting of Observational Studies in Epidemiology (STROBE; Appendix D), which sets out guidelines for the design and reporting of studies (Von Elm et al., 2007). However, few of the included studies met these criteria.

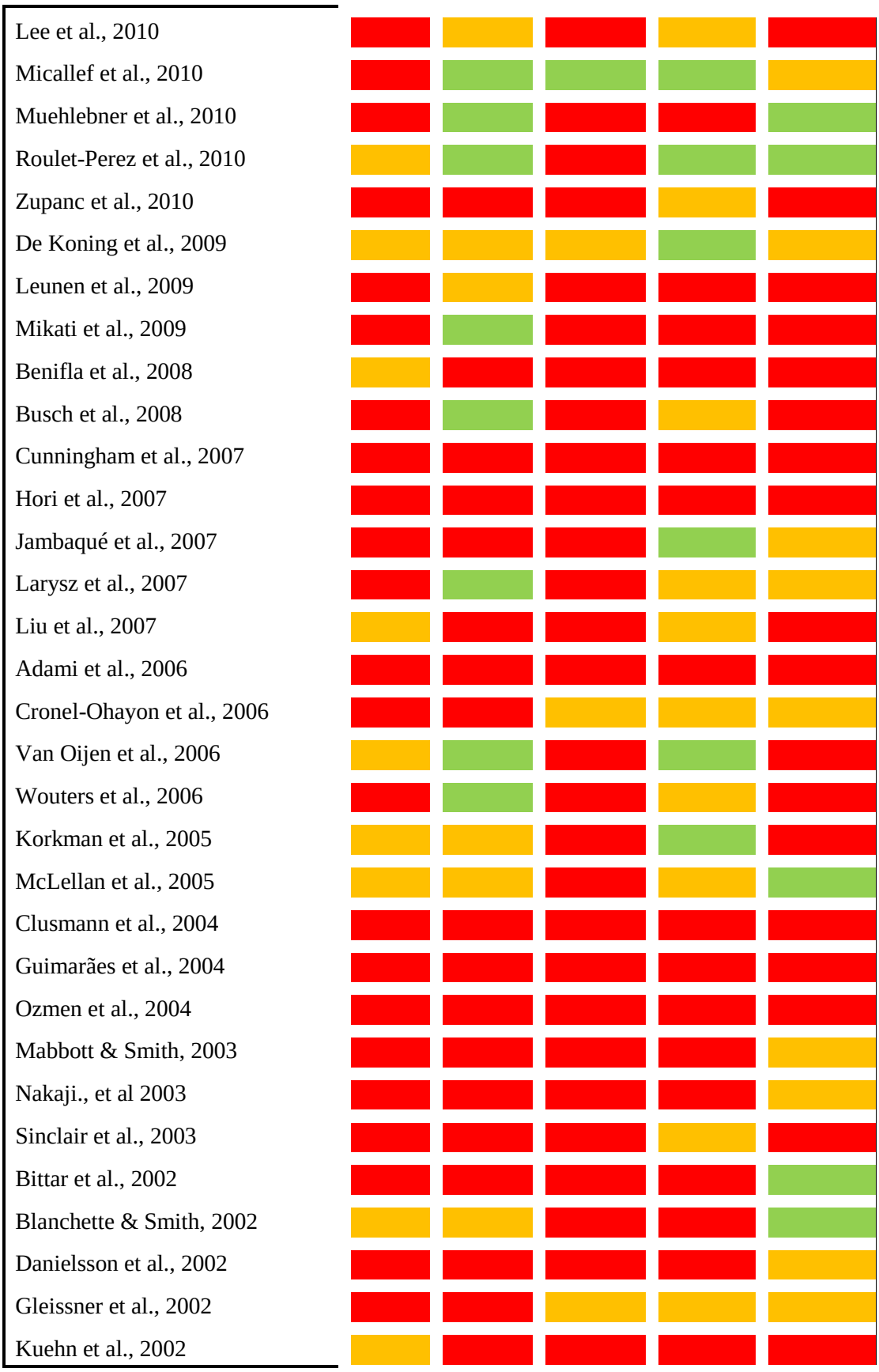
3.3.6 Validity of claims made

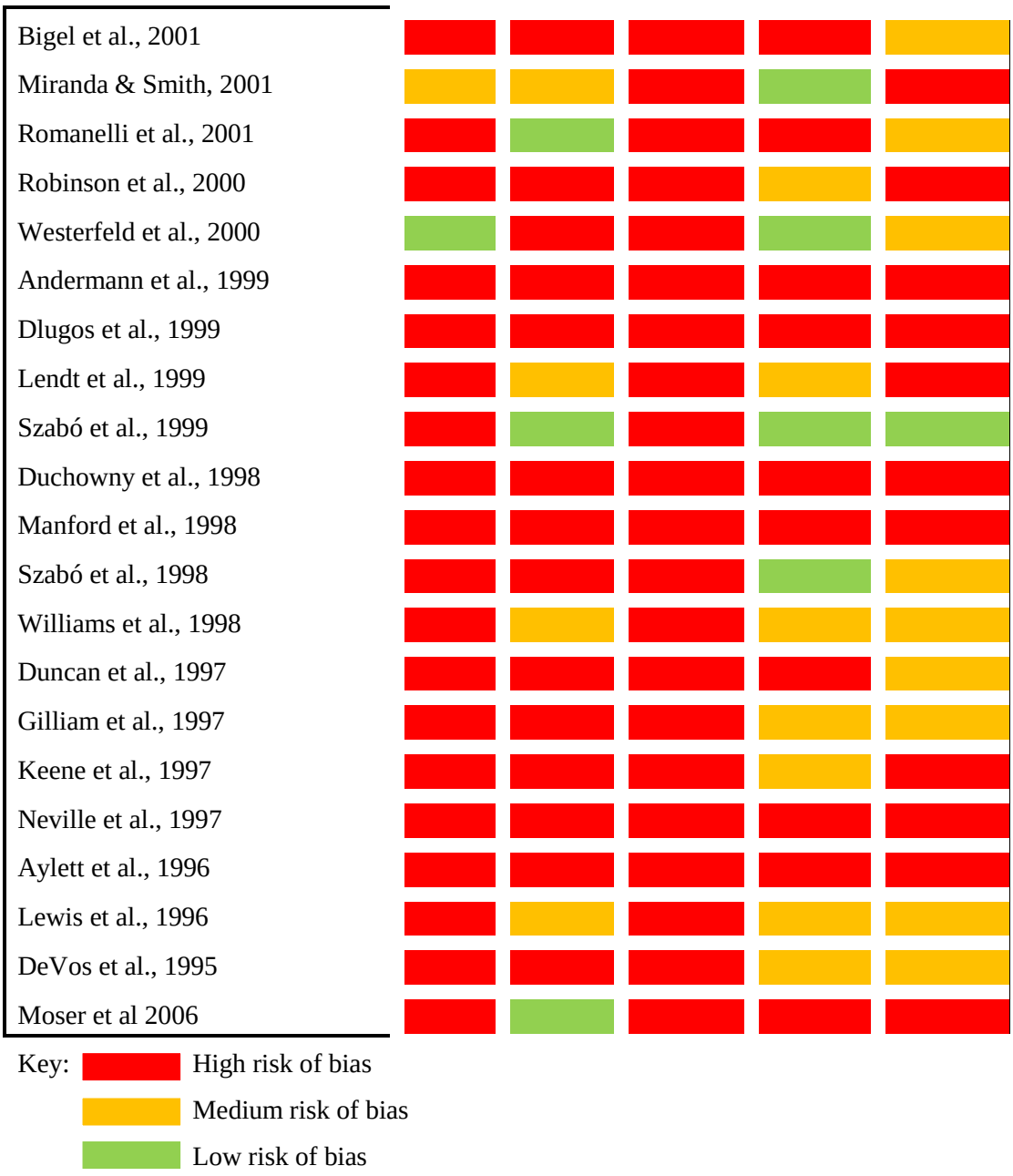
Thirty nine (54%) studies were at high risk of overstating claims based on the results, twenty six (35%) at medium risk and eight (11%) at low risk. Those at low risk were only rated as such because they made no real claims that results could be generalised (e.g. Blanchette et al., 2002). Most papers overstated the extent to which the outcomes could be attributed to the surgery, without adequately controlling for confounding factors. For example, Zupanc et al. (2010) claimed that QoL improved after surgery, when there was no pre-surgical assessment of QoL. Whilst many studies did acknowledge their limitations, they then went on to overstate the generalisability of their results. The majority of papers pooled data from participants with heterogeneous ages, surgeries, and characteristics, thereby yielding conclusions that cannot be applied to aid clinical decision making about a specific age of child or type of resection. Even if studies were able to establish a causal link between the outcomes measured and the surgery, most studies lacked adequate follow up (which was less than one year in many cases) to make firm conclusions about the long term consequences of the surgery for each outcome domain. Furthermore, the majority of studies only measured less than three outcome domains, and as such they neglected the effect of the surgery on other outcome domains. Whilst it is understandable that small-scale studies choose to focus on just one or two

outcome domains, advocating for or against surgery should be based upon the appraisal of results across all domains that may be important to a developing young person. This is particularly evident in the paediatric epilepsy surgery literature as a whole, as described in Section 3.1, 811 (64%) of the 1259 studies reporting paediatric epilepsy surgery outcome did not report neurocognitive and psychosocial outcomes at all, and most claims of beneficial outcome from surgery are frequently based only on seizure outcome. The results presented above demonstrate, albeit with limited quality, that beneficial seizure outcome following surgery does not always preclude the development of other problems that may have a major impact on a child's life. The ratings for each category of bias are displayed in Table 3.11.

Table 3.11 Risk of bias ratings for all included studies

Study (author, year)	Sample Bias	Attrition bias	Con-founding	Measure-ment bias	Validity of reporting/ claims
Lah & Smith, 2015					
Lee et al., 2015					
Skirrow et al., 2015					
Andresen et al., 2014					
Ghatan et al., 2014					
Grosmaitre et al., 2014					
Berl et al., 2013					
Boronat et al., 2013					
Meekes et al., 2013					
Miserocchi et al., 2013					
Taylor et al., 2013					
Beaton et al., 2012					
Moseley et al., 2012					
Vadera et al., 2012					
Bird-Lieberman et al., 2011					
Gagliardi et al., 2011					
Garcia-Fernandez et al., 2011					
Lee et al., 2011					
Skirrow et al., 2011					
Jarrar et al., 2010					


Lee et al., 2010
Micallef et al., 2010
Muehlebner et al., 2010
Roulet-Perez et al., 2010
Zupanc et al., 2010
De Koning et al., 2009
Leunen et al., 2009
Mikati et al., 2009
Benifla et al., 2008
Busch et al., 2008
Cunningham et al., 2007
Hori et al., 2007
Jambaqué et al., 2007
Larysz et al., 2007
Liu et al., 2007
Adami et al., 2006
Cronel-Ohayon et al., 2006
Van Oijen et al., 2006
Wouters et al., 2006
Korkman et al., 2005
McLellan et al., 2005
Clusmann et al., 2004
Guimarães et al., 2004
Ozmen et al., 2004
Mabbott & Smith, 2003
Nakaji., et al 2003
Sinclair et al., 2003
Bittar et al., 2002
Blanchette & Smith, 2002
Danielsson et al., 2002
Gleissner et al., 2002
Kuehn et al., 2002



3.3.7 Common sources of bias in included studies

A number of more specific potential sources of bias were repeatedly observed in studies. These are displayed in Table 3.12, which records which studies had each source of bias and journal in which they were published. Within the same paper, the measurement of different outcomes sometimes varied in methodological quality. Many of the studies had higher methodological quality for seizure outcomes than neuropsychological outcomes and within neuropsychological outcomes, some studies reported pre-and post- surgical assessment for cognition but not for psychosocial measures (e.g. Lendt et al., 1996). The ratings provided in Table 3.12 were decided based upon the neuropsychological outcome domain reported with the highest methodological quality, i.e. Lendt et

al. (1996) was not rated as having the bias source "no pre- and post- measurement" because they did have these assessments for cognition. This further illustrates the complexity and heterogeneity of the literature when collecting data on a broad range of outcomes after paediatric epilepsy surgery.

Table 3.12 Common sources of bias in studies, and publication

Author, Year	Retrospective design	Unvalidated measures	No pre- and post- assessment	Variable follow-up	No control group	Pooling across surgery types	Patient details omitted	Sample size of N<3	Journal
Lah et al 2015	X			X	X		X		Epilepsy & Behavior
Lee et al 2015	X			X	X				Pediatric Neurology
Skirrow et al 2015	X			X					Brain
Andreson et al 2014	X			X	X		X		Frontiers in Neurology
Ghatan et al 2014	X	X			X	X			Journal of Neurosurgery: Pediatrics
Grosmaitre et al 2014	X							X	Neurocase
Berl et al 2013	X				X		X	X	Book chapter
Boronat et al 2013	X	X	X		X			X	Childs Nervous System
Meekes et al 2013									Epilepsy Research
Miserocchi et al 2013	X			X	X				Journal of Neurosurgery: Pediatrics
Taylor et al 2013	X	X	X		X			X	Journal of Neurosurgery: Pediatrics
Beaton et al 2012	X			X	X				Seizure
Vadera et al 2012	X			X	X				Journal of Neurosurgery: Pediatrics
Bird-Lieberman et al 2011	X	X	X	X	X			X	Journal of Neurosurgery: Pediatrics
Gagliardi et al 2011	X			X	X		X		Arquiva Neuropsiquiatra
Garcia-Fernandez et al 2011	X	X		X	X	X	X		Seizure
Lee et al 2011	X	X	X	X	X		X		Childs Nervous System
Skirrow et al 2011	X			X					Neurology
Lee et al 2010	X			X	X				Childs Nervous System
Micallef et al 2010			X	X					Epilepsia
Muehlebner et al 2010	X	X			X			X	Epilepsy Research
Roulet-Perez et al 2010	X			X	X				Epilepsia
Zupanc et al 2010	X			X	X	X	X		Pediatric Neurology
de Koning et al	X				X				Epilepsia

Author, Year	Retrospective design	Unvalidated measures	No pre- and post- assessment	Variable follow-up	No control group	Pooling across surgery types	Patient details omitted	Sample size of N<3	Journal
2009									
Leunen et al 2009	X		X	X			X		Epilepsy & Behavior
Mikati et al 2009	X	X			X			X	Epilepsy & Behavior
Benifla et al 2008	X			X	X				Epilepsy Research
Busch et al 2008	X			X	X			X	Epileptic Disorders
Cunningham et al 2007	X	X			X		X	X	Journal of Developmental & Behavioral Pediatrics
Hori et al 2007	X			X	X			X	Journal of Neurosurgery
Jambaqué et al 2007	X			X	X		X		Neuropsychologia
Jarrar et al 2007	X		X	X	X		X		Neurology
Larysz et al 2007	X	X			X	X		X	Childs Nervous System
Liu et al 2007	X			X	X		X		Brain & Development
Adami et al 2006	X	X	X		X			X	Acta Psychiatrica Scandinavica
Cronel-Ohayon et al 2006	X							X	Neuropediatrics
Joudan Moser et al 2006	X				X			X	Acta Paediatrica
Van Oijen et al 2006	X			X	X		X		European Journal of Pediatric Neurology
Wouters et al 2006	X				X			X	Developmental Medicine & Child Neurology
Korkman et al 2005	X				X		X		Pediatric Neurology
McLellan et al 2005	X	X		X	X		X		Developmental Medicine & Child Neurology
Clussman et al 2004	X				X				Neurosurgery
Guimarães et al 2004	X	X			X		X	X	Epilepsy & Behavior
Ozmen et al 2004	X	X	X		X			X	Epilepsy & Behavior
Mabbott et al 2003	X			X	X		X		Neuropsychologia
Nakaji et al 2003	X	X	X		X			X	Pediatrics
Sinclair et al 2003	X				X				Pediatric Neurosurgery
Bittar et al 2002	X	X	X	X	X				Journal of Clinical Neuroscience
Danielsson et al 2002	X				X				Epilepsy & Behavior

Author, Year	Retrospective design	Unvalidated measures	No pre- and post- assessment	Variable follow-up	No control group	Pooling across surgery types	Patient details omitted	Sample size of N<3	Journal
Gleissner et al 2002	X			X	X		X		Epilepsy Research
Kuehn et al 2002	X			X	X		X		Child's Nervous System
Bigel et al 2001	X			X	X		X	X	Brain and Cognition
Blanchette et al 2001	X			X	X		X		Brain and Cognition
Miranda et al 2001	X			X	X				Epilepsy & Behavior
Romanelli et al 2001	X	X	X		X			X	Neurosurgery
Moseley et al 2000	X	X	X		X			X	Journal of Child Neurology
Robinson et al 2000	X				X		X		Journal of Neurosurgery
Westerfeld et al 2000	X			X	X		X		Journal of Neuropsychology
Andermann et al 1999	X	X	X		X			X	Epilepsia
Dlugos et al 1999	X			X	X				Pediatric Neurology
Lendt et al 1999	X								Epilepsia
Szabó et al 1999	X			X	X				Pediatric Neurology
Duchowny et al 1998	X	X		X	X		X		Epilepsia
Manford et al 1998	X	X			X			X	J. Am. Acad. Child Adolesc. Psychiatry
Szabó et al 1998	X			X	X				Epilepsia
Williams et al 1998	X			X	X				Pediatric Neurology
Duncan et al 1997	X	X	X	X	X		X		Pediatric Neurosurgery
Gilliam et al 1997	X			X	X	X			Neurology
Keene et al 1997	X		X	X	X	X			Child's Nervous System
Neville et al 1997	X	X			X			X	Pediatric Neurology
Aylett et al 1996	X	X	X		X			X	European Child & Adolescent Psychiatry
Lewis et al 1996	X			X	X				Journal of Epilepsy
DeVos et al, 1995	X			X	X	X			Neurology

Table 3.12 does not contain methodological quality items that are commonly rated within systematic reviews, such as allocation concealment or masking of outcomes, because there were no randomised controlled trials in the included studies and none of the studies had these features. Only one study (Meekes et al, 2013), had none of the common sources of bias displayed in Table 3.12 and one (Lewis et al., 1996) had one. Nine studies had two of the common bias sources, 17 had three, 22 had four, 19 had five and four had six bias sources. Many of the common potential sources of bias in Table 3.11, for example, N<3 and retrospective design, are not necessarily methodological limitations, depending on the aim of the study, however, they become problematic when authors attempt to extrapolate, generalise, or make claims for the significance of their findings. As shown in Table 3.11, a number of studies were rated as making claims that overstretched their results.

A Spearman's Rank correlation coefficient was calculated to investigate the relationship between the average number of common bias sources per study found from each publication and the publication's impact factor (the book chapter was omitted). Impact factors were obtained from the 2014 Journal Citation Reports (Thomson Reuters, 2015). No significant correlation [ρ=-0.06, n=34, p=0.740] was found between number of study biases and publication impact factor, as displayed in Figure 3.8.

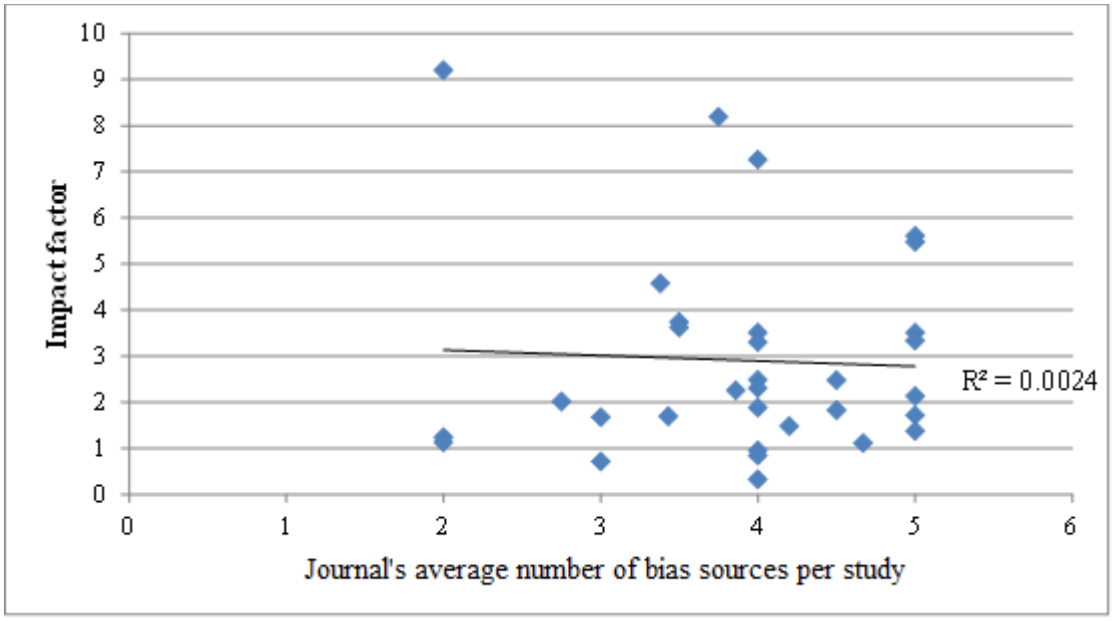


Figure 3.8 Scatter graph with trend line to show relationship between journal impact factor and average number of common bias sources in their studies

3.4 Highest quality evidence and synthesis

Three of the included studies (Meekes et al., 2013; Micallef et al., 2010; Skirrow et al., 2011) were deemed to be of sufficient quality to be included in the final synthesis of the best quality evidence, based upon an aggregate reporting and methodological quality assessment, which took into account the risk of bias ratings provided for each study in Table 3.11 and the ratings of common sources of bias provided in Table 3.12. Unfortunately, these studies each reported on different outcome domains so their results cannot be pooled. Nevertheless, their results are summarised here before findings of the review are concluded.

Micallef et al. (2010) conducted a prospective longitudinal study of children with TLE and followed their psychosocial functioning, measured by semi-structured interviews and self-report questionnaires. This design allowed comparisons to be drawn between the outcomes of young people who proceeded to surgery and those who did not undergo surgery, and these groups were found to be matched for age at onset, gender, follow-up time from seizure onset and rate of intellectual disability. Thus the design allowed for control of some of the confounding factors that could affect outcomes, although there was no blinding of outcome measurement, and there may have been inherent differences between children who were suitable candidates for surgery and the non-surgical group, so confounding was not eliminated. As discussed in Section 3.2.4.5, they found that participants who achieved seizure freedom following surgery did not have significantly different scores in depression, self-esteem or anxiety compared to chronic epilepsy non-surgical controls, but participants who underwent surgery but did not achieve seizure freedom had significantly lower self-esteem and increased depression compared to the other groups, despite having the same seizure burden as the chronic epilepsy group. This finding points to a possible effect of disappointment at failed treatment in developing psychological difficulties post-surgery, or to a negative experience of undergoing surgery, which is not outweighed by positive effects. The authors reported that the not-seizure free group reported a sense of being "changed" after the surgery and reference studies pointing to the role of temporal lobe surgery in potentially causing neurobiological changes that contribute to depression (e.g. Wrench et al., 2004), in addition to the psychological experience of failed surgery. A strength of this study was its appreciation of the complexity of psychological distress and although subjective, the authors' choice to employ semi-structured interviews to explore the psychological changes after surgery allowed for a richer dataset to be developed than simply using standardised outcome measures of psychological constructs. For example, they found that, although those who achieved seizure freedom following surgery had improved self-esteem, identity and sense of a "cure", some participants felt pressure to increase their activity levels, which was linked to worsening mood. Overall, they found that the surgical seizure free group did not differ in depression, self-esteem or anxiety compared to the spontaneous

remission group or the chronic epilepsy group, and the surgical non-seizure free group was significantly worse, suggesting an overall negative effect following surgery on these outcomes. However, a major limitation in this study is the variable length of follow-up after surgery, which ranged from 3 months to 14 years, and individual data were not available for participants with different follow-up durations. Length of follow-up may have had a significant impact on reported outcome as it seems likely that any effect of surgery on depression or anxiety may take some time to emerge, and because the process of psychological adjustment to surgery and the effects of seizure burden or cognitive change after surgery, are likely to be gradual. Therefore, further studies with analysis of follow-up at set times after surgery are required before results can be generalizable.

