Neurobiological, cognitive, and psycho-social determinants of paediatric temporal lobe epilepsy surgery outcomes.

Francesca Cacucci

DClinPsy thesis (Volume 1), 2022

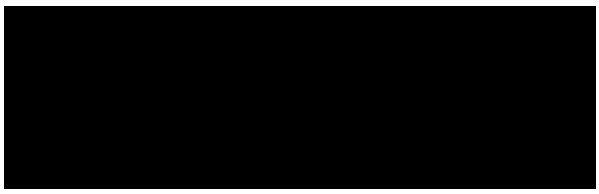
University College London

UCL Doctorate in Clinical Psychology

Thesis declaration form

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

Signature:



Name:

Francesca Cacucci

Date: 29.07.22

Overview

This thesis investigates neurobiological, cognitive, and psycho-social determinants of surgical outcome in paediatric epilepsy.

Part 1 offers a systematic review of studies employing quality-of-life measures to assess resective surgery efficacy in the management of medically resistant childhood epilepsy.

It reports that the largest quality-of-life improvements are most likely observed 6-months to 2-years following surgery in the health, social and behavioural domains. The most robust determinant of quality-of-life improvement following surgery is seizure freedom and its effect is likely mediated by mood. Cognitive variables are not associated with quality-of-life outcomes.

Part 2 reports the findings of a quantitative study focusing on brain correlates of cognitive outcomes in paediatric temporal lobe epilepsy. The findings demonstrate that paediatric temporal lobe epilepsy is characterised by a degree of hippocampal atrophy, associated with age at epilepsy onset. In patients with lesions in the left hemisphere, residual left hippocampal volumes are associated with post-surgical verbal memory function. In this patient group, extent of surgical resection was the only significant predictor of post-surgical verbal memory function. These results suggest that pre-operative verbal memory ability is likely supported by functional tissue in the ipsilesional hemisphere and highlights the value of monitoring hippocampal volume/function before surgery. The study also reports an overall (small) decline in verbal function and memory, at relatively short follow up periods (~1-year), regardless of lesion laterality. Children with higher pre-operative scores are most vulnerable to post-operative decline in performance across all cognitive domains.

Part 3 provides some reflections on the process of engaging with this research.

Impact statement

This thesis investigates surgical outcomes in paediatric epilepsy.

The literature review focuses on the use of quality-of-life measures to track general well-being following paediatric epilepsy surgery.

The literature review highlights that childhood epilepsy surgery has overall excellent medical outcomes in terms of seizure freedom and concurrent quality of life improvement. We show that seizure freedom is the most studied and most robust determinant of quality-of-life improvement following surgery, with mood likely mediating this effect. Surprisingly, cognitive variables are not associated with quality-of-life outcomes following epilepsy surgery.

Clinical assessment of psychosocial factors (including mood) before and after epilepsy surgery is of fundamental importance both to track surgical outcomes and to design clinical interventions. These results are likely to have most profound impact on clinical management of paediatric epilepsy patients.

Our literature review identified several methodological factors that should be considered in the design of surgical outcome studies (choice of qualitative/quantitative approach, heterogeneity of available quality-of-life measures, duration of follow up). Findings from the systematic review are well placed to inform research practices in the field of paediatric epilepsy, and, more broadly, in the field of chronic neurodevelopmental disorders.

The empirical study focuses on brain correlates of cognitive outcomes in temporal lobe epilepsy. Our findings demonstrate that paediatric temporal lobe epilepsy is often characterised

by a degree of hippocampal atrophy, associated with age at epilepsy onset. Before surgery we observed that general intellectual function and verbal reasoning are affected, regardless of whether epilepsy originates in the left or the right hemisphere. Following surgery, we observed a decline in verbal function and memory, regardless of lesion laterality. Children with higher pre-operative scores are most vulnerable to post-operative decline in performance across all cognitive domains.

These results could be applied to clinical practice and could inform clinical counselling during the process of assessment of eligibility for resective surgery. As a note of caution, considering the substantial inter-individual differences observed, clinical counselling should continue to emphasise the large inter-individual variability in surgical outcomes.

In patients with lesions in the left hemisphere, residual left hippocampal volumes were associated with verbal memory scores following surgery, and extent of surgical resection was the only significant predictor of post-surgical verbal memory function. These results suggest that pre-operative verbal memory ability is supported by functional tissue in the ipsilesional hemisphere and indicate that there is value in monitoring hippocampal volume/function before surgery. Moreover, our work demonstrates that if memory outcomes are to be prioritised in paediatric epilepsy of left temporal lobe origin, it would be important to focus on conservative surgical methods which allow preservation of healthy hippocampal tissue.

From the point of view of further research, our study clearly exemplifies the most common limitations to current clinical paediatric epilepsy research. Sample size limitations, combined with significant clinical complexity, represent the most urgent issue to be solved.

Overall, the results of this thesis have clear implications in the realm of both clinical and research practice in the field of paediatric epilepsy and its surgical management.

Table of Contents

Acknowledgments

I dedicate this thesis to all the young patients, their family and friends who are affected by epilepsy.

A special thanks goes to all those who have agreed to participate in this study.

This thesis is the fruit of the generosity of several people, who dedicated their time and care. It is not possible to make justice to all of you, but I would like to name my family (a special thanks goes to my daughters and partner, who have patiently put up with a busy mother/partner); the neuropsychology team at GOSH, who have welcomed me with warmth and guided me when I moved my first steps in the realm of clinical paediatric neuropsychology; the larger epilepsy surgery MDT at GOSH who have given me the possibility to learn about the difficult decisions they have to navigate each week; and the academic team at the Institute of Child Health, for offering intellectual (and practical) support before and throughout my DClinPsy studies.

Special thanks to Patricia Martin-Sanfilippo for her help with the curation of the patient database, Tina O'Mahony for spending hours identifying MRI patient scans and sharing them with me, and to Rory Piper for sharing his knowledge on how best to analyse structural MRI scans of epilepsy patients.

Thanks to Angela Simcox and Daniel Stark for supervising me during my paediatric neuropsychology placement.

A significant mention goes to the UCL Estates Division without whose forward planning skills my DClinPsy journey would not have been possible. A warm acknowledgment goes to Trevor

Smart, for the support and generosity he consistently showed me at a very difficult time in my career. Tara Keck for being the strongest of allies throughout this and Geraint Rees for his foresight and flexibility in finding solutions to my predicament.

I would like to thank my DClinPsy tutor, Miriam Fornells-Ambrojo, my MPR visitor, Josh Sott, and Henry Clements – for spending hours of their lives to support my journey during the DClinPsy programme. Special thanks go to Zaariyah Bashir, fellow trainee, for her patience, insights and support.

A special acknowledgement goes to John King, my DClinPsy research supervisor, for his support and guidance, and for the meeting we had several years ago in Planet Organic which started all of this.

Finally, a very special mention goes to Faraneh Vargha-Khadem, intellectual and spiritual beacon, for her irreplaceable guidance and boundless generosity.

Part 1: Literature Review

Evaluation of epilepsy surgery outcomes in paediatric populations: the use of quality-of-life measures in monitoring treatment efficacy.

.

Abstract

Aims

Paediatric epilepsy surgery outcomes have most commonly been studied with reference to seizure freedom, cognitive, and academic outcomes. Quality-of-life has more recently emerged as a relevant construct in tracking epilepsy surgery outcomes in children and adolescents. Our aims were to critically review the literature and to investigate the factors related to quality-of-life outcomes following childhood epilepsy surgery.

Method

Medline and Embase literature searches were conducted for peer reviewed studies of quality-of-life outcomes following paediatric epilepsy surgery. Searches identified 36 eligible studies.

Results

The largest quality-of-life improvements are most likely observed six months to two years following surgery in the health, social and behavioural domains. Seizure freedom is the most robust determinant of quality-of-life improvement following surgery, with mood likely mediating this effect. Cognitive variables are not associated with quality-of-life outcomes following epilepsy surgery at either short- (1-2 years) or longer (>5 years) follow up periods. Significant improvements in quality-of-life are routinely observed in children with pre-surgical IQ < 70, even in the absence of an improvement in IQ post-surgery.

Conclusions

Childhood epilepsy surgery has overall excellent medical outcomes in terms of seizure freedom and concurrent quality-of-life improvement.

This systematic review strongly indicates that it is vital for children undergoing epilepsy surgery, and their families, to be assessed for psychosocial difficulties, with the aim to tailor interventions to improve their quality of life.

Introduction

Epilepsy is one of the most common chronic neurological conditions of childhood, affecting 1/177 children (Joint Epilepsy Council of the UK and Ireland, 2011).

A significant proportion of children (estimated to vary between 4-20%) do not become seizure-free upon pharmacological treatment alone (Camfield et al., 1993; Sillanpää & Schmidt, 2006). Drug-resistant epilepsy (DRE) is defined as failure of two appropriately chosen/dosed antiepileptic drugs (AEDs) to provide adequate seizure control. The chances of obtaining seizure freedom in DRE upon further medication trials is minimal (e.g. Kwan & Brodie, 2000).

Children with poorly controlled seizures are at increased risk of premature death, poor long-term medical, cognitive, academic, and psychosocial outcomes (Engel, 2016).

Resective surgery in appropriately selected children suffering from DRE has been proven to be safe and effective, with rates of seizure freedom reported, in a relatively recent randomised controlled trial (Dwivedi et al., 2017), to be 77% in the surgery group vs 7% in the medically treated group. A recent systematic review of 182 studies (West et al., 2019) reported that seizure freedom was achieved in up to 64% of children undergoing epilepsy surgery. This review, however, also highlights the large variability in seizure outcomes (13-92% range of incidence of post-surgical seizure freedom). Research is ongoing to identify the most important clinical variables responsible for this variability in outcome.

Emphasis on seizure freedom as the preeminent outcome against which to measure epilepsy surgery effectiveness has dominated the design of clinical trials both in adult and paediatric populations – with epilepsy surgery outcomes classified according to the extent of residual seizures (using the Engel or ILAE classifications systems; Engel, 1993; Wieser et al., 2001).

In paediatric populations, Intelligence Quotient (IQ) and academic achievement, are also commonly reported as a primary outcomes of epilepsy surgery (see, e.g. Skirrow et al., 2011).

However, there is growing recognition of the value of examining the impact of epilepsy surgery beyond seizure control and intellectual function, as this will help to comprehensively inform and counsel patients and their families (e.g. Perry & Duchowny, 2013; Speechley, 2013).

Health-related quality of life (HR-QOL) is progressively becoming an important outcome measure in the assessment of the impact of epilepsy surgery in children. QOL is a broad construct, encompassing physical health, cognitive function, mental health, social function, and independence. The World Health Organisation definition of QOL places the individual's subjective perception at the core of the concept (World Health Organisaion, 2012). In clinical practice, in the UK, it is currently common to administer QOL questionnaires to parents and (whenever possible) children pre- and post-surgically, to capture the broader impact seizures and their treatment have on the quality of life of children and their families.

Here we review studies of quality-of-life outcomes following paediatric epilepsy surgery, highlighting their strengths and limitations, to paint a picture of current knowledge of a more holistic assessment of epilepsy surgery outcomes, to discuss current knowledge gaps and suggest future research directions.

We will focus on two main research questions:

1- Does undergoing epilepsy surgery during childhood result in improvements in QOL?

2- What factors are associated with changes in QOL outcomes following paediatric epilepsy surgery?

Before reviewing the available evidence, we will: a- provide a summary of common factors which previous literature suggests affect QOL and psychosocial function in children and adolescents with epilepsy; b- provide a brief overview of how QOL is most commonly conceptualised and which measurement instruments are most commonly used in clinical and research practice.

Common factors affecting quality of life and psychosocial function in children and adolescents with epilepsy

Epilepsy in childhood has a significant effect on the quality of life of children and their families, with an impact that is greater than in other chronic conditions like diabetes, cerebral palsy, or asthma (Moreira et al., 2013). Even a single seizure can have negative effects on quality of life (Modi et al., 2009), and epilepsy can have a life-long impact on quality of life (Sillanpää et al., 2004).

Childhood onset epilepsy is associated with increased risk of adverse mental health and behavioural outcomes, cognitive impairment, and educational under-attainment and underemployment – with all these factors impacting on reduced quality of life.

Some of these changes may even predate the time of seizure onset (pointing at underlying neural dysfunction as the driver of some of these changes – see Baum et al., 2007; Fastenau et al., 2009). Social stigma is also an important factor in mediating QOL in children and families living with epilepsy (for a recent report see Kwon et al., 2022).

Here we will first summarise current knowledge of the impact of epilepsy/epilepsy surgery in children on those variables known to have a direct impact on quality of life (mental health, cognitive function, and academic and employment outcomes). We will then discuss how the quality of life (QOL) construct is most commonly operationalised and measured in this patient population. Finally, we will review evidence for the impact of epilepsy surgery on quality of life in children.

Mental health and behaviour

Mental health problems are common in children and adolescents living with epilepsy (Besag et al., 2016; McLellan, 2015; Scott et al., 2020), with rates of psychiatric diagnoses 3-6 times higher than those in the general population (Reilly et al., 2019).

Psychiatric diagnoses include emotional disorders (anxiety/depression), conduct disorders, psychosis and conversion disorders (McLellan, 2015).

Childhood-onset epilepsy is also associated with neuro-behavioural disorders with intellectual disability, attention-deficit/hyperactivity disorder (ADHD), and autism spectrum disorder the most common neurobehavioral diagnoses (see, for example, Reilly et al., 2014).

Importantly, adverse mental health/neurobehavioural outcomes have a significant impact on quality of life, often larger than the seizures themselves (Baca et al., 2011; Reilly et al., 2015). For example, a relatively recent study (Bilgiç et al., 2018) reported that psychiatric factors were the largest contributors (when compared to number of anti-epileptic drugs and seizure frequency) to health-related quality of life outcomes as reported both by children and their mothers.

A recent systematic review of the prevalence of anxiety and depressive disorders in children with epilepsy (Scott et al., 2020) reported prevalence of 18.9% and 13.5% for anxiety and depression respectively, rates that are 5 times higher than in the general paediatric population. Rates of generalised anxiety disorder and separation anxiety are particularly elevated. Longer epilepsy duration and older age were associated with lower anxiety and depressive symptoms.

Children who undergo resective epilepsy surgery are at even higher risk of neurobehavioural and mental health difficulties, as, by definition, they represent a subset of children with epilepsy for whom structural brain abnormalities have been identified. Temporal lobe lesions are associated with higher rates of neurobehavioural/psychiatric adverse outcomes than extratemporal lesions (McLellan, 2015).

Studies addressing psychiatric and behavioural outcomes following epilepsy surgery are growing in numbers, but results, overall, provide a mixed picture (McLellan, 2015). A recent systematic review of behavioural and emotional outcomes following paediatric epilepsy surgery (Reilly et al., 2019) found that parents of children undergoing epilepsy surgery report improvement in emotional and behavioural functioning. However, this is not reflected by a decrease in psychiatric diagnoses. A small number of children receives new psychiatric diagnoses post-surgery, with explanations for this phenomenon ranging from – difficulties adjusting to life without epilepsy (the "burden of normality", Wilson et al., 2001), absence of medication and seizures "unmasking" underlying mental health difficulties, and chance.

In addition, caregivers of children with epilepsy also experience increased severity and prevalence of symptoms of anxiety and depression (for a systematic review, see Jones & Reilly,

2016) and this, in turn, is known to have a negative impact on family functioning and quality of life for caregivers, siblings and children with epilepsy (e.g. Mendes et al., 2017; Puka et al., 2017). A recent study of caregiver depression and anxiety in families of children who underwent epilepsy surgery (Phillips et al., 2019) reported decreased depressive symptoms in caregivers and improved family functioning at follow up (1 year), irrespective of treatment type (surgery vs pharmacological), and, importantly, found that low family resources predicted higher caregiver anxiety and depression. Parental coping (e.g., feeling of helplessness) is significantly related to quality of life in children and adolescents (McLaughlin et al., 2018).

Overall, evidence is clear that children with epilepsy, and more specifically those who undergo epilepsy surgery are at higher risk of mental health and neurobehavioural difficulties, so it is clinically important to screen for mental health/behavioural disorders in this patient population and provide adequate supportive treatment, alongside any medical intervention. Additionally, caregiver mental health and family functioning are also important predictors of quality of life in children with epilepsy, highlighting the importance of providing support to the whole family when providing care to children with epilepsy.

Cognitive outcomes

Epilepsy in children is associated with a wide spectrum of cognitive disorders (Berg et al., 2008; MacAllister & Schaffer, 2007), with several factors involved (seizures related factors, effect of medication, Lenck-Santini & Scott, 2015; Ulate-Campos & Fernández, 2017). Cognitive impairment (IQ <85) has been shown to have an independent impact on quality of life in children with epilepsy (Reilly et al., 2015) and to be associated with deterioration of quality-of-life overtime (Speechley et al., 2012).

Intellectual disability (IQ <70) in children with epilepsy has been shown to independently decrease quality of life (Sabaz et al., 2001), but children with low intellectual ability can achieve similar postsurgical quality of life improvement as children with average intelligence (Conway et al., 2018).

Most reviews (e.g., Flint et al., 2017) and a recent randomised controlled study (Dwivedi et al., 2017) conclude that there is very little consistent change in intellectual function after epilepsy surgery when follow up duration is short (< 4 years). Factors that increase the chances of improvement in cognitive function are seizure freedom and completeness of resection (Lah, 2004; Van Schooneveld & Braun, 2013).

There is still a relative paucity of long-term studies of the impact of resective surgery on cognitive function (Baldeweg, 2015; Moosa & Wyllie, 2017). Baldeweg, 2015 reviewed 31 studies reporting long term outcomes after epilepsy surgery (> 4 years) and concluded that, overall, results are mixed, with studies reporting both improvement and decline in IQ scores across children. Freedom from seizure and AED withdrawal tend to correlate with higher proportion of patients with cognitive improvement after epilepsy surgery. Surgery type is also an important variable, with patients receiving hemispherotomy faring generally worse in terms of long-term post-surgical IQ outcome as opposed to children undergoing focal resections (this likely reflects more marked cognitive impairments even before surgery, Lindsay et al., 1987). A particularly notable study (Skirrow et al., 2011) reported IQ and quality of life outcomes after an average post-surgical period of 9 years in a cohort of children who received temporal lobe surgery. Both IQ and quality of life improved in the surgical group (when compared to a nonsurgical control group). Improvements in quality of life correlated most with seizure freedom (rather than surgery itself).

Taken together, these studies illustrate how long term follow up is necessary to detect significant post-surgical changes in both intellectual and quality of life outcomes.

Academic and employment outcomes

Childhood epilepsy has documented negative impacts on educational achievements and occupational outcomes (e.g., Jennum et al., 2016; Sillanpää et al., 1998).

Academic and occupational difficulties in children with epilepsy are not simply due to the effects of epilepsy on cognitive function: academic impairments exceed those expected based on intellectual function (Fastenau et al., 2008) and educational and occupational difficulties are prevalent even among children with normal intelligence (Jalava et al., 1997).

Employment outcomes in children who received resective surgery during childhood are generally reported to be superior to those of adults (Skirrow, 2015). This is especially notable in recent studies which reported long term outcomes (20 years follow-up) and considered the impact of seizure freedom as a mediator of the improved outcomes (Nickels, 2020; Reinholdson et al., 2020). In general, there are indications that early surgery, in children with normal intelligence, may promote improved academic and employment outcomes, via seizure cessation. However, few studies include a control cohort of medically treated patients, thus leaving open the possibility that superior academic and employment outcomes may reflect better presurgical function.

The literature reporting long term academic and employment outcomes in children with epilepsy does not generally include information regarding quality-of-life indicators – so no

direct conclusions can be drawn on the effect of employment and academic achievement on perceived quality of life in childhood-onset epilepsy.

What is quality of life and how is it measured?

The discussion has so far focused on some of the challenges experienced by children living with epilepsy and their families. There is growing recognition that the impact of epilepsy on children and families' wellbeing goes way beyond medical and seizure related factors, and that clinical management of the disorder needs to take into consideration psychosocial as well as medical factors (Ronen et al., 2003).

This recognition has brought about a focus on health-related quality of life as a key outcome in the medical (and surgical) management of paediatric epilepsy.

Quality of life (QOL) is a multi-faceted construct and is commonly thought to encompass psychosocial wellbeing, physical health, independence, and spiritual beliefs.

The WHO definition of QOL (World Health Organisation, 2012) tries to capture its breadth: "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns".

The question of how to capture quality of life in children with epilepsy has a long tradition and two main approaches can be recognised in the literature.

