# Cognitive Outcomes in Children with Temporal Lobe Epilepsy: Predictors of Academic Attainment

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Thesis submitted in partial fulfilment for the degree of Doctor in Clinical Psychology (DClinPsy) to the University of East London

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## DECLARATION

I, Jennifer Black, confirm that the work herein is entirely my own. I can confirm that where information has been used from other sources it has been indicated in the text. The work has not been submitted, in whole or in part, towards any previous degree or qualification.

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*Although an organ may not have been originally formed for some special purpose, if it now serves for this end we are justified in saying that it is specially contrived for it. On the same principle, if a man were to make a machine for some special purpose, but were to use old wheels, springs, and pulleys, only slightly altered, the whole machine, with all its parts, might be said to be specially adapted for that purpose. Thus throughout nature almost every part of each living being has probably served, in a slightly modified condition, for diverse purposes, and has acted in the living machinery of many ancient and distinct specific forms.*

— Charles Darwin (1862, p. 348)

## ABSTRACT

**Objectives:** Children with temporal lobe epilepsy (TLE) are at a significant risk of cognitive disability and academic underachievement. Where medicines have proven ineffective for seizure management, surgical intervention has proven to be valuable treatment; nevertheless, the long-term cognitive and academic outcomes for this group of children are unclear.

**Method:** Clinical data on 72 children who underwent surgical resection for unilateral TLE were reviewed at around 12-months post-surgery. Pre- versus post-surgery cognitive and achievement assessments were compared to investigate outcomes and the contributions of demographic and epilepsy-related variables.

**Results:** The findings suggest overall modest improvements in test scores, but with some areas of greater change, including decline in some domains. The picture is dominated, however, by substantial individual variability.

**Conclusions:** Epilepsy surgery for TLE in childhood does not, in general, have a significant deleterious or positive effect on cognition or academic achievement, in the short-medium term. Marked individual variation is the norm. Research and clinical implications, particularly a need for longitudinal studies, are discussed.



Key words: *Temporal lobe epilepsy, neuropsychology, epilepsy surgery, cognition, memory, achievement, academic, outcomes.*


**Main Points:**

- Group analyses suggested that children largely remained stable across all neuropsychological measures at post-operative assessment.
- There is some evidence for the effect of lesion side and aetiology on cognitive outcomes.
- Significant variation exists in cognitive outcomes following surgery
- Limitations of existing literature indicates more longitudinal studies are needed.
- Large scale, multi-centre research with agreed core outcome measures would allow for greater quality of evidence.

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| | |
|---|---|
| AED | Antiepileptic drug |
| ATL | Anterior temporal lobe |
| ANOVA | Analysis of variance |
| CAVLT | Children's Auditory Verbal Learning Task |
| CESS | Children's Epilepsy Surgery Service |
| CMS | Children's Memory Scale |
| DNET | Dysembryoplastic Neuroepithelial Tumour |
| DQ | Developmental Quotient |
| EDA | Exploratory data analysis |
| EEG | Electroencephalography |
| FCD | Focal cortical dysplasia |
| fMRI | Functional magnetic resonance imaging |
| FSIQ | Full Scale Intelligence Quotient |
| GLM | General linear model |
| GOSH | Great Ormond Street Hospital |
| ILAE | International League Against Epilepsy |
| IQ | Intelligence quotient |
| LTL | Left temporal lobe |
| M | Mean |
| MRI | Magnetic Resonance Imaging |
| MTS | Mesial temporal sclerosis |

| | |
|---|---|
| NEPSY | A Developmental Neuropsychological Assessment |
| NICE | National Institute for Health and Care Excellence |
| PIQ | Performance Intelligence Quotient |
| PRI | Perceptual Reasoning Index |
| PSI | Processing Speed Index |
| RTL | Right temporal lobe |
| SD | Standard Deviation |
| SPSS | Statistical Package for Social Sciences |
| TL | Temporal Lobe |
| TLE | Temporal Lobe Epilepsy |
| TLR | Temporal Lobe Resection |
| VCI | Verbal Comprehension Index |
| VIQ | Verbal Intelligence Quotient |
| WAIS | Wechsler Adult Intelligence Scale |
| WASI | Wechsler Abbreviated Scale of Intelligence |
| WHO | World Health Organisation |
| WIAT | Wechsler Individual Achievement Test |
| WISC | Wechsler Intelligence Scale for Children |
| WMI | Working Memory Index |
| WMS | Wechsler Memory Scale |
| WOND | Wechsler Objective Numerical Dimensions |
| WORD | Wechsler Objective Reading Dimensions |
| WPPSI | Wechsler Preschool and Primary Scale of Intelligence |

# 1. INTRODUCTION

## 1.1 Structure of the Thesis

Chapter 1 provides a general overview of paediatric epilepsy, including the classification, incidence, prevalence, aetiology and treatment. The focus will then move specifically to epilepsy of the temporal lobe (TL) and the role of neuropsychological assessment. An extensive review of the literature on cognitive and academic outcomes after surgical intervention is provided in Chapter 2, offering a summary of the current state of play in the field of paediatric temporal lobe epilepsy (TLE), considering both empirical evidence and theoretical understandings. The rationale and aims for the current study will be outlined. Chapter 3 will describe the method employed and the main results will be summarised in Chapter 4. The results will be discussed in relation to the literature and clinical implications in Chapter 5.

## 1.2 Paediatric Epilepsy: Classification and Treatment

### 1.2.1 Definition and Classification

Epilepsy has been defined as “a disorder of the brain characterised by an enduring predisposition of the brain to generate seizures and by the neurobiologic, cognitive, psychological and social consequences of this condition” (Fisher et al., 2005, p.471). In order to meet the criteria for epilepsy, the International League Against Epilepsy (ILAE) states that at least one epileptic seizure must have occurred (Fisher et al., 2014). A seizure has been defined as “an excessive burst of abnormal synchronised neuronal activity affecting small or large neuronal networks that result in clinical manifestations that are sudden, transient and usually brief” (Tamber & Mountz, 2012). Epilepsy represents a symptom, rather than a cause, of brain dysfunction of which there can be many different aetiologies (Anderson, Northam & Wrennall, 2019).

Epilepsy has been classified in terms of seizure type, epilepsy type and epilepsy syndrome and this reflects contemporary ideas in practice (Scheffer et al., 2017). It is necessary to identify the presence, aetiology, and type of seizures being experienced at the diagnostic assessment. This is determined by clinical information about the seizure semiology gathered by the physician and supported by evidence from electroencephalographic (EEG) examination (Saad, 2014). The classification system published by the ILAE (Fisher et al., 2017) is used to determine the seizure type (*Figure 1).* Once the seizure type has been classified, the epilepsy type must then be established.

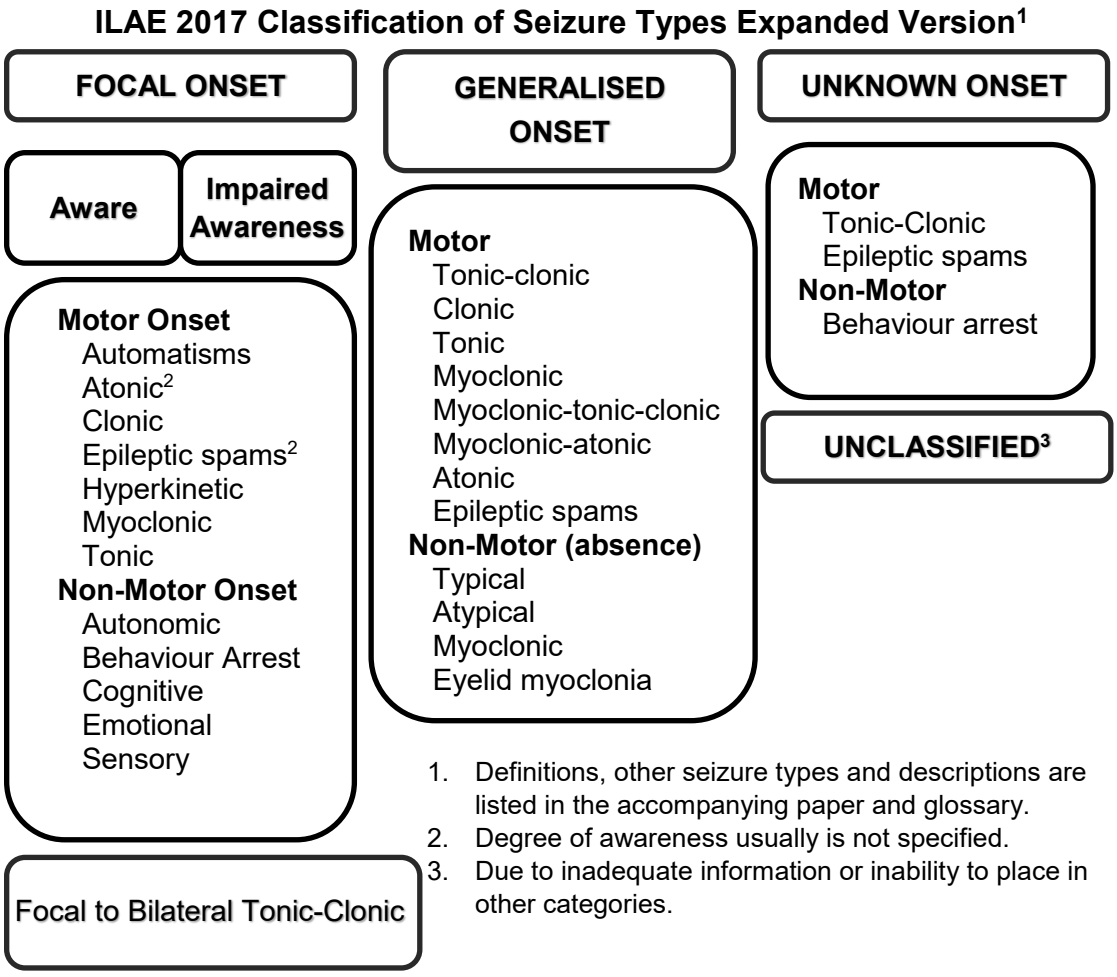



**Figure 1. ILAE Revised classification of seizures (based on Fisher et al., 2017).**

The functional and structural interconnectivity of brain regions has led to current understandings of epilepsy as a disease of *networks*. The epileptogenic activity occurs in the context of large, interconnected neuronal networks which involve several cortical, sub-cortical and bilateral regions (Stafstrom & Carmant, 2015). Evidence for structural and functional connectivity has been demonstrated through intracranial EEG, fMRI, clinical observations, and response to invasive treatment aimed at network disruption (Spencer, 2002). To support this, studies investigating cognitive impairment in TLE have identified widespread compromise in performance on neuropsychological tests, including memory (Menlove & Reilly, 2015), language (Bell, Seidenberg, Hermann & Douville, 2003; Boscariol et al., 2015; Lendt, Helmstaedter & Elger, 1999), and executive function (Rzezak et al., 2007; Rzezak, Valente & Duchowny, 2014; Sepeta et al., 2017), suggestive of impairment in cerebral areas not limited to the TLs (Guimarães et al., 2007).

### 1.2.2 Prevalence

Epilepsy is the most common paediatric neurological condition (Anderson et al., 2019). It affects 0.5-1% of children and occurs most frequently during infancy and early childhood (1-10 years) with an incidence rate of approximately 58 per 100,000 (Aaberg et al., 2017). In 2016, the number of children in the UK living with epilepsy was estimated to be over 50,000 (NHS England, 2016). Children under the age of one have the highest incidence of epilepsy and the overall rate is slightly higher for boys (Hermann, Seidenberg & Jones, 2008; Wirrell, Grossardt, Wong-Kisiel & Nickels, 2012). Epilepsy and seizures in children are markedly diverse, with varying aetiologies, comorbidities, prognoses, age of onset and seizure characteristics (Saad, 2014). Focal onset is the most common type of epilepsy in the paediatric population, as shown in population-based studies, accounting for almost two-thirds of patients (Camfield & Camfield, 2015; Wirrell et al., 2012). The World Health Organisation (WHO, 2019) have identified the global burden of epilepsy and raised its priority on the global agenda.

## 1.3 Temporal Lobe Epilepsy

TLE represents the presence of recurrent epileptic seizure activity that emanates from the TL (Panayiotopoulos, 2005) and makes up the most common type of focal seizures (Hermann, Meador, Gaillard & Cramer, 2010). Epidemiological studies vary in the reported rates of incidence of TLE in the paediatric population due to the non-specification of the lobe of onset in most incidence studies (Nickels, Wong-Kisiel, Moseley & Wirrell, 2011). While the exact incidence is unknown, estimations in the literature range from 8-20% (Lee & Lee, 2013; Nickels et al., 2011). The most frequent aetiologies in medically refractory childhood TLE are focal cortical dysplasia (FCD) (Bartolini et al., 2017; Harvey, Cross, Shinnar & Mathern, 2008; Kabat & Król, 2012) and low-grade tumours (Dysembryoplastic Neuroepithelial Tumour (DNET) and gangliogioma) (Rzezak et al., 2014). FCD represents an abnormality of cortical development (Kabat & Król, 2012), DNETs and gangliogiomas are brain tumours (Sukheeja & Mehta, 2016) classified as grade I and II neuronal tumours under the WHO classification of primary intracranial tumours (Louis et al., 2016). TLE shows a markedly different clinical picture in children compared to the relatively homogeneous syndrome in adults (Nickels et al., 2011).

### 1.3.1 Treatment

Given the potential for negative cognitive, behavioural, and psychosocial sequelae of paediatric epilepsy throughout childhood and into adulthood, it is vital that efforts are made to reduce or prevent seizures; thus the goal for epilepsy management is seizure freedom with little or no considerable unwanted outcomes (Panayiotopoulos, 2005). Prolonged, untreated epileptic discharges can have a profound impact on the developing brain and potentially lead to epileptic encephalopathy, whereby the seizures themselves can have negative consequences across cognitive, emotional, behavioural and psychosocial domains, beyond what would be expected from the underlying pathology itself (Berg, 2011). Increased epilepsy-related morbidity and mortality warrant further consideration for intervention to address the seizure activity (Dodrill, 2004; Hauptman & Mathern, 2012). Early intervention has been advocated due to the

noticeably harmful effects of ongoing seizure activity from a neurodevelopmental perspective (Cross et al., 2006; Mittal et al., 2005).

#### *1.3.1.1 Anti-Epileptic Drugs*

Medical management through prescribed anti-epileptic drugs (AEDs) is usually the first line of treatment for children with TLE. Although the precise mechanisms of many AEDs are not completely known, it is thought they act on gamma-aminobutyric acid (GABA) receptors to counteract neuronal excitability and modify inhibitory neurotransmission at voltage-gated ion channels (e.g. calcium and sodium) in order to target the neuronal activity that cause seizures (Anderson et al., 2019). For most children, response to drug therapy and seizure freedom is achieved early in the course of the disease (Dragoumi et al., 2013). However, a proportion of children will continue to experience medically refractory seizures (Wirrell, Wong-Kisiel, Mandrekar & Nickels, 2013), with estimates ranging from 10-40% (Baca, Vickrey, Caplan, Vassar & Berg, 2011). The likelihood of seizure freedom declines with each successive drug regime treatment (Brodie, Barry, Bamagous, Norrie & Kwan, 2012) and when two or more AED trials have been tried without favourable outcome, the likelihood of seizure freedom is low (Park, Kim & Lee, 2019). Furthermore, AEDs are associated with risk for detrimental cognitive side effects. An early influential paper investigated cognitive side effects of phenobarbital, prescribed to treat seizures in children (Farwell et al., 1990). The researchers randomly assigned 217 children, who had experienced at least one febrile seizure, to either a phenobarbital treatment group or a placebo group, and reported that full scale intelligence quotients (FSIQs) in children treated with phenobarbital were approximately half a standard deviation lower than the placebo group. Recent evidence has also demonstrated impairment in memory, language and attention, associated with AED use in children (Ijff & Aldenkamp, 2013).

In addition, there is a growing evidence base that demonstrates improvement in cognitive functioning following AED withdrawal after successful surgical intervention (Boshuisen et al., 2015). To substantiate the futility of prolonged AED use, Wiebe, Blume, Girvin and Eliasziw (2001) conducted a randomized controlled trial (RCT) to investigate the efficacy of surgery for TLE in a mixed

group of adults and children. Eighty participants were randomly assigned to either a surgical treatment group or an AED treatment group. At one year, the cumulative percentage of those who underwent surgery and achieved seizure freedom was 58% compared to only 8% in the AED group. In conclusion, the side effects of older drugs and the increased risk for cognitive impairment and other health risks in newly developed drugs can make them an overall unfavourable treatment option compared to surgical intervention (Nickels et al., 2011).

#### *1.3.1.2 Surgical Intervention*

Epilepsy surgery, once considered to be a last resort after years of unsuccessful medical treatment, is now considered a mainstream choice over prolonged courses of failed AED regimes (Hermann, Loring & Wilson, 2017). It is well documented that surgery is a safe and effective treatment for epilepsy remediation and seizure control (Lee & Lee, 2013; Ormond et al., 2019), which has been linked to greater quality of life (Alexiades & McKhann, 2018) and better overall social wellbeing (Lach et al., 2010), compared to pharmacological intervention alone (Dwivedi et al., 2017). When compared to patients with continued seizures, surgery is associated with improved intellectual function (Puka, Tavares & Smith, 2017). The primary goal of epilepsy surgery is to eradicate seizures and minimise cognitive and psychosocial morbidity (Mittal et al., 2005). Seizure outcome following epilepsy surgery has been reported in the literature in accordance with either the Engel (Engel, Cascino, Ness, Rasmussen & Ojemann, 1993) or ILAE classification systems (Wieser et al., 2001), which have shown significant correlation and acceptable inter-rater reliability (Durnford et al., 2011).

Neurosurgery for TLE involves the resection, removal or disconnection of brain tissue in the epileptogenic region (Al-Otaibi, Baeesa, Parrent, Girvin & Steven, 2012). The amount of tissue removed during temporal lobe resection (TLR) in children can vary (Flint et al., 2017). The average procedure removes approximately 1.5% of the total brain volume (Skirrow et al., 2011) and can involve medial and lateral tissue, and sometimes the amygdala and hippocampus too. A combination of medical and neuropsychological advances informs the decision process as to whether a child is a suitable candidate for surgical

treatment. In order to establish the area from which the seizures originate, known as the epileptogenic zone, an extensive pre-surgical assessment is required (Rosenow & Luders, 2008).

The identification of a clearly identifiable focal unilateral lesion from where the seizure activity originates is necessary for surgery, however emerging technologies have suggested that surgical treatment for generalised epilepsy may also be an option (Englot, 2018). The type of surgery undertaken is determined by the identification and documentation of the seizure onset zone (Mansouri, Fallah & Valiante, 2012). Information from magnetic resonance imaging (MRI), functional magnetic resonance imaging (fMRI), Video-EEG monitoring, neuropsychological assessment and clinical history gathering is combined to support the identification of the site and side of lesions and of key areas involved in language and motor function. The extent of the resection is influenced by the location of the epileptogenic region in relation to the eloquent cortex, which is implicated in essential cortical functions such as speech and language and motor functions (Englot, 2018), in order to preserve function and reduce post-operative morbidity (Kreidenhuber, De Tiège & Rampp, 2019). Determination of cerebral language dominance using language fMRI examination to identify cerebrovascular changes in response to cognitive activation is therefore an important phase of the pre-surgical assessment (Hermann et al., 2017; Silva, See, Essayed, Golby & Tie, 2018).

European trends in paediatric epilepsy surgery over recent years have shown a considerable increase in the number of surgical procedures and stability in Engel Class I outcomes (free of disabling seizures) (Barba et al., 2016). Improved post-surgical seizure outcomes showing 88% Engel Class I outcomes have been recorded for children, compared to 63% of adults (Gleissner, Sassen, Schramm, Elger & Helmstaedter, 2005), demonstrating the relative effectiveness of surgical intervention for childhood epilepsy. Good long-term seizure outcomes have also been reported after 10-year follow-up (Hosoyama et al., 2017). When compared to the risks associated with the chronic use of AEDs and the potential progression of epilepsy and associated prolonged seizures, the relatively low risks of neurosurgery make it a favourable option (Dwivedi et al., 2017;

Hauptman & Mathern, 2012). In addition, studies have found that longer duration of epilepsy prior to surgery is linked to detrimental pre-surgical development (Kadish et al., 2019), poorer long-term cognitive outcomes (Chaix et al., 2006; Nolan et al., 2004; Ramantani et al., 2013), and lower likelihood of seizure freedom at follow-up (Bjellvi, Olsson, Malmgren & Wilbe Ramsay, 2019). The evidence base has offered further support for early surgery and, consequently, there is increasing advocacy for earlier referral for pre-surgical assessment (Cross et al., 2006; Engel, 2019; Lee & Lee, 2013; Saad, 2014; Sugano & Arai, 2015).

However, despite the evidence of the efficacy for surgical intervention to treat TLE, the number of children who undergo surgery in the UK is low (approximately 110 children per year) and lower than what would be expected based on epidemiology data (NHS Commissioning Board, 2013; Shastin et al., 2015). Despite reports of better cognitive and psychosocial outcomes, reduced morbidity and mortality, and improvements in surgical technique, epilepsy surgery is considered to be the most under-utilised of all medical interventions (Engel, 2013). There are a number of reasons why surgery may be declined, including fear of complications and doubts about the benefits (Vakharia et al., 2018), however mortality and morbidity from chronic seizures and medical treatment are much higher than from surgery (Sperling, Barshow, Nei & Asadi-Pooya, 2016). Misconceptions by non-specialist physicians about which patients may benefit from surgery may also contribute to the low referral rate (Vakharia et al., 2018).

It is important to note that neurosurgery also carries a risk for loss of cognitive function (Helmstaedter & Kockelmann, 2006). Neurosurgery is an elective procedure and children and families must be informed of the potential risks and benefits involved in order to support the decision-making process. Pre-surgical counselling should include the potential for decline in function with the removal of tissue that is critical for support of that function (Witt et al., 2014, 2015). However, this may be balanced with the possibility that the affected tissue may have been functionally defective prior to surgery, in which case it may not have been effective at supporting that function beforehand and hence a decline may not be apparent after surgery (Vakharia et al., 2018). Despite good evidence showing

positive seizure outcome following TLR, a recent Cochrane Review highlighted mixed findings in the literature on cognitive outcomes, providing limited evidence to guide surgical candidacy and prediction of likely outcomes (West et al., 2019). While seizure freedom is one of the main goals of surgical intervention, clinicians also aim to prevent cognitive decline and ensure retention of as much cognitive function as possible (Hermann, Meador, Gaillard & Cramer, 2010).

### 1.3.2 Neuropsychological Assessment

A long and interdependent relationship has been documented between neuropsychology and epilepsy (Hermann et al., 2017). Early contributions from neuropsychology to epilepsy syndromes helped to advance understanding of the epilepsies from a disease of progressive cognitive decline to a surgically remediable syndrome that does not result in significant post-surgical deterioration (Loring, 2010).

The neuropsychological assessment is an essential component in contemporary epilepsy evaluation and management, offering a significant contribution to pre- and post-operative assessments (Loring, 2010). Guidance from the National Institute for Health and Care Excellence (NICE, 2012) on epilepsy assessment and treatment recommends neuropsychological assessment for “children, young people and adults in whom it is important to evaluate learning disabilities and cognitive dysfunction, particularly with regard to language and memory” (p.23). For children with medically retractable epilepsy, a neuropsychological assessment can contribute to pre-surgical evaluation to determine surgical candidacy. At the pre-operative assessment, relative weaknesses can be triangulated with findings from other neurological investigations in order to support the identification of the epileptogenic zone and associated deficits (Rankin & Vargha-Khadem, 2007). It also offers a means of risk stratification and prediction of cognitive impact following epilepsy surgery (Anderson & Brandt, 2014). Post-operative neuropsychological assessment can be carried out to monitor cognitive outcomes following surgery, as well as identifying those whose trajectories indicate risk of regression or decline (Rankin & Vargha-Khadem, 2007). The identification of strengths and weaknesses in a child’s cognitive profile aids in the determination of an appropriate rehabilitative intervention (Jones-

Gotman et al., 2010; Lezak, Howieson, Loring, Hannay & Fischer, 2004) and guides recommendations for families and educational institutions. This is particularly useful where specific cognitive deficits are present alongside grossly intact global intellectual ability (Kernan et al., 2012) in order to support the identification of impairment which may impact educational and occupational attainment.

The strength of the neuropsychological assessment lies in the “consideration of the whole person embedded within a broader social and cultural context, bringing together complex, interacting processes of mind, brain and behaviour that directly inform diagnosis, prognosis and treatment” (Wilson et al., 2015, p.680). However, it is important to consider the validity of the tools used in the assessment. Most neuropsychological tests involve the employment of more than one, isolated cognitive function, thus requiring different brain regions (Zucchella et al., 2018). For example, it has been noted that few, if any, memory tasks administered as part of neuropsychological assessment access a single memory system (Tulving, 2002). Furthermore, in view of epilepsy as a disease of networks, it is not unusual to find an array of neuropsychological deficits across cognitive domains. Neuropsychology has often focused its clinical and research efforts on structure-function relationships; however, it has become apparent that cognitive and structural abnormalities can be observed beyond the zone of seizure onset (Hermann et al., 2017). As such, neuropsychological assessment in TLE has illustrated impairment across cerebral regions and identified cognitive dysfunction in domains other than the those thought to be represented in the TLs, pointing to dysfunction in other cerebral regions or connections (Guimarães et al., 2007). Anderson (2010) has highlighted the necessity to abandon assumptions of selectivity and localisation that have long guided clinical neuroscience research, considering the evidence suggestive of cortical circuits that support multiple domains. One of the best recognised and investigated neural network systems in human epilepsy is the medial temporal/limbic network, which involves the amygdalae, the hippocampi, the entorhinal cortex, the lateral temporal neocortices, the inferios frontal lobes, and the extratemporal area of the medial thalamus (Spencer, 2002).

In conclusion, the mutually beneficial relationship between neuropsychology and epilepsy may be extended as knowledge is obtained about the cognitive outcomes from the paediatric population. For clinical neuropsychologists working with children with TLE, the contributions of neuropsychological assessments are important aspects of the multi-disciplinary assessment for consideration of surgical candidacy and post-operative cognitive outcome monitoring. In order to hold in mind TLE as a disease of networks, it is important for neuropsychologists to maintain an understanding of the different ‘systems’ that a single psychometric test may draw upon. Furthermore, it is important that clinical neuropsychologists work within a biopsychosocial framework, which allows for multiple factors to be considered at each stage of the child’s surgical journey.

# 2. REVIEW OF THE LITERATURE

## 2.1 Chapter Overview

This review will aim to outline the evidence from the literature on the cognitive and academic profiles of children who undergo resective surgery for TLE. Outcomes in relation to cognitive functions and academic attainment will be addressed in turn. The current agreed upon theory underpinning paediatric neurodevelopment in the context of TLE will be discussed. The review will highlight the difficulties in studying outcomes in this group of children and the disparities across studies, illustrating the heterogeneity of this population.

## 2.2 Data Sources

Initial searches were carried out using EBSCO electronic database to identify relevant research published up to March 2020. This was followed by narrative and snowballing methods to identify further relevant literature. A diagram of the study selection process can be found in *Figure 2*. The literature search was conducted using combinations of the following key words: *"children"; "paediatric"; "child"; "adolescents"; "epilepsy"; "seizures"; "temporal lobe"; "IQ"; "intelligence"; "memory", "academic achievement"; "academic attainment";* "*cognitive ability*"; *"neurosurgery",* and *"brain surgery".* Studies written in English and in peer-reviewed journals that described the cognitive assessment of children with TLE were included. The reference lists from the identified articles were hand-searched in order to find any studies that were not identified in the electronic database search. An additional search for any remaining literature was carried out in Google Scholar.

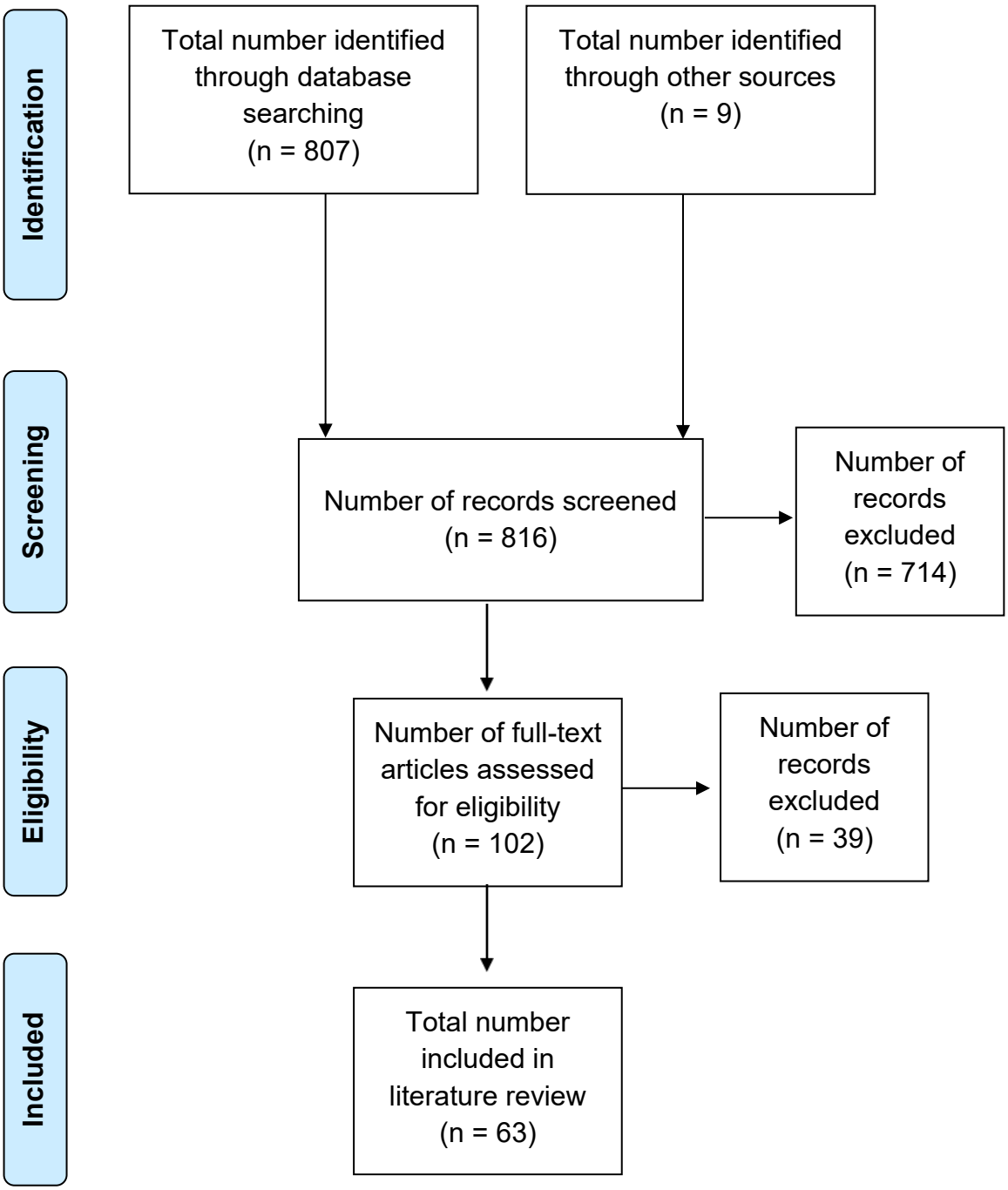



**Figure 2. Flow Diagram of Study Selection Process (adapted from Moher, Liberati, Tetzlaff, Altman & Prisma Group, 2009).**

## 2.3 Cognitive and Academic Outcomes in Temporal Lobe Epilepsy

The impact epilepsy has on cognition can often be more debilitating than the syndrome itself (Aldenkamp, 2006). As such, many studies have attempted to capture the observed influence of epilepsy across several cognitive domains. There is a wealth of evidence that has demonstrated the association between paediatric TLE and disruption across a number of cognitive processes, with adverse effects on academic skills (Puka, Khattab, Kerr & Smith, 2015), memory (Cormack, Vargha-Khadem, Wood, Cross & Baldeweg, 2012), language (Wheless, Simos & Butler, 2002), attention, executive function and processing speed (Flint et al., 2017), and quality of life (Elliott, Lach & Smith, 2005). It is appreciated that numerous interacting factors influence cognitive outcomes to produce a unique clinical picture for each child (Westerveld, 2010). Epilepsy factors including age of onset, pathology, age at surgery, duration of epilepsy, frequency of seizures, side and site of lesion, degree of localisation, and AED load have been attributed to such outcomes (Berg, Zelko, Levy & Testa, 2012; Kim & Ko, 2016; Lordo, Van Patten, Sudikoff & Harker, 2017). However, the reported influence of epilepsy-related variables on cognitive outcomes following neurosurgery to treat TLE are not consistent and the literature is reflective of this. Understandings of the impact of brain insult on the undeveloped brain have traditionally been derived from adult models, however contemporary knowledge has evidenced important differences between the child and adult brain (Smith, 2010).

Childhood TLE can disrupt normative development and long-term social and psychological development which may not become evident until a child reaches maturity (Ounstead, Lindsay & Richards, 1987; Wilson et al., 2012). Considering the far-reaching impact, studies have attempted to predict which factors contribute to less favourable outcomes. An area of empirical interest has been the impact of neurosurgical intervention for TLE on the developing brain. Some of the key papers in the literature which have investigated memory, intellectual function and academic outcomes in paediatric TLE will be discussed here.

### 2.3.1 Memory

Memory impairment in patients with TLE is well-documented in the literature (Law, Benifla, Rutka & Smith, 2017; Meekes, Braams, Braun, Jennekens-Schinkel & van Nieuwenhuizen, 2013; Sherman et al., 2011). The structures known to be implicated in learning, storage and retrieval of information are located in the medial temporal structures, including the temporal neocortex, hippocampus, parahippocampus, and the amygdala (Galanopoulou & Moshé, 2014). The relatively circumscribed nature of TLE pathology, involving such structures, has in turn provided an exemplary platform on which to investigate memory function (Leritz, Grande & Bauer, 2006). Considering the critical role of the TLs in memory (Skirrow et al., 2015), it is therefore not surprising to observe that the most frequent finding among children with TLE has been memory impairment, compared to adult and child controls as well as normative scores (Hermann, Seidenberg & Jones, 2008; Menlove & Reilly, 2015). The literature has explored the influence of various clinical variables on cognitive outcomes, including lesion side, aetiology, epilepsy duration, and age of onset.

In the study of adults, patterns of lateralisation have frequently and consistently been observed, whereby verbal memory deficits have been associated with left-sided lesions and visual memory deficits have been associated with right-sided lesions (Willment & Golby, 2013). Many paediatric TLE studies have also demonstrated lateralised hemisphere involvement for memory; however, such findings are less consistent in children. In a systematic review with weighted estimates, risk of memory impairment was stratified according to side of lesion in children and adults following TL surgery (Sherman et al., 2011). A 44% risk to verbal memory for left-sided TL surgery was reported, compared to a 20% risk for right-sided surgery. However, the review was based largely on studies drawn from the adult literature, with just a few paediatric studies contributing to the findings and should therefore be interpreted with caution. The authors stated that conclusions regarding outcomes for children should remain tentative due to the paucity of studies upon which the review was based.

Studies that have investigated the impact of lesion side on memory outcomes in children have generally shown mixed findings. Meekes et al. (2013) assessed

verbal memory in 21 children before epilepsy surgery and at 6, 12 and 24 months after, and used a comparison group of gender and age matched healthy controls. In the study the authors concluded that, for the sample overall, verbal memory was not impacted by surgery; however, for those who underwent left-sided TL surgery verbal memory remained vulnerable. The authors highlighted the need to set modest verbal memory expectations when counselling parents of children due to undergo left TL surgery. These findings should, however, be interpreted with caution due to the heterogeneity of aetiology, epilepsy type and small sample size, limiting the power to detect the possible effects of confounding epilepsy variables.

#### *2.3.1.1 Role of mesial structures*

Similar findings were observed in a sample of children who underwent TL surgery with hippocampectomy and subsequently experienced seizure remission (Jambaqué et al., 2007). In this study material specific effects were observed following surgery, whereby 9 out of 12 children who had left TLR had worse verbal memory outcomes and 5 out of 8 children who had right TLR had worse visual memory performance. However, the small size and pathological diversity of the sample limits the generalisability of the findings. Furthermore, the extent of the excision in their sample, involving hippocampectomy, may represent a key contribution to memory outcomes in this study. It has been posited that the effect of TLE on memory is due to the involvement of the mesial structures of the TLs, in particular the amygdalae and hippocampi, which appear to be critical for recovery of memory function (Zeman, Kapur & Jones-Gotman, 2012). Witt et al. (2015) investigated the relevance of hippocampal integrity following surgery for unilateral mesial TLE in adults and found that the integrity of the hippocampus was a key factor for determining the degree of verbal memory decline in the left dominant hemisphere. In children, smaller resection volumes and greater temporal pole integrity have been related to improved outcomes for memory, attributed to the capacity for compensatory mechanisms to draw on the tissue that remains in the operated TL (Skirrow et al., 2015). The clinical picture of children with TLE is said to be less specified because the cognitive deficits implicated often involve structures beyond the temporal and mesial temporal regions (Rzezak et al., 2014).

*2.3.1.2 Role of neuropathology*

Underlying pathology has also been reported as a relevant contributor to memory outcomes for children who undergo TLR, although studies have not been able to reliably and consistently differentiate between pathology types. Previous research has often used samples of mixed underlying pathology which has several implications as the pathology represents different underlying neurological processes and has been found to relate to differences in cognitive outcomes (Bigel & Smith, 2001). Memory deficits in mesial temporal sclerosis (MTS) have been well-documented in the neuropsychological evaluation of adults with epilepsy (Engel, 2001), predictably, given the involvement of the hippocampus and associated temporolimbic structures that are crucial for learning and memory. A recent study by (Law et al., 2017) investigated post-operative memory outcomes in children with MTS and found that memory outcomes were mediated by the structural involvement of the mesial temporal lobes. In a sample of 53 children, for those where mesial structures were spared (*n* = 13), there was less risk of verbal memory decline. However, for children who underwent left TLR that involved mesial temporal structures, there was a significant risk for verbal memory decline. This was particularly evident in those who had left language lateralisation and intact pre-operative verbal memory. This research suggests that the extent of resection is a relevant factor in post-operative memory outcomes for children with MTS.