Meekes et al. (2013) undertook a prospective controlled study to investigate verbal memory after epilepsy surgery in childhood. Unfortunately, the control group consisted only of healthy children; it would have been useful to have a 'seizure' group as well as a 'chronic seizure' control group in order to control for confounding factors such as the influence of underlying pathology on memory development, or the effect of continued seizures over the follow-up period. In addition, the study was not limited to temporal lobe surgery so results also included children who had undergone other surgeries for epilepsy. However, results were calculated for TLE separately, albeit this group having a small sample size of ten. A strength of this study was a consideration of practice effects and predicted development; they compared obtained scores at follow-up to predicted scores which were extrapolated from baseline with adjustment for retest effects and expected development, using standardized regression-based analysis (Duff, 2012; McSweeny et al., 1993). At the individual level, Meekes et al. (2013) found that 4 participants had significantly deteriorated in verbal memory relative to their projected scores (all left sided temporal surgical candidates) and 6 had no significant change in verbal memory relative to their projected score (2 left and 4 right temporal candidates). Meekes et al. (2013) also found that temporal lobe surgery candidates performed significantly worse on verbal memory assessment at follow-up at the group level compared to that predicted from their pre-surgical scores. As discussed in Section 3.2.4.2.1, this effect remained after preverbal IQ, age at surgery and AED use were accounted for. Another strength of this study was that it presented limitations, and did not make any claims of its generalisability. However, further studies with a larger sample size of temporal lobe surgery candidates, that use chronic epilepsy control groups, are required in order to obtain generalizable results about the impact of TLE surgery on verbal memory.

Skirrow et al. (2011) conducted a follow-up study of intellectual outcome for 42 young people who underwent temporal lobe surgery in childhood and 11 matched non-surgical controls. A strength of

this study was its long term follow-up, however this varied between participants (mean 9 years old, range 5-15 years). As discussed in Section 3.2.4.1, left temporal lobe resection patients showed statistically significant improvement in intellectual function after surgery at the group level and right temporal lobe resected patients and non-surgical controls did not. At the individual level, 17 (41%) surgery patients had gained more than 10 FSIQ points at follow-up, 24 (57%) had not changed significantly and 1 had deteriorated more than ten points. These individual results were more positive than the majority of individual results presented in Section 3.2.4.1. Within the control participants, one participant improved more than ten points and the results for the other control participants were not provided. This study was unique among included studies of intellectual outcome in the number of variables it investigated for a predictive relationship with intellectual outcome. They found that higher preoperative FSIQ negatively predicted positive FSIQ change, current AED use was a negative predictor of FSIQ (specifically Topirimate) and they found no significant effect of seizure duration or post-operative seizure status. Quality of life assessment was undertaken only at follow-up, so group differences on this measure may have been the result of other factors that existed pre-surgery. Authors recognised the limitations of their study, pointing to the small sample size, and identifying that EEG findings differed between the non-surgical controls and surgical participants, which may have meant that observed differences in results were due to pre-existing differences in the groups. The authors conclude that the intellectual gains observed in the study were striking in comparison to the risk of cognitive deterioration of conventionally treated children with TLE. However, the size of the control group is small so the difference detected between groups may be spurious, as this group may be representative of children with chronic TLE who do not undergo surgery. Although this was the most appropriately designed study for measuring change in intellectual function, further studies with a larger non-surgical control group must be conducted to assess if this finding is generalizable.

In summary, the results of these selected studies suggest that for each outcome, most children remained stable, some improved and some deteriorated. The studies found that temporal lobe epilepsy surgery may have beneficial effects for intellectual outcome but that it may contribute to verbal memory deterioration for children who are not seizure free after surgery. However, these results are from studies with small samples and are not generalizable. Overall, for each outcome, most children remained stable, some improved and some deteriorated.

CHAPTER FOUR: DISCUSSION

This chapter will use the evidence from the systematic review of the temporal lobe epilepsy surgery literature to address the research questions and project aims laid out in Chapter One. Sections 4.1 and 4.2 will address each of the research questions in turn, before Section 4.3 addresses the limitations of the review. Section 4.4 makes a number of recommendations for current clinical practice, researchers at individual centres and to the wider research community.

4.1 What are the long term neuropsychological outcomes after temporal lobe epilepsy surgery in childhood?

This systematic review found that for each neuropsychological outcome domain, the majority of young people remained stable after surgery, some young people improved and some deteriorated. As this same pattern was found across neuropsychological domains, each domain will not be discussed in detail. These findings are more conservative than some reviews report, for example Baldeweg and Skirrow (2015) found that half of the participants in their included studies showed improved IQ from pre-surgical assessment to follow-up. This discrepancy may be because this thesis focussed only on temporal lobe surgery, whereas others (e.g. Baldeweg & Skirrow, 2015) include other surgical types, including hemispherectomy, which has been associated with lower risk of reduced cognitive outcome (e.g. Baldeweg & Skirrow, 2015; Vining et al., 1997). This review was unable to analyse the effect sizes of the improvements and deteriorations in function experienced by some individuals after surgery because data about the number of participants experiencing improvement and decline was generally presented categorically, rather than as individual participant results. Therefore, this thesis cannot make conclusions about the severity of possible post-surgical impairment or the magnitude of potential improvement, which would be useful information for families who are deciding whether or not to proceed with surgery. Analysis of the evidence retrieved in this review did not enable conclusions to be drawn about long-term outcomes because studies had variable, and often short, follow-up periods, which ranged from less than one year in many participants to 27 years for one participant; if that participant was aged 18 at the time of surgery, the maximum possible age at follow-up would be 45, so no studies examined outcomes in later life. Therefore, it is not possible to assess the very long term neuropsychological outcomes of temporal lobe epilepsy surgery in childhood. Furthermore, because most study samples varied in both age at surgery and follow-up assessment time-points, and because they generally pooled outcomes so that long-term outcomes were generally combined with results from candidates who had only recently undergone surgery, the relationship between surgery and magnitude of change or developmental progress could not be investigated. It is possible that the full impact of surgery may manifest later and these late effects were not captured in the review. Therefore, the

review was unable to answer this research question fully. However, as most children remain stable, some improve, and some deteriorate, it is important to investigate which children are likely to experience which outcome so that decisions to proceed with surgery are based on accurate evidence. Potential predictors of neuropsychological outcome are addressed in the next sections.

4.1.1 Is earlier better?

From the included studies it was not yet possible to answer this research question about whether earlier age at temporal lobe epilepsy surgery leads to better neuropsychological outcomes. Other authors (Dunkley et al., 2011; Loddenkemper et al., 2007; Steinbok et al., 2009) have noted that reports of epilepsy studies have generally not shown clear stratification for age at surgery, neurosurgical technique, follow-up duration and age of onset so these factors may be conflated in results. Therefore, the review was unable to contribute to the debate over whether earlier surgery allows reduced seizure burden and easier recovery, or whether earlier insult conveys vulnerability. These limitations are discussed further in Section 4.3. In the present review, only studies of cognitive outcome reported the predictive effect of age at surgery and these studies had mixed results that could not be generalised, as discussed in Section 3.2.4.1.1. This may be a result of a lack of studies with long-enough follow-up periods and matched non-surgical control groups which would have allowed the effect of years with reduced seizure burden to appear. Berl (2014) makes a compelling case for the need for earlier intervention, in her commentary on Skirrow et al. (2015), citing Skirrow et al.'s finding of improved memory after long-term follow-up in the contralateral hemisphere-mediated memory function (i.e. right operated participants improved in verbal memory). These findings are indeed promising, and Berl (2014) raises a number of questions about whether a broad range of social, QoL and cognitive outcomes would be improved with earlier surgery. Berl (2014) uses the rationale that if children have surgery before plastic compensatory reorganisation of functions due to seizure activity had occurred, this would reduce the demand placed on global brain functions and therefore may lead to more typical development. It is certainly important to pursue this theory in further research, however, it must be noted that Skirrow et al. (2015) had a small sample, with unequal group sizes, so their results may not be generalizable. Furthermore, they did not themselves find a significant effect of age at surgery on memory outcome, and only found a significant association of seizure duration, with one verbal memory measure, which was taken post-surgery only, and therefore may not represent outcome of surgery but rather pre-existing differences between children. Therefore, Berl's urgent calls for earlier surgery may require further evidence. The findings of this review therefore cannot support or reject Cross's (2006) assertion that earlier surgery leads to better cognitive outcomes.

4.1.2 Factors predictive of neuropsychological outcome after paediatric temporal lobe epilepsy surgery

In addition to age, the associations between neuropsychological outcome and a number of other participant factors were investigated. Among the studies that investigated the predictive effects of seizure duration, age at onset or age at surgery upon neuropsychological outcome, no clear pattern of predictive effect was found. Therefore, these are not considered further, but a number of other participant characteristics that may have a bearing on neuropsychological outcomes are discussed below. The factors discussed represent both potential moderating factors on outcome of surgery, and potential confounding factors that may bias results if not adequately measured and controlled for in the analysis of studies.

4.1.2.1 Side of surgery

Results suggest that surgery on the left temporal lobe may be related to poorer language and verbal memory outcome compared to surgery on the right temporal lobe, although not all studies found these results. Those with left TLE generally had poorer language or verbal memory than those with right TLE even before surgery, but these material specific deficits were increased after surgery. As noted above, Skirrow et al.'s (2015) findings went further and found that the memory functions of the contralateral hemisphere could be enhanced after surgery. As discussed above, the effect of side of surgery may be influenced by age at onset of seizures, as early damage caused by seizures may lead to the reorganisation of functions so that lateralisation of verbal functions is transferred (Saykin, 1992). The effect of side of surgery may have been obscured as many studies reported their outcomes according to left and right hemisphere, rather than in groups according to language-dominant and non-dominant hemispheres, and these are not always concordant. The effect of side of surgery was rarely investigated for other outcome domains, such as psychological wellbeing or quality of life.

4.1.2.2 Pre-surgical ability level

Many of the studies reporting cognitive outcomes reported that participants with lower pre-surgical baseline scores on assessments achieved a more positive change in score post-surgery. This is at odds with the cognitive reserve hypothesis, which suggests that that those with higher cognitive ability levels have greater neuronal reserves and so are more resilient to the effects of brain damage (Katzman et al., 1988). The cognitive reserve effect was originally described for older adults with Alzheimer's disease but has been observed in children who have sustained brain injury (Kesler, 2010). More specifically, the functional reserve hypothesis, originally described by Scoville and Milner (1952), describes the findings of those with better memory functioning pre-surgery being

less likely to acquire global amnesia following temporal lobectomy (Barr & Morrison, 2010). This theory posits that functional reserve is determined by the integrity of the contralateral (un-operated) hippocampus, which is able to compensate after surgery to preserve some memory function (Barr & Morrison, 2010), and therefore predicts that higher pre-surgical memory would result in more positive memory outcome. However, as Busch et al. (2008) notes, the findings of more positive memory outcomes for lower pre-surgical outcomes fits better with the functional adequacy hypothesis (Chelune, 1995), which posits that material-specific deficits after temporal lobectomy depend to an extent of the integrity of the ipsilateral (operated) hippocampus, and predicts that those with lower functioning pre-surgical memory will experience less decline; resecting a hippocampus that is functioning well is likely to have a greater impact on memory function than resecting a hippocampus that is already compromised. Although these findings appear to provide support for the cognitive adequacy hypothesis, it should be noted that the findings of studies may reflect bias, as discussed in Section 4.2, and as such they should be interpreted with caution.

4.1.2.3 Gender

The majority of studies did not report on sex differences in neuropsychological outcome after temporal lobe surgery; of those that did, five found no significant effect (Blanchette & Smith, 2002; De Koning et al. 2009; Gleissner et al., 2002; Korkman et al., 2005; Miranda & Smith, 2001) and one (Westerveld et al., 2001) found slightly greater positive change in VIQ for males than females. These results do not support any convincing conclusions about the effect of gender on neuropsychological outcome. This may be because gender does not affect outcome, it may be that the sample sizes of studies are not large enough to detect an effect, or it may be that the follow-up period is not long enough for gender-related differences in outcomes to emerge. Gender differences have been reported in rates of anxiety difficulties (Bender et al., 2012), patterns of emotional expression (Chaplin & Aldao, 2013), and cognitive abilities among children. There is debate about the extent to which these differences are innate and how much they are related to social expectations and gender roles (Lippa, 2010; Rosenfeld & Smith, 2010), but whatever the cause of these differences, they may cause surgery to have a different effect on males and females. Indeed, men and women show some differences in expectations prior to surgery (Bower et al., 2009) and gender differences in outcome have been found for adults (Burneo et al., 2006) so gender may be relevant to neuropsychological outcomes and for children.

4.1.2.4 Family relationships and SES

None of the temporal case series evaluated the relationship between pre-surgical parental anxiety and outcome, although this has been shown to predict the post-surgical emotional response of

children after anaesthetic (Bevan et al., 1990). Furthermore, studies did not consider family SES, which influences children's long term outcomes in education (Morgan et al., 2009; Palardy, 2008), reading (Aikens & Barbarin, 2008) and Mathematics skill acquisition (Coley, 2002), behaviour at school (Morgan et al 2009), language development (Clark, 2009; Farrant & Zubrick, 2012; Hart, 1995) and vulnerability to mental health problems (Bradley & Corwyn, 2002; Hudson, 2005). These social variables may represent potential moderators of long-term neuropsychological outcomes after epilepsy surgery, and there is a lack of exploration of these factors in the evidence base. Further research is warranted to explore the relationship between these factors and surgical outcome and to detect any outcome inequalities as a results of SES.

4.1.3 Are studies focussing solely on seizure frequency and is it important to consider other outcomes?

The majority of studies returned from the database searches that reported any outcomes of paediatric epilepsy surgery did not report any neuropsychological outcomes in their abstracts, focussing instead on seizure outcome, including a number of recent papers (e.g. Englot, et al., 2015; Benedetti-Isaac et al., 2013). In part this may be due to the aims of the studies to focus on seizure outcome specifically, however, psychosocial outcomes are considered a key outcome of paediatric epilepsy surgery and, as such, should be widely reported (NHS Commissioning Board, 2013). Claims for success of epilepsy surgery are often made on the basis of seizure frequency, and it may be assumed that successful seizure cessation corresponds to positive outcomes after surgery for other areas of life (Baxendale, 2015). Therefore, an aim of this review was to investigate how far seizure frequency was associated with broader neuropsychological outcomes, and if it can be used as a proxy for some outcome domains. The results showed that overall, seizure outcome was the most consistent predictor of neuropsychological outcome, with those who achieved seizure freedom having more positive outcome than those who continued to have seizures on measures of quality of life, parental satisfaction and social, behavioural, educational, vocational and psychological wellbeing. The relationship between seizure outcome and the cognitive outcomes of IQ, memory and language were less clear; potentially the beneficial effects of reduced seizure burden on cognition are tempered by the effects of the resection of temporal structures that are important for cognition, such as the hippocampus. Alternatively, the effects of reduced seizure burden may only become apparent at longer follow-up than was available for most of the included participants. Although there is an intuitive logic that seizure freedom results in improved outcomes for psychological wellbeing, most studies did not have non-surgical control groups and so did not control for confounding variables, which may have led to differences in both seizure outcomes after surgery and psychological wellbeing, so no causal inference can be drawn. This problem is

compounded by the lack of reported pre-surgical data in many studies for many of these outcomes, so differences between participants may have been pre-existing before the surgery. Micallef et al.'s (2010) exploration of the mechanisms that may underlie this difference suggests that if surgery is undertaken, seizure freedom results in more positive psychological outcomes than non-seizure free outcome after surgery, but there was no significant difference in mood outcome between young people who were seizure free after surgery and young people with chronic seizures who remained on AEDs without surgery. The relationship between seizure outcome and neuropsychological outcome is not straight-forward. It is highly unlikely that reduced seizure burden always leads to improved psychosocial outcome, because psychological wellbeing in epilepsy is multifactorial and is influenced by environmental, social and historical factors in addition to changes in the brain (Carlton-Ford et al., 1995). Anderson et al. (2011) presents the idea of a continuum of recovery possibilities for early brain insult, that depends on multiple factors, including injury and social factors; it seems likely that the factors contributing to neuropsychological outcome after epilepsy surgery are just as numerous. Therefore, the review was able to answer this research question; many studies do still focus on seizure freedom and, although seizure freedom is strongly associated with some neuropsychological outcomes, it is still necessary to measure a broad range of neuropsychological outcomes.

4.1.4 Relationships between neuropsychological variables

The relationships between neuropsychological domains are complex and an aim of this thesis was to investigate these relationships, if possible from the literature. A clear pattern of three outcome groups emerged across outcome domains: there was a group who remained stable (the largest proportion); a group who improved; and a group who deteriorated. This common pattern raises the possibility that the same young people would have fallen into each of these outcome groups across outcome domains, i.e. those who deteriorated in language may also have deteriorated in IQ and mood. Unfortunately, the review was unable to investigate this question, as individual level results were generally presented separately for each outcome within papers, without reference to participant characteristics, and many of the studies only reported one outcome domain. Furthermore, within-subject comparisons to investigate the relationships between outcome domains were rarely performed by studies. Additionally, study authors did not always adequately consider other causal explanations for their findings other than the effect of resection. For example, most studies that reported psychological wellbeing outcomes referenced a biological account of mental health outcome after TLE surgery, due to the disruption of mesiotemporal networks. However, any paediatric surgery can be a traumatic event in the life of a child which may have long-term effects (Lerwick, 2013), so studies comparing outcomes of temporal lobe epilepsy surgery with outcomes

of other surgeries are warranted. In sum, further appropriately designed studies are required to find out the effects of epilepsy on children's lives and the mechanisms for these effects, so that young people, families and clinicians can make a fully informed decision about the risks and benefits of proceeding with surgery. The logic model in Figure 4.1 is presented as a tentative framework for further exploration of the surgical, child and outcome variables that may shape long-term outcomes to surgery, so that future research can explore these relationships. Logic models present relationships between inputs and outputs in a systematic and visual way (Kellogg WK Foundation, 2004) and they have been used in a number of health-related systematic reviews (Anderson et al., 2011). Logic models can be useful for planning analyses (Anderson et al., 2011) and the model in Figure 4.1 may be helpful for shaping further investigations of the relationship between variables. Figure 4.1 shows variables that were investigated in the studies, displayed in bold text, and also variables that are recommended as a focus for further research, not in bold.

Ultimately, this review was unable to construct an account in the narrative synthesis of how the intervention works and for whom, in terms of the neuropsychological outcomes of TLE surgery, which is the stated aim of narrative synthesis according to the Cochrane collaboration (Ryan, 2013). However, its findings on the methodological and reporting quality were perhaps more significant. The recommendations arising from these findings are outlined in Section 4.4.

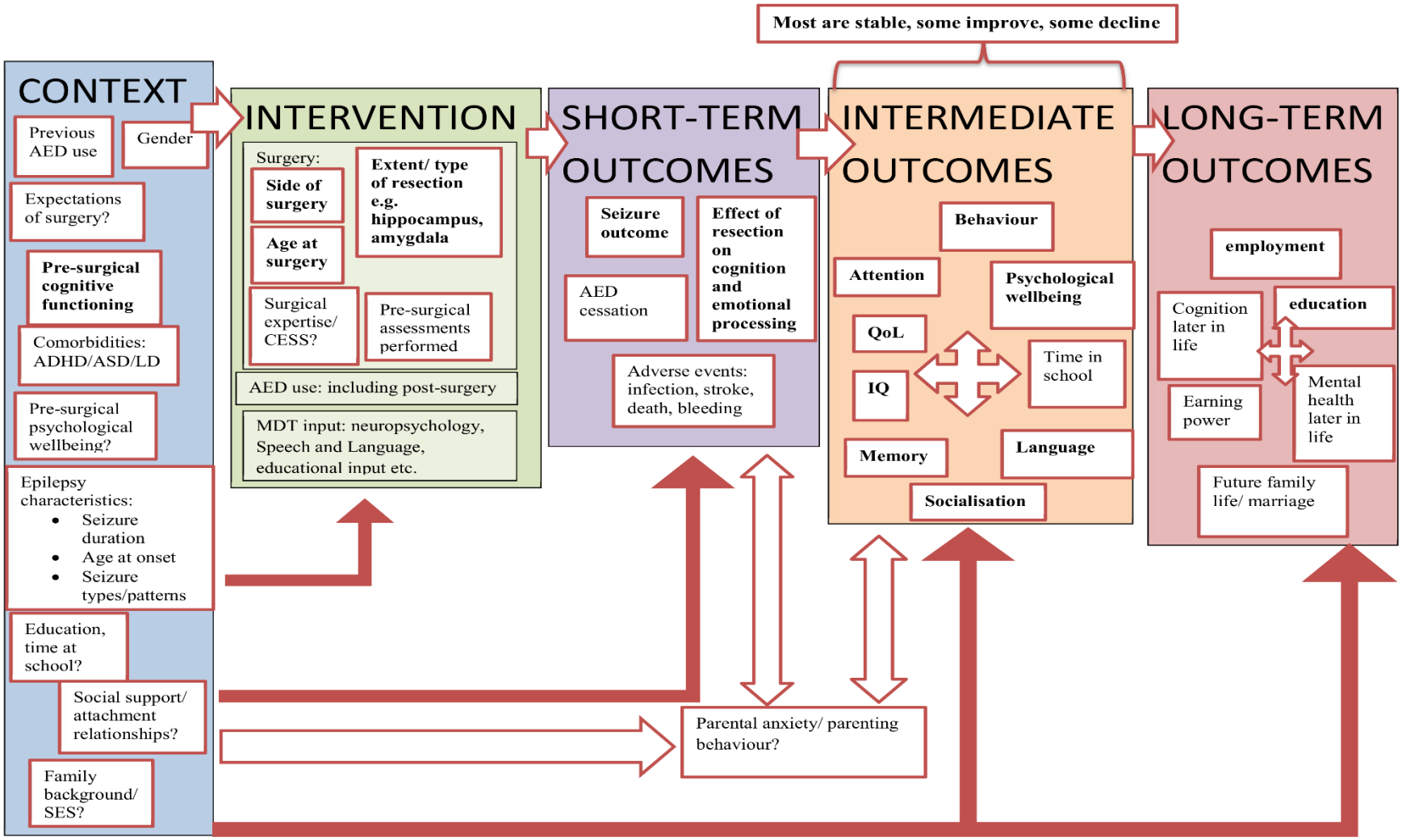


Figure 4.1 Logic model for understanding potential relationships between outcomes of paediatric epilepsy surgery, for further investigation. Variables that were explored in studies are displayed in bold.

4.2 Are limitations in reporting and study design biasing conclusions drawn about the efficacy of temporal lobe epilepsy surgery in children?