Qualitative approaches have made use of individual or group interviews (focus groups) to explore the experiences of children and families affected by epilepsy (e.g., Baker et al., 2008; Elliott et al., 2005; McEwan et al., 2004; Moffat et al., 2009). Themes emerging from these

studies are distress at the unpredictability of seizure occurrence, social stigma, erosion of self-confidence, social isolation, frustration at the restriction of activities brought about by seizure burden. Adolescents report specific concerns related to identity formation, difficulties in developing independence and worries about the future. This approach leads to rich descriptions and, crucially, brings with it the centrality of the voice of the children and their families.

This review will mainly focus on quantitative approaches to measuring QOL in children with epilepsy – as these remain the main driver behind the development of the most utilised instruments currently used in clinical practice. Efforts are ongoing to develop a core outcome set as this would reduce heterogeneity across studies (e.g., Crudgington et al., 2019). A relatively recent meta-analysis (Maragkos et al., 2019) included data pertaining to 890 children who had undergone resective epilepsy surgery, across 18 retrospective studies. The authors concluded that only the patients who achieved total seizure freedom after surgery benefited from significant postoperative QOL improvement.

The National Institute for Health Care and Excellent (NICE) research recommendations used to suggest that research should include seizure freedom as primary outcome, and seizure reduction, quality of life and cognitive outcome as secondary outcomes (CG 137, NICE 2012). However, these recommendations have been superseded very recently by new guidelines (NG217, NICE, 2022) that make no reference to quality-of-life monitoring (but still include medical and mental health/neuro-behavioural monitoring in the management of adults and children with epilepsy). The International League Against Epilepsy (ILAE) regularly publishes guidance on which outcome measures to include in clinical trials and QOL is an indicator that features in most of them (e.g., Chadwick D, 1998; Modi et al., 2017). In the US, the Common Data Element project (run by the National institute of Neurological Disorders and Stroke;

Loring et al., 2011) aims to develop common standards for clinical neuroscience research. QOL is included in their comprehensive list of indicators (which was, however, developed without family/children input).

This brief overview exemplifies how reporting of QOL has gained significant traction as a measure of epilepsy treatment efficacy. However, there is no consensus, as yet, relating to which measures best capture QOL.

A recent systematic review selected 11 patient-report outcome measures commonly used to assess QOL in children with epilepsy and assessed their measurement properties (validity, reliability, precision, and responsiveness, see Table 1 in Crudgington, Rogers, et al., 2020 for the list of reviewed instruments). They concluded that there is good evidence for the use of two questionnaires: the QoLCE-55 (Goodwin et al., 2015; good evidence of structural validity, construct validity, and internal consistency) and the CHEQoL (Ronen et al., 2003 good evidence of content validity, structural validity, and construct validity), with the latter capturing both child and parent reported QOL (while the former only captures parent reported QOL). The PedsQL epilepsy module (Follansbee-Junger et al., 2016) was also mentioned (among other questionnaires), as good evidence of its content validity is available.

In an accompanying article (Crudgington, Collingwood, et al., 2020) the authors report the results of a consultation exercise (which involved medical professionals, parents and children) aimed at understanding whether the content of the questionnaires selected by Crudgington, Rogers, et al., 2020 captured the core outcome set of measures which was agreed on the basis of a Delphi consensus process (seizures, sleep, social functioning, mental health, cognition, physical functioning, behaviour, adverse events, family life, and global quality of life; Crudgington et al., 2019) which involved both professional and service-user input. The authors

concluded that "both QOLCE-55 (parent-report) and CHEQOL (parent and child report) were considered acceptable for research use in the context of the UK National Health Service (NHS)", while also mentioning that the selected questionnaires did not include information about the constructs of "independence", "future concerns", or "worries".

An important consideration is that both the QOLCE-55 and the CHEQOL have been developed and are mainly used in North America (Canada and the US), whilst current clinical practice in the UK privileges other instruments (e.g., PedsQL, IPES). At the present moment, it is unclear whether a shift in clinical practice can be achieved such that a common set of QOL instruments can be used across clinical centres.

In conclusion, there are several quantitative instruments that are available to researchers and clinicians to monitor QOL in children with epilepsy. Efforts to reach a consensus as to the use of common instruments are laudable, in a field where heterogeneity (of aetiology, medical course, interventions, etc) has already hampered research and, indirectly, the introduction of improvements in clinical practice.

Methods

Sources

Articles were searched using a priori defined search strings on MEDLINE (1985- March 2022), and EMBASE (1985- March 2022). These databases were chosen as most publications pertaining to QOL assessment following paediatric epilepsy surgery are expected to be published in medical journals. Moreover, these databases are those commonly searched by

clinicians who provide care for children with epilepsy in a professional capacity and therefore have highest probability to influence standards of care. It is possible, however, that restricting searches to medical databases will have missed publications with an emphasis on different approaches (e.g. sociological, anthropological).

Search strategy

The systematic search strategy employed consisted of combination of terms related to:

1- paediatric literature (e.g. “child”, “adolescent”, “paediatric/pediatric”)

2- epilepsy surgery (e.g. “epilepsy surgery”, “resective surgery”)

3- quality of life outcomes (e.g. “quality of life”, “psychosocial”).

Searches were complemented with citation tracking of primary research articles and scanning reference list from book chapters. Relevant articles were also sought by consulting reviews, commentaries, and clinical guidelines.

A meta-analysis of the findings was deemed to be inappropriate due to heterogeneity in study quality, with most studies not reporting measures of precision of the reported effects, significant design variability and clinical diversity (e.g. diversity in etiology, timing and course of disease, surgical approaches, follow up time) and heterogeneity of outcome measures (e.g. diversity of QOL measures employed).

Inclusion criteria

Articles were included based on the following criteria:

1- they included an outcome measure of quality of life.

2- they included participants who had received resective epilepsy surgery before they reached 18 years of age.

Articles were included only if they were published in English and had been subjected to peer-review. Conference proceedings, case studies, reviews/commentaries/opinion pieces were not included.

Data collection and analysis

Titles and abstracts for each study were studied for eligibility for inclusion. Whenever information from abstracts was not sufficient to determine an inclusion/exclusion decision, full text versions of the articles were reviewed.

For each study which was deemed fit for inclusion in the review the following information was recorded (whenever available):

1- authors
2- date of publication
3- Study setting and geographical location
4- Study design
5- N participants in active group
6- Follow up duration
7- Surgery type/epilepsy aetiology

8- Quality of life outcome variables employed

9- Rater identity (Parent and/or child)

10- Main findings

11- Factors significantly associated (or not) with outcome

Quality appraisal was conducted in a narrative manner, without the employment of a formal quality appraisal tool. This was due to the lack of appropriate tools specifically developed to assess study quality in the context of paediatric epilepsy QOL outcomes. Although one quality appraisal tool, the EBNP checklist (Hrabok et al., 2013) has been developed to assess quality of primary studies reporting neuropsychological outcomes after epilepsy surgery, we opted not to employ this tool after consideration of some of its characteristics (some items are difficult to interpret or too general, e.g. "Did you believe the results?", "What are the implication for practice?"; instrument gives same weight to minor concerns and serious flaws). In this context, it is notable that this instrument has not been employed since its publication in 2013.

More generally, the lack of information provided by most studies included in this systematic review precluded employment of formal quality assessment tools.

Criteria for assessing quality of studies included: study design (e.g. inclusion of appropriate control groups), number of participants, hetero- or homogeneity of population with respect to epilepsy and demographic factors, statistical tools/analysis adopted, type of outcome measures employed, rater identity (parent/patients).

Results

A flowchart outlining the selection process for inclusion in the review is presented in Figure 1.

Following screening for eligibility a total of 36 studies met selection criteria. Publication dates ranged from 1996-2021.

General characteristics of reviewed studies

The studies reviewed were heterogeneous with respect to both design and measures used.

Of the thirty-six studies reviewed, only eight had a prospective design and two of these were Randomly Controlled Trials (RCTs). Twenty-six studies had a cross-sectional design, with QOL measured only after surgery, thus not including baseline measures of QOL ahead of the surgical procedure. Ten studies adopted a more robust longitudinal design, with QOL measured both pre- and post-surgically. Two studies adopted a qualitative design.

Only a subset of studies (fourteen) included both a surgical (active) group and a medication-only (control) group. The other studies analysed variation of surgical subgroups across epilepsy (e.g. seizure outcome), surgical (location, type), neuropsychological (e.g. IQ), psychological (e.g. mood) and demographic variables (e.g. gender).

There was significant variation across studies in terms of post-surgical follow up duration.

Sixteen studies included data referring to follow up durations 2 years or shorter. Thirteen studies reported mean follow up periods between 2 and 5 years, six studies reported follow up durations longer than 5 years. One study did not include information regarding follow up duration.

Studies also varied with respect to the number of participants included. The average number of participants who had received surgery (active group) was 54 (range 7-262) across all

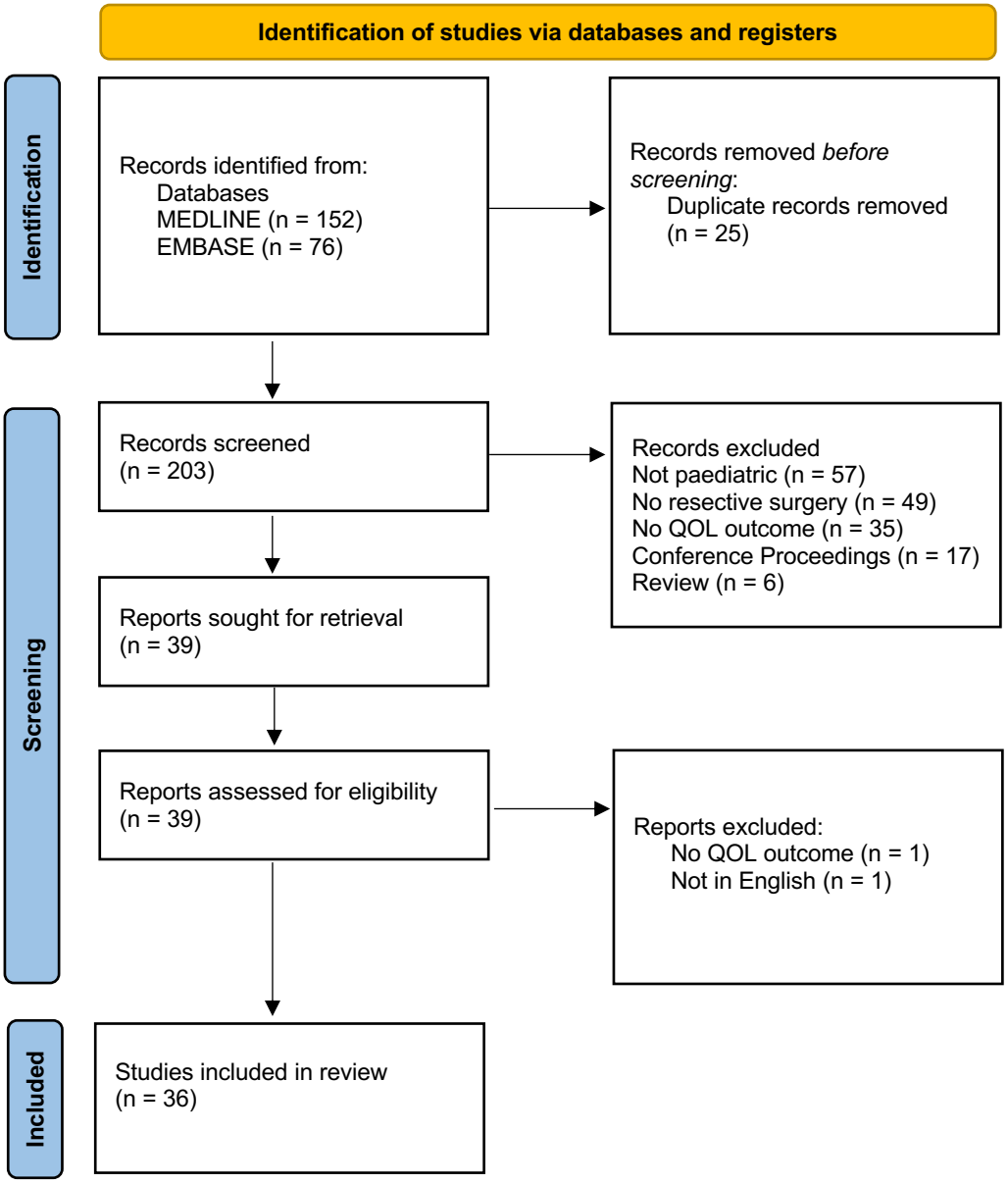


Figure 1. Results of the systematic search and screening of citations.

reviewed studies, with ten studies collating data from 25 participants or fewer, fourteen studies between 25 and 50, six studies from between 51 and 100 participants and five studies reporting data relating to more than 100 participants.

There was considerable heterogeneity across studies in terms of inclusion criteria relating to epilepsy aetiology and surgery type. Of the thirty-six reviewed studies seven focused on specific aetiologies (1 on focal cortical dysplasia, 1 on Landau-Kleffner disorder, 2 on Lennox-Gastaux disorder and 3 on Tuberous Sclerosis Complex); six focused on a specific surgical approach (3 on hemispherectomies/hemispherotomies, 2 on Corpus callosotomy, 1 on anterior temporal lobectomy), whilst the remaining twenty-three studies reported included participants more heterogeneous across epilepsy aetiology and surgical approaches adopted.

There was considerable across-study heterogeneity in terms of QOL measures adopted. Most studies opted for inclusion of standardised measures with only six studies (two of which were qualitative) including data related to unstandardised instruments/semi-structured interviews. A variety of standardised instruments were employed across studies, with thirteen studies employing the QOLIE, nine studies the QOLCE, two studies the PedsQL. The remaining twelve studies employed other instruments (for complete list see Table 1, Appendix).
Out of thirty-six studies, only seven studies included child-rated outcomes, with twenty-seven studies including only parental/carer-rated outcomes. Two studies included only child-ratings.

A subset of studies (thirty) directly addressed the question of which factors were associated with QOL outcomes following epilepsy surgery in children. Post-surgical seizure status and IQ were the most studied factors. Children and carers' mental health factors (anxiety and depression) and other family variables were studied by only a minority of studies.

Studies were conducted across several geographical locations. The geographical distribution was the following: fourteen studies were conducted in North America (8 Canada, 6 US), ten in Asia (4 China, 3 India, 2 Taiwan, 1 Japan,); six in Europe (3 UK, 2 Germany, 1 Netherlands); two in the Middle East (Lebanon); two in South America (Brazil), and one in Africa (Uganda). One additional study was conducted as part of large consortium spanning several continents.

For a full list of studies and more detailed information, see Table 1 (in Appendix).

Effects of surgery on QOL

Twenty-five studies reported the effects of epilepsy surgery on QOL outcomes. Of these, eleven included a nonsurgical epilepsy control group. Inclusion of such a group is essential to dissect the specific effects of surgery on QOL controlling for the natural progression of epilepsy and/or child development per se. This is particularly important for long-term follow up studies, as children suffering from epilepsy often show improvements, even in the absence of surgery.

Summary of results reported by studies which did not include a non-surgical epilepsy group

Results from the thirteen studies which did not include a nonsurgical epilepsy group cannot be unequivocally interpreted as indicating that post-operative QOL changes are to be attributed to surgery. It is, however, still valuable to report their findings, as they are indicative of how children undergoing epilepsy surgery may fare in terms of QOL at different time points after surgery.

The picture the results paint is, overall, one of improvement in QOL.

Of the thirteen studies which reported effects of epilepsy surgery on QOL outcomes (but did not include a nonsurgical control group) twelve reported improvements in at least some aspects of QOL. The only study which did not report an improvement in QOL post-surgery, Gilliam et al., 1997 had a cross-sectional design and reported parental ratings of QOL (CHQ questionnaire; n=33) of children who underwent epilepsy surgery, comparing them to those of a healthy control group. Perhaps unsurprisingly, they reported that ratings in the domains of physical function, general behaviour, general health, self-esteem, emotional impact on parents and time impact on parents were significantly lower in the epilepsy surgery group than in the healthy control group, even after an average of 3 years post-surgery (follow up range 7 months – 6 years). This indicates long lasting problems in this patient population. However, 85% of parents reported satisfaction with the results of surgery, providing an indirect indication that surgery was seen as having had a beneficial impact on quality of life.

Out of the twelve studies reporting improvements in QOL after surgery, four (Ciliberto et al., 2012; Roth et al., 2011; Hum et al., 2011; O'Brien et al., 2020) had a cross-sectional design, measuring QOL outcomes only after surgery. Ciliberto et al., 2012 reported that all the parents of the children included in their study (N=7) "indicated that the QOL of both their children and themselves was "much better" after surgery" (follow up duration ranged from 2 to 5.3 years). It is of note that Ciliberto et al., 2012 report on the results of a specific surgical approach, functional hemispherotomy, which is indicated in more pervasive/disabling childhood epilepsy presentations. Roth et al., 2011 administered unstandardised questionnaires to the parents of 39 children suffering from Tuberous sclerosis complex and who therefore underwent multiple

surgeries (multi-stage surgical resections; mean follow up period was 3.9 years). They reported that 46-85% experienced at least a moderate improvement in QOL following surgery.

Hum et al., 2011 and O'Brien et al., 2020 adopted a qualitative approach. Hum et al., 2011 conducted semi-structured interviews with 27 children and adolescents, 2 years after they had undergone epilepsy surgery. They probed the participants' perception of their quality of life, in the social domain. Although improvements in social function and greater independence were reported (especially by seizure-free adolescents), most participants continued to report social isolation and problems with their peers (regardless of seizure status).

O'Brien et al., 2020 adopting a similar qualitative approach, conducted semi structured interviews of both parents and children (n=16, 7 children), following epilepsy surgery (follow up duration ranging from 6 months to 3 years). In agreement with Hum et al., 2011 they reported nuanced findings regarding improvement in quality of life after epilepsy surgery: families and children both reported that surgery had had a positive impact on their lives, whilst highlighting continuing difficulties in adapting to "normal" life.

Taken together, the studies reviewed thus far offer indications that quality of life improves after epilepsy surgery, but that some difficulties are present even after relatively long follow up periods (> 3 years).

Eight studies which reported improvements in QOL after surgery (but did not include a nonsurgical epilepsy control group) had a longitudinal design, measuring QOL both before and after surgery and could therefore statistically test whether QOL had significantly changed following surgery. The studies were heterogeneous with respect to the QOL instruments employed and duration of follow up. Most studies reported post-operative improvement in

QOL, especially at longer follow up durations (e.g. 2 years vs 6 months, Leal et al., 2020), but with improvements in selected QOL domains already detectable at short intervals after surgery (e.g. at 6 months, improvement in the frequency of activities and more frequent positive emotions were reported by van Empelen et al., 2005).

Notable was also that improvement in QOL occurred also in children with lower cognitive ability (e.g., Titus et al., 2013; Leal et al., 2020; Panigrahi et al., 2016; Conway et al., 2018; Reilly et al., 2020). In particular, two studies (Titus et al., 2013; Conway et al., 2018), reported specific improvements in physical activity and social ability around 1 year following epilepsy surgery, in the absence of changes in the cognitive and emotional domains.

Significant behavioural improvement after epilepsy surgery was reported by at least three studies (Sabaz et al., 2006; Conway et al., 2018; Reilly et al., 2020), with Reilly et al., 2020 reporting a significant association between behaviour improvement and post-surgical QOL changes.

Taken together, the results reviewed thus far point to overall favourable QOL outcomes following epilepsy surgery. Cumulative evidence suggests that physical, social, and behavioural domains are more often the first to improve with improvements being more notable 2 or more years after surgery. Improvements in the cognitive domains are instead less likely to be observed, especially at short intervals after surgery.

The two qualitative studies reviewed here point to the fact that this overall positive picture of increased social competence and life enjoyment post-surgery is balanced against continuing difficulties that families and children face adapting to life after surgery: peer difficulties, social isolation, pressure to adapt to “normal” life (the “burden of normality” effect –Wilson et al., 2001 which we will return to in the discussion).

However, as mentioned above, due to the lack of inclusion of a nonsurgical control group, the changes in QOL reported by the studies reviewed thus far cannot be definitively attributed to the specific effect of epilepsy surgery. For this reason, we now turn our attention to studies which have included such a control group.

Summary of results reported by studies which included a non-surgical epilepsy group

Overall, twelve studies which met inclusion criteria reported on the effect of surgery on QOL. Of these, five had a cross-sectional design, reporting only post-surgical QOL outcomes. Whilst the lack of preoperative assessment of QOL precludes the possibility to assess whether participants improved, deteriorated, or experienced no change following surgery, the average follow up duration of cross-sectional studies reviewed here was longer than that of studies with a longitudinal design. These cross-sectional studies therefore offer the opportunity to explore the mid to long-term effects of epilepsy surgery.