Cormack, Vargha-Khadem, Wood, Cross and Baldeweg (2012) also investigated the influence of pathology on cognitive outcomes and identified a distinct pattern of memory impairment according to the underlying pathology, and to a lesser degree the side of seizure onset. In a pre-operative sample of 44 children with hippocampal sclerosis (HS) or DNET and 22 healthy controls, different memory profiles were reported. Irrespective of side, delayed verbal paired-associate and story recall performance was more impaired in patients with HS compared to those with DNET. Children with HS and left-sided DNET also demonstrated impairment in verbal semantic memory. Other evidence from adults with childhood onset epilepsy has produced similar findings and identified different patterns of lateralised memory impairment in DNET compared to HS (Baxendale,

Donnachie, Thompson & Sander, 2013). In patients with left TLE, significantly lower scores were reported for the HS group compared to the DNET group on measures of verbal learning. For the patients with right sided TLE lower scores were reported for the HS group than the DNET group on measures of general cognition, verbal learning and visual learning. However, it is important to note that a long history of seizures prior to pre-surgical assessment was observed in the sample, therefore the effect of additional clinical variables should be considered.

Despite the preponderance of research emphasising the lateralisation of material-specific memory function, some authors have demonstrated bilateral contributions of the left and right hemispheres to memory performance, suggesting a more complex picture. Rice, Caswell, Moore, Hoffman and Lambon Ralph (2018) investigated semantic memory in 40 children who underwent unilateral left and right sided anterior temporal lobe (ATL) resection to treat epilepsy. The authors demonstrated mild impairment in both the left and right-side resected children, which increased as the degree of difficulty of the semantic tasks became more challenging. The findings provided partial support for the specialisation of function of the left ATL for verbal information and of the right ATL for non-verbal information. Conclusions drawn indicated bilateral contribution of left and right ATLs to a singular semantic memory system. The importance of these findings lies in the notable context of ongoing research endeavours to categorise effects of epilepsy surgery by side of lesion and determine links to lateralisation effects yet have produced inconsistent findings.

#### *2.3.1.3 Role of lateralisation*

Conflicting evidence for lateralisation has come from studies that have failed to find material specific differences based on lesion side. Mabbott and Smith (2003) evaluated the memory of 44 children and young people who underwent surgical resection to either the left temporal, right temporal, or extratemporal region for focal epilepsy. No pre- or post-operative group differences were found in the sample for verbal memory or design recall. On a facial recognition task, all groups showed improvement, apart from the right temporal group who displayed poorer performance. The substantial variability in the performance among the groups suggested that cognitive profiles following TLR are not uniform. Early age

of onset was related to poorer performance on verbal memory and face recognition than those who experienced seizure onset at an older age. In addition, increased AED use and greater duration of epilepsy were also found to relate to outcomes.

Non-lateralising memory effects were also observed in a study by Martin et al. (2016) who observed a significant decline in performance on memory tests that was similar for patients with right and left TLE across all memory tests. Although significant declines in memory were observed in the TLE group compared to groups with seizure onset in other regions, no material specific lateralising deficits were found in the TLE group. In cases where memory improved, this was associated with reduction in seizure frequency and decrease in AEDs. Pre-surgical performance was found to be the best predictor of declines in memory test scores.

Similarly, Sepeta et al. (2017) investigated memory and executive functioning in 70 children with focal epilepsy and 70 age-matched healthy controls. Memory performance was similar regardless of seizure foci, showing age-related expectations in most areas apart from delayed memory which showed impairment compared to controls. They argued that these findings were crucial as they highlighted that the severity and pattern of learning and memory impairment previously seen in children with focal epilepsy is unclear. This research offers insights into the possibility of a much more complex understanding of the development of the child brain following insult. It challenges popular understandings extracted from the homogeneous syndrome typically observed in adults (Nickels et al., 2011). A notable criticism of the study, however, is that not all participants had video-EEG confirmed localisation of seizures which is the most robust tool for confirming seizure foci (Staljanssens et al., 2017), hence qualifying the reliability of the origin of the seizures. Further, high variability in lobe localisation within the sample limits the applicability of findings to children with TLE.

*2.3.1.4 Positive versus negative outcomes*

While most of the research into memory outcomes following TLR for childhood epilepsy has indicated a detrimental impact on performance, some studies have shown evidence to the contrary. In a systematic review by Menlove and Reilly (2015), 50% of studies reported an improvement in memory scores after paediatric epilepsy surgery. The variables found to be predictive of memory impairment included greater number of AEDs, earlier age at seizure onset, longer duration of epilepsy, and higher seizure frequency. The impact of AEDs on cognition has been well documented in the literature, although the findings remain inconclusive and subject to methodological limitations (Bourgeois, 2002). Bourgeois (2002) highlighted that it cannot be assumed that no drug causes cognitive deficits in every child and no drug can be presumed to never cause cognitive impairment.

A study by Skirrow et al. (2015) assessed 53 children who underwent assessment for epilepsy surgery, 42 of whom underwent unilateral TLRs. The researchers found no decline in memory from pre- to post-surgical assessments. Rather, an improvement in verbal episodic memory was observed following right TLR and visual episodic memory was improved following left TLR. Verbal memory improvement was related to greater hippocampal residual volume after surgery. The authors concluded that the findings indicated compensatory function in the un-operated TL, which was constrained by the quantity of tissue remaining in the operated TL, and so warrants careful tailoring of resection in TL surgery. It has also been suggested that memory deficits of the contralateral TL in unilateral TLE may show improvements in patients with a shorter duration of seizures, owing to greater cognitive capacity for compensation (Baxendale, Thompson & Duncan, 2008).

While some studies have showed gains, and others have indicated loss in memory function following TLR, the most frequently observed outcome in childhood epilepsy surgery outcome studies is no significant change (Moosa & Wyllie, 2017). An early study by Lendt et al. (1999) evaluated the pre- and post-operative neuropsychological performance of 20 children with TLE and a group of age-matched controls. The findings showed no differences between patients and

controls pre-operatively, and at one year post-operatively memory performance showed no change for the patient group. Individual evaluations showed some children made gains in memory performance and others showed losses. The factor which determined memory loss from memory gain in this study was the presence of ongoing seizures. This was replicated in a study by Kuehn, Keene, Richards and Ventureyra (2002) who assessed 26 children following cortical resection for TLE and found no significant change in performance on memory or intellectual functioning.

A consistent pattern in recent evidence suggests that individual developmental trajectories are influenced by a number of epilepsy-related factors, such as the degree of pre-surgical impairment, use of AEDs, seizure status, age at time of surgery, and extent of surgical excision (Ramantani & Reuner, 2018). The multifactorial, complex and interacting nature of multiple variables appear to produce different outcomes for each child. Overall, the variation in studies, accounted for by the employment of different neuropsychological tests, aetiological diversity, mixed lobar and underlying pathology types, and small sample sizes, results in inconsistent findings across the literature on memory outcomes following surgery for paediatric TLE. Although many studies have identified memory impairment, the findings are inconsistent and, therefore, the exact nature and prevalence of memory impairment is unknown for this population (Menlove & Reilly, 2015).

### 2.3.2 Intellectual Function

While memory deficits are the most commonly associated problem in TLE, more diffuse neuropsychological impairments are also apparent, including overall intellectual ability (Hermann et al., 2002; Bjornaes, Stabell, Henriksen & Loyning, 2001). Intellectual ability is not a single cognitive operation, rather a general factor that affects one's performance on most other tasks such as those underpinning performance on neuropsychological tests of IQ. Performance on IQ tests following surgery for TLE in children show a relatively low prevalence of adverse effects (Sherman et al., 2003). Guimarães et al. (2007) assessed 25 children with TLE and compared their neuropsychological test performance to 25 normally developing children. Their findings showed that, although the patients

with TLE had a lower IQ than the control group, they still had scores within the normal range.

Similar to the outcome studies on memory performance, material-specific patterns of deficits in verbal and non-verbal intelligence that are observed in adults have not been consistently replicated in children. Given that in the typically-developing brain the LTL becomes associated with language function and the RTL with visual functions, children with unilateral left-sided lesions do not display verbal intellectual deficits relative to non-verbal intellect as observed in adults (Rankin & Vargha-Khadem, 2007). Compared to adults, children show greater aptitude for improved post-surgical outcomes in intellectual function. In a systematic review of children and adults who underwent epilepsy surgery, weighted estimates indicated the highest rate of gain in IQ scores among children (Sherman et al., 2011). It has been hypothesised that less exposure to the negative effects of chronic seizure activity during sensitive periods of development in childhood (Smith, Elliott & Lach, 2002) and cognitive morbidity associated with prolonged AED use (Hermann, Meador, Gaillard & Cramer, 2010) can lead to better cognitive outcomes for the developing brain.

*2.3.2.1 Follow-up period*

Children with epilepsy often obtain scores within the average range on neuropsychological tests of IQ (Berg et al., 2008). In addition, much of the literature on post-surgical IQ in children with TLE has demonstrated no change in scores over time (Gleissner, Clusmann, Sassen, Elger & Helmstaedter, 2006; Korkman et al., 2005; Smith, Elliott & Lach, 2006). It has been argued that most studies have been based on relatively short follow-up periods, which may not be a long enough duration to observe the long-term effects of neurosurgery on intellectual outcomes. One study evaluated the impact of surgery on IQ in 42 children after an average of 9 years following TL surgery (Skirrow et al. 2011).The findings suggested a significant increase in IQ only after an extended follow-up period of 6 years or more. Increases in IQ were best predicted by cessation of AEDs. No increase in IQ was observed in the children who underwent non-surgical intervention. The authors concluded that an extended

time period is required in order for cognitive recovery to take place (Skirrow et al., 2011).

In another long-term follow-up study, Puka et al. (2017) assessed a group of 97 patients (mean age 20.08) at a follow-up period of 4-11 years following resective surgery for childhood TLE. An interaction effect was observed between time and seizure status, where seizure freedom was associated with improvements in IQ at follow-up, regardless of whether seizure-free status was obtained through surgical or medical intervention. These studies indicate that seizure status and cessation of AEDs are important factors for improvements in intellectual ability at a sufficient post-operative follow-up period. Research into the long-term (>5 years) cognitive outcomes following childhood TLE surgery is scarce (Spencer & Huh, 2008), although the few existing studies have demonstrated improved post-surgical intellectual outcome at longer follow-up periods, suggesting that studies with shorter follow-up durations are less likely to reveal improvements.

#### *2.3.2.2 Individual variation*

The inability of studies to detect reliable cognitive change after epilepsy surgery may, on the other hand, be reflective of the approach used in the analyses. Outcome studies that have reported both group and individual level results have shown more detailed differences in analyses of individual performances. In an attempt to investigate the cognitive risks associated with TL surgery, changes in IQ were assessed before and after surgery in a sample of 82 children (Westerveld et al., 2000). No significant declines were observed following surgery in the sample at the group level; however, a closer inspection of the findings suggested significant gains as well as significant losses upon individual analysis. Analysis of individual scores showed that 10% achieved a significant improvement in verbal IQ while 9% achieved a significant decline. Non-verbal IQ saw a significant improvement in 16% of the sample and a significant decline in 2% of the sample. Overall, the authors concluded that a modest improvement in global intellectual ability was more likely than a decline following TL surgery. These results suggest that group analysis may not reveal the individual variation in changes following TL surgery.

#### *2.3.2.3 Role of pre-surgery ability level*

In general, the risk for decline in IQ following TL surgery is low (Kuehn et al., 2002); however, the literature does suggest that higher pre-operative abilities increase the risk for post-operative decline in intellectual function (Szabo et al., 1998). Skirrow et al. (2011) reported pre-surgical baseline IQ to be a significant factor in determining long-term outcomes. Children with a lower pre-surgical IQ showed greater improvement than those with average to high average IQ's. This pattern between lower pre-operative performance and greater improvement in post-operative outcomes has also been recorded in other studies (e.g. Puka et al., 2017; Rudebeck et al., 2018). Liang et al. (2012) examined pre and post-operative neuropsychological assessment scores in a sample of 206 children and found that those with lower pre-operative IQ scores who became seizure free achieved improvements post-operatively after 2 years. A recent systematic review provided corresponding evidence demonstrating better intellectual outcomes for children who had lower pre-surgical ability (Flint et al., 2017). These findings have also been replicated in a sample of 50 children who underwent TL surgery for epilepsy, where increases in verbal IQ were related to lower verbal IQ before surgery, older age at surgery, and better post-operative seizure outcome (Miranda & Smith, 2001). The inverse relationship between pre-operative ability and post-operative outcomes challenges the hypothesis that higher cognitive ability indicates greater cognitive reserve and resilience to the effects of brain insult; rather, the risk for decline is determined by the functional adequacy of the resected tissue (Chelune, 1995). Taken together, pre-operative ability and seizure status appear to be important for IQ outcomes in children who undergo surgery for TLE.

#### *2.3.2.4 Age of onset and duration of epilepsy*

Several studies have reported associations between a range of clinical epilepsy variables and intellectual function. A recent review of the literature looked at predictors of change in IQ for children after epilepsy surgery. The authors found the following factors to be predictive of post-operative neurodevelopmental gains: unilobar pathology; shorter duration of epilepsy; younger age at surgery; fewer AEDs; decrease in seizure frequency post-operatively, and longer duration of follow-up (Datta & Wong, 2017). Age at seizure onset has also been explored in

relation to intellectual outcomes and has been repeatedly found to be associated with poorer cognitive functioning. In a study that compared early and late epilepsy onset in childhood, patients with late onset exhibited fewer cognitive deficits. In contrast, poorer performance across all cognitive domains, including IQ, language, memory, visuoperception, and executive function, was observed in the early-onset group, due to the adverse effects of epilepsy on neurodevelopment (Hermann et al., 2002). Similar findings were replicated in a study by Berg et al. (2012) who assessed a group of 198 children to test whether earlier onset carried greater vulnerability to the effects of uncontrolled seizures. Their study indicated that intellectual function was impacted by uncontrolled seizures, most severely in those with seizure onset in infancy and lessening as age of onset increased. The impact of seizure frequency was also demonstrated in a study by Puka et al. (2017) who found that seizure freedom was linked to improved intellectual function at long-term follow-up, regardless of whether obtained through surgical or medical management. Overall, these studies suggest that age at epilepsy onset and seizure status may be important in determining IQ outcomes for children with TLE.

A large population-based study found that IQ was negatively correlated to seizure frequency in patients who underwent TLR and suggested that seizure free rates may be lower in those with an IQ <70 (Malmgren, Olsson, Engman, Flink & Rydenhag, 2008). There is relatively little research on children with intellectual disability in the TLE population, perhaps reflecting findings that global intellectual disability is not typically associated with paediatric TLE (Laurent & Arzimanoglou, 2006). However, one study, using a cut-off IQ score of <79, found intellectual dysfunction to be predicted by age at seizure onset (Cormack et al., 2007). The authors reported that 57% of children with unilateral TLE who underwent neuropsychological assessment and subsequent TLR were reported to have intellectual dysfunction. Furthermore, for those with onset in the first year of life, impaired intellectual function was observed in over 80% of children. A similar finding was documented by Matsuzaka et al. (2001) who studied the developmental quotient (DQ) of children who underwent epilepsy surgery, type unspecified by the authors. Earlier age at seizure onset was related to lower DQ. Additionally, age at onset of developmental delay was positively correlated with

seizure onset, suggesting that seizures may cause developmental delay or regression, sustained until surgical intervention. The authors in these studies highlighted the vulnerability of the infant brain to the sequelae of epilepsy and the importance of early identification of developmental problems. These studies suggest that onset of epilepsy in early infancy is related to poorer cognitive outcomes. Anatomic reduction in brain volume, particularly in grey and white matter at early onset can have a detrimental impact on cognition and result in worse IQ test scores compared with those with a late onset (Hermann et al., 2002).

Intellectual outcomes for children with TLE are particularly vulnerable to greater duration and subsequent, recurrent seizure activity. Evidence supportive of early surgical intervention comes from studies which have demonstrated worse outcomes for those with a longer duration of epilepsy prior to surgical intervention. Children aged 2-6 years with early onset of focal epilepsy who underwent surgery were followed up by Shurtleff et al. (2015) for neuropsychological evaluation. Children who had a duration of epilepsy less than 6 months prior to surgery, compared to those who had a duration greater than 6 months, showed improved overall and non-verbal intellectual function. Similarly, a study of children who underwent surgical resection for FCD in a mixed lobar sample found that those who had a seizure duration less than two years demonstrated improved seizure control, better cognitive outcomes, and quality of life (Chen et al., 2014). These findings have been repeatedly shown in studies of children with mixed lobar seizure foci, as well as in TLE samples, demonstrating the negative consequences of longer duration of pre-operative epilepsy (Hermann et al., 2002; Lee & Lee, 2013; Mittal et al., 2005; Rzezak et al., 2007; Smith, Elliott & Lach, 2002). Meyer, Marsh, Laws and Sharbrough (1986) assessed a sample of 50 children who underwent temporal lobectomy and found that, although no significant change was observed in IQ, the shorter duration from epilepsy onset to epilepsy surgery, the greater chance of improvement in verbal and non-verbal intellectual function. A longer duration of epilepsy can therefore lead to potentially irreversible effects from AED and prolonged seizures on brain function (Datta & Wong, 2017). On the other hand, other research has indicated no link between duration of epilepsy and IQ in children with TLE (Baxendale,

Heaney, Thompson & Duncan, 2010; Miranda & Smith, 2001). Baxendale et al (2010) suggest that this was a result of pre-established TLE-associated cognitive deficits as children enter adulthood, however it is important to note that their study was based on retrospective analysis. None of the sample had undergone surgical intervention and all continued to be prescribed AEDs.

*2.3.2.5 Role of neuropathology*

Research that has found a high incidence of cognitive difficulties in the early stages of epilepsy (Witt & Helmstaedter, 2012) has suggested that cognitive difficulties may predate seizure onset (Fastenau et al., 2009; Hermann et al., 2006; Hermann, Jones, Jackson & Seidenberg, 2012; Hermann, Jones, Sheth & Seidenberg, 2007; Schouten, Oostrom, Pestman, Peters & Jennekens-Schinkel, 2002; Van Schooneveld & Braun, 2013; Zeman, Kapur & Jones-Gotman, 2012). Approximately 25% of children with idiopathic epilepsy show cognitive impairment and require special education services prior to seizure onset, suggesting that cognitive sequelae may predate the onset of epilepsy (Berg et al., 2005). Of relevance is that the age at lesion onset is not equitable to age at seizure onset. Such findings may be partially explained by the pathophysiology underlying the epilepsy syndrome (Greener, 2013; Hermann & Seidenberg, 2007) and represent antecedent neurobiological damage of unknown aetiology (Hermann, Jones, Sheth & Seidenberg, 2007). Underlying epileptogenesis, by which the brain is functionally biased toward the generation of abnormal neuronal excitation that subserves seizure activity (Coulter & Goldberg, 2013), may play a role in the foundation of neuropsychological deficits studied in the post-onset and post-surgical outcome studies (Kim & Ko, 2016).

Taken together, the research into verbal and non-verbal ability outcomes in childhood TLE has indicated relatively little impact on IQ following unilateral TL surgery. Follow-up period, pre-morbid IQ and some epilepsy variables have been found to account for the marginal variation in the population and have advanced knowledge of risk factors that may moderate post-surgical outcomes. There are several methodological limitations to be considered; most considerably, the short post-surgical follow-up durations, the heterogeneity of the sample and relatively small sample sizes.

### 2.3.3 Academic Attainment

An understanding of the academic attainment difficulties observed in children with epilepsy is important as they have been found to contribute to a number of negative consequences in adulthood, including social and employment outcomes (McNelis, Johnson, Huberty & Austin, 2005). The influence of epilepsy on academic attainment is well documented in the literature and specific learning difficulties have been reported in children with TLE (Fawi et al., 2019). In comparison to the general population, children with epilepsy have higher rates of educational difficulties (Fastenau et al., 2009), with increased prevalence of reading, writing and math difficulties (Fastenau et al., 2004; Lah, Castles & Smith, 2017). Although educational attainment deficits may be present, not all children will show global cognitive impairment (Beghi, Cornaggia, Frigeni & Beghi, 2006). In children with epilepsy whose IQ falls within the normal range, neuropsychological assessment can identify specific learning difficulties found to be predictive of academic underachievement (Dunn & Kronenberger, 2005).

#### *2.3.3.1 Academic attainment and IQ*

There has been extensive debate concerning the separateness of academic achievement and psychometric IQ (Watkins, Lei, & Canivez, 2007). Historically, IQ tests were used to measure students' scholastic abilities, which assumes that intelligence underpins academic achievement (Kamphaus, Petoskey, & Rowe, 2000). Research has also demonstrated the predictive ability of psychometric IQ to academic attainment in healthy children (Lynn & Mikk, 2009; te Nijenhuis, Tolboom, Resing & Bleichrodt, 2004; te Nijenhuis, van Vianen & van der Flier, 2007). However, the relationship between IQ and academic attainment has been extensively debated (Watkins, Lei & Canivez, 2007). Watkins et al. (2007) investigated the relationship between academic test performance and psychometric IQ in a sample of 289 children assessed for special educational needs. The children completed tests of IQ and academic attainment at two time points with an average test-retest interval of 2.8 years. The researchers used confirmatory factor analysis and concluded that psychometric IQ has a causal effect on academic attainment, whereas academic attainment does not predict future psychometric IQ.

On the other hand, the causal precedence of IQ to academic attainment has not been consistently observed and evidence to the contrary has shown that psychometric IQ may also be a questionable indicator of academic attainment. A study by Bailet and Turk (2000) assessed a sample of 74 children with epilepsy who had good seizure control. In this study, despite obtaining average IQ (≥80) on psychometric testing, the authors found high rates of placement in special education and attainment gaps between the children with epilepsy and their school peers.

While academic attainment difficulties within this group of children are likely to be multifactorial, there is evidence to suggest patterns of specific deficits (in the context of average IQ) which may point to a specific learning disability (Breier et al., 2000). In a study by Oostrom, Smeets-Schouten, Kruitwagen, Peters and Jennekens-Schinkel (2003), the researchers investigated educational difficulties in children with epilepsy and found that 51% of children with epilepsy had additional educational needs, compared to 27% of controls, despite similar educational background and intelligence. This literature may suggest that there are factors other than general intelligence contributing to academic outcomes in the paediatric epilepsy population.

Research has consistently suggested the presence of a relationship between various aspects of cognition and academic ability, however questions remain about the specific factors and underlying mechanisms that contribute to academic vulnerability in paediatric TLE populations (Williams et al., 2001). Despite often obtaining an IQ within the normal range (Berg et al., 2008; Oostrom et al., 2003), research has suggested that children with TLE may present with several specific neuropsychological impairments, including attention, language, executive function, sensorimotor skills, and visuoconstructive praxis (which are not directly addressed in the WISC or the WAIS) (Hermann, Seidenberg, Lee, Chan & Rutecki, 2007; Laurent & Arzimanoglou, 2006; Reyes et al., 2019; Rzezak, Guimarães, Fuentes, Guerreiro & Valente, 2012; Zhao, Kang, You, Venkatesh & Chandra, 2014; Zilli, Zanini, Conte, Borgatti & Urgesi, 2015).

This was demonstrated in a study by (Fastenau et al., 2009) who completed a neuropsychological test battery with 282 children who had experienced seizures (compared to 147 healthy siblings). Neuropsychological deficits in either language, processing speed, verbal memory, attention, construction, or executive functioning, alongside normal IQ, were observed at epilepsy onset in 40% of the sample. Risk factors for deficits included multiple seizures, AED use, symptomatic/cryptogenic aetiology, and epileptiform EEG activity. In this sample, academic attainment was not affected at epilepsy onset, suggesting that the impact of school performance may not be apparent early in the disorder. The authors highlighted the significance of this finding for educational providers, suggesting that the influence of neuropsychological deficits on academic attainment may be observed to develop over time. It has been proposed that there might be a window of opportunity in which educational interventions could be effective in preventing or minimising the deleterious effect on academic attainment (Lah & Smith, 2015). These findings may be relevant to understanding why children may display a discrepancy between general intellectual ability and achievement in education settings.

*2.3.3.2 Academic difficulties that pre-date epilepsy onset*

Evidence to the contrary has concluded children with epilepsy show risk of academic predicament even in the earliest stages of the syndrome (Oostrom et al., 2003). To substantiate the claim that academic difficulties predate epilepsy onset, Berg et al. (2005) conducted a prospective, community-based study of 542 children diagnosed with epilepsy. The authors contrasted two forms of epilepsy aetiology: cryptogenic/idiopathic (labelled ‘neurologically intact’) versus remote symptomatic and/or epileptic encephalopathy. Access to special education services was higher in the latter group (88% of the sample compared to 49% of the controls) and the proportion of the epilepsy sample increased with age (7.3% for <5 years, 19.9% for age 5-9 years, and 15% for >10 years). This was also found in a sample of 53 children aged 8-18 years with recent onset idiopathic epilepsy (Hermann et al., 2006). It was concluded that the children with a history of educational difficulties had the most impaired cognitive function, with significant reductions in posterior left hemisphere grey matter volume, irrespective of the epilepsy syndrome. These studies suggest that cognitive

deficits do not necessarily result as a direct consequence of epilepsy itself, but as a consequence of the (perhaps unknown) neuropathology (Hermann et al., 2012).

#### *2.3.3.3 Academic attainment and memory*

Other studies have investigated the role of learning and memory and have found certain aspects to be implicated in the development of academic abilities (Alloway & Alloway, 2010; Gathercole, Pickering, Knight & Stegmann, 2004; Lah & Smith, 2015). Differentiated associations between semantic and episodic memory to academic attainment were identified in a study of 57 children with unilateral TLE who were administered tests of verbal memory and literacy skills (Lah & Smith, 2014). Semantic memory was found to account for over 30% of the variance in each literacy domain (reading and spelling accuracy, reading comprehension). This has been supported by further evidence demonstrating the relationship between semantic memory and reading comprehension in typically developing children (Nouwens, Groen & Verhoeven, 2017). Differential performance has also been observed between free recall and recognition memory. Children with epilepsy demonstrate stronger recognition skills than long-term/delayed recall skills (Williams et al., 2001), which may be equal to that of controls (Sepeta et al., 2017). Applied to academic settings, this might suggest that memory performance may be improved for these children when a multiple-choice format is available. The role of memory performance in academic attainment outcomes has also been demonstrated by Harrison, Cross, Harkness and Vargha-Khadem (2013). The authors examined the neuropsychological performance of 390 children with focal epilepsy as part of neurosurgical evaluation. The results showed that between 38% (word reading) and 47% (reading comprehension) of the sample had significantly impaired scores for academic attainment compared to the population mean. Memory impairment was found to be predictive of impairment in reading comprehension. Cautionary interpretation of these findings is necessary when considering the generalisability of the findings due to the diversity of lobar epilepsy foci within the sample.

#### *2.3.3.4 Role of lateralisation*

In addition to the predictive ability of other aspects of cognition on academic outcomes, research has also demonstrated a relationship between epilepsy variables and academic outcomes. The effect of lobar region and side was demonstrated in a study by Chaix et al. (2006) who investigated the academic performance of children with three forms of epilepsy syndrome: TLE, generalised epilepsy, or benign idiopathic epilepsy with Rolandic spikes. Of the three groups, children with TLE had significantly lower performance on tests of reading speed and comprehension, associated with seizure activity and duration of epilepsy, with the left TL group showing worse performance than the right. This is not the only study to demonstrate effects of the laterality of seizure focus. Aldenkamp, Weber, Overweg-Plandsoen, Reijs and van Mil (2005) found higher levels of educational problems in children with localised and symptomatic generalised epilepsy, indicating an effect of underlying neuropathology. In a recent study by Fawi et al. (2019), the authors note a much greater frequency of learning difficulties in the left-side group (79%) versus the right-side seizure onset (50%). Of the children with seizure onset in the temporal lobe, those with learning difficulties made up over half of the children (52.6%). This was also found in an adult study by Butterbaugh et al. (2004) which found those with left TLE had higher rates of reading comprehension, calculation, and reading comprehension difficulties in comparison to the right side. The authors also concluded that seizure focus in the language-dominant hemisphere was associated with specific learning disability. Although these studies are based on small samples, they provide some evidence for the role of seizure onset and lobar region.

#### *2.3.3.5 Seizure status*

Other studies have related seizure status to academic attainment. The magnitude of academic difficulties has also been found to be dependent on the severity of seizures (Austin, Huberty, Huster & Dunn, 1999). In a 4-year follow-up study of 98 children with epilepsy, no changes in academic attainment were observed over time. Children with high seizure severity did not show improvement, nor did they show a continuing decline. A further 44% of the sample had repeated at least one grade at school. This was further evidenced in a study by Aldenkamp, Overweg-Plandsoen and Arends (1999) who assessed children with epilepsy and

co-morbid educational delay, compared with a matched sample of children with educational delay but without epilepsy. The authors found the main factor that contributed to learning problems in epilepsy was a higher seizure frequency. Unsurprisingly, when generalised and localisation epilepsy groups were compared, the group with generalised epilepsy showed significantly lower academic achievement. These studies offer some evidence for the effects of recurrent seizures on educational outcomes; however, their use of mixed aetiology and epilepsy types limit their generalisability to those with unilateral TLE. The importance of the influence of seizure freedom on academic attainment for long-term outcomes has also been evidenced. In a recent study by Reinholdson, Olsson, Edelvik Tranberg and Malmgren (2020) that compared the long-term educational and employment outcomes after childhood epilepsy surgery, it was found that those who became seizure-free had similar educational attainment to the general population.

#### *2.3.3.6 Age of onset*

Research has also found age of seizure onset to be a significant factor in academic attainment outcomes. The prevalence of learning difficulties is reported to be higher in children with early age at seizure onset (Beghi et al., 2006). In an early study by Seidenberg et al., (1988) it was concluded that, of the individual variables, age of onset was one of the strongest correlates of academic attainment. This study was based on a mixed sample who had generalised and partial seizures, which limit the generalisability of the findings to children with unilateral TLE. If earlier age of onset is related to worse academic outcomes, these studies provide rationale for the early identification of children who will show greater vulnerability to academic underachievement. Furthermore, deterioration in academic attainment scores in children who do not undergo surgery has demonstrated the risk of continued seizure activity and prolonged seizure activity to outcomes (Martin et al., 2016), giving further support for early recognition and referral for surgical intervention.

Overall, it has been concluded that no definitive patterns with regard to the identification of the correlates of academic underachievement have emerged (Reilly & Neville, 2011) and the relationship between TLE and specific learning

disorders is uncertain (Breier et al., 2000). This has been echoed in a systematic review of the effect of epilepsy on academic outcomes in children, which reported some cognitive and epilepsy variables to be related to educational attainment in some studies, and not in others (Wo, Ong, Low & Lai, 2017). Lah et al. (2017) highlight the lack of statistical power in the research into academic attainment in childhood epilepsy, which limits the ability to investigate the relationship between epilepsy-related factors, cognitive variables, and academic attainment. The variability of tests used to measure academic attainment across studies may also influence the detection of learning disorders in the literature (Beghi et al., 2006). Such methodological flaws have resulted in inconsistencies in the literature around memory and reading ability in childhood epilepsy.

However, the presence of childhood epilepsy has been consistently associated with poorer academic attainment compared to controls. The importance of the evaluation of memory and intellectual abilities in order to plan appropriate educational support, is highlighted in the research. It is important for clinicians to understand the trajectories of children with TLE who undergo surgery. The knowledge of which groups plateau, which groups decline, and which groups improve are essential for intervention planning and allocation of resources to support education. Deterioration of academic performance has been reported in children who do not proceed to surgery and shows the potential for detrimental consequences of prolonged seizures and continued AED use (Martin et al., 2016). This provides further rationale for referral to surgical intervention.

Although not within the scope of the current study, it is acknowledged that there is a large and growing literature base on the impact of psychological and behavioural factors on academic underachievement. A child's ability to access the educational curriculum can be impacted by the cognitive effects of AEDs, the effects of seizure activity, absenteeism, adaptation and attitudes towards epilepsy, family socioeconomic status (SES) and resources, understanding and expectations of teachers, and acceptance from peers (McNelis et al., 2005; Reilly & Ballantine, 2011).

## 2.4 A Summary of the Outcome Studies

Overall, the literature reviewing outcomes in children with epilepsy who undergo TLR does not yield a consensus on the impact of surgery on cognitive, memory and academic outcomes. Research into post-surgical cognitive outcomes for children with TLE has historically been guided by adult models, although contemporary knowledge has reflected substantial differences between the mature and the developing brain (Smith, 2010). There is little evidence concerning lateralisation effects in the paediatric population or reliable evidence for which groups experience cognitive improvement, decline, or no change in post-operative outcomes.

Literature on memory and academic outcomes has been variable. While some studies have identified a vulnerability for verbal memory deficits following left TLR, others have found no lateralising effects. Several studies have also reported evidence of no change in memory, and even improvement, after TLR. Some studies have suggested underlying aetiology, the extent of surgical excision, duration of epilepsy, and other epilepsy variables to be associated with memory test performance. Studies that reported a decline in memory are limited by their small sample sizes.

Outcome studies that have explored the impact of TLR on verbal and non-verbal intellectual function have shown relatively little change in IQ scores for children after surgery. Children with TLE are often reported to have general intellectual abilities at least within the average range; however, despite this, poorer academic attainment has been demonstrated. It has therefore been suggested that academic difficulties in this population result from specific learning difficulties or deficits in other cognitive domains. Earlier seizure onset, presence of seizures and use of AEDs have all been linked to intellectual outcomes while pre-operative IQ has been related to the magnitude of change in post-surgical IQ.

Research into the academic performance of children with epilepsy has consistently reported worse attainment outcomes than that of healthy children. Most studies have reported academic attainment difficulties in the context of

normal IQ test performance, suggestive of the presence of specific learning difficulties. Other studies have raised the issue of academic attainment problems which pre-date the onset of seizures and raise the possibility of the effect of underlying aetiology on academic ability. Research demonstrating a link between poor academic attainment and negative outcomes in adulthood provides good rationale for the early identification of cognitive deficits and remedial support for children identified as having academic difficulties.

### 2.4.1 Methodological Issues in the Literature

Altogether, the research has drawn links between various epilepsy variables and cognitive outcomes; however, the sample sizes included in these studies are often small, lack appropriate control groups (Hermann & Seidenberg, 2007), and are based on heterogeneous samples with vast clinical and aetiological diversity (Jambaqué et al., 2007). The study of cognitive problems in paediatric epilepsy is complex owing to the numerous factors that influence cognition (Hermann & Seidenberg, 2007). It is not easy to disentangle the multiple, interacting and cumulative effects of the epilepsy and seizure related variables on cognitive outcomes, all of which influence the extent to which a child is able to engage and access education (Reilly & Ballantine, 2011), potentially creating a greater gap between this population and those without chronic neurological presentations. Many researchers have attempted to understand the relationship between the multiple contributing variables to cognitive outcomes in epilepsy. However, many of the epilepsy variables are often confounding. For example, age at seizure onset is linked to duration of epilepsy, which is likely related to the longer duration of AED regime, which can increase risk of adverse effects of prolonged AED use and the detrimental effects of epileptic discharge activity on the developing brain. Studies that have linked post-operative cessation of AEDs to better cognitive outcomes are likely to also be capturing the effects of seizure freedom and the impact of surgery itself.

Control groups in the existing research into the cognitive outcomes of children with TLE usually involve adults with epilepsy, children with other forms of focal or generalized epilepsy who are not eligible for surgery, or healthy children without a history of neurological disorder. The groups of children with epilepsy who are not

eligible for neurosurgery are likely to differ significantly from children with TLE who undergo surgery, as the factors that make children a non-candidate for surgery are reflective of different underlying pathology and epilepsy characteristics. For children with focal epilepsy involving brain regions other than the temporal lobes, removal of tissue from other lobar regions is likely to show a very different clinical picture. The outcomes following surgery for other epilepsy types should be studied separately. The most reliable findings in this area of research would involve comparisons with a similar group of children who are matched based on age, clinical and epilepsy characteristics, but who do not proceed to surgery. Clearly, because these children may benefit from surgical intervention, it would be unethical to withhold treatment. Despite this, it is important that outcomes for children who undergo surgery for TLE are reported and published in order to inform parents and children who may be faced with making such an important decision about the management of the condition. Given the mixed findings, a greater understanding of the neuropsychological outcomes following TLR is required. Increased knowledge of the effect of surgery on the cognitive developmental trajectory for this population may highlight an increased role for neuropsychology to support children, for example in education.

### 2.4.2 Clinical Implications

Given the mixed findings in the literature, it is unclear exactly which combination of variables lead to worse outcomes for children who undergo surgery for TLE. Clinically, a comprehensive neuropsychological assessment should reflect biopsychosocial factors and take into account a range of factors that have the potential to influence post-surgical outcomes. Gonzalez and Wrennall (2019) offer a neuropsychological model for the pre-surgical assessment of children which covers a number of relevant dimensions (*Figure 3*). Other factors found to relate to outcomes, though not explored in this review, include family stressors, attitude to the child's problem, coping and adjustment, and social context (Anderson et al., 2019; Austin & Caplan, 2007; Gonzalez & Wrennall, 2019). The contemporary view of epilepsy as a network disorder should inform and support pre-surgical decision-making and consider issues beyond localisation and lateralisation of function (Gonzalez & Wrennall, 2019).