As discussed in Section 3.3, all of the studies reporting neuropsychological outcomes of temporal lobe epilepsy surgery in children carried significant risk of bias. Some bias may have been caused by features of the study design, some by the quality of reporting. Key limitations in study design were as follows:

- Nearly all studies were retrospective, which may have biased results as data were not collected at standardised time points, and because the sample may be biased because only those who receive follow-up are included, and data for those lost-to-follow-up may be missing.
- Study methods did not adequately control for other variables that may explain intervention effects. As Hermann et al. (2002) and Strauss et al. (2000) note, studies measuring cognitive outcome of paediatric epilepsy surgery rarely include a control group of age-matched children with comparable epilepsies, who undergo neuropsychological assessment at the same time-points as the surgical group. Therefore, it is not possible to disentangle the effects of surgery from expected cognitive development during that time without surgery. This review, like others (Sherman et al., 2011; Tellez-Zenteno et al., 2007), found that these types of medical control group are rare, so methods were unable to distinguish outcomes of surgery from outcomes of AEDs as usual.
- The results of participants with a range of resection types, ages, seizure durations and follow-up durations, so the outcomes associated with each of these characteristics were hidden.
- For some outcome domains, there was a lack of pre-surgical assessment, so the reported outcome data may have been due to pre-existing differences between young people.
- Studies generally lacked enough participants for the sample to be considered representative or for statistical tests to yield meaningful results.
- Follow-up durations were inappropriately short for the variables being measured, such as intellectual functioning and psychological functioning, which are likely to change over the long term as the young person develops.

It should be noted that the conclusions of simple uncontrolled case studies are not necessarily biased, if they do not make claims of generalisability or causation, and if they have a well-defined cohort and assessment procedures and analyses used are adequately reported, as defined by

STROBE (Appendix D). However, the studies were not concordant with STROBE and key limitations in reporting quality were as follows:

- Individual participant data was not presented, so it was not possible to disaggregate outcome information for participants with different resections, ages, or other characteristics. For some studies this included reporting results for adults and children combined together.
- Key demographic variables, such as age and side of surgery, were not reported, meaning that the results of the participants cannot be generalised.
- The nature of the intervention or assessments undertaken were not adequately reported.
- A thorough history of other interventions, including AEDs was not presented. For example, many children remain on antiepileptic drugs after surgery and it is difficult to disentangle whether outcomes are the result of surgical intervention, medication, or even maturation of the child's brain with the passage of time (Schmidt, Baumgartner, & Loscher, 2004). As other reviews have noted (Tellez-Zenteno, Dhar, Hernandez-Ronquillo, & Wiebe, 2007) AED use is sometimes inadequately reported in paediatric epilepsy surgery literature; authors may neglect to mention how many AEDs were tried, and for how long, before surgical candidacy of participants was assessed, and whether participants remain on AEDs after surgery.

Therefore, the review was able to answer this research question, with the finding that limitations in reporting and study design are likely to bias conclusions drawn about the efficacy of temporal lobe surgery for neuropsychological functioning in children.

Despite these limitations to methodological and reporting quality of the studies included in this review, centres should be commended for publishing their studies and it should be appreciated that not all studies had the expressed aim of assessing the efficacy of temporal lobe epilepsy surgery, rather most study aims were simply to present the findings from their recent case series of epilepsy surgery patients. It is positive that surgical centres communicate their outcomes, for the purpose of quality assurance, service improvement and to highlight training needs. It should also be noted that many surgical centres were not represented in the included studies, suggesting that many centres do not routinely publish their outcomes, as noted by Shastin et al. (2015), or that their published outcomes did not meet the criteria of this review, perhaps not presenting results for temporal surgery separately, or not presenting neuropsychological outcome. The reporting of routine outcome data represents a valuable opportunity for practice-based evidence to complement the results of trials, which have strong internal validity but may lack external validity (Barkham et al., 2010). This fusion of evidence-based medicine and practice-based evidence approaches allows the

best available evidence to be collected from rigorous research conducted in routine clinical settings (Barkham & Margison, 2007).

However, the conclusions of the included published case series often overstated their findings, and implied a causal link between outcome at follow-up and surgery, which could not safely be inferred from their results due to the method used. Although most studies documented their limitations and many used tentative language when drawing their conclusions, these papers may then be cited as supporting evidence by further studies, without reference to their methodological limitations (e.g. Spencer et al., 2008), and used to support stronger conclusions. This may contribute to the emergence of a consensus that has a spurious certainty that is not based on evidence at the ground level of research.

The review raised epistemological questions about the nature of what is considered as evidence. Despite many of the studies having high risk of bias, it should be noted that they all passed through the peer review process, and, as shown in Section 3.3.7, the average number of identified biases per paper from each journal did not correlate with journal's impact factor. This finding is important as it casts doubt upon the assumption made by some clinicians that impact factor can be seen as a measure of journal quality (Saha et al., 2003), at least for the literature concerning neuropsychological outcomes of paediatric epilepsy surgery. The implications of the methodological limitations in this literature may not be fully appreciated and may not be communicated to the family when they are deciding whether or not to proceed with temporal lobe surgery. Clinical implications and recommendations for study design, reporting and new ways to develop high quality evidence are presented in Section 4.4.

4.3 Limitations

4.3.1 Limitations of systematic review methodology

Systematic reviews are vulnerable to bias, just as the included studies were. For example, the reviewer defines the problem and sets the key variables that the review will focus on at the start of the review, which shapes the eventual review findings and conclusions (Alliance for Health Policy and Systems Research, 2009). In addition, systematic reviews can be affected by the "file draw" problem (Rosenthal, 1979) as studies that do not show the desired effect on an intervention are less likely to be published and unpublished studies may not be captured during the search. Ultimately, the conclusions of systematic reviews are only as good as the included studies, and for this reason the term "garbage in-garbage out" (GIGO) was coined (Yuan & Hunt, 2009) to describe the inappropriate pooling of heterogeneous data from low quality studies in meta-analysis. For this

reason, many systematic reviews set strict methodological quality criteria for inclusion. However, this means that it is difficult to gather data about outcomes for interventions where the conduct of RCTs is difficult or rare. Guidance for systematic reviews is largely based around specific, focused questions and RCTs (Higgins & Green, 2011), which makes the analysis of surgical interventions with few RCTs difficult. Similarly, for meta-analysis to be valid, studies must not be too heterogeneous and must each set out to answer the same question (Bartolucci & Hillegass 2010). Systematic reviews that do not allow for meta-analysis frequently use narrative synthesis, like this one, which may be more prone to bias because of its reliance on the reviewer's interpretation of the salient points to draw from the literature. Furthermore, due to the wide variety in potential review topics, formats and findings, guidance on narrative synthesis is necessarily non-specific (Ryan et al., 2013), making it difficult to ensure that a transparent protocol for analysis is followed. Therefore, a recommendation from this review is that further guidance should be produced for the narrative review of studies reporting varied intervention outcomes. Additionally, much of the systematic review guidance (e.g. CRD, 2009; Higgins & Green, 2011) suggests reviewing only studies with the highest quality, such as RCTs. However, RCTs are also open to bias, from sources such as reporting bias, publication bias and conflict of interest, and the conducting of large enough RCTs with high methodological quality is likely to be limited due to a lack of available funding and research infrastructure within surgical centres. Perhaps a more fruitful approach than conducting further systematic reviews of the small sampled studies with high risk of bias, is the development of open data repositories for the collection of practice based evidence, which would ultimately allow enough data to be collected from multiple centres to allow for analyses of the various long term outcomes of epilepsy surgery for young people with different ages, epilepsy characteristics, social backgrounds, and at a range of follow-up durations. This recommendation is discussed further in Section 4.4.

4.3.2 Limitations of this review

The methods used in this review were compared to the PRISMA statement checklist (Liberati et al., 2009), which is designed for the critical appraisal of systematic reviews. Appendix C shows where in this review each point on the checklist was met. However, it must be noted that there were two deviations from the checklist. Firstly, the research questions were not defined with reference to a specific comparator group (the C in PICO), as studies without comparison groups were included. The implicit primary comparator group in studies reporting the outcomes of children with TLE who undergo epilepsy surgery is children with TLE who do not undergo surgery, although other control groups may also be useful, such as children with epilepsy who undergo other types of surgery that require general anaesthetic. Secondly, no registration number was obtained and the review protocol

was not registered. The review was otherwise PRISMA concordant. The limitations of the review will be discussed in the format recommended by the Cochrane Consumers and Communication Review Group (Ryan, 2013) in Sections 4.3.2.1 to 4.3.2.3.

4.3.2.1 Overall completeness and applicability of evidence

The studies were not able to sufficiently address the objectives of the review, and important gaps remain in the literature, because study designs and reported data did not allow the research questions to be answered, as discussed in Sections 4.1 and 4.2. It would have been useful to extract individual participant data from included studies in order to investigate the factors that predict neuropsychological outcomes after surgery, so that findings could be applicable to clinical decision making about surgical candidacy so that expectations can be managed about neuropsychological outcomes. However, the heterogeneity of participant characteristics and follow-up durations included in each study and lack of individual data did not allow this. This review looked at a broad array of neuropsychological outcomes, and grouped areas of functioning into different outcome domains, such as IQ, attention and psychological wellbeing. In so doing it is in danger of repeating the mistakes of the included papers, as these outcome domains have multiple components that have been combined for the purposes of the review. For example, attention can be divided into sustained attention, divided attention and so on, and it may have been helpful for a review to consider each of these outcomes individually, as they may be affected differently after temporal lobe surgery for epilepsy. Similarly, the review included participants with TLE, but this form of epilepsy is variable, and the review could have looked at specific types of epileptogenic foci separately. However, the measures used, participants included and data reported by included studies would not have allowed this level of analysis.

The completeness and applicability of the evidence presented in this review relies upon the completeness and applicability of the evidence base. It is likely there are psychosocial outcomes of interest to children with epilepsy that have not been studied, for example, none of the studies focussed on family relationships after surgery. Likewise, it may be that the outcomes that are routinely studied may not be the ones that are most appropriate or applicable to children's lives. For example, many studies used measures of IQ, which has been criticised for not being a relevant or sufficient measure of cognitive abilities for children, as it does not include aspects of functioning such as creativity (Kim, 2005), and may introduce cultural bias (Neissner, 1997). However, standardised IQ tests at least allow measurement of a common set of abilities, and is strongly associated with other outcomes of interest such as educational attainment (Dreary & Johnson, 2010). Another example of outcomes that may not have real-world applicability are psychiatric

diagnoses, such as those reported by McLellan et al. (2005), which have been found to have poor validity (Bentall, 2009; Kinderman et al., 2013). They are perhaps particularly problematic for children, where models of resilience and vulnerability might be more appropriate (Luthar, 2003). Overall, the review was not able to provide complete, generalizable and applicable results about the neuropsychological outcomes of temporal lobe epilepsy surgery in childhood but it was able to provide a realistic picture of the methodological and reporting quality of research in the field. The research questions posed at the outset of this review could be better answered by outcome measure agreement and planned analysis (see Section 4.4).

4.3.2.2 Quality of the evidence

As discussed extensively in Section 3.3 and 4.2, the included studies had high risk of bias and this impacted heavily on the conclusions that could be drawn in the review.

4.3.2.3 Potential biases in the review process

This review required some deviation from the guidance for systematic reviews, as discussed in Chapter 2, due to the broad nature of its research questions and the type of studies included. This may have introduced some potential for bias in the way the studies were selected and handled. However, a review protocol was developed to ensure a rigorous and transparent approach, and this was shared with members of the multidisciplinary neurosurgical team, to ensure that the review would be rigorous and clinically relevant. There were three main processes in the review that may have increased risk of bias:

- It is probable that the review did not include all relevant studies as the grey literature was not included, and this may have biased the results as studies with negative or 'non-significant' results may have been less likely to be published.
- The systematic review process may have been threatened by sample bias; is possible that search terms and database searches did not find all relevant literature. However, search terms were designed via a rigorous and methodical approach of testing, as detailed in Chapter Two, and an inclusive approach was taken to maximise the sensitivity of the search. Guidance was sought from specialist scientific librarians to ensure the use of appropriate search strategies. It is also possible that studies that reported neuropsychological outcomes in the full body of the paper may have been excluded if these outcomes were not referred to in the title or abstract. However, this would also denote that these outcomes were not a central part of the study. Alternatively, non-significant findings may not have been considered as prominent, and therefore be less likely to be included in the abstract, and thus within-study reporting bias may have influenced review findings.

- The method of narrative analysis was at risk of bias, as a single reviewer drew out the salient points from studies and made judgements on their methodological quality, and there was no masking of study author. However, attempts were made to make this process as transparent and standardised as possible, and there were no conflicts of interest.

In addition to these potential causes bias, which could systematically influence results, there were two main aspects of the review process that may have introduced random error:

- Study authors were not contacted to obtain details where studies reported only pooled outcome data of participants with mixed characteristics, or where participant data was missing. This may have increased the risk of error, and reduced the ability of the thesis to answer the research questions. However, as nearly all studies met this description, contacting all authors to obtain such data would have been beyond the scope of this project.
- Both the study selection and data extraction phase may have contributed to random error (McDonagh et al., 2010) because these processes were performed by just one reviewer, increasing the risk of human error.

4.4 Recommendations

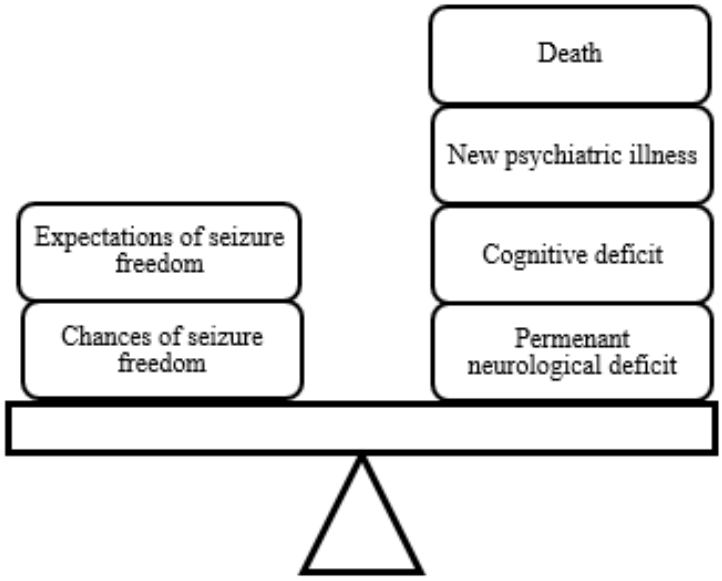
A number of recommendations are made based on the findings of this review. These are discussed below, with reference to the changing landscape of paediatric epilepsy surgery in the UK with the introduction of CESS.

4.4.1 Clinical recommendations

4.4.1.1 Clinical discussions and managing expectations

Given the complexity and methodological variability of the paediatric epilepsy surgery literature, the heterogeneity of the intervention and population, and the excessive claims sometimes made by study authors, it may be difficult for clinicians to clearly communicate the evidence on the potential risks and benefits of undergoing and not undergoing epilepsy surgery to young people with epilepsy and their families. Managing expectations for neuropsychological outcomes is important, as seizure improvement with surgery is not always associated with other broader life improvements often hoped for by candidates (Baxendale, 2015). Providing accurate information about the many outcomes of epilepsy surgery to young people and their families is important to ensure that they are able to accurately weigh the potential benefits and costs of proceeding with surgery. Baxendale (2015) presents a diagrammatic representation of the decisional balance for young people deciding whether or not to undergo surgery, displayed in Figure 4.2.

Figure 4.2 Diagrammatic representation of risk-benefit ratio of deciding on epilepsy surgery, from Baxendale (2015)



Baxendale (2015) notes that there are no empirical studies of surgical expectations for children so this is an important area of further research, including studies to investigate the effect of unrealistic pre-surgical expectations on post-operative psychological outcome. The poor psychological outcomes of children who were not seizure free post-surgery compared to non-surgical candidates, reported by Micallef et al. (2013), may have been in part related to this. The CESS service specification states that CESS should "provide high quality information for patients, families and carers in appropriate and accessible formats and media" (NHS Commissioning Board, 2013, p.4). In an attempt to contribute to this aim, the results of this review were translated for family use (Appendix E); however, the low quality of the evidence meant that this family translation required so many notes of caution that it may not communicate clear messages to families and may increase anxiety. This review found that while most young people remain stable in neuropsychological outcomes or improve after surgery, some deteriorate; it is important that the individual and surgical predictors of these negative neuropsychological outcomes are better understood so that children at greater risk of post-surgical deterioration are provided with information on the costs of surgery to help them reach an informed decision, which will require appropriately designed and reported research, as recommended below.

4.4.1.2 Role of Clinical Neuropsychology

Neuropsychology services could play a key role in a number of areas of the care of young epilepsy candidates, not only limited to cognitive assessments, but also to support the young person and their

family during the journey of surgery and follow-up. This review did not assess the efficacy of neuropsychology interventions but the varied potential neuropsychological outcomes may require a range of different types of input from specialised services:

- Facilitating discussions around expectations of surgery and assessing young peoples' level of understanding and capacity to make the decision
- Assessing pre-existing social support, resilience and coping
- Completing thorough neuropsychological assessments pre- and post-surgery and explaining them
- Providing follow-up and neuropsychological rehabilitation
- Providing evidence-based psychotherapeutic interventions in response to epilepsy or surgery related mood difficulties, individually or with the family
- Signposting young people to support organisations or setting up groups in order that young people and families can meet others in their situation.
- Input to schools to support educational adjustments so that learning, behaviour and wellbeing can be better supported at school

Neuropsychology should also be involved in researching evidence-based interventions post-surgery, and should contribute to the research output of neurosurgical centres. Psychological research, including qualitative methods, may help to map out the relationships between outcomes outlined in Figure 4.1. It is also important to measure and report neuropsychological outcomes to better understand the expected cognitive and psychosocial effects of surgery, the factors affecting these outcomes, and mechanisms that lead to their development, in order that neuropsychological, educational and social interventions can be designed and services can be better placed to support young people to achieve their full potential after temporal lobe surgery for epilepsy. Within some of the studies reviewed, there appeared to be a hierarchy of research design and reporting quality amongst outcome domains, where quality of life was often not as rigorously assessed as cognitive outcome, which was often not as carefully assessed compared to seizure outcome within the same study. For example, in some studies, psychosocial measures were taken only at follow-up, perhaps as an afterthought, whereas seizure and cognitive outcomes were assessed both pre- and post-surgery (e.g. Gilliam et al 1997; Skirrow et al., 2011). This suggests that surgical centres may not all consider psychosocial outcomes to be key outcomes of epilepsy surgery, for routine measurement at pre- and post-surgical assessment. Greater MDT collaboration between neurosurgery and neuropsychology in the preparation of publications may allow for greater parity of reporting for neuropsychological and seizure outcomes.

4.4.2 Research design recommendations

The evidence gathered in this review was limited due to the methods used in the studies, which were unable to provide generalizable results. It should be appreciated that conducting rigorous and well-designed studies in this field is very difficult undertaking, due to the heterogeneity of participants, epilepsies and surgeries. The highest level of evidence for the effect of epilepsy surgeries on neuropsychological outcome would be provided through RCTs. However, RCTs may not be feasible due to the difficulty in finding well-defined cohorts of similar participants to undergo identical interventions, and there are potential ethical considerations around ensuring that surgery is offered to all suitable surgery candidates who wish to proceed with surgery, rather than allocating the to a control arm of an RCT. However, prospectively planned multi-centre follow-up studies with appropriately chosen non-surgical quasi-control participants would allow firmer conclusions to be drawn. Studies that include both pre-and post- surgical assessments of outcome are required, particularly for outcomes such as QoL, which was often assessed only post-surgery, so that outcomes can be related to the intervention and the effects of pre-surgical differences between children can be controlled. There should be consistency between pre- and post-surgical assessments performed where possible. If centres are to be able to accomplish the recommendation for large prospective controlled studies, they will require further support in conducting research, including the necessary research infrastructure. This includes employment of a database manager and funding for adequate follow-up of participants into adulthood, in order to record their longer term outcomes, and therefore, this recommendation is resource-dependent. It is hoped that this will be more feasible with the centralisation of services into CESS, as resources will be more concentrated in one place. Further recommendations on outcome measurement and follow-up are provided in Section 4.4.4 and 4.4.5.

4.4.3 Reporting recommendations

Despite the need for higher quality research, the publication of routine outcome data should not be discouraged; it should be both welcomed and required, as this allows for greater transparency for quality assurance and service improvement. Reporting of outcomes from individual centres also potentially enables a larger dataset of surgical outcomes to be developed for later analysis, as discussed in Sections 4.4.4 and 4.4.6. However, these data are of limited utility if key details about the intervention and participant are omitted. Therefore, a number of reporting recommendations are suggested:

- Publications of case studies should aim to be concordant with STROBE (Appendix D) so that their methodology and study aims are transparent for the reader.

- Studies should publish individual participant data for participant characteristics, surgery details and outcomes.
- Studies should publish individual participants' data for the following participant characteristics: perinatal history, seizure onset, seizure types, medication history / treatment history, neurodevelopmental progress, family history, other medical problems, investigation history, neurological examination treatment/medication history, neurodevelopmental progress, family history, comorbid conditions, investigation history and details of their neurological examination. All of this information is required at referral to the CESS (NHS Commissioning Board, 2013) so it is likely that it will already be available to clinicians, but was often missing from reported studies. Although it may be controversial to record participant characteristics such as ethnicity and SES and there are difficulties in the validity of assigning discrete labels for these variables (Braveman et al., 2001), reporting these variables would increase knowledge about how long term outcomes of young people after epilepsy surgery are affected by health inequalities (Begley et al., 2009; Burneo et al., 2009).
- The details and locations of resections should be reported for each participant
- The pre-surgical imaging evaluations undertaken should be reported. The CESS service specification (NHS Commissioning Board, 2013) states that pre-surgical assessment must include interictal sleep EEG recording, video EEG recording of seizures, MRI, functional imaging if required, neuropsychological assessment, advice on educational interventions, neuropsychiatry assessment and treatment. The CESS specification (NHS Commissioning Board, 2013) states that pre-surgical investigations will vary according to individual need, but that access to 3T, MRI, SPECT, PET, fMRI and MEG are required. However, the included studies did not always report which pre-operative imaging assessments were used for each individual, so it was not possible for this review to investigate the effect of different pre-surgical assessments on neuropsychological outcomes. Pre-surgical assessment details should be recorded so that they can be considered in meta-analysis.
- Abstracts should provide the participants' information such as age range, side of surgery, and type of surgery. This information was frequently missing from abstracts, for example many studies made no reference to the age of their participants when the sample contained both adults and children, this is likely to lead to 'research waste', as the results of these children will likely be missed in reviews of paediatric epilepsy surgery studies, which meant that they may be missed out of reviews of child surgery.

- Studies should provide individual participant data. Combining outcome data from heterogeneous samples (including participants who underwent surgery on different lobes of the brain, or combining results of adults and children) contributes to 'research waste' (Equator Network, 2009), as these studies are unable to answer the question of which surgery works for whom.
- Studies should report their drop-out rate with reasons if known, and characteristics of those who dropped-out if possible
- Studies should report the method of outcome assessment, and use agreed definitions when referring to concepts such as Quality of Life, rather than using terms informally, for example recording improvement in quality of life as an assumed result of reduced seizures.
- Most importantly, individual surgical centres should all be publishing their paediatric epilepsy surgery outcomes.
- Authors should state if other outcomes of the reported cohort of patients has also been reported elsewhere, so that this is readily accessible.

Authors of routine small uncontrolled case series papers may find it difficult to meet all of the above recommendations, particularly if they are not based within a CESS, and this should not preclude them from publishing their findings. However, it would be helpful for to provide a data supplement of whatever individual participant data they were able to collect, and to be careful in their discussion not to overstate the generalisability of their findings, or to make claims about epilepsy surgery efficacy as a whole based upon their sample.