Four out of five studies with a cross-sectional design reported significantly higher QOL outcomes in surgical vs nonsurgical epilepsy patient groups on at least some QOL domains. Mikati et al., 2008, 2010 conducted two retrospective studies on relatively small cohorts of children who underwent epilepsy surgery (n=17 and N=19 respectively for 2008 and 2010). No information is provided as to how much (if any) overlap exists across the cohorts included in the 2008 and 2010 study. They reported parent rated QOL outcomes (QOLCE-91), 2 years or longer after epilepsy surgery (follow up duration 2 years for Mikati et al., 2008; 3-5 years for Mikati et al., 2010). Mikati et al., 2010 reported improvements in total QOLCE, general health, physical activities, well-being, but not on social functioning, behavioural and cognitive

functioning in the surgical group, when compared to the nonsurgical epilepsy group. For Mikati et al., 2010, surgery participants scored better than non-surgery participants across the behavioural domain and the side effects scale score only. This latter study also included a healthy participant group. Authors report that after surgery patients were similar to healthy subjects in social, emotional, cognitive, behavioural, and overall QOL, but had lower scores in total QOL, physical and health domains, whilst non surgery patients scored worse than healthy participants in total QOL, physical, behavioural, health and overall QOL.

Fletcher et al., 2015 conducted a retrospective, cross-sectional study of 19 children who underwent temporal lobe epilepsy surgery in Uganda. They reported that quality of life (measured via child and parent-rated instruments at least 5 years after surgery) was significantly higher in the surgical vs the nonsurgical group. Perceived stigma was lower in the surgical group than in the non-surgical group. Interestingly, self-esteem (rated by both parents and children) did not differ across the surgical and non-surgical groups, with all participants reporting high or normal self-esteem.

Puka et al., 2015 conducted a larger (N=71) retrospective, cross-sectional, study on the long term (follow up duration ranging from 4-11 years) effects of epilepsy surgery on QOL. They reported that the only differences related to surgical status were greater concerns reported by nonsurgical patients on seizure worry and medication effect subscales.

Downes et al., 2015 is the only cross-sectional study which included a nonsurgical epilepsy group and did not find statistical differences between the groups in terms of cognition, adaptive behaviour and QOL at follow up (18 months - 5 years; PedsQL and VABS-II for QOL and behavioural functioning, respectively). They studied a cohort of children (N=14) affected by

Landau-Kleffner syndrome, a disorder commonly associated with electrical status epilepticus during sleep (ESES), and with marked cognitive regression. Children received multiple subpial transection surgery. These results therefore apply to a specific population of children living with epilepsy and cannot be generalised to more common forms of childhood epilepsies.

Overall, results from cross-sectional studies including a nonsurgical epilepsy group strongly support the view that surgery has a positive effect on QOL at mid- to long-term follow up durations. As mentioned above, these studies do not provide information on extent of *change* in QOL outcomes following surgery. For this reason, we will now turn to the discussion of longitudinal studies which include a nonsurgical epilepsy control group.

Two studies focused on QOL outcomes following epilepsy surgery for children suffering from Lennox-Gastaut syndrome. This is a rare and severe form of epilepsy that typically affects children during infancy or early childhood. Liang et al., 2014 is a prospective study which included 23 children who had undergone anterior corpus callosotomy. They obtained parental QOL (QOLIE-31) ratings and IQ scores before and 1, 2 and 5-years following surgery and reported that both overall QOL and IQ were higher in the surgical group (vs the nonsurgical epilepsy group) at the 2-year follow up time point. They also reported that these changes were not related to the degree of seizure freedom. Ding et al., 2016 adopted an RCT design, which included 43 children affected by LGS. They included one nonsurgical epilepsy group, and two surgical groups (resective approach with or without anterior corpus callosotomy). Parental ratings of QOL (QOLIE-31) were obtained before and 3-5 years following surgery. Similarly to Liang et al., 2014, Ding et al., 2016 reported better QOL and FSIQ outcomes in the surgical vs the nonsurgical groups, with the combined surgical approach (resection + CCT) outperforming the resection only approach on both outcome measures – as per Liang et al.,

2014, there was no significant effect of seizure outcome on QOL and/or IQ outcomes. Taken together these studies, which focus on a specific and severe childhood epilepsy disorder, suggest that surgery is superior to pharmacological only treatment in terms of both cognitive and QOL outcomes – and that these outcomes are not directly linked to post-surgical seizure status.

More recently, Dwivedi et al., 2017 reported the results of an RCT study, with broader inclusion criteria (including all <18 patients with drug resistant epilepsy randomly assigned to surgery and non-surgical management groups). Follow up period was one year. The authors reported that between-group differences in the change in QOL (PedsQL), behaviour (Child Behaviour Checklist) and Social maturity (VSMS), but not IQ (Binet-Kamat test) pre-/post-surgery favoured surgery over pharmacological management alone. This study did not explore whether seizure freedom was associated with QOL and other adaptive functioning outcomes.

Results from several longitudinal studies which include a nonsurgical epilepsy control group (Markand et al., 2000; Skirrow et al., 2011; Jain et al., 2020; Philips et al., 2019) converge on the finding that the treatment (surgery vs medial management) is not independently associated with improved QOL. Jain et al., 2020 is the only study that finds an independent effect of surgery (over medical management) on social function. Overall, these studies provide evidence that it is seizure freedom, rather than surgery per se, that is associated with better post-surgical QOL outcomes. These results are all the more convincing if one takes into consideration the heterogeneity in surgical approaches (temporal lobectomy for Skirrow et al., 2011; anterior temporal lobectomy for Markand et al., 2000; mixed surgical approaches for Jain et al., 2020 and Philips et al., 2020b), follow up durations (from 1 year – Jain et al., 2020; Phillips et al., 2020b; to 1-2 years for Markand et al., 2000; and over 5 years for Skirrow et al., 2011),

demographic characteristics of the participants, and QOL instruments employed across these studies.

In summary, the evidence reviewed thus far suggests that QOL outcomes are superior following surgery vs exclusive medical management in childhood epilepsy and suggest that post-surgical improvement in QOL is probably to be imputed to the superiority of surgery over medical management in resulting in seizure freedom.

We will now review evidence that speaks towards which factors are more likely to be associated with QOL outcomes following paediatric epilepsy surgery.

Factors associated with changes in QoL outcomes following paediatric epilepsy surgery

The role of epilepsy and surgery related factors as determinants of QOL

A majority of studies reviewed here (Chen et al., 2014; Conway et al., 2018; Downes et al., 2015; Elliott et al., 2012; Griffiths et al., 2007; Hum et al., 2010; Jain et al., 2020; Keene et al., 1997; Leal et al., 2020; Liang et al., 2012; Liu et al., 2020; Markand et al., 2000; Mikati et al., 2010; Roth et al., 2011; Sabaz et al., 2006; Skirrow et al., 2011; Titus et al., 2013; Yang et al., 1996; Zupanc et al., 2010; twenty out of thirty-six) report an association between QOL outcome and seizure outcome following paediatric epilepsy surgery. In some studies, a specific association between post-surgical seizure severity/frequency (often measured using the Engel classification system; (Engel, 1993) and QOL outcome was noted (Roth et al., 2011; Markand et al., 2000; Mikati et al., 2010; Griffiths et al., 2007; Fletcher et al., 2015; Downes et al., 2015), with most studies reporting an association between QOL outcomes and seizure freedom (Engel class I; Keene et al., 1997, Reilly et al., 2020, Hum et al., 2010, Sabaz et al., 2006, Liang et al.,

2012; Liu et al., 2020; Skirrow et al., 2011; Jain et al., 2020; Philips et al., 2020b) but this was not a universal finding. For instance, Titus et al., 2013 reported that better seizure outcome correlated with improvement in QOL, but there was no significant difference between QOL improvement across participants falling in the different Engel categories, following surgery. The association between seizure outcome and changes in QOL may not be as evident in the case of the most severe forms of childhood epilepsies. For instance, Liang et al., 2014 who studied a cohort of children affected by Lennox-Gastaut syndrome reported a lack of association between seizure control and post-surgical QOL/IQ outcomes, although this finding could also be due to lack of statistical power. Clearly more research is needed to ascertain the possible determinants of QOL and IQ outcomes in these more selected groups of children living with syndromic epilepsies.

Overall, there is a strong consensus that seizure outcome is strongly associated with QOL in paediatric surgical epilepsy. These results are also corroborated by a meta-analysis by Maragkos et al., 2019, which concluded that only the patients who achieved total seizure freedom after surgery benefited from significant postoperative QOL improvement.

The association between QOL improvement and seizure freedom might be mediated, at least in part, by decrease in AED load. The relationship between AED load and QOL outcomes was directly studied only by a subset of the reviewed reports – whose results paint, overall, a mixed picture. Griffiths et al., 2007 reported that both residual seizure frequency and higher AED load predicted worse QOL in a cohort of patients who had undergone hemispherectomy. Puka et al., 2015 in a broader surgical cohort, reported that AED use was associated with the social functioning, medication effects and seizure worry components of the QOLIE. However, Mikati et al., 2008 in a similar (but smaller) mixed surgical cohort failed to find an association between

AED load and QOL outcomes in both the surgical and non-surgical groups. Reilly et al., 2020 reported on a large mixed epilepsy surgery cohort (n=107). They found that AED reduction contributed to reduced behavioural difficulties, which, in turn, translated to significant improvement in QOL at follow up. Taken together these studies suggest that AED reduction plays an important part in QOL improvements in children who have undergone epilepsy surgery.

Some studies have also explored the role of other epilepsy related factors in determining QOL outcomes following epilepsy surgery. Downes et al., 2015 noted that earlier age of epilepsy onset and continuing seizures were the most predictive of poorer quality of life at long-term follow-up in a small cohort of children affected by Landau-Kleffner disorder. Moritake et al., 2009 similarly found that later age at onset of epilepsy correlated with higher QOL increases post-surgery, in a cohort of 47 children which had undergone epilepsy surgery (mixed surgical approaches). However, Reilly et al., 2020 in a similar but larger cohort of children (N=107) failed to find an association between age at onset and QOL outcomes.

Surgery related factors have been explored in a very small subset of the studies reviewed, with Moritake et al., 2009 reporting that the location of lesion (temporal vs extra-temporal) and the nature of the pathological changes (non-dysplastic vs dysplastic) were associated with QOL outcomes, with significantly higher QOL scores in the temporal resection group and extratemporal resection of non-dysplastic cortical pathology group vs the extratemporal resection of dysplastic cortical pathology group.

Dagar et al., 2011 did not find a correlation between side of surgery and QOL outcomes. This is the only study (among those included in this review) that has explored whether there are hemispheric differences in terms of post-surgical QOL outcomes.

Overall, seizure outcome is the most studied factor in the search for determinants of QOL changes following epilepsy surgery in children. This is also a clear strong determinant of QOL outcomes. There is also some support for AED load as a determinant of QOL outcomes.
Much less data are available in terms of other surgical and epilepsy related factors and their association with QOL outcomes. There are some indications that, as expected from developmental neuropsychological principles, earlier age at onset is often associated with poorer QOL outcomes. Evidence is inconclusive with respect to the effects of side of lesion, nature of pathology/aetiology on QOL outcomes.

Demographic factors and follow up duration and QOL

Some of the studies reviewed here explored the association between demographic variables and QOL outcomes. They mostly reported no effect of age and gender on QOL outcome (e.g. Dagar et al., 2011; Markand et al., 2000). An exception to this is Griffiths et al., 2007, which reported that female gender was associated with worse QOL outcomes in a relatively small cohort (N=26) of children who had undergone hemispherectomy. Elliott et al., 2012 reported similar findings on a broader (mixed surgery approaches) and larger (N=69). In their long term follow up (average FU duration 9 years, range 2-22 years) they found that sex independently predicted only QOLIE-31 Energy/Fatigue scores, with male patients reporting higher levels of QOL. Overall, there is inconsistent evidence with regards to the role of demographic factors in contributing to QOL following epilepsy surgery.

Duration of post-surgical follow up was found to be significantly associated with the degree of QOL change by Markand et al., 2000 and van Empelen et al., 2005. Both studies found that QOL had improved more at longer follow up durations (2 years vs 1 year for Markand et al., 2000, 2 years vs 6 months for van Empelen et al., 2005). Leal et al., 2020 found improvements in QOL at 2 years but not at 6 months following surgery.

Puka et al., 2015 studied a relatively large cohort of children (N=71) who underwent epilepsy surgery (mixed approaches) and assessed QOL outcomes 5 or more years after surgery. They reported that follow up duration did not affect QOL outcomes.

Overall, these results suggest that some improvement in QOL is already detectable 6 months after epilepsy surgery and that more profound improvements can be observed up to 2 years post-surgery. The results are consistent with serial follow-up studies of QOL in adult populations, which show that QOL improves during the first 6 months to 2 years after surgery and stabilizes thereafter (Spencer et al., 2007).

Neuropsychological factors/cognition/IQ

A few studies included here have explored the role of cognitive function (mostly operationalised as IQ) in determining post-surgical QOL outcomes.

Strikingly only two studies, (Liu et al., 2020; Stomberg et al., 2021), both reporting QOL outcomes following surgery in children affected by tuberous sclerosis, reported an effect of IQ on QOL.

Liu et al., 2020 concluded that post-surgical "QOL improvements were frequently observed in patients with postoperative seizure freedom and preoperative low intelligence quotient".

Stomberg et al., 2021 reported that higher developmental level at follow up was associated with improved quality of life, social adaptation, impact on family and parental concerns.

The other studies which explored whether an association between IQ and QOL outcomes in surgical epilepsy patients could not find one (Conway et al., 2018; Leal et al., 2020; Liang et al., 2014; Puka & Smith, 2015; Skirrow et al., 2011; Titus et al., 2013; Yang et al., 1996). These results all the more remarkable as these studies differ in terms of length of follow up duration (Conway et al., 2018; Leal et al., 2020; Titus et al., 2013; Yang et al., 1996 shorter FU <2years; Skirrow et al., 2011 FU >5years), and surgical approach/aetiology studied (mixed in Conway et al., 2018; Leal et al., 2020; Liang et al., 2014; Puka & Smith, 2015; Skirrow et al., 2011; Titus et al., 2013; Yang et al., 1996; TLE for Skirrow et al., 2011, corpus callosotomies for Liang et al., 2014; Yang et al., 1996). It is known that changes in IQ are not generally observed at shorter follow up durations (up to 5 years) following epilepsy surgery. However, both Skirrow et al., 2011 and Puka et al., 2015, focused on long term effects on QOL and IQ (> 5 years) and yet could not find an association between IQ and QOL outcomes. Overall, these results suggest that IQ is not strongly associated with QOL outcomes following epilepsy surgery.

Psychosocial factors

A relatively small subset of studies has explicitly addressed whether post-surgical QOL outcomes are associated with psychosocial factors.

Titus et al., 2013 reported that whilst QOL outcomes, including the depression subscale of the QOLCE-76 demonstrated a significant post-surgical improvement (average FU 1 year), there

was no corresponding improvement in Depression Subscale of the BASC-2. They concluded that this discrepancy implied that the improvements in mood reported using the QOL instrument reflected "subjective observations about happiness rather than being indicative of a reduction in clinical symptoms of depression". However, a more recent study (Elliott et al., 2012), which included much longer follow up duration (average FU 9 years – range 2-22 years) concluded that mood (measured via the Profile of Mood States, POMS, McNair et al., 1989) was the most consistent independent predictor of QOL.

Similarly, Puka et al., 2015 (with an Average FU of 7 years and range 4-11 years) employed mediation analyses methods and found that internalising behaviour (anxiety/depression, measured with the State Trait Anxiety Inventory and the ABCL/CBCL respectively) mediated the relationship between seizure freedom and better QOL, where seizure freedom led to better ratings of anxiety/depression, which in turn led to better ratings of QOL.

Evidence is mounting, therefore, in support of the relevance and importance of mood in mediating QOL outcomes, especially at longer follow-up durations.

Looking at the broader psychosocial impact of family factors on QOL outcomes following epilepsy surgery, Leal et al., 2020 noted that parental level of education (but not family income) was correlated with post-surgical QOL outcomes at 2 years follow up. Philips et al., 2020b conducted a moderation analysis and reported that whilst seizure outcome was the most robust predictor of post-surgical overall QOL outcomes (1-year post-surgery), family resources moderated the association between seizure freedom and QOL, such that for children with limited family resources achieving seizure freedom was only weakly linked to QOL improvements. They therefore conclude that "achieving seizure freedom may not be enough to improve overall HRQOL in children who do not have adequate social support and family resources".

Overall, there are indications that both psychological (mood) and psychosocial (family resources) factors are associated with QOL outcomes following epilepsy surgery.

Discussion

A systematic review of the literature identified 36 studies which examined QOL outcomes following resective epilepsy surgery in paediatric populations. Close examination of the articles provided answers to the research questions posed.

1- Does undergoing epilepsy surgery during childhood result in improvements in QOL?

The systematic review provides evidence that QOL outcomes improve following epilepsy surgery in childhood.

The vast majority of studies reported increased overall QOL following epilepsy surgery. Improvements were most often observed in the physical health, social and behavioural domains. Improvements in the cognitive and emotional domains were least likely to be observed. Improvements were most likely in the first 6 months to 2 years following surgery, plateauing afterwards. This is consistent with results observed in adult populations (Spencer et al., 2007).

Only a subset of studies had a longitudinal design and included a control group of children whose epilepsy was medically managed, thus offering an opportunity to answer the question of whether QOL changes were specifically associated with epilepsy surgery. Overall, these

studies suggest that QOL improves post-surgery, but that these improvements are not directly attributable to surgery per se, but rather to the fact that surgery affords higher rates of seizure freedom than exclusive pharmacological management of epilepsy in children affected by refractory epilepsy.

Two of the reviewed studies adopted a qualitative design (Hum et al., 2010; O'Brien et al., 2020) and provided richer descriptions of QOL changes following epilepsy surgery. Both studies reported improvements in the social domain but converged in highlighting ongoing difficulties following epilepsy surgery. They indicated that children and their families continued to face challenges due to social isolation, difficulties in interacting with peers and significant problems in adapting to a life without seizures. This latter phenomenon has been observed also in adult populations and has been referred to as "the burden of normality" (Wilson et al., 2001). Indeed, there are indications in the literature that it may be difficult to predict psychosocial outcomes following epilepsy surgery in children and adolescents, with most patients and their families, reporting difficulties in adapting to the transition from refractory epilepsy to a life without seizures (Derry & Wiebe, 2000; Dupont et al., 2006; Kemp et al., 2016). The adult literature is richer in qualitative studies which have also explored, for instance, issues of identity changes following epilepsy surgery (Coleman et al., 2021). More emphasis on qualitative approaches to explore children and young people's lived experience of life following epilepsy surgery are likely to provide important insights.

2- What factors are associated with changes in QoL outcomes following paediatric epilepsy surgery?

Seizure outcome following epilepsy surgery is, by far, the most explored and reported factor associated with changes in QOL following surgery.

Most studies reported that QOL improvements are higher in children who have achieved seizure freedom over those who experience residual seizures following surgery. As mentioned above, there is mounting evidence that it is indeed seizure freedom, rather that surgery per se which is associated to QOL gains following epilepsy surgery. These results are also corroborated by a recent meta-analysis of 18 studies focused on QOL outcomes following paediatric epilepsy surgery (Maragkos et al., 2019, N=890). They concluded that only children who were seizure free after surgery experienced significant QOL improvements, whilst for their counterparts who still experienced residual seizures after surgery QOL improvements did not reach statistical significance.

Overall, evidence is mixed with regards to other epilepsy related factors and their association with QOL outcomes following surgery. Higher post-surgical AED load has been found to be significantly associated with poorer QOL outcomes, but this is not a universal finding, and it is unclear how much of this effect is imputable to seizure outcome rather than any direct effects of AED burden on QOL outcomes.

Earlier age at epilepsy onset has also been reported to correlate with worse QOL outcomes following surgery. In general, however, participant heterogeneity with respect to epilepsy related factors (age at epilepsy onset, duration of epilepsy, aetiology, etc) is too large to be able to detect significant associations between these factors and post-surgical QOL outcomes.

Heterogeneity of participant samples also largely precludes analysis of association between surgery related factors (age at surgery, location, surgery type) and QOL outcomes. A small group of studies have reported on selected patient populations undergoing specific surgical interventions and provide valuable insights with regards to surgical management of specific patient populations (e.g., RCT superiority of corpus callosotomy and resection over resection only approach, Ding et al., 2016), but overall, these represent the exception rather than the norm.

Demographic factors have not been systematically explored as determinants of QOL outcomes following epilepsy surgery. A small number of studies reviewed here reported worse QOL outcomes in girls vs boys. However, several of the studies reviewed here reported no association between gender (and age) and QOL outcomes. Overall, the evidence reviewed here is inconsistent with respect to potential associations between demographic factors and QOL outcomes.