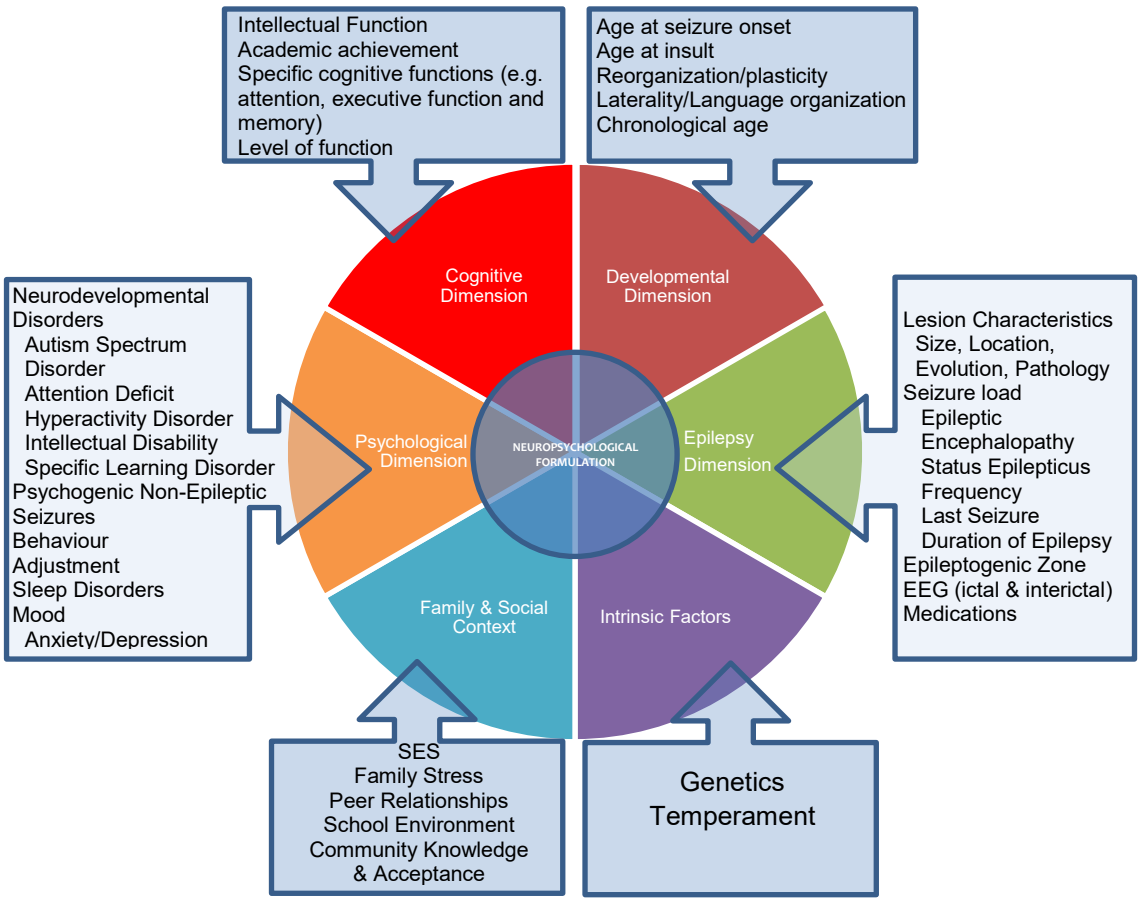



**Figure 3. A child specific model of pre-surgical neuropsychological assessment (based on Gonzalez & Wrennall, 2019).**

## 2.5 Neuroplasticity and Reorganisation

In light of the evidence showing better outcomes for children who undergo surgery at an earlier age, early referral and assessment for surgical intervention is recommended (Flint et al., 2017). Epilepsy surgery is no longer considered a last resort for the treatment of drug resistant epilepsy (Braun & Cross, 2018). To reflect this, national guidelines have set out to increase the number of children under age 6 who undergo surgery for epilepsy (NHS England, 2016). The underlying premise is that early surgery allows for re-localisation of functions and prevention of developmental regression or arrest (Cross et al., 2006). Evidence of developmental benefits of early surgical treatment on cognition warrants consideration of theories of neuroplasticity and reorganisation.

Child neuropsychology has a shorter history than adult neuropsychology. It has built its foundations on adult models, drawing on ideas of lateralisation and functional and structural organisation (Lajiness-O'Neill, Pawluk & Jacobson, 2011). Early findings from adult studies used the lesion method to map brain-behaviour relationships (Moses & Stiles, 2002) and research from rodent and adult human brains described a topographical model of the brain, identifying relationships between structure and function (e.g. Maguire et al., 2000; Richardson & Price, 2009; Straathof et al., 2020). However; despite its static anatomy, there is a general consensus that cognition is highly distributed and depends on the interaction between many brain regions (Gläscher et al., 2012) and it is understood that higher cognitive functions are supported by widespread, distributed cortical networks (Jung, Visser, Binney & Lambon Ralph, 2018).

It has become increasingly evident that adult models are not applicable to the child population (Anderson et al., 2019; Wood et al., 2020). Rather, children exhibit a broad spectrum of cognitive impairments beyond those implicated in the epileptogenic region. More so in children than in adults, a combination of biological, psychosocial, cognitive and environmental factors interacts to influence outcomes and there is no definitive formula for predicting outcomes following early brain insult. The impact of early insult to the developing brain is much more complex and likely to represent an interaction between the neuropathology and normal neurocognitive development mechanisms (Moses & Stiles, 2002). Cognitive skills are less differentiated in children (Westerveld, 2010) and hence a more holistic view of the child at post-injury assessment is essential in order to understand the factors which influence later outcomes (Anderson et al., 2019).

There is a common assumption that the immature brain has greater capacity for the recovery of function as a result of neuroplasticity. Early child neuropsychology theories declared that the child brain was capable of reorganisation following insult, unlike the mature, adult brain which would suffer much more severe consequences from the same insult. These ideas were first described in early theoretical contributions to the neuropsychology literature by Kennard (1942) who studied the effect of timing of brain injury in monkeys and this led to the discovery

that the younger the brain, the greater potential for reorganisation of function. The negative linear relationship between age at brain insult and outcomes became known as the 'Kennard Principle'. Teuber (1974) concluded, based on Kennard's work, "if you're going to have brain damage, have it early" (Anderson et al., 2019, p. 4). Both researchers offered the notion that less differentiation of functions in the immature brain allows for increased capability of transferring functions from damaged to healthy cerebral tissue.

Evidence for reorganisation of function has been demonstrated in unilateral TLE studies of children. For most healthy individuals, language function is lateralised to the left hemisphere of the brain (Knecht et al., 2000). In children with epilepsy originating in the left hemisphere, evidence has shown that chronic seizure activity can lead to a shift of language function from the left to the right side of the brain (Hamberger & Cole, 2011). Atypical language lateralisation provides evidence to support the ability of the developing brain to re-organise language function, demonstrating the effects of neuroplasticity (Yuan et al., 2006).

The idea that the developing brain is malleable to surgical resection is often referred to in comparison studies of adults and children who undergo surgery for focal epilepsy. Research has demonstrated differences in functional recovery between the developing and the adult brain, and children show favourable outcomes and better compensation for post-surgical deficits (Ramantani & Reuner, 2018). Gleissner et al. (2005) assessed a group of adults and children matched on pathology, age of onset, side of lesion and type of surgery. Neuropsychological assessment demonstrated a significant decline in verbal learning capacity in both left-resected groups at 3 months post-surgery. However, one-year post-surgery, while the children recovered to their pre-surgical level, the adults who had left resection remained low on verbal learning capacity, and were worse than pre-surgical status. For the right-resected groups, adults showed a decline in visual memory, while the children improved. The findings of this research were interpreted by the authors as indicative of plasticity and conclusions were drawn pertaining to a more rapid and complete restitution of functions following childhood focal insult, compared to adults. The literature has suggested that improved cognitive outcomes for children may be attributed to a

constitution of shorter epilepsy duration and greater brain plasticity, compared to adults (Lee & Lee, 2013).

While damage to the adult brain may result in a loss of previously acquired functions, in the child brain there may be interference with cognitive development rather than a remarkable loss of function (Smith, 2010). Interference in cognitive development has been demonstrated in a study that compared patients who had early onset (7.8 years) and late onset (23.3 years) TLE (Hermann et al., 2002). The authors found more widespread cognitive deficits in the early onset group, which they conclude was the result of adverse neurodevelopmental impact on cognition and brain structure.

Another important factor when considering the capacity for post-surgical cognitive change is the level of reorganisation that may have occurred during the period that the child was living with seizures. Two effects may be observed; the effect of the removal of the affected brain tissue and the effect of seizure freedom. If reorganisation was already taking place, then little effect may be seen post-surgery if the region of the brain affected was not supporting function (Moosa and Wyllie, 2017). The effects of surgery may depend on the level of functional deficit within and outside of the epileptogenic zone removed during TLR. In post-operative studies of children following unilateral TLR, less pronounced material-specific, hemispheric differences have been shown compared to adults (Lendt et al., 1999) and it has been suggested that these differences may be due to reorganizational capacity of brain function in children (Lee, Lee, Seo, Baumgartner & Westerveld, 2019).

Theories of neuroplasticity have suggested that the earlier the surgery takes place in a child's life, the greater the advantage for compensation of function. This provides a strong argument for early neurosurgical intervention. However, despite their popularity, there is much controversy around neuroplasticity theories. Although early theorists claimed that the earlier insult in childhood yielded less significant deficits than in adulthood, advances in the research have considered this view overly optimistic (Anderson et al., 2019). The overemphasis

on young age neuroplasticity may create a more hopeful picture for post-surgical cognitive outcomes.

There is accumulating evidence that disruption to neurodevelopment in the immature brain has been linked to detrimental effects on the development of neuronal networks and their underlying functions (Anderson et al., 2019). Recent research has observed a negative correlation between age of onset and cognitive outcomes. Anderson, Catroppa, Morse, Haritou and Rosenfeld (2005) investigated the impact of age of injury on cognitive outcomes and offered contributions to the ongoing debate around the capacity for plasticity in children following brain insult. The authors suggested that there are two sides to the coin; children who experience early and severe brain insult (age 3-7 years) and children who experience later, mild-moderate brain insult (age 8-12 years) may be vulnerable to lasting cognitive impairment. While this research was conducted with children who had traumatic brain injuries (TBI), there may be some translatable principles, however it is acknowledged that TBI represents a much more diffuse injury to focal TLE. Research has also demonstrated this finding in TLE and indicated that early seizure onset is related to considerable cognitive deficits. Rather than benefitting from reorganisation and increased plasticity, the impact of recurrent seizures has been associated with detrimental effects on cognitive function (Hermann et al., 2002). The immature brain may be more vulnerable to the effects of prolonged seizures, owing to the firing of synapses from epileptic activity which may be indiscriminate from meaningful synaptic activity (Anderson et al., 2019).

The developing brain has unique vulnerabilities and the potential for early injury to cause irreversible deficits that create problems in higher-order functions in the damaged region (Kolb & Whilshaw, 1998). To reflect advances in the conceptualisation of the effects of early brain insult, research into the impact of brain insult on language development identified that time since insult was a crucial factor in determining outcomes. Rather than recovering function, Dennis et al., (2014) described a trajectory of increasing impairment over time as children ‘grow into’ their deficits. Therefore, the full extent of the impact of brain insult cannot be known until the brain reaches maturation in early adulthood. In

clinical practice, repeated post-operative assessments over time showing a decline in performance may be indicative of this process of emerging difficulties, rather than one of deterioration (Anderson et al., 2019).

Alternative theories on neurodevelopment have been proposed. The ontogenetic specialisation model (Vargha-Khadem, Isaacs, Watkins & Mishkin, 2000) offers one explanation of how the paediatric brain responds to injury. It posits that hemispheric specialisation is genetically determined and that functional expression of this disposition is regulated by the interaction between neural plasticity and environmentally induced neural activity. Childhood trauma or injury to the brain can affect the typical trajectory of brain development and the interaction between this trajectory and the environment. This indicates a non-linear relationship between plasticity and age (Anderson et al., 2019). Other theories put forward have proposed a recovery continuum model of plasticity and vulnerability based on the injury, the cognitive skill, development of the child, and the influence of the environment (Anderson, Spencer-Smith & Wood, 2011). The developmental stage at which the pathology occurs is said to be a key determinant for outcomes (Westerveld, 2010). Seizure activity during critical periods of brain development can lead to adverse effects on synaptic and axon maturation, negatively influencing cognition and behaviour (Hauptman & Mathern, 2012). Purves (2010) defined a critical developmental period as “a restricted developmental period during which the nervous systems of humans or other animals are particularly sensitive to the effects of experience” (p. 247). It has been hypothesised that recurrent seizure activity during such periods can lead to impairment in cognitive function (Campiglia et al., 2014). The type and magnitude of impairment will reflect different consequences at different developmental stages (Dennis et al., 2014). Conclusions drawn from these ideas suggest that the integrity of cerebral structures involved in the critical development periods may be important, such that functions dependent on the affected structures may be more negatively impacted (Anderson et al., 2019).

## 2.6 Overall Conclusions and Rationale for Study

Epilepsy in children is often associated with interference in cognitive development compared to typically developing, age-matched peers (Kellermann, Bonilha, Lin & Hermann, 2015). There is considerable research and agreement that childhood TLE is associated with disruption across developmental cognitive processes, with adverse effects on general cognition (Nolan et al., 2004), academic skills (Puka et al., 2015), memory (Cormack et al., 2012), language (Wheless et al., 2002), attention, processing speed and executive functioning (Flint et al., 2017); and quality of life (Elliott et al., 2005). An understanding of the impact of surgery on cognition, memory and academic attainment is essential, firstly, to identify predictors which can help guide pre-operative counselling and provide information on the risk of cognitive morbidity and, secondly, to understand how children can be supported effectively in the education system.

Taken together, the theoretical and empirical literature suggest neurodevelopment in TLE and post-TLR to be complex and multifactorial. Research to date has attempted to categorise cognitive outcomes following the diagnosis and treatment of the epilepsies, although challenges such as small sample sizes, methodological limitations, and the heterogeneous nature of the group have made this a difficult endeavour. The literature to date is somewhat inconclusive with regards to the relationship between epilepsy variables and cognitive outcomes, with some studies claiming relationships and others not (Hermann et al., 2006).

To date, no theoretical framework has prevailed in offering an integrated model that combines biological, environmental and psychological factors in order to predict outcomes in a clinically meaningful way (Anderson et al., 2019). Taxonomic approaches to the presentation and course of cognitive impairment in paediatric TLE have rarely advanced understandings in the field (Hermann & Seidenberg, 2007). It is clear however, that one common theme throughout these models is that it is the interaction of numerous factors that produce a unique clinical picture for each child (Westerveld, 2010). The mixed clinical picture on post-operative outcomes in children may be explained by the fact that the

developing brain incorporates information into its function and structure differently to the mature brain. It is also widely agreed that age at time of lesion is an important factor, which may represent a window of opportunity for some, and a period of vulnerability for others. (Andersen, 2003).

Overall, children with epilepsy have worse educational outcomes than controls. Performance on intelligence tests has shown to be the best predictor of academic abilities (Watkins et al., 2007) although there is a paucity of evidence demonstrating the relationship these variables in the paediatric TLE population. Further, academic attainment difficulties have been observed in children whose IQ falls within the normal range. Academic underachievement is linked to poor social outcomes and contributes to unemployment in adulthood (McNelis et al., 2005) and these are an important consideration for parents and families of children under assessment for surgical candidacy. There is limited knowledge on employment outcomes for adults who undergo epilepsy surgery in childhood due to the scarcity of long-term follow-up studies (Reinholdson et al., 2020), however some evidence has suggested significantly lower income in this population, despite having similar educational attainment to the general population (Puka & Smith, 2016).

Epilepsy is considered an *invisible* disability as no symptoms are present except during a seizure (Hills, 2007); however, seizures and their consequences contribute to the burden of the syndrome due to the considerable impact on disability and mortality (Beghi et al., 2019). It may go unaddressed in educational systems where specific cognitive impairments exist alongside otherwise grossly intact global cognitive abilities (Kernan et al., 2012; Reilly & Neville, 2011). Neuropsychological assessment is therefore important to identify strengths and weaknesses in cognitive profiles in order to support the child's educational attainment.

Neuropsychological performance is often articulated around separate cognitive domains of functioning; and assessments are developed to measure these apparently discrete abilities (Lezak, Howieson, Bigler & Tranel, 2012). However, it is widely understood test specificity is poor and the domains targeted are not

independent of each other (Lopez-Garcia et al., 2016). Contemporary knowledge has demonstrated activation and interaction of neural circuits, providing evidence of the complex organisation structures involved in cognitive tasks (Harvey, 2019). One must remain critical of the tools available and their underlying epistemological and ontological assumptions. In addition, an established evidence based now exists in the adult literature suggesting that neuropsychological test performance may not be fully explained by neurological deficits alone (e.g. Green, Rohling, Lees-Haley & Allen, 2001). Educational opportunity, language, culture, medical and psychological condition can also influence test performance. For example, performance validity is increasingly being found to explain test score variance in the adult literature (McMillan et al., 2009), although it is unlikely that effort was considered in the paediatric studies described.

## 2.7 Present Study

The aim of the current study is to extend findings of previous research into cognitive outcomes following TLR for paediatric TLE. Previous studies have been subject to methodological limitations arising from the recruitment of small samples and participants with a range of lobar regions of epilepsy onset. The present study will address these gaps by its use of a larger sample than in previous studies of children with TLE, all of whom have unilateral onset, drawing upon a sizeable data set of pre- and post-operative neuropsychological assessment scores. Participants included 72 children who underwent TLR for TLE. All participants underwent neuropsychological assessments prior to surgery and approximately one year after. Cognitive variables of interest were verbal and non-verbal intelligence, memory, and academic attainment. Based on findings from the existing outcomes literature in paediatric epilepsy, epilepsy-related variables of interest were side of pathology, duration of epilepsy, and type of pathology. The outcome variable was academic attainment, yielding scores for numeracy, literacy and reading comprehension.

The current study offers the potential to increase the understanding of which children display better outcomes following TL surgery. The findings will also have implications for researchers and scholars, as the data will serve to potentially offer a foundation upon which further research can emerge. The results of this study may offer insight into the cognitive outcomes for children who undergo surgery for TLE. This may be beneficial for physicians through building on existing understanding of post-surgical outcomes and informing pre-surgical counselling. It is hoped that the findings will contribute to the literature on outcomes for children who undergo TLR and consider the type of support that academic institutions can put in place to support the additional learning needs of children with TLE. Implications for practice in paediatric neuropsychology services will be considered. A greater understanding of the impacted networks in childhood TLE might inform a neuropsychological assessment that identifies specific effects of the epilepsy, as well as to inform and evaluate therapeutic interventions designed to alleviate the neuropsychological effects of epilepsy.

# 3. METHOD

## 3.1 Chapter Overview

This chapter will outline the method for this study and describe each stage of the research. Section 3.2 provides the aims and objectives of the study. Section 3.3 outlines the epistemological foundations upon which the research is positioned. Section 3.4 and 3.5 detail some key ethical considerations. Sections 3.6 and 3.7 detail the national service context to the research and the participants who were involved in the study. Section 3.8 and 3.9 describe the process of data collection. Section 3.10 outlines the instruments administered and the epilepsy variables are discussed in 3.11. Finally, 3.12 details some preliminary considerations for the analyses.

## 3.2 Research Aims and Objectives

The lack of consensus regarding outcomes following surgery to treat paediatric TLE is reflective of the multiple and often confounding findings in the literature. There are some obvious gaps in the evidence base that are currently unable to be directly addressed due to the lack of longitudinal designs, methodological limitations and the unavoidable fact that children with TLE represent a heterogeneous group. It was hoped that the current study could provide some evidence to demonstrate the cognitive, memory and academic outcomes following TLR and the influence of epilepsy variables by using a larger sample than those commonly reported in the literature thus far. This led to the following research questions:

1. What are the cognitive, memory and academic outcomes for children who undergo neurosurgery for TLE?

2. What are the contributions of epilepsy-related factors to memory, cognitive and academic outcomes?

## 3.3 Ontology and Epistemology

Ontology is a branch of philosophy that is concerned with the nature of existence and what constitutes reality (Richards, 2003). Two broad, overarching positions that guide one's ontological stance are realism and relativism. Realism assumes an external reality that exists independent of people's understanding and beliefs about it, whereas relativism exerts that reality is dependent on socially constructed meanings (Ormston, Spencer, Barnard & Snape, 2013). The current study assumed a realist ontology; the phenomena under investigation occurred independently of influence from the researcher. The clinical and neuropsychological assessment data recorded in the patients' clinical notes is seen to be a reflection of 'real' events observed in the world.

Epistemology is an area of philosophy that is concerned with "the very bases of knowledge – its nature and forms, how it can be acquired, and how communicated to other human beings" (Cohen, Manion & Morrison, 2007, p.7). It is important for researchers to be explicit about their epistemological position, as it is the guiding principle for the methodological concerns of research; from the research questions, to the choice of measurement, analysis and interpretation (Willig, 2001). Inherent in quantitative research is the assumption that phenomenon can be directly observed in order to enhance one's understanding about the world. Its positivist positioning assumes knowledge to be derived from observable 'truths' and realities (Scotland, 2012). Neuropsychology has its roots in scientific positivism where biology meets psychology (de la Miyar & Moes, 2014). It rests upon the assumption that cognitive processes that take place at the neurobiological and chemical level can be observed, measured and categorised according to pre-assessed standardised norms. The selection of a representative sample allows for inferential statistical analyses (Scotland, 2012). Relationships between variables are considered to represent meaningful constructs and differences that can be generalised to the larger population (Kukull & Ganguli, 2012). It is assumed that cognitive constructs defined in neuropsychology can be inferred from performance on neuropsychological tests (Schoenberg & Scott, 2011).

The current research draws upon a critical realist epistemological stance. Inherent in this is the assumption that, while it is not possible to tangibly observe the processes behind the constructs that have been defined, outputs are measured by neuropsychological tests which offer true representations of what is intended to be measured. For example, in measuring 'encoding', 'storage' and 'recall' of verbal and visual information, the outputs, measured by delayed recall tasks, are assumed to access these complex neuropsychological processes that support the recall of previously learnt information. As such, while it is not possible to directly observe such phenomena, one can only deduce from responses and make inferences about such processes (Popovic, 2005). The research questions of the current study lend themselves to this approach due to the reliance on test performance data as a measure of observable phenomenon, allowing for a theory-driven approach. In doing so, the study aims to quantify phenomena that might exist independently across time and within a social and material reality. Furthermore, epilepsy is a recognised medical condition with distinct, observable physical and neurological manifestations with symptoms that are not present for those without the syndrome. Alongside this, the current study is aligned with the perspective that neuropsychological constructs exist within a cultural, historical, and socio-political context, whereby definitions of what is considered the 'norm', in reference to intelligence, alter over time (Flynn, 1984). The value and contributions of inductive research based on experimentation and observation to science is acknowledged, though it has been recognised that induction is not infallible and not to be taken for granted (Popovic, 2005); therefore, all knowledge and research should therefore be interpreted in context. As the current study was based on the secondary analysis of existing data, the epistemological stance was guided and limited by this methodology. The approach has greater allegiance with positivist assumptions and methodology associated with the natural sciences, such as observing, testing and measuring.

## 3.4 Ethical Considerations

The current study was based on the analysis of secondary data derived from an existing database of pre-surgical and post-surgical neuropsychological

assessment outcomes of children who underwent neurosurgery for TLE at Great Ormond Street Hospital (GOSH). NHS ethical approval was obtained under a pre-existing application approved by GOSH and the Institute for Child Health (ICH) (REC reference: 05/Q0502/88) *(Appendix A)*. An application was made to the Ethics Committee at the University of East London's School of Psychology Research Ethics Committee and ethical approval for secondary data analysis was granted on 7/10/2019 *(Appendix B)*.

### 3.5 Confidentiality and Data Protection

The data was anonymised, and any identifiable information was removed. Each child was given a unique number which linked to the anonymised data, which was stored separately under data protection regulations. All data was stored securely and protected with passwords. The anonymised data was stored electronically on the secure servers at the university. The data was coded and entered into a database for analysis with no identifiable information.

### 3.6 National Service Context

In order to set GOSH within the national clinical context for paediatric epilepsy, it is necessary to consider the reform of UK paediatric epilepsy services following the *Safe and Sustainable Review* of neurological children's services in 2012 (NHS England, 2016; NHS Specialised Services, 2012). Children's Epilepsy Surgery Services (CESS) were established across the UK as specialist centres performing the majority of surgeries and consulting to other hospitals (NHS England, 2018). This was based on evidence that optimal care for children with epilepsy is best provided by experienced paediatric care units with specialist expertise, highlighting the necessity for dedicated centres (Cross et al., 2006). National standards for best care were agreed and specialist staff were put in place to set up an expert workforce in line with the requirements of the Department of Health (DoH, 2008) *Commissioning Safe and Sustainable Specialised Paediatric Services* framework. GOSH became one of the CESS centres following this centralisation. Between 2012 and 2013, the year during

which the CESS centres were established, 64% of all surgeries were carried out at GOSH (Shastin et al., 2015).

### 3.7 Participants

The sample was drawn from a clinical population of children who were seen at GOSH CESS between 1999 and 2019. Children were referred by neurologists for pre-operative neuropsychological assessment as part of routine evaluation for epilepsy surgery. The neuropsychological assessment combined with other investigations during an inpatient admission (MRI, EEG, fMRI) contributed to discussions at large multi-disciplinary epilepsy surgery meetings where children were considered for suitability to proceed to surgery. Pre-operative neuropsychological assessments also represented a baseline of the children's abilities prior to surgical intervention. For those who had multiple pre-operative assessments, usually due to inability to identify a focal lesion at initial assessment, or a decision to not go ahead with the procedure following an initial pre-operative assessment, the most recent pre-operative neuropsychological assessment results were used.

Children were referred for a second neuropsychological assessment approximately one year post-operatively. The post-operative assessment served as a measure of current ability which could be compared to the children's pre-operative baseline assessment and to identify strengths and weaknesses in the cognitive profile. Where areas of difficulty were identified, recommendations were made in in the neuropsychological assessment reports to support the children's education and learning at school.

For those who had more than one post-operative assessment, often due to concerns around cognitive developmental trajectory following surgery or in cases where seizures were not remediated, the results from the initial one-year follow-up neuropsychological assessment were used. All neuropsychological measures were administered by clinicians who were trained in the administration and

scoring of the tests, under the supervision of experienced clinical or educational psychologists.

The sample consisted of 72 children and adolescents who underwent surgery prior to age 18. The ages of the children at each evaluation were calculated based on the method provided in the Wechsler scales (Wechsler, 2014). All children were diagnosed with TLE, according to the ILAE guidelines (Fisher et al., 2017). Epilepsy diagnoses were made by paediatric neurologists based on MRI findings, EEG investigations, seizure semiology and clinical history. All children involved in the study had an identified structural abnormality detected by MRI scanning. All children were diagnosed with drug resistant epilepsy, which is defined as a failure to achieve seizure freedom with 2 adequate AED schedules (whether as monotherapy or polytherapy; Kwan et al., 2010). All the children underwent surgical intervention. Only participants with outcome data from neuropsychological assessments carried out both pre- and post-surgery were included in the study.

### 3.7.1 Inclusion and Exclusion Criteria

Criteria applied by clinicians when considering suitability for surgical intervention guided the inclusion and exclusion criteria for the database. Children and young people up to the age of 18 at the time of surgery were included.

Inclusion Criteria

i) Diagnosis of TLE.
ii) Up to age 18 at the time of surgery.
iii) Underwent both pre- and post-operative neuropsychological assessment.

Exclusion Criteria

i) Children with generalised or multifocal epilepsy.
ii) Children without a clear identified structural abnormality on MRI or EEG.
iii) Children with a Learning Disability and/or FSIQ or VIQ/VCI <70.
iv) Children with a major sensory deficit sufficient to significantly impact performance on neuropsychological assessment.
v) Presence of another neurological disorder.

vi) Children with co-morbid physical health diagnoses that are known to impact neuropsychological test performance.

vii) Children who underwent more than one neurosurgical procedure, for example: one child in the sample underwent two surgical interventions in between their pre- and post- operative neuropsychological assessments, due to insufficient removal of tissue during the initial surgical procedure and continuation of seizures.

### 3.8 Missing data

In clinical and epidemiological research, missing data are ubiquitous (Sterne et al., 2009). In the current study, not all children completed all measures of the standard service test battery protocol. A reduced protocol was used for some children due to inability to access the tests due to abilities, inattentiveness, or fatigue. Those for whom a neuropsychological assessment was available at only one time-point (either pre-operative or post-operative) were not included in the final sample. Children who completed a pre-operative assessment, but no post-operative assessment may not have proceeded to surgery and so this data was excluded. One reason for not proceeding to surgery may be due to the absence of an identified focal lesion, hence a child would not be a candidate for TL resective surgery. In addition, a non-focal epilepsy syndrome would produce a very different clinical and cognitive picture to a unilateral TLE (van Rijckevorsel, 2006).

### 3.9 Procedure

A trawl of the electronic medical files was completed and information from the neuropsychological assessment reports was extracted and entered into a database. The data included neuropsychological test scores and demographic information, including sex, age and handedness. Information relating to epilepsy variables and clinical characteristics (diagnosis, pathology, age at seizure onset, AED load, date and type of surgery, and side/site of lesion) was taken from

medical letters by the neurologists. A thorough process of scrutinising the dataset and entering missing data was undertaken.

The final version of the database contained 72 eligible participants. The choice of variables was rooted in evidence from the literature which has demonstrated the effect and contributions of the variables to cognitive outcomes post TLR, including duration of epilepsy, type of pathology, side of pathology, and seizure frequency.

## 3.10 Instruments

The participants underwent standardised assessments according to a neuropsychological test battery agreed within the CESS. The measures spanned verbal and non-verbal intellectual abilities, verbal and visual memory, and literacy and numeracy attainments, and are described in detail below. All measures were administered, scored, and interpreted in line with the guidelines provided by the test manuals. All raw scores were converted into age-appropriate scaled and index scores based on standardised normative data. Due to either the age of the participants, or the version of the test used by the department at the time of the children's assessments, not all participants completed the same version of a given measure. It is acknowledged that there is likely to be lack of equivalence between the different test versions. Neuropsychological tests are refined and re-standardised to reflect updated conceptualisations of intelligence (Taub & Benson, 2013). Further, the Flynn Effect may demonstrate inflated scores that are artificially reflective of individuals who may have taken the same test but at a later date and are being compared to older norms (Flynn, 1984). This is an unavoidable, but potential limitation of the current study.

### 3.10.1 Assessment of Intellectual Function

Participants' general intellectual ability (verbal and visuo-spatial attention and reasoning skills; IQ) were obtained using the age appropriate form of the Wechsler Intelligence Scales. The data was collected over an extended time period which meant that different test versions were used. Most of the sample

completed the *Wechsler Intelligence Scale for Children 4th edition* (WISC-IV$^{UK}$; Wechsler, 2003). Some of the participants completed the following versions:

- *Wechsler Preschool and Primary Scale of Intelligence Revised* (WPPSI-R$^{UK}$; Wechsler, 1989*).*
- *Wechsler Preschool and Primary Scale of Intelligence 3rd edition* (WPPSI-III$^{UK}$; Wechsler, 2002*).*
- *Wechsler Preschool and Primary Scale of Intelligence* 4th edition (WPPSI-IV$^{UK}$; Wechsler, 2012*).*
- *Wechsler Intelligence Scale for Children 3rd edition* (WISC-III$^{UK}$; Wechsler, 1991).
- *Wechsler Intelligence Scale for Children 5th edition* (WISC-V$^{UK}$; Wechsler, 2014).
- *Wechsler Adult Intelligence Scale 3rd edition* (WAIS-III$^{UK}$; Wechsler, 1997).
- *Wechsler Abbreviated Scale of Intelligence* (WASI$^{UK}$; Wechsler, 1999).
- *Wechsler Adult Intelligence Scale 4th edition* (WAIS-IV$^{UK}$; Wechsler, 2008).

As an example, the most commonly administered was the WISC-IV$^{UK}$. The WISC-IV$^{UK}$ was designed for ages 6 years 0 months – 16 years 11 months. It was normed on a representative UK sample of 780 children (368 boys, 412 girls) and has good evidence for reliability and validity. The WISC-IV provides an overall general ability score (FSIQ) that comprises four composite scores; *Verbal Comprehension Index* (VCI), *Processing Speed Index* (PSI), *Perceptual Reasoning Index* (PRI) and *Working Memory Index* (WMI). The VCI is composed of the *Similarities, Vocabulary* and *Comprehension* subtests. The PSI is composed of the *Coding* and *Symbol Search* subtests. The PRI is composed of the *Block Design, Matrix Reasoning* and *Picture Concepts* subtests. The WMI is comprised of the *Digit Span* and *Letter-Number Sequencing* subtests.

3.10.2 Assessment of Memory

Learning and memory functions were assessed using the *Children's Memory Scale* (CMS; Cohen, 1997), or *Wechsler Memory Scale* (WMS$^{UK}$) as appropriate to their age. The CMS was used for children aged 5-16 years and the WMS-III$^{UK}$

(Wechsler, 1997) or WMS-IV$^{UK}$ (Wechsler, 2009) were used for children aged 16 +. *The CMS was standardized on a sample of 1000 children* (Cohen, 1997), the WMS-III$^{UK}$ was standardised on 1250 adults (age range 16-89) (Wechsler, 1998) and the WMS-IV$^{UK}$ was standardized on 900 adults (age range 16-89) (Wechsler, 2009). All have good evidence of reliability and validity. In all cases, immediate and delayed recall of prose stories and a list of word pairs was used to assess verbal episodic learning and memory (*CMS Stories; CMS Word Pairs; WMS Logical Memory; WMS Verbal Paired Associates*). Visuo-spatial learning and memory were assessed with the *Family Pictures* (WMS-III$^{UK}$), and *Faces* (CMS; WMS-III$^{UK}$) or *Dot Locations* (CMS), or *Visual Reproduction* (WMS-IV$^{UK}$) subtests of the age-appropriate instrument. In line with recommendations in the manual, the *Children's Auditory Verbal Learning Test* (CAVLT-2; Talley, 1993) was used for some children as a measure of verbal memory.

Of the total number of participants who completed a measure of learning and memory pre-operatively, 58 completed the CMS and 4 completed the CAVLT-2. A small proportion of the participants completed WMS-IV$^{UK}$ (n=2). Post-operatively, 55 completed the CMS, 5 completed the WMS-III, 8 completed the WMS-IV, and 1 completed the NEPSY-2 (Korkman, Kirk & Kemp, 2007).

3.10.3 Assessment of Academic Achievement

Participants' academic skills were assessed using subtests of the *Weschler Individual Attainment Test 2nd UK Edition* (WIAT-II$^{UK}$; Wechsler, 2005) *Word Reading, Reading Comprehension* and *Pseudoword Decoding* tasks or the *Wechsler Objective Reading Dimensions* (WORD; Rust, Golombok & Trickey, 1993) *Basic Reading, Spelling* and *Reading Comprehension* tasks. The separate dimensions provide overall reading composite scores.

Participants' numeracy attainments were assessed using the *Numerical Operations* and *Mathematics Reasoning* subtests of the *Wechsler Individual Attainment Test-2nd Edition* (WIAT-II$^{UK}$; Wechsler, 2005), the *Wechsler Individual Attainment Test-3rd Edition* (WIAT-III$^{UK}$; Wechsler, 2018) or the *Wechsler Objective Numerical Dimensions* (WOND; Rust, 1996).

The WIAT-II$^{UK}$ was used for children aged 4 years to 16 years 11 months. The WIAT-III$^{UK}$ was used for children aged 4 years to 25 years 11 months. The WORD and the WOND were originally used for children aged 6-16 years.

The WIAT-II$^{UK}$ was standardised on a UK sample of 892 individuals, during the same period of standardisation as the WISC-IV$^{UK}$ and has good evidence for reliability and validity. Inter-item consistency within subtests showed strong reliability coefficients (on average, ranging from .80 to .98) and strong interscorer reliability (overall reliability of .94) has been demonstrated. Evidence of validity (construct, content, and criterion) was also demonstrated.

The WIAT-II$^{UK}$ consists of four composite scores; *Reading, Mathematics, Written Language* and *Oral Language*. In the current sample, all subtests from the Reading (*Word Reading, Pseudoword Decoding, Reading Comprehension*) and Mathematics (*Numerical Operations* and *Mathematical Reasoning*) domains were routinely administered. For some of the sample, the *Spelling* subtest from the Written Language composite was also administered.

The WORD and WOND were standardised on a UK sample of 418 children who represented each of the 11 age groups from ages 6-16. Both have good evidence for reliability and validity (Rust, 1996). The WIAT-III$^{UK}$ was normed on a stratified sample of 744 children, based on the UK census data from 2011, and has good evidence for reliability and validity (Wechsler, 2018). The WORD and the WOND are co-normed with the WISC-III$^{UK}$ and the WIAT-II$^{UK}$ is co-normed with the WISC-IV$^{UK}$.

The subtests used from the WORD, WOND and the WIAT were equivalent across all tests. In all cases, a numerical operations task was used to assess numeracy, a single word reading task was used as a measure of reading ability, and spelling was used as a measure of written language ability.

These three together are not combined in the usual composite scoring procedures, so Pearson's correlation was undertaken to determine whether they are related. Results show not only *Spelling* and *Word Reading* were correlated

(.793), but *Numeracy* was also correlated to *Word Reading* (.604) and *Spelling* (.676). Accordingly, the three measures are strongly correlated and this allowed for all three to represent a composite of all for overall academic attainment (*Table 1).*

**Table 1. Correlations between the academic attainment dimensions.**

| | 1 | 2 |
|---|---|---|
| **1. Word Reading (Pre)** | - | |
| **2. Numerical Operations (Pre)** | .604** | - |
| **3. Spelling (Pre)** | .793** | .676** |

** p < 0.01 level (2-tailed).

Given that the current study was based on clinical data, variability existed in the tests administered and there were instances of missing data. Therefore, the number of participants in each group is variable across analyses. Those whose neuropsychological test battery included at least one measure of intellectual ability, memory, or academic attainment were included and their scores were entered into the final database. Of the pre-operative group, 71/72 completed a measure of intellectual abilities, 60/72 completed a measure of memory (constituted on both verbal and visual), and 65/72 completed a measure of academic attainment. Of the post-operative group, 72/72 completed a measure of intellectual abilities, 69/72 completed a measure of memory (constituted on both verbal and visual), and 70/72 completed a measure of academic attainment. Measures for all three domains at both time points constituted a complete dataset and this was obtained for 49/72 of the participants.

### 3.11 Epilepsy Variables

Epilepsy-related variables which have been found to be related to cognitive outcomes in children with TLE were recorded. The following data were collected:

### 3.11.1 Duration of Epilepsy

*Age at onset*, confirmed by parent report, and age at surgery were recorded and used to calculate the *duration of epilepsy*, in years and months.

### 3.11.2 Seizure Frequency

Given that seizure freedom is the main goal for surgical intervention, *seizure frequency* was recorded before and after surgery. Seizure frequency indicates the behavioural manifestation of epilepsy, offering a proxy measure for the severity of the epilepsy (Berto, 2002). However it has been suggested that seizure frequency in children should be interpreted with caution due to significant under-reporting of seizures (Akman et al., 2009). The seizure frequency data was obtained from parent reports. The Engel classification system *(Appendix C)* (Engel, Cascino, Ness, Rasmussen & Ojemann, 1993) was used to categorise post-operative seizure frequency based on parent reports of seizure frequency.

### 3.11.3 Side of Lesion

*Side of lesion* was recorded at the children's pre-operative inpatient assessment following Video-EEG monitoring and MRI investigation.

### 3.11.4 Pathology

*Pathology* was determined by MRI investigations carried out prior to surgery and confirmed by histopathological examination. Neuropathic examination of brain tissue aids the identification of the clinicopathologic substrate of the epilepsy and advances understanding of epilepsy through the inspection of well-characterised brain tissue (Blümcke et al., 2016). Results from histopathologic examination, EEG and MRI offer complementary information on the structural and functional neuropathology. This contributes to both clinical decisions about appropriate intervention and research strategies that account for group comparisons (Pittau et al., 2014; Wang et al., 2013).