4.4.4 Outcome measure agreement and data collection

In terms of outcome measurement, the service specification (NHS Commissioning Board, 2013) states that the CESS will monitor performance in terms of mortality, post-operative morbidity, neurological (seizure) outcome, neurodevelopmental/cognitive/ neurobehavioral, QoL, patient/carer satisfaction, reoperation rate, waiting times, adverse events and near misses. However, despite outlining the outcomes to be measured, the CESS service specification does not specify the outcome measures to be used. Individual patient characteristics, surgical details and outcome data from surgical candidates in England is collected in the nationwide Orion database for the purpose of audit, and measures used have gradually converged through a series of national meetings to try to standardise the data collected (V. Gray, personal communication, 27 June 2016). However, internationally there is little agreement in measures used. The studies included in this review assessed a wide variety of outcome domains, and for each domain, studies used a wide variety of outcome measures, many of which measured slightly different things. A core set of outcome measures would ensure that all relevant outcomes are consistently reported, simplify reporting of

results, allow data to be better compared between centres, improve quality assurance for centres, and make possible further systematic reviews with meta-analyses to determine the efficacy of epilepsy surgery for children with particular characteristics, or for particular outcome domains. The task of agreeing on outcome measures is a particularly difficult one, given the variety in the characteristics of each child's brain, life, epilepsy and surgery, in addition to language and cultural differences internationally. This recommendation fits with the approach taken by the Core Outcome Measures in Effectiveness Trails (COMET) group (COMET Initiative, 2016). COMET's aim is to support researchers working in a number of areas of health research to develop core outcome sets that are collected and reported as a minimum, whilst trials are free to explore additional outcomes as well, and storing these outcome sets in a searchable database (COMET Initiative, 2016). For example, a recent study registered on the COMET website (Noble & Marson, 2016) surveyed adults with epilepsy and their carers, and found that patients and carers wanted to add "Depression", "Anxiety" and "Independence/need for support" as important outcomes for measurement in addition to the outcomes identified by the International League Against Epilepsy's Commission on Outcome Measurement (COME) which were "Seizure severity", "Seizure frequency", "Quality of life", "Cognitive function", and "Adverse events" (Baker et al., 1998). It is likely that outcomes of importance may differ for children due the developmental challenges they face. A similar survey should be conducted amongst children with epilepsy, young people, parents and carers in order to identify the outcome domains that are most important to them. The ILAE COME (Baker et al., 1998) stated that outcome measures chosen for research on outcomes for people with epilepsy should be applicable for answering questions with respect to epilepsy, should have good construct validity (they measure the functions they are intended to measure) and that the information gathered should be useful and relevant to the lives of people with epilepsy. Cross et al (2006) concluded that there was not yet enough Class 1 evidence to develop recommended practice guidance for evaluation of children for epilepsy surgery. However, this situation leads to a circular problem, in which poor matching of evaluation protocols and outcome measures between studies makes the gathering of high quality evidence difficult. The COMET group provide guidance for the process of arriving at agreed outcome measures, and recommend processes such as the Delphi technique, which involves presenting questionnaires to subject experts over a number of rounds to arrive at a consensus. Considering the results of this thesis, it is recommended that this process be conducted for paediatric epilepsy surgery outcomes. The ILAE suggest that paediatric epilepsy surgery outcome measures should include seizure frequency, antiepileptic drug (AED) use, quality of life (QoL), development, cognition, behaviour, and psychosocial adjustment (NHS Commissioning Board, 2013). However, the suggested neuropsychological outcome domains are poorly specified, and as shown in the included studies, measures of all of these domains are rarely reported, and

follow-up design is variable. As a starting point the following neuropsychological outcome domains and measures are proposed in addition to seizure outcomes, in Table 4.1, with suggested outcome measures. These outcome measures were chosen due to the routine use of many of them in neuropsychology services and collection on the Orion database (V. Gray, personal communication, 27 June 2016), their established reliability and validity for young people with epilepsy (Barr & Morrison, 2010; Berl et al., 2015; Cohen, 1997; Duan et al., 2012; Parrish et al., 2007; Sherman et al., 2012) and in the cases of the Wechsler scales because tests of memory and intellectual functioning are co-normed to allow the calculation of any discrepancy between performance and expected scores. It is understood that the measures used will necessarily vary internationally, for language and cultural appropriateness, and for age, both between patients and for the same patient as they grow older over the follow-up period, and it is likely that test versions may vary between studies as new editions are released. However, where possible, outcome measure agreement allows more valid comparisons to be drawn between centers, and allows results to be pooled across studies for the purposes of meta-analysis. It is understood that some study authors will choose to focus on only one outcome of interest, and so may not use the whole of the outcome measure framework proposed in Table 4.1, and that there is likely to be some distinction between the outcome dataset of funded large research trials and published routine clinical follow-up data. However, published routine clinical data will be much more useful for research purposes if it can be somewhat standardized, and it would be useful for such studies to choose measures from the commonly agreed set of measures where possible, if they are appropriate for the outcomes that they are measuring.

The Orion database is potentially a rich data source for research as well as its intended purpose of audit, and therefore its accessibility to research teams should be maximized. However, there are intrinsic compromises between the level of data collected by such databases and the burden on clinician time for data entry and computational resources required. For example, the WISC and Children's Memory Scale (CMS) are reported on Orion in terms of index scores but not at the level of subtest scores (V. Gray, personal communication, 27 June 2016), which may be of interest to researchers, particularly in the investigation of material-specific deficits after temporal lobe resection. It is also inevitable that large datasets may result in some reductionism of the experience and outcomes of each child. Therefore, it remains important for clinical research teams to continue to collect their own fuller datasets that include additional outcomes and measures of interest in addition to that collected by the database. This may include qualitative research to investigate young people's experience of the patient journey.

Table 4.1 Proposed neuropsychological outcome measures for studies of paediatric epilepsy surgery

Outcome domain	Proposed measures
Seizures	Engel's classifications
IQ/developmental level	WAIS/WISC/WIPPSI
Quality of life	Pediatric Quality of Life Questionnaire (PedsQL).
Memory	Children's Memory Scale (CMS)/ Wechsler Memory Scale (WMS)
Attention	Computerised Performance Test (CPT) Test of Everyday Attention for Children (TEA-Ch2)
Executive function	Delis-Kaplan Executive Function System (D-KEFS)
Visuomotor skills	Wide Range Assessment of Visual Motor Ability (WRAVMA); Vineland II (Motor Skills domain)
Language	Vineland II (Communication domain) Clinical Evaluation of Language Fundamentals - Fourth Edition UK (CELF-4 UK) or CELF-Preschool 2 UK
Psychological wellbeing/ vulnerability	Strengths and Difficulties Questionnaire (SDQ); neuropsychological interview; Revised Children's Anxiety and Depression Scale (RCADS)
Educational attainment	Wechsler Individual Achievement Test, 2nd Edition (WIAT II).
Education/ Vocational outcome	Record of schooling – e.g. special school, requiring extra support or mainstream school Record of work – full time/ part-time /unemployed
Social	Vineland II (Socialization domain)
Behaviour	Strength and Difficulties questionnaire, Vineland II (Maladaptive Behaviour Index)
Functional independence	Vineland II (Daily Living Skills domain) WeeFIM/ Functional Independence Measure (FIM)
Satisfaction with surgery	Questionnaire for parents/carers and children

4.4.5 Follow-up Recommendations

Outcome measures should be conducted both pre- and post- surgery and at longer-term follow up, wherever possible, so that the change in the child's functioning after surgery can be measured. It may also be helpful to measure some additional outcomes at follow-up only, for example longer-term outcomes such as work type or earnings as an adult. However, it would be important for such research to also include the pre- and post- neuropsychological outcomes of those participants. The duration of follow-up is likely to depend on available funding but studies that include prospective follow-up across multiple time points at agreed intervals, for example at age 1 year, 5 years and 10 years post-surgery, would be very helpful for identifying potential clinical need and late effects of surgery. However, studies that are only able to report neuropsychological outcomes over shorter and varied follow-up durations should still be published so long as they do not make claims that are not supported by their findings. It is anticipated that there may be some barriers to adopting these

follow-up recommendations, as follow-up of paediatric patients as they transition to adult services may be difficult if research is conducted by clinical teams within a paediatric service, so close links between paediatric and adult services for this research. Furthermore, there is a potential funding gap for the follow-up of surgical candidates within paediatric services; CESS are currently funded for pre-surgical work-up, and some children who have positive outcome after surgery may not be followed up in the longer term if they do not require input from services. The CESS service specification (NHS Commissioning Board, 2013) also states that ongoing monitoring of children's development should be offered where appropriate by local centres, including assessing educational progress, neuropsychological problems and psychiatric disorders. It would be helpful for this local data to be published, using agreed outcome measures where possible, so that it can contribute to a growing body of outcome data that may help to unpick the factors related to long-term neuropsychological outcomes after surgery. Very long-term follow-up, for example 25 or 50 years post-surgery would be helpful for expanding knowledge about the long-term outcomes after paediatric epilepsy surgery, although this this would be very expensive and with longer follow-up there may be increased requirement to control for other life events which may affect outcomes, so this recommendation may not be feasible. There is already guidance from the CESS service specification as to the nature of follow-up at CESS; it specifies that the neurodevelopmental/cognitive/neurobehavioural outcome of children should be measured at pre-surgical assessment and at 2- and 5-years post-surgery and given a rating of 'better', 'no change' or 'deterioration', but the timing of other outcome domain assessments, such as QoL is not specified. Further guidance for long-term follow-up should be developed, as has been developed for children with cancers by the Children's Oncology Group (Armenian et al., 2013).

4.4.6 Transparency, collaboration and big data in clinical research

The above recommendations for consistency in outcome measurement and follow-up also links with a wider picture of re-thinking how knowledge is created in the clinical sciences. There has been recent attention paid to the 'research waste' (Equator Network, 2009) created by research that is inappropriately designed, asks the wrong questions or is inadequately reported and therefore unusable (e.g. Chalmers et al 2014; Ioannidis et al., 2014; Salman et al., 2014). In order to combat this research waste, there has been a movement towards combining results from multiple research groups or clinical centres in order to produce larger datasets. For example, the Human Connectome project (Van Essen et al., 2013) has been set up as a repository of fMRI datasets, in order that enough data can be collected for later analyses to learn about the neural pathways underlying brain function and behaviour. When publishing in scientific journals there is a requirement for authors to provide novel answers to research questions, in order that the research appears worthwhile. This

may lead to overstating of claims, or only presenting some outcomes with significant results (Ioannidis et al., 2014). Shared outcome measures and open reviews, in which multiple trials make their datasets available for individual participant analysis (IPA; Stewart & Tierney, 2002; Vale et al., 2015) would provide a way for individual centres to contribute to knowledge and report their outcomes without the need to overstate claims or present data selectively. This requires a spirit of transparency and cooperation, which may require a culture shift within scientific publishing, which sometimes rewards competition and prestige (Ioannidis et al., 2014). The Orion database, and any similar international research databases that may be developed for paediatric epilepsy surgery outcomes, will require continual assessment of their utility and workability by the wider clinical and research community. The CESS service specification requires that research activity within CESS must have a "focus on contributing to a few high-quality multi-centre epilepsy research projects, rather than single centre case series" and that "all CESS centres nationally with academic links will be expected to initiate and coordinate studies and collaborate together on research-proposals" (NHS Commissioning Board, 2013, p.39). As this data is published it will be important to investigate whether the outcomes of paediatric epilepsy surgery improve, as was the aim of the centralisation of services. It may be that this has different effects on different outcome domains; for example, centralisation may mean that there is a higher rate of successful seizure reduction, but a negative impact on QoL when families have to travel further from home.

The key outcomes of paediatric epilepsy surgery are to "reduce seizures", "optimise development potential" and "improve QoL" (NHS Commissioning Board, 2013). However, in order to know whether these aims are accomplished in the longer term, and for which children, higher quality evidence is required. Therefore, a spirit of cooperation between surgical centres must be adopted in order to find out which surgeries work, in which ways for which children. This will help to inform young people and their families about the likely consequences of undergoing surgery so that they can weigh up these risks and benefits and decide what is right for them.

REFERENCES

Abrami, P. C., Cohen, P. A., & d'Apollonia, S. (1988). Implementation problems in meta-analysis. Review of Educational Research, 58, 151–179.

Ackers, R., Besag, F. M., Hughes, E. et al. (2011). Mortality Rates and Causes of Death in Children with Epilepsy Prescribed Antiepileptic Drugs. *Drug safety*, *34*(5), 403-413.

Adami, P., König, P., Vetter, Z. et al. (2006). Post-traumatic stress disorder and amygdala-hippocampectomy. *Acta Psychiatrica Scandinavica*, *113*(4), 360-363.

Aicardi, J., & Chevrie, J. J. (1970). Convulsive status epilepticus in infants and children. *Epilepsia*, *11*(2), 187-197.

Aikens, N. L., & Barbarin, O. (2008). Socioeconomic differences in reading trajectories: The contribution of family, neighborhood, and school contexts. *Journal of Educational Psychology*, *100*(2), 235.

Alliance for Health Policy and Systems Research (2009) Briefing Note 4: Systematic Reviews in Health Policy and Systems Research. World Health Organisation. http://www.who.int/alliance-hpsr/resources/AllianceHPSR_Brief_Note4_ENG.pdf

Al-Mufti, F., & Claassen, J. (2014). Neurocritical care: status epilepticus review. *Critical care clinics*, *30*(4), 751-764.

Andermann, L. F., Savard, G., Meencke, H. J. et al. (1999). Psychosis after resection of ganglioglioma or DNET: evidence for an association. *Epilepsia*, *40*(1), 83-87.

Anderson, L. M., Petticrew, M., Rehfuess, E., et al. (2011) Using logic models to capture complexity in systematic reviews. *Res Synth Methods*, *2*, 33–42.

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*, awr103.

Andresen, E. N., Ramirez, M. J., Kim, K. H. et al. (2014). Effects of surgical side and site on mood and behavior outcome in children with pharmacoresistant epilepsy.*Frontiers in neurology*, *5*.

Andrewes, D. G., Bullen, J. G., Tomlinson, L. et al. (1986). A comparative study of the cognitive effects of phenytoin and carbamazepine in new referrals with epilepsy. *Epilepsia*, *27*(2), 128-134.

Arzimanoglou, A., Aldenkamp, A., Cross, H., & Lassonde, M. (2005). *Cognitive dysfunction in children with temporal lobe epilepsy* (Vol. 1). John Libbey Eurotext.

Armenian, S. H., Landier, W., Hudson, M. M., & Robison, L. L. (2013). Children's Oncology Group's 2013 Blueprint for Research: Survivorship and Outcomes. *Pediatric Blood & Cancer*, *60*(6), 1063–1068.

Austin, J. K., Harezlak, J., Dunn, D. W. et al. (2001). Behavior problems in children before first recognized seizures. *Pediatrics, 107*(1), 115-122.

Austin, J. K., & McDermott, N. (1988). Parental attitude and coping behaviors in families of children with epilepsy. *Journal of Neuroscience Nursing*, *20*(3), 174-179.

Austin, J. K., Smith, M. S., Risinger, M. W., & McNelis, A. M. (1994). Childhood epilepsy and asthma: comparison of quality of life. *Epilepsia*, *35*(3), 608-615.

Aylett, S. E., Cross, J. H., Taylor, D. C. et al. (1996). Epileptic akinetic mutism: following temporal lobectomy for Rasmussen's syndrome. *European child & adolescent psychiatry*, *5*(4), 222-225.

Bais, A. S., Sardana, P., & Arora, M. (2003). Osteopetrosis-variable otorhinolaryngological manifestations. *Indian Journal of Otolaryngology and Head and Neck Surgery*, *55*(2), 113-116.

Baker, G. A., Camfield, C., Camfield, P. et al. (1998). Commission on outcome measurement in epilepsy, 1994–1997: final report. *Epilepsia*, *39*(2), 213-231.

Baldeweg, T., & Skirrow, C. (2015). Long-Term Cognitive Outcomes After Epilepsy Surgery in Children. In *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 85-101). Springer International Publishing.

Banerjee, P., & Crain, B. (2008). 2-year-old girl with right leg weakness. *Brain Pathology*, *18*(4), 608-610.

Banks, J. L., & Marotta, C. A. (2007). Outcomes validity and reliability of the modified Rankin scale: Implications for stroke clinical trials a literature review and synthesis. *Stroke*, *38*(3), 1091-1096.

Bannerman, D. M., Rawlins, J. N. P., McHugh, S. B., et al. (2004). Regional dissociations within the hippocampus—memory and anxiety. *Neuroscience & Biobehavioral Reviews*, *28*(3), 273-283.

Barkham, M., Hardy, G. E., & Mellor-Clark, J. (2010). *Developing and delivering practice-based evidence*. Chichester: Wiley.

Barkham, M., & Margison, F. (2007). Practice-based evidence as a complement to evidence-based practice: From dichotomy to chiasmus. *Handbook of evidence-based psychotherapies: A guide for research and practice*, 443-476.

Barr, W. B., & Morrison, C. (Eds.). (2010). *Handbook on the Neuropsychology of Epilepsy*. Springer.

Bartolucci, A. A., & Hillegass, W. B. (2010). Overview, strengths, and limitations of systematic reviews and meta-analyses. In *Evidence-Based Practice: Toward Optimizing Clinical Outcomes* (pp. 17-33). Springer Berlin Heidelberg.

Baxendale, S. (2015). Managing Expectations of Epilepsy Surgery. In *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 243-253). Springer International Publishing.

Beaton, A. E., Durnford, A., Heffer-Rahn, P. E. et al. (2012). Transsylvian selective amygdalohippocampectomy in children with hippocampal sclerosis: Seizure, intellectual and memory outcome. *Seizure*, *21*(9), 699-705.

Beghi, E. (2004). Efficacy and tolerability of the new antiepileptic drugs: comparison of two recent guidelines. *The Lancet Neurology*, *3*(10), 618-621.

Begley, C. E., Basu, R., Reynolds, T., Lairson, D. R. et al. (2009). Sociodemographic disparities in epilepsy care: results from the Houston/New York City health care use and outcomes study. *Epilepsia*, *50*(5), 1040-1050.

Bender, P. K., Reinholdt-Dunne, M. L., Esbjørn, B. H., & Pons, F. (2012). Emotion dysregulation and anxiety in children and adolescents: Gender differences. *Personality and Individual Differences*, *53*(3), 284-288.

Benifla, M., Rutka, J. T., Otsubo, H., Lamberti-Pasculli, M.et al. (2008). Long-term seizure and social outcomes following temporal lobe surgery for intractable epilepsy during childhood. *Epilepsy research*, *82*(2), 133-138.

Bercovici, E., Kumar, B.S. & Mirsattari, S.M., 2012. Neocortical temporal lobe epilepsy. *Epilepsy research and treatment*, *2012*.

Berg, A. T., Berkovic, S. F., Brodie, M. J. et al. (2010). Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. *Epilepsia*, *51*(4), 676-685.

Berg, A. T., Caplan, R., & Hesdorffer, D. C. (2011). Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy. *Epilepsy & Behavior*, *20*(3), 550-555.

Berg, A. T., Langfitt, J. T., Testa, F. M., Levy, S. R., DiMario, F., Westerveld, M., & Kulas, J. (2008). Global cognitive function in children with epilepsy: a community-based study. *Epilepsia*, *49*(4), 608-614.

Berg, A. T., Mathern, G. W., Bronen, R. A. et al. (2009). Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. *Brain*, *132*(10), 2785-2797.

Berl, M., Kenealy, L., & Salpekar, J. (2013). A case study: Seizure disorders *Psychopathology of childhood and adolescence: A neuropsychological approach* (pp. 723-727). New York, NY: Springer Publishing Co; US.

Berl, M., Terwilliger, V., Scheller, A. et al. (2015). Speed and Complexity Characterize Attention Problems in Children with Localization-Related Epilepsy. *Epilepsia*, *56*(6), 833–840. http://doi.org/10.1111/epi.12985

Bevan, J. C., Johnston, C., Haig, M. J. et al. (1990). Preoperative parental anxiety predicts behavioural and emotional responses to induction of anaesthesia in children. *Canadian Journal of Anaesthesia*, *37*(2), 177-182.

Bigel, M. G., & Smith, M. L. (2001). The impact of different neuropathologies on pre-and postsurgical neuropsychological functioning in children with temporal lobe epilepsy. *Brain and cognition*, *46*(1), 46-49.

Binder, J. R., Desai, R. H., Graves, W. W., & Conant, L. L. (2009). Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. *Cerebral Cortex*, *19*(12), 2767-2796.

Bird-Lieberman, G., Sethi, K., Childs, A. M. et al. (2011). Diffuse hemispheric dysembryoplastic neuroepithelial tumor: a new radiological variant associated with early-onset severe epilepsy: Report of 3 cases. *Journal of Neurosurgery: Pediatrics*,*7*(4), 416-420.

Bittar, R. G., Rosenfeld, J. V., Klug, G. L. et al. (2002). Resective surgery in infants and young children with intractable epilepsy. *Journal of clinical neuroscience*, *9*(2), 142-146.

Blake R. V., Wroe S. J., Breen E. K., & McCarthy R.A. Accelerated forgetting in patients with epilepsy: Evidence for an impairment in memory consolidation. *Brain*. 2000;123 Pt 3:472–83

Blanchette, N., & Smith, M. L. (2001). Language after temporal or frontal lobe surgery in children with epilepsy. *Brain and cognition*, *48*(2-3), 280-284.

BMA Library - MEDLINE Plus (2012). *Basic Course: Notes for OvidSP*. BMA.

Bolton, P., & Griffiths, P. (1997). Association of tuberous sclerosis of temporal lobes with autism and atypical autism. Lancet, 349 (9049), 392–395.

Boluyt, N., Tjosvold, L., Lefebvre, C. et al. (2008). Usefulness of systematic review search strategies in finding child health systematic reviews in MEDLINE. *Archives of pediatrics & adolescent medicine*, *162*(2), 111-116.

Boronat, S., Newberry, P., Mehan, W. et al. (2013). Klüver–Bucy syndrome after unilateral frontotemporal resection in a child with tuberous sclerosis. *Child's Nervous System*, *29*(8), 1391-1394.

Boshuisen, K., Lamberink, H.J., van Schooneveld, M.M., et al. (2015). Cognitive consequences of early versus late antiepileptic drug withdrawal after pediatric epilepsy surgery, the TimeToStop (TTS) trial: study protocol for a randomized controlled trial. *Trials*, *16*(1), p.482.

Bradley, R. H., & Corwyn, R. F. (2002). Socioeconomic status and child development. *Annual review of psychology*, *53*(1), 371-399.

Bramer, W. M., Giustini, D., Kramer, B. M., & Anderson, P. (2013). The comparative recall of Google Scholar versus PubMed in identical searches for biomedical systematic reviews: a review of searches used in systematic reviews. *Systematic Reviews*, *2*, 115. http://doi.org/10.1186/2046-4053-2-115

Braveman, P., Cubbin, C., Marchi, K. et al. (2001). Measuring socioeconomic status/position in studies of racial/ethnic disparities: maternal and infant health. *Public health reports*, *116*(5), 449.

Breslau, N. (1985). Psychiatric disorder in children with physical disabilities. *Journal of the American Academy of Child Psychiatry*, *24*(1), 87-94.

Brodie, M. J., & Holmes, G. L. (2008). Should all patients be told about sudden unexpected death in epilepsy (SUDEP)? Pros and Cons. *Epilepsia*, *49*(s9), 99-101.