One important finding that emerges from this systematic review is that, overall, there seems to be a dissociation between QOL and cognitive outcomes following epilepsy surgery. This finding has been observed not only by short term (1-2 years) and longer term (>5 years) follow up studies. Overall, there are good indications that post-surgical QOL outcomes in epilepsy surgery are largely independent of IQ scores and IQ changes following epilepsy surgery in paediatric populations.

A small, but recently growing, number of studies has explored the association between QOL outcomes and psychosocial factors. Mood (anxiety/depression) has been highlighted as an important mediator of the effect of seizure freedom on post-surgical QOL outcomes. Of the broader psychosocial factors, family resources have been shown to be significant moderators of QOL improvements following epilepsy surgery, indicating that pre-surgical family interventions could be important determinants of QOL outcomes following epilepsy surgery.

Methodological considerations and quality of studies reviewed

The number of studies focusing on QOL outcomes following paediatric epilepsy surgery has increased steadily during the last two decades. It is only in the last 5 years, however, that interest has grown in exploring non-medical determinants of QOL outcomes. This research area is particularly vital to inform clinical decision making and interventions. Here we will discuss methodological considerations regarding the reviewed studies, with a view to illustrate current research challenges, highlight gaps in current knowledge, with the aim to inform future research strategies.

Study design and statistical considerations

Many studies included in this review (15 out of 36) adopted a cross-sectional design. The advantages of cross-sectional designs are that they facilitate the inclusion of larger samples, their relative low costs and time-efficiency. It is also the case that, due to practical considerations, most of the studies which report long term follow up durations are cross-sectional in design. However, a cross-sectional design precludes analysis of causality and the study of QOL *changes* following surgery.

An important methodological consideration is choice of control group. Some studies reviewed here reported comparisons with healthy participants. The inclusion of a control group including exclusively medically managed epilepsy is crucial as it allows exploration of the effect of surgery on QOL outcomes. This is particularly important as there is extensive evidence in the literature showing QOL improvements across time for children affected by epilepsy, regardless of surgical intervention. Of the studies reviewed here only 12 out of 36 studies reviewed here included such a medically managed epilepsy group (and of those only 7 adopted a longitudinal design).

Small sample sizes were relatively common in the reviewed studies, potentially leading to low statistical power/type II errors (failure to find statistically significant effects where there would have been some). Studies which included larger sample had often a medical focus, often reporting QOL outcomes alongside medical variables (e.g., seizure freedom) rather than exploring broader psychosocial factors.

A very small number of studies did not employ statistical methods, and only reported descriptive results.

Only 2 of the 36 studies reviewed here adopted a qualitative design. Qualitative studies are important as they offer much richer and in-depth descriptions of QOL, and therefore can provide important clues as that might aid the further design/refinement of quantitative QOL instruments and suggest useful suggestions for further research. For instance, both qualitative studies reviewed here highlighted the presence of social barriers (isolation and specific

difficulties with peer-interactions) and identity issues (adaptation to life without seizures) as important determinants of QOL outcomes following epilepsy surgery.

Heterogeneity

Most studies were characterised by large within and across group variability with respect to epilepsy-related, surgical-related, and demographic factors. This heterogeneity largely prevented drawing firm conclusions with respect to the contribution of these factors to QOL outcomes following epilepsy surgery.

Most larger sample studies included children who underwent resective surgery targeting a wide variety of brain targets, thus precluding the possibility of investigating whether differences in QOL outcomes are driven by location of pathology. For instance, in the adult populations there are reports that indicate that temporal epilepsy carries more risks to QOL outcomes than extra-temporal epileptic foci (Jones, 2015).

Measurement issues

This review highlights the large variety of instruments used to monitor QOL. Studies included here used both standardised and unstandardised measures.

Of note, most studies included parental reports of QOL outcomes, with only a subset of studies also reporting children's reports (7 out 36 studies). Of these, only van Empelen et al., 2005 systematically assessed level of agreement between child and parent raters. They concluded that whilst overall children and parent ratings were positively correlated, children were less positive regarding their physical, cognitive, and social activities than their parents. Although there are reports of substantial agreement between parental and children QOL variables (Puka

et al., 2018), there is also evidence in the literature pointing at differences (Ferro et al., 2017). Overall, multi-informant assessment of QOL is best placed to capture this potential variability. In addition, there are indications that there is variability across developmental times as to what is prioritised in terms of QOL. For instance, O'Brien et al., 2020 and Zupanc et al., 2010 highlighted differences in QOL ratings across adolescents and children, with adolescents reporting worse social outcomes than children.

Clinical implications

The findings from this review highlight the need for quality of life and psychosocial factors to be routinely included in the assessment of surgical intervention in children with epilepsy. Standardised measures should be routinely administered to children, their carers and teachers (whenever possible), in order to ensure that several perspectives are incorporated. Measures should include family as well as child-centred factors, such that tailored interventions can be designed and implemented both pre- and post-surgically, to maximise the chances of positive clinical outcomes.

Assessment and discussion of QOL should be encouraged at the pre-surgical stage, so that patients, their family and medical professionals can make informed decisions regarding treatment, having considered potential outcomes across broader psycho-social domains.

As this review highlighted, growing consensus points to the role of mental-health related factors (e.g. anxiety, mood) as mediators of QOL outcomes of paediatric epilepsy surgery. The paradoxical increase in anxiety that is often observed following epilepsy surgery has been interpreted as reflecting, at least partially, the “burden of normality”, difficulties of the family and patient to adapt to a post-surgical seizure-free identity. This interpretation is corroborated both by quantitative and qualitative research, some of which was reviewed here (e.g. Hum et

al., 2010; O'Brien et al., 2020). These difficulties in adapting to a "seizure-free identity" are most likely exacerbated by the fact that post-surgical follow up is often restricted to few appointments with the medical and neuropsychology team in the tertiary care setting where surgery has taken place. At least in the UK, the dearth of community neuropsychology services, and the reluctance of clinical psychology professionals to care for children with brain injury/disease has meant that longitudinal and holistic psycho-social support of paediatric epilepsy patients, post-surgery, in the community, is often not available. Patients are often referred to 3rd sector organisations, which are underfunded and cannot adequately meet the complex needs of the young patients and their families.

Moreover, more can be done in terms of empowering and educating school staff on how best to support children with epilepsy, and specifically children who are due to or have undergone epilepsy surgery. This could be achieved via forging more direct links between neuropsychology, educational psychology and clinical psychology teams across tertiary care, local authority, and school settings.

In order to target the broader QOL of young patients living epilepsy or any other brain disorder/injury it is paramount for mental health professionals to feel competent and capable of supporting the mental wellbeing of children with brain injury/disease. Emphasis should be put on integrating neuropsychology and mental health curricula for clinical, counselling and educational psychologists. Unfortunately, in the UK, a worrying trend of specialisation rather than integration is slowly taking hold. Children with brain injury/disease encounter often insurmountable difficulties in obtaining adequate recognition, care and support of their mental health needs in the community. There is therefore an urgent need to revise curricula, to make psychology training more inter-disciplinary, avoiding the mind/brain duality trap.

Lastly, evidence reviewed here points to the need to incorporate interventions that are mindful of the larger social circumstances of young epilepsy patients. A nascent research field is exploring how social factors (e.g. family resources, Leal, 2020, Philips et al., 2020b) interact with medical factors (e.g. seizure freedom) in determining QOL outcomes following epilepsy surgery. These results have clear implications for the design of clinical interventions which enhance access to resources (financial, educational, etc.) for the families of children affected by epilepsy.

Future research

The results reviewed here and the methodological considerations above point to several recommendations for further research:

1- It is important to include a non-surgical control group whenever assessing QOL outcomes, in order to be able to attribute findings specifically to surgical intervention. It is also advisable to adopt a longitudinal design, whenever possible, such that QOL *change* following surgery can be monitored.

2- The design of studies focusing on QOL outcomes in populations differing across locus of pathology (e.g., temporal vs extra-temporal) might uncover differences in QOL improvements/vulnerabilities across children.

3- It is advisable to reach a consensus on a smaller set of objective QOL instruments, via professionals/carers and patients forums, whilst continuing to research the sensitivity and cultural appropriateness of the instruments in use currently.

4- There is a relative dearth of longer follow up studies of QOL outcomes following epilepsy surgery in children. Design of multi-centre, prospective long-term follow up

studies is therefore recommended. In particular, it would be important to focus attention on different developmental transition periods (from primary to secondary school, from school to further education/employment and transition to adulthood).

5- There is a nascent research interest in studying psychosocial determinants of QOL. Further research in this field should be nurtured, and a focus on family factors is also advisable.

6- Lastly, a qualitative approach to future research with regards to psychosocial outcomes would be valuable to capture the richness of the lived experience of children undergoing epilepsy surgery and their families. As highlighted in this review, findings from qualitative studies have great potential at providing clues as to what variables, beyond medical ones, determine QOL outcomes in paediatric populations undergoing epilepsy surgery.

Conclusions

Childhood epilepsy surgery has overall excellent medical outcomes in terms of seizure freedom and concurrent QOL improvement.

This review indicates that the largest QOL improvements are most likely observed 6-months to 2 years following surgery in the health, social and behavioural domains.

The most robust determinant of QOL improvement following surgery is seizure freedom.

The effect of seizure freedom on QOL improvement is likely mediated by mood, with seizure freedom directly improving mood and this, in turn translating into QOL improvements.

It is likely that family resources moderate the effect of seizure freedom on QOL improvement following surgery.

Cognitive variables, and in particular IQ, are not associated with QOL outcomes following epilepsy surgery at either short- (1-2 years) or longer (>5 years) follow up periods. Moreover, significant improvements in QOL are routinely observed in children with pre-surgical IQ < 70, even in the absence of an improvement in IQ post-surgery.

This systematic review strongly indicates that it is vital for children undergoing epilepsy surgery, and their families, to be assessed for psychosocial difficulties, with the aim to tailor interventions to improve their quality of life.

Bibliography

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), e1532-1543. https://doi.org/10.1542/peds.2011-0245

Baker, G. A., Hargis, E., Hsih, M. M., Mounfield, H., Arzimanoglou, A., Glauser, T., Pellock, J., & Lund, S. (2008). Perceived impact of epilepsy in teenagers and young adults: an international survey. *Epilepsy Behav*, *12*(3), 395-401. https://doi.org/10.1016/j.yebeh.2007.11.001

Baldeweg, T. a. S., C. (2015). *Long-term cognitive outcomes after epilepsy surgery in children*. Springer International Publishing.

Baum, K. T., Byars, A. W., deGrauw, T. J., Johnson, C. S., Perkins, S. M., Dunn, D. W., Bates, J. E., & Austin, J. K. (2007). Temperament, family environment, and behavior problems in children with new-onset seizures. *Epilepsy Behav*, *10*(2), 319-327. https://doi.org/10.1016/j.yebeh.2006.12.007

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

Besag, F., Aldenkamp, A., Caplan, R., Dunn, D. W., Gobbi, G., & Sillanpää, M. (2016). Psychiatric and Behavioural Disorders in Children with Epilepsy: an ILAE Task Force Report. *Epileptic Disord*, *18 Suppl 1*, 1-86. https://doi.org/10.1684/epd.2016.0809 (Psychiatric and Behavioural Disorders in Children with Epilepsy: an ILAE Task Force Report.)

Bilgiç, A., Işık, Ü., Çolak, R. S., Derin, H., & Çaksen, H. (2018). Psychiatric symptoms and health-related quality of life in children with epilepsy and their mothers. *Epilepsy & Behavior*, *80*, 114-121.

Camfield, C., Camfield, P., Gordon, K., Smith, B., & Dooley, J. (1993). Outcome of childhood epilepsy: A population-based study with a simple predictive scoring system for those treated with medication. *The Journal of Pediatrics*, *122*(6), 861-868. https://doi.org/https://doi.org/10.1016/S0022-3476(09)90008-7

Chadwick D, B. E., Callaghan N, et al. (1998). Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia*, *39*(7), 799-803. https://doi.org/10.1111/j.1528-1157.1998.tb01167.x

Chen, H. H., Chen, C., Hung, S. C., Liang, S. Y., Lin, S. C., Hsu, T. R., Yeh, T. C., Yu, H. Y., Lin, C. F., Hsu, S. P., Liang, M. L., Yang, T. F., Chu, L. S., Lin, Y. Y., Chang, K. P., Kwan, S. Y., Ho, D. M., Wong, T. T., & Shih, Y. H. (2014). Cognitive and epilepsy outcomes after epilepsy surgery caused by focal cortical dysplasia in children: early intervention maybe better. *Childs Nerv Syst*, *30*(11), 1885-1895. https://doi.org/10.1007/s00381-014-2463-y

Coleman, H., McIntosh, A., Rayner, G., & Wilson, S. J. (2021). Understanding long-term changes in patient identity 15-20 years after surgery for temporal lobe epilepsy. *Epilepsia*, *62*(10), 2451-2462. https://doi.org/10.1111/epi.17027

Conway, L., Widjaja, E., & Smith, M. L. (2018). Impact of resective epilepsy surgery on health-related quality of life in children with and without low intellectual ability. *Epilepsy Behav*, *83*, 131-136. https://doi.org/10.1016/j.yebeh.2018.03.036

Crudgington, H., Collingwood, A., Bray, L., Lyle, S., Martin, R., Gringras, P., Pal, D. K., & Morris, C. (2020). Mapping epilepsy-specific patient-reported outcome measures for children

to a proposed core outcome set for childhood epilepsy. *Epilepsy Behav*, *112*, 107372. https://doi.org/10.1016/j.yebeh.2020.107372

Crudgington, H., Rogers, M., Bray, L., Carter, B., Currier, J., Dunkley, C., Gibbon, F. M., Hughes, D., Lyle, S., Roberts, D., Tudur Smith, C., Gringras, P., Pal, D. K., & Morris, C. (2019). Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus. *Epilepsia*, *60*(5), 857-871. https://doi.org/10.1111/epi.14735

Crudgington, H., Rogers, M., Morris, H., Gringras, P., Pal, D. K., & Morris, C. (2020). Epilepsy-specific patient-reported outcome measures of children's health-related quality of life: A systematic review of measurement properties. *Epilepsia*, *61*(2), 230-248. https://doi.org/10.1111/epi.16430

Dagar, A., Chandra, P. S., Chaudhary, K., Avnish, C., Bal, C. S., Gaikwad, S., Garg, A., Sarkar, C., Srivastava, A., Padma, M. V., Rekha, D., Gulati, S., Paul, V., Prasad, K., Singh, M. B., & Tripathi, M. (2011). Epilepsy surgery in a pediatric population: a retrospective study of 129 children from a tertiary care hospital in a developing country along with assessment of quality of life. *Pediatr Neurosurg*, *47*(3), 186-193. https://doi.org/10.1159/000334257

Derry, P. A., & Wiebe, S. (2000). Psychological adjustment to success and to failure following epilepsy surgery. *Canadian journal of neurological sciences*, *27*(S1), S116-S120.

Ding, P., Liang, S., Zhang, S., Zhang, J., Hu, X., & Yu, X. (2016). Resective surgery combined with corpus callosotomy for children with non-focal lesional Lennox-Gastaut syndrome. *Acta Neurochir (Wien)*, *158*(11), 2177-2184. https://doi.org/10.1007/s00701-016-2947-5

Downes, M., Greenaway, R., Clark, M., Helen Cross, J., Jolleff, N., Harkness, W., Kaliakatsos, M., Boyd, S., White, S., & Neville, B. G. (2015). Outcome following multiple subpial transection in Landau-Kleffner syndrome and related regression. *Epilepsia*, *56*(11), 1760-1766. https://doi.org/10.1111/epi.13132

Dupont, S., Tanguy, M.-L., Clemenceau, S., Adam, C., Hazemann, P., & Baulac, M. (2006). Long-term Prognosis and Psychosocial Outcomes after Surgery for MTLE. *Epilepsia*, *47*(12), 2115-2124. https://doi.org/https://doi.org/10.1111/j.1528-1167.2006.00852.x

Dwivedi, R., Ramanujam, B., Chandra, P. S., Sapra, S., Gulati, S., Kalaivani, M., Garg, A., Bal, C. S., Tripathi, M., Dwivedi, S. N., Sagar, R., Sarkar, C., & Tripathi, M. (2017). Surgery for Drug-Resistant Epilepsy in Children. *N Engl J Med*, *377*(17), 1639-1647. https://doi.org/10.1056/NEJMoa1615335

Elliott, I., Kadis, D. S., Lach, L., Olds, J., McCleary, L., Whiting, S., Snyder, T., & Smith, M. L. (2012). Quality of life in young adults who underwent resective surgery for epilepsy in childhood. *Epilepsia*, *53*(9), 1577-1586. https://doi.org/10.1111/j.1528-1167.2012.03594.x

Elliott, I. M., Lach, L., & Smith, M. L. (2005). I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. *Epilepsy Behav*, *7*(4), 664-678. https://doi.org/10.1016/j.yebeh.2005.07.004

Engel, J. (1993). *Surgical Treatment of the Epilepsies, 2nd ed.* Raven Press.

Engel, J., Jr. (2016). What can we do for people with drug-resistant epilepsy? The 2016 Wartenberg Lecture. *Neurology*, *87*(23), 2483-2489. https://doi.org/10.1212/wnl.0000000000003407

Fastenau, P. S., Jianzhao, S., Dunn, D. W., & Austin, J. K. (2008). Academic underachievement among children with epilepsy: proportion exceeding psychometric criteria for learning disability and associated risk factors. *J Learn Disabil*, *41*(3), 195-207. https://doi.org/10.1177/0022219408317548

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

Ferro, M. A., Avery, L., Fayed, N., Streiner, D. L., Cunningham, C. E., Boyle, M. H., Lach, L., Glidden, G., Rosenbaum, P. L., Ronen, G. M., & group, Q. (2017). Child- and parent-reported quality of life trajectories in children with epilepsy: A prospective cohort study. *Epilepsia*, *58*(7), 1277-1286. https://doi.org/10.1111/epi.13774

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. *Seizure - European Journal of Epilepsy*, *52*, 89-116. https://doi.org/10.1016/j.seizure.2017.09.011

Follansbee-Junger, K. W., Mann, K. A., Guilfoyle, S. M., Morita, D. A., Varni, J. W., & Modi, A. C. (2016). Development of the PedsQL™ Epilepsy Module: Focus group and cognitive interviews. *Epilepsy Behav*, *62*, 115-120. https://doi.org/10.1016/j.yebeh.2016.06.011

Goodwin, S. W., Lambrinos, A. I., Ferro, M. A., Sabaz, M., & Speechley, K. N. (2015). Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). *Epilepsia*, *56*(6), 864-872. https://doi.org/10.1111/epi.13000

Griffiths, S. Y., Sherman, E. M., Slick, D. J., Eyrl, K., Connolly, M. B., & Steinbok, P. (2007). Postsurgical health-related quality of life (HRQOL) in children following hemispherectomy for intractable epilepsy. *Epilepsia*, *48*(3), 564-570. https://doi.org/10.1111/j.1528-1167.2006.00966.x

Hrabok, M., Dykeman, J., Sherman, E. M., & Wiebe, S. (2013, Dec). An evidence-based checklist to assess neuropsychological outcomes of epilepsy surgery: how good is the evidence? Epilepsy Behav, 29(3), 443-448. https://doi.org/10.1016/j.yebeh.2013.08.035

Hum, K. M., Smith, M. L., Lach, L., & Elliott, I. M. (2010). Self-perceptions of social function 2years after pediatric epilepsy surgery. *Epilepsy & Behavior*, *17*(3), 354-359. https://doi.org/https://doi.org/10.1016/j.yebeh.2009.11.022

Joint Epilepsy Council of UK and Norther Ireland (2011). *Epilepsy prevalence, incidence and other statistics*.

Jain, P., Smith, M. L., Speechley, K., Ferro, M., Connolly, M., Ramachandrannair, R., Almubarak, S., Andrade, A., Widjaja, E., & Pepsqol Study, T. (2020). Seizure freedom improves health-related quality of life after epilepsy surgery in children. *Dev Med Child Neurol*, *62*(5), 600-608. https://doi.org/10.1111/dmcn.14390

Jalava, M., Sillanpää, M., Camfield, C., & Camfield, P. (1997). Social adjustment and competence 35 years after onset of childhood epilepsy: a prospective controlled study. *Epilepsia*, *38*(6), 708-715. https://doi.org/10.1111/j.1528-1157.1997.tb01241.x

Jennum, P., Christensen, J., Ibsen, R., & Kjellberg, J. (2016). Long-term socioeconomic consequences and health care costs of childhood and adolescent-onset epilepsy. *Epilepsia*, *57*(7), 1078-1085. https://doi.org/10.1111/epi.13421

Jones, C., & Reilly, C. (2016). Parental anxiety in childhood epilepsy: A systematic review. *Epilepsia*, *57*(4), 529-537. https://doi.org/10.1111/epi.13326

Jones, J. H., M. (2015). *Quality-of-life outcomes in adults following epilepsy surgery*. Springer International Publishing.