### 3.11.5 AED Load

*AED load* was recorded at the time of the pre and post-operative neuropsychological assessments. They were recorded by actual number of AEDs and categorised into three groups; none, monotherapy, and polytherapy for the analysis.

## 3.12 Statistical Analyses

IBM Statistical Package for Social Sciences (SPSS, version 26) (IBM Corporation, 2019) was used to perform statistical analysis on the data.

### 3.12.1 Data Preparation

Raw scores on the tests used in the neuropsychological assessment were converted into standard scores and scaled sores using age-matched norms published in the test manuals. Conversion of the scores allowed for comparison across measures by using a single metric. All index scores had a mean of 100 and a standard deviation of 15. In addition, new variables were generated in order to analyse the predictors of change in test performance after surgery. These variables were created using a calculation of the difference between the *z*-scores from the post- and pre-operative assessments for each domain and accounted for loss or gain over time.

Exploratory data analysis (EDA) was conducted using Tukey's EDA model (Tukey, 1977). The data was screened for any univariate outliers and any administrative errors were corrected. Missing composite scores were calculated for all participants and were pro-rated on subscale sums where necessary. Missing values of continuous variables due to omission of administration was denoted by '999' in SPSS. Pairwise deletion was employed for missing data-points, in order to make efficient use of the available data. Whilst this method has its merits in preserving more data than listwise deletion, the model parameters are based on different data sets with different sample sizes, means and standard errors (Kang, 2013).

### 3.12.2 Testing for Assumptions

Analyses were undertaken to ensure the data met assumptions for multivariate analysis (Field, 2018). Unusually low or high scores on boxplots were checked for accuracy of scoring and data entry and all values were determined to be correct. Measures of frequency and distribution were generated in order to check data were normally distributed, in accordance with methods outlined by Field (2018). Shapiro-Wilk's test suggested that all neuropsychological test outcome variables were normally distributed. Upon visual inspection, histograms were symmetric and normally distributed without significant outliers. The epilepsy variables were assessed for departure from normality. *Duration of epilepsy, age at onset* and pre-operative *seizure frequency* were found to be asymmetrical and not normally distributed. These variables were transformed using normal score by Blom's formula to ensure they met normality and subsequent EDA confirmed showed a highly symmetrical bell-shaped curve. The results are presented in both transformed and non-transformed format *(Figure A – Figure F, Appendix D).*

### 3.12.3 Data Analysis

To address the first research question, which sought to ascertain the cognitive, memory and academic outcomes following neurosurgery for TLE, descriptive statistics were collected for the neuropsychological test variables for both the left and right TLE groups and for the three pathology groups (MTS, FCD and tumour). A series of paired t-tests were used to determine change over time within the pathology and lesion side groups. Between group differences along the neuropsychological test domains were then analysed using a series of One-Way ANOVAs. The second question, to establish any unique and combined contributions of epilepsy variables, *duration of epilepsy, seizure frequency, lesion side* and *pathology*, to cognitive outcomes, was addressed using general linear model (GLM).

# 4. RESULTS

## 4.1 Chapter Overview

This chapter provides the results for the research questions of the study. The demographic and clinical characteristics of the sample are described to give an overview of the epilepsy and neuropsychological test variables. One-way ANOVAs are used to compare the samples by lesion side and pathology groups. A series of GLMs are then then applied in order to identify the unique and combined contributions of the epilepsy variables to cognitive outcomes.

## 4.2 Sample Characteristics

*Table 2* shows a summary of the descriptive and clinical data for the sample by lesion side implicated in TLE. For the overall sample there was a fairly even distribution of males (*n* = 34) and females (*n* = 38). The average age at surgery was marginally higher for the right group than the left group. The average post-surgical follow-up for the entire sample was 1.47 years. Seventy children had data for seizure outcome following surgery and the majority of children achieved seizure freedom after surgery (Engel Class I).

Of the children with seizures emanating from the left hemisphere, the majority had right hand dominance (*n* = 40), with a minority showing left hand dominance (*n* = 5) and ambidexterity (*n* = *1).* Of the children with seizures emanating from the right hemisphere, a majority right-hand dominance was again observed (*n* = 22), a minority showed left-hand dominance (*n* = 3) and ambidexterity (*n* = 1). One child was reported to have changed dominant hand from left to right following left-sided surgery.

Of the total sample, the great majority were taking AEDs prior to surgery (*n* = 68) and, among those, the majority were taking multiple medications (*n* = 43). The

number of children taking AEDs at follow-up was reduced compared to before surgery (*n* = 48) and the number of those on polytherapy was almost equal to monotherapy.

The groups were not homogeneous for lesion side or pathology. Of the total sample, 46 had seizures emanating from the LTL and 26 from the RTL. Most underwent lesionectomy (*n*=29; left = 16. Right = 13) or lobectomy (*n*=32; left = 22, right = 10), some underwent amygdalohippocampectomy (*n*=10; left = 8, right = 2), and 1 patient underwent a right-sided temporal disconnection. The sample had histopathologic findings consistent with one of the three following diagnoses: MTS, low-grade tumour (DNET or gangliogioma), or FCD. The FCD cases were all but one to the left side.

The average age of onset was similar for both the left and right groups, which ranged from 0.33 to 14 years for the left side and 0.5 to 14 years for the right side. The mode for age of onset for the whole sample was 1 year; the majority of children experienced their first seizure before the age of 1 year (Figure A, Appendix D), although this differed between the left (1 year) and right group (8 years). Descriptive statistics suggested that age at seizure onset appears younger in the MTS group (M 3.16, SD 2.93) than in the tumour group (M 6.21, SD 4.24) and the FCD group (M 4.64, SD 3.49). Duration of epilepsy was similar for both the right and left group.

There was significant variation in pre-operative seizure frequency. The data collected from parental report by clinicians at the time of the pre- and post-surgical assessments were not reported along a single metric. For the analysis, seizure frequency was converted to obtain a number of seizures per calendar month. The mean pre-operative seizure frequency for the left group was considerably greater than the right group and showed much greater individual variation. Post-operatively, the mean seizure frequency and individual variation was much lower for both the right and the left group, with considerably less variation within the groups.

**Table 2. Demographic and clinical characteristics of the whole sample and by lesion side**

| | Whole sample (*n*=72) | Right temporal (*n*=26) | Left temporal (*n*=46) |
|---|---|---|---|
| *Sex, n* | | | |
| Male | 34 | 12 | 22 |
| Female | 38 | 14 | 24 |
| Age at seizure onset, y, *mean (SD)* | 4.87 (3.943) | 4.88 (3.974) | 4.87 (3.969) |
| Age at seizure onset (mode) | 1.00 | 8.00 | 1.00 |
| Age at surgery, y, *mean (SD)* | 12.10 (3.676) | 12.32 (4.097) | 11.97 (3.457) |
| Duration of epilepsy, y, *mean (SD)* | 7.22 (3.924) | 7.43 (4.27) | 7.10 (3.758) |
| *Pathology, n* | | | |
| Tumour | 37 | 12 | 25 |
| MTS | 28 | 13 | 15 |
| FCD | 7 | 1 | 6 |
| | | | |
| ***Pre-surgery*** | | | |
| *Handedness, n* | | | |
| Right | 61 | 22 | 39 |
| Left | 9 | 3 | 6 |
| Ambidextrous | 2 | 1 | 1 |
| *AED load, n* | | | |
| None | 4 | 0 | 4 |
| Mono | 25 | 9 | 16 |
| Poly | 43 | 17 | 26 |
| AED medication, *mean (SD)* | 1.71 (.863) | 1.77 (.710) | 1.67 (.944) |
| Seizure frequency, m, *mean (SD)* (*n*=55) | 42.41 (64.091) | 35.69 (51.842) | 46.57 (71.037) |
| | | | |
| ***Post-surgery*** | | | |
| Age at follow-up, y, *mean (SD)* | 13.65 (3.46) | 13.88 (3.89) | 13.52 (3.224) |
| Time since surgery, y, *mean (SD)* | 1.47 (.913) | 1.41 (.755) | 1.50 (.998) |
| *AED load, n* | | | |
| None | 24 | 7 | 17 |
| Mono | 22 | 9 | 13 |
| Poly | 26 | 10 | 16 |
| AED medication, *mean (SD)* | 1.08 (.931) | 1.19 (.939) | 1.02 (.931) |
| *Handedness, n* | | | |
| Right | 62 | 22 | 40 |
| Left | 8 | 3 | 5 |
| Ambidextrous | 2 | 1 | 1 |
| Seizure frequency, m, *mean (SD)* (*n*=64) | .70 (3.905) | .041 (.204) | 1.10 (4.917) |

## 4.3 Research Question 1

**What are the cognitive, memory and academic outcomes for children who undergo neurosurgery for TLE?**

Descriptive statistics for the sample change scores on IQ, memory and academic attainment can be found in *Table 3* and *Table 4.* Change scores were derived from the difference between the individual pre- and post-operative standard scores across domain and composite standard scores. Inspection of the descriptive statistics for the entire sample, and when broken down by lesion side and pathology showed substantial individual variation as observed in the large SDs. For example, the mean for *Verbal Delayed Memory* change for the whole sample is 2.69 with a SD of 15.27. For greater transparency, the individual variation across the overall domain change scores (for the left and right groups) can be found in *Appendix D.* The general trend is for small improvements in scores with several exceptions. While some children improved in performance over time, others declined, and some showed no difference. The mean and SD for lesion side and pathology groups by each neuropsychological test domain, pre- and post-operatively, are given in *Tables B – F, Appendix D).*

Comparisons were then made to determine whether differences in neuropsychological test performance over time were reliable. A series of paired samples t-tests were conducted for the left and right groups, and the three pathology groups. The results of the analysis show that for the LTL group there was a decline from pre- and post-operative scores for *VCI* (t(32) = 2.351, d = .346, p = .023) (*Table K*. Paired T-tests to examine differences between the pre and post op test scores for the left TLE group.). In the pathology groups, there was a decline between pre- and post-operative performance on *Word Reading* in the tumour group (t(32) = 2.135, d = .371, p = .041) (*Table M*. Paired T-tests to examine differences between the pre and post op test scores for the tumour group). The pre- and post-operative scores for *VCI* (t(27) = 2.410, d = .455, p = .023) and *Verbal Delayed Memory* (t(25) = 2.292, d = .449, p = .031) showed decline in the MTS group

(*Table N*. Paired T-tests to examine differences between the pre and post op test scores for the MTS group).

**Table 3. Means and Standard Deviations for the neuropsychological test variables (pre-post differences) for whole sample, left TLE group and right TLE group.**

| | Whole sample | LTL | RTL |
|---|---|---|---|
| **IQ composites** | | | |
| FSIQ change (n = 71; 45; 26) mean (SD) | 1.66 (9.991) | 1.33 (9.332) | 2.23 (11.212) |
| VCI change (n = 71; 46; 25) mean (SD) | 3.37 (8.367) | 2.76 (7.964) | 4.48 (9.125) |
| PRI change (n = 70; 45; 25) mean (SD) | 0.23 (11.642) | 0.42 (10.922) | -0.12 (13.068) |
| PSI change (n = 64; 42; 22) mean (SD) | -.53 (11.021) | -0.79 (10.98) | -0.05 (11.341) |
| WMI change (n = 67; 43; 24) mean (SD) | 1.87 (13.234) | 3.16 (12.96) | -0.46 (13.679) |
| **Memory composites** | | | |
| Overall memory change (n = 57; 38; 19) mean (SD) | 0.46 (14.876) | 0.95 (14.547) | -0.53 (15.872) |
| Visual immediate change (n = 61; 41; 20) mean (SD) | -1.44 (18.011) | -1.22 (17.439) | -1.9 (19.59) |
| Visual delayed change (n = 57; 38; 19) mean (SD) | -0.86 (14.419) | -2.74 (13.5) | 2.89 (15.808) |
| Verbal immediate change (n = 61; 41; 20) mean (SD) | 0.2 (16.862) | 2.2 (15.616) | -3.9 (18.926) |
| Verbal delayed change (n = 61; 41; 20) mean (SD) | 2.69 (15.27) | 3.68 (13.207) | 0.65 (19.044) |
| **Academic attainment** | | | |
| Word reading change (n = 64; 42; 22) mean (SD) | 2.81 (10.8) | 2.26 (9.713) | 3.86 (12.804) |
| Numerical operations change (n = 58; 38; 20) mean (SD) | -0.5 (12.765) | -0.05 (10.75) | -1.35 (16.207) |
| Spelling change (n = 61; 41; 20) mean (SD) | 0.26 (10.968) | -0.9 (11.382) | 2.65 (9.912) |
| Academic achievement change (n = 64; 42; 22) mean (SD) | -0.18 (8.269) | 0.00 (8.663) | -0.56 (7.617) |

**Table 4. Means and Standard Deviations for the neuropsychological test variables (pre-post differences) for the tumour, MTS and FCD groups.**

| | Tumour | MTS | FCD |
|---|---|---|---|
| IQ composites | | | |
| FSIQ change (n = 36; 28; 7) mean (SD) | 1.83 (11.106) | 0.57 (9.016) | 5.14 (7.712) |
| VCI change (n = 36; 28; 7) mean (SD) | 2.61 (8.617) | 4 (8.781) | 4.71 (5.407) |
| PRI change (n = 35; 28; 7) mean (SD) | 1.17 (11.155) | -0.79 (12.891) | -0.43 (9.761) |
| PSI change (n = 33; 26; 5) mean (SD) | -1.03 (12.1) | -0.04 (10.482) | 0.2 (7.12) |
| WMI change (n = 34; 27; 6) mean (SD) | 1.32 (13.213) | 0.37 (13.159) | 11.67 (11.396) |
| Memory composites | | | |
| Overall memory change (n = 27; 25; 5) mean (SD) | 0.37 (11.923) | 2.68 (15.429) | -10.2 (23.931) |
| Visual immediate change (n = 30; 26; 5) mean (SD) | 0.77 (15.743) | -1.73 (20.859) | -13.2 (11.819) |
| Visual delayed change (n = 27; 25; 5) mean (SD) | 0.22 (12.479) | 0.52 (14.748) | -13.6 (19.256) |
| Verbal immediate change (n = 30; 26; 5) mean (SD) | -1.57 (16.444) | 3.5 (17.249) | -6.4 (17.213) |
| Verbal delayed change (n = 30; 26; 5) mean (SD) | -1.03 (14.613) | 6.19 (13.775) | 6.8 (23.637) |
| Academic attainment | | | |
| Word reading change (n = 33; 26; 5) mean (SD) | 3.79 (10.194) | 2.27 (12.065) | -0.8 (8.349) |
| Numerical operations change (n = 29; 24; 5) mean (SD) | -0.28 (10.707) | -0.67 (15.15) | -1 (14.107) |
| Spelling change (n = 32; 25; 4) mean (SD) | 0.19 (12.827) | 1.2 (8.893) | -5 (5.354) |
| Academic achievement change (n = 33; 26; 5) mean (SD) | -0.57 (8.804) | 0.04 (8.071) | 1.25 (7.136) |

## 4.4 Research Question 2

**What are the contributions of epilepsy-related factors to memory, cognitive and academic outcomes?**

A series of one-way ANOVAs were performed to investigate the effects of lesion side and underlying pathology on test outcomes pre-operatively, post-operatively, and the difference between the two time-points. There was no reliable difference between the left and right groups on any of the variables when pre-operative scores *(Table G, Appendix D)* and change in performance over time (pre-post) (*Table 5*) were analysed. Post-operatively, there was a reliable difference between the left and right groups on *Visual Delayed Memory* performance (F (1,67) = 7.436, eta = .316, *p* = .008) *(Table H, Appendix D)*. The RTL group had poorer *Visual Delayed Memory* performance than the LTL group post-operatively.

When the pathology groups were compared on pre-post differences there was no difference between the three groups (MTS, tumour and FCD) (*Table 6)*. Pre-operatively, the pathology groups did not differ on test performance *(Table I, Appendix D)*. Post-operatively there was a difference between the three groups on measures of *Overall Memory* performance (F (2,66) = 3.585, eta = .313, *p* = .033) and *Visual Delayed Memory* performance (F (2,66) = 4.828, eta = .357, *p* = .011), *(Table J, Appendix D).* A Tukey post-hoc test for post-operative *Visual Delayed Memory* performance revealed that the MTS group differed from the tumour group (-9.311 ± 3.542, p = .028) and the FCD group (-14.397 ± 5.866, p = .044). Exploration of the group means showed that the MTS group performed worse than both the FCD and tumour groups for *Visual Delayed Memory* performance at post-operative assessment. However, there was no difference between the FCD and tumour groups (5.086 ± 5.726, p = .650). A Tukey post-hoc test for *Overall Memory* showed that the FCD group had the largest change in *Overall Memory* from pre to post-operative assessment. The tumour group showed the least change. Both the MTS and tumour groups showed a positive change, whereas the FCD group showed a decline. None of the *Overall Memory* differences were statistically significant.

**Table 5. One-way ANOVA with eta and Levene's tests on pre-post differences for the *left* versus *right* side lesion groups**

| | | One-Way ANOVA | | | | Levene's Test | | |
|---|---|---|---|---|---|---|---|---|
| | ***N*** | ***df*** | ***F*** | ***Sig.*** | ***eta*** | ***df*** | ***Statistic*** | ***Sig.*** |
| FSIQ difference | 71 | 1,69 | 0.131 | .718 | .044 | 1,69 | .420 | .519 |
| VCI difference | 71 | 1,69 | 0.681 | .412 | .099 | 1,69 | .193 | .662 |
| PRI difference | 70 | 1,68 | 0.034 | .853 | .022 | 1,68 | .209 | .649 |
| PSI difference | 64 | 1,62 | 0.064 | .801 | .032 | 1,62 | .031 | .861 |
| WMI difference | 67 | 1,65 | 1.156 | .286 | .132 | 1,65 | .038 | .846 |
| Overall Memory difference | 57 | 1,55 | 0.122 | .728 | .047 | 1,55 | 1.016 | .318 |
| Visual Immediate difference | 61 | 1,59 | 0.019 | .891 | .018 | 1,59 | 0.088 | .768 |
| Visual Delayed difference | 57 | 1,55 | 1.966 | .167 | .186 | 1,59 | 0.202 | .655 |
| Verbal Immediate difference | 61 | 1,59 | 1.779 | .187 | .171 | 1,59 | 0.510 | .478 |
| Verbal Delayed difference | 61 | 1,59 | 0.526 | .471 | .094 | 1,59 | 3.044 | .086 |
| Academic Overall difference | 55 | 1,53 | 0.054 | .818 | .032 | 1,53 | 0.120 | .740 |
| Word Reading difference | 64 | 1,62 | 0.314 | .577 | .071 | 1,62 | 2.678 | .107 |
| Numerical Operations difference | 58 | 1,56 | 0.133 | .716 | .049 | 1,56 | 6.334 | .015 |
| Spelling difference | 61 | 1,59 | 1.420 | .238 | .153 | 1,59 | 0.421 | .519 |

**Table 6. One-way ANOVA with eta and Levene's tests on pre-post differences for the *MTS, Tumour* and *FCD* groups**

| | | One-Way ANOVA | | | | Levene's Test | | |
|---|---|---|---|---|---|---|---|---|
| | ***N*** | ***df*** | ***F*** | ***Sig.*** | ***eta*** | ***df*** | ***Statistic*** | ***Sig.*** |
| FSIQ difference | 71 | 2,68 | 0.590 | .557 | .131 | 2,68 | 2.140 | .126 |
| VCI difference | 71 | 2,68 | 0.312 | .733 | .095 | 2, 68 | 0.691 | .505 |
| PRI difference | 70 | 2,67 | 0.227 | .798 | .082 | 2, 67 | 0.025 | .975 |
| PSI difference | 64 | 2,61 | 0.069 | .934 | .047 | 2, 61 | 0.840 | .437 |
| WMI difference | 67 | 2,64 | 1.896 | .158 | .056 | 2, 64 | 0.070 | .933 |
| Overall Memory difference | 57 | 2,54 | 1.596 | .212 | .236 | 2,54 | 3.631 | .033 |
| Visual Immediate difference | 61 | 2,58 | 1.308 | .278 | .208 | 2,58 | 2.368 | .103 |
| Visual Delayed difference | 57 | 2,54 | 2.237 | .117 | .277 | 2,54 | 0.891 | .416 |
| Verbal Immediate difference | 61 | 2,58 | 1.047 | .357 | .187 | 2,58 | 0.105 | .900 |
| Verbal Delayed difference | 61 | 2,58 | 1.804 | .174 | .242 | 2,58 | 1.878 | .162 |
| Academic Overall difference | 55 | 2,52 | 0.096 | .908 | .061 | 2,52 | 0.024 | .976 |
| Word Reading difference | 64 | 2,61 | 0.439 | .647 | .119 | 2,61 | 0.435 | .649 |
| Numerical Operations difference | 58 | 2,55 | 0.010 | .990 | .019 | 2,55 | 0.725 | .489 |
| Spelling difference | 61 | 2,58 | 0.544 | .583 | .136 | 2,58 | 3.051 | .055 |

In order to establish the contribution of the epilepsy-related variables to outcomes, a series of GLM analyses were performed on the data. The differences between pre-operative and post-operative performance on the domain composites were used as the criterion variables. The GLMs were undertaken with *duration of epilepsy, age of onset* and *seizure frequency* as co-variates and lesion side and pathology as fixed factors. Four models were computed in order to observe the influence of pathology and lesion side on 1) Wechsler indices (*VCI, PRI, PSI, WMI*), 2) memory (*Visual Immediate, Visual Delayed, Auditory Immediate, Auditory Delayed*), 3) academic achievement (*Word Reading, Spelling, Numerical Operations)*, and 4) full scale composites for all (*FSIQ, Overall Memory,* and *Overall Academic Achievement*).

In predicting the outcomes of interest, the models included estimates of eta-squared in order to examine the contribution of explained variance per predictor after adjustment for all others included. Eta-squared signifies the explained variance per unique co-variate (*age of onset, duration of epilepsy, and seizure frequency*) in predicting the outcome variables (change in neuropsychological test performance). The values for the overall model, intercept and errors are not reported for clarity.

### 4.4.1 Model 1: Cognition Change

A GLM containing the Wechsler indices (*VCI, PRI, PSI* and *WMI*) showed that there were no main effects or interactions observed in the data. None of the covariates uniquely predicted any of the neuropsychological outcome variables (*Table 7*).

### 4.4.2 Model 2: Memory Change

*Table 8* shows the contributions to memory domain score differences. The data showed no main effects or interactions. None of the covariates uniquely predicted any of the neuropsychological variables.

### 4.4.3 Model 3: Academic Attainment Change

*Table 9* shows the contributions to academic attainment difference scores. There was a moderate main effect of *age of onset* on *Word Reading* difference (F(1) =

5.927, eta-squared = .135, p = .020) and *Spelling* difference (F(1) = 5.937, eta-squared = .135, p = .020). Older age at onset was associated with a decrease in performance on *Word Reading* and *Spelling* from pre- to post-operative assessment. Inspection of a scatterplot suggested a negative relationship; as age of onset went up, Word Reading and Spelling scores went down.

#### 4.4.4 Model 4: Overall Scores (FSIQ, Overall Memory, Overall Academic Achievement)

*Table 10* shows the contributions to the domain composites (*FSIQ, Overall Memory* and *Overall Academic Attainment*) difference scores. There were no main effects or interactions observed in the data. None of the covariates uniquely predicted any of the neuropsychological test outcome variables.

**Table 7. GLM of between-subjects effects using lesion side (left vs. right) and aetiology (MTS vs. tumour vs. FCD) to determine the contribution of epilepsy variables to change in IQ over time.**

| Source | Dependent Variable | *Type III Sum of Squares* | *df* | *Mean Square* | *F* | *Sig.* | *Partial Eta Squared* |
|---|---|---|---|---|---|---|---|
| **Duration of Epilepsy** | VCI difference (Pre-Post) | 35.407 | 1 | 35.407 | .524 | .473 | .012 |
| | PRI difference (Pre-Post) | 235.424 | 1 | 235.424 | 1.435 | .237 | .031 |
| | PSI difference (Pre-Post) | 1.890 | 1 | 1.890 | .014 | .905 | .000 |
| | WMI difference (Pre-Post) | 73.035 | 1 | 73.035 | .406 | .527 | .009 |
| **Age of Onset** | VCI difference (Pre-Post) | 253.486 | 1 | 253.486 | 3.753 | .059 | .077 |
| | PRI difference (Pre-Post) | 27.975 | 1 | 27.975 | .170 | .682 | .004 |
| | PSI difference (Pre-Post) | 7.916 | 1 | 7.916 | .061 | .807 | .001 |
| | WMI difference (Pre-Post) | 507.372 | 1 | 507.372 | 2.823 | .100 | .059 |
| **Seizure Frequency (Pre)** | VCI difference (Pre-Post) | 196.596 | 1 | 196.596 | 2.911 | .095 | .061 |
| | PRI difference (Pre-Post) | 55.015 | 1 | 55.015 | .335 | .565 | .007 |
| | PSI difference (Pre-Post) | 298.781 | 1 | 298.781 | 2.289 | .137 | .048 |
| | WMI difference (Pre-Post) | 251.123 | 1 | 251.123 | 1.397 | .243 | .030 |
| **Lesion Side** | VCI difference (Pre-Post) | 61.004 | 1 | 61.004 | .903 | .347 | .020 |
| | PRI difference (Pre-Post) | 22.974 | 1 | 22.974 | .140 | .710 | .003 |
| | PSI difference (Pre-Post) | 18.253 | 1 | 18.253 | .140 | .710 | .003 |
| | WMI difference (Pre-Post) | 98.661 | 1 | 98.661 | .549 | .463 | .012 |
| **Pathology** | VCI difference (Pre-Post) | 84.723 | 2 | 42.362 | .627 | .539 | .027 |
| | PRI difference (Pre-Post) | 377.526 | 2 | 188.763 | 1.150 | .326 | .049 |
| | PSI difference (Pre-Post) | 179.933 | 2 | 89.967 | .689 | .507 | .030 |
| | WMI difference (Pre-Post) | 728.667 | 2 | 364.334 | 2.027 | .144 | .083 |
| **Lesion Side * Pathology** | VCI difference (Pre-Post) | 128.741 | 1 | 128.741 | 1.906 | .174 | .041 |
| | PRI difference (Pre-Post) | 24.804 | 1 | 24.804 | .151 | .699 | .003 |
| | PSI difference (Pre-Post) | 197.518 | 1 | 197.518 | 1.513 | .225 | .033 |
| | WMI difference (Pre-Post) | 105.196 | 1 | 105.196 | .585 | .448 | .013 |

**Table 8. GLM of between-subjects effects using lesion side (left vs. right) and aetiology (MTS vs. tumour vs. FCD) to determine the contribution of epilepsy variables to change in memory over time.**

| Source | Dependent Variable | *Type III Sum of Squares* | *df* | *Mean Square* | *F* | *Sig.* | *Partial Eta Squared* |
|---|---|---|---|---|---|---|---|
| **Duration of Epilepsy** | Visual Immediate difference (Pre-Post) | 240.863 | 1 | 240.863 | .707 | .406 | .018 |
| | Visual Delayed difference (Pre-Post) | 2.581 | 1 | 2.581 | .012 | .912 | .000 |
| | Verbal Immediate difference (Pre-Post) | .382 | 1 | .382 | .002 | .969 | .000 |
| | Verbal Delayed difference (Pre-Post) | 1.926 | 1 | 1.926 | .010 | .923 | .000 |
| **Age of Onset** | Visual Immediate difference (Pre-Post) | 86.127 | 1 | 86.127 | .253 | .618 | .007 |
| | Visual Delayed difference (Pre-Post) | 3.094 | 1 | 3.094 | .015 | .904 | .000 |
| | Verbal Immediate difference (Pre-Post) | 16.170 | 1 | 16.170 | .064 | .801 | .002 |
| | Verbal Delayed difference (Pre-Post) | 152.031 | 1 | 152.031 | .751 | .392 | .019 |
| **Seizure Frequency (Pre)** | Visual Immediate difference (Pre-Post) | 19.700 | 1 | 19.700 | .058 | .811 | .002 |
| | Visual Delayed difference (Pre-Post) | 8.808 | 1 | 8.808 | .042 | .839 | .001 |
| | Verbal Immediate difference (Pre-Post) | .051 | 1 | .051 | .000 | .989 | .000 |
| | Verbal Delayed difference (Pre-Post) | 240.767 | 1 | 240.767 | 1.189 | .282 | .030 |
| **Lesion Side** | Visual Immediate difference (Pre-Post) | 106.617 | 1 | 106.617 | .313 | .579 | .008 |
| | Visual Delayed difference (Pre-Post) | 380.491 | 1 | 380.491 | 1.812 | .186 | .046 |
| | Verbal Immediate difference (Pre-Post) | 423.048 | 1 | 423.048 | 1.686 | .202 | .042 |
| | Verbal Delayed difference (Pre-Post) | 1.148 | 1 | 1.148 | .006 | .940 | .000 |
| **Pathology** | Visual Immediate difference (Pre-Post) | 619.351 | 2 | 309.675 | .909 | .411 | .046 |
| | Visual Delayed difference (Pre-Post) | 99.809 | 2 | 49.905 | .238 | .790 | .012 |
| | Verbal Immediate difference (Pre-Post) | 27.905 | 2 | 13.953 | .056 | .946 | .003 |
| | Verbal Delayed difference (Pre-Post) | 805.530 | 2 | 402.765 | 1.988 | .151 | .095 |
| **Lesion Side * Pathology** | Visual Immediate difference (Pre-Post) | 272.003 | 1 | 272.003 | .799 | .377 | .021 |
| | Visual Delayed difference (Pre-Post) | 128.026 | 1 | 128.026 | .610 | .440 | .016 |
| | Verbal Immediate difference (Pre-Post) | 343.250 | 1 | 343.250 | 1.368 | .249 | .035 |
| | Verbal Delayed difference (Pre-Post) | 87.508 | 1 | 87.508 | .432 | .515 | .011 |

**Table 9. GLM of between-subjects effects using lesion side (left vs. right) and aetiology (MTS vs. tumour vs. FCD) to determine the contribution of epilepsy variables to change in academic attainment over time.**

| Source | Dependent Variable | *Type III Sum of Squares* | *df* | *Mean Square* | *F* | *Sig.* | *Partial Eta Squared* |
|---|---|---|---|---|---|---|---|
| **Duration of Epilepsy** | Word Reading difference (Pre-Post) | 83.839 | 1 | 83.839 | .758 | .390 | .020 |
| | Numerical Ops difference (Pre-Post) | 37.883 | 1 | 37.883 | .197 | .660 | .005 |
| | Spelling difference (Pre-Post) | 333.936 | 1 | 333.936 | 3.477 | .070 | .084 |
| **Age of Onset** | Word Reading difference (Pre-Post) | 655.765 | 1 | 655.765 | 5.927 | .020 | .135 |
| | Numerical Ops difference (Pre-Post) | .006 | 1 | .006 | .000 | .996 | .000 |
| | Spelling difference (Pre-Post) | 570.140 | 1 | 570.140 | 5.937 | .020 | .135 |
| **Seizure Frequency** | Word Reading difference (Pre-Post) | 65.464 | 1 | 65.464 | .592 | .447 | .015 |
| | Numerical Ops difference (Pre-Post) | 10.896 | 1 | 10.896 | .057 | .813 | .001 |
| | Spelling difference (Pre-Post) | 4.830 | 1 | 4.830 | .050 | .824 | .001 |
| **Lesion Side** | Word Reading difference (Pre-Post) | 1.625 | 1 | 1.625 | .015 | .904 | .000 |
| | Numerical Ops difference (Pre-Post) | 44.669 | 1 | 44.669 | .232 | .633 | .006 |
| | Spelling difference (Pre-Post) | 84.944 | 1 | 84.944 | .885 | .353 | .023 |
| **Pathology** | Word Reading difference (Pre-Post) | 248.577 | 2 | 124.289 | 1.123 | .336 | .056 |
| | Numerical Ops difference (Pre-Post) | 207.796 | 2 | 103.898 | .539 | .588 | .028 |
| | Spelling difference (Pre-Post) | 12.847 | 2 | 6.423 | .067 | .935 | .004 |
| **Lesion Side * Pathology** | Word Reading difference (Pre-Post) | 16.795 | 1 | 16.795 | .152 | .699 | .004 |
| | Numerical Ops difference (Pre-Post) | 88.016 | 1 | 88.016 | .457 | .503 | .012 |
| | Spelling difference (Pre-Post) | 29.747 | 1 | 29.747 | .310 | .581 | .008 |

**Table 10. GLM of between-subjects effects using lesion side (left vs. right) and aetiology (MTS vs. tumour vs. FCD) to determine the contribution of epilepsy variables to change in composite domain scores over time.**

| Source | Dependent Variable | *Type III Sum of Squares* | *df* | *Mean Square* | *F* | *Sig.* | *Partial Eta Squared* |
|---|---|---|---|---|---|---|---|
| **Duration of Epilepsy** | FSIQ Pre-post Difference | 38.763 | 1 | 38.763 | .432 | .515 | .013 |
| | Overall memory difference (Pre-Post) | 55.779 | 1 | 55.779 | .313 | .579 | .009 |
| | Overall Achievement Difference (pre-post) | 6.784 | 1 | 6.784 | .075 | .786 | .002 |
| **Age of Onset** | FSIQ Pre-post Difference | 106.119 | 1 | 106.119 | 1.183 | .285 | .035 |
| | Overall memory difference (Pre-Post) | 11.265 | 1 | 11.265 | .063 | .803 | .002 |
| | Overall Achievement Difference (pre-post) | 334.084 | 1 | 334.084 | 3.693 | .063 | .101 |
| **Seizure Frequency (Pre)** | FSIQ Pre-post Difference | 58.792 | 1 | 58.792 | .655 | .424 | .019 |
| | Overall memory difference (Pre-Post) | .299 | 1 | .299 | .002 | .968 | .000 |
| | Overall Achievement Difference (pre-post) | 5.298 | 1 | 5.298 | .059 | .810 | .002 |
| **Lesion Side** | FSIQ Pre-post Difference | 14.619 | 1 | 14.619 | .163 | .689 | .005 |
| | Overall memory difference (Pre-Post) | 15.258 | 1 | 15.258 | .086 | .772 | .003 |
| | Overall Achievement Difference (pre-post) | 25.633 | 1 | 25.633 | .283 | .598 | .009 |
| **Pathology** | FSIQ Pre-post Difference | 68.016 | 2 | 34.008 | .379 | .687 | .022 |
| | Overall memory difference (Pre-Post) | 78.092 | 2 | 39.046 | .219 | .804 | .013 |
| | Overall Achievement Difference (pre-post) | 139.993 | 2 | 69.996 | .774 | .469 | .045 |
| **Lesion Side * Pathology** | FSIQ Pre-post Difference | 134.983 | 1 | 134.983 | 1.505 | .229 | .044 |
| | Overall memory difference (Pre-Post) | 35.477 | 1 | 35.477 | .199 | .658 | .006 |
| | Overall Achievement Difference (pre-post) | 16.218 | 1 | 16.218 | .179 | .675 | .005 |

# 5. DISCUSSION

## 5.1 Chapter Overview

This section will consider the extent to which the current study was able to answer the research questions. A summary of the findings in relation to the existing literature will feature along with how this sits in relation to current theoretical understandings of the brain and neurodevelopment. Implications for practice and recommendations for professionals who work with children with TLE will be offered. Finally, the strengths and limitations of the current study will be outlined and possible directions for future research will be suggested.

The research described in this thesis arose from the existing limitations of current research into cognitive outcomes following surgery for paediatric TLE. A noteworthy limitation of the existing literature is the use of heterogeneous samples with varied aetiological and clinical diversity and small sample sizes. Consequently, the purpose of this study was to investigate the relationship between epilepsy variables and neuropsychological test performance, and to analyse their contributions to academic attainment outcomes in a larger sample of children who underwent surgical treatment for unilateral TLE. Measures of memory, cognition, and academic attainment were considered as well as epilepsy variables; *duration of epilepsy, age at onset, lesion side, seizure frequency*, and *pathology*. Accordingly, the following research questions were addressed:

1. What are the cognitive, memory, and academic outcomes for children who undergo neurosurgery for TLE?

2. What are the contributions of epilepsy-related factors to memory, cognitive and academic outcomes?

## 5.2 Summary of the Main Findings

### 5.2.1 Cognitive Outcomes Following TLR

The findings of the current study show that there were, overall, very modest improvements in test scores, but with some areas of greater change, including decline in some domains. Although there was a general trend for slight improvement, the overall picture is dominated by substantial individual variability, a feature previously noted in the literature review. This variation was evident for the entire sample, as well as within the lesion side and pathology groups. These findings are consistent with previous research. The most commonly reported finding in post-surgical paediatric epilepsy research is no significant change (approximately 70% of children, alongside decline in 10-15% and improvement in 10-15%; Moosa & Wyllie, 2017). Individual variation in this population may be one of the most consistently reported findings over the last three decades of research into cognitive outcomes (Dlugos, Moss, Duhaime, & Brooks-Kayal, 1999; Mabbott & Smith, 2003; Miranda & Smith, 2001; Sherman et al., 2011; Skirrow et al., 2019; Szabo et al., 1998). In respect of the considerable individual variation observed in the current findings, the results are broadly consistent with existing literature.

#### *5.2.1.1 Memory*

In contrast to previous research, the current study did not identify any reliable pre- to post-operative differences for the memory domains for both the LTL and RTL groups. These findings correspond to early research that has reported preserved memory functions at a similar follow-up period (Lendt et al., 1999). However the findings contrast with more recent studies which have reported that verbal memory, in particular, is vulnerable to decline following LTL surgery for epilepsy (e.g. Gleissner et al., 2002; Meekes et al., 2013; Sherman et al., 2011). It is possible that the differences are due to methodological variations (e.g. the variables included in the analyses, the measures used). It should also be noted that the relatively short follow-up period may also explain the absence of reliable difference, which will be discussed further at 5.2.3.

Consistent with previous research conducted by Law et al. (2017), a diagnosis of MTS appeared to carry a greater risk for verbal memory decline in the current study. It has been suggested that underlying pathology represents differentiated disease processes that manifest in different cognitive outcomes for the different pathology groups (Bigel & Smith, 2001). MTS is a process of hippocampal neuron atrophy associated with reduced hippocampal volume, whereas FCD and low-grade tumours are cortically based (Hsu, Stenberg, & Krings, 2020). A degree of impairment in the MTS group was, therefore, not an unexpected finding, given the role of hippocampal regions in memory functions (Lee & Lee, 2013; Leritz et al., 2006; Jambaqué et al., 2007; Skirrow et al., 2015). It is possible that the decline in verbal memory for the MTS group in the current study resulted from the primary involvement in hippocampal pathology, which was not observed in the other groups. The current study offers preliminary findings for different patterns of cognitive impairment based on underlying pathology.