Browne, T. R., & Holmes, G. L. (2008). *Handbook of epilepsy*. Jones & Bartlett Learning.

Burneo, J. G., Black, L., Martin, R. et al. (2006) Race/Ethnicity, Sex, and Socioeconomic Status as Predictors of Outcome After Surgery for Temporal Lobe Epilepsy. *Arch Neurol.*63(8):1106-1110.

Burneo, J. G., Jette, N., Theodore, W. et al. for the Task Force on Disparities in Epilepsy Care, on behalf of the North American Commission of the International League Against Epilepsy (2009), Disparities in epilepsy: Report of a systematic review by the North American Commission of the International League Against Epilepsy. *Epilepsia*, 50: 2285–2295.

Burneo, J. G., Villanueva, V., Knowlton, R. C. et al. (2008). Kaplan–Meier analysis on seizure outcome after epilepsy surgery: Do gender and race influence it?. *Seizure*, *17*(4), 314-319.

Busch, R. M., Chapin, J. S., Umashankar, G. et al. (2008). Poor presurgical performance on both verbal and visual memory measures is associated with low risk for memory decline following left temporal lobectomy for intractable epilepsy. *Epileptic Disorders*,*10*(3), 199-205.

Cadman, D., Boyle, M., Szatmari, P., & Offord, D. R. (1987). Chronic illness, disability, and mental and social well-being: findings of the Ontario Child Health Study. *Pediatrics*, *79*(5), 805-813.

Calandre, E. P., Dominguez-Granados, R., Gomez-Rubio, M., & Molina-Font, J. A. (1990). Cognitive effects of long-term treatment with phenobarbital and valproic acid in school children. *Acta Neurologica Scandinavica*, *81*(6), 504-506.

Camfield PR, Gates R, Ronen G, Camfield C. et al. (1984). Comparison of cognitive ability, personality profile and school succes in epileptic children with pure right versus left temporal lobe EEG foci. *Ann Neurol*. 1(15), 122-6.

Caplan, R., Shields, W. D., Mori, L., & Yudovin, S. (1991). Middle childhood onset of interictal psychosis. *Journal of the American Academy of Child & Adolescent Psychiatry*, *30*(6), 893-896.

Carlton-Ford, R. Miller, M. Brown, N. et al. (1995) Epilepsy and children's social and psychological adjustment. *J Health Soc Behav;* 36(3): 285–301.

Carpay, H. A., Vermeulen, J., Stroink, H. et al.(1997). Disability due to restrictions in childhood epilepsy. *Developmental Medicine & Child Neurology*, *39*(8), 521-526.

Cataltepe, O., & Jallo, G. I. (2010). *Pediatric Epilepsy Surgery: Preoperative Assessment and Surgical Treatment*: Thieme.

Centre for reviews, & dissemination (CRD). (2009). *Systematic reviews: CRD's guidance for undertaking reviews in health care*. Centre for Reviews and Dissemination.

Chalmers, I., Bracken, M. B., Djulbegovic, B. et al.. (2014). How to increase value and reduce waste when research priorities are set. *The Lancet*, *383*(9912), 156-165.

Chaplin, T. M., & Aldao, A. (2013). Gender differences in emotion expression in children: a meta-analytic review. *Psychological Bulletin*, *139*(4), 735.

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology*, *10*(5), 413-432.

Chelune, G. J., Naugle, R. I., Lüders, H. et al. (1993). Individual change after epilepsy surgery: Practice effects and base-rate information. *Neuropsychology*, *7*(1), 41.

Christie, D. & Khatun, H. (2012) Adjusting to life with chronic illness. *The Psychologist*, 25(3), 194-197.

Ciesielski A.S., Samson S.,& Steinhoff B.J. (2006) Neuropsychological and psychiatric impact of add-on titration of pregabalin versus levetiracetam: a comparative short-term study. Epilepsy Behav 9: 424–431

Clark, Eve (2009). *First Language Acquisition.* New York, (pp. 44–46). NY: Cambridge University Press.

Clarke, D. F., Roberts, W., Daraksan, M., et al. (2005). The prevalence of autistic spectrum disorder in children surveyed in a tertiary care epilepsy clinic. *Epilepsia*, *46*(12), 1970-1977.

Clusmann, H., Kral, T., Gleissner, U. et al.. (2004). Analysis of different types of resection for pediatric patients with temporal lobe epilepsy. *Neurosurgery*, *54*(4), 847-860.

Cochrane Collaboration. (2014). Review Manager (RevMan)[Computer Program] Version 5.2. 3. Copenhagen: The Nordic Cochrane Centre; 2012.

Cochrane Consumers & Communication Review Group (2013) *Study Quality Guide: Guide for review authors on assessing study quality.* The Cochrane Collaboration.

Cohen, M. J. (1997). *CMS: Children's Memory Scale: Manual*. Psychological Corporation.

Coley, R. J. (2002). An Uneven Start: Indicators of Inequality in School Readiness. Policy Information Report.

Concato, J. (2012). Is it time for medicine-based evidence? *JAMA, 307*(15), 1641-1643.

Concato, J. (2013). Study Design and "Evidence" in Patient-oriented Research. *American Journal of Respiratory and Critical Care Medicine, 187*(11), 1167-1172.

Cormack, F., Cross, H. J., Isaacs, E. et al. (2007). The development of intellectual abilities in pediatric temporal lobe epilepsy. *Epilepsia, 48*(1), 201-204.

Cramer, J. A., De Rue, K., Devinsky, O. et al. (2003). A systematic review of the behavioral effects of levetiracetam in adults with epilepsy, cognitive disorders, or an anxiety disorder during clinical trials. *Epilepsy & Behavior, 4*(2), 124-132.

Cronel-Ohayon, S., Zesiger, P., Davidoff, V. et al. (2006). Deficit in memory consolidation (abnormal forgetting rate) in childhood temporal lobe epilepsy. Pre and postoperative long-term observation. *Neuropediatrics, 37*(06), 317-324.

Cross, J. H. (2011). Epilepsy surgery in children: are we doing enough? *Epilepsy Professional*.

Cross, J. H., Jayakar, P., Nordli, D. et al. (2006). Proposed criteria for referral and evaluation of children for epilepsy surgery: recommendations of the Subcommission for Pediatric Epilepsy Surgery. *Epilepsia, 47*(6), 952-959.

Cross, J. H., Kluger, G., & Lagae, L. (2013). Advancing the management of childhood epilepsies. *European Journal of Paediatric Neurology, 17*(4), 334-347.

Cunningham, C., Tuxhorn, I., Kotagal, P et al. (2007). Epilepsy surgery in an 8-year-old boy with intractable seizures. *Journal of Developmental & Behavioral Pediatrics*, *28*(4), 330-333.

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC medicine, 11*(1), 126.

Danielsson, S., Rydenhag, B., Uvebrant, P., et al. (2002). Temporal lobe resections in children with epilepsy: neuropsychiatric status in relation to neuropathology and seizure outcome. *Epilepsy & Behavior, 3*(1), 76-81.

Davies, K.G., Risse, G.L. & Gates, J.R., 2005. Naming ability after tailored left temporal resection with extraoperative language mapping: increased risk of decline with later epilepsy onset age. *Epilepsy & Behavior, 7*(2), pp.273-278.

De Koning, T., Versnel, H., Jennekens-Schinkel, A., et al. (2009). Language development before and after temporal surgery in children with intractable epilepsy. *Epilepsia, 50*(11), 2408-2419.

Dennis, M., Spiegler, B. J., Juranek, J. J. et al. (2013). Age, Plasticity, and Homeostasis In Childhood Brain Disorders. *Neuroscience and biobehavioral reviews, 37*(10 0 2),

DeVos, K. J., Wyllie, E., Geckler, C., et al. (1995). Language dominance in patients with early childhood tumors near left hemisphere language areas. *Neurology, 45*(2), 349-356.

Dlugos, D. J., Moss, E. M., Duhaime, A. C., & Brooks-Kayal, A. R. (1999). Language-related cognitive declines after left temporal lobectomy in children. *Pediatric neurology, 21*(1), 444-449.

Dodrill C.B., Arnett J.L., Hayes A.G., et al. (1999) Cognitive abilities and adjustment with gabapentin: results of a multisite study. Epilepsy Res 35: 109–121

Donati F., Gobbi G., Campistol J.et al. (2006) Effects of oxcarbazepine on cognitive function in children and adolescents with partial seizures. Neurology 67: 679–682

Donati F., Gobbi G., Campistol J. et al. (2007) The cognitive effects of oxcarbazepine versus carbamazepine or valproate in newly diagnosed children with partial seizures. *Seizure* 16: 670–679

Donner, E. J., Smith, C. R., & Snead, O. C. (2001). Sudden unexplained death in children with epilepsy. *Neurology*, *57*(3), 430-434.

Downs, S. H., & Black, N. (1998). The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health*, *52*(6), 377-384

Deary, I. J., & Johnson, W. (2010). Intelligence and education: causal perceptions drive analytic processes and therefore conclusions. *International Journal of Epidemiology*, *39*(5), 1362-1369.

Duan, X., Zhang, S., & Xiao, N. (2012). Reliability and validity of the PedsQL™ Generic Core Scales 4.0 for Chinese children with epilepsy. *Epilepsy & Behavior*, *23*(4), 431-436.

Duchowny, M., & Cross, J. H. (2012). Preoperative evaluation in children for epilepsy surgery. *Handbook of clinical neurology*, *108*, 829.

Duchowny, M., Jayakar, P., Resnick, T. et al. (1998). Epilepsy surgery in the first three years of life. *Epilepsia*, *39*(7), 737-743.

Duff, K. (2012). Evidence-based indicators of neuropsychological change in the individual patient: relevant concepts and methods. *Archives of Clinical Neuropsychology*, *27*(3), 248-261.

Duncan, J. D., Moss, S. D., Bandy, D. J. et al. (1997). Use of positron emission tomography for presurgical localization of eloquent brain areas in children with seizures. *Pediatric neurosurgery*, *26*(3), 144-156.

Dunkley, C., Kung, J., Scott, R. C. et al. (2011). Epilepsy surgery in children under 3 years. *Epilepsy research*, *93*(2), 96-106.

Dyson, L. L. (1996). The experiences of families of children with learning disabilities: Parental stress, family functioning, and sibling self-concept. *Journal of learning disabilities*, *29*(3), 280-286.

Eddy, C. M., Rickards, H. E., & Cavanna, A. E. (2011). The cognitive impact of antiepileptic drugs. *Therapeutic advances in neurological disorders*, *4*(6), 385-407.

Elliott, I. M., Lach, L., & Smith, M. L. (2005). I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. *Epilepsy & Behavior*, *7*(4), 664-678.

Elliott, R. E., Morsi, A., Kalhorn, S. P. et al. (2011). Vagus nerve stimulation in 436 consecutive patients with treatment-resistant epilepsy: long-term outcomes and predictors of response. *Epilepsy & Behavior*, *20*(1), 57-63

Elliott, R. E., Rodgers, S. D., Bassani, L. et al. (2011). Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases: Clinical article. *Journal of Neurosurgery: Pediatrics*, *7*(5), 491-500.

Ellis, N., Upton, D., & Thompson, P. (2000). Epilepsy and the family: a review of current literature. *Seizure*, *9*(1), 22-30.

Engel, J. (1987). Approaches to localization of the epileptogenic lesion. *Surgical Treatment of the Epilepsies, Raven Press, New York*, 75-95.

Engel, J. (2001). A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. *Epilepsia*, *42*(6), 796-803.

Engel Jr, J. (1996). Surgery for seizures. *New England Journal of Medicine*, *334*(10), 647-653.

Epilepsy Action (2013a). A guide for Paediatricians: Children's Epilepsy Surgery Service (CESS). Guidelines for children's epilepsy brain surgery referrals in England. URL: https://www.epilepsy.org.uk/sites/epilepsy/files/professionals/cess-practioners-booklet.pdf

Epilepsy Action (2013b). Children's Epilepsy Surgery Service (CESS) in England. URL: https://www.epilepsy.org.uk/sites/epilepsy/files/epilepsy-action-children-epilepsy-surgery-parents-booklet.pdf

EPPI-centre methods for conducting systematic reviews (2010). *EPPI-Centre Methods for Conducting Systematic Reviews.* EPPI-centre, Social Science Research Unit, Institute of Education, University of London

Equator Network (2009). *Enhancing the quality and transparency of health research.* Available at www. equator-network.org. [Accessed Date 20.06.2016]

Ettinger, A. B., Jandorf, L., Berdia, A. et al. (1996). Felbamate-Induced Headache. *Epilepsia*, *37*(5), 503-505.

Ewart, H. (2009). The Relation Between Volume and Outcome in Paediatric Neurosurgery: A Literature Review for the National Specialised Commissioning Group. Public Health Resource Unit. Retrieved from: http://www.webarchive.org.uk/wayback/archive/20130325152435/http://www.specialisedservices.nhs.uk/library/31/The_Relation_Between_Volume_and_Outcome_in_Paediatric_Neurosurgery__A_Literature_Review_for_the_National_Specialised_Commissioning_Group_Henrietta_Ewart_Consultant_in_Public_Health_Medicine_PHRU_Oxford__September_2009.pdf

Farrant, B. & Zubrick, S. (2012). "Early vocabulary development: The importance of joint attention and parent-child book reading*". First Language: 343–364.*

Farwell, J. R., Lee, Y. J., Hirtz, D. G. et al. (1990). Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. *New England Journal of Medicine*,*322*(6), 364-369.

Fedio, P. & Mirsky, A. F. Selective intellectual deficits in children with temporal lobe or centrencephalic epilepsy. Neuropsychologia. 1969; 7:287-300.

Fisher, R. S., Acevedo, C., Arzimanoglou, A. et al. (2014). ILAE official report: a practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475-482.

Fisher, R., Salanova, V., Witt, T. et al. (2010). Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia*, *51*(5), 899-908.

French, J. A., Kanner, A. M., Bautista, J. et al. (2004). Efficacy and tolerability of the new antiepileptic drugs II: Treatment of refractory epilepsy: The TTA and QS Subcommittees of the AAN and the American Epilepsy Society. *NEUROLOGY-MINNEAPOLIS-*, *62*(8), 1261-1273.

Fried, I. (1995). Magnetic resonance imaging and epilepsy: neurosurgical decision making. *Magnetic resonance imaging*, *13*(8), 1163-1170.

Gagliardi, I. C., Guimarães, C. A., Souza, E. A., et al. (2011). Quality of life and epilepsy surgery in childhood and adolescence. *Arquivos de neuro-psiquiatria*, *69*(1), 23-26.

Gallagher, J. (2013). Child heart surgery reform suspended. *BBC News Health*. Retrieved from http://www.bbc.co.uk/news/health-22857214

García-Fernández, M., Fournier-Del Castillo, C., Ugalde-Canitrot, A., et al. (2011). Epilepsy surgery in children with developmental tumours. *Seizure*, *20*(8), 616-627.

Gayatri, N. A., Morrall, M. C., Jain, V., et al. (2010). Parental and physician beliefs regarding the provision and content of written sudden unexpected death in epilepsy (SUDEP) information. *Epilepsia*, *51*(5), 777-782.

Ghatan, S., McGoldrick, P., Palmese, C., et al. (2014). Surgical management of medically refractory epilepsy due to early childhood stroke: Clinical article. *Journal of Neurosurgery: Pediatrics*, *14*(1), 58-67.

Gilliam, F., Wyllie, E., Kashden, J., et al. (1997). Epilepsy surgery outcome Comprehensive assessment in children. *Neurology*, *48*(5), 1368-1374.

Gleissner, U., Sassen, R., Lendt, M., et al. (2002). Pre-and postoperative verbal memory in pediatric patients with temporal lobe epilepsy. *Epilepsy research*, *51*(3), 287-296.

Gonzalez, L. M., Anderson, V. A., Wood, S. J., et al. (2007), The Localization and Lateralization of Memory Deficits in Children with Temporal Lobe Epilepsy. Epilepsia, 48: 124–132.

Groesbeck, D. K., Bluml, R. M., & Kossoff, E. H. (2006). Long-term use of the ketogenic diet in the treatment of epilepsy. *Developmental Medicine & Child Neurology*, *48*(12), 978-981.

Grosmaitre, C., Auclair, L., Dorfmuller, G., et al. (2014). Reading impairment in an adolescent with temporo-occipital epilepsy. Pre-and post-surgical evaluation. *Neurocase*, *20*(1), 87-99.

Gross, F. L. (1987). *Introducing Erik Erikson: An invitation to his thinking*. Univ Pr of Amer.

Guerrini, R., Scerrati, M., Rubboli, G., et al. (2013). Overview of presurgical assessment and surgical treatment of epilepsy from the Italian League Against Epilepsy. *Epilepsia*, *54*(s7), 35-48.

Guimarães, C.A., Min, L. L., Rzezak, P., et al. (2006). Memory impairment in children with temporal lobe epilepsy: a review. *Journal of Epilepsy and Clinical Neurophysiology*, *12*(1, Suppl. 1), 22-25.

Guimarães, C. A., Franzon, R. C., Souza, E. A., et al. (2004). Abnormal behavior in children with temporal lobe epilepsy and ganglioglioma. *Epilepsy & Behavior*, *5*(5), 788-791.

Hamiwka, L., Macrodimitris, S., Tellez-Zenteno, J. F., et al. (2011). Social outcomes after temporal or extratemporal epilepsy surgery: a systematic review. *Epilepsia*, *52*(5), 870-879.

Harbord, M. G. (2000). Significant anticonvulsant side-effects in children and adolescents. *Journal of clinical neuroscience*, *7*(3), 213-216.

Hart, Betty (1995). *Meaningful Differences in the Everyday Experience of Young American Children.*

Harvey, A. S., Cross, J. H., Shinnar, S., & Mathern, G. W. (2008). Defining the spectrum of international practice in pediatric epilepsy surgery patients. *Epilepsia*, *49*(1), 146-155.

Hauptman, J. S. & Mathern, G. W. (2016) Epilepsy Surgery in Children, in The Treatment of Epilepsy, Third Edition (eds S. Shorvon, E. Perucca and J. Engel), Wiley-Blackwell, Oxford, UK.

Heiman, T., & Berger, O. (2008). Parents of children with Asperger syndrome or with learning disabilities: Family environment and social support. *Research in Developmental Disabilities*, *29*(4), 289-300.

Heinrich, L. M., & Gullone, E. (2006). The clinical significance of loneliness: A literature review. *Clinical psychology review*, *26*(6), 695-718.

Helmstaedter, C., & Elger, C. E. (2009). Chronic temporal lobe epilepsy: A neurodevelopmental or progressively dementing disease? Brain, 132(10), 2822- 2830.

Henderson, C. B., Filloux, F. M., Alder, S. C., et al. (2006). Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. *Journal of child neurology*, *21*(3), 193-198.

Hennessy, M. J., Langan, Y., Elwes, R. D. C., et al. (1999). A study of mortality after temporal lobe epilepsy surgery. *Neurology*, *53*(6), 1276-1276.

Hermann, B. P., Dabbs, K., Becker, T., et al. (2010). Brain development in children with new onset epilepsy: a prospective controlled cohort investigation. *Epilepsia*,*51*(10), 2038-2046.

Hermann, B., Jones, J., Sheth, R., et al. (2006). Children with new-onset epilepsy: neuropsychological status and brain structure. *Brain*, *129*(10), 2609-2619.

Hermann, B. P., Jones, J. E., Sheth, R., et al. (2008). Growing up with epilepsy: a two-year investigation of cognitive development in children with new onset epilepsy. *Epilepsia, 49*(11), 1847-1858.

Hermann, B., & Seidenberg, M. (2007). Epilepsy and Cognition. *Epilepsy Currents*, *7*(1), 1–6.

Hermann, B., Seidenberg, M., Bell, B., et al. (2002). The Neurodevelopmental Impact of Childhood-onset Temporal Lobe Epilepsy on Brain Structure and Function. *Epilepsia, 43*(9), 1062-1071.

Hermann, B. P., Seidenberg, M., Schoenfeld, J., & Davies, K. (1997). Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. *Arch Neurol, 54*(4), 369-376.

Hermann, B. P., Whitman, S., Hughes, J. R.,et al. (1988). Multietiological determinants of psychopathology and social competence in children with epilepsy. *Epilepsy research*, *2*(1), 51-60.

Higgins, J.P.T. & Green, S. (Eds.) (2011). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Höller, Y., Kutil, R., Klaffenböck, L., et al. (2015). High-frequency oscillations in epilepsy and surgical outcome. A meta-analysis. *Frontiers in human neuroscience*, *9*.

Holmes, T. R., Browne, G. L., & Gregory, L. (2008). Handbook of epilepsy.*Philadelphia: Lippincott Williams and Wilkins. ISBN*, *1141240981*.

Hori, T., Yamane, F., Ochiai, T., et al. (2007). Selective subtemporal amygdalohippocampectomy for refractory temporal lobe epilepsy: operative and neuropsychological outcomes. *Journal of neurosurgery*, *106*(1), 134-141.

Hrabok, M., Dykeman, J., Sherman, E. M. S., & Wiebe, S. (2013). An evidence-based checklist to assess neuropsychological outcomes of epilepsy surgery: How good is the evidence?. *Epilepsy & Behavior*, *29*(3), 443-448.

Huang C.-W., Pai M.-C., Tsai J.-J. (2008) Comparative cognitive effects of levetiracetam and topiramate in intractable epilepsy. Psychiatr Clin Neurosci 62: 548–553

Hudson, C. G. (2005). Socioeconomic status and mental illness: tests of the social causation and selection hypotheses. *American journal of Orthopsychiatry*, *75*(1), 3.

Ioannidis, J. P. (2005). Why most published research findings are false. *PLoS Med*, *2*(8), e124.

Ioannidis, J. P. (2011). Excess significance bias in the literature on brain volume abnormalities. *Archives of General Psychiatry*, *68*(8), 773-780.

Ioannidis, J. P., Greenland, S., Hlatky, M. A., et al. (2014). Increasing value and reducing waste in research design, conduct, and analysis. *The Lancet*, *383*(9912), 166-175.

Ipsos MORI (2011). Safe and Sustainable Review of Children's Congenital Heart Services in England: report of the public consultation (executive summary).

Joint Epilepsy Council. (2011). Epilepsy Prevalence. Incidence, and Other Statistics (Joint Epilepsy Council Publication).

Jambaqué, I., Dellatolas, G., Dulac, O., et al. (1993). Verbal and visual impairment in children with epilepsy. *Neuropsychology;*31, 1321-7.

Jambaqué, I., Dellatolas, G., Fohlen, M., et al. (2007). Memory functions following surgery for temporal lobe epilepsy in children. *Neuropsychologia*, *45*(12), 2850-2862.

Jarrar, R. G., Buchhalter, J. R., Meyer, F. B., et al. (2002). Long-term follow-up of temporal lobectomy in children. *Neurology*,*59*(10), 1635-1637.

Jones, J. E., Watson, R., Sheth, R., et al. (2007). Psychiatric comorbidity in children with new onset epilepsy. *Developmental Medicine & Child Neurology*, *49*(7), 493-497.

Kaindl, A. M., Asimiadou, S., Manthey, D., et al. (2006). Antiepileptic drugs and the developing brain. *Cellular and Molecular Life Sciences CMLS*, *63*(4), 399-413.

Kandratavicius, L., Hallak, J. E., Young, L. T., et al. (2012). Differential aberrant sprouting in temporal lobe epilepsy with psychiatric co-morbidities. *Psychiatry research*, *195*(3), 144-150.