Keene, D. L., Higgins, M. J., & Ventureyra, E. C. (1997). Outcome and life prospects after surgical management of medically intractable epilepsy in patients under 18 years of age. *Childs Nerv Syst*, *13*(10), 530-535. https://doi.org/10.1007/s003810050132

Kemp, S., Garlovsky, J., Reynders, H., Caswell, H., Baker, G., & Shah, E. (2016). Predicting the psychosocial outcome of epilepsy surgery: A longitudinal perspective on the 'burden of normality'. *Epilepsy & Behavior*, *60*, 149-152. https://doi.org/https://doi.org/10.1016/j.yebeh.2016.04.029

Kwan, P., & Brodie, M. J. (2000). Early identification of refractory epilepsy. *N Engl J Med*, *342*(5), 314-319. https://doi.org/10.1056/nejm200002033420503

Kwon, C.-S., Jacoby, A., Ali, A., Austin, J., Birbeck, G. L., Braga, P., Cross, J. H., de Boer, H., Dua, T., Fernandes, P. T., Fiest, K. M., Goldstein, J., Haut, S., Lorenzetti, D., Mifsud, J., Moshe, S., Parko, K. L., Tripathi, M., Wiebe, S., & Jette, N. (2022). Systematic review of frequency of felt and enacted stigma in epilepsy and determining factors and attitudes toward persons living with epilepsy—Report from the International League Against Epilepsy Task Force on Stigma in Epilepsy [https://doi.org/10.1111/epi.17135]. *Epilepsia*, *63*(3), 573-597. https://doi.org/https://doi.org/10.1111/epi.17135

Lah, S. (2004). Neuropsychological outcome following focal cortical removal for intractable epilepsy in children. *Epilepsy Behav*, *5*(6), 804-817. https://doi.org/10.1016/j.yebeh.2004.08.005

Leal, S. T. F., Santos, M. V., Thome, U., Machado, H. R., Escorsi-Rosset, S., Dos Santos, A. C., Wichert-Ana, L., Leite, J. P., Fernandes, R. M. F., Sakamoto, A. C., & Hamad, A. P. A. (2020). Impact of epilepsy surgery on quality of life and burden of caregivers in children and adolescents. *Epilepsy Behav*, *106*, 106961. https://doi.org/10.1016/j.yebeh.2020.106961

Lenck-Santini, P. P., & Scott, R. C. (2015). Mechanisms Responsible for Cognitive Impairment in Epilepsy. *Cold Spring Harb Perspect Med*, *5*(10). https://doi.org/10.1101/cshperspect.a022772

Liang, S., Wang, S., Zhang, J., Ding, C., Zhang, Z., Fu, X., Hu, X., Meng, X., Jiang, H., & Zhang, S. (2012). Long-term outcomes of epilepsy surgery in school-aged children with partial epilepsy. *Pediatr Neurol*, *47*(4), 284-290. https://doi.org/10.1016/j.pediatrneurol.2012.06.014

Liang, S., Zhang, S., Hu, X., Zhang, Z., Fu, X., Jiang, H., & Xiaoman, Y. (2014). Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. *Eur J Paediatr Neurol*, *18*(6), 670-676. https://doi.org/10.1016/j.ejpn.2014.05.004

Lindsay, J., Ounsted, C., & Richards, P. (1987). Hemispherectomy for childhood epilepsy: a 36-year study. *Dev Med Child Neurol*, *29*(5), 592-600. https://doi.org/10.1111/j.1469-8749.1987.tb08501.x

Liu, S., Yu, T., Guan, Y., Zhang, K., Ding, P., Chen, L., Shan, Y., Guo, Q., Liu, Q., Yao, Y., Yang, M., Zhang, S., Lin, Y., Zhao, R., Mao, Z., Zhang, J., Zhang, C., Zhang, R., Yang, Z., . . . Liang, S. (2020). Resective epilepsy surgery in tuberous sclerosis complex: a nationwide multicentre retrospective study from China. *Brain*, *143*(2), 570-581. https://doi.org/10.1093/brain/awz411

Loring, D. W., Lowenstein, D. H., Barbaro, N. M., Fureman, B. E., Odenkirchen, J., Jacobs, M. P., Austin, J. K., Dlugos, D. J., French, J. A., Gaillard, W. D., Hermann, B. P., Hesdorffer, D. C., Roper, S. N., Van Cott, A. C., Grinnon, S., & Stout, A. (2011). Common data elements in epilepsy research: development and implementation of the NINDS epilepsy CDE project. *Epilepsia*, *52*(6), 1186-1191. https://doi.org/10.1111/j.1528-1167.2011.03018.x

MacAllister, W. S., & Schaffer, S. G. (2007). Neuropsychological deficits in childhood epilepsy syndromes. *Neuropsychol Rev*, *17*(4), 427-444. https://doi.org/10.1007/s11065-007-9048-4

Maragkos, G. A., Geropoulos, G., Kechagias, K., Ziogas, I. A., & Mylonas, K. S. (2019). Quality of Life After Epilepsy Surgery in Children: A Systematic Review and Meta-Analysis. *Neurosurgery*, *85*(6), 741-749. https://doi.org/10.1093/neuros/nyy471

Markand, O. N., Salanova, V., Whelihan, E., & Emsley, C. L. (2000). Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. *Epilepsia*, *41*(6), 749-759. https://doi.org/10.1111/j.1528-1157.2000.tb00238.x

McEwan, M. J., Espie, C. A., Metcalfe, J., Brodie, M. J., & Wilson, M. T. (2004). Quality of life and psychosocial development in adolescents with epilepsy: a qualitative investigation using focus group methods. *Seizure*, *13*(1), 15-31. https://doi.org/https://doi.org/10.1016/S1059-1311(03)00080-3

McLaughlin, R. M., Schraegle, W. A., Nussbaum, N. L., & Titus, J. B. (2018). Parental coping and its role in predicting health-related quality of life in pediatric epilepsy. *Epilepsy Behav*, *87*, 1-6. https://doi.org/10.1016/j.yebeh.2018.08.009

McLellan, A. (2015). *Long-term psychiatric and behavior outcomes in children following epilepsy surgery*. Springer International Publishing.

McNair, D., Lorr, M., & Droppleman, L. (1989). Profile of mood states (POMS).

Mendes, T. P., Crespo, C. A., & Austin, J. K. (2017). Family Cohesion, Stigma, and Quality of Life in Dyads of Children With Epilepsy and Their Parents. *J Pediatr Psychol*, *42*(6), 689-699. https://doi.org/10.1093/jpepsy/jsw105

Mikati, M. A., Ataya, N., Ferzli, J., Kurdi, R., El-Banna, D., Rahi, A., Shamseddine, A., Sinno, D., & Comair, Y. (2010). Quality of life after surgery for intractable partial epilepsy in children: a cohort study with controls. *Epilepsy Res*, *90*(3), 207-213. https://doi.org/10.1016/j.eplepsyres.2010.05.002

Modi, A. C., King, A. S., Monahan, S. R., Koumoutsos, J. E., Morita, D. A., & Glauser, T. A. (2009). Even a single seizure negatively impacts pediatric health-related quality of life. *Epilepsia*, *50*(9), 2110-2116. https://doi.org/10.1111/j.1528-1167.2009.02149.x

Modi, A. C., Wagner, J., Smith, A. W., Kellermann, T. S., & Michaelis, R. (2017). Implementation of psychological clinical trials in epilepsy: Review and guide. *Epilepsy & Behavior*, *74*, 104-113. https://doi.org/https://doi.org/10.1016/j.yebeh.2017.06.016

Moffat, C., Dorris, L., Connor, L., & Espie, C. A. (2009). The impact of childhood epilepsy on quality of life: A qualitative investigation using focus group methods to obtain children's perspectives on living with epilepsy. *Epilepsy & Behavior*, *14*(1), 179-189. https://doi.org/https://doi.org/10.1016/j.yebeh.2008.09.025

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/https://doi.org/10.1016/j.spen.2017.10.010

Moreira, H., Carona, C., Silva, N., Frontini, R., Bullinger, M., & Canavarro, M. C. (2013). Psychological and quality of life outcomes in pediatric populations: a parent-child perspective. *J Pediatr*, *163*(5), 1471-1478. https://doi.org/10.1016/j.jpeds.2013.06.028

National Institute for Health and Care Excellence, (2022). *NG 217 Epilepsies in children, young people and adults*.

O'Brien, J., Gray, V., & Woolfall, K. (2020). Child and parent experiences of childhood epilepsy surgery and adjustment to life following surgery: A qualitative study. *Seizure*, *83*, 83-88. https://doi.org/10.1016/j.seizure.2020.10.006

Perry, M. S., & Duchowny, M. (2013). Surgical versus medical treatment for refractory epilepsy: outcomes beyond seizure control. *Epilepsia*, *54*(12), 2060-2070. https://doi.org/10.1111/epi.12427

Phillips, N. L., Widjaja, E., & Smith, M. L. (2019). Impact of resective surgery for pediatric drug-resistant epilepsy on emotional functioning. *Epilepsy Behav*, *101*(Pt A), 106508. https://doi.org/10.1016/j.yebeh.2019.106508

Puka, K., & Smith, M. L. (2015). Predictors of long-term quality of life after pediatric epilepsy surgery. *Epilepsia*, *56*(6), 873-881. https://doi.org/10.1111/epi.13004

Puka, K., Tavares, T. P., Anderson, K. K., Ferro, M. A., & Speechley, K. N. (2018). A systematic review of quality of life in parents of children with epilepsy. *Epilepsy & Behavior*, *82*, 38-45.

Puka, K., Widjaja, E., & Smith, M. L. (2017). The influence of patient, caregiver, and family factors on symptoms of anxiety and depression in children and adolescents with intractable epilepsy. *Epilepsy Behav*, *67*, 45-50. https://doi.org/10.1016/j.yebeh.2016.12.011

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & Neville, B. G. (2014). Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics*, *133*(6), e1586-1593. https://doi.org/10.1542/peds.2013-3787

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & Neville, B. G. (2015). Factors associated with quality of life in active childhood epilepsy: a population-based study. *Eur J Paediatr Neurol*, *19*(3), 308-313. https://doi.org/10.1016/j.ejpn.2014.12.022

Reilly, C., Baldeweg, T., Stewart, N., Wadhwani, S., Jones, C., Helen Cross, J., & Heyman, I. (2019). Do behavior and emotions improve after pediatric epilepsy surgery? A systematic review. *Epilepsia*, *60*(5), 885-897. https://doi.org/10.1111/epi.14737

Ronen, G. M., Streiner, D. L., & Rosenbaum, P. (2003). Health-related quality of life in childhood epilepsy: Moving beyond 'seizure control with minimal adverse effects'. *Health and Quality of Life Outcomes*, *1*(1), 36. https://doi.org/10.1186/1477-7525-1-36

Roth, J., Olasunkanmi, A., MacAllister, W. S., Weil, E., Uy, C. C., Devinsky, O., & Weiner, H. L. (2011). Quality of life following epilepsy surgery for children with tuberous sclerosis complex. *Epilepsy Behav*, *20*(3), 561-565. https://doi.org/10.1016/j.yebeh.2010.11.003

Sabaz, M., Cairns, D. R., Lawson, J. A., Bleasel, A. F., & Bye, A. M. (2001). The health-related quality of life of children with refractory epilepsy: a comparison of those with and without intellectual disability. *Epilepsia*, *42*(5), 621-628. https://doi.org/10.1046/j.1528-1157.2001.25200.x

Sabaz, M., Lawson, J. A., Cairns, D. R., Duchowny, M. S., Resnick, T. J., Dean, P. M., Bleasel, A. F., & Bye, A. M. (2006). The impact of epilepsy surgery on quality of life in children. *Neurology*, *66*(4), 557-561. https://doi.org/10.1212/01.wnl.0000197788.38783.09

Scott, A. J., Sharpe, L., Loomes, M., & Gandy, M. (2020). Systematic Review and Meta-Analysis of Anxiety and Depression in Youth With Epilepsy. *J Pediatr Psychol*, *45*(2), 133-144. https://doi.org/10.1093/jpepsy/jsz099

Sillanpää, M., Haataja, L., & Shinnar, S. (2004). Perceived impact of childhood-onset epilepsy on quality of life as an adult. *Epilepsia*, *45*(8), 971-977. https://doi.org/10.1111/j.0013-9580.2004.44203.x

Sillanpää, M., Jalava, M., Kaleva, O., & Shinnar, S. (1998). Long-term prognosis of seizures with onset in childhood. *N Engl J Med*, *338*(24), 1715-1722. https://doi.org/10.1056/nejm199806113382402

Sillanpää, M., & Schmidt, D. (2006). Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. *Brain*, *129*(3), 617-624. https://doi.org/10.1093/brain/awh726

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. B., T. (2015). *Educational and employment outcomes following epilepsy surgery in children*. Springer International Publishing.

Speechley, K. (2013). *What if quality of life better expressed outcomes for epilepsy?* . John Libbey Eurotext.

Speechley, K. N., Ferro, M. A., Camfield, C. S., Huang, W., Levin, S. D., Smith, M. L., Wiebe, S., & Zou, G. (2012). Quality of life in children with new-onset epilepsy: a 2-year

prospective cohort study. *Neurology*, *79*(15), 1548-1555. https://doi.org/10.1212/WNL.0b013e31826e25aa

Spencer, S. S., Berg, A. T., Vickrey, B. G., Sperling, M. R., Bazil, C. W., Haut, S., Langfitt, J. T., Walczak, T. S., & Devinsky, O. (2007). Health-related quality of life over time since resective epilepsy surgery. *Ann Neurol*, *62*(4), 327-334. https://doi.org/10.1002/ana.21131

Stomberg, M., Bien, C. G., Kalbhenn, T., Polster, T., & May, T. W. (2021). Epilepsy associated with tuberous sclerosis complex in childhood: Long-term outcome in children after epilepsy surgery and children non-eligible for epilepsy surgery. *Epilepsy Behav*, *122*, 108210. https://doi.org/10.1016/j.yebeh.2021.108210

Titus, J. B., Lee, A., Kasasbeh, A., Thio, L. L., Stephenson, J., Steger-May, K., Limbrick, D. D., Jr., & Smyth, M. D. (2013). Health-related quality of life before and after pediatric epilepsy surgery: the influence of seizure outcome on changes in physical functioning and social functioning. *Epilepsy Behav*, *27*(3), 477-483. https://doi.org/10.1016/j.yebeh.2013.03.003

Ulate-Campos, A., & Fernández, I. S. (2017). Cognitive and Behavioral Comorbidities: An Unwanted Effect of Antiepileptic Drugs in Children. *Semin Pediatr Neurol*, *24*(4), 320-330. https://doi.org/10.1016/j.spen.2017.10.011

van Empelen, R., Jennekens-Schinkel, A., van Rijen, P. C., Helders, P. J., & van Nieuwenhuizen, O. (2005). Health-related quality of life and self-perceived competence of children assessed before and up to two years after epilepsy surgery. *Epilepsia*, *46*(2), 258-271. https://doi.org/10.1111/j.0013-9580.2005.27304.x

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

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*(6). https://doi.org/10.1002/14651858.CD010541.pub3

Wieser, H. G., Blume, W. T., Fish, D., Goldensohn, E., Hufnagel, A., King, D., Sperling, M. R., Lüders, H., & Pedley, T. A. (2001). ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*, *42*(2), 282-286.

Wilson, S. J., Bladin, P. F., Saling, M. M., McIntosh, A. M., & Lawrence, J. A. (2001). The longitudinal course of adjustment after seizure surgery. *Seizure*, *10*(3), 165-172. https://doi.org/10.1053/seiz.2000.0491

World Health Organization (2012) The World Health Organization Quality of life (WHOQOL) , Retrieved 3rd of June from https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03

Yang, T. F., Wong, T. T., Kwan, S. Y., Chang, K. P., Lee, Y. C., & Hsu, T. C. (1996). Quality of life and life satisfaction in families after a child has undergone corpus callostomy. *Epilepsia*, *37*(1), 76-80. https://doi.org/10.1111/j.1528-1157.1996.tb00515.x

Zupanc, M. L., Rubio, E. J., Werner, R. R., Schwabe, M. J., Mueller, W. M., Lew, S. M., Marcuccilli, C. J., O'Connor, S. E., Chico, M. S., Eggener, K. A., & Hecox, K. E. (2010). Epilepsy surgery outcomes: quality of life and seizure control. *Pediatr Neurol*, *42*(1), 12-20. https://doi.org/10.1016/j.pediatrneurol.2009.07.018

Part 2: Empirical Paper

Brain correlates of neuropsychological outcome following paediatric temporal lobe epilepsy surgery.

Abstract

Aims

We set out to identify neurobiological factors which may explain some of the observed individual variability in post-surgical cognitive outcomes in children who have undergone resective surgery to treat temporal lobe epilepsy.

Method

This retrospective study included 81 patients with medication-resistant temporal lobe epilepsy and 20 aged-matched healthy participants. Pre- and post-surgical hippocampal volumes and surgical resection volumes were obtained and studied for their association with neuropsychological variables.

Results

In our cohort of paediatric temporal lobe epilepsy patients, we observed a variable degree of pre-surgical hippocampal atrophy. Atrophy extent was associated with age at epilepsy onset.

Following surgery, we showed a decline in verbal function and verbal memory, regardless of lesion laterality. Children with higher pre-operative scores were most vulnerable to post-operative decline in performance across all cognitive domains.

In patients with left hemisphere lesions, extent of surgical resection was the only significant predictor of post-surgical verbal memory function.

Conclusions

Paediatric temporal lobe epilepsy is associated with impairments to general cognitive function and variable degree of hippocampal atrophy.

Resective surgery can result in small cognitive declines at short follow up intervals (around 1 year).

Our results are indicative that pre-operative verbal memory ability is supported by functional brain tissue in the ipsilesional hemisphere.

Surgical methods which allow preservation of healthy hippocampal and cortical tissue are best employed if verbal memory outcomes are to be prioritised in paediatric epilepsy of left temporal lobe origin.

List of Tables

List of Figures

Introduction

Temporal lobe epilepsy (TLE) is the most common form of focal epilepsy (Maizuliana et al., 2020). Whilst the exact incidence rate of TLE in paediatric populations is unknown, a large retrospective study reported paediatric TLE incidence at around 8% (Wirrell et al., 2011), and estimates range between 8-20% (Lee & Lee, 2013; Nickels et al., 2012).

Cognitive dysfunction is a major complication of childhood epilepsy, with impairments documented even before overt seizures occur (e.g., Bruce et al., 2012; Fastenau et al., 2009a and worsening with ongoing seizures (Baldeweg, 2015; Berg et al., 2008; Hermann et al., 2002; Reilly et al., 2014).

First line treatment for TLE is pharmacological, through prescription of anti-epileptic drugs (AEDs). However, in a subset of children (estimates ranging from 10-40%, Baca et al., 2011; Wirrell, 2013) pharmacological treatment alone does not result in adequate seizure control, with each subsequent AED trial carrying a smaller likelihood to achieve seizure freedom (Brodie et al., 2012). Medication-resistant epilepsy is defined as lack of adequate seizure control upon trial of at least two different AEDs and TLE is thought to be the most common cause of medication-resistant epilepsy, at least in the adult population (Engel, Jr., 1993).

During the last two decades, resective surgery has emerged as a safe and effective treatment of medication-resistant epilepsy in children, with overall reported rates of post-surgical seizure freedom of around 60% (across temporal and extra-temporal surgery, see Dwivedi et al., 2017; Téllez-Zenteno et al., 2005; West et al., 2019). Resective surgery has become the mainstay

treatment for medication-resistant epilepsy in children, with alternative approaches under consideration (e.g., see Khan et al., 2021 for deep brain stimulation). The two most common surgical approaches for epilepsy of temporal lobe origin are anterior temporal lobectomy (indicated when seizure onset occurs in lateral temporal structures) and amygdalohippocampectomy, which involves the selective removal of mesial temporal lobe structures (Wirrell et al., 2011). In selected cases, lesionectomy can be performed, aimed at selective removal of any structural abnormality observed via diagnostic imaging.

Cognitive dysfunction in TLE: verbal and visuo-spatial memory

Cognitive dysfunction in TLE is most often characterised by memory impairment (Bell et al., 2011; Lenck-Santini & Scott, 2015; Sherman et al., 2011), reflecting the critical role of mesial temporal lobe structures in human memory (e.g., Burgess et al., 2002; Tulving & Markowitsch, 1998).