The individual variation observed in the memory performance in the present study, overall, was consistent with the substantial variability in post-surgical memory performance reported by Mabbott and Smith (2003) at a similar follow-up duration to the current study. The key finding was that the children did not show uniformly poor or good performance across all tasks, instead it was noted that children did better in some tasks than others. Accordingly, this suggests post-operative memory performance is varied both within and between children following TLR. As highlighted in the literature review, the exact nature and prevalence of memory deficits are reported to be unknown for this population due to the inconsistencies in the literature (Menlove & Reilly, 2015). Therefore, while the findings from the current study suggest an overall general trend of no reliable change in memory outcomes at one-year post-surgery, the substantial individual variability indicates that a range of outcomes can be observed.

#### *5.2.1.2 Cognition*

The current study revealed that children who undergo surgery for TLE to the LTL experienced a post-operative decline in verbal intellectual functioning based on their pre-operative performance. These findings are inconsistent with previous

literature, which has often reported either no change or an improvement in verbal intellectual abilities for children who undergo neurosurgery to the LTL for TLE (Korkman et al., 2005; Miranda & Smith, 2001; Westerveld et al., 2000). Although the direction of change was dissimilar, the overall conclusions of prior research were supported by the present study; despite the overall positive change of surgery on cognition, the magnitude of change was small and the significant individual variation within the domain and composite scores of the current study should be noted. Although group analyses did not yield reliable change in the current study, findings revealed that while some children showed increase in verbal and non-verbal intellectual functioning, others showed decline. A decline from pre- to post-operative verbal intellectual functioning was also observed for the MTS group in the current study. This finding has not previously been reported in the literature. One possible explanation for this finding is that the hippocampus, implicated in MTS, is involved in semantic and declarative memory and has been found to relate to verbal intellectual functioning (Amat et al., 2008; Schumann et al., 2007).

#### *5.2.1.3 Academic Attainment*

In general, the current study showed no reliable pre-post differences in academic attainment, with the exception of a decline in one aspect of literacy for the tumour group. The latter finding is inconsistent with research that has reported no significant declines in academic abilities for children with low-grade tumours one-year after surgery (García-Fernández et al., 2011). Overall, the current findings are consistent with previous research that has identified no change over time in academic attainment, such as that by Lah and Smith (2015) who found that Reading Comprehension and Spelling remained stable one year after TLR for epilepsy in children. In addition, the current findings substantiate existing research that has demonstrated significant individual variation in academic attainment (Puka et al., 2015).

### 5.2.2 The Contributions of Epilepsy-Related Factors to Post-Surgical Cognitive Outcomes.

#### *5.2.2.1 Memory*

In examining the change in memory performance, right-sided TLR was associated with poorer *Visual Delayed Memory* post-operatively, compared to the left TLR group. The current study is consistent with research that has compared children with left and right TLE and found poorer visuo-spatial memory performance for those where the right hemisphere of the brain is implicated (Jambaqué et al., 2007). Although no significant differences in change in performance over time were observed within the left and right groups in the current study, the reliable difference between the groups on post-operative *Visual Delayed Memory* could suggest the early emergence of a lateralised pattern of memory impairment. However, it is important to note that the extant literature on the presence of laterality effects in children is inconsistent.

In the current study, MTS was associated with poorer *Overall Memory* and *Visual Delayed Memory* post-operatively, when compared to the other pathology groups. As previously noted, different underlying pathologies represent different disease processes and the primary involvement of the hippocampus in MTS may explain poorer memory performance, as suggested in the current findings. Research into adult patients has indicated a differential cognitive profile based on underlying aetiology (Engel, 2001), suggesting that underlying pathology may influence outcomes. Underlying pathology has implications for neurodevelopmental trajectory and can influence neuropsychological functioning at both pre- and post-operative assessments and cognitive outcomes following surgery (Kim & Ko, 2016), however there is significantly less research identifying such differences in children. The current findings could imply that children with MTS show a different pattern of cognitive deficits to those with pathologies that are more cortical in nature.

#### *5.2.2.2 Cognition*

In examining change in general cognition, it is notable that the children did not display a lateralised pattern of cognitive impairment on verbal and non-verbal

functioning. These findings were expected given the abundance of research that has indicated a low prevalence of adverse effects of surgery on general intellectual functioning (Sherman et al., 2003) and absence of lateralisation effects (Westerveld, 2010). The current results are consistent with most previous studies that have examined post-operative cognitive outcomes following TL surgery in children (e.g. Miranda & Smith, 2001). The results of the current study accompany existing findings concluded by Miranda and Smith (2001) that indicate intelligence tests are not a reliable tool to assess differential engagement or lateralisation in dysfunction of the left and right hemispheres in children with TLE.

#### *5.2.2.3 Academic Attainment*

As noted in the literature review, many studies have related epilepsy variables to cognitive outcomes. Research into academic difficulties in children with epilepsy has suggested that age at seizure onset may contribute to specific cognitive deficits, independent of global cognitive impairment (e.g. Reilly et al., 2014). Consistent with existing research in which age of onset emerges as a factor that influences post-surgical outcomes, older age of onset in the current study was associated with a decrease in performance on *Word Reading* and *Spelling* from pre- to post-operative assessment. However, research has consistently reported an alternative relationship; earlier seizure onset has been related to poorer cognitive outcomes, including higher rates of learning difficulties (Beghi et al., 2006; Cormack et al., 2007; Mabbott & Smith, 2003; Menlove & Reilly, 2015). Neuroplasticity theories have provided explanation for this finding; early seizure onset disrupts typical neurodevelopment (Holmes, 2016), which reflects reorganisation of structural and functional connectivity among neural networks (Doucet et al., 2015; Sebastianelli et al., 2017). However, the current study could imply that there is greater 'laying down' of cognitive functions as neurodevelopment unfolds. The immature brain may, therefore, have greater capacity for the uptake of function in the unaffected regions, which decreases as the brain develops. Furthermore, other research has suggested no influence of age of onset to academic outcomes (e.g. Lah & Smith, 2015). Taken together,

the relationship between age of onset and cognitive outcomes may reflect a complex interplay of inter-related seizure variables.

### 5.2.3 Theoretical Context

Theoretically, the conservative findings observed in the current study may be explained by the protracted trajectory of early insult to the immature brain. As in acquired brain impairment more generally, early post-injury assessment may show few problems, but the full impact on cognition may not be apparent until many years later (Anderson et al., 2011). Skirrow et al. (2011) suggest that in order to see an improvement in cognition, a follow-up period greater than six years post-surgery is required. Similar findings were reported by Puka et al. (2017) where the authors concluded that time was a critical factor for improvements in IQ scores. Furthermore, Dodrill (2004) proposed that in order to adequately assess the impact of seizures, children should be followed up for a period of at least 25 years. Studies that have a short duration following surgery are unlikely to demonstrate such improvements. This may explain the absence of significant change in the current research.

If the case regarding the necessity of a reliable post-operative follow-up time period stands true, then research that reports findings after a shorter follow-up duration, such as in the present study, should be cautious with regards to any hypotheses that can be drawn (Skirrow et al., 2011). It is widely accepted that the human brain follows a protracted course of development, which begins approximately two weeks after conception and reaches maturity in the third decade of life (Bick & Nelson, 2016). Normative patterns of neurodevelopment can be compromised following TLE surgery and the cognitive trajectory may look very different for this population as they enter early adulthood and reach neurodevelopmental maturity. As with much of the research into the effects of surgery for TLE in the paediatric population to date, this study captured only an early snapshot of the child's post-surgical trajectory. The individual variation in the current findings may reflect only the beginning of the children's post-surgical recovery trajectory, which could look vastly different at long-term follow-up.

A wide range of developmental stages were included in the sample in the current study, with respect to age at onset and age at surgery. There emerged great variability within the sample for almost all the neuropsychological domain, composite and change scores, which may be explained by the impact of epilepsy onset and surgical intervention occurring at potentially different developmental stages. Variation in post-operative cognitive trajectories may be explained by the developmental stage of particular abilities at the time of surgery (e.g. language skills already established at time of injury have been associated with better recovery of those skills; Dennis et al., 2014). While some children will show early decline and may later improve, others may 'grow into' cognitive deficits. Other children may show early improvement in cognitive functioning, followed by a plateau with an increasing gap observed between the child and their peers, and some children may show improvement over time (see Skirrow et al., 2015). Early critical periods of development set the foundation for later development of higher-order skills; therefore, neural insult during critical periods of neurodevelopment can result in more pronounced neuropsychological deficits later in life (Cormack et al., 2007; Knudsen, 2004).

In the current study, older age of onset was associated with poorer performance in some areas of academic attainment offering potential evidence for greater plasticity at an earlier age. Age of onset has been contentious, with mixed reports of its influence overall. For focal lesions, early onset has been associated with good prognosis due to greater distribution of function in the immature brain, allowing for restitution of impaired functions (Helmstaedter & Kockelmann, 2006). On the other hand, researchers have warned that the immaturity of the paediatric brain should not be seen as a protective factor against damage as injury to the developing brain may disrupt skills in the process of acquirement and those yet to be acquired (Gil, 2003). Overall, it has been concluded that there is no general advantage to the onset of insult to the brain at either young or old age, as at every age the risk of cognitive impairment is mitigated by plasticity and intelligence reserves (Dennis, Spiegler & Hetherington, 2000).

To conclude, group level analysis suggests the risk of overall developmental arrest or cognitive decline following epilepsy surgery for TLE is moot when

assessed at one-year post-operatively. However, group analysis does not adequately capture the individual variation in outcomes and so conclusions of the risk factors for cognitive and academic morbidity should be tentative. The inherent, heterogeneity within the paediatric TLE population is an important consideration in paediatric TLE research. Furthermore, given the protracted course of neurodevelopment in children, this study offers only a snapshot of the post-operative cognitive outcomes.

## 5.3 Implications

### 5.3.1 Clinical Implications

The application of the current findings to clinical practice should be tentative, not only due to the large individual variation in outcomes, but also in the context of a largely inconsistent evidence base. Consistent with the majority of the literature that has reported mean differences based on group data, it is difficult to translate the current findings into clinically reliable estimates of the benefits and risks of undergoing TLE surgery in childhood for children and families faced with the decision of whether or not to proceed with surgical intervention: the group-level analyses conceal individual cognitive outcomes by combining patients who improve, decline and show no change following surgery (Sherman et al., 2011). Although the dilemma exists in extracting the results from group analysis to provide individualised, clinically meaningful advice on surgical risk of cognitive morbidity, the likelihood of seizure freedom is more positive and predictable (Ormond et al., 2019; Widjaja et al., 2020). For some patients, seizure freedom may be favourable despite a risk to cognitive function (Loring, Meador, Lee, & Smith, 2004).

The results from the current study are not unexpected given the empirical and theoretical evidence that suggests the effects of childhood brain surgery or insult show a protracted course (Anderson et al., 2011; Dennis et al., 2014; Skirrow et al., 2011). Currently, routine 12-month follow-up appointments for neuropsychological assessment are the norm in clinical practice for children following TLR (NHS England, 2018). However, the current evidence suggests

that a longer follow-up period is necessary in order to observe the full effects of epilepsy and surgical intervention. Extended follow-ups would serve to advance clinical practice by enhancing the understanding of individual neurodevelopmental trajectories. Consequently, neuropsychological rehabilitation strategies could then be tailored to an individual child's needs. Relatedly, children who experience specific learning difficulties alongside overall average cognitive functions may require alternative teaching strategies that are moderated to meet their educational needs. For clinical neuropsychologists working with this population, it would be important for a child's cognitive difficulties to be identified and documented in educational needs statements. The necessity for ongoing consultation to education providers in order to support and enhance children's learning following TL surgery for epilepsy may also be indicated.

### 5.3.2 Research Implications

The interplay between science and knowledge sets the foundations for optimal clinical practice within a healthcare system (Green & Johnson, 2015). There is a rich history of epilepsy's contribution to knowledge of the relationships between the brain and behaviour (Loring, 2010; Westerveld et al., 2000). It is essential that clinical practice and research continue to share a bi-directional relationship in paediatric epilepsy. The current findings provide some early support for researchers interested in exploring the combination of factors which interact to influence cognitive outcomes after paediatric surgery for TLE. As noted by Cabeza and Nyberg (2000), given the considerable variability that is characteristic of this population, there is much to be learned from focusing on the variability in findings rather than the inconsistency.

While paediatric studies of epilepsy have drawn on the structure-function mapping, typically used in adult studies, the current study reveals that children with TLE may have variable patterns of cognitive morbidities. This suggests the presence of distributed neural networks which subserve cognitive development. Research that focusses on structure-function relationships does not provide information about the functional relations between regions (Cabeza & Nyberg, 2000) and will limit accurate attribution and contribution of cortical circuits to multiple cognitive domains (Anderson, 2010). Furthermore, domain-specific

research limits the widespread acceptability of theoretical positions that underpin circuit-based understandings of neural-overlap in the brain. Test specificity and sensitivity is, therefore, essential for drawing conclusions about impacted cognitive functions. For example, traditional IQ tests may not map on to a child's day-to-day function or pedagogical environment (Moosa & Wyllie, 2017; Szulevicz & Tanggaard, 2017). They also measure a range of 'abilities' that do not rely solely on one cognitive function and may draw on various structural and functional brain regions.

## 5.4 Strengths and Limitations

### 5.4.1 Sample Size and Characteristics

Although small, the sample size was comparable to, or exceeded, those typically reported in the literature on paediatric TLE. In addition, previous literature on children with focal epilepsy has grouped together participants who have varied pathology and lobar regions of onset. The inherent heterogeneity of this population is acknowledged, although there is rather less variability in the current study given that it was based solely on children whose seizures emanated from a single TL.

It should be acknowledged that the number of participants relative to the number of variables included in the study limited the statistical power that could be attributed to the results and may have impacted the ability of the analysis to detect reliable effect sizes. In order to examine the potential confounding effects of inter-related epilepsy variables, a larger sample of participants with equal sub-groups representing lesion side and underlying pathology is required.

### 5.4.2 Cross-Sectional Design

A further methodological limitation lies in the cross-sectional nature of the design which limits the applicability of findings from the current study. The assessment of outcomes at a single time point limits the interpretation of any cognitive deficits as potentially emerging and declining, delayed with likelihood for improvement, or a representation of permanent and static deficits (Anderson et al., 2011). The

current findings represents a single point on the child's developmental curve, which will not reliably indicate the cognitive outcome, or the pattern and direction of a child's developmental trajectory (Dennis et al., 2014). Given the multiple, interacting factors that contribute to cognitive outcomes following TL surgery, a cross-sectional design makes it difficult to clarify the contribution of each of the factors on outcomes (Moosa & Wyllie, 2017).

### 5.4.3 Follow-up Duration

In the evaluation of the cognitive effects of paediatric neurosurgery for TLE, the full extent of cognitive outcomes following epilepsy surgery may not be manifest for several years (Hermann et al., 2010; Moosa & Wyllie, 2017). Research into the long-term (>5 years) cognitive outcomes following childhood TLE surgery is scarce (Spencer & Huh, 2008), although the few existing studies have demonstrated improved post-surgical intellectual outcomes at longer follow-up periods, suggesting that studies with shorter follow-up durations are less likely to reveal improvements (Puka et al., 2017; Skirrow et al., 2011). Unfortunately, the current study was unable to address this problem as the data were taken from routine clinical practice whereby the children are followed up at one time point, one-year post-operatively. Post-operative cognitive trajectories are said to proceed at a stable rate in most children (Freitag & Tuxhorn, 2005); therefore, the findings from the current study that showed no reliable change in most areas of assessment over time may not be an accurate reflection of the full extent of the outcomes following surgery. It may be speculated that the lack of significant change observed in the current study may be due to the follow-up period that was too short to allow for functional reorganisation to take place.

### 5.4.4 Neuropsychological Assessment

This retrospective study spans 20 years of data collected as part of clinical evaluation for surgical candidacy, thus the instruments used, and their contents, have changed over time. In the current study, different versions of tests were used to assess the same construct, of which operationalisations have changed over time (e.g. development of the Wechsler intelligence scales from measurement of only verbal and performance indices, to the inclusion of processing speed and working memory indices). Furthermore, consideration of

the ability of a neuropsychological assessment to produce reliably differentiated cognitive profiles based upon the current conceptualisations of domain-based measures of impairment is warranted. The current study assumes that the tests administered access constructs that are somehow differentiated from one another. However, evidence suggestive of widespread dysfunction as a result of focal brain damage provides rationale for an assessment based on distributed networks (Anderson, 2010). Patients are supposedly best categorised according to affected networks rather than affected regions, due to the evidenced remote effects on network function, and complex interaction between the structural and functional cortical networks (Carter, Shulman, & Corbetta, 2012). It has also been suggested that even when seizures remain focal, widespread network disruption can be observed (Liou et al., 2020).

### 5.4.5 Exclusion of important variables

Although the study is limited to the data available, there are of course many variables (not included here) that have been found to be of relevance to an individual's post-surgical cognitive outcomes. Clinically, family and psychosocial variables, such as attitudes towards epilepsy, family stressors, mood, access to resources, social context, and coping and adjustment to the condition have been related to child outcomes (Anderson et al., 2019; Austin & Caplan, 2007; Gonzalez & Wrennall, 2019; Wilson et al., 2015). In addition, the experiences and attitudes of family members, school teachers, and peers will have a great influence on how a child copes with the syndrome (Abulhamail et al., 2014; Ziegler et al., 2000). This highlights the importance of the role for coherent and cohesive support from professionals, families, and schools, thus providing tailored and focussed support for the development of cognitive and academic outcomes, for affected children (England et al., 2012). An awareness of possible psychosocial problems can aid clinicians in the identification of risk factors for poorer cognitive outcomes and guide targeted and appropriate individual support.

Further, as highlighted in a recent Cochrane Review (West et al., 2019), neurobiological data including the type of excision, size and precise location of lesions, and amount of residual brain tissue are suggested to influence cognitive

outcomes. In addition, almost all the children in the current study were taking AEDs at the pre-operative assessment, and some continued to take AEDs at the post-operative assessment. This was not accounted for in the analyses. Importantly, it is known that AEDs have a heterogeneous effect on individuals and can alter cognition (Witt & Helmstaedter, 2017). It was therefore difficult to eliminate the effects of medication and other clinical variables on performance.

## 5.5 Directions for Future Research

At present, advances in paediatric epilepsy that drive the development of new knowledge about pathophysiology, aetiology and management continue to require large-scale collaboration in order to capture meaningful data, as noted by Perucca and O'Brie (2015). Due to the heterogeneous nature of this population, large, prospective, multi-site and inter-professional research that covers medical imaging, pathology, and neuropsychological findings would be beneficial. Multi-site study requires careful planning in order to ensure that the avoidable limitations of previous research can be overcome. The literature would benefit from a core battery of tests for more robust conclusions to be drawn and to take advantage of international collaborations and the use of large data (Hermann et al., 2017). A recent study indicated that 186 different tests are used for the assessment of surgical candidates across epilepsy centres in Europe (Vogt et al., 2017), although efforts are being made in order to formalise recommendations for clinicians working around the world in epilepsy services (Wilson et al., 2015). In addition, a longitudinal model that incorporates multiple variables to identify risk factors for cognitive morbidity in children with TLE would help to identify those who are most vulnerable and who would benefit from intervention. This may also improve insight into neurodevelopmental trajectories following surgery and facilitate exploration into the individual differences and sample variation. This may also go some way to advancing not only the clinical care for this population, but also in advancing the knowledge base from which further research can be conducted.

However, while longitudinal assessment of outcomes may be theoretically desirable (as this provides information about the neurodevelopmental trajectories; Karmiloff-Smith, 2010), longitudinal research is very difficult to undertake. In light of the substantial individual variation observed in the current data and in previous research, the field would benefit from adoption of single case study designs in order to highlight, reflect and preserve the individual variability of outcomes following surgical intervention. It would be important for authors to report patient

characteristics in sufficient detail in order to allow readers to determine the likely cognitive outcomes for patients on an individual basis (Romeiser, Slaughter & Hickman, 2017). In addition, primary differences in patient characteristics may represent useful predictors for who is likely to benefit from surgical intervention, and of what kind. Case-series analysis designs will allow clinicians in practice to see how individual features will matter for outcomes.

The investigation of children with an equitable sample who have a diagnosis of FCD (which represented a relatively small proportion of the total sample in the current study) will be important in order to elucidate pathology differences, which are thought to be a primary determinant of post-surgical cognitive outcomes (Westerveld, 2010). The possibility of different patterns of cognitive strengths and weaknesses is of interest to researchers and clinicians. In addition, with the recruitment of an overall larger sample, further research could build on these preliminary findings on risk factors driving individual variation.

In the absence of large-scale, multi-site research, it would be beneficial to this population to see advances in the field of neurorehabilitation. Variables that influence and optimise a child's trajectory after surgery warrant further attention. As highlighted by Hermann and Seidenberg (2007), the literature is saturated with studies that focus on the description and characterization of the epilepsies, while research into the treatment and remediation of epilepsy or associated cognitive deficits following surgery has been largely omitted.

The utility of just one post-operative, neuropsychological follow-up assessment, at a given time, provides limited insight in to how an individual child will be affected by surgery. Reflections on clinical observations when working with children following TLR for epilepsy has highlighted the multiple demands this group of children face; the mastery of normative psychosocial developmental tasks alongside increasing academic demands. Disruption to psychosocial development often goes unrecognised from a broader lifespan perspective and should be met with assessment across the lifespan, offering a practical framework for the development and targeting appropriate support (Wilson et al., 2012). Greater integration of the ongoing, variable and changing cognitive,

psychological and social needs is required and illustrate the necessity for consultation by clinical neuropsychologists to families and schools for children following surgery for TLE.

## 5.6 Conclusions

The current findings offer some confirmatory evidence for the effects of lesion side and preliminary findings suggestive of differentiated cognitive outcomes based on underlying pathology. Cognitive outcomes and the factors which contribute to academic attainment outcomes remain somewhat elusive in paediatric TLE research. In conclusion, epilepsy and its effects during child development may increase vulnerability to a range of cognitive deficits resulting in variable prognoses following surgery. Each child may have their own post-surgical cognitive journey and the current study highlights the need to attend to individual variation when conducting group-based research with this group of children.

## REFERENCES


Aaberg, K. M., Gunnes, N., Bakken, I. J., Soraas, C. L., Berntsen, A., Magnus, P., … Suren, P. (2017). Incidence and prevalence of childhood epilepsy: A nationwide cohort study. *Pediatrics*, *139*(5). https://doi.org/10.1542/peds.2016-3908

Abulhamail, A. S., Al-Sulami, F. E., Alnouri, M. A., Mahrous, N. M., Joharji, D. G., Albogami, M. M., & Jan, M. M. (2014). Primary school teacher's knowledge and attitudes toward children with epilepsy. *Seizure*, *23*(4), 280-283.

Akman, C. I., Montenegro, M. A., Jacob, S., Eck, K., Chiriboga, C., & Gilliam, F. (2009). Seizure frequency in children with epilepsy: Factors influencing accuracy and parental awareness. *Seizure*, *18*(7), 524–529. https://doi.org/10.1016/j.seizure.2009.05.009

Al-Otaibi, F., Baeesa, S. S., Parrent, A. G., Girvin, J. P., & Steven, D. (2012). Surgical Techniques for the Treatment of Temporal Lobe Epilepsy. *Epilepsy Research and Treatment*, *2012*, 1–13. https://doi.org/10.1155/2012/374848

Aldenkamp, A.P., Overweg-Plandsoen, W. C. G., & Arends, J. (1999). An open, nonrandomized clinical comparative study evaluating the effect of epilepsy on learning. *Journal of Child Neurology*, *14*(12), 795–800. https://doi.org/10.1177/088307389901401205

Aldenkamp, A. P. (2006). Cognitive impairment in epilepsy: State of affairs and clinical relevance. *Seizure*, *15*(4), 219–220. https://doi.org/10.1016/j.seizure.2006.02.010

Aldenkamp, A. P., Weber, B., Overweg-Plandsoen, W. C. G., Reijs, R., & van Mil, S. (2005). Educational underachievement in children with epilepsy: A model to predict the effects of epilepsy on educational achievement. *Journal of Child Neurology*, *20*(3), 175–180. https://doi.org/10.1177/08830738050200030101

Alexiades, N. G., & McKhann, G. M. (2018). Seizing the moment: A randomized trial of surgery for drug-resistant pediatric epilepsy. *Clinical Neurosurgery*,

*82*(3), N31–N32. https://doi.org/10.1093/neuros/nyx600

Alloway, T. P., & Alloway, R. G. (2010). Investigating the predictive roles of working memory and IQ in academic attainment. *Journal of Experimental Child Psychology*, *106*(1), 20–29. https://doi.org/10.1016/j.jecp.2009.11.003

Amat, J. A., Bansal, R., Whiteman, R., Haggerty, R., Royal, J., & Peterson, B. S. (2008). Correlates of intellectual ability with morphology of the hippocampus and amygdala in healthy adults. *Brain Cognition*, *66*(2), 105–114. https://doi.org/10.1038/jid.2014.371

Andersen, S. L. (2003). Trajectories of brain development: Point of vulnerability or window of opportunity? *Neuroscience and Biobehavioral Reviews*, *27*(1–2), 3–18. https://doi.org/10.1016/S0149-7634(03)00005-8

Anderson, M. L. (2010). Neural reuse: A fundamental organizational principle of the brain. *Behavioral and Brain Sciences*, *33*(4), 245–266. https://doi.org/10.1017/S0140525X10000853

Anderson, V., Northam, E., & Wrennall, J. (2019). *Developmental Neuropsychology A Clinical Approach* (Second edi). Oxon: Routledge.

Anderson, V., Catroppa, C., Morse, S., Haritou, F., & Rosenfeld, J. (2005). Functional plasticity or vulnerability after early brain injury? *Pediatrics*, *116*(6), 1374–1382. https://doi.org/10.1542/peds.2004-1728

Anderson, V., Spencer-Smith, M., & Wood, A. (2011). Do children really recover better? Neurobehavioural plasticity after early brain insult. *Brain*, *134*(8), 2197–2221. https://doi.org/10.1093/brain/awr103

Anderson, W. S., & Brandt, J. (2014). The role of neuropsychological evaluation in epilepsy surgery candidates. *Neurosurgery Quarterly*, *24*(4), 301–305. https://doi.org/10.1097/wnq.0000000000000124

Austin, J. K., & Caplan, R. (2007). Behavioral and psychiatric comorbidities in pediatric epilepsy: Toward an integrative model. *Epilepsia*, *48*(9), 1639–1651. https://doi.org/10.1111/j.1528-1167.2007.01154.x

Austin, J. K., Huberty, T. J., Huster, G. A., & Dunn, D. W. (1999). Does academic

achievement in children with epilepsy change over time? *Developmental Medicine and Child Neurology*, *41*(7), 473–479. https://doi.org/10.1017/S0012162299001024

Baca, C. B., Vickrey, B. G., Caplan, R., Vassar, S. D., & Berg, A. T. (2011). Psychiatric and medical comorbidity and quality of life outcomes in childhood-onset epilepsy. *Pediatrics*, *128*(6). https://doi.org/10.1542/peds.2011-0245

Bailet, L. L., & Turk, W. R. (2000). The impact of childhood epilepsy on neurocognitive and behavioral performance: A prospective longitudinal study. *Epilepsia*, *41*(4), 426–431. https://doi.org/10.1111/j.1528-1157.2000.tb00184.x

Barba, C., Rheims, S., Minotti, L., Guénot, M., Hoffmann, D., Chabardès, S., … Ryvlin, P. (2016). Reply: Temporal plus epilepsy is a major determinant of temporal lobe surgery failures. *Brain*, *139*(7), e36. https://doi.org/10.1093/brain/aww047

Bartolini, L., Whitehead, M. T., Ho, C. Y., Sepeta, L. N., Oluigbo, C. O., Havens, K., … Gaillard, W. D. (2017). Temporal lobe epilepsy and focal cortical dysplasia in children: A tip to find the abnormality. *Epilepsia*, *58*(1), 113–122. https://doi.org/10.1111/epi.13615

Baxendale, S., Thompson, P., & Duncan, J. (2008). The role of the Wada test in the surgical treatment of temporal lobe epilepsy: an international survey. *Epilepsia*, *49*(4), 715–720.

Baxendale, S., Donnachie, E., Thompson, P., & Sander, J. W. (2013). Dysembryoplastic neuroepithelial tumors: A model for examining the effects of pathology versus seizures on cognitive dysfunction in epilepsy. *Epilepsia*, *54*(12), 2214–2218. https://doi.org/10.1111/epi.12425

Baxendale, S., Heaney, D., Thompson, P. J., & Duncan, J. S. (2010). Cognitive consequences of childhood-onset temporal lobe epilepsy across the adult lifespan. *Neurology*, *75*(8), 705–711. https://doi.org/10.1212/WNL.0b013e3181eee3f0

Beghi, E., Giussani, G., Abd-Allah, F., Abdela, J., Abdelalim, A., Abraha, H. N., … Murray, C. J. L. (2019). Global, regional, and national burden of epilepsy, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet Neurology*, *18*(4), 357–375. https://doi.org/10.1016/S1474-4422(18)30454-X

Beghi, M., Cornaggia, C. M., Frigeni, B., & Beghi, E. (2006). Learning disorders in epilepsy. *Epilepsia*, *47*(SUPPL. 2), 14–18. https://doi.org/10.1111/j.1528-1167.2006.00681.x

Bell, B. D., Seidenberg, M., Hermann, B. P., & Douville, K. (2003). Visual and auditory naming in patients with left or bilateral temporal lobe epilepsy. *Epilepsy Research*, *55*(1–2), 29–37. https://doi.org/10.1016/S0920-1211(03)00110-4

Berg, A. T. (2011). Epilepsy, cognition, and behavior: The clinical picture. *Epilepsia*, *52*(SUPPL. 1), 7–12. https://doi.org/10.1111/j.1528-1167.2010.02905.x

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. https://doi.org/10.1111/j.1528-1167.2007.01461.x

Berg, A. T., Smith, S. N., Frobish, D., Levy, S. R., Testa, F. M., Beckerman, B., & Shinnar, S. (2005). Special education needs of children with newly diagnosed epilepsy. *Developmental Medicine and Child Neurology*, *47*(11), 749–753. https://doi.org/10.1017/S001216220500157X

Berg, A. T., Zelko, F. A., Levy, S. R., & Testa, F. M. (2012). Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes: A prospective cohort study. *Neurology*, *79*(13), 1384–1391. https://doi.org/10.1212/WNL.0b013e31826c1b55

Berto, P. (2002). Quality of life in patients with epilepsy and impact of treatment. *Pharmacoeconomics*, *20*(15), 1039–1059. https://doi.org/10.17352/jnnsd.0000024

Bick, J., & Nelson, C. A. (2016). Early adverse experiences and the developing brain. *Neuropsychopharmacology*, *41*(1), 177–196. https://doi.org/10.1038/npp.2015.252

Bigel, M. G., & Smith, M. Lou. (2001). Single and Dual Pathologies of the Temporal Lobe: Effects on Cognitive Function in Children with Epilepsy. *Epilepsy and Behavior*, *2*(1), 37–45. https://doi.org/10.1006/ebeh.2000.0146

Bjellvi, J., Olsson, I., Malmgren, K., & Wilbe Ramsay, K. (2019). Epilepsy duration and seizure outcome in epilepsy surgery: A systematic review and meta-Analysis. *Neurology*, *93*(2), E159–E166. https://doi.org/10.1212/WNL.0000000000007753

Blümcke, I., Aronica, E., Miyata, H., Sarnat, H. B., Thom, M., Roessler, K., … Spreafico, R. (2016). International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia*, *57*(3), 348–358. https://doi.org/10.1111/epi.13319

Boscariol, M., Casali, R. L., Amaral, M. I. R., Lunardi, L. L., Matas, C. G., Collela-Santos, M. F., & Guerreiro, M. M. (2015). Language and central temporal auditory processing in childhood epilepsies. *Epilepsy and Behavior*, *53*, 180–183. https://doi.org/10.1016/j.yebeh.2015.10.015

Boshuisen, K., Lamberink, H. J., van Schooneveld, M. M. J., Cross, J. H., Arzimanoglou, A., van der Tweel, I., … Braun, K. P. J. (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), 1–9. https://doi.org/10.1186/s13063-015-0989-2

Bourgeois, B. F. D. (2002). Differential cognitive effects of antiepileptic drugs. *Journal of Child Neurology*, *17*(SUPPL. 2), 28–33. https://doi.org/10.1177/08830738020170020901

Braun, K. P. J., & Cross, J. H. (2018). Pediatric epilepsy surgery: the earlier the better. *Expert Review of Neurotherapeutics*, *18*(4), 261–263.

https://doi.org/10.1080/14737175.2018.1455503

Breier, J. I., Fletcher, J. M., Wheless, J. W., Clark, A., Cass, J., & Constantinou, J. E. C. (2000). Profiles of cognitive performance associated with reading disability in temporal lobe epilepsy. *Journal of Clinical and Experimental Neuropsychology*, *22*(6), 804–816. https://doi.org/10.1076/jcen.22.6.804.948

Brodie, M. J., Barry, S. J. E., Bamagous, G. A., Norrie, J. D., & Kwan, P. (2012). Patterns of treatment response in newly diagnosed epilepsy. *Neurology*, *78*(20), 1548–1554. https://doi.org/10.1212/WNL.0b013e3182563b19

Butterbaugh, G., Olejniczak, P., Roques, B., Costa, R., Rose, M., Fisch, B., … Skinner, J. (2004). Lateralization of temporal lobe epilepsy and learning disabilities, as defined by disability-related civil rights law. *Epilepsia*, *45*(8), 963–970. https://doi.org/10.1111/j.0013-9580.2004.29803.x

Cabeza, R., & Nyberg, L. (2000). Imaging cognition II: An empirical review of 275 PET and fMRI studies. *Journal of Cognitive Neuroscience*, *12*(1), 1–47. https://doi.org/10.1162/08989290051137585

Camfield, P., & Camfield, C. (2015). Incidence, prevalence and aetiology of seizures and epilepsy in children. *Epileptic Disorders*, *17*(2), 117–123. https://doi.org/10.1684/epd.2015.0736

Campiglia, M., Seegmuller, C., Le Gall, D., Fournet, N., Roulin, J. L., & Roy, A. (2014). Assessment of everyday executive functioning in children with frontal or temporal epilepsies. *Epilepsy and Behavior*, *39*, 12–20. https://doi.org/10.1016/j.yebeh.2014.07.023

Carter, A. R., Shulman, G. L., & Corbetta, M. (2012). Why use a connectivity-based approach to study stroke and recovery of function? *Computer*, *62*(4), 2271–2280. https://doi.org/10.1038/jid.2014.371

Chaix, Y., Laguitton, V., Lauwers-Cancès, V., Daquin, G., Cancès, C., Démonet, J. F., & Villeneuve, N. (2006). Reading abilities and cognitive functions of children with epilepsy: Influence of epileptic syndrome. *Brain and Development*, *28*(2), 122–130. https://doi.org/10.1016/j.braindev.2005.06.004

Chelune, G. J. (1995). Hippocampal adequacy versus functional reserve: Predicting memory functions following temporal lobectomy. *Archives of Clinical Neuropsychology*, *10*(5), 413–432. https://doi.org/10.1016/0887-6177(95)00015-V

Chen, H. H., Chen, C., Hung, S. C., Liang, S. Y., Lin, S. C., Hsu, T. R., … Shih, Y. H. (2014). Cognitive and epilepsy outcomes after epilepsy surgery caused by focal cortical dysplasia in children: early intervention maybe better. *Child's Nervous System*, *30*(11), 1885–1895. https://doi.org/10.1007/s00381-014-2463-y

Cohen, M. J. (1997). *Children's Memory Scale*. San Antonio, TX: The Psychological Corporation.

Cohen, L., Manion, L., & Morrison, K. (2007). *Research Methods in Education*. London: Routledge.

Cormack, F., Cross, J. H., Isaacs, E., Harkness, W., Wright, I., Vargha-Khadem, F., & Baldeweg, T. (2007). The development of intellectual abilities in pediatric temporal lobe epilepsy. *Epilepsia*, *48*(1), 201–204. https://doi.org/10.1111/j.1528-1167.2006.00904.x

Cormack, F., Vargha-Khadem, F., Wood, S. J., Cross, J. H., & Baldeweg, T. (2012). Memory in paediatric temporal lobe epilepsy: Effects of lesion type and side. *Epilepsy Research*, *98*(2–3), 255–259. https://doi.org/10.1016/j.eplepsyres.2011.09.004

Coulter, E. M., & Goldberg, D. A. (2013). Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction. *Nat Rev Neurosci.*, *14*(5), 337–349. https://doi.org/10.1038/nrn3482

Cross, J. H., Jayakar, P., Nordli, D., Delalande, O., Duchowny, M., Wieser, H. G., … Mathern, G. W. (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. https://doi.org/10.1111/j.1528-1167.2006.00569.x

Darwin, C. (1862). *On the various contrivances by which British and foreign*

*orchids are fertilised by insects*. London: John Murray.

Datta, K., & Wong, P. K. H. (2017). Predictors of IQ after Pediatric Epilepsy Surgery. *Scientific Times Journal of Paediatrics*, *2*(1).

de la Miyar, C. G. A., & Moes, E. J. (2014). Perspectivas epistemológicas no estudo científico e a avaliação clínica das funções executivas. *Acta Colombiana de Psicologia*, *17*(2), 69–79. https://doi.org/10.14718/ACP.2014.17.2.8

Dennis, M., Spiegler, B. J., Simic, N., Sinopoli, K. J., Wilkinson, A., Yeates, K. O., … Fletcher, J. M. (2014). Functional Plasticity in Childhood Brain Disorders: When, What, How, and Whom to Assess. *Neuropsychol Rev*, *24*(4), 389–408. https://doi.org/10.1038/jid.2014.371

Dennis, M., Spiegler, B. J., & Hetherington, R. (2000). New survivors for the new millennium: Cognitive risk and reserve in adults with childhood brain insults. *Brain and Cognition*, *42*(1), 102–105. https://doi.org/10.1006/brcg.1999.1174

Department of Health (DoH). (2008). *Commissioning safe and sustainable specialised paediatric services: A framework of critical interdependencies*.