Katzman, R., Terry, R., DeTeresa, R., et al. (1988). Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Annals of neurology*, *23*(2), 138-144.

Keene, D. L., Higgins, M. J., & Ventureyra, E. C. (1997). Outcome and life prospects after surgical management of medically intractable epilepsy in patients under 18 years of age. *Child's Nervous System*, *13*(10), 530-535.

Kellogg WK Foundation (2004) Logic model development guide. In: Knowledge Centre, WK Kellogg Foundation. http://www.wkkf.org/knowledge-center/resources/2006/02/wk-kellogg-foundationlogic-model-development-guide.aspx

Kernan, C. L., Asarnow, R., Siddarth, P., et al. (2012), Neurocognitive profiles in children with epilepsy. Epilepsia, 53: 2156–2163.

Kesler, S. R., Tanaka, H., & Koovakkattu, D. (2010). Cognitive reserve and brain volumes in pediatric acute lymphoblastic leukaemia. *Brain imaging and behavior*, *4*(3-4), 256-269.

Kim, K. H. (2005). Can only intelligent people be creative? A meta-analysis. *Prufrock Journal*, *16*(2-3), 57-66.

Korkman, M., Granström, M. L., Kantola-Sorsa, E., et al. (2005). Two-year follow-up of intelligence after pediatric epilepsy surgery. *Pediatric neurology*, *33*(3), 173-178.

Krsek, P., Kudr, M., Jahodova, A., et al. (2013). Localizing value of ictal SPECT is comparable to MRI and EEG in children with focal cortical dysplasia. *Epilepsia*, *54*(2), 351-358

Kuehn, S. M., Keene, D. L., Richards, P. M., & Ventureyra, E. C. (2002). Are there changes in intelligence and memory functioning following surgery for the treatment of refractory epilepsy in childhood?. *Child's nervous system*, *18*(6-7), 306-310.

Kwan, P., & Brodie, M. J. (2000). Early identification of refractory epilepsy. *New England Journal of Medicine*, *342*(5), 314-319.

Lah, S. (2004). Neuropsychological outcome following focal cortical removal for intractable epilepsy in children. *Epilepsy & Behavior*, *5*(6), 804-817.

Lah, S., & Smith, M. L. (2015). Verbal memory and literacy outcomes one year after pediatric temporal lobectomy: a retrospective cohort study. *Epilepsy & Behavior*, *44*, 225-233.

Larysz, D., Larysz, P., & Mandera, M. (2007). Evaluation of quality of life and clinical status of children operated on for intractable epilepsy. *Child's Nervous System*, *23*(1), 91-97.

LeDoux, J. (2003). The emotional brain, fear, and the amygdala. *Cellular and molecular neurobiology*, *23*(4-5), 727-738.

Lee, Y. J., Kang, H. C., Bae, S. J., et al. (2010). Comparison of temporal lobectomies of children and adults with intractable temporal lobe epilepsy. *Child's Nervous System*, *26*(2), 177-183.

Lee, Y. J., Kang, H. C., Kim, H. D., et al. (2015). Neurocognitive Function in Children After Anterior Temporal Lobectomy with Amygdalohippocampectomy. *Pediatric neurology*, *52*(1), 88-93.

Lee, J. Y., Phi, J. H., Wang, K. C., et al. (2011). Transsylvian-transcisternal selective lesionectomy for pediatric lesional mesial temporal lobe epilepsy. *Neurosurgery*, *68*(3), 582-587.

Lendt, M., Helmstaedter, C., & Elger, C. E. (1999). Pre-and Postoperative Neuropsychological Profiles in Children and Adolescents with Temporal Lobe Epilepsy. *Epilepsia*, *40*(11), 1543-1550.

Lerwick, J. L. (2013, August). Psychosocial implications of pediatric surgical hospitalization. In *Seminars in pediatric surgery* (Vol. 22, No. 3, pp. 129-133). WB Saunders.

Leunen, D., Caroff, X., Chmura, S., et al. (2009). Verbal and spatial learning after temporal lobe excisions in children: An adaptation of the Grober and Buschke procedure. *Epilepsy & Behavior*, *16*(3), 534-538.

Levisohn P.M., Mintz M., Hunter S.J., et al. (2009) Neurocognitive effects of adjunctive levetiracetam in children with partial-onset seizures: A randomized, double-blind, placebo-controlled, noninferiority trial. Epilepsia 50: 2377–2389

Lewis, D. V., Thompson, R. J., Santos, C. C., et al. (1996). Outcome of temporal lobectomy in adolescents. *Journal of Epilepsy*, *9*(3), 198-205.

Liberati, A., Altman, D. G., Tetzlaff, J., et al. (2009). The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration. *PLos Medicine*, *6*(7), 1-6.

Lippa, R. A. (2010). Gender differences in personality and interests: when, where, and why?. *Social and personality psychology compass*, *4*(11), 1098-1110.

Liu, S., An, N., Yang, H., et al. (2007). Pediatric intractable epilepsy syndromes: reason for early surgical intervention. *Brain and Development*, *29*(2), 69-78.

Loddenkemper, T., Holland, K. D., Stanford, L. D., et al. (2007). Developmental outcome after epilepsy surgery in infancy. *Pediatrics*, *119*(5), 930-935.

Lopez-Ojeda, P., Labib, M., Burneo, J., & Lownie, S. P. (2013). Temporal lobe arteriovenous malformations: surgical outcomes with a focus on visual field defects and epilepsy. *Neurosurgery*, *73*(5), 854-862

Luthar, S. S. (2003). *Resilience and vulnerability: Adaptation in the context of childhood adversities*. Cambridge University Press.

Mabbott, D. J., & Smith, M. L. (2003). Memory in children with temporal or extra-temporal excisions. *Neuropsychologia*, *41*(8), 995-1007.

Manford, M., Cvejic, H., Minde, K., et al. (1998). Case study: neurological brain waves causing serious behavioral brainstorms. *Journal of the American Academy of Child & Adolescent Psychiatry*, *37*(10), 1085-1090.

May, T. W., Bulmahn, A., Wohlhueter, M., & Rambeck, B. (1992). Effects of withdrawal of phenytoin on cognitive and psychomotor functions in hospitalized epileptic patients on polytherapy. *Acta neurologica scandinavica*, *86*(2), 165-170.

Maguire, M. J., Hemming, K., Hutton, J. L., & Marson, A. G. (2008). Overwhelming heterogeneity in systematic reviews of observational anti-epileptic studies. *Epilepsy research*, *80*(2), 201-212.

McCandless, D. W. (2012). Simple Partial Seizures. In *Epilepsy* (pp. 143-152). Springer New York.

McDonagh, M., Peterson, K., Raina, P., et al. (2006) Avoiding Bias in Selecting Studies. 2013 Feb 20. In: *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK126701/

McEwan, M. J., Espie, C. A., Metcalfe, J., et al. (2004). Quality of life and psychosocial development in adolescents with epilepsy: a qualitative investigation using focus group methods. *Seizure*, *13*(1), 15-31.

McLellan, A. (2015). Long-Term Psychiatric and Behaviour Outcomes in Children Following Epilepsy Surgery. In K. Malgrem, S. Baxendale, J. H. Cross (Eds.) *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 115-124). Springer International Publishing.

McLellan, A., Davies, S., Heyman, I., et al. (2005). Psychopathology in children with epilepsy before and after temporal lobe resection. *Developmental Medicine & Child Neurology*, *47*(10), 666-672.

McLoyd, V. C. (1998). Socioeconomic disadvantage and child development. *American psychologist*, *53*(2), 185.

McSweeny, A. J., Naugle, R. I., Chelune, G. J., & Lüders, H. (1993). "T scores for change": An illustration of a regression approach to depicting change in clinical neuropsychology. *The Clinical Neuropsychologist*, *7*(3), 300-312.

Meador K.J., Loring D.W., Ray P.G., et al. (1999) Differential cognitive effects of carbamazepine and gabapentin. Epilepsia 40: 1279–1285

Meekes, J., Braams, O., Braun, K. P., et al. (2013). Verbal memory after epilepsy surgery in childhood. *Epilepsy research*, *107*(1), 146-155.

Meline, T. (2006). Selecting studies for systematic review: Inclusion and exclusion criteria. *Contemporary Issues in Communication Science and Disorders*, *33*(21-27).

Mhaskar, R., Emmanuel, P., Mishra, S., et al. (2009). Critical appraisal skills are essential to informed decision-making. *Indian journal of sexually transmitted diseases*, *30*(2), 112.

Miatton, M., Van Roost, D., Thiery, E., et al. (2011). The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. *Epilepsy & Behavior*, *22*(4), 759-764.

Micallef, S., Spooner, C. G., Simon Harvey, A., et al. (2010). Psychological outcome profiles in childhood-onset temporal lobe epilepsy. *Epilepsia*, *51*(10), 2066-2073.

Mikati, M. A., El-Bitar, M. K., Najjar, M. W., et al. (2009). A child with refractory complex partial seizures, right temporal ganglioglioma, contralateral continuous electrical status epilepticus, and a secondary Landau–Kleffner autistic syndrome. *Epilepsy & Behavior*, *14*(2), 411-417.

Mims, J. (1997). Self-esteem, behavior, and concerns surrounding epilepsy in siblings of children with epilepsy. *Journal of Child Neurology*, *12*(3), 187-192.

Miranda, C., & Smith, M. L. (2001). Predictors of intelligence after temporal lobectomy in children with epilepsy. *Epilepsy & Behavior*, *2*(1), 13-19.

Miserocchi, A., Cascardo, B., Piroddi, C., et al. (2013). Surgery for temporal lobe epilepsy in children: relevance of presurgical evaluation and analysis of outcome: Clinical article. *Journal of Neurosurgery: Pediatrics*, *11*(3), 256-267.

Mitchell, W. G., Chavez, J. M., Lee, H., & Guzman, B. L. (1991). Academic underachievement in children with epilepsy. *Journal of Child Neurology*, *6*(1), 65-72.

Morgan, P. L., Farkas, G., Hillemeier, M. M., & Maczuga, S. (2009). Risk factors for learning-related behavior problems at 24 months of age: Population-based estimates. *Journal of abnormal child psychology*, *37*(3), 401-413.

Morris, G. L., Gloss, D., Buchhalter, J., et al. (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*(16), 1453-1459.

Moseley, B. D., Dhamija, R., & Wirrell, E. C. (2012). The cessation of continuous spike wave in slow-wave sleep following a temporal lobectomy. *Journal of child neurology*, *27*(1), 113-116.

Moser, S. J., Schneider, J., Lütschg, J. & Weber, P. (2006), Fast improvement of verbal memory function after left temporal tumour resection. Acta Paediatrica, 95: 1306–1309.

Muehlebner, A., Groeppel, G., Pahs, G., et al. (2010). Beneficial effect of epilepsy surgery in a case of childhood non-paraneoplastic limbic encephalitis. *Epilepsy research*, *90*(3), 295-299.

Nadkarni, S., & Devinsky, O. (2005). Psychotropic effects of antiepileptic drugs. *Epilepsy Currents*, *5*(5), 176-181.

Nakaji, P., Meltzer, H. S., Singel, S. A., & Alksne, J. F. (2003). Improvement of aggressive and antisocial behavior after resection of temporal lobe tumors. *Pediatrics*, *112*(5), e430-e430.

National Specialised Services (2012) *Safe & Sustainable Children's Neurosurgical Services Review* (http://www.specialisedservices.nhs.uk/safe_sustainable/childrens- neurosurgical-services). Accessed 23 March 2013.

Neal, E. G., Chaffe, H., Schwartz, R. H., et al. (2008). The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *The Lancet Neurology*, *7*(6), 500-506.

Neisser, U., Boodoo, G., Bouchard Jr, T. J., et al. (1996). Intelligence: knowns and unknowns. *American psychologist*, *51*(2), 77.

Neville, B. G., Harkness, W. F., Cross, J. H., et al. (1997). Surgical treatment of severe autistic regression in childhood epilepsy. *Pediatric neurology*, *16*(2), 137-140.

Neyens L.G.J., Alpherts W.C.J., Aldenkamp A.P. (1995) Cognitive effects of a new pyrrolidine derivative (levetiracetam) in patients with epilepsy. Prog Neuropsychopharmacol Biol Psychiatr 19: 411–419

NHS Commissioning Board (2013) *2013/14 NHS standard contract for children's epilepsy surgery service* http://www.england.nhs.uk/wp-content/uploads/2013/06/e09-child-epilepsy-surg.pdf. Accessed 10 June 2016.

Nicholas, K. K., & Pianta, R. C. (1994). Mother-child interactions and seizure control: relations with behavior problems in children with epilepsy. *Journal of Epilepsy*, *7*(2), 102-107.

Nickels, K. C., Wong-Kisiel, L. C., Moseley, B. D., & Wirrell, E. C. (2011). Temporal lobe epilepsy in children. *Epilepsy research and treatment*, *2012*

Nikcevic, A. V., Kuczmierczyk, A. R., & Bruch, M. (Eds.). (2009). *Formulation and treatment in clinical health psychology*. Routledge.

Noble, A. J., & Marson, A. G. (2016). Which outcomes should we measure in adult epilepsy trials? The views of people with epilepsy and informal carers. *Epilepsy & Behavior*, *59*, 105-110.

Nolan, M. A., Redoblado, M. A., Lah, S., et al. (2004) Memory function in childhood epilepsy syndromes. J

Paediatr Child Health, 40, 20-7.

OCEBM Levels of Evidence Working Group. (2011). The Oxford 2011 levels of evidence.

Ochi, A., Hung, R., Weiss, S., et al. (2011). Lateralized interictal epileptiform discharges during rapid eye movement sleep correlate with epileptogenic hemisphere in children with intractable epilepsy secondary to tuberous sclerosis complex. *Epilepsia*, *52*(11), 1986-1994.

Ødegård, W. (2005). Chronic illness as a challenge to the attachment process. *Clinical child psychology and psychiatry*, *10*(1), 13-22.

Oostrom, K. J., Smeets-Schouten, A., Kruitwagen, C. L., et al. (2003). Not only a matter of epilepsy: early problems of cognition and behavior in children with "epilepsy only"—a prospective, longitudinal, controlled study starting at diagnosis. *Pediatrics*, *112*(6), 1338-1344.

Ott, D., Caplan, R., Guthrie, D., et al. (2001). Measures of psychopathology in children with complex partial seizures and primary generalized epilepsy with absence. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(8), 907-914.

Ott, D., Siddarth, P., Gurbani, S., et al. (2003). Behavioral disorders in pediatric epilepsy: unmet psychiatric need. *Epilepsia*, *44*(4), 591-597.

Ozmen, M., Erdogan, A., Duvenci, S., et al. (2004). Excessive masturbation after epilepsy surgery. *Epilepsy & Behavior*, *5*(1), 133-136.

Pagliaro, L., Bruzzi, P., & Bobbio, M. (2010). Why are Cochrane hepato-biliary reviews undervalued by physicians as an aid for clinical decision-making? *Digestive and Liver Disease*, *42*(1), 1-5.

Palardy, G. J. (2008). Differential school effects among low, middle, and high social class composition schools: A multiple group, multilevel latent growth curve analysis. *School Effectiveness and School Improvement*, *19*(1), 21-49.

Pariante CM (August 2003). "Depression, stress and the adrenal axis". *Journal of Neuroendocrinology* 15 (8): 811–2.

Parrish, J., Geary, E., Jones, J., et al. (2007). Executive functioning in childhood epilepsy: parent-report and cognitive assessment. *Developmental Medicine & Child Neurology*, *49*(6), 412-416.

Pascual-Leone, A, Amedi, A, Fregni. F. & Merabet, L. (2005). The plastic human brain cortex. *Ann Rev Neurosci. (*28), 377-401.

Pinquart, M. (2013) Do the parent–child relationship and parenting behaviors differ between families with a child with and without chronic illness? A meta-analysis. *Journal of pediatric psychology*, *38*(7), 708-721.

Placidi F., Marciani M.G., Diomedi M., et al. (2000) Effects of lamotrigine on nocturnal sleep, daytime somnolence and cognitive functions in focal epilepsy. Acta Neurol Scand 102: 81–86

Pokharel, S., Parker, J. R., Parker, J. C.,et al. (2011). Angiocentric glioma with high proliferative index: case report and review of the literature. *Annals of Clinical & Laboratory Science, 41*(3), 257-261.

Popay, J., Roberts, H., Sowden, A., et al. (2006). Guidance on the conduct of narrative synthesis in systematic reviews. *A product from the ESRC methods programme. Lancaster: Institute of Health Research*.

Prabhu, S., & Mahomed, N. (2015). Imaging of intractable paediatric epilepsy. *South African Journal of Radiology*, *19*(2), 10-pages.

Pritchard, P. B., Lombroso, C. T., & McIntyre, M. (1980). Psychological complications of temporal lobe epilepsy. *Neurology*, *30*(3), 227-227.

Pulliainen, V., & Jokelainen, M. (1995). Comparing the Cognitive Effects of Phenytoin and Carbamazepine in Long-Term Monotherapy: A Two-Year Follow-Up. *Epilepsia*, *36*(12), 1195-1202.

Pulsipher, D. T., Seidenberg, M., Guidotti, L., et al. (2009) Thalamofrontal circuitry and executive dysfunction in recent-onset juvenile myoclonic epilepsy. Epilepsia 50:1210–1219.

Quyen, M. L. V., Navarro, V., Martinerie, J., et al. (2003). Toward a neurodynamical understanding of ictogenesis. *Epilepsia*, *44*(s12), 30-43.

Rantanen, K., Eriksson, K., & Nieminen, P. (2011). Cognitive impairment in preschool children with epilepsy. *Epilepsia*, *52*(8), 1499-1505.

Raybaud, C., Shroff, M., Rutka, J. T., & Chuang, S. H. (2006). Imaging surgical epilepsy in children. *Child's Nervous System*, *22*(8), 786-809.

Reynolds, C. R., & Fletcher-Janzen, E. (2009). Handbook of clinical child neuro psychology: springer science, business media.

Robinson, S., Park, T. S., Blackburn, L. B., et al. (2000). Transparahippocampal selective amygdalohippocampectomy in children and adolescents: efficacy of the procedure and cognitive morbidity in patients. *Journal of neurosurgery*, *93*(3), 402-409.

Roeschl-Heils A, Bledowski C, Elger CE, et al. (2002). Neuropsychological functioning among 32 patients with temporal lobe epilepsy and their discordant siblings. *Epilepsia*, *43*(suppl 7):85.

Romanelli, P., Weiner, H. L., Najjar, S., & Devinsky, O. (2001). Bilateral resective epilepsy surgery in a child with tuberous sclerosis: case report. *Neurosurgery*, *49*(3), 732-735.

Ronen, G. M., Streiner, D. L., Rosenbaum, P. (2003). Health-related quality of life in children with epilepsy: development and validation of self-report and parent proxy measures. *Epilepsia*, *44*(4), 598-612.

Rosenfield, S., & Smith, D. (2010). Gender and mental health: Do men and women have different amounts or types of problems. *A handbook for the study of mental health: Social contexts, theories, and systems*, 256-267.

Rosenow, F., & Lüders, H. (2001). Presurgical evaluation of epilepsy. *Brain*, *124*(9), 1683-1700.

Rosenthal, R. (1979). The file drawer problem and tolerance for null results. *Psychological bulletin*, *86*(3), 638.

Roulet-Perez, E., Davidoff, V., Mayor-Dubois, C., et al. (2010). Impact of severe epilepsy on development: recovery potential after successful early epilepsy surgery. *Epilepsia*, *51*(7), 1266-1276.

Roy, H., Lippé, S., Lussier, F., et al. (2011). Developmental outcome after a single episode of status epilepticus. *Epilepsy & Behavior*, *21*(4), 430-436.

Rutter, M., Tizard, J., & Whitmore, K. (1970). *Education, health and behaviour*: Longman Publishing Group.

Sackett, D. L., Rosenberg, W. M., Gray, J. M., et al. (1996). Evidence based medicine: what it is and what it isn't. *Bmj*, *312*(7023), 71-72.

Saha, S., Saint, S., & Christakis, D. A. (2003). Impact factor: a valid measure of journal quality? *Journal of the Medical Library Association*, *91*(1), 42.

Salman, R. A. S., Beller, E., Kagan, J., et al. (2014). Increasing value and reducing waste in biomedical research regulation and management. *The Lancet*, *383*(9912), 176-185.

Salpekar, J. A., Berl, M. M., Havens, K., et al. (2013). Psychiatric symptoms in children prior to epilepsy surgery differ according to suspected seizure focus. *Epilepsia*, *54*(6), 1074-1082.

Sanchez-Gistau, V., Pintor, L., Sugranyes, G., et al. (2010). Prevalence of interictal psychiatric disorders in patients with refractory temporal and extratemporal lobe epilepsy in Spain. A comparative study. *Epilepsia*, *51*(7), 1309-1313.

Sayin, U., Sutula, T. P., & Stafstrom, C. E. (2004). Seizures in the Developing Brain Cause Adverse Long-term Effects on Spatial Learning and Anxiety. *Epilepsia*, *45*(12), 1539-1548.

Schmidt, D., Baumgartner, C., & Löscher, W. (2004). Seizure recurrence after planned discontinuation of antiepileptic drugs in seizure-free patients after epilepsy surgery: a review of current clinical experience. *Epilepsia*, *45*(2), 179-186.

Scoville, W. B. & Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. *The Journal of Neuropsychiatry and Clinical Neuroscienves*, *12*, 103-113.

Sills, G. J. (2011). Mechanisms of action of antiepileptic drugs. In J.W. Sander, M. C. Walker & J. E. Smalls (Eds.) *Epilepsy 2011: From Science to Society. A Practical Guide to Epilepsy*. London, UK: ILAE, National Society for Epilepsy.

Shastin, D., Chandrasekaran, S., Ferrie, C., Vadlamani, G., et al. (2015). Monitoring the changing pattern of delivery of paediatric epilepsy surgery in England—an audit of a regional service and examination of national trends. *Child's Nervous System*, *31*(6), pp.931-939.

Sherman, E., Brooks, B. L., Fay-McClymont, T. B., & MacAllister, W. S. (2012). Detecting epilepsy-related cognitive problems in clinically referred children with epilepsy: Is the WISC-IV a useful tool?. *Epilepsia*, *53*(6), 1060-1066.

Sherman, E. M., Wiebe, S., Fay-McClymont, T. B., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., . . . Jette, N. (2011). Neuropsychological outcomes after epilepsy surgery: systematic review and pooled estimates. *Epilepsia*, *52*(5), 857-869.

Shorvon, S. (2015). Definition (Terminology) and Classification in Epilepsy: A Historical Survey and Current Formulation, with Special Reference to the ILAE. *The Treatment of Epilepsy*, *4*, 1-23.

Sinclair, D. B., Aronyk, K., Snyder, T., et al. (2003). Pediatric temporal lobectomy for epilepsy. *Pediatric neurosurgery*, *38*(4), 195-205.

Skirrow, C., & Baldeweg, T. (2015). Educational and Employment Outcomes Following Epilepsy Surgery in Childhood. In *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 151-164). Springer International Publishing.

Skirrow, C., Cross, J. H., Cormack, F., et al. (2011). Long-term intellectual outcome after temporal lobe surgery in childhood. *Neurology*, *76*(15), 1330-1337.

Skirrow, C., Cross, J. H., Harrison, S., et al. (2015). Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome. *Brain*, *138*(1), 80–93.

Slim, K., Nini, E., Forestier, D., et al. (2003). Methodological index for non-randomized studies (minors): development and validation of a new instrument. *ANZ J Surg*, *73*(9), 712-716.