In adults with TLE, there is substantial evidence for material specific impairment across the memory domain, depending on laterality of seizure origin. Verbal memory deficits are consistently observed in left lateralised epilepsy in adult TLE (Saghafi et al., 2018; Willment & Golby, 2013; Witt et al., 2019). Consistently with this, rates of verbal memory decline following temporal lobe resective surgery (TLR) vary depending on side of surgery: a meta-analysis (Sherman et al., 2011) reported that 44% of patients receiving left TLR vs 20% of patients receiving right TLE present with verbal memory decline. These data reflect the fact that, in adults, the temporal lobe in the language dominant (often left) hemisphere is specialised for auditory verbal processing. However, the evidence for the preponderance of visuo-spatial deficits in right TLE/TLR is inconclusive (Willment & Golby, 2013). For instance, the same

meta-analysis demonstrating higher rates of verbal memory decline following left TLR (Sherman et al., 2011) reported equal rates of postsurgical visual memory declines (around 20%) for both right and left sided TLR (see also Kennepohl et al., 2007; Vaz, 2004). The lack of clear lateralisation effect for visuo-spatial memory can at least partly be attributed to neuropsychological task structure, as ostensive visual tasks often include a verbal component (Saling, 2009).

There is evidence for cognitive dysfunction also in children affected by TLE. As in adults, memory is the cognitive domain which is most likely to be affected in children suffering from TLE (Flint et al., 2017; Menlove & Reilly, 2015). Memory impairments brought about by TLE can have negative impacts on daily functioning and academic achievement in children and adolescents (e.g., Fastenau et al., 2009a; Schouten et al., 2002).

The evidence in support of material-specificity and lateralisation of memory function in children either before or after surgery is less clear cut than in adults.

Post-surgical verbal memory outcomes have been extensively studied in paediatric TLE populations. Some studies have reported declines in verbal memory following left sided TLR in children (Jambaqué et al., 2007; Meekes et al., 2013), whilst others have not (Gonzalez et al., 2012; Mabbott & Smith, 2003). Flint et al, 2017 conducted a systematic review of neuropsychological outcomes following paediatric TLR surgery and concluded that there was a trend for left sided surgery to result in deterioration of verbal memory and for right sided surgical candidates to have less favourable visual memory outcome. Flint et al, 2017 however, acknowledged that the large heterogeneity across studies in terms of neuropsychological measures employed, methodological approach, and sample sizes, precludes the possibility to draw firm conclusions on the matter of material-specificity and side of lesion in paediatric TLE.

A recent meta-analysis of pre- and post-surgical memory function in children with TLE concluded that 55% of the studies reviewed reported lower presurgical verbal memory function in children with left hemisphere TLE (Levy et al., 2021). Authors reported verbal memory (but not visuo-spatial memory) declines following left TLR, whilst right TLR had no significant effect on either verbal or visual memory TLE (Levy et al 2021).

Overall, there is strong evidence for lateralisation of verbal memory to the dominant hemisphere in adults, with consequent verbal memory dysfunction in left TLE and significant declines in verbal memory outcomes following left temporal lobe resections in adult TLE patients. In paediatric populations, the evidence for lateralisation and material specificity of memory is mixed. Several studies show lower verbal memory scores in children with left TLE and verbal memory declines following left sided paediatric temporal lobe resective surgery. There is, however, large variability in reported memory outcomes in paediatric populations. This likely reflects the additional challenges of studying the impact of chronic disease against the backdrop of developmental change – which in turn results in large methodological heterogeneity across studies (in term of e.g., length of follow up periods, neuropsychological measures employed, demographic and other clinical variables – age at surgery, age at seizure onset, etc.).

As for adults, no clear lateralisation effect is observed in pre-surgical visuo-spatial memory in children with TLE. No significant differences are generally reported on visuo-spatial memory performance in children with left or right lateralised TLE (Engle & Smith, 2010; Gonzalez et al., 2007).

The effect of resective surgery on visuo-spatial memory in children is unclear (for reviews of longitudinal studies see Guimarães et al., 2007; Menlove & Reilly, 2015). Most studies report no significant changes in visual memory outcomes following temporal lobe surgery. Of note, some longitudinal studies have reported selective post-surgical improvements in facial recognition, a task which taps specifically into configural memory (Beardsworth & Zaidel, 1994; Mabbott & Smith, 2003).

Overall, the evidence for lateralisation of function of visual memory to the non-dominant (often right) hemisphere is weaker than for that for lateralisation of verbal memory to the dominant hemisphere in both adults and children with TLE. Accumulating evidence points to a lack of change in visual memory following temporal lobe surgery in children, with the possible exception of improvement in facial recognition.

The role of integrity of mesial temporal structures on verbal and visuospatial memory outcomes

One of the factors that may moderate the effect of TLR on verbal memory is the extent of preservation of hippocampal and other mesial temporal structures in the dominant hemisphere. In adults, Witt et al., 2014 found that, in a large cohort of mesial TLE patients, higher cellular density in the resected left hippocampus was associated with larger declines in verbal memory. This evidence is consistent with results showing that in patients with more severe sclerosis of hippocampal tissue pre-operatively, no appreciable memory change is observed following resective surgery (Bell et al., 2011). These results suggest that it is the extent of resection of functional hippocampal tissue which is a strong determinant of post-surgical verbal memory function in adult TLE.

This hypothesis is consistent with evidence gathered in paediatric TLE. For instance, Skirrow et al., 2015 reported that better post-surgical verbal memory outcomes were associated with larger post-surgical residual hippocampal volumes in children with TLE.

More broadly, a growing number of studies report an association between larger hippocampal resections and poorer verbal memory outcomes in paediatric TLE (Gleissner et al., 2005; Lah & Smith, 2015; Law et al., 2017; but see Lah & Smith, 2015 – reporting similar post-surgical verbal memory outcomes regardless of extent of hippocampal resection).
Consistent with this growing evidence associating hippocampal volumes and verbal memory function following temporal lobe resective surgery in children, Danguecan & Smith, 2019 showed that post-surgical verbal associative memory outcomes were worse in children with left hemisphere resections involving mesial temporal structures (as compared to those for whom only lateral mesial temporal structures were resected), and that this effect was present only in children displaying typical left hemispheric language dominance.

Taken together these results suggest that the extent of preservation of hippocampal tissue is an important factor in verbal memory outcomes in both adult and paediatric TLE.

With regards to the role of mesial temporal structures in mediating visuo-spatial memory outcomes following paediatric temporal resective surgery, accumulating evidence suggests that visuospatial memory performance does not decline following surgery, regardless of whether resections involve or not mesial temporal structures (Kuehn et al., 2002; Martin et al., 2016; Stewart & Smith, 2019).

Overall, the evidence reviewed thus far suggests that integrity of mesial temporal structures is associated with verbal (but not visual) memory outcomes following paediatric TL surgery.

The role of aetiology/neuropathology

The underlying aetiology of TLE is variable, including focal cortical dysplasia (cortical malformation of developmental origin), tumours and hippocampal sclerosis (progressive neuronal cell loss and gliosis of the hippocampus and neighbouring structures). There is evidence that neuropathology type is a critical variable to consider when assessing degree of memory impairment in both adult and paediatric TLE. In adults, it is well established that memory deficits are more pronounced in TLE patients displaying mesial temporal sclerosis (MTS), which can be bilateral in a high percentage of cases (~30-40%; Engel, 2001). Law et al., 2017 studied post-operative memory outcomes in children affected by mesial temporal sclerosis. They concluded that memory outcomes were less favourable in the group of children who sustained resections involving mesial temporal structures – whilst preservation of these structures was associated with lower risk of verbal memory decline. Cormack et al., 2012 reported that children affected by hippocampal sclerosis (irrespective of side of lesion) had lower verbal paired-associates memory scores than children affected by DNET (Dysembroblastic neuro-epithelial tumours; low grade tumours).

Overall, these studies implicate aetiology, and in particular extent of hippocampal sclerosis, in the degree of verbal memory decline following temporal lobe surgery in children as well as in adults. Children (and adults) with smaller pre-surgical volumes of functional (non-sclerotic) hippocampal tissue fare better post-surgery than those with relatively preserved hippocampal tissue before surgery – as in the latter group a larger portion of healthy tissue will have been

resected during surgery. It is likely that the amount of healthy hippocampal tissue that is resected during surgery may at least explain the common observation that children and adults with higher pre-operative verbal memory scores are at higher risk to experience declines in memory function following surgery (Bauman et al., 2019; Helmstaedter et al., 2011).

It is well recognised that both in the case of the broader TLE diagnostic category, and in its "purer" form of mesial temporal lobe epilepsy with hippocampal sclerosis, widespread extrahippocampal structural alterations are routinely reported in adult populations (Blümcke et al., 2012; Bonilha & Keller, 2015). The most commonly reported alterations detected via the application of Voxel Based Morphometry in adult TLE are volume loss in ipsilateral hippocampus and mediodorsal thalamic nuclei, with bilateral cortical thinning observed in a widespread and multilobar network of brain areas (involving temporal, parietal and occipital cortices, e.g. see Bernhardt et al., 2016; Bernhardt et al., 2010; Bonilha & Keller, 2015; Whelan et al., 2018).

A recent report demonstrates more restricted cortical thinning, limited to the ipsilateral temporal pole, in paediatric TLE (Adler et al., 2018), indicating more limited pathological involvement in paediatric vs adult TLE. However, Adler et al., 2018, reported the presence of bilateral FLAIR/T2 hyperintensities (thought to reflect gliosis) in lateral temporal, insular and cingulate cortices (a finding also reported in adult TLE). There are also several reports of structural alterations extending beyond the temporal lobes in paediatric TLE (contralateral frontal lobe - Guimarães et al., 2007; ipsilateral inferior frontal gyrus - Chen et al., 2020).

Overall, there is substantial evidence that structural alterations in both paediatric and adult TLE extend beyond the hippocampus and the temporal lobes – with involvement of both the ipsi- and contra-lesional hemispheres.

Given the well-established role of the hippocampus in supporting declarative memory both in adults and children, the focus of this study is the relationship between hippocampal integrity and memory function before and after paediatric TL epilepsy surgery. It is however important to keep in mind that TLE is a circuit disorder, characterised by chronic and widespread functional alterations that emanate from epileptogenic foci in the temporal lobes but that involve large areas of ipsi- and contra-lateral brain territories (Bonilha et al., 2015). Any behavioural/neuropsychological changes in TLE cannot therefore easily and directly attributed to pathology in a single brain area but more likely reflect generalised functional alterations extending across several cortical and subcortical circuit nodes.

Cognitive dysfunction in paediatric TLE, beyond memory

Whilst TLE, in adults, is often associated with selective memory deficits in the context of normal intelligence, overall intellectual ability can be affected in children with TLE (Berg et al., 2008). Reports have demonstrated that up to 50-60% of children suffering from TLE present with intellectual dysfunction when compared to healthy controls or their own siblings (Cormack et al., 2007; Helmstaedter et al., 2020; Helmstaedter & Kockelmann, 2006). Earlier age of onset is associated with most pervasive intellectual deficits, with seizure onset in the first year of life being associated with the highest incidence (82%) of intellectual impairment (Cormack et al., 2007).

Overall, studies investigating IQ outcomes following resective surgery for temporal lobe epilepsy have generally shown no significant change (Gleissner et al., 2005; Korkman et al., 2005; Smith et al., 2006). This may be at least partly explained by the relatively short follow up periods reported in most studies. When Skirrow et al., 2011 evaluated the impact of temporal

lobe surgery on IQ at average follow up duration of 9 years, data showed that non-verbal IQ increases could only be detected in the surgical cohort (as compared to children who underwent medical management alone) 6 or more years after the surgery had taken place. IQ improvements were associated with cessation of anti-epileptic medication (AED).

In a similar long term follow up study of surgical outcomes in children affected by temporal and extra-temporal epilepsy (follow up duration 4-11 years) Puka et al., 2017 reported post-surgical cognitive improvements over time. Importantly, seizure freedom, but not seizure status was associated with cognitive improvement. This indicates that cessation of seizures was the main driver behind cognitive improvement, rather than surgery itself.

Paediatric TLE, similarly to adult TLE, is also characterised by executive dysfunction (for a review see Rzezak et al., 2014, with children with hippocampal sclerosis showing more profound executive impairments than those with other aetiologies Igarashi et al., 2002). Children with TLE also present attentional impairments, to a larger extent than those reported in children with generalised epilepsy (Rzezak et al., 2014).

Paediatric TLE is therefore not to be thought of as a strictly focal disorder, as there is ample evidence for widespread circuit dysfunction well beyond the temporal lobes (e.g., Cormack et al., 2005). The extent of these more widespread deficits depends on a host of factors, including age at onset, severity and duration of seizures (Berg et al., 2012; Puka et al., 2017) and anti-epileptic drug load (Boshuisen et al., 2015; Helmstaedter et al., 2016).

Rationale for current study

The impact of epilepsy of temporal lobe origin and the effects of temporal lobe surgery on memory function in adults are relatively well understood, with most patients with left TLE

demonstrating verbal memory difficulties pre-operatively and experiencing declines in verbal memory following surgery (Sherman et al., 2011). Post-surgical changes can be prolonged with reports showing that short-term memory declines can be followed by stabilisation or improvement across 6-10 years (Alpherts et al., 2006; Andersson-Roswall et al., 2010). The degree of post-operative memory decline has been linked, in adults, to the extent of resection (Helmstaedter et al., 2002), the degree of pre-operative hippocampal sclerosis (Hermann et al., 1992) and the size of the residual hippocampus following surgery (Baxendale et al., 2000). Right temporal epilepsy and surgery are only sometimes associated with non-verbal memory impairments in adults (Sherman et al., 2011; Vaz, 2004).

Literature on the impact of temporal lobe epilepsy and surgery on memory circuits in childhood is more limited with an effect of left temporal surgeries on verbal memory reported by some studies (e.g., Jambaqué et al., 2007; Meekes et al., 2013) but not others (e.g. Gonzalez et al., 2012; Oitment et al., 2013). The nature of these verbal memory declines may be temporary, with reports of memory function recovery 1 year after surgery (Gleissner et al., 2005). The degree of integrity of mesial temporal lobe structures in supporting verbal memory following temporal lobe surgery is emerging as an important factor (Skirrow et al., 2015).

Here we set out to attempt to fill the knowledge gap related to potential links between neuroanatomical parameters and neuropsychological variables in determining post-surgical cognitive and memory outcome in paediatric temporal lobe epilepsy. We use a combination of cross-sectional and longitudinal analyses, in a relatively large paediatric TLE patient cohort, to examine:

1- The impact of epilepsy of temporal lobe origin on general cognition and memory, with special focus on any laterality effects.
2- The association between pre-surgical integrity of hippocampal circuits and baseline intellectual function/memory.
3- The role of clinical and demographic factors as predictors of pre-surgical hippocampal integrity.
4- Surgical impact on intellectual function and memory.
5- Association of surgical resection volumes and residual hippocampal volumes with cognitive and memory outcomes.

Methods

Study design

The study employed a longitudinal retrospective design to investigate the association between hippocampal volume and neuropsychological function in paediatric patients who underwent epilepsy surgery for medication-resistant temporal lobe epilepsy.

Participants

81 patients with medication-resistant temporal lobe epilepsy underwent epilepsy surgery between 1999 and 2020 at Great Ormond Street Hospital NHS Trust.

Inclusion Criteria were:

- Diagnosis of temporal lobe epilepsy (TLE).
- Maximum age 18 at the time of surgery
- Presence of both pre- and post-operative neuropsychological assessment.
- Presence of both pre- and post-operative MRI imaging.

Exclusion Criteria were:

- Children with generalised or multifocal epilepsy.
- Children without a clear MRI identified structural abnormality.
- Children with extra temporal lobe abnormality on MRI and/or with motor deficits.
- Children with a Learning Disability and/or FSIQ or VIQ/VCI <70.
- Children with a major sensory deficit sufficient to significantly impact performance on neuropsychological assessment.
- Presence of another neurological disorder.

Demographic and clinical details of the patients are provided in Table 1.

In addition, 20 healthy children, with no history of psychiatric or neurological disorder, aged between 8 and 16 years (mean age 12.77, range 8.33-16.33) were identified as potential control subjects for this study. This pool of healthy children represents a subset of children who underwent neuropsychological testing drawn from a larger population of healthy children recruited by Buck et al., 2021.

Ethics

This study involved secondary analysis of clinical and demographic data which had already been collected (secondary data analysis).

Ethics permission for the studies which originally reported on these patient and control populations Buck et al., 2021; Skirrow et al., 2015 was granted by the UCL Research Ethics Committee (REC; REC references 7447/002 and 16NP03 respectively) and fully informed written consent was obtained from each participant.

All patients underwent:

- A presurgical evaluation which included neuropsychological assessment, neurophysiological assessment (ictal and inter-ictal EEG), and imaging assessment (MRI as standard practice, with additional PET in a subset of cases)
- Epilepsy resective surgery – surgical approach varied across patients, depending on clinical need, and included: temporal lobectomy (with and without amigdalectomy and hippocampectomy) and lesionectomy.
- A follow up evaluation (mean interval between surgery and follow up was 1.5 years (range 0.25- 5.42 years). The follow up evaluation included neuropsychological and imaging assessment (MRI).

Neuropsychological assessment

Patients' neuropsychological assessments were conducted by members of the clinical neuropsychology team at Great Ormond Street Hospital. Healthy control participants' neuropsychological assessments were conducted by Sarah Buck from the Institute of Child Health, UCL.

Healthy control participants

The neuropsychological testing battery for healthy control participants included:

- Weschler Abbreviated Scale of Intelligence (WASI; Weschler, 1999) – for each participant measures of Full Scale Intellectual Quotient (FSIQ), Verbal Cognitive Index (VCI) and Perceptual Reasoning Index (PRI) were derived.
- Children's Memory Scale (CMS; Cohen, 1997) – Dot Locations and Word Pairs subtests.

Temporal Lobe Patients

The neuropsychological testing battery for temporal lobe patients included:

Intellectual function. Several different Wechsler intelligence scales were used, depending on patient age:

- Weschler Preschool and Primary Scale of Intelligence (WIPPSI) 3rd and 4th editions (WIPPSI-III and WIPPSI-IV; Weschler, 2002, 2012).
- Weschler Intelligence Scale for Children (WISC) 3rd, 4th and 5th editions (WISC-III, WISC-IV and WISC V; Weschler, 1991, 2003, 2014).
- Weschler Adult Intelligence Scale (WAIS) 3rd and 4th editions (WAIS-III and WAIS-IV; Weschler, 1997a, 2008);
- Weschler Abbreviated Scale of Intelligence (WASI; Weschler, 1999).

The following indices were derived whenever possible: Verbal Comprehension (VCI), Perceptual Reasoning (PRI), Working Memory (WMI), Processing Speed (PSI).

Memory function. Different memory scales were employed:

- Children's Memory Scale (CMS; Cohen, 1997), including Dot Location, Faces, Stories and Word Pairs subtests.
- Wechsler Memory Scale (WMS) 3rd and 4th edition (WMS-III and WMS IV; Weschler, 1997b, 2009), including Logical Memory I and II and Verbal Paired Associates.

Visual memory.

Visuospatial memory: The Dot Location test is a test of visuo-spatial memory, during which children are asked to reproduce visual patterns using tokens on a board, after a short (SD condition) and long delay (LD condition) following a demonstration.

Configural memory: During the face recognition test children are asked to select photographs of faces (presented interspersed with foils) after a short (SD condition) or long delay (LD condition) from original presentation.

Verbal memory.

Narrative memory: Stories (CMS), Logical Memory I and II (WMS): children are asked to recollect a story which has been read to them, after a short (SD condition) and a long (LD condition) delay.

Paired associates: Word Pairs (CMS), Verbal Paired Associates (WMS): children are asked to recall pairs of semantically related and unrelated words which have been presented over repeated trials after a short (SD condition) and long (LD condition) delay.

Imaging

Acquisition: TLE Patients

Whole brain structural MRI scans acquired prior to 2007 (n =11; 17% of total number of scans) were obtained on a 1.5-T Siemens Vision System and included a volume T1- weighted scan using a three- dimensional magnetization- prepared rapid gradient echo sequence (repetition time = 10 milliseconds, echo time = 4 milliseconds, flip angle = 12°, voxel size = 1.0 × 1.0 × 1.25 mm). Scans acquired after 2007, were obtained on a 1.5-T Siemens Avanto System. Three-dimensional volume T1- weighted scans were acquired using a 3DFLASH sequence (repetition time = 11 milliseconds, echo time = 5 milliseconds, flip angle = 15°, voxel size = 1.0 × 1.0 × 1.0 mm).