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. https://doi.org/10.1016/S0887-8994(99)00032-6

Dodrill, C. B. (2004). Neuropsychological effects of seizures. *Epilepsy and Behavior*, *5*(SUPPL. 1), 21–24. https://doi.org/10.1016/j.yebeh.2003.11.004

Doucet, G. E., Sharan, A., Pustina, D., Skidmore, C., Sperling, M. R., & Tracy, J. I. (2015). Early and Late Age of Seizure Onset have a Differential Impact on Brain Resting-State Organization in Temporal Lobe Epilepsy. *Brain Topography*, *28*, 113–126. https://doi.org/10.1007/s10548-014-0366-6

Dragoumi, P., Tzetzi, O., Vargiami, E., Pavlou, E., Krikonis, K., Kontopoulos, E., & Zafeiriou, D. I. (2013). Clinical course and seizure outcome of idiopathic childhood epilepsy: Determinants of early and long-term prognosis. *BMC*

*Neurology*, *13*, 1–12. https://doi.org/10.1186/1471-2377-13-206

Dunn, D. W., & Kronenberger, W. G. (2005). Childhood Epilepsy, Attention Problems, and ADHD: Review and Practical Considerations. *Seminars in Pediatric Neurology*, *12*(4), 222–228. https://doi.org/10.1016/j.spen.2005.12.004

Durnford, A. J., Rodgers, W., Kirkham, F. J., Mullee, M. A., Whitney, A., Prevett, M., … Gray, W. P. (2011). Very good inter-rater reliability of Engel and ILAE epilepsy surgery outcome classifications in a series of 76 patients. *Seizure*, *20*(10), 809–812. https://doi.org/10.1016/j.seizure.2011.08.004

Dwivedi, R., Ramanujam, B., Chandra, P. S., Sapra, S., Gulati, S., Kalaivani, M., … Tripathi, M. (2017). Surgery for drug-resistant epilepsy in children. *New England Journal of Medicine*, *377*(17), 1639–1647. https://doi.org/10.1056/NEJMoa1615335

Elliott, I. M., Lach, L., & Smith, M. Lou. (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 and Behavior*, *7*(4), 664–678. https://doi.org/10.1016/j.yebeh.2005.07.004

Engel J. (2001). Mesial temporal lobe epilepsy: What have we learned? *Neuroscientist*, *7*(4), 340–352. https://doi.org/10.1177/107385840100700410

Engel, J. (2013). Why is there still doubt to cut it out? *Epilepsy Currents*, *13*(5), 198–204. https://doi.org/10.5698/1535-7597-13.5.198

Engel, J. (2019). Evolution of concepts in epilepsy surgery*. *Epileptic Disorders*, *21*(5), 391–409. https://doi.org/10.1684/epd.2019.1091

Engel, J., Van Ness, P. C., Rasmussen, T. B., & Ojemann, L. M. (1993). Outcome with respect to epileptic seizures. In Engel, J. (Ed.), *Surgical treatment of the epilepsies* (pp. 609–621). New York: Raven Press.

England, M. J., Liverman, C. T., Schultz, A. M., & Strawbridge, L. M. (2012). Epilepsy across the spectrum: Promoting health and understanding.: A summary of the Institute of Medicine report. *Epilepsy & Behavior*, *25*(2), 266-

276.

Englot, D. J. (2018). A Modern Epilepsy Surgery Treatment Algorithm: Incorporating Traditional and Emerging Technologies. *Epilepsy Behav*, *80*, 68–74. https://doi.org/10.1016/j.physbeh.2017.03.040

Farwell, J. R., Lee, Y. J., Hirtz, D. G., Sulzbacher, S. I., Ellenberg, J. H., & Nelson, K. B. (1990). Phenobarbital for febrile seizures - effects on intelligence and on seizure recurrence. *The New England Journal of Medicine*, *322*(6), 364–369.

Fastenau, P. S., Johnson, C. S., Perkins, S. M., Byars, A. W., DeGrauw, T. J., Austin, J. K., & Dunn, D. W. (2009). Neuropsychological status at seizure onset in children: Risk factors for early cognitive deficits. *Neurology*, *73*(7), 526–534. https://doi.org/10.1212/WNL.0b013e3181b23551

Fastenau, P. S., Shen, J., Dunn, D. W., Perkins, S. M., Hermann, B. P., & Austin, J. K. (2004). Neuropsychological predictors of academic underachievement in pediatric epilepsy: Moderating roles of demographic, seizure, and psychosocial variables. *Epilepsia*, *45*(10), 1261–1272. https://doi.org/10.1111/j.0013-9580.2004.15204.x

Fawi, G., Mohamed, A.-A. B., Sedky, A., Hassan, A. B., Abdelhameed, S. G., Mosa, A. M., & Hussein, G. M. (2019). Relationship between learning disabilities and the laterality of epileptic discharges in young patients with idiopathic focal epilepsy. *Journal of Medical Science And Clinical Research*, *7*(4), 542–553. https://doi.org/10.18535/jmscr/v7i4.93

Field, A. (2018). *Discovering statistics using IBM SPSS statistics* (Fifth). London: SAGE Publications.

Fisher, R. S., Acevedo, C., Arzimanoglou, A., Bogacz, A., Cross, J. H., Elger, C. E., … Wiebe, S. (2014). ILAE Official Report: A practical clinical definition of epilepsy. *Epilepsia*, *55*(4), 475–482. https://doi.org/10.1111/epi.12550

Fisher, R. S., Cross, J. H., D'Souza, C., French, J. A., Haut, S. R., Higurashi, N.,

… Zuberi, S. M. (2017). Instruction manual for the ILAE 2017 operational classification of seizure types. *Epilepsia*, *58*(4), 531–542. https://doi.org/10.1111/epi.13671

Fisher, R. S., Van Emde Boas, W., Blume, W., Elger, C., Genton, P., Lee, P., & Engel, J. (2005). Response: Definitions proposed by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) [4]. *Epilepsia*, *46*(10), 1701–1702. https://doi.org/10.1111/j.1528-1167.2005.00273_4.x

Flint, A. E., Waterman, M., Bowmer, G., Vadlamani, G., Chumas, P., & Morrall, M. C. H. J. (2017). Neuropsychological outcomes following paediatric temporal lobe surgery for epilepsies: Evidence from a systematic review. *European Journal of Epilepsy*, *52*, 89–116. https://doi.org/https://doi.org/10.1016/j.seizure.2017.09.011

Flynn, J. R. (1984). The mean IQ of Americans: Massive gains 1932 to 1978. *Psychological Bulletin*, *95*(1), 29–51. https://doi.org/10.1037/0033-2909.95.1.29

Freitag, H., & Tuxhorn, I. (2005). Cognitive function in preschool children after epilepsy surgery: Rationale for early intervention. *Epilepsia*, *46*(4), 561–567. https://doi.org/10.1111/j.0013-9580.2005.03504.x

Galanopoulou, A. S., & Moshé, S. L. (2014). Neuronal Network Mechanisms-Sex and Development. *Neuronal Networks in Brain Function, CNS Disorders, and Therapeutics*, 145–155. https://doi.org/10.1016/B978-0-12-415804-7.00011-3

García-Fernández, M., Fournier-Del Castillo, C., Ugalde-Canitrot, A., Pérez-Jiménez, Á., Álvarez-Linera, J., De Prada-Vicente, I., … Villarejo-Ortega, F. (2011). Epilepsy surgery in children with developmental tumours. *Seizure*, *20*(8), 616–627. https://doi.org/10.1016/j.seizure.2011.06.003

Gathercole, S. E., Pickering, S. J., Knight, C., & Stegmann, Z. (2004). Working memory skills and educational attainment: Evidence from national curriculum assessments at 7 and 14 years of age. *Applied Cognitive Psychology*, *18*(1),

1–16. https://doi.org/10.1002/acp.934

Gil, A. M. (2003). Neurocognitive outcomes following pediatric brain injury: A developmental approach. *Journal of School Psychology*, *41*(5), 337–353. https://doi.org/10.1016/S0022-4405(03)00085-2

Gläscher, J., Adolphs, R., Damasio, H., Bechara, A., Rudrauf, D., Calamia, M., … Tranel, D. (2012). Lesion mapping of cognitive control and value-based decision making in the prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(36), 14681–14686. https://doi.org/10.1073/pnas.1206608109

Gleissner, U., Sassen, R., Lendt, M., Clusmann, H., Elger, C. E., & Helmstaedter, C. (2002). Pre- and postoperative verbal memory in pediatric patients with temporal lobe epilepsy. *Epilepsy Research*, *51*(3), 287–296. https://doi.org/10.1016/S0920-1211(02)00158-4

Gleissner, U., Sassen, R., Schramm, J., Elger, C. E., & Helmstaedter, C. (2005). Greater functional recovery after temporal lobe epilepsy surgery in children. *Brain*, *128*(12), 2822–2829. https://doi.org/10.1093/brain/awh597

Gleissner, U., Clusmann, H., Sassen, R., Elger, C. E., & Helmstaedter, C. (2006). Postsurgical outcome in pediatric patients with epilepsy: A comparison of patients with intellectual disabilities, subaverage intelligence, and average-range intelligence. *Epilepsia*, *47*(2), 406–414. https://doi.org/10.1111/j.1528-1167.2006.00436.x

Gonzalez, L. M., & Wrennall, J. A. (2019). A neuropsychological model for the pre-surgical evaluation of children with focal-onset epilepsy: An integrated approach. *Seizure*, (September), 0–1. https://doi.org/10.1016/j.seizure.2018.12.013

Green, B. N., & Johnson, C. D. (2015). Interprofessional collaboration in research, education, and clinical practice: working together for a better future . *Journal of Chiropractic Education*, *29*(1), 1–10. https://doi.org/10.7899/jce-14-36

Green, P., Rohling, M. L., Lees-Haley, P. R., & Allen, L. M. (2001). Effort has a

greater effect on test scores than severe brain injury in compensation claimants. *Brain Injury*, *15*(12), 1045–1060. https://doi.org/10.1080/02699050110088254

Greener M. (2013). Beyond seizures: Understanding cognitive deficits in epilepsy. *Progress in Neurology and Psychiatry*, *17*(3), 31–32.

Guimarães, C. A., Li, L. M., Rzezak, P., Fuentes, D., Franzon, R. C., Augusta Montenegro, M., … Guerreiro, M. M. (2007). Temporal lobe epilepsy in childhood: Comprehensive neuropsychological assessment. *Journal of Child Neurology*, *22*(7), 836–840. https://doi.org/10.1177/0883073807304701

Hamberger, M. J., & Cole, J. (2011). Language organization and reorganization in epilepsy. *Neuropsychology Review*, *21*(3), 240–251. https://doi.org/10.1007/s11065-011-9180-z

Harrison, S., Cross, H., Harkness, W., & Vargha-Khadem, F. (2013). Pre-operative educational status of children with focal epilepsy. *Epilepsy & Behavior*, *28*(2), 328. https://doi.org/10.1016/j.yebeh.2012.04.096

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. https://doi.org/10.1111/j.1528-1167.2007.01421.x

Harvey, P. D. (2019). Domains of cognition and their assessment. *Dialogues in Clinical Neuroscience*, *21*(3), 227–237. https://doi.org/10.31887/DCNS.2019.21.3/pharvey

Hauptman, J. S., & Mathern, G. W. (2012). Epilepsy neurosurgery in children. In *Handbook of Clinical Neurology*. https://doi.org/10.1016/B978-0-444-52899-5.00034-4

Helmstaedter, C., & Kockelmann, E. (2006). Cognitive outcomes in patients with chronic temporal lobe epilepsy. *Epilepsia*, *47*(SUPPL. 2), 96–98. https://doi.org/10.1111/j.1528-1167.2006.00702.x

Hermann, B. P., Jones, J. E., Jackson, D. C., & Seidenberg, M. (2012). Starting at the beginning: The neuropsychological status of children with new-onset

epilepsies. *Epileptic Disorders*, *14*(1), 12–21. https://doi.org/10.1684/epd.2012.0483

Hermann, B. P., Jones, J., Sheth, R., & Seidenberg, M. (2007). Cognitive and Magnetic Resonance Volumetric Abnormalities in New Onset Pediatric Epilepsy. *Semin Pediatr Neurol*, *14*(4), 173–180.

Hermann, B. P., Seidenberg, M., & Bell, B. (2002). The neurodevelopmental impact of childhood onset temporal lobe epilepsy on brain structure and function and the risk of progressive cognitive effects. *Progress in Brain Research*, *135*(9), 429–438. https://doi.org/10.1016/S0079-6123(02)35040-4

Hermann, B., Seidenberg, M., & Jones, J. (2008). The neurobehavioural comorbidities of epilepsy: can a natural history be developed? *The Lancet Neurology*, *7*(2), 151–160. Retrieved from http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L351106399%5Cnhttp://dx.doi.org/10.1016/S1474-4422(08)70018-8%5Cnhttp://cy7sh3vq3t.search.serialssolutions.com?sid=EMBASE&sid=EMBASE&issn=14744422&id=doi:10.1016/S1474-4422(08)70018-

Hermann, B., Jones, J., Sheth, R., Dow, C., Koehn, M., & Seidenberg, M. (2006). Children with new-onset epilepsy: Neuropsychological status and brain structure. *Brain*, *129*(10), 2609–2619. https://doi.org/10.1093/brain/awl196

Hermann, B., Loring, D. W., & Wilson, S. (2017). Paradigm shifts in the neuropsychology of epilepsy. *Journal of the International Neuropsychological Society*, *23*(9-10 Special Issue), 791–805. https://doi.org/10.1017/S1355617717000650

Hermann, B., Meador, K. J., Gaillard, W. D., & Cramer, J. A. (2010). Cognition across the lifespan: Antiepileptic drugs, epilepsy, or both? *Epilepsy and Behavior*, *17*(1), 1–5. https://doi.org/10.1016/j.yebeh.2009.10.019

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

Hermann, B., Seidenberg, M., Lee, E. J., Chan, F., & Rutecki, P. (2007). Cognitive phenotypes in temporal lobe epilepsy. *Journal of the International*

*Neuropsychological Society*, *13*(1), 12–20. https://doi.org/10.1017/S135561770707004X

Hills, M. D. (2007). The psychological and social impact of epilepsy. *Neurology Asia*, *12*(Suppl. 1), 10–12.

Holmes, G. L. (2016). Effect of Seizures on the Developing Brain and Cognition. *Semin Pediatr Neurol*, *23*(2), 120–126. https://doi.org/10.1016/j.physbeh.2017.03.040

Hosoyama, H., Matsuda, K., Mihara, T., Usui, N., Baba, K., Inoue, Y., … Arita, K. (2017). Long-term outcomes of epilepsy surgery in 85 pediatric patients followed up for over 10 years: A retrospective survey. *Journal of Neurosurgery: Pediatrics*, *19*(5), 606–615. https://doi.org/10.3171/2016.12.PEDS16197

Hsu, C. C. T., Stenberg, L., & Krings, T. (2020). Imaging the Patient with Epilepsy. In *Diseases of the Brain, Head and Neck, Spine 2020–2023* (pp. 111–130). Springer.

IBM Corp. (2019). *IBM Statistics for Windows, Version 26.0*. Armonk, NY: IBM Corp.

Ijff, D. M., & Aldenkamp, A. P. (2013). Cognitive side-effects of antiepileptic drugs in children. In *Handbook of Clinical Neurology* (1st ed., Vol. 111). https://doi.org/10.1016/B978-0-444-52891-9.00073-7

Jambaqué, I., Dellatolas, G., Fohlen, M., Bulteau, C., Watier, L., Dorfmuller, G., … Delalande, O. (2007). Memory functions following surgery for temporal lobe epilepsy in children. *Neuropsychologia*, *45*(12), 2850–2862. https://doi.org/10.1016/j.neuropsychologia.2007.05.008

Jones-Gotman, M., Smith, M. Lou, Risse, G. L., Westerveld, M., Swanson, S. J., Giovagnoli, A. R., … Piazzini, A. (2010). The contribution of neuropsychology to diagnostic assessment in epilepsy. *Epilepsy and Behavior*, *18*(1–2), 3–12. https://doi.org/10.1016/j.yebeh.2010.02.019

Jung, J. Y., Visser, M., Binney, R. J., & Lambon Ralph, M. A. (2018). Establishing

the cognitive signature of human brain networks derived from structural and functional connectivity. *Brain Structure and Function*, *223*(9), 4023–4038. https://doi.org/10.1007/s00429-018-1734-x

Kabat, J., & Król, P. (2012). Focal cortical dysplasia - review. *Polish Journal of Radiology*, *77*(2), 35–43. https://doi.org/10.12659/PJR.882968

Kadish, N. E., Bast, T., Reuner, G., Wagner, K., Mayer, H., Schubert-Bast, S., … Ramantani, G. (2019). Epilepsy Surgery in the First 3 Years of Life: Predictors of Seizure Freedom and Cognitive Development. *Clinical Neurosurgery*, *84*(6), E368–E377. https://doi.org/10.1093/neuros/nyy376

Kamphaus, R. W., Petoskey, M. D., & Rowe, E. W. (2000). Current trends in psychological testing of children. *Professional Psychology: Research and Practice.*, *31*(2), 155–164.

Kang, H. (2013). The prevention and handling of the missing data. *Korean Journal of Anesthesiology*, *64*(5), 402–406. https://doi.org/10.4097/kjae.2013.64.5.402

Karmiloff-Smith, A. (2010). Neuroimaging of the developing brain: Taking “developing” seriously. *Human Brain Mapping*, *31*(6), 934–941. https://doi.org/10.1002/hbm.21074

Kellermann, T. S., Bonilha, L., Lin, J. J., & Hermann, B. P. (2015). Mapping the landscape of cognitive development in children with epilepsy. *Cortex*, *66*, 1–8. https://doi.org/10.1016/j.cortex.2015.02.001

Kennard, M. A. (1942). Cortical Reorganisation of Memory Function: Studies on series of monkeys of various ages from infancy to maturity. *Archives of Neurology and Psychiatry*, *48*(2), 227–240.

Kernan, C. L., Asarnow, R., Siddarth, P., Gurbani, S., Lanphier, E. K., Sankar, R., & Caplan, R. (2012). Neurocognitive profiles in children with epilepsy. *Epilepsia*, *53*(12), 2156–2163. https://doi.org/10.1111/j.1528-1167.2012.03706.x

Kim EH, & Ko TS. (2016). Cognitive impairment in childhood onset epilepsy: Up-

to-date information about its causes. *Korean Journal of Pediatrics*, *59*(4), 155–164. http://dx.doi.org/10.3345/kjp.2016.59.4.155

Knecht, S., Drager, B., Deppe, M., Bobe, L., Lohmann, H., Floel, A., … Henningsen, H. (2000). Handedness and hemispheric language dominance in healthy humans. *Brain*, *123*, 2512–2518. https://doi.org/10.1515/9783110259032

Knudsen, E. I. (2004). Sensitive Periods in the Development of the Brain and Behavior," Journal of Cognitive Neuroscience, 16(8): 1412-1425, 2004. *Journal of Cognitive Neuroscience*, 1412–1425. Retrieved from http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.467.1663&rep=rep1&type=pdf%0Ahttp://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.467.1663

Kolb, B., & Whilshaw, I. Q. (1998). Brain Plasticity and Behavior. *Annu. Rev. Psychol.*, *49*, 43–64. https://doi.org/10.1007/978-3-642-70644-8_20

Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY– II*: *Second edition*. San Antonio, TX: The Psychological Corporation.

Korkman, M., Granström, M. L., Kantola-Sorsa, E., Gaily, E., Paetau, R., Liukkonen, E., … Blomstedt, G. (2005). Two-year follow-up of intelligence after pediatric epilepsy surgery. *Pediatric Neurology*, *33*(3), 173–178. https://doi.org/10.1016/j.pediatrneurol.2005.04.006

Kreidenhuber, R., De Tiège, X., & Rampp, S. (2019). Presurgical functional cortical mapping using electromagnetic source imaging. *Frontiers in Neurology*, *10*(June), 1–14. https://doi.org/10.3389/fneur.2019.00628

Kuehn, S. M., Keene, D. L., Richards, P. M. P., & Ventureyra, E. C. G. (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. https://doi.org/10.1007/s00381-002-0599-7

Kukull, W. A., & Ganguli, M. (2012). Generalizability: The trees, the forest, and the low-hanging fruit. *Neurology*, *78*(23), 1886–1891. https://doi.org/10.1212/WNL.0b013e318258f812

Kwan, P., Arzimanoglou, A., Berg, A. T., Brodie, M. J., Hauser, W. A., Mathern, G., … French, J. (2010). Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. *Epilepsia*, *51*(6), 1069–1077. https://doi.org/10.1111/j.1528-1167.2009.02397.x

Lach, L. M., Elliott, I., Giecko, T., Olds, J., Snyder, T., McCleary, L., … Smith, M. Lou. (2010). Patient-reported outcome of pediatric epilepsy surgery: Social inclusion or exclusion as young adults? *Epilepsia*, *51*(10), 2089–2097. https://doi.org/10.1111/j.1528-1167.2010.02584.x

Lah, S., Castles, A., & Smith, M. Lou. (2017). Reading in children with temporal lobe epilepsy: A systematic review. *Epilepsy and Behavior*, *68*, 84–94. https://doi.org/10.1016/j.yebeh.2016.12.021

Lah, S., & Smith, M. Lou. (2014). Semantic and episodic memory in children with temporal lobe epilepsy: Do they relate to literacy skills? *Neuropsychology*, *28*(1), 113–122. https://doi.org/10.1037/neu0000029

Lah, S., & Smith, M. Lou. (2015). Verbal memory and literacy outcomes one year after pediatric temporal lobectomy: A retrospective cohort study. *Epilepsy and Behavior*, *44*, 225–233. https://doi.org/10.1016/j.yebeh.2014.12.040

Lajiness-O'Neill, R., Pawluk, L., & Jacobson, D. (2011). Past, present and future of pediatric neuropsychology. In A. S. Davis (Ed.), *Handbook of Pediatric Neuropsychology*. New York: Springer Publishing.

Laurent, A., & Arzimanoglou, A. (2006). Cognitive impairments in children with nonidiopathic temporal lobe epilepsy. *Epilepsia*, *47*(SUPPL. 2), 99–102. https://doi.org/10.1111/j.1528-1167.2006.00703.x

Law, N., Benifla, M., Rutka, J., & Smith, M. Lou. (2017). Verbal memory after temporal lobe epilepsy surgery in children: Do only mesial structures matter? *Epilepsia*, *58*(2), 291–299. https://doi.org/10.1111/epi.13635

Lee, K. H., Lee, Y.-J., Seo, J. H., Baumgartner, J. E., & Westerveld, M. (2019). Epilepsy Surgery in Children versus Adults. *Journal of Korean Neurosurgical Society*, *62*(3), 328–335. https://doi.org/10.3340/jkns.2019.0026

Lee, Y. J., & Lee, J. S. (2013). Temporal lobe epilepsy surgery in children versus adults: From etiologies to outcomes. *Korean Journal of Pediatrics*, *56*(7), 275–281. https://doi.org/10.3345/kjp.2013.56.7.275

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. https://doi.org/10.1111/j.1528-1157.1999.tb02038.x

Leonardi, M., & Ustun, T. B. (2002). The global burden of epilepsy. *Epilepsia*, *43*(Suppl.6), 21–25. https://doi.org/10.1046/j.1528-1157.43.s.6.11.x

Leritz, E. C., Grande, L. J., & Bauer, R. M. (2006). Temporal lobe epilepsy as a model to understand human memory: The distinction between explicit and implicit memory. *Epilepsy and Behavior*, *9*(1), 1–13. https://doi.org/10.1016/j.yebeh.2006.04.012

Lezak, M. D., Howieson, D. B., Loring, D. W., Hannay, H. J., & Fischer, J. S. (2004). *Neuropsychological assessment* (Fourth). New York: Oxford University Press.

Lezak, M., Howieson, D., Bigler, E., & Tranel, D. (2012). *Neuropsychological assessment* (Fifth). New York: Oxford University Press.

Liang, S., Wang, S., Zhang, J., Ding, C., Zhang, Z., Fu, X., … Zhang, S. (2012). Long-term outcomes of epilepsy surgery in school-aged children with partial epilepsy. *Pediatric Neurology*, *47*(4), 284–290. https://doi.org/10.1016/j.pediatrneurol.2012.06.014

Liou, J. Y., Smith, E. H., Bateman, L. M., Bruce, S. L., McKhann, G. M., Goodman, R. R., … Abbott, L. F. (2020). A model for focal seizure onset, propagation, evolution, and progression. *ELife*, *9*, 1–27. https://doi.org/10.7554/eLife.50927

Lopez-Garcia, P., Lesh, T. A., Salo, T., Barch, D. M., MacDonald, A. W., Gold, J. M., … Carter, C. S. (2016). The neural circuitry supporting goal maintenance during cognitive control: a comparison of expectancy AX-CPT and dot probe expectancy paradigms. *Cogn Affect Behav Neurosci*, *16*(1), 164–175.

https://doi.org/10.3758/s13415-015-0384-1

Lordo, D. N., Van Patten, R., Sudikoff, E. L., & Harker, L. (2017). Seizure-related variables are predictive of attention and memory in children with epilepsy. *Epilepsy and Behavior*, *73*, 36–41. https://doi.org/10.1016/j.yebeh.2017.05.017

Loring, D. W. (2010). History of neuropsychology through epilepsy eyes. *Archives of Clinical Neuropsychology*, *25*(4), 259–273. https://doi.org/10.1093/arclin/acq024

Loring, D. W., Meador, K. J., Lee, G. P., & Smith, J. R. (2004). Structural versus functional prediction of memory change following anterior temporal lobectomy. *Epilepsy and Behavior*, *5*(2), 264–268. https://doi.org/10.1016/j.yebeh.2004.01.001

Louis, D. N., Perry, A., Reifenberger, G., von Deimling, A., Figarella-Branger, D., Cavenee, W. K., … Ellison, D. W. (2016). The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathologica*, *131*(6), 803–820. https://doi.org/10.1007/s00401-016-1545-1

Lynn, R., & Mikk, J. (2009). National IQs predict educational attainment in math, reading and science across 56 nations. *Intelligence*, *37*(3), 305–310. https://doi.org/10.1016/j.intell.2009.01.002

Mabbott, D. J., & Smith, M. Lou. (2003). Memory in children with temporal or extra-temporal excisions. *Neuropsychologia*, *41*(8), 995–1007. https://doi.org/10.1016/S0028-3932(02)00318-4

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S. J., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences of the United States of America*, *97*(8), 4398–4403. https://doi.org/10.1073/pnas.070039597

Malmgren, K., Olsson, I., Engman, E., Flink, R., & Rydenhag, B. (2008). Seizure outcome after resective epilepsy surgery in patients with low IQ. *Brain*,

*131*(2), 535–542. https://doi.org/10.1093/brain/awm296

Mansouri, A., Fallah, A., & Valiante, T. A. (2012). Determining Surgical Candidacy in Temporal Lobe Epilepsy. *Epilepsy Research and Treatment*, *2012*, 1–16. https://doi.org/10.1155/2012/706917

Martin, R., Cirino, P., Hiscock, M., Schultz, R., Collins, R., & Chapieski, L. (2016). Risks and benefits of epilepsy surgery in a pediatric population: Consequences for memory and academic skills. *Epilepsy and Behavior*, *62*, 189–196. https://doi.org/10.1016/j.yebeh.2016.06.028

Matsuzaka, T., Baba, H., Matsuo, A., Tsuru, A., Moriuchi, H., Tanaka, S., & Kawasaki, C. (2001). Developmental assessment-based surgical intervention for intractable epilepsies in infants and young children. *Epilepsia*, *42*(SUPPL. 8), 9–12. https://doi.org/10.1046/j.1528-1157.2001.05403.x

McMillan, T. M., Anderson, S., Baker, G., Berger, M., Powell, G. E., & Knight, R. (2009). Assessment of effort in clinical testing of cognitive functioning for adults. *Professional Practice Board-British Psychological Society*, (October), 1–27. https://doi.org/ISBN 978-1-85433-497-8

McNelis, A. M., Johnson, C. S., Huberty, T. J., & Austin, J. K. (2005). Factors associated with academic achievement in children with recent-onset seizures. *Seizure*, *14*(5), 331–339. https://doi.org/10.1016/j.seizure.2005.04.005

Meekes, J., Braams, O., Braun, K. P. J., Jennekens-Schinkel, A., & van Nieuwenhuizen, O. (2013). Verbal memory after epilepsy surgery in childhood. *Epilepsy Research*, *107*(1–2), 146–155. https://doi.org/10.1016/j.eplepsyres.2013.08.017

Menlove, L., & Reilly, C. (2015). Memory in children with epilepsy: A systematic review. *Seizure*, *25*, 126–135. https://doi.org/10.1016/j.seizure.2014.10.002

Meyer, F. B., Marsh, W. R., Laws, E. R., & Sharbrough, F. W. (1986). Temporal lobectomy in children with epilepsy. *Journal of Neurosurgery*, *64*(3), 371–376. https://doi.org/10.3171/jns.1986.64.3.0371

Miranda, C., & Smith, M. Lou. (2001). Predictors of Intelligence after Temporal Lobectomy in Children with Epilepsy. *Epilepsy and Behavior*, *2*(1), 13–19. https://doi.org/10.1006/ebeh.2000.0142

Mittal, S., Montes, J. L., Farmer, J. P., Rosenblatt, B., Dubeau, F., Andermann, F., … Olivier, A. (2005). Long-term outcome after surgical treatment of temporal lobe epilepsy in children. *Journal of Neurosurgery*, *103 PEDIAT*(SUPPL. 5), 401–412. https://doi.org/10.3171/ped.2005.103.5.0401

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Prisma Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS med*, *6*(7), e1000097.

Moosa, A. N. V., & Wyllie, E. (2017). Cognitive Outcome After Epilepsy Surgery in Children. *Seminars in Pediatric Neurology*, *24*(4), 331–339. https://doi.org/10.1016/j.spen.2017.10.010

Moses, P., & Stiles, J. (2002). The lesion methodology: Contrasting views from adult and child studies. *Developmental Psychobiology*, *40*(3), 266–277. https://doi.org/10.1002/dev.10031

NHS Commissioning Board (2013). NHS standard contract for children's epilepsy surgery service http://www.england.nhs.uk/wpcontent/uploads/2013/06/e09-child-epilepsy-surg.pdf.

NHS England. (2016). *Proposed changes to service specification for Children's Epilepsy Surgery: Consultation outcome report*.

NHS England (2018). *Children's Epilepsy Surgery Service (CESS). Service specification publication.* Retrieved from https://www.england.nhs.uk/wp-content/uploads/2018/01/service-spec-childrens-epilepsy-surgery-service.pdf.

NHS Specialised Services. (2012). *Safe and Sustainable Children's Neurosurgical Services Review*. Retrieved from http://www.specialisedservices.nhs.uk/safe_sustainable/childrens-neurosurgical-services.

NICE (2012). *Epilepsies: diagnosis and management.* Clinical guideline [CG137] Published date: 11 January 2012 Last updated: 11 February 2020.

Nickels, K. C., Wong-Kisiel, L. C. L., Moseley, B. D., & Wirrell, E. C. (2011). Temporal lobe epilepsy in children. *Epilepsy Research and Treatment*, *6*(2), 201–213. https://doi.org/10.1155/2012/849540

Nolan, M. A., Redoblado, M. A., Lah, S., Sabaz, M., Lawson, J. A., Cunningham, A. M., … Bye, A. M. E. (2004). Memory function in childhood epilepsy syndromes. *Journal of Paediatrics and Child Health*, *40*(1–2), 20–27. https://doi.org/10.1111/j.1440-1754.2004.00284.x

Nouwens, S., Groen, M. A., & Verhoeven, L. (2017). How working memory relates to children's reading comprehension: the importance of domain-specificity in storage and processing. *Reading and Writing*, *30*(1), 105–120. https://doi.org/10.1007/s11145-016-9665-5

Oostrom, K. J., Smeets-Schouten, A., Kruitwagen, C. L. J. J., Peters, A. C. B., & Jennekens-Schinkel, A. (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 I), 1338–1344. https://doi.org/10.1542/peds.112.6.1338

Ormond, D. R., Clusmann, H., Sassen, R., Hoppe, C., Helmstaedter, C., Schramm, J., & Grote, A. (2019). Pediatric temporal lobe epilepsy surgery in bonn and review of the literature. *Clinical Neurosurgery*, *84*(4), 844–856. https://doi.org/10.1093/neuros/nyy125

Ormston, R., Spencer, L., Barnard, M., & Snape, D. (2013). The Foundations of Qualitative Research. In J. Ritchie, J. Lewis, C. Nicholls, & R. Ormston (Eds.), *Qualitative research practice: a guide for social science students and researchers*. Sage.

Panayiotopoulos, C. P. (2005). *The Epilepsies: Seizures, Syndromes and Management.* Oxfordshire: Bladon Medical Publishing.

Park, K. M., Kim, S. E., & Lee, B. I. (2019). Antiepileptic Drug Therapy in Patients with Drug-Resistant Epilepsy. *Journal of Epilepsy Research*, *9*(1), 14–26.

https://doi.org/10.14581/jer.19002

Perucca, P., & O'Brien, T. J. (2015). Epilepsy in 2014: Novel and large collaborations drive advances in epilepsy. *Nature Reviews Neurology*, *11*(2), 74–76. https://doi.org/10.1038/nrneurol.2014.255

Pittau, F., Grouiller, F., Spinelli, L., Seeck, M., Michel, C. M., & Vulliemoz, S. (2014). The role of functional neuroimaging in pre-surgical epilepsy evaluation. *Frontiers in Neurology*, *5 MAR*(March), 1–16. https://doi.org/10.3389/fneur.2014.00031

Popovic, N. (2005). *Personal Synthesis*. London: PWBC.

Puka, K., Khattab, M., Kerr, E. N., & Smith, M. Lou. (2015). Academic achievement one year after resective epilepsy surgery in children. *Epilepsy and Behavior*, *47*, 1–5. https://doi.org/10.1016/j.yebeh.2015.04.062

Puka, K., & Smith, M. Lou. (2016). Where are they now? Psychosocial, educational, and vocational outcomes after epilepsy surgery in childhood. *Epilepsia*, *57*(4), 574–581. https://doi.org/10.1111/epi.13327

Puka, K., Tavares, T. P., & Smith, M. Lou. (2017). Development of intelligence 4 to 11 years after paediatric epilepsy surgery. *Journal of Neuropsychology*, *11*(2), 161–173. https://doi.org/10.1111/jnp.12081

Purves, D. (2010). *Brains: how they seem to work*. New Jersey: FT Press.

Ramantani, G., Kadish, N. E., Strobl, K., Brandt, A., Stathi, A., Mayer, H., … Bast, T. (2013). Seizure and cognitive outcomes of epilepsy surgery in infancy and early childhood. *European Journal of Paediatric Neurology*, *17*(5), 498–506. https://doi.org/10.1016/j.ejpn.2013.03.009

Ramantani, G., & Reuner, G. (2018). Cognitive Development in Pediatric Epilepsy Surgery. *Neuropediatrics*, *49*(2), 93–103. https://doi.org/10.1055/s-0037-1609034

Rankin, P.M. & Vargha-Khadem, F. (2007) Neuropsychological evaluation - children. In: Engel, J. & Pedley, T., A. (Eds.) *Epilepsy: A Comprehensive Textbook*. Lippincott Williams & Wilkins.

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F. C., Aylett, S. E., Burch, V., … Neville, B. G. R. (2014). Academic achievement in school-aged children with active epilepsy: A population-based study. *Epilepsia*, *55*(12), 1910–1917. https://doi.org/10.1111/epi.12826

Reilly, C., & Ballantine, R. (2011). Epilepsy in school-aged children: More than just seizures? *Support for Learning*, *26*(4), 144–151. https://doi.org/10.1111/j.1467-9604.2011.01501.x

Reilly, C., & Neville, B. G. R. (2011). Academic achievement in children with epilepsy: A review. *Epilepsy Research*, *97*(1–2), 112–123. https://doi.org/10.1016/j.eplepsyres.2011.07.017

Reinholdson, J., Olsson, I., Edelvik Tranberg, A., & Malmgren, K. (2020). Long-term employment outcomes after epilepsy surgery in childhood. *Neurology*, *94*(2), e205–e216. https://doi.org/10.1212/WNL.0000000000008681

Reyes, A., Kaestner, E., Bahrami, N., Balachandra, A., Hegde, M., Paul, B. M., … Mcdonald, C. R. (2019). Cognitive phenotypes in temporal lobe epilepsy are associated with distinct patterns of white matter network abnormalities. *Neurology*, *92*(17), E1957–E1968. https://doi.org/10.1212/WNL.0000000000007370

Rice, G. E., Caswell, H., Moore, P., Hoffman, P., & Lambon Ralph, M. A. (2018). The roles of left versus right anterior temporal lobes in semantic memory: A neuropsychological comparison of postsurgical temporal lobe epilepsy patients. *Cerebral Cortex*, *28*(4), 1487–1501. https://doi.org/10.1093/cercor/bhx362

Richards, K. (2003). *Qualitative Inquiry in TESOL*. New York: Palgrave Macmillan.

Richardson, F. M., & Price, C. J. (2009). Structural MRI studies of language function in the undamaged brain. *Brain Structure and Function*, *213*(6), 511–523. https://doi.org/10.1007/s00429-009-0211-y

Rosenow, F., & Luders, H. (2008). Presurgical evaluation of epilepsy patients. *Medicina*, *44*(8), 585–592. https://doi.org/10.3390/medicina44080076

Romeiser-Logan, L., Slaughter, R., & Hickman, R. (2017). Single-subject research designs in pediatric rehabilitation: a valuable step towards knowledge translation. *Developmental Medicine & Child Neurology*, *59*(6), 574-580. https://doi.org/10.1111/dmcn.13405

Rudebeck, S. R., Shavel-Jessop, S., Varadkar, S., Owen, T., Cross, J. H., Vargha-Khadem, F., & Baldeweg, T. (2018). Pre- and postsurgical cognitive trajectories and quantitative MRI changes in Rasmussen syndrome. *Epilepsia*, *59*(6), 1210–1219. https://doi.org/10.1111/epi.14192

Rust, J. (1996). *Wechsler Objective Numerical Dimensions (WOND)*. London: The Psychological Corporation.

Rust, J., Golombok, S., & Trickey, G. (1993). *Wechsler Objective Reading Dimension (WORD)*. London: The Psychological Corporation.