Smith, M. L., Elliott, I. M., & Lach, L. (2002). Cognitive skills in children with intractable epilepsy: comparison of surgical and nonsurgical candidates. *Epilepsia*, *43*(6), 631-637.

Smith, M. L., & Puka, K. (2015). Quality of Life and Psychosocial Outcomes in Children Following Epilepsy Surgery. In K. Malmgren, S. Baxendale & J. H. Cross (Eds.) *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 193-207). Springer International Publishing.

Smith, S. M., & Vale, W. W. (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. *Dialogues in clinical neuroscience*, *8*(4), 383.

Spencer, S., & Huh, L. (2008). Outcomes of epilepsy surgery in adults and children. *The Lancet Neurology*, *7*(6), 525-537.

Spencer RL, Hutchison KE (1999). "Alcohol, aging, and the stress response". *Alcohol Research & Health* 23 (4): 272–83.

Stefanatos, A. K. (2015). *Neurocognitive and psychosocial functions in children with frontal and temporal lobe epilepsy* (Doctoral dissertation).

Steinbok, P., Gan, P. Y., Connolly, M. B., et al. (2009). Epilepsy surgery in the first 3 years of life: a Canadian survey. *Epilepsia*, *50*(6), 1442-1449.

Sterne, J. A. C., Higgins, J.P.T., Reeves, B.C. on behalf of the development group for ACROBATNRSI (2014). A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBATNRSI), Version 1.0.0, 24 September 2014. Available from http://www.riskofbias.info [accessed date Mar 20 2015]

Stewart, L. A., & Tierney, J. F. (2002). To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Evaluation & the health professions*, *25*(1), 76-97.

Szabó, C. Á., Wyllie, E., Dolske, M., et al. (1999). Epilepsy surgery in children with pervasive developmental disorder. *Pediatric neurology*, *20*(5), 349-353.

Szabó, C. A., Wyllie, E., Stanford, L. D., et al. (1998). Neuropsychological effect of temporal lobe resection in preadolescent children with epilepsy. *Epilepsia*, *39*(8), 814-819.

Taylor, D. C., Neville, B. G. R., & Cross, J. H. (1999). Autistic spectrum disorders in childhood epilepsy surgery candidates. *European child & adolescent psychiatry*, *8*(3), 189-192.

Taylor, J., Jacoby, A., Baker, G. A., & Marson, A. G. (2011). Self-reported and parent-reported quality of life of children and adolescents with new-onset epilepsy. *Epilepsia*, *52*(8), 1489-1498.

Taylor, D. R., Wait, S. D., Wheless, J. W., & Boop, F. A. (2013). Amygdalar neuromelanosis intractable epilepsy without leptomeningeal involvement: Case report. *Journal of Neurosurgery: Pediatrics*, *12*(1), 21-24.

Tellez-Zenteno, J. F., Dhar, R., Hernandez-Ronquillo, L., & Wiebe, S. (2007). Long-term outcomes in epilepsy surgery: antiepileptic drugs, mortality, cognitive and psychosocial aspects. *Brain*, *130*(Pt 2), 334-345.

Tellez-Zenteno, J. F., Dhar, R., & Wiebe, S. (2005). Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain*, *128*(Pt 5), 1188-1198.

Tellez-Zenteno, J. F., Hernandez Ronquillo, L., Moien-Afshari, F., & Wiebe, S. (2010). Surgical outcomes in lesional and non-lesional epilepsy: a systematic review and meta-analysis. *Epilepsy Res*, *89*(2-3), 310-318.

Terra, V. C., Cysneiros, R., Cavalheiro, E. A., & Scorza, F. A. (2013). Sudden unexpected death in epilepsy: From the lab to the clinic setting. *Epilepsy & Behavior*, *26*(3), 415-420.

Terra, V. C., Furlanetti, L. L., Nunes, A. A., et al. (2014). Vagus nerve stimulation in pediatric patients: Is it really worthwhile?. *Epilepsy & Behavior*, *31*, 329-333.

Thomas, L., Trimble, M., Schmitz, B., & Ring, H. (1996). Vigabatrin and behaviour disorders: a retrospective survey. *Epilepsy research*, *25*(1), 21-27.

Thome-Souza, S., Kuczynski, E., Assumpção, F., et al. (2004). Which factors may play a pivotal role on determining the type of psychiatric disorder in children and adolescents with epilepsy?. *Epilepsy & Behavior*, *5*(6), 988-994.

Thomson Reuters (2015). 2014 Journal Citation Reports® Science Edition.

Vadera, S., Kshettry, V. R., Klaas, P., & Bingaman, W. (2012). Seizure-free and neuropsychological outcomes after temporal lobectomy with amygdalohippocampectomy in pediatric patients with hippocampal sclerosis: Clinical article. *Journal of Neurosurgery: Pediatrics*, *10*(2), 103-107.

Vale, C. L., Rydzewska, L. H., Rovers, M. M., et al. (2015). Uptake of systematic reviews and meta-analyses based on individual participant data in clinical practice guidelines: descriptive study. *bmj*, *350*, h1088.

Van Essen, D. C., Smith, S. M., Barch, D. M., et al. (2013). The WU-Minn human connectome project: an overview. *Neuroimage*, *80*, 62-79.

Van Oijen, M., De Waal, H., Van Rijen, P. C., et al. (2006). Resective epilepsy surgery in childhood: the Dutch experience 1992–2002. *European Journal of Paediatric Neurology*, *10*(3), 114-123.

Vaz, S. A. M. (2004). Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. *Seizure*, *13*(7), 446-452.

Vining, E. P. G., Freeman, J. M., Pillas, D. J., et al. (1997). Why would you remove half a brain? The outcome of 58 children after hemispherectomy ? The Johns Hopkins experience: 1968 to 1996. Pediatrics, 100, 163-171.

Vining, E. P., Mellits, E. D., Dorsen, M. M., et al. (1987). Psychologic and behavioral effects of antiepileptic drugs in children: a double-blind comparison between phenobarbital and valproic acid. *Pediatrics*, *80*(2), 165-174.

Von Elm, E., Altman, D. G., Egger, M., et al. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Preventive medicine*, *45*(4), 247-251.

Wechsler, D. (2002). *WPPSI-III administration and scoring manual*. Psychological Corporation.

Wechsler, D. (2003). *WISC-IV Wechsler Intelligence Scale for Children: Technical and Interpretative: Manual*. Pearson.

Wechsler, D. (2014). Wechsler intelligence scale for children-fifth edition. Bloomington, MN: Pearson.

Wells, G. A., Shea, B., O'connell, D., et al. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses.URL: http://www.medicine.mcgill.ca/rtamblyn/Readings/The%20Newcastle%20-%20Scale%20for%20assessing%20the%20quality%20of%20nonrandomised%20studies%20in%20meta-analyses.pdf

Wesnes, K. A., Edgar, C., Dean, A. D. P., & Wroe, S. J. (2009). The cognitive and psychomotor effects of remacemide and carbamazepine in newly diagnosed epilepsy. *Epilepsy & behavior*, *14*(3), 522-528.

Westerveld, M., Sass, K. J., Chelune, G. J., et al. (2000). Temporal lobectomy in children: cognitive outcome. *Journal of neurosurgery*, *92*(1), 24-30.

Williams, J., Griebel, M. L., Sharp, G. B., & Boop, F. A. (1998). Cognition and behavior after temporal lobectomy in pediatric patients with intractable epilepsy. *Pediatric neurology*, *19*(3), 189-194.

Williams, J., Lange, B., Sharp, G., et al. (2000). Altered sleeping arrangements in pediatric patients with epilepsy. *Clinical Pediatrics*, *39*(11), 635-642.

Wiebe, S. (2000). Epidemiology of temporal lobe epilepsy. Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques,27(S1), S6-S10.

Wouters, H., Fonteyne, A., Lagae, L., & Stiers, P. (2006). Specific memory impairment in a multiple disabled male with fragile X syndrome and temporal lobe epilepsy. *Developmental medicine and child neurology*, *48*(5), 378.

Wrench, J., Wilson, S. J., & Bladin, P. F. (2004). Mood disturbance before and after seizure surgery: a comparison of temporal and extratemporal resections. *Epilepsia*, *45*(5), 534-543.

Wyllie, E., Comair, Y. G., Kotagal, P., Raja, S., & Ruggieri, P. (1996). Epilepsy surgery in infants. *Epilepsia*, *37*(7), 625-637.

Yates, D. (2015). Neural circuits: A nucleus of fear. *Nature Reviews Neuroscience*, *16*(3), 121-121.

Yeo, M., & Sawyer, S. (2005). 5 Chronic illness and disability. *ABC of Adolescence*, *98*, 16.

Young, A. E. (2014). Designing a safe and sustainable pediatric neurosurgical practice: the English experience. *Pediatric Anesthesia*, *24*(7), 649-656.

Young, H. K., & Johnston, H. (2004). Intracranial tumors in infants. *Journal of child neurology*, *19*(6), 424-430.

Yuan, Y., & Hunt, R. H. (2009). Systematic reviews: the good, the bad, and the ugly. *The American journal of gastroenterology*, *104*(5), 1086-1092.

Zeiler, F. A., McDonald, P. J., Kaufmann, A., et al. (2011). Gamma knife for cerebral arteriovenous malformations at a single centre. *Canadian Journal of Neurological Sciences/Journal Canadien des Sciences Neurologiques*, *38*(06), 851-857.

Zeman, A., Kapur, N., & Jones-Gotman, M. (2012). *Epilepsy and memory*. Oxford University Press.

Zhao, F., Kang, H., You, L., et al. (2014). Neuropsychological deficits in temporal lobe epilepsy: A comprehensive review. *Annals of Indian Academy of Neurology*, *17*(4), 374

Zupanc, M. L., dos Santos Rubio, E. J., Werner, R. R., et al. (2010). Epilepsy surgery outcomes: quality of life and seizure control. *Pediatric neurology*, *42*(1), 12-20.

APPENDIX A: CATEGORIZATION OF THE EPILEPSIES

Epilepsies can broadly be characterised as having seizures that are generalised, i.e. they quickly engage bilaterally distributed brain networks (Berg et al., 2010) or localised, i.e. they start unilaterally and each seizure type has a consistent site where the seizure starts (Berg et al., 2010). However, these categories are not dichotomous and some children present with epilepsies that show both generalised and focal epileptiform patterns on scalp electroencephalography (EEG) (Scheffer, Berkovic, Capovilla, & Connolly, 2014). Figure A.1 in Appendix A shows the organisation of seizure categories, as defined by the International League against Epilepsy (International League against Epilepsy, 2014).

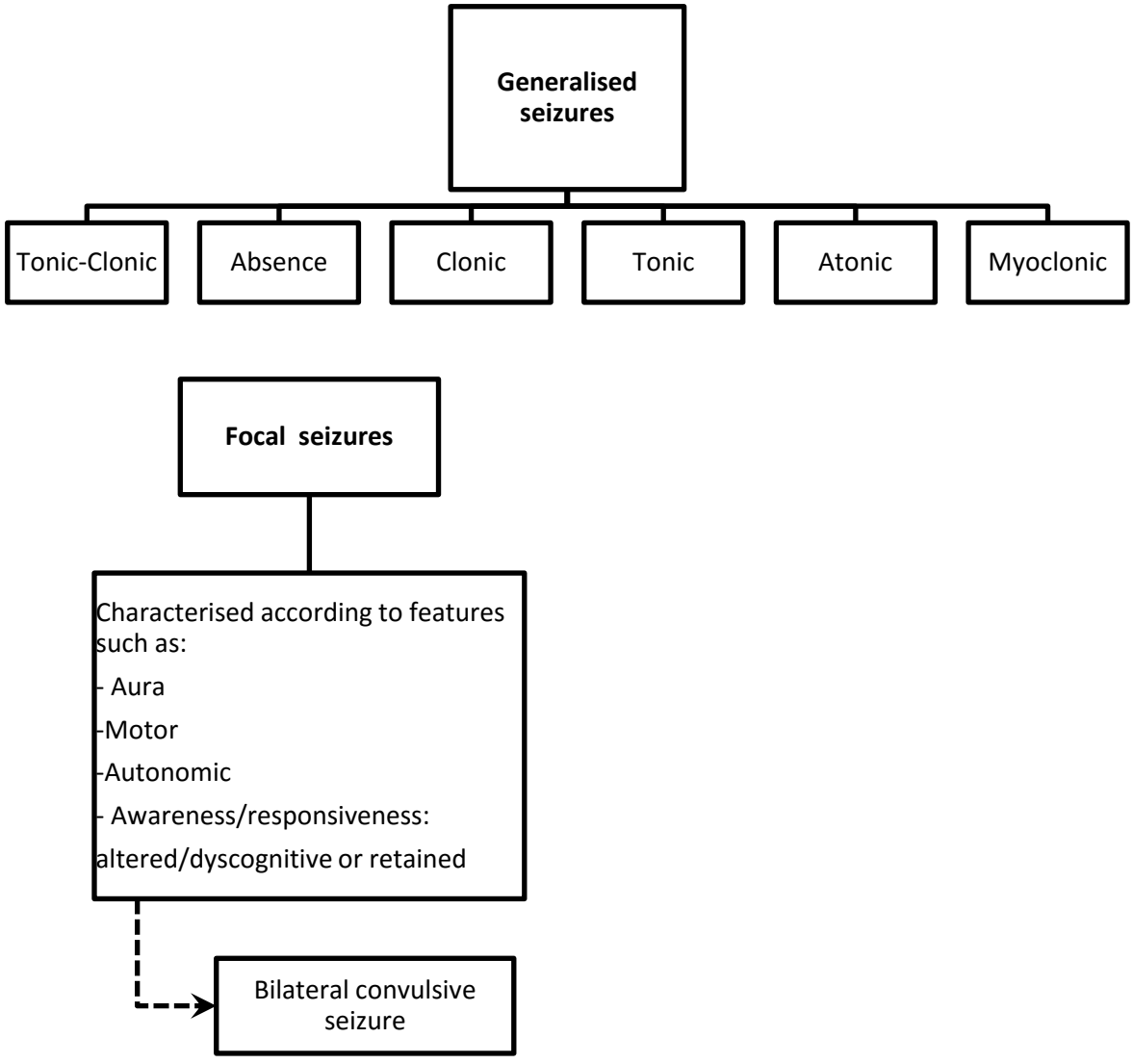


Figure A.1 Organisation of seizure types, after International League against Epilepsy (2014).

The many types of seizure have markedly different presentations, and some children exhibit a number of different seizure types. Generalised seizures generally involve some loss of consciousness (International League against Epilepsy, 2015). Tonic seizures involve increased tone in the limbs bilaterally for a period of up to approximately one minute whereas clonic seizures are characterised by bilateral jerking of the limbs in a rhythmic motion. Children with tonic-clonic seizures alternate between these two phases (International League against Epilepsy, 2015). Absence seizures are characterised by a period of altered awareness, usually accompanied by clonic movement of the facial muscles (International League against Epilepsy, 2015). Myoclonic seizures involve brief jerks of the limbs, and these can sometimes co-occur with generalised absence seizures (International League against Epilepsy, 2015). By contrast, atonic seizures are characterised by a sudden loss of muscle tone. Epilepsies can further be categorised according to their electro-clinical syndromes, i.e. a description of the presentation and type of seizures, age of onset, EEG patterns and comorbidities, or according to their aetiologies, i.e. the underlying cause of the epilepsy (Scheffer et al., 2014). These categories of organisation are overlapping but different. Figure A.2 shows the range of electro-clinical syndromes, arranged by typical age at onset and Figure A.3 shows the range of aetiologies underlying childhood epilepsies. Epilepsies have been associated with genetic abnormalities, structural abnormalities, metabolic disturbances, auto-immune activity or infections. A structural cause means that there is a structural abnormality in the brain that gives rise to the child's seizures. Common examples of these are focal cortical dysplasias, where small areas of the cortex have not formed properly, and hippocampal sclerosis, in which there is neuronal cell loss in the hippocampus. Finally, for approximately one third of epilepsies, the aetiology is unknown (Shinnar & Pellock, 2002).

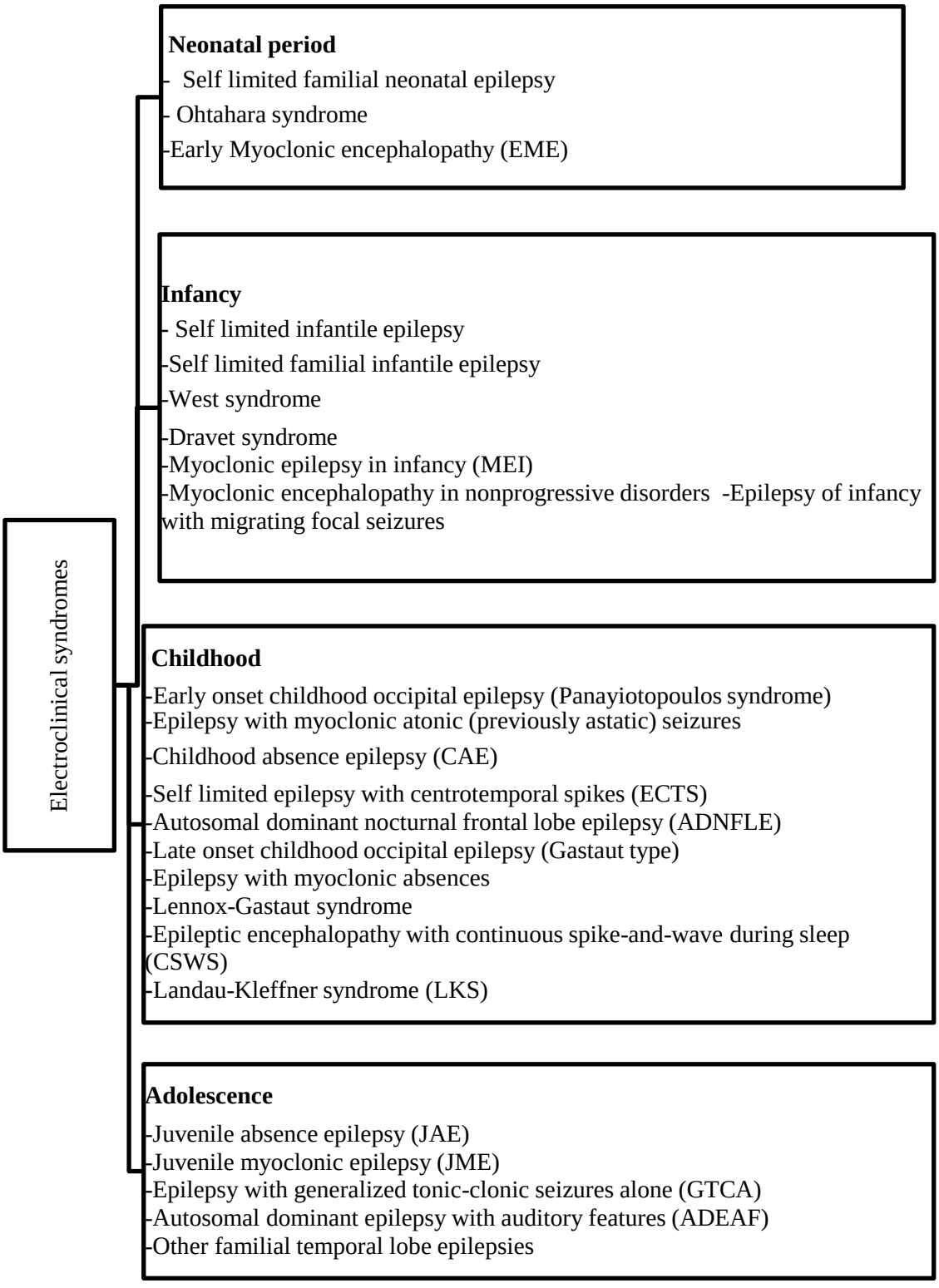


Figure A.2 Organisation of epilepsies according to electroclinical syndrome, after (ILAE, 2014)

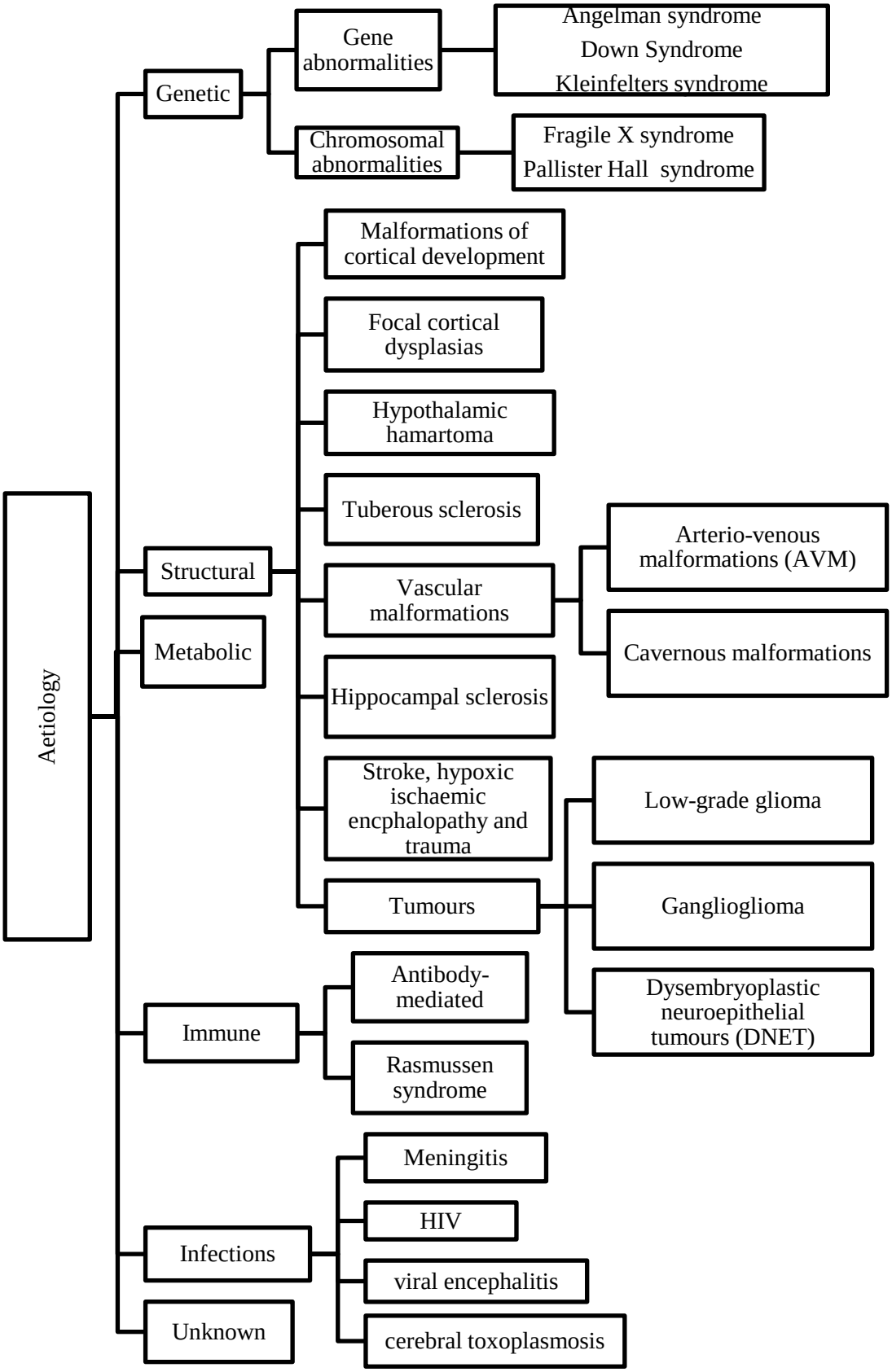


Figure A.3 Organisation of epilepsies according to aetiology, after (ILAE, 2014)