Acquisition: Healthy control participants

Whole brain structural 3T-MRI scans were obtained using a 3T Siemens MRI system with a 20-channel head coil. A T1-weighted magnetization prepared rapid gradient-echo (MPRAGE) scan was acquired with the following parameters: in-plane resolution of 1mmx1mm; slice thickness of 1mm; repetition time of 2,300ms; echo time of 2.74ms.

Hippocampal volume extraction

For the measurement of pre-surgical hippocampal volumes, an automated parcellation tool was used – the "Hipposeg" extraction tool (Winston et al, 2013) freely available from the NiftyWeb UCL CMIC service (University College London Centre for Medical Imaging Computing: http://niftyweb.cs.ucl.ac.uk/; Prados, 2016). Hipposeg is based on Similarity and Truth Estimation for Propagated Segmentation approach (STEPS, Cardoso et al., 2013) and has been developed from epilepsy clinical databases – it has been shown to be robust in patients displaying hippocampal atrophy (e.g., hippocampal sclerosis).

Hippocampal segmentations were then manually curated using ITK-SNAP (version 3.8.0; Yushkevich et al., 2006; www.itksnap.org).

Intra-cranial volume (ICV) was obtained from the sagittal imaging dataset, using a 1 in 10 sampling strategy. Hippocampal volumes were corrected for ICV volume, using the formula $\Delta V=1.81x10^{-3}(\Delta ICV)$. This formula was derived from the regression line of control hippocampus volume (V) versus ICV.

Estimation of total surgical resection volume

Surgical cavity was estimated using "resseg" (https://github.com/fepegar/resseg; Pérez-García et al., 2021), a freely available, self-supervised Convolutional Neural Network (CNN) algorithm, which was originally trained on EPISURG a large database comprising pre- and post-operative MRIs from 430 refractory epilepsy patients (Pérez-García et al, 2020).
Surgical cavities were then manually curated using ITK-SNAP (version 3.8.0; Yushkevich et al., 2006; www.itksnap.org).

Post-surgical residual hippocampal volume estimation

Post-surgical residual hippocampal volume was obtained by registering post-surgical with pre-surgical scans for each patient which allowed derivation of surgical cavity masks in pre-surgical image coordinates (FSL software was employed, Jenkinson et al., 2012, modified from original code obtained from Rory Piper and Kiran Seuranine, UCL). Residual hippocampal volume was then obtained by computing the difference between the surgical cavity in the pre-surgical space with the pre-surgical hippocampal mask.

Statistical analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 25.0.

Group differences in demographic, cognitive and psychosocial data were tested using independent samples t-tests, analysis of variance, chi-squared or Fisher exact tests as appropriate.

Group differences with respect to brain volumes (pre-surgical/baseline hippocampal volume; post-surgical residual hippocampal volume, total surgical resection volume) were analysed using independent samples t-tests and analysis of variance, as appropriate.

Neuropsychological (intellectual and memory function) change indices were calculated by subtracting baseline from follow-up values (positive values index increases, negative values index decrements).

Potential association between brain volumes and neuropsychological variables was explored employing Pearson's correlations.

Comparison of intellectual and memory across healthy participant and patient groups was performed employing ANOVA testing.

Longitudinal analyses were conducted to study changes in intellectual and memory function following epilepsy surgery by employing 2x2 mixed design ANOVA testing (surgery – within subject factor, 2 levels – pre and post-surgery; Lesion side – between-subjects factor, 2 groups – Left and Right temporal lobe lesions).

Stepwise linear regression analyses (backward method on SPSS) were employed to identify clinical predictors of pre-surgical ipsilesional hippocampal volumes and post-surgical memory

outcome in the patient group. Diagnostic analyses included examination of influential points, normality or residuals and multicollinearity.

The false discovery rate approach (FDR, Benjamini & Hochberg, 1995) was employed to correct for multiple comparisons within each family of tests (detection threshold 0.05-0.1).

Results

Participant groups: demographic and clinical measures

Study participants were grouped into three groups: Left Temporal epilepsy patients, Right Temporal epilepsy patients and a Healthy Control group (see Table 1 for demographic details and statistical results). The Healthy Control group included children who were aged matched to epilepsy patients and were recruited from London schools (see methods section for more details).

Age and gender did not significantly differ across groups (age: one-way ANOVA, $F(2,51.7)=2.14$, $p=.128$, eta squared = 0.03; gender: Fisher's exact test, two-tailed, $p=.836$).

Left and Right Temporal patient groups did not differ across several demographic and epilepsy related variables (see Table 1).

		Left Temporal (N=50)	Right Temporal (N=31)	Healthy Controls (N=20)	*p-value*
Age		12.77 (2.7)	11.23 (3.4)	11.38 (4.1)	0.128
Sex, n,(% female)		28(56.0)	15(48.4)	10 (50.0)	0.836
Pathology, n (%)					0.355
	Focal Cortical Dysplasia	10(20.0)	3(9.6)		
	Hippocampal Sclerosis	17(34.0)	14(45.2)		
	Tumour	19(38.0)	9(29.0)		
	Other	4(8.0)	5(16.1)		
Age at epilepsy onset		5.18(3.9)	4.79(4.0)		0.663
Duration of Epilepsy		6.93(4.2)	7.32(4.2)		0.691
Age at evaluation (pre-surgical)		11.14(3.4)	11.54(4.1)		0.643
Age at evaluation (post-surgical)		13.73(3.3)	13.51(3.9)		0.795
Age at surgery		12.12(3.5)	12.20(3.9)		0.921

Table 1. Demographic and Clinical Data

Pre-surgical hippocampal volumes

Hippocampal volumes across participant groups

Left and Right hippocampal volumes (corrected for intra-cranial volumes - ICVs, see methods section for details) differed significantly across the control and patient groups. A mixed design ANOVA, with hemisphere (left, right) as within subject factor and participant group as between subject factor (Healthy Control - HC, Left Temporal – LT, Right Temporal, RT) revealed that there was no significant main effect of hemisphere ($F(1,80) = 1.61 *10^{-5}$, $p = .990$), but a statistically significant hemisphere*participant group interaction ($F(2,80) = 7.55$, $p = .001$). Analysis of simple main effects showed that left hippocampal volumes significantly differed between the Healthy Control and Left Temporal patient groups ($p = .012$, with Sidak

correction), and right hippocampal volumes significantly differed between the Healthy Control and Right Temporal patient groups (p = .016, Sidak correction; see Figure 1A).

These results indicate that hippocampal volumes, ipsilateral to the lesion site, are significantly smaller in temporal epilepsy patients than in healthy control participants.

Hippocampal volumes and aetiology

Ipsilesional hippocampal volumes differed significantly across aetiology groups (2x2 between-subjects ANOVA, main effect of lesion type – $F(3,49)= 11.579$, $p < .001$; lesion type had four levels: FCF, HS, Tumour and Other), but no differences between epilepsy groups (epilepsy group had two levels: Left Temporal – LT; and Right Temporal - RT) or interaction between lesion type and epilepsy group were detected (main effect epilepsy group, $F(1,49) = .028$, $p =.869$; epilepsy group*lesion type, $F(3,49) = 1.013$, $p =.395$; see Figure 1B). Post-hoc analyses revealed that pre-surgical ipsilesional hippocampal volumes in the hippocampal sclerosis aetiology group differed significantly from those in the FCD ($p <.001$, Sidak corrected), Tumour ($p <.001$, Sidak corrected) and Other ($p = .005$, Sidak corrected) aetiology groups.

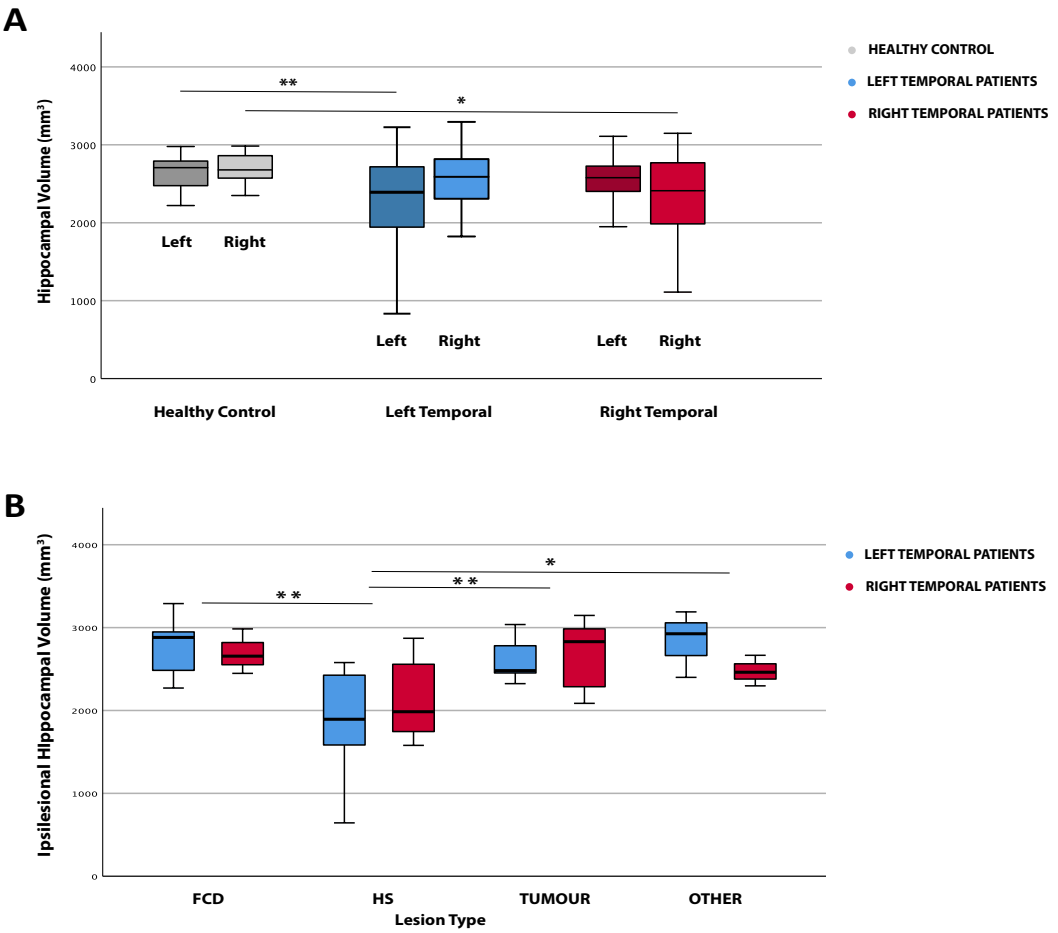


Figure 1. Pre-surgical Hippocampal Volumes **(A)** Left and Right hemisphere ICV corrected presurgical hippocampal volumes (in mm3) for Healthy Control (grey), Left Temporal (blue) and Right Termporal (red) epilepsy patient groups. **(B)** Ipsilesional ICV corrected presurgical hippocampal volumes (in mm3) in Left Temporal (blue) and Right Tempoarl (Red) epilepsy patient groups, across different Lesion Types: Focal Cortical Dysplasia (FCD), Hippocampal Sclerosis (HS), Tumour and miscellaneous category (Other). * p<0.05; ** p<0.001.

Figure 1. Pre-surgical hippocampal volumes

Epilepsy factors and pre-surgical hippocampal volumes

Backward stepwise linear regression analysis was used to determine clinical predictors (age at seizure onset, duration of epilepsy, lesion type and pre-surgical AED load) of pre-surgical ipsilesional hippocampal volumes. Younger age at onset of epilepsy was the only predictor to be significantly associated with smaller ipsilesional hippocampal volumes.

Presurgical intellectual and memory function

Intellectual function

Significant differences across control/patient groups were found for Full scale IQ (FSIQ), Verbal comprehension index (VCI) and Perceptual Reasoning index (PRI). One-way ANOVA, FSIQ: $F(2,52.23) = 16.12$, $p < 0.0001$, eta squared = 0.18; VCI: $F(2,53.09) = 19.71$, $p < .0001$; PRI $F(2,52.92) = 4.51$, $p = .016$). Post-hoc analyses (Games-Howell post-hoc tests) revealed that FSIQ and VCI were higher in control participants when compared to both Left ($p<.0001$) and Right Temporal patients ($p<.0001$) patients. PRI in Right Temporal patients was lower than in control participants ($p = .013$) but did not differ between Left Temporal patients and control participants (see Figure 2A-C).

Memory

With regards to performance on memory tests, significant differences across control/patient groups were found for Visual Memory Long Delay (LD) and Verbal Memory Short Delay (SD, Word paired associates; one-way ANOVA, Visual Memory LD: $F(2,40.32) = 5.17$, $p =.010$,

eta squared = 0.14; Verbal Memory SD: F(2,44.44) = 4.77, p =.013). Games-Howell post-hoc tests revealed that Right Temporal patients had lower Visual Memory LD scores when compared to Healthy Control participants (p=.011) and Left Temporal patients (p=.020). Left Temporal patients had lower Verbal Memory SD than Healthy Control participants (p=.010; see Figure 2D-G).

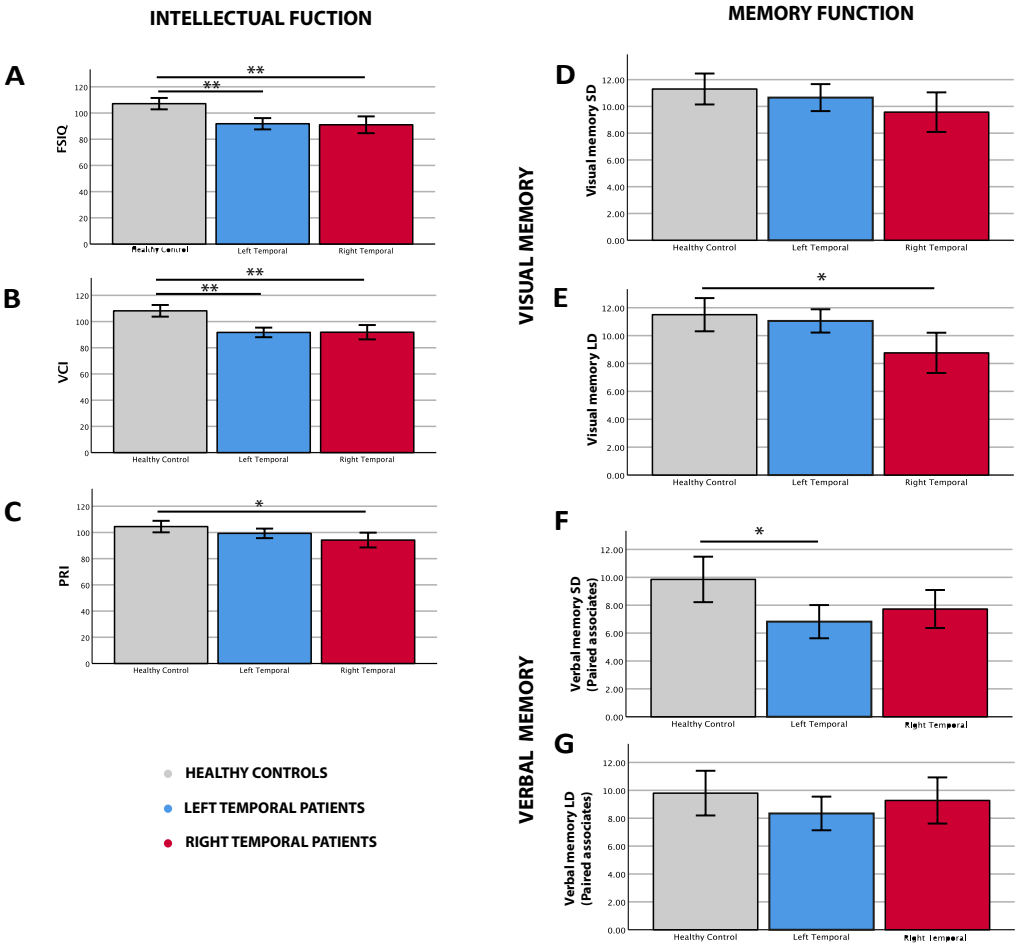


Figure 2. Pre-surgical Cognitive Function. Intellectual Function (Left): Full Scale Intellectual Quotient (FSIQ, A), Verbal Comprehension Index (VCI, B) and Perceptual Reasoning Index (PRI) in Healthy Control (grey), Left Temporal (blue) and Right Temporal (red) Patient Groups. Memory Function (Right): Visual Memory Short Delay (D), Visual Memory Long Delay (E), Verbal Memory Short Delay (F) andVerbal Memory Long Delay (G) in Healthy Control (grey), Left Temporal (blue) and Right Temporal (red) Patient Groups. Visual Memory was assessed with Dot Location Task, Verbal Memory with Word Paired Associate Task, from Children Memory Scale Battery. Bar Charts display mean and 95% CI. * p<0.05; ** p<0.001.

Figure 2. Pre-surgical Cognitive Function

Hippocampal volume and pre-surgical cognitive function

Right hippocampal volumes were significantly associated with FSIQ and VCI (FSIQ: N=21 r=0.495, p = .023; VCI: N=24, r=0.526, p = .008), in Right Temporal patients. No other significant associations were found between intellectual function and presurgical hippocampal volume (see Figure 3).

Verbal memory Short Delay scores (Word Paired Associates SD) were significantly associated with pre-surgical right hippocampal volumes in Right Temporal patients (N = 20, r=0.532, p = .016). No other significant associations were found between pre-surgical hippocampal volume and memory function (see Figure 4).

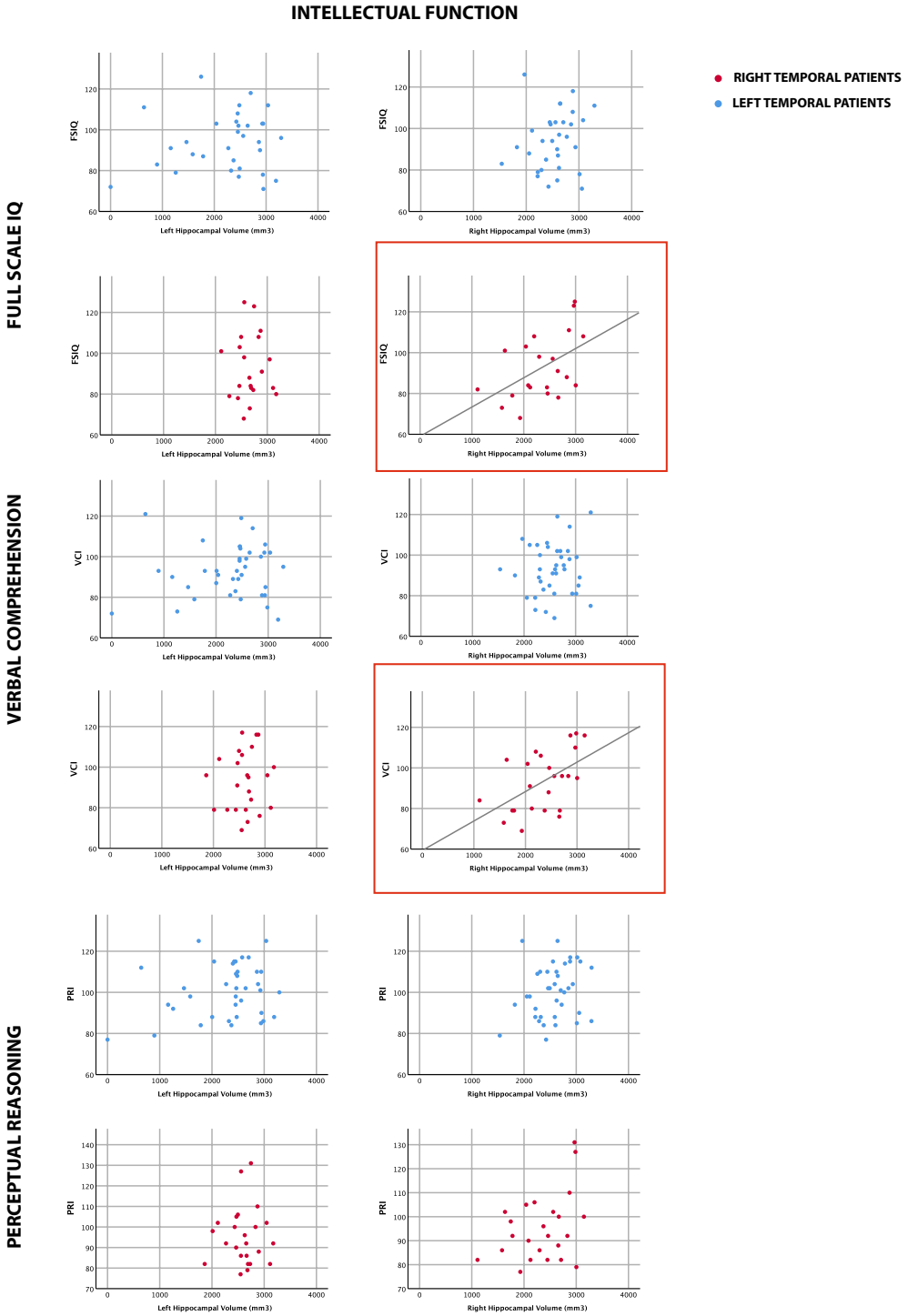


Figure 3. Association between pre-surgical hippocampal volume and Intellectual function. Scatterplots of Left (Left Column) and Right (Right Column) Pre-surgical ICV corrected Hippocampal volumes and Full Scale IQ (FSIQ, top two rows), Verbal Comprehension Index (VCI, middle two rows) and Perceptual Reasoning Index (PRI, Bottom two rows) in Left (blue) and Right (red) Temporal epilepsy patient groups. Plots of significant Pearson's correlations are highlighted by red frames (FSIQ: N=21 r=0.495, p = 0.023; VCI: N=24, r=0.526, p = 0.008).