Rzezak, P., Fuentes, D., Guimarães, C. A., Thome-Souza, S., Kuczynski, E., Li, L. M., … Valente, K. D. (2007). Frontal Lobe Dysfunction in Children With Temporal Lobe Epilepsy. *Pediatric Neurology*, *37*(3), 176–185. https://doi.org/10.1016/j.pediatrneurol.2007.05.009

Rzezak, P., Guimarães, C. A., Fuentes, D., Guerreiro, M. M., & Valente, K. D. (2012). Memory in children with temporal lobe epilepsy is at least partially explained by executive dysfunction. *Epilepsy and Behavior*, *25*(4), 577–584. https://doi.org/10.1016/j.yebeh.2012.09.043

Rzezak, P., Valente, K. D., & Duchowny, M. S. (2014). Temporal lobe epilepsy in children: Executive and mnestic impairments. *Epilepsy and Behavior*, *31*, 117–122. https://doi.org/10.1016/j.yebeh.2013.12.005

Saad, K. (2014). Childhood Epilepsy: An update on diagnosis and management. *American Journal of Neuroscience*, *5*(2), 36–51. https://doi.org/10.31128/AJGP-06-19-4957

Scheffer, I. E., Berkovic, S., Capovilla, G., Connolly, M. B., Guilhoto, L., Hirsch, E., … Solomon, L. (2017). Commission for Classification and Terminology. *Epilepsia*, *58*(4), 512–521. https://doi.org/10.1111/epi.13709.ILAE

Schoenberg, M. R., & Scott, J. G. (2011). *The little black book of neuropsychology: A syndrome-based approach*. New York: Springer.

Schouten, A., Oostrom, K. J., Pestman, W. R., Peters, A. C. B., & Jennekens-Schinkel, A. (2002). Learning and memory of school children with epilepsy: A prospective controlled longitudinal study. *Developmental Medicine and Child Neurology*, *44*(12), 803–811. https://doi.org/10.1017/S0012162201002973

Schumann, C. M., Hamstra, J., Goodlin-Jones, B. L., Kwon, H., Reiss, A. L., & Amaral, D. G. (2007). Hippocampal Size Positively Correlates With Verbal IQ in Male Children. *Hippocampus*, *17*, 486–493. https://doi.org/10.1002/hipo

Scotland, J. (2012). Exploring the philosophical underpinnings of research: Relating ontology and epistemology to the methodology and methods of the scientific, interpretive, and critical research paradigms. *English Language Teaching*, *5*(9), 9–16. https://doi.org/10.5539/elt.v5n9p9

Sebastianelli, L., Versace, V., Nothdurfter, W., Saltuari, L., Taylor, A., Trinka, E., … Trinka, E. (2017). Functional reorganization after hemispherectomy in humans and animal models: What can we learn about the brain's resilience to extensive unilateral lesions? *Brain Research Bulletin*, *131*(January), 156–167. https://doi.org/10.1016/j.brainresbull.2017.04.005

Seidenberg, M., Beck, N., Geisser, M., O'Leary, D. S., Giordani, B., Berent, S., … Boll, T. J. (1988). Neuropsychological correlates of academic achievement of children with epilepsy. *Journal of Epilepsy*, *1*(1), 23–29. https://doi.org/10.1016/S0896-6974(88)80029-X

Sepeta, L. N., Casaletto, K. B., Terwilliger, V., Facella-Ervolini, J., Sady, M., Mayo, J., … Berl, M. M. (2017). The role of executive functioning in memory performance in pediatric focal epilepsy. *Epilepsia*, *58*(2), 300–310. https://doi.org/10.1111/epi.13637

Shastin, D., Chandrasekaran, S., Ferrie, C., Vadlamani, G., Morrall, M., Warren, D., … Chumas, P. (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), 931–939.

https://doi.org/10.1007/s00381-015-2686-6

Sherman, E. M. S., Slick, D. J., Connolly, M. B., Steinbok, P., Martin, R., Strauss, E., … Farrell, K. (2003). Reexamining the effects of epilepsy surgery on IQ in children: Use of regression-based change scores. *Journal of the International Neuropsychological Society*, *9*(6), 879–886. https://doi.org/10.1017/S1355617703960085

Sherman, E. M. S., Wiebe, S., Fay-Mcclymont, T. B., Tellez-Zenteno, J., Metcalfe, A., Hernandez-Ronquillo, L., … Jetté, N. (2011). Neuropsychological outcomes after epilepsy surgery: Systematic review and pooled estimates. *Epilepsia*, *52*(5), 857–869. https://doi.org/10.1111/j.1528-1167.2011.03022.x

Shurtleff, H. A., Barry, D., Firman, T., Warner, M. H., Aguilar-Estrada, R. L., Saneto, R. P., … Ojemann, J. G. (2015). Impact of epilepsy surgery on development of preschool children: Identification of a cohort likely to benefit from early intervention. *Journal of Neurosurgery: Pediatrics*, *16*(4), 383–392. https://doi.org/10.3171/2015.3.PEDS14359

Silva, M. A., See, A. P., Essayed, W. I., Golby, A. J., & Tie, Y. (2018). Challenges and techniques for presurgical brain mapping with functional MRI. *NeuroImage: Clinical*, *17*, 794–803. https://doi.org/10.1016/j.nicl.2017.12.008

Skirrow, C., Cross, J. H., Cormack, F., Harkness, W., Vargha-Khadem, F., & Baldeweg, T. (2011). Long-term intellectual outcome after temporal lobe surgery in childhood. *Neurology*, *76*(15), 1330–1337. https://doi.org/10.1212/WNL.0b013e31821527f0

Skirrow, C., Cross, J. H., Harrison, S., Cormack, F., Harkness, W., Coleman, R., … Baldeweg, T. (2015). Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome. *Brain*, *138*(1), 80–93. https://doi.org/10.1093/brain/awu313

Skirrow, C., Cross, J. H., Owens, R., Weiss-Croft, L., Martin-Sanfilippo, P., Banks, T., … Baldeweg, T. (2019). Determinants of IQ outcome after focal epilepsy surgery in childhood: A longitudinal case-control neuroimaging

study. *Epilepsia*, *60*(5), 872–884. https://doi.org/10.1111/epi.14707

Smith, M. L. (2010). Neuropsychology in epilepsy: Children are not small adults. *Epilepsia*, *51*(Suppl. 1), 68–69. https://doi.org/10.1111/j.1528-1167.2009.02451.x

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. https://doi.org/10.1046/j.1528-1157.2002.26101.x

Smith, M. L., Elliott, I., & Lach, L. (2006). Memory outcome after pediatric epilepsy surgery: Objective and subjective perspectives. *Child Neuropsychology*, *12*(3), 151–164. https://doi.org/10.1080/09297040591001076

Spencer, S., & Huh, L. (2008). Outcomes of epilepsy surgery in adults and children. *The Lancet Neurology*, *7*(6), 525–537. https://doi.org/10.1016/S1474-4422(08)70109-1

Spencer, S. S. (2002). Neural networks in human epilepsy: Evidence of and implications for treatment. *Epilepsia*, *43*(3), 219–227. https://doi.org/10.1046/j.1528-1157.2002.26901.x

Sperling, M. R., Barshow, S., Nei, M., & Asadi-Pooya, A. A. (2016). A reappraisal of mortality after epilepsy surgery. *Neurology*, *86*(21), 1938–1944. https://doi.org/10.1212/WNL.0000000000002700

Stafstrom, C. E., & Carmant, L. (2015). Seizures and epilepsy: An overview for Neuroscientists. *Epilepsy: The Intersection of Neurosciences, Biology, Mathematics, Engineering, and Physics*, *5*, 1–18. https://doi.org/10.1101/cshperspect.a022426

Staljanssens, W., Strobbe, G., Van Holen, R., Keereman, V., Gadeyne, S., Carrette, E., … van Mierlo, P. (2017). EEG source connectivity to localize the seizure onset zone in patients with drug resistant epilepsy. *NeuroImage: Clinical*, *16*(May), 689–698. https://doi.org/10.1016/j.nicl.2017.09.011

Sterne, J. A., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G.,

… Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *British Medical Journal*, *338*(b2393). https://doi.org/10.1136/bmj.b2393

Straathof, M., Sinke, M. R. T., Roelofs, T. J. M., Blezer, E. L. A., Sarabdjitsingh, R. A., van der Toorn, A., … Dijkhuizen, R. M. (2020). Distinct structure-function relationships across cortical regions and connectivity scales in the rat brain. *Scientific Reports*, *10*(1), 1–14. https://doi.org/10.1038/s41598-019-56834-9

Sugano, H., & Arai, H. (2015). Epilepsy surgery for pediatric epilepsy: Optimal timing of surgical intervention. *Neurologia Medico-Chirurgica*, *55*(5), 399–406. https://doi.org/10.2176/nmc.ra.2014-0369

Sukheeja, D., & Mehta, J. (2016). Dysembryoplastic neuroepithelial tumor: A rare brain tumor not to be misdiagnosed. *Asian Journal of Neurosurgery*, *11*(2), 174.

Szabo, C. A., Wyllie, E., Stanford, L. D., Geckler, C., Kotagal, P., Comair, Y. G., & Thornton, A. E. (1998). Neuropsychological Effect of Temporal Lobe Resection in Preadolescent Children with Epilepsy. *Epilepsia*, *39*(8), 814–819. https://doi.org/10.1111/j.1528-1157.1998.tb01174.x

Szulevicz, T., & Tanggaard, L. (2017). *Educational psychology practice. A new theoretical framework*, *Cultural psychology of education, vol. 4*. Cham: Springer.

Talley, J. L. (1993). Children's Auditory Verbal Learning Test - 2 (CAVLT-2). Odessa, FL: Psychological Assessment Resources.

Tamber, M. S., & Mountz, J. M. (2012). Advances in the diagnosis and treatment of epilepsy. *Seminars in Nuclear Medicine*, *42*(6), 371–386. https://doi.org/10.1053/j.semnuclmed.2012.06.005

Taub, G. E., & Benson, N. (2013). Matters of Consequence: An Empirical Investigation of the WAIS-III and WAIS-IV and Implications for Addressing the Atkins Intelligence Criterion. *Journal of Forensic Psychology Practice*, *13*(1), 27–48. https://doi.org/10.1080/15228932.2013.746913

Te Nijenhuis, J., Tolboom, E., Resing, W., & Bleichrodt, N. (2004). Does Cultural Background Influence the Intellectual Performance of Children from Immigrant Groups? The RAKIT Intelligence Test for Immigrant Children. *European Journal of Psychological Assessment*, *20*(1), 10–26. https://doi.org/10.1027/1015-5759.20.1.10

te Nijenhuis, J., van Vianen, A. E. M., & van der Flier, H. (2007). Score gains on g-loaded tests: No g. *Intelligence*, *35*(3), 283–300. https://doi.org/10.1016/j.intell.2006.07.006

Tukey, J. (1977). *Exploratory data analysis*. Don Mills: Addison-Wesley Publishing Company.

Tulving, E. (2002). Episodic Memory: From Mind to Brain. *Annu. Rev. Psychol.*, *53*, 1–25. https://doi.org/10.1146/annurev.psych.53.100901.135114

Vakharia, V. N., Duncan, J. S., Witt, J. A., Elger, C. E., Staba, R., & Engel, J. (2018). Getting the best outcomes from epilepsy surgery. *Annals of Neurology*, *83*(4), 676–690. https://doi.org/10.1002/ana.25205

van Rijckevorsel, K. (2006). Cognitive problems related to epilepsy syndromes, especially malignant epilepsies. *Seizure*, *15*(4), 227–234. https://doi.org/10.1016/j.seizure.2006.02.019

Van Schooneveld, M. M. J., & Braun, K. P. J. (2013). Cognitive outcome after epilepsy surgery in children. *Brain and Development*, *35*(8), 721–729. https://doi.org/10.1016/j.braindev.2013.01.011

Vargha-Khadem, F., Isaacs, E., Watkins, K. E., & Mishkin, M. (2000). Ontogenetic specialisation of hemispheric function. In J. Oxbury, C. E. Polkey, & M. Duchowny (Eds.), *Intractable focal epilepsy.* (First, pp. 405–418). London: W.B. Saunders.

Vogt, V. L., Äikiä, M., del Barrio, A., Boon, P., Borbély, C., Bran, E., … Helmstaedter, C. (2017). Current standards of neuropsychological assessment in epilepsy surgery centers across Europe. *Epilepsia*, *58*(3), 343–355. https://doi.org/10.1111/epi.13646

Wang, Z. I., Alexopoulos, A. V., Jones, S. E., Jaisani, Z., Najm, I. M., & Prayson, R. A. (2013). The pathology of magnetic-resonance-imaging-negative epilepsy. *Modern Pathology*, *26*(8), 1051–1058. https://doi.org/10.1038/modpathol.2013.52

Watkins, M. W., Lei, P. W., & Canivez, G. L. (2007). Psychometric intelligence and achievement: A cross-lagged panel analysis. *Intelligence*, *35*(1), 59–68. https://doi.org/10.1016/j.intell.2006.04.005

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV).* San Antonio, TX: Pearson Assessment.

Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI).* San Antonio, TX.: The Psychological Corporation.

Wechsler, D. (2005). *Wechsler Individual Achievement Test-Second Edition (WIAT II)*. London: The Psychological Corp.

Wechsler, D. (2018). *Wechsler Individual Achievement Test-Third Edition (WIAT III).* London: The Psychological Corp.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children- Third Edition (WISC-III).* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2003). *Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV).* San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2014). *Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V).* San Antonio, TX: NCS Pearson.

Wechsler, D. (1997). *Wechsler Memory Scale-Third Edition (WMS-III)*. San Antonio, TX: Psychological Corporation

Wechsler, D. (2009). *Wechsler Memory Scale-Fourth edition (WMS-IV).* San Antonio, TX: Pearson.

Wechsler, D. (1989). *Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R).* San Antonio, Tx: The Psychological Corporation.

Wechsler, D. (2002). *Wechsler Preschool and Primary Scale of Intelligence-Third Edition (WPPSI-III)*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (2012). *Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition (WPPSI-IV)*. San Antonio, TX: The Psychological Corporation.

West, S., Nevitt, S. J., Cotton, J., Gandhi, S., Weston, J., Sudan, A., Ramirez, R. & Newton, R. (2019). Surgery for epilepsy. *Cochrane Database of Systematic Reviews*, *2019*(6). https://doi.org/10.1002/14651858.CD010541.pub3.

Westerveld, M., Sass, K. J., Chelune, G. J., Hermann, B. P., Barr, W. B., Loring, D. W., … Spencer, D. D. (2000). Temporal lobectomy in children: cognitive outcome. *Journal of Neurosurgery*, *92*(1), 24–30. https://doi.org/10.3171/jns.2000.92.1.0024.

Westerveld, M. (2010). Childhood Epilepsy. In K. O. Yeates, M. D. Ris, H. G. Taylor, & B. F. Pennington (Eds.), *Pediatric neuropsychology: Research, theory, and practice.* 2nd edn. (pp. 71–91). New York: Guilford Press.

Wheless, J. W., Simos, P. G., & Butler, I. J. (2002). Language dysfunction in epileptic conditions. *Seminars in Pediatric Neurology*, *9*(3), 218–228. https://doi.org/10.1053/spen.2002.35504

Widjaja, E., Jain, P., Demoe, L., Guttmann, A., Tomlinson, G., & Sander, B. (2020). Seizure outcome of pediatric epilepsy surgery: Systematic review and meta-analyses. *Neurology*, *94*(7), 311–321.

Wiebe, S., Blume, W. T., Girvin, J. P., & Eliasziw, M. (2001). A randomized, controlled trial of surgery for temporal-lobe epilepsy. *New England Journal of Medicine*, *345*(5), 311–318. https://doi.org/10.1056/NEJM200108023450501

Wieser, H. G., Blume, W. T., Fish, D., Goldensohn, E., Hufnagel, A., King, D., …

Pedley, T. A. (2001). Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*, *42*(2), 282–286. https://doi.org/10.1046/j.1528-1157.2001.35100.x

Williams, J., Phillips, T., Griebel, M. L., Sharp, G. B., Lange, B., Edgar, T., & Simpson, P. (2001). Factors Associated with Academic Achievement in Children with Controlled Epilepsy. *Epilepsy and Behavior*, *2*(3), 217–223. https://doi.org/10.1006/ebeh.2001.0166

Willig, C. (2001). *Qualitative research in Psychology: A practical guide to theory and method.* Buckingham: Open University Press.

Willment, K. C., & Golby, A. (2013). Hemispheric lateralization interrupted: Material-specific memory deficits in temporal lobe epilepsy. *Frontiers in Human Neuroscience*, *7*, 1–8. https://doi.org/10.3389/fnhum.2013.00546

Wilson, S. J., Baxendale, S., Barr, W., Hamed, S., Langfitt, J., Samson, S., Watanabe, M., Baker, G. A., Helmstaedter, C., Hermann, B. P., & Smith, M. L. (2015). Indications and expectations for neuropsychological assessment in routine epilepsy care: Report of the ILAE Neuropsychology Task Force, Diagnostic Methods Commission, 2013-2017. *Epilepsia*, *56*(5), 674–681. https://doi.org/10.1111/epi.12962

Wilson, S. J., Micallef, S., Henderson, A., Rayner, G., Wrennall, J. A., Spooner, C., & Harvey, A. S. (2012). Developmental outcomes of childhood-onset temporal lobe epilepsy: A community-based study. *Epilepsia*, *53*(9), 1587–1596. https://doi.org/10.1111/j.1528-1167.2012.03632.x

Wirrell, E. C., Grossardt, B. R., Wong-Kisiel, L. C. L., & Nickels, K. C. (2012). Incidence and Classification of New-Onset Epilepsy and Epilepsy Syndromes in Children in Olmsted County, Minnesota from 1980–2004: A population-based study. *Epilepsy Research*, *95*(1–2), 110–118. https://doi.org/10.1016/j.eplepsyres.2011.03.009

Wirrell, E. C., Wong-Kisiel, L. C. L., Mandrekar, J., & Nickels, K. C. (2013). What Predicts Enduring Intractability in Children Who Appear Medically Intractable In The First Two Years After Diagnosis? *Epilepsia*, *54*(6), 1056–1064.

https://doi.org/10.1111/epi.12169

Witt, J. A., Coras, R., Schramm, J., Becker, A. J., Elger, C. E., Blümcke, I., & Helmstaedter, C. (2014). The overall pathological status of the left hippocampus determines preoperative verbal memory performance in left mesial temporal lobe epilepsy. *Hippocampus*, *24*(4), 446–454. https://doi.org/10.1002/hipo.22238

Witt, J. A., Coras, R., Schramm, J., Becker, A. J., Elger, C. E., Blümcke, I., & Helmstaedter, C. (2015). Relevance of hippocampal integrity for memory outcome after surgical treatment of mesial temporal lobe epilepsy. *Journal of Neurology*, *262*(10), 2214–2224. https://doi.org/10.1007/s00415-015-7831-3

Witt, J. A., & Helmstaedter, C. (2012). Should cognition be screened in new-onset epilepsies? A study in 247 untreated patients. *Journal of Neurology*, *259*(8), 1727–1731. https://doi.org/10.1007/s00415-012-6526-2

Witt, J. A., & Helmstaedter, C. (2017). How can we overcome neuropsychological adverse effects of antiepileptic drugs? *Expert Opinion on Pharmacotherapy*, *18*(6), 551–554. https://doi.org/10.1080/14656566.2017.1309025

Wo, S. W., Ong, L. C., Low, W. Y., & Lai, P. S. M. (2017). The impact of epilepsy on academic achievement in children with normal intelligence and without major comorbidities: A systematic review. *Epilepsy Research*, *136*(May), 35–45. https://doi.org/10.1016/j.eplepsyres.2017.07.009

Wood, A. G., Foley, E., Virk, P., Ruddock, H., Joshee, P., Murphy, K., & Seri, S. (2020). Establishing a Developmentally Appropriate fMRI Paradigm Relevant to Presurgical Mapping of Memory in Children. *Brain Topography*, *33*(2), 267–274. https://doi.org/10.1007/s10548-019-00751-7

World Health Organisation. (2019). *Epilepsy. A Public Health Imperative*. Geneva: World Health Organization. https://doi.org/10.1525/sp.2007.54.1.23.

Yuan, W., Szaflarski, J. P., Schmithorst, V. J., Schapiro, M., Anna, W., Strawsburg, R. H., & Holland, S. K. (2006). *NIH Public Access*. *47*(3), 593–600.

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

Zhao, F., Kang, H., You, L., Venkatesh, D., & Chandra, M. (2014). Neuropsychological deficits in temporal lobe epilepsy: a comprehensive review. *Annals of Indian Academy of Neurology*, *17*(4), 374. https://doi.org/10.4103/0972-2327.144003

Ziegler, R. G., Erba, G., Holden, L., & Dennison, H. (2000). The coordinated psychosocial and neurologic care of children with seizures and their families. *Epilepsia*, *41*(6), 732-743.

Zilli, T., Zanini, S., Conte, S., Borgatti, R., & Urgesi, C. (2015). Neuropsychological assessment of children with epilepsy and average intelligence using NEPSY II. *Journal of Clinical and Experimental Neuropsychology*, *37*(10), 1036–1051. https://doi.org/10.1080/13803395.2015.1076380

Zucchella, C., Federico, A., Martini, A., Tinazzi, M., Bartolo, M., & Tamburin, S. (2018). Neuropsychological testing. *Practical Neurology*, *18*(3), 227–237. https://doi.org/10.1136/practneurol-2017-001743

**APPENDICES**

**APPENDIX A: NHS ETHICAL APPROVAL**

NHS
Health Research Authority

**London - Harrow Research Ethics Committee**
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

24 May 2016

[redacted]

Dear Professor [redacted]

| | |
|---|---|
| **Study title:** | **Hypoxia-ischaemia in children: patterns of neuropathology and associated memory impairment.** |
| **REC reference:** | **05/Q0502/88** |
| **Amendment number:** | **22** |
| **Amendment date:** | **31 March 2016** |
| **IRAS project ID:** | |

The above amendment was reviewed by the Sub-Committee in correspondence.

**ETHICAL OPINION**

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

The Sub-Committee reviewed the following:

1. Broadening inclusion criteria.
2. Updates to description of study.

3. Store personally identifiable data in UCL Data Safe Haven.
4. Extend provision of sharing anonymised data to include other collaborating institutions.
5. Documents updated with current name of section- 'Cognitive Neuroscience and Neuropsychiatry Section'.

**APPROVED DOCUMENTS**

The documents reviewed and approved at the meeting were:

| *Document* | *Version* | *Date* |
|---|---|---|
| GP/consultant information sheets or letters [LETTER TO GP patients and controls_8-17] | 2 | 31 March 2016 |
| Letters of invitation to participant [Letter to Adults_patients_ver2] | 2 | 31 March 2016 |
| Letters of invitation to participant [LETTER TO PARENTS of patients] | 4 | 31 March 2016 |
| Notice of Substantial Amendment (non-CTIMP) [IRAS submission] | 22 | 31 March 2016 |
| Other [Confirmation letter to parents] | 2 | 31 March 2016 |
| Other [LETTER TO HEAD TEACHER agreed] | 1 | 31 March 2016 |
| Other [LETTER TO HEAD TEACHER information] | 3 | 31 March 2016 |
| Other [LETTER TO PARENTS controls_8-18] | 2 | 31 March 2016 |
| Other [FLYER controls_8-18] | 3 | 31 March 2016 |
| Other [Hanging ad - adult controls] | 1 | 31 March 2016 |
| Other [HANGING AD controls_8-18] | 3 | 31 March 2016 |
| Participant consent form [Consent form - Adults] | 3 | 31 March 2016 |
| Participant consent form [Consent form - Parent or Guardian] | 7 | 31 March 2016 |
| Participant information sheet (PIS) [INFORMATION SHEET (young children 8-13), v3] | 3 | 31 March 2016 |
| Participant information sheet (PIS) [INFO SHEET (14-17, controls), v2] | 2 | 15 March 2016 |
| Participant information sheet (PIS) [INFO SHEET controls_18+] | 3 | 31 March 2016 |
| Participant information sheet (PIS) [INFO SHEET parents of controls] | 6 | 31 March 2016 |
| Participant information sheet (PIS) [INFO SHEET parents of patients] | 6 | 31 March 2016 |
| Participant information sheet (PIS) [INFO SHEET patient_14-17] | 2 | 31 March 2016 |
| Participant information sheet (PIS) [INFO SHEET patients 18+] | 3 | 31 March 2016 |

**Membership of the Committee**
The members of the Committee who took part in the review are listed on the attached sheet.

## R&D APPROVAL

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

## STATEMENT OF COMPLIANCE

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

**05/Q0502/88: Please quote this number on all correspondence**

Yours sincerely,

[redacted]

**London - Harrow Research Ethics Committee**
**Attendance at Sub-Committee of the REC meeting via correspondence**

**Committee Members:**

| *Name* | *Profession* | *Present* | *Notes* |
|---|---|---|---|
| [redacted] | Consultant in Pharmaceutical and Translational Medicine | Yes | |
| [redacted] | Consultant Anaesthetist (Chair) | Yes | |
| [redacted] | Consultant Psychologist | Yes | |

**Also in attendance:**

| *Name* | *Position (or reason for attending)* |
|---|---|
| [redacted] | REC Assistant |

**National Research Ethics Service**

NHS Health Research Authority

## NOTICE OF SUBSTANTIAL AMENDMENT (non-CTIMP)

*For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) available in the Integrated Research Application System (IRAS) at http://www.myresearchproject.org.uk or on the EudraCT website at https://eudract.ema.europa.eu/document.html.*

*To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.*

*Further guidance is available at http://www.nres.nhs.uk/applications/after-ethical-review/notification-of-amendments/.*

| | |
|---|---|
| **Details of Chief Investigator:** | Professor of Developmental Neuroscience<br><br>Head of the Cognitive Neuroscience and Neuropsychiatry Section, UCL Institute of Child Health |
| *Name:* | [redacted] |
| *Address:* | [redacted] |
| *Telephone:* | [redacted] |

| | |
|---|---|
| *E-mail:* | [redacted] |
| *Fax:* | [redacted] |

| | |
|---|---|
| **FULL TITLE OF STUDY:** | Hypoxia/ischaemia in children: Patterns of neuropathology and associated memory impairment |
| **LEAD SPONSOR:** | R&D for UCL Institute of Child Health & Great Ormond Street Hospital |
| **NAME OF REC:** | Previously: UCL/UCLH Committee Alpha<br>Currently: London-Bentham Research Ethics Committee |
| **REC REFERENCE NUMBER:** | 05/Q0502/88 |
| **NAME OF LEAD R&D OFFICE:** | R&D for UCL Institute of Child Health & Great Ormond Street Hospital |
| **DATE STUDY COMMENCED:** | 01/11/2005 |
| **PROTOCOL REFERENCE (IF APPLICABLE), CURRENT VERSION AND DATE:** | MRC Protocol version 3 revised 13th January 2012 |
| **AMENDMENT NUMBER AND DATE:** | Amendment 22, 31st March 2016 |

| |
|---|
| **Type of amendment (indicate all that apply in bold)**<br><br>*(a) Amendment to information previously given on the REC Application Form* |

***Yes***

*If yes, please refer to relevant sections of the REC application in the "summary of changes" below.*

*(b) Amendment to the protocol*

***No***

*If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.*

*(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting documentation for the study*

***Yes***

*If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.*

**Is this a modified version of an amendment previously notified to the REC and given an unfavourable opinion?**

***No***

**SUMMARY OF CHANGES**

*Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study.*

*If this is a modified amendment, please explain how the modifications address concerns raised previously by the ethics committee.*

*If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific*

*information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.*

1. We began our research programme on the effects of hypoxia on cognitive development by investigating different cohorts of children and adolescents with cardiorespiratory conditions.

   Although recruitment to some of our cohorts (e.g. prematurity and cardiac arrest) is now complete, our overall programme is ongoing, and recruitment is continuing. In the course of our investigations we have become aware that some of our patients who meet our inclusionary criteria have a history of hypoxia arising from aetiologies other than cardiorespiratory problems. We now have to take account of this finding by recruiting patients from a broader spectrum of conditions, as investigating these patients is fundamental to the fulfilment of our research objective. At the same time this expansion will improve our recruitment rates and will enable us to meet our targets. The addition of patients from other aetiological categories will require a small change in our study description in the supporting documents, but it will not affect our protocols. We have enclosed all updated documents for your consideration.

   Firstly, we need to update the description of our study to be more inclusive of the broader spectrum of aetiologies, and the proposed amendments have been highlighted in the enclosed documents. Secondly, some of our participants are now over the age limit we were initially recruiting from, but they are still actively taking part in our ongoing research. Therefore, we would like to amend the supporting documents to remove the upper age limit of 18-22 years. Again, these changes have been highlighted for your attention.

2. We would like to store personally identifiable data in UCL Data Safe Haven (this is a UCL computer system designed to keep health research data secure). UCL researchers collecting and using personally identifiable information are advised to use the data safe haven to satisfy data security requirements. Safe Haven is ISO27001 certified and conforms to the NHS Information Governance Toolkit. Having access to identifiable data for the duration of the project makes the work of researchers easier and more efficient, it also leaves less scope for errors. There are also concerns that referring to audio visual recorded

data as anonymised is misleading, as it is not anonymous by virtue of showing the face of the participant. Please see the amended information sheets below for your review.

3. We currently have a provision to share anonymised data with the custodians of other ethically approved studies within UCL, which we would like to extend to include other collaborating institutions. We have been advised by our Data Protection Office at UCL that as the provision concerns fully anonymised data, it is not covered by the DPA and should not form part of the consent form. Therefore we removed this clause from our consent forms, but included it in the information sheets. Please find updated consent forms and information sheets attached.

4. All documents will also need to be updated with the current name of the section – 'Cognitive Neuroscience and Neuropsychiatry Section' (formerly 'Developmental Cognitive Neuroscience Unit'). Please find the amended documents included.

**ANY OTHER RELEVANT INFORMATION**

**Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.**

**List of enclosed documents**

| *Document* | *Version* | *Date* |
|---|---|---|
| 1. Confirmation letter to parents | 2 | 31 March 2016 |
| 2. Consent form (adults) | 3 | 31 March 2016 |
| 3. Consent form (parent or guardian) | 7 | 31 March 2016 |
| 4. Flyer (ages 8-18, controls) | 3 | 31 March 2016 |
| 5. Recruitment advertisement (adults, controls) | 1 | 31 March 2016 |
| 6. Recruitment advertisement (ages 8-18, controls) | 3 | 31 March 2016 |
| 7. Information sheet for control children (ages 14-17) | 2 | 31 March 2016 |
| 8. Information sheet for children (ages 8-13) | 3 | 31 March 2016 |

| | | |
|---|---|---|
| 9. Information sheet for adults (control) | 3 | 31 March 2016 |
| 10. Information sheet for parents of controls | 6 | 31 March 2016 |
| 11. Information sheet for parents of patients | 6 | 31 March 2016 |
| 12. Information sheet for children (patients, ages 14-17) | 2 | 31 March 2016 |
| 13. Information sheet for adult patients | 3 | 31 March 2016 |
| 14. Letter to adult patients | 2 | 31 March 2016 |
| 15. Letter to GP | 2 | 31 March 2016 |
| 16. Letter to head teacher (no. 1) | 3 | 31 March 2016 |
| 17. Letter to head teacher (no. 2) | 2 | 31 March 2016 |
| 18. Letter to parents of controls | 2 | 31 March 2016 |
| 19. Letter to parents of patients | 4 | 31 March 2016 |

**DECLARATION BY CHIEF INVESTIGATOR**

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.

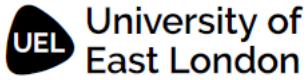
- I consider that it would be reasonable for the proposed amendment to be implemented.

*Signature of Chief Investigator:*  ……

*Print name:* [redacted]

*Date of submission: 31st March 2016*

## APPENDIX B: UEL BOARD OF ETHICS LETTER




Dear Jennifer,

**Application ID: ETH1819-0083**

Project title: COGNITIVE OUTCOMES IN CHILDREN WITH TEMPORAL LOBE EPILEPSY: PREDICTORS OF ACADEMIC ATTAINMENT

Lead researcher: Miss Jennifer Black

Your application to Research, Research Degrees and Ethics Sub-Committee meeting was considered on the 7th of October 2019.

The decision is: **Approved**

The Committee's response is based on the protocol described in the application form and supporting documentation.

Your project has received ethical approval for 2 years from the approval date.

If you have any questions regarding this application please contact the Research, Research Degrees and Ethics Sub Committee meeting.

Approval has been given for the submitted application only and the research must be conducted accordingly.

Should you wish to make any changes in connection with this research project you must complete 'An application for approval of an amendment to an existing application'.

The approval of the proposed research applies to the following research site.

Research site: UCL Institute of Child Health/Great Ormond Street Hospital

Principal Investigator / Local Collaborator: Miss Jennifer Black

Approval is given on the understanding that the UEL Code of Practice for Research and the Code of Practice for Research Ethics is adhered to.

Any adverse events or reactions that occur in connection with this research project should be reported using the University's form for Reporting an Adverse/Serious Adverse Event/Reaction.

The University will periodically audit a random sample of approved applications for ethical approval, to ensure that the research projects are conducted in compliance with the consent given by the Research Ethics Committee and to the highest standards of rigour and integrity.

Please note, it is your responsibility to retain this letter for your records.

With the Committee's best wishes for the success of the project

Yours sincerely

[redacted]

Research, Research Degrees and Ethics Sub-Committee

## APPENDIX C: ENGEL CLASSIFICATION SYSTEM

| | |
|---|---|
| **Class I** | Seizure free or no more than a few early, non-disabling seizures; or seizures upon drug withdrawal only. |
| **Class II** | Disabling seizures occur rarely during a period of at least 2 years; disabling seizures may have been more frequent soon after surgery; nocturnal seizures. |
| **Class III** | Worthwhile improvement; seizure reduction for prolonged periods but less than 2 years. |
| **Class IV** | No worthwhile improvement; some reduction, no reduction, or worsening are possible. |

**Table A.** ***Engel classification of seizure outcomes following neurosurgical resection (based on Engel, Cascino, Ness, Rasmussen & Ojemann, 1993)***