APPENDIX B: Electronic search strategies

Appendix B.1: Medline search strategy

1. seizure*.ti,ab.
2. epilep*.ti,ab.
3. exp *Epilepsy/
4. 1 or 2 or 3
5. surger*.ti,ab.
6. surgical*.ti,ab.
7. operati*.ti,ab.
8. (resecti* or disconnect*).ti,ab.
9. (hemispherectomy or callosotomy or hemispherotomy or MST or "multiple subpial transection" or "temporal lobectomy" or "focal neocortical resection").ti,ab.
10. exp *Neurosurgery/
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp "Quality of Life"/
13. "Quality of Life".ti,ab.
14. exp Treatment Outcome/
15. exp Follow-Up Studies/
16. Outcome.ti,ab.
17. exp Prognosis/
18. Prognosis.ti,ab.
19. (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Visual* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*).ti,ab.
20. (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD).ti,ab.
21. (seizure adj2 free*).ti,ab.
22. (seizure adj2 freq*).ti,ab.
23. exp Mental Disorders/
24. (Mortal* or Death* or Die or Dies or Died or Morbid* or Infect* or Stroke* or Complicat*).ti,ab.
25. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. limit 41 to humans
27. limit 42 to english language
28. limit 43 to yr="1995 -Current"
29. seizure*.ti,ab.
30. epilep*.ti,ab.
31. exp *Epilepsy/
32. 29 or 30 or 31
33. surger*.ti,ab.
34. surgical*.ti,ab.
35. operati*.ti,ab.
36. (resecti* or disconnect*).ti,ab.
37. (hemispherectomy or callosotomy or hemispherotomy or MST or "multiple subpial transection" or "temporal lobectomy" or "focal neocortical resection").ti,ab.
38. exp *Neurosurgery/
39. 33 or 34 or 35 or 36 or 37 or 38

40. exp "Quality of Life"/
41. "Quality of Life".ti,ab.
42. exp Treatment Outcome/
43. exp Follow-Up Studies/
44. Outcome.ti,ab.
45. exp Prognosis/
46. Prognosis.ti,ab.
47. (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Visual* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*).ti,ab.
48. (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD).ti,ab.
49. (seizure adj2 free*).ti,ab.
50. (seizure adj2 freq*).ti,ab.
51. exp Mental Disorders/
52. (Mortal* or Death* or Die or Dies or Died or Morbid* or Infect* or Stroke* or Complicat*).ti,ab.
53. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. (infancy or Newborn* or New-born* or Baby* or Babies or Neonat* or Neo-nat* or Preterm* or Pre-term* or Prematur* or Pre-matur* or Postmatur* or Post-matur*).ti,ab.
55. Child/
56. Infant/
57. (Infant* or Child* or Juvenile* or Junior* or Young person or Young people or Schoolchild* or School-child* or School age* or School-age* or Preschool* or Pre-school* or Kid or kids or Toddler*).ti,ab.
58. Adolescent/
59. (Adoles* or Teen* or Boy* or Girl*).ti,ab.
60. Minors/
61. Minor*.ti,ab.
62. Puberty/
63. (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*).ti,ab.
64. Pediatrics/
65. (Paediatric* or Pediatric* or Peadiatric*).ti,ab.
66. Schools/
67. (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool* or High-school*).ti,ab.
68. 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67
69. 32 and 39 and 53 and 68
70. limit 69 to humans
71. limit 70 to english language
72. limit 71 to yr="1995 -Current"
73. (letter or editorial or comment or "historial article").ti,ab.
74. biography/ or comment/ or editorial/ or letter/
75. "review"/
76. 73 or 74 or 75
77. 72 not 76

Appendix B.2: Embase search strategy

1. "Seizure*".ti,ab.
2. "Epilep*".ti,ab.
3. exp *epilepsy/
4. 1 or 2 or 3
5. "Surger*".ti,ab.
6. "Surgical*".ti,ab.
7. "Operati*".ti,ab.
8. (Resecti* or Disconnect*).ti,ab.
9. (hemispherectomy or callosotomy or hemispherotomy or MST or "Multiple subpial transection" or "Temporal lobectomy" or "Focal neocortical resection").ti,ab.
10. exp *neurosurgery/
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp "quality of life"/
13. "Quality of life".ti,ab.
14. exp treatment outcome/
15. exp follow up/
16. "Outcome*".ti,ab.
17. exp prognosis/
18. Prognosis.ti,ab.
19. (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or Self-esteem or "Self esteem" or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*).ti,ab.
20. (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD).ti,ab.
21. (Seizure adj2 free*).ti,ab.
22. (Seizure adj2 freq*).ti,ab.
23. exp mental disease/
24. (Mortal* or Death* or Die or Dies or Died or Morbid* or Infect* or Stroke* or Complicat*).ti,ab.
25. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (Infancy or Newborn* or New-born* or Baby* or Babies or Neonat* or Neo-nat* or Preterm* or Prematur* or Pre-matur* or Postmatur* or Post-matur*).ti,ab.
27. child/
28. infant/
29. (Infant* or Child* or Juvenile* or Junior* or Young person or Young people or School child* or School-child* or School age* or School-age* or Preschool* or Pre-school* or Kid or Kids or Toddler*).ti,ab.
30. adolescent/
31. (Adoles* or Teen* or Boy* or Girl*).ti,ab.
32. exp "minor (person)"/
33. "Minor*".ti,ab.
34. exp puberty/
35. (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*).ti,ab.
36. exp pediatrics/
37. (Paediatric* or Pediatric* or Peadiatric*).ti,ab.
38. exp school/

39. (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school or High-school* or Highschool*).ti,ab.
40. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41. 4 and 11 and 25 and 40
42. limit 41 to english language
43. limit 42 to human
44. limit 43 to yr="1995 -Current"
45. (letter or editorial or comment or "historial article").ti,ab.
46. letter/
47. editorial/
48. "review"/
49. 45 or 46 or 47 or 48
50. 44 not 49

Appendix B.3 PsycINFO search strategy
1. seizure*.ti,ab.
2. epilep*.ti,ab.
3. exp *Epilepsy/
4. 1 or 2 or 3
5. surger*.ti,ab.
6. surgical*.ti,ab.
7. operati*.ti,ab.
8. (resecti* or disconnect*).ti,ab.
9. (hemispherectomy or callosotomy or hemispherotomy or MST or "multiple subpial transection" or "temporal lobectomy" or "focal neocortical resection").ti,ab.
10. exp *Neurosurgery/
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp "Quality of Life"/
13. "Quality of life".ti,ab.
14. exp Treatment Outcomes/
15. exp Followup Studies/
16. Outcome*.ti,ab.
17. exp Prognosis/
18. Prognosis.ti,ab.
19. (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct* or Cogniti* or Neurocogniti* or Executive function* or Language or Social* or Visuo-spatial* or Spatial* or Attent* or Processing Speed* or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*).ti,ab.
20. (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD).ti,ab.
21. (seizure adj2 free*).ti,ab.
22. (seizure adj2 freq*).ti,ab.
23. exp Mental Disorders/
24. (Mortal* or Death* or Die or Died or Dies or Morbid* or Infect* or Stroke* or Complicat*).ti,ab.
25. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26. (infancy or Newborn* or New-born* or Baby* or Babies or Neonat* or Neo-nat* or Preterm* or Pre-term* or Prematur* or Pre-matur* or Postmatur* or Post-matur*).ti,ab.

27. (Infant* or Child* or Juvenile* or Junior* or Young person or Young people or Schoolchild* or School-child* or School age* or School-age* or Preschool* or Pre-school* or Kid or kids or Toddler*).ti,ab.
28. (Adoles* or Teen* or Boy* or Girl*).ti,ab.
29. Minor*.ti,ab.
30. exp Puberty/
31. (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*).ti,ab.
32. Pediatrics/
33. (Paediatric* or Pediatric* or Peadiatric*).ti,ab.
34. exp Schools/
35. (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school or High-school* or Highschool*).ti,ab.
36. 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
37. 4 and 11 and 25 and 36
38. limit 37 to english language
39. limit 38 to yr="1995 -Current"
40. (letter or editorial or comment or "historial article").ti,ab.
41. "literature review"/
42. 40 or 41
43. 39 not 42

Appendix B.4: Global Health search strategy

1. seizure*.ti,ab.
2. Epilep*.ti,ab.
3. exp *epilepsy/
4. 1 or 2 or 3
5. Surger*.ti,ab.
6. Surgical*.ti,ab.
7. Operat*.ti,ab.
8. (Resecti* or Disconnect*).ti,ab.
9. (hemispherectomy or callosotomy or hemispherotomy or MST or "multiple subpial transection" or "temporal lobectomy" or "focal neocortical resection").ti,ab.
10. exp *surgery/
11. 5 or 6 or 7 or 8 or 9 or 10
12. exp "quality of life"/
13. "quality of life".ti,ab.
14. exp follow up/
15. Outcome.ti,ab.
16. exp prognosis/
17. Prognosis.ti,ab.
18. (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Visual* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*).ti,ab.
19. (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD).ti,ab.
20. (seizure adj2 free*).ti,ab.
21. (seizure adj2 freq*).ti,ab.

22. exp mental disorders/
23. (Mortal* or Death* or Die or Dies or Died or Morbid* or Infect* or Stroke* or Complicat*).ti,ab.
24. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25. (infancy or Newborn* or New-born* or Baby* or Babies or Neonat* or Neo-nat* or Preterm* or Pre-term* or Prematur* or Pre-matur* or Postmatur* or Post-matur*).ti,ab.
26. Children/
27. Infants/
28. (Infant* or Child* or Juvenile* or Junior* or Young person or Young people or Schoolchild* or School-child* or School age* or School-age* or Preschool* or Pre-school* or Kid or kids or Toddler*).ti,ab.
29. Adolescents/
30. (Adoles* or Teen* or Boy* or Girl*).ti,ab.
31. Minors*.ti,ab.
32. Puberty/
33. (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*).ti,ab.
34. Paediatrics/
35. (Paediatric* or Pediatric* or Peadiatric*).ti,ab.
36. Schools/
37. (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High-school* or High school* or Highschool*).ti,ab.
38. 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. 4 and 11 and 24 and 38
40. limit 39 to english language
41. limit 40 to yr="1995 -Current"
42. (letter or editorial or comment or "historial article").ti,ab.
43. "letters (correspondence)"/
44. editorials/
45. exp reviews/
46. 42 or 43 or 44 or 45
47. 41 not 46

Appendix B.5: Web of Science search strategy

#9	**(#6 NOT #7)** ***AND*** LANGUAGE: **(English)** **Refined by:** PUBLICATION YEARS: **(2013 OR 2008 OR 2015 OR 2011 OR 2004 OR 1997 OR 2014 OR 2005 OR 1998 OR 2009 OR 2002 OR 1995 OR 2012 OR 2003 OR 1996 OR 2010 OR 2001 OR 2006 OR 2000 OR 2007 OR 1999)** ***DocType=All document types; Language=All languages;***
#8	(#6 NOT #7) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#7	(TS=(letter or editorial or comment or "historical article")) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#6	#5 AND #4 AND #3 AND #2 *DocType=All document types; Language=All languages;*
#5	(TS=(Infancy OR Newborn* OR New-born* OR Baby* OR Babies OR Neonat* OR Neo-nat* OR Preterm* OR Prematur* OR Pre-matur* OR Postmatur* OR Post-matur* OR Infant* OR Child* OR Juvenile* OR Junior* OR "Young person" OR "Young people" OR "School child*" OR School-child* OR "School age*" OR School-age* OR Preschool* OR Pre-school* OR Kid OR Kids OR Toddler* OR Adoles* OR Teen* OR Boy* OR Girl OR Minor* OR Pubert* OR Pubescen* OR Prepubescen* OR Pre-pubescen* OR Paediatric* OR Pediatric* OR Peadiatric* OR Nursery school* OR Kindergar* OR Primary school* OR Secondary

	school* OR Elementary school* OR High school OR High-school* OR Highschool*)) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#4	(TS=("Quality of life" OR Outcome* OR Prognosis OR Follow-up OR "Follow up" OR Emotion* OR Affect* OR Psycholog* OR Psychiatr* OR Behavio?r* OR Conduct OR Cogniti* OR Neurocogniti* OR Neuropsycholog* OR Learning OR Memory OR "Executive function*" OR Language OR Social* OR Visuo-spatial* OR Spatial* OR Attent* OR "Processing speed" OR Psychosocial OR Psycho-social OR Self-esteem OR "Self esteem" OR Ruminat* OR Attachment OR Parenting OR Parental OR "Body image" OR Body-image OR "Self image" OR Self-image or Sleep OR Educat* OR Anxiety OR Anxious OR Depress* OR Psychosis OR Psychotic OR Schizo* OR "Mental health" OR "Mental illness" OR "Attention deficit disorder" OR "Attention deficit hyperactivity disorder" OR "ADD" OR ADHD OR (Seizure NEAR/2 free*) OR (Seizure NEAR/2 freq*) OR Mortal* OR Death* OR Die OR Dies OR Died OR Morbid* OR Infect* OR Stroke* OR Complicat*)) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#3	(TS=(Surger* OR Surgical* OR Operati* OR Resecti* OR Disconnect* OR Hemispherectomy OR Callosotomy OR Hemispherotomy OR MST OR "Multiple subpial transection" OR "Temporal lobectomy" OR "Focal neocortical resection")) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#2	(TS=(Seizure* OR Epilep*)) *AND* **LANGUAGE:** (English) *DocType=All document types; Language=All languages;*
#1	**TOPIC:** (Seizure*) *DocType=All document types; Language=All languages;*

Appendix B.6: CINAHL search strategy

Search ID#	Search Terms
S42	S38 NOT S41
S41	S39 OR S40
S40	(MM "Literature Review+")
S39	TI (Comment* OR "Historical article" OR Editorial OR Review) OR AB (Comment* OR "Historical article" OR Editorial OR Review)
S38	S4 AND S8 AND S22 AND S37
S37	S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36
S36	TI (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool* or High-school) OR AB (Nursery school* or Kindergar* or Primary school* or Secondary school* or Elementary school* or High school* or Highschool* or High-school)
S35	(MH "Schools+")
S34	TI (Paediatric* or Pediatric* or Peadiatric*) OR AB (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*)
S33	(MH "Pediatrics+")
S32	TI (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*) OR AB (Pubert* or Pubescen* or Prepubescen* or Pre-pubescen*)
S31	(MH "Puberty+")
S30	TI Minor* OR AB Minor*
S29	(MH "Minors (Legal)")

S28	TI (Adoles* or Teen* or Boy* or Girl*) OR AB (Adoles* or Teen* or Boy* or Girl*)
S27	(MH "Adolescence+")
S26	TI (Infant* or Child* or Juvenile* or Junior* or Young person or Young people or Schoolchild* or School-child* or School age* or School-age* or Preschool* or Pre-school* or Kid or kids or Toddler*) OR AB (Infant* or Child* or Juvenile* or Junior* or Young person or Young people or Schoolchild* or School-child* or School age* or School-age* or Preschool* or Pre-school* or Kid or kids or Toddler*)
S25	(MH "Infant+")
S24	(MH "Child+")
S23	TI (infancy or Newborn* or New-born* or Baby* or Babies or Neonat* or Neo-nat* or Preterm* or Pre-term* or Prematur* or Pre-matur* or Postmatur* or Post-matur*) OR AB (infancy or Newborn* or New-born* or Baby* or Babies or Neonat* or Neo-nat* or Preterm* or Pre-term* or Prematur* or Pre-matur* or Postmatur* or Post-matur*)
S22	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
S21	TI (Mortal* or Death* or Die or Dies or Died or Morbid* or Infect* or Stroke* or Complicat*) OR AB (Mortal* or Death* or Die or Dies or Died or Morbid* or Infect* or Stroke* or Complicat*)
S20	(MH "Mental Disorders+")
S19	TI (seizure* n2 freq*) OR AB (seizure* n2 freq*)
S18	TI (seizure* n2 free*) OR AB (seizure* n2 free*)
S17	TI (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD) OR AB (Anxiety or Anxious or Depress* or Psychosis or Psychotic or Schizo* or "Mental health" or "Mental illness" or "Attention deficit disorder" or "Attention deficit hyperactivity disorder" or "ADD" or ADHD)
S16	TI (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Visual* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*) OR AB (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Visual* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*)TI (Emotion* or Affect* or Psycholog* or Psychiatr* or Behavio?r* or Conduct or Cogniti* or Neurocogniti* or Neuropsycholog* or Learning or Memory or Executive function* or Language or Social* or Visuo-spatial* or Visual* or Spatial* or Attent* or Processing speed or Psychosocial or Psycho-social or "Self esteem" or Self-esteem or Ruminat* or Attachment or Parenting or Parental or "Body image" or Body-image or "Self image" or Self-image or Sleep or Educat*) OR AB (Emotion* or Affect* or Psycholo ...Show Less
S15	TI Prognosis OR AB Prognosis
S14	(MH "Prognosis+")
S13	TI Outcome* OR AB Outcome*
S12	(MH "Prospective Studies+")
S11	(MH "Treatment Outcomes+")
S10	TI "quality of life" OR AB "quality of life"
S9	(MH "Quality of Life+")

S8	S5 OR S6 OR S7
S7	(MM "Neurosurgery+")
S6	TI ("multiple subpial transection" or "temporal lobectomy" or "focal neocortical resection") OR AB ("multiple subpial transection" or "temporal lobectomy" or "focal neocortical resection")
S5	TI (surger* or surgical* or operat* or resecti* or disconnect* or hemispherectomy or callosotomy or hemispherotomy or MST) OR AB (surger* or surgical* or operat* or resecti* or disconnect* or hemispherectomy or callosotomy or hemispherotomy or MST)
S4	S1 OR S2 OR S3
S3	(MM "Epilepsy+")
S2	TI Epilep* OR AB Epilep*
S1	TI Seizure* OR AB Seizure*

APPENDIX C: PRISMA Checklist

Table C.1 PRISMA 2009 Checklist (Moher et al., 2009)

Section/Topic	#	Checklist Item	Reported on page
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rational	3	Describe the rationale for the review in the context of what is already known.	27-29
Objective	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	28-37

Methods			
Protocols and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No registered protocol, however protocol discussed on page 42-43
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	34-37
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	37-43 and 49
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix B

APPENDIX D: : Strengthening the reporting of observational studies in epidemiology (STROBE) statement

Table D.1 Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies, from Von Elm et al., (2007)

	Item No	Recommendation
Title and abstract		
	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*? Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. *Case-control study*? Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. *Cross sectional study*? Give the eligibility criteria, and the sources and methods of selection of participants (*b*) *Cohort study*? For matched studies, give matching criteria and number of exposed and unexposed. *Case-control study*? For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/	8*	For each variable of interest, give sources of data and details of

measurement		methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) *Cohort study*? If applicable, explain how loss to follow-up was addressed *Case-control study*? If applicable, explain how matching of cases and controls was addressed *Cross sectional study*? If applicable, describe analytical methods taking account of sampling strategy (*e*) Describe any sensitivity analyses
Results		
Participants	13*	(*a*) Report numbers of individuals at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (*b*) Give reasons for non-participation at each stage (*c*) Consider use of a flow diagram
Descriptive data	14*	(*a*)Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders (*b*) Indicate number of participants with missing data for each variable of interest (*c*) *Cohort study*? Summarise follow-up time (e.g. average and total amount)
Outcome data	15*	*Cohort study*? Report numbers of outcome events or summary measures over time *Case-control study?* Report numbers in each exposure category,

		or summary measures of exposure *Cross sectional study?* Report numbers of outcome events or summary measures
Main results	16	(*a*) Report the numbers of individuals at each stage of the study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (*b*) Give reasons for non-participation at each stage (*c*) Consider use of a flow diagram
Other analyses	17	Report other analyses done e.g. analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

***Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.**

Psychological abilities, skills and experiences after temporal lobe epilepsy surgery

This review looked at the evidence from 72 clinical studies about how children and young people perform psychologically in the longer term after temporal lobe surgery for epilepsy. This review focussed on how the surgery affects young people's psychological abilities, skills and experiences:

- Thinking skills
- Memory
- Attention and concentration
- Problem solving and planning
- Language
- Quality of life
- Education
- Jobs
- Psychological wellbeing and mood
- Behaviour
- Social skills and social life
- Independence with everyday tasks
- Satisfaction with surgery

The key findings were:

- Almost three quarters (74%) of young people were seizure free after temporal lobe epilepsy surgery at their last follow-up assessment.
- The majority of young people did not change in any of these psychological abilities and skills after surgery, a minority showed improvement and a minority worsened.
- Young people who have operations that include removing part of a brain structure called the hippocampus may have worse affected verbal memory afterwards than children whose operations do not include the hippocampus.
- Young people who have temporal lobe operations on the left side of their brain may have worse verbal memory and language outcome than people who have operations on the right side of their brain.

- Young people who stop having seizures after their surgery have a higher quality of life than young people who have surgery and continue to have seizures. However, it is not known from these studies if children who are seizure free after surgery have higher quality of life than young people with temporal lobe epilepsy who do not have surgery at all.
- Young people who stop having seizures after surgery had better mood than young people who continued to have seizures after surgery. However, there was no difference in mood between young people with epilepsy who had not had surgery and young people who were seizure free after surgery. So overall surgery does not appear to affect mood, but there may be a risk of worsened mood if young people have surgery and seizures continue.
- The studies could not tell us if surgery on the left or right side of the brain makes a difference to mood.
- The studies could not tell us if it is better for young people to have surgery at an earlier age.
- The majority of young people who had temporal lobe epilepsy surgery were found to be doing well at participation in education and work, but studies were not able to link this to the surgery, as children who had surgery were not compared to children who did not have surgery.
- Some studies reported that young people improved in the social interaction after surgery, but these studies may be biased
- More research is needed to find out about the impact of surgery on independence with everyday activities.
- Parents are more likely to be satisfied with surgery if their child becomes seizure free but none of the studies asked the young people themselves about their satisfaction with surgery.
- Most children were not followed up after surgery for long enough so we do not know how they do in the long-term.

The review found that the studies on surgery for temporal lobe epilepsy in children were not designed to be able to tell if these skills and abilities were impacted by the surgery of if young people would have had the same outcomes without surgery. This is because:

- Many studies did not compare the results of children who had surgery to children who did not have surgery
- Psychological skills, abilities and experiences were only measured after the surgery and so could not be compared to their skills, abilities and experiences before the surgery
- Young people of very different ages, or who had different types of surgery were grouped together so that we do not know which surgery will work for which children.
- There were no studies that provided high quality evidence about the psychological outcomes of temporal lobe epilepsy surgery in children.

However, we know from previous research that children who continue to have seizures often experience difficulties with their development, psychosocial skills and wellbeing.

Recommendations

- Researchers should plan their studies in advance and follow-up the young people over a longer time.
- Researchers should compare young people's psychological skills and abilities from before and after surgery, and with children with temporal lobe epilepsy who have not had surgery.
- Researchers should record and report details about the surgery, age and epilepsy characteristics of the young people who have surgery more carefully.
- Researchers should share data from individual participants and collaborate so that results from all young people who have epilepsy surgery can be combined and analysed together so that we can find out which surgeries work best for which young people and how this affects their lives over the long term.
- Neurosurgical teams should make sure that you have all available information on how epilepsy surgery may affect young people before deciding whether or not to have surgery.