## APPENDIX D: SPSS DATA OUTPUT

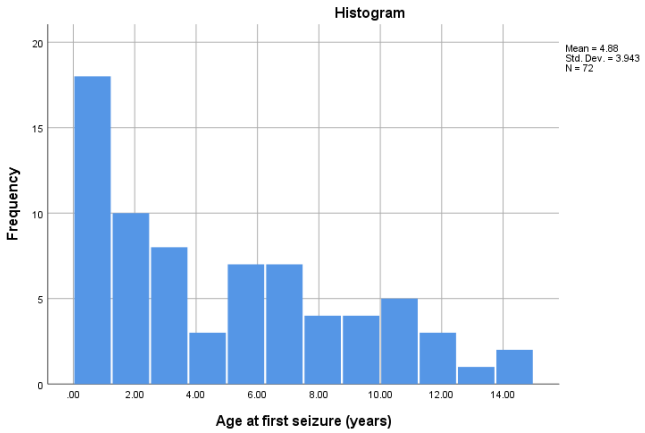



**Figure A. Age at seizure onset (whole sample) prior to Blom transformation.**

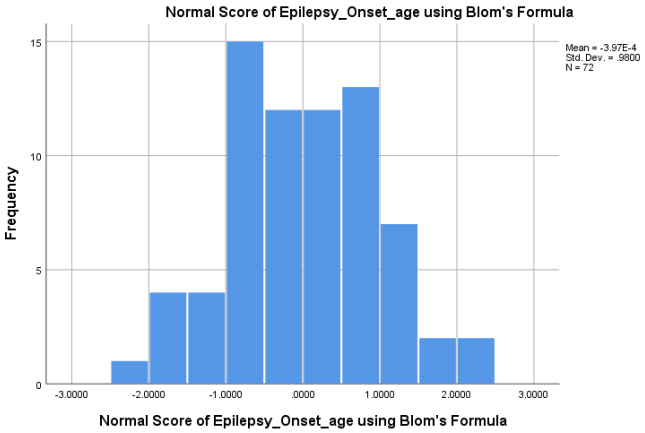



**Figure B. Age at seizure onset (whole sample) with Blom transformation.**

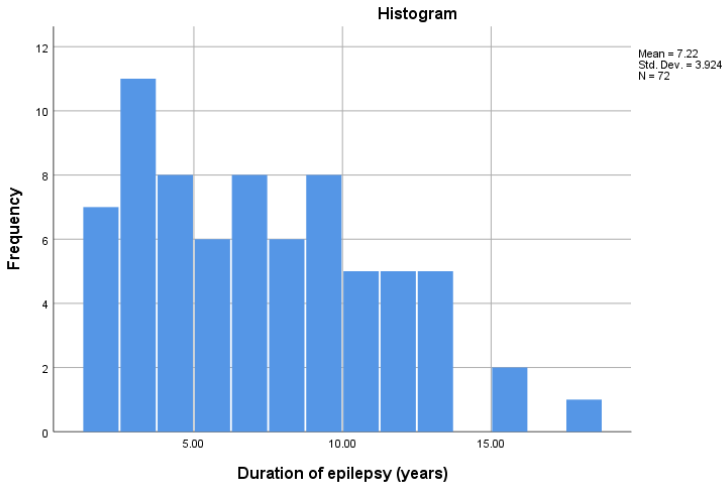



**Figure C. Duration of epilepsy (whole sample) prior to Blom transformation.**

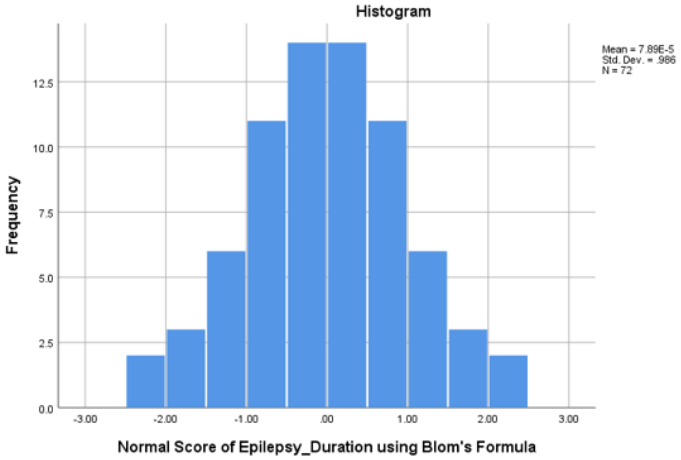



**Figure D. Duration of epilepsy (whole sample) with Blom transformation.**

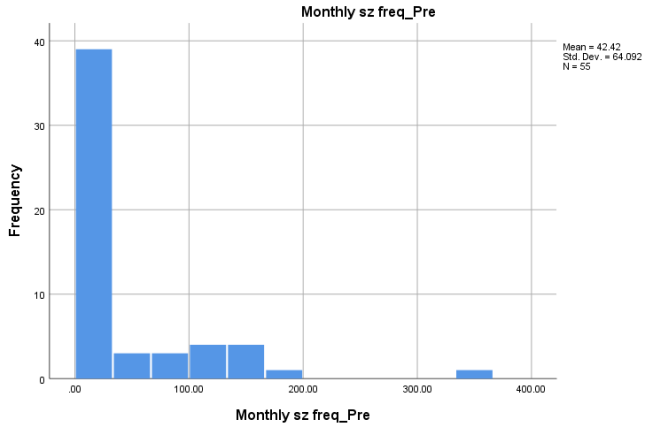



**Figure E. Monthly seizure frequency (whole sample) prior to Blom transformation.**

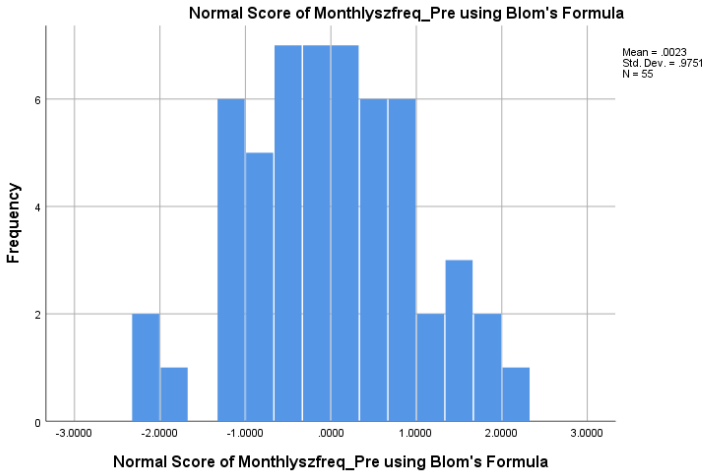



**Figure F. Monthly seizure frequency (whole sample) with Blom transformation.**

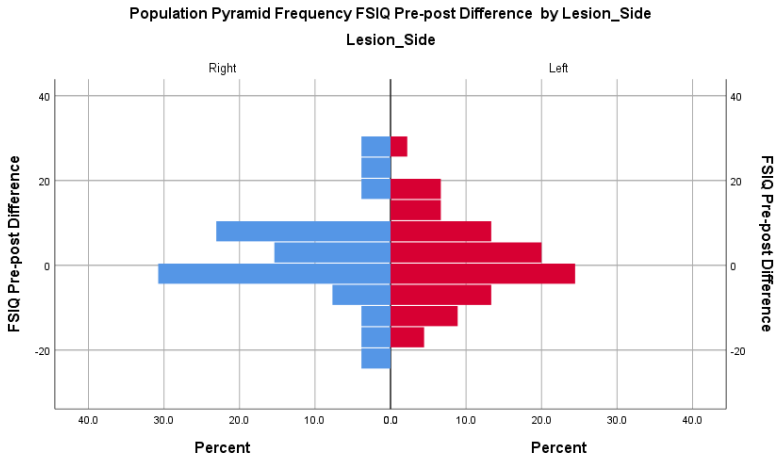



**Figure G. Population pyramid showing individual variability for FSIQ difference (Pre-Post)**

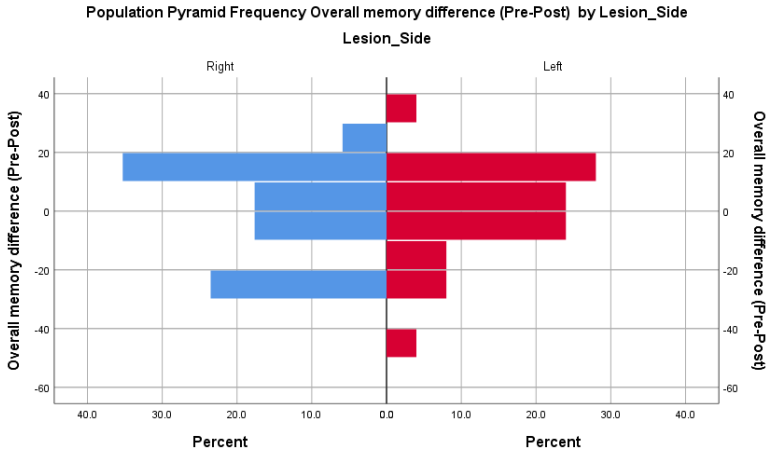



**Figure H. Population pyramid showing individual variability for overall memory difference (Pre-Post)**

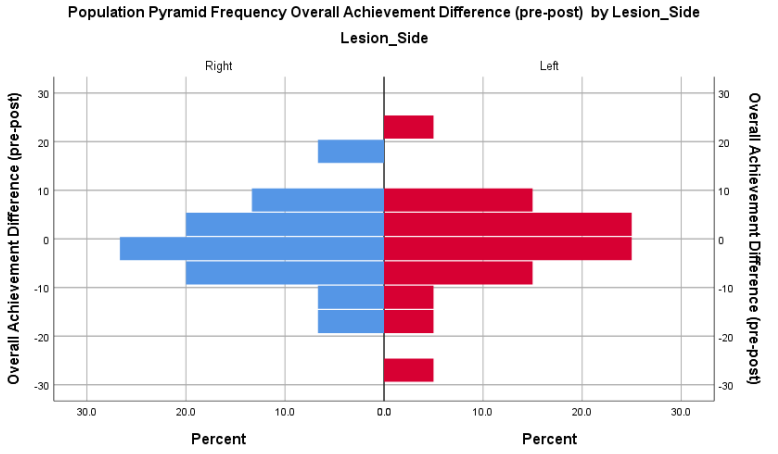



**Figure I. Population pyramid showing individual variability for academic attainment difference (Pre-Post)**

**Table B. Means and SD of Pre and Post-operative scores for the right TLE group.**

| | *N* | *Mean* | *Std. Deviation* |
|---|---|---|---|
| FSIQ (Pre) | 26 | 91.27 | 16.161 |
| FSIQ (Post) | 26 | 89.69 | 15.283 |
| VCI (Pre) | 26 | 92.92 | 14.897 |
| VCI (Post) | 25 | 90.32 | 13.795 |
| PRI (Pre) | 26 | 95.27 | 15.924 |
| PRI (Post) | 25 | 96.52 | 14.592 |
| PSI (Pre) | 24 | 87.79 | 15.921 |
| PSI (Post) | 24 | 87.13 | 14.272 |
| WMI (Pre) | 26 | 90.31 | 13.962 |
| WMI (Post) | 24 | 92.13 | 17.063 |
| Overall Memory (Pre) | 20 | 84.70 | 22.882 |
| Overall Memory (Post) | 25 | 87.76 | 19.193 |
| Visual Immediate (Pre) | 21 | 90.43 | 21.262 |
| Visual Delayed (Pre) | 20 | 91.85 | 18.027 |
| Visual Immediate (Post) | 25 | 92.08 | 14.227 |
| Visual Delayed (Post) | 25 | 90.00 | 16.998 |
| Verbal Immediate (Pre) | 21 | 81.86 | 18.040 |
| Verbal Delayed (Pre) | 21 | 87.29 | 21.900 |
| Verbal Immediate (Post) | 25 | 88.20 | 17.270 |
| Verbal Delayed (Post) | 25 | 91.20 | 19.162 |
| Overall Achievement (Pre) | 21 | 94.05 | 19.164 |
| Overall Achievement (Post) | 22 | 91.86 | 16.921 |
| Word Reading (Pre) | 23 | 95.91 | 18.251 |
| Word Reading (Post) | 25 | 92.60 | 15.300 |
| Numerical Operations (Pre) | 22 | 92.00 | 17.763 |
| Numerical Operations (Post) | 23 | 93.96 | 15.879 |
| Spelling (Pre) | 22 | 94.82 | 12.868 |
| Spelling (Post) | 23 | 91.74 | 17.062 |

**Table C. Means and SD of Pre and Post-operative scores for the left TLE group.**

| | *N* | *Mean* | *Std. Deviation* |
|---|---|---|---|
| FSIQ (Pre) | 45 | 91.16 | 13.683 |
| FSIQ (Post) | 46 | 89.76 | 15.652 |
| VCI (Pre) | 46 | 91.54 | 12.968 |
| VCI (Post) | 46 | 88.78 | 15.223 |
| PRI (Pre) | 45 | 98.76 | 12.149 |
| PRI (Post) | 46 | 98.13 | 14.874 |
| PSI (Pre) | 42 | 91.43 | 12.745 |
| PSI (Post) | 46 | 91.20 | 14.621 |
| WMI (Pre) | 43 | 92.12 | 15.48 |
| WMI (Post) | 46 | 88.72 | 13.065 |
| Overall Memory (Pre) | 40 | 86.13 | 18.503 |
| Overall Memory (Post) | 44 | 88.14 | 17.430 |
| Visual Immediate (Pre) | 43 | 95.65 | 14.003 |
| Visual Delayed (Pre) | 40 | 95.10 | 13.030 |
| Visual Immediate (Post) | 44 | 97.66 | 14.464 |
| Visual Delayed (Post) | 44 | 99.52 | 11.902 |
| Verbal Immediate (Pre) | 43 | 82.33 | 18.461 |
| Verbal Delayed (Pre) | 43 | 86.07 | 18.335 |
| Verbal Immediate (Post) | 44 | 81.95 | 18.703 |
| Verbal Delayed (Post) | 44 | 84.23 | 19.460 |
| Overall Achievement (Pre) | 39 | 93.97 | 16.803 |
| Overall Achievement (Post) | 43 | 93.47 | 17.355 |
| Word Reading (Pre) | 42 | 92.62 | 13.074 |
| Word Reading (Post) | 45 | 89.69 | 15.337 |
| Numerical Operations (Pre) | 39 | 96.54 | 18.983 |
| Numerical Operations (Post) | 43 | 95.60 | 17.885 |
| Spelling (Pre) | 41 | 92.34 | 13.685 |
| Spelling (Post) | 45 | 92.84 | 14.808 |

**Table D. Means and SD of Pre and Post-operative scores for the Tumour group.**

| | *N* | *Mean* | *Std. Deviation* |
|---|---|---|---|
| FSIQ (Pre) | 36 | 92.83 | 14.604 |
| FSIQ (Post) | 37 | 90.89 | 17.298 |
| VCI (Pre) | 37 | 92.78 | 14.193 |
| VCI (Post) | 36 | 90.67 | 16.209 |
| PRI (Pre) | 36 | 98.44 | 13.179 |
| PRI (Post) | 36 | 97.44 | 16.366 |
| PSI (Pre) | 35 | 91.51 | 13.813 |
| PSI (Post) | 35 | 91.74 | 14.875 |
| WMI (Pre) | 36 | 92.56 | 14.256 |
| WMI (Post) | 35 | 92.09 | 16.105 |
| Overall Memory (Pre) | 29 | 86.83 | 20.242 |
| Overall Memory (Post) | 35 | 90.63 | 19.353 |
| Visual Immediate (Pre) | 32 | 96.59 | 15.819 |
| Visual Delayed (Pre) | 29 | 97.45 | 13.956 |
| Visual Immediate (Post) | 35 | 96.06 | 15.237 |
| Visual Delayed (Post) | 35 | 99.20 | 14.192 |
| Verbal Immediate (Pre) | 32 | 81.38 | 20.009 |
| Verbal Delayed (Pre) | 32 | 84.22 | 21.823 |
| Verbal Immediate (Post) | 35 | 85.80 | 21.420 |
| Verbal Delayed (Post) | 35 | 88.83 | 23.540 |
| Overall Achievement (Pre) | 31 | 95.03 | 16.646 |
| Overall Achievement (Post) | 34 | 92.47 | 17.122 |
| Word Reading (Pre) | 34 | 94.38 | 12.223 |
| Word Reading (Post) | 36 | 90.78 | 14.606 |
| Numerical Operations (Pre) | 31 | 95.97 | 17.348 |
| Numerical Operations (Post) | 35 | 95.17 | 17.643 |
| Spelling (Pre) | 34 | 94.12 | 13.495 |
| Spelling (Post) | 35 | 93.46 | 14.288 |

**Table E. Means and SD of Pre and Post-operative scores for the MTS group.**

| | *N* | *Mean* | *Std. Deviation* |
|---|---|---|---|
| FSIQ (Pre) | 28 | 88.25 | 13.232 |
| FSIQ (Post) | 28 | 87.68 | 12.561 |
| VCI (Pre) | 28 | 91.39 | 12.591 |
| VCI (Post) | 28 | 87.39 | 12.420 |
| PRI (Pre) | 28 | 95.54 | 14.380 |
| PRI (Post) | 28 | 96.32 | 11.944 |
| PSI (Pre) | 26 | 87.31 | 12.441 |
| PSI (Post) | 28 | 87.54 | 13.240 |
| WMI (Pre) | 27 | 88.07 | 13.123 |
| WMI (Post) | 28 | 87.71 | 12.159 |
| Overall Memory (Pre) | 26 | 83.96 | 19.615 |
| Overall Memory (Post) | 27 | 81.74 | 16.124 |
| Visual Immediate (Pre) | 27 | 91.04 | 18.007 |
| Visual Delayed (Pre) | 26 | 90.69 | 15.579 |
| Visual Immediate (Post) | 27 | 92.96 | 14.471 |
| Visual Delayed (Post) | 27 | 89.89 | 14.672 |
| Verbal Immediate (Pre) | 27 | 82.89 | 16.496 |
| Verbal Delayed (Pre) | 27 | 87.41 | 16.425 |
| Verbal Immediate (Post) | 27 | 79.85 | 13.939 |
| Verbal Delayed (Post) | 27 | 82.48 | 14.588 |
| Overall Achievement (Pre) | 24 | 89.75 | 15.400 |
| Overall Achievement (Post) | 24 | 90.00 | 13.387 |
| Word Reading (Pre) | 26 | 91.38 | 17.468 |
| Word Reading (Post) | 27 | 88.67 | 15.307 |
| Numerical Operations (Pre) | 25 | 91.12 | 19.053 |
| Numerical Operations (Post) | 24 | 92.83 | 15.107 |
| Spelling (Pre) | 25 | 90.84 | 12.233 |
| Spelling (Post) | 26 | 88.69 | 16.171 |

**Table F. Means and SD of Pre and Post-operative scores for the FCD group.**

| | *N* | *Mean* | *Std. Deviation* |
|---|---|---|---|
| FSIQ (Pre) | 7 | 94.57 | 18.955 |
| FSIQ (Post) | 7 | 91.86 | 16.497 |
| VCI (Pre) | 7 | 90.71 | 16.173 |
| VCI (Post) | 7 | 90.14 | 15.805 |
| PRI (Pre) | 7 | 100.29 | 14.009 |
| PRI (Post) | 7 | 103.14 | 16.426 |
| PSI (Pre) | 5 | 94.80 | 22.095 |
| PSI (Post) | 7 | 89.14 | 18.398 |
| WMI (Pre) | 6 | 99.83 | 22.921 |
| WMI (Post) | 7 | 87.57 | 15.339 |
| Overall Memory (Pre) | 5 | 87.60 | 22.93 |
| Overall Memory (Post) | 7 | 99.00 | 6.658 |
| Visual Immediate (Pre) | 5 | 92.60 | 15.900 |
| Visual Delayed (Pre) | 5 | 91.40 | 13.722 |
| Visual Immediate (Post) | 7 | 103.86 | 7.515 |
| Visual Delayed (Post) | 7 | 104.29 | 5.469 |
| Verbal Immediate (Pre) | 5 | 83.40 | 18.008 |
| Verbal Delayed (Pre) | 5 | 95.80 | 18.254 |
| Verbal Immediate (Post) | 7 | 93.14 | 12.980 |
| Verbal Delayed (Post) | 7 | 92.86 | 9.940 |
| Overall Achievement (Pre) | 5 | 108.00 | 26.739 |
| Overall Achievement (Post) | 7 | 105.14 | 24.654 |
| Word Reading (Pre) | 5 | 102.2 | 18.86 |
| Word Reading (Post) | 7 | 98.43 | 18.329 |
| Numerical Operations (Pre) | 5 | 107.2 | 20.729 |
| Numerical Operations (Post) | 7 | 101.86 | 21.396 |
| Spelling (Pre) | 4 | 100.25 | 19.050 |
| Spelling (Post) | 7 | 101.57 | 16.369 |

**Table G. One-way ANOVA with eta and Levene's tests on pre-surgery scores for the *left* versus *right* side lesion groups**

| | | One-Way ANOVA | | | | Levene's Test | | |
|---|---|---|---|---|---|---|---|---|
| | ***N*** | ***df*** | ***F*** | ***Sig.*** | ***eta*** | ***df*** | ***Statistic*** | ***Sig.*** |
| FSIQ (Pre) | 71 | 1,69 | 0.001 | .975 | .004 | 1,69 | 0.394 | .532 |
| VCI (Pre) | 72 | 1,70 | 0.169 | .682 | .049 | 1,70 | 1.451 | .232 |
| PRI (Pre) | 71 | 1,69 | 1.077 | .303 | .124 | 1,69 | 0.964 | .330 |
| PSI (Pre) | 66 | 1,64 | 1.035 | .313 | .126 | 1,64 | 1.195 | .278 |
| WMI (Pre) | 69 | 1,67 | 0.238 | .627 | .059 | 1,67 | 0.958 | .331 |
| Overall Memory (Pre) | 60 | 1,58 | 0.067 | .796 | .034 | 1,58 | 0.287 | .594 |
| Visual Immediate (Pre) | 64 | 1,62 | 1.381 | .244 | .148 | 1,62 | 3.770 | .057 |
| Visual Delayed (Pre) | 60 | 1,58 | 0.638 | .428 | .104 | 1,58 | 1.857 | .178 |
| Verbal Immediate (Pre) | 64 | 1,62 | 0.009 | .924 | .012 | 1,62 | 0.009 | .925 |
| Verbal Delayed (Pre) | 64 | 1,62 | 0.005 | .816 | .030 | 1,62 | 0.616 | .435 |
| Academic Overall (Pre) | | | | | | | | |
| Word Reading (Pre) | 65 | 1,63 | 0.709 | .403 | .105 | 1,63 | 2.453 | .122 |
| Numerical Operations (Pre) | 61 | 1,59 | 0.841 | .363 | .119 | 1,59 | 0.097 | .757 |
| Spelling (Pre) | 63 | 1,61 | 0.488 | .487 | .089 | 1,61 | 0.550 | .461 |

**Table H. One-way ANOVA with eta and Levene's tests on post-surgery scores for the *left* versus *right* side lesion groups**

| | | One-Way ANOVA | | | | Levene's Test | | |
|---|---|---|---|---|---|---|---|---|
| | ***N*** | ***df*** | ***F*** | ***Sig.*** | ***eta*** | ***df*** | ***Statistic*** | ***Sig.*** |
| FSIQ (Post) | 72 | 1,70 | 0.000 | .986 | .002 | 1,70 | 0.433 | .513 |
| VCI (Post) | 71 | 1,69 | 0.176 | .676 | .050 | 1,69 | 0.117 | .733 |
| PRI (Post) | 71 | 1,69 | 0.192 | .662 | .053 | 1,69 | 0.120 | .730 |
| PSI (Post) | 70 | 1,68 | 1.242 | .269 | .134 | 1,68 | 0.174 | .678 |
| WMI (Post) | 70 | 1,68 | 0.866 | .355 | .112 | 1,68 | 1.113 | .295 |
| Overall Memory (Post) | 69 | 1,67 | 0.007 | .934 | .010 | 1,67 | 0.579 | .450 |
| Visual Immediate (Post) | 69 | 1,67 | 2.400 | .126 | .186 | 1,67 | 0.083 | .775 |
| Visual Delayed (Post) | 69 | 1,67 | 7.436 | .008 | .316 | 1,67 | 5.770 | .019 |
| Verbal Immediate (Post) | 69 | 1,67 | 1.877 | .175 | .165 | 1,67 | 0.131 | .718 |
| Verbal Delayed (Post) | 69 | 1,67 | 2.069 | .155 | .173 | 1,67 | 0.005 | .941 |
| Academic Overall (Post) | | | | | | | | |
| Word Reading (Post) | 70 | 1,68 | 0.580 | .449 | .092 | 1,68 | 0.233 | .631 |
| Numerical Operations (Post) | 66 | 1,64 | 0.137 | .712 | .046 | 1,64 | 0.974 | .328 |
| Spelling (Post) | 68 | 1,66 | 0.076 | .783 | .034 | 1,66 | 0.576 | .450 |

**Table I. One-way ANOVA with eta and Levene's tests on pre-surgery scores for the *MTS, Tumour* and *FCD* pathology groups**

| | | One-Way ANOVA | | | | Levene's Test | | |
|---|---|---|---|---|---|---|---|---|
| | ***N*** | ***df*** | ***F*** | ***Sig.*** | ***eta*** | ***df*** | ***Statistic*** | ***Sig.*** |
| FSIQ (Pre) | 71 | 2,68 | 0.994 | .376 | .168 | 2,68 | 0.357 | .701 |
| VCI (Pre) | 72 | 2,69 | 0.117 | .890 | .058 | 2,69 | 0.446 | .642 |
| PRI (Pre) | 71 | 2,68 | 0.515 | .600 | .122 | 2,68 | 0.258 | .773 |
| PSI (Pre) | 66 | 2,63 | 0.981 | .381 | .174 | 2,63 | 1.306 | .278 |
| WMI (Pre) | 69 | 2,66 | 1.795 | .174 | .227 | 2,66 | 2.220 | .117 |
| Overall Memory (Pre) | 60 | 2,57 | 0.164 | .849 | .076 | 2,57 | 0.032 | .968 |
| Visual Immediate (Pre) | 64 | 2,61 | 0.819 | .446 | .162 | 2,61 | 0.159 | .854 |
| Visual Delayed (Pre) | 60 | 2,57 | 1.540 | .223 | .226 | 2,57 | 0.138 | .872 |
| Verbal Immediate (Pre) | 64 | 2,61 | 0.061 | .941 | .045 | 2,61 | 0.758 | .473 |
| Verbal Delayed (Pre) | 64 | 2,61 | 0.820 | .445 | .162 | 2,61 | 1.215 | .304 |
| Academic Overall (Pre) | 60 | 2,57 | 2.479 | .093 | .283 | 2,57 | 2.357 | .104 |
| Word Reading (Pre) | 65 | 2,62 | 1.144 | .325 | .189 | 2,62 | 1.521 | .227 |
| Numerical Operations (Pre) | 61 | 2,58 | 1.712 | .189 | .236 | 2,58 | 0.110 | .896 |
| Spelling (Pre) | 63 | 2,60 | 1.029 | .364 | .182 | 2,60 | 1.056 | .354 |

**Table J. One-way ANOVA with eta and Levene's tests on post-surgery scores for the *MTS, Tumour* and *FCD* pathology groups**

| | | One-Way ANOVA | | | | Levene's Test | | |
|---|---|---|---|---|---|---|---|---|
| | ***N*** | ***df*** | ***F*** | ***Sig.*** | ***eta*** | ***df*** | ***Statistic*** | ***Sig.*** |
| FSIQ (Post) | 72 | 2,69 | 0.413 | .663 | .109 | 2,69 | 1.227 | .299 |
| VCI (Post) | 71 | 2,68 | 0.398 | .673 | .108 | 2,68 | 1.158 | .320 |
| PRI (Post) | 71 | 2,68 | 0.599 | .552 | .132 | 2,68 | 1.918 | .155 |
| PSI (Post) | 70 | 2,67 | 0.653 | .524 | .138 | 2,67 | 0.457 | .635 |
| WMI (Post) | 70 | 2,67 | 0.798 | .454 | .153 | 2,67 | 1.154 | .322 |
| Overall Memory (Post) | 69 | 2,66 | 3.585 | .033 | .313 | 2,66 | 3.563 | .034 |
| Visual Immediate (Post) | 69 | 2,66 | 1.622 | .205 | .216 | 2,66 | 1.237 | .297 |
| Visual Delayed (Post) | 69 | 2,66 | 4.828 | .011 | .357 | 2,66 | 2.081 | .133 |
| Verbal Immediate (Post) | 69 | 2,66 | 1.767 | .179 | .225 | 2,66 | 4.027 | .022 |
| Verbal Delayed (Post) | 69 | 2,66 | 1.195 | .309 | .187 | 2,66 | 5.816 | .005 |
| Academic Overall (Post) | 65 | 2,62 | 2.234 | .116 | .259 | 2,62 | 2.575 | .084 |
| Word Reading (Post) | 70 | 2,67 | 1.140 | .326 | .181 | 2,67 | 0.123 | .884 |
| Numerical Operations (Post) | 66 | 2,63 | 0.751 | .476 | .153 | 2,63 | 0.795 | .456 |
| Spelling (Post) | 68 | 2,65 | 2.122 | .128 | .248 | 2,65 | 0.243 | .785 |

**Table K. Paired T-tests to examine differences between the pre and post op test scores for the left TLE group.**

| | | | | Paired Samples T-test | | | |
|---|---|---|---|---|---|---|---|
| | ***N*** | ***Mean*** | ***SD*** | ***t*** | ***df*** | ***Sig (2-tailed)*** | ***Cohen's d*** |
| FSIQ (Pre) | 45 | 91.16 | 13.683 | 0.958 | 44 | 0.343 | 0.142 |
| FSIQ (Post) | 45 | 89.82 | 15.823 | | | | |
| VCI (Pre) | 46 | 91.54 | 12.968 | 2.351 | 45 | 0.023 | 0.346 |
| VCI (Post) | 46 | 88.78 | 15.223 | | | | |
| PRI (Pre) | 45 | 98.76 | 12.149 | 0.259 | 44 | 0.797 | 0.038 |
| PRI (Post) | 45 | 98.33 | 14.977 | | | | |
| PSI (Pre) | 42 | 91.43 | 12.745 | -0.464 | 41 | 0.645 | -0.071 |
| PSI (Post) | 42 | 92.21 | 14.738 | | | | |
| WMI (Pre) | 43 | 92.12 | 15.48 | 1.600 | 42 | 0.117 | 0.244 |
| WMI (Post) | 43 | 88.95 | 13.18 | | | | |
| Overall Memory (Pre) | 38 | 87.47 | 17.983 | 0.401 | 37 | 0.690 | 0.065 |
| Overall Memory (Post) | 38 | 86.53 | 16.479 | | | | |
| Visual Immediate (Pre) | 41 | 96.41 | 13.887 | -0.448 | 40 | 0.657 | -0.069 |
| Visual Immediate (Post) | 41 | 97.63 | 14.931 | | | | |
| Visual Delayed (Pre) | 38 | 96.32 | 12.11 | -1.250 | 37 | 0.219 | -0.202 |
| Visual Delayed (Post) | 38 | 99.05 | 11.889 | | | | |
| Verbal Immediate (Pre) | 41 | 82.83 | 18.72 | 0.900 | 40 | 0.373 | 0.140 |
| Verbal Immediate (Post) | 41 | 80.63 | 17.731 | | | | |
| Verbal Delayed (Pre) | 41 | 87.2 | 18.017 | 1.786 | 40 | 0.082 | 0.278 |
| Verbal Delayed (Post) | 41 | 83.51 | 18.155 | | | | |
| Word Reading (Pre) | 42 | 92.62 | 13.074 | 1.509 | 41 | 0.139 | 0.232 |
| Word Reading (Post) | 42 | 90.36 | 15.544 | | | | |
| Numerical Operations (Pre) | 38 | 97.34 | 18.553 | -0.030 | 37 | 0.976 | -0.004 |
| Numerical Operations (Post) | 38 | 97.39 | 18.256 | | | | |
| Spelling (Pre) | 41 | 92.34 | 13.685 | -0.508 | 40 | 0.614 | -0.079 |
| Spelling (Post) | 41 | 93.24 | 15.155 | | | | |

**Table L. Paired T-tests to examine differences between the pre and post op test scores for the right TLE group.**

| | *N* | *Mean* | *SD* | **Paired Samples T-test** | | | |
|---|---|---|---|---|---|---|---|
| | | | | ***t*** | ***df*** | ***Sig (2-tailed)*** | ***Cohen's d*** |
| FSIQ (Pre) | 26 | 91.27 | 16.161 | 0.753 | 25 | 0.458 | 0.147 |
| FSIQ (Post) | 26 | 89.69 | 15.283 | | | | |
| VCI (Pre) | 25 | 93.64 | 14.739 | -0.31 | 24 | 0.759 | 0.315 |
| VCI (Post) | 25 | 90.32 | 13.795 | | | | |
| PRI (Pre) | 25 | 95.72 | 16.082 | -0.365 | 23 | 0.718 | -0.062 |
| PRI (Post) | 25 | 96.52 | 14.592 | | | | |
| PSI (Pre) | 22 | 87.59 | 13.835 | -0.434 | 19 | 0.669 | -0.004 |
| PSI (Post) | 22 | 87.64 | 14.032 | | | | |
| WMI (Pre) | 24 | 91.13 | 13.901 | -0.922 | 19 | 0.368 | -0.074 |
| WMI (Post) | 24 | 92.13 | 17.063 | | | | |
| Overall Memory (Pre) | 19 | 84.47 | 23.486 | 1.415 | 21 | 0.172 | -0.033 |
| Overall Memory (Post) | 19 | 85.00 | 19.061 | | | | |
| Visual Immediate (Pre) | 20 | 89.20 | 21.035 | 1.196 | 19 | 0.247 | -0.097 |
| Visual Immediate (Post) | 20 | 91.10 | 15.331 | | | | |
| Visual Delayed (Pre) | 19 | 91.58 | 18.479 | 1.577 | 24 | 0.128 | 0.183 |
| Visual Delayed (Post) | 19 | 88.68 | 16.418 | | | | |
| Verbal Immediate (Pre) | 20 | 82.15 | 18.457 | -0.019 | 21 | 0.985 | -0.206 |
| Verbal Immediate (Post) | 20 | 86.05 | 17.590 | | | | |
| Verbal Delayed (Pre) | 20 | 87.55 | 22.435 | -0.145 | 18 | 0.887 | 0.034 |
| Verbal Delayed (Post) | 20 | 86.90 | 17.921 | | | | |
| Word Reading (Pre) | 22 | 96.36 | 18.549 | 0.798 | 18 | 0.435 | 0.301 |
| Word Reading (Post) | 22 | 92.50 | 15.753 | | | | |
| Numerical Operations (Pre) | 20 | 93.15 | 18.172 | 0.153 | 19 | 0.880 | -0.083 |
| Numerical Operations (Post) | 20 | 94.50 | 16.64 | | | | |
| Spelling (Pre) | 20 | 94.60 | 13.112 | -0.373 | 19 | 0.714 | 0.267 |
| Spelling (Post) | 20 | 91.95 | 16.901 | | | | |

**Table M. Paired T-tests to examine differences between the pre and post op test scores for the tumour group**

| | *N* | *Mean* | *Std. Deviation* | **Paired Samples T-test** | | | |
|---|---|---|---|---|---|---|---|
| | | | | *t* | *df* | *Sig (2-tailed)* | *Cohen's d* |
| FSIQ (Pre) | 36 | 92.83 | 14.604 | 0.990 | 35 | 0.329 | 0.165 |
| FSIQ (Post) | 36 | 91.00 | 17.53 | | | | |
| VCI (Pre) | 36 | 93.28 | 14.068 | 1.818 | 35 | 0.078 | 0.303 |
| VCI (Post) | 36 | 90.67 | 16.209 | | | | |
| PRI (Pre) | 35 | 98.86 | 13.133 | 0.621 | 34 | 0.539 | 0.104 |
| PRI (Post) | 35 | 97.69 | 16.54 | | | | |
| PSI (Pre) | 33 | 91.61 | 12.096 | -0.489 | 32 | 0.628 | -0.085 |
| PSI (Post) | 33 | 92.64 | 14.684 | | | | |
| WMI (Pre) | 34 | 93.26 | 14.126 | 0.584 | 33 | 0.563 | 0.100 |
| WMI (Post) | 34 | 91.94 | 16.324 | | | | |
| Overall Memory (Pre) | 27 | 87.67 | 20.411 | 0.161 | 26 | 0.873 | 0.031 |
| Overall Memory (Post) | 27 | 87.30 | 18.252 | | | | |
| Visual Immediate (Pre) | 30 | 96.47 | 15.763 | 0.267 | 29 | 0.792 | 0.049 |
| Visual Immediate (Post) | 30 | 95.70 | 16.270 | | | | |
| Visual Delayed (Pre) | 27 | 98.63 | 13.048 | 0.093 | 26 | 0.927 | 0.018 |
| Visual Delayed (Post) | 27 | 98.41 | 13.543 | | | | |
| Verbal Immediate (Pre) | 30 | 81.67 | 20.652 | 0.522 | 29 | 0.606 | -0.096 |
| Verbal Immediate (Post) | 30 | 83.23 | 20.821 | | | | |
| Verbal Delayed (Pre) | 30 | 84.90 | 22.293 | 0.387 | 29 | 0.701 | -0.071 |
| Verbal Delayed (Post) | 30 | 85.93 | 21.438 | | | | |
| Word Reading (Pre) | 33 | 94.64 | 12.321 | 2.135 | 32 | 0.041 | 0.371 |
| Word Reading (Post) | 33 | 90.85 | 15.085 | | | | |
| Numerical Operations (Pre) | 29 | 97.03 | 17.379 | -0.139 | 28 | 0.891 | -0.025 |
| Numerical Operations (Post) | 29 | 97.31 | 18.432 | | | | |
| Spelling (Pre) | 32 | 93.94 | 13.669 | 0.083 | 31 | 0.935 | 0.014 |
| Spelling (Post) | 32 | 93.75 | 14.723 | | | | |

**Table N. Paired T-tests to examine differences between the pre and post op test scores for the MTS group**

| | N | Mean | SD | Paired Samples T-test | | | |
|---|---|---|---|---|---|---|---|
| | | | | t | df | Sig (2-tailed) | Cohen's d |
| FSIQ (Pre) | 28 | 88.25 | 13.232 | 0.335 | 27 | 0.740 | 0.063 |
| FSIQ (Post) | 28 | 87.68 | 12.561 | | | | |
| VCI (Pre) | 28 | 91.39 | 12.591 | 2.410 | 27 | 0.023 | 0.455 |
| VCI (Post) | 28 | 87.39 | 12.420 | | | | |
| PRI (Pre) | 28 | 95.54 | 14.380 | -0.323 | 27 | 0.750 | -0.061 |
| PRI (Post) | 28 | 96.32 | 11.944 | | | | |
| PSI (Pre) | 26 | 87.31 | 12.441 | -0.019 | 25 | 0.985 | 0.000 |
| PSI (Post) | 26 | 87.35 | 13.597 | | | | |
| WMI (Pre) | 27 | 88.07 | 13.123 | 0.146 | 26 | 0.885 | 0.029 |
| WMI (Post) | 27 | 87.70 | 12.390 | | | | |
| Overall Memory (Pre) | 25 | 84.96 | 19.334 | 0.868 | 24 | 0.394 | 0.173 |
| Overall Memory (Post) | 25 | 82.28 | 16.620 | | | | |
| Visual Immediate (Pre) | 26 | 91.54 | 18.171 | -0.423 | 25 | 0.676 | 0.082 |
| Visual Immediate (Post) | 26 | 93.27 | 14.668 | | | | |
| Visual Delayed (Pre) | 25 | 91.20 | 15.679 | 0.176 | 24 | 0.862 | 0.035 |
| Visual Delayed (Post) | 25 | 90.68 | 14.801 | | | | |
| Verbal Immediate (Pre) | 26 | 83.54 | 16.466 | 1.035 | 25 | 0.311 | 0.202 |
| Verbal Immediate (Post) | 26 | 80.04 | 14.180 | | | | |
| Verbal Delayed (Pre) | 26 | 88.46 | 15.792 | 2.292 | 25 | 0.031 | 0.449 |
| Verbal Delayed (Post) | 26 | 82.27 | 14.834 | | | | |
| Word Reading (Pre) | 26 | 91.38 | 17.468 | 0.959 | 25 | 0.347 | 0.188 |
| Word Reading (Post) | 26 | 89.12 | 15.428 | | | | |
| Numerical Operations (Pre) | 24 | 92.17 | 18.714 | -0.216 | 23 | 0.831 | -0.044 |
| Numerical Operations (Post) | 24 | 92.83 | 15.107 | | | | |
| Spelling (Pre) | 25 | 90.84 | 12.233 | 0.675 | 24 | 0.506 | 0.135 |
| Spelling (Post) | 25 | 89.64 | 15.750 | | | | |

**Table O. Paired T-tests to examine differences between the pre and post op test scores for the FCD group**

| | *N* | *Mean* | *SD* | **Paired Samples T-test** | | | |
|---|---|---|---|---|---|---|---|
| | | | | *t* | *df* | *Sig (2-tailed)* | *Cohen's d* |
| FSIQ (Pre) | 7 | 94.57 | 18.955 | 1.523 | 6 | 0.179 | 0.575 |
| FSIQ (Post) | 7 | 91.86 | 16.497 | | | | |
| VCI (Pre) | 7 | 90.71 | 16.173 | 0.134 | 6 | 0.898 | 0.050 |
| VCI (Post) | 7 | 90.14 | 15.805 | | | | |
| PRI (Pre) | 7 | 100.29 | 14.009 | -0.892 | 6 | 0.407 | -0.337 |
| PRI (Post) | 7 | 103.14 | 16.426 | | | | |
| PSI (Pre) | 5 | 94.80 | 22.095 | 0.063 | 4 | 0.953 | 0.028 |
| PSI (Post) | 5 | 94.60 | 18.229 | | | | |
| WMI (Pre) | 6 | 99.83 | 22.921 | 1.861 | 5 | 0.122 | 0.759 |
| WMI (Post) | 6 | 90.33 | 14.774 | | | | |
| Overall Memory (Pre) | 5 | 87.60 | 22.930 | -0.953 | 4 | 0.395 | -0.426 |
| Overall Memory (Post) | 5 | 97.80 | 7.727 | | | | |
| Visual Immediate (Pre) | 5 | 92.60 | 15.900 | -2.497 | 4 | 0.067 | -1.116 |
| Visual Immediate (Post) | 5 | 105.80 | 7.759 | | | | |
| Visual Delayed (Pre) | 5 | 91.40 | 13.722 | -1.579 | 4 | 0.189 | -0.706 |
| Visual Delayed (Post) | 5 | 105.00 | 6.285 | | | | |
| Verbal Immediate (Pre) | 5 | 83.40 | 18.008 | -0.831 | 4 | 0.453 | -0.371 |
| Verbal Immediate (Post) | 5 | 89.80 | 14.237 | | | | |
| Verbal Delayed (Pre) | 5 | 95.80 | 18.254 | 0.643 | 4 | 0.555 | 0.287 |
| Verbal Delayed (Post) | 5 | 89.00 | 8.944 | | | | |
| Word Reading (Pre) | 5 | 102.20 | 18.86 | -0.214 | 4 | 0.841 | -0.095 |
| Word Reading (Post) | 5 | 103.00 | 16.867 | | | | |
| Numerical Operations (Pre) | 5 | 107.20 | 20.729 | -0.159 | 4 | 0.882 | -0.071 |
| Numerical Operations (Post) | 5 | 108.20 | 21.879 | | | | |
| Spelling (Pre) | 4 | 100.25 | 19.050 | -1.868 | 3 | 0.159 | -0.934 |
| Spelling (Post) | 4 | 105.25 | 18.839 | | | | |