Figure 3. Association between pre-surgical hippocampal volume and Intellectual Function.

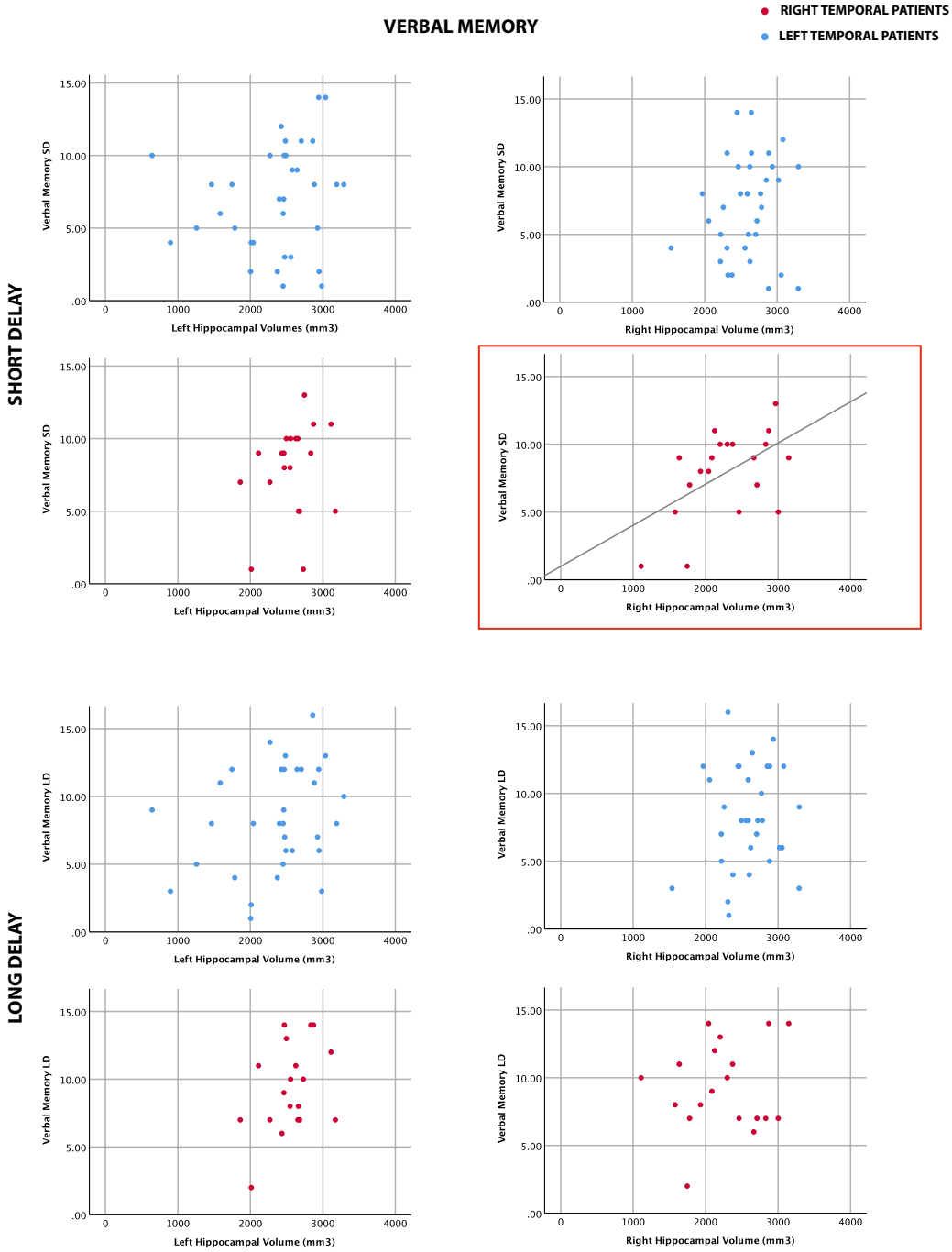


Figure 4. Association between pre-surgical hippocampal volume and memory function. Scatterplots of Left (Left Column) and Right (Right Column) Pre-surgical ICV corrected Hippocampal volumes and Verbal Memory Short Delay (top two rows), Verbal Memory Long Delay (bottom two rows) in Left (blue) and Right (red) Temporal epilepsy patient groups. Plot of significant Pearson's correlation is highlighted by a red frame (Verbal Memory SD: N = 20, r=0.532, p = 0.016). Verbal Memory was assessed with the Word Paired Associate Task, from the Children Memory Scale Battery.

Figure 4. Association between pre-surgical hippocampal volume and memory function

Surgical resections

Surgical resections were variable, being tailored to individual pathological findings.

Total resection volumes and residual hippocampal volumes did not differ across Left and Right Temporal lobe epilepsy patients (independent t-tests, Total resection volume: $t(36) = 0.364$, $p = .346$; residual hippocampal volume: $t(35)=1.675$, $p = 0103$). There was no association between total resection volume/residual hippocampal volumes and age at surgery (resection volume: $r= -0.073$, $p = .667$; residual hippocampus: $r = -0.005$, $p = .978$).

Total resection volumes did not vary across epilepsy aetiology (one-way ANOVA: $F(3,13.45) = 2.32$, $p = .122$). Residual hippocampal volumes were significantly smaller in patients with hippocampal sclerosis (HS) and in those with tumours (one-way ANOVA: $F(3,15) = 28.261$, $p<.0001$; Games-Howell post-hoc tests HS: $p<.0001$; tumour: $p = .008$).

Longitudinal changes in intellectual and memory function (pre-surgical vs post-surgical)

Results of statistical analyses of longitudinal changes in intellectual and memory function are summarised in Table 2, and Figure 5 (2 x 2 mixed design ANOVAs).

	Surgery (p-value)	Lesion Side (p-value)	Surgery x Lesion Side (p- value)
INTELLECTUAL FUNCTION			
FSIQ (Full scale IQ)	0.315	0.720	0.746
VCI (Verbal Comprehension Index)	**0.005****	0.897	0.475
PRI (Perceptual Reasoning Index)	0.887	0.143	0.450
WMI (Working Memory Index)	0.317	0.974	0.120
PSI (Processing Speed Index)	0.320	0.185	0.818
MEMORY			
Verball Memory			
Stories Short Delay	**0.044***	0.451	0.497
Stories Long Delay	**0.041***	0.532	0.787
Word Pairs Short Delay	0.347	0.101	0.257
Word Pairs Long Delay	0.642	0.403	0.642
Visual Memory			
Dot Location Short Delay	**0.032***	**0.004***	0.112
Dot Location Long Delay	0.393	**0.002***	0.514
Face Recognition Short Delay	**0.013***	0.890	0.194
Face Recognition Long Delay	**0.026***	0.979	0.160

*p<0.1,**p<0.05 (FDR-adjusted)

Table 2. Longitudinal changes in intellectual and memory function (2 x 2 mixed design ANOVAs – FDR- adjusted p-values for main effects of Surgery and Lesion Side, and interaction Surgery x Lesion Side).

Analysis of general intellectual function (FSIQ), Perceptual Reasoning (PRI), Working Memory (WMI) and Processing Speed (PSI), revealed no significant effect of surgery and lesion side.

A significant main effect of surgery on Verbal Comprehension was seen, with lower VCI scores at 1-year post-surgical follow up (main effect of surgery, p = .005; no main effect of lesion side or surgery x lesion side interaction were observed).

Short and Long Delay Verbal Memory scores (Stories subtest of CMS battery) were significantly lower at 1-year post-surgical follow up (main effect of surgery, Stories Short

Delay, p = .044; Stories Long Delay, p = .041; no significant main effect of lesion side/ surgery x lesion side interaction).

Short Delay Visual Memory scores (Dot Location) were significantly lower post-surgery (main effect of surgery, p = .032).

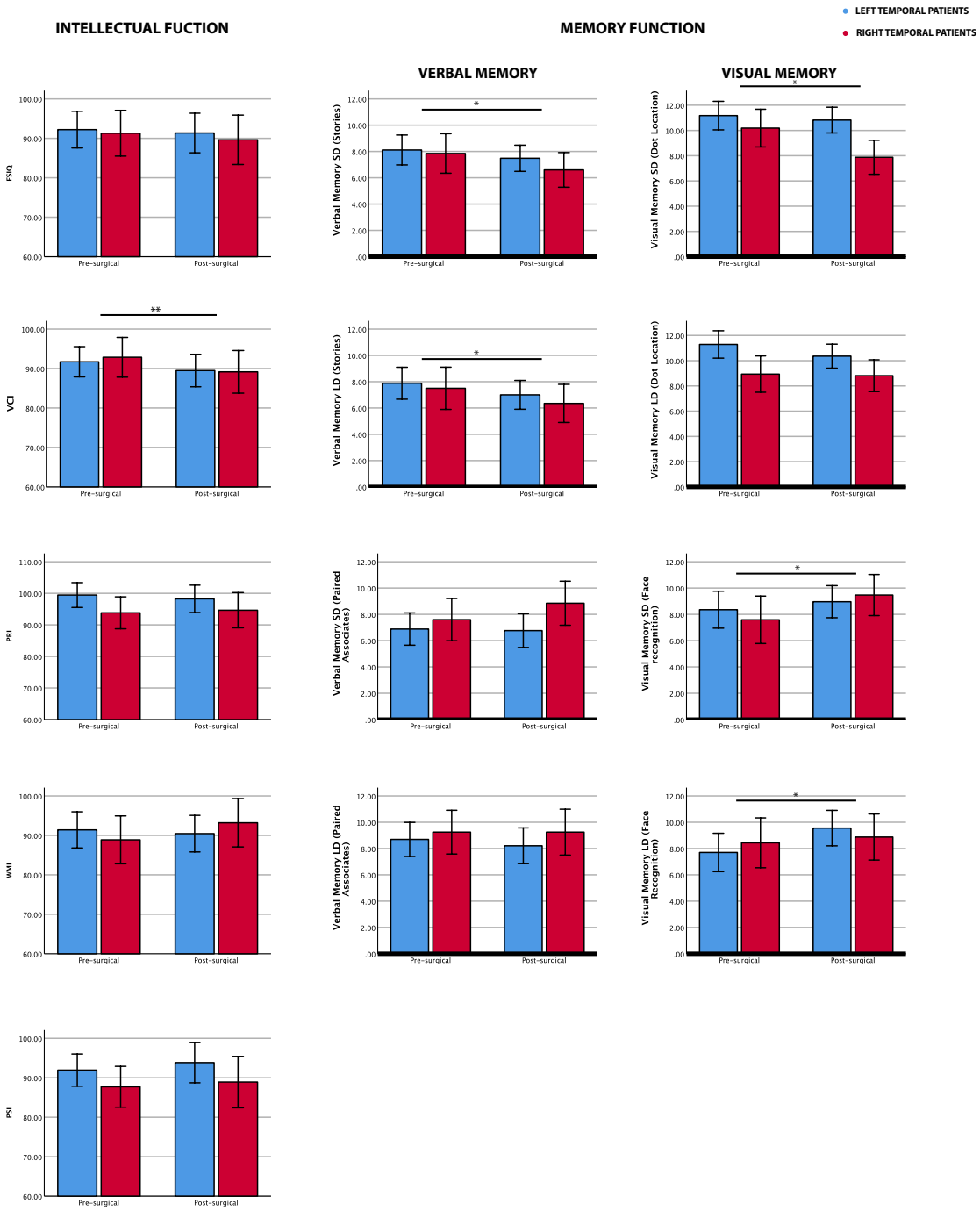


Figure 5. Longitudinal Changes in Intellectual and Memory Function following resective epilepsy surgery. Intellectual Function (Left): Full Scale Intellectual Quotient (FSIQ), Verbal Comprehension Index (VCI) and Perceptual Reasoning Index (PRI) in Left Temporal (blue) and Right Temporal (red) Patient Groups. Verbal Memory Function (Middle Column): Verbal Memory Short and Long Delay (Stories test, top two rows; Paired Associates, bottom two rows) in Left Temporal (blue) and Right Temporal (red) Patient Groups. Visual Memory Short and Long Delay (Dot Location test, top two rows; Face Recognition test, bottom two rows) in Left Temporal (blue) and Right Temporal (red) Patient Groups. Bar Charts display mean and 95% CI. * p<0.05; ** p<0.001.

Figure 5. Longitudinal Changes in Intellectual and Memory Function following resective epilepsy surgery

Significant main effects of lesion side were observed for both Short and Long Delay Visual Memory (Dot Location), with Right Temporal patients faring worse than Left Temporal patients (Dot Location Short Delay post-surgical, p = .004; Dot Location Long Delay, p = .002; no significant surgery x lesion side effects were observed).

Short and Long Delay Face Recognition scores significantly improved after surgery (main effect of surgery, Face Recognition Short Delay, p = .013, Long Delay, p = .026; no significant effect of lesion side/surgery x lesion side interaction).

Correlational analyses revealed that the greater improvements in both visual and verbal memory occurred for individuals who had lower pre-surgical scores (Table 3 and Figure 6 provide summary results of correlations between pre-surgical scores and post-surgical change).

	Left Temporal (Pearson's r)	Left Temporal (p-value)	Right Temporal (Pearson's r)	Right Temporal (p-value)
INTELLECTUAL FUNCTION				
VCI (Verbal Comprehension Index)	-0.049	0.734	-0.406	0.029
MEMORY				
Verball Memory				
Stories Short Delay	-0.56	<0.001	-0.672	0.001
Stories Long Delay	-0.433	0.008	-0.688	0.001
Visual Memory				
Dot Location Short Delay	-0.735	<0.001	-0.699	0.003
Face Recognition Short Delay	-0.506	0.006	-0.785	<0.001
Face Recognition Long Delay	-0.552	0.003	-0.447	0.082

Table 3. Correlations between pre-surgical cognitive scores and post-surgical change.

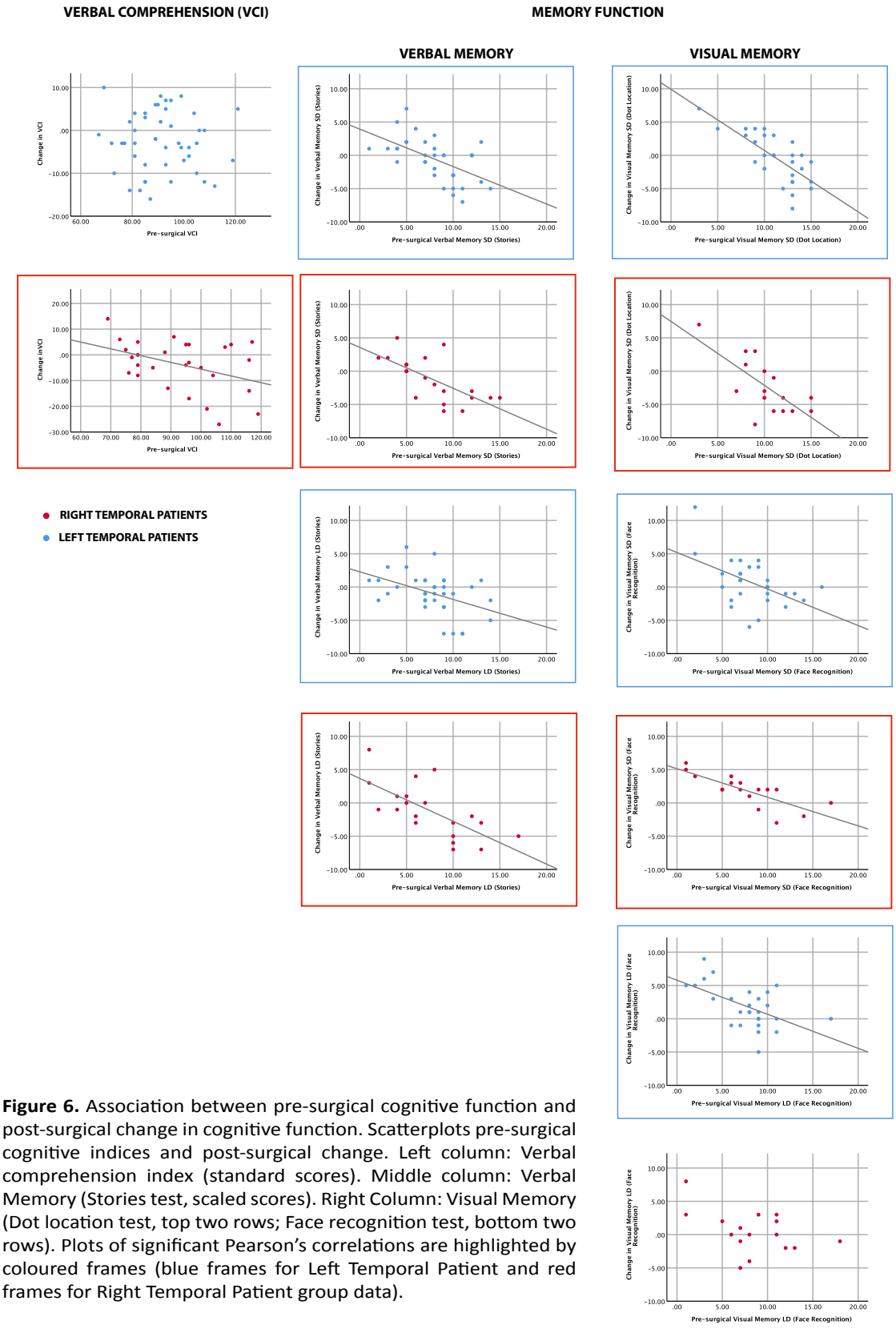


Figure 6. Association between pre-surgical cognitive function and post-surgical change in cognitive function. Scatterplots pre-surgical cognitive indices and post-surgical change. Left column: Verbal comprehension index (standard scores). Middle column: Verbal Memory (Stories test, scaled scores). Right Column: Visual Memory (Dot location test, top two rows; Face recognition test, bottom two rows). Plots of significant Pearson's correlations are highlighted by coloured frames (blue frames for Left Temporal Patient and red frames for Right Temporal Patient group data).

Figure 6. Association between pre-surgical cognitive function and post-surgical change in cognitive function.

Brain correlates of post-surgical memory change

Post-surgical change in Short and Long Delay Verbal Memory scores (Stories test) and residual left hippocampal volume in Left Temporal patients were significantly correlated (see Figure 7) with patients with larger residual left hippocampal volumes showing larger post-surgical verbal memory improvements (Stories Short Delay: N = 18, r = .562, p = .015; Stories Long Delay N = 19, r = .625, p = .004).

No significant associations were observed between total resection volume and post-surgical memory change scores.

Brain correlates of post-surgical memory outcome

In the Left Temporal patient group, post-surgical Short and Long Delay Verbal Memory (Stories) outcome scores were significantly associated with residual Left Hippocampal volume and Total Resection volume (see Figure 8). Patients with larger residual left hippocampal volumes displayed higher post-surgical memory scores (Stories Short Delay, N= 20, r = .523, p = .22; Stories Long Delay, N = 20, r = .577, p = .010).

Patients with smaller resection extent showing higher post-surgical verbal memory scores (Stories Short Delay N = 20, r = -.505, p = .023; Stories Long Delay N = 20, r = -.482, p = .31).

Clinical predictors of post-surgical memory outcome

Backward stepwise linear regression analysis was used to determine clinical predictors (age at seizure onset, duration of epilepsy, pre-surgical FSIQ, post-surgical AED load, total resection

volume, residual hippocampal volume) of memory outcomes in the surgical groups. For the Left Temporal patient group smaller total surgical resection volumes predicted better post-surgical Verbal memory outcomes (Stories test, short and long delay conditions). In the Right Temporal patient group higher presurgical FSIQ predicted better post-surgical Verbal memory outcomes (Stories test, short and long delay conditions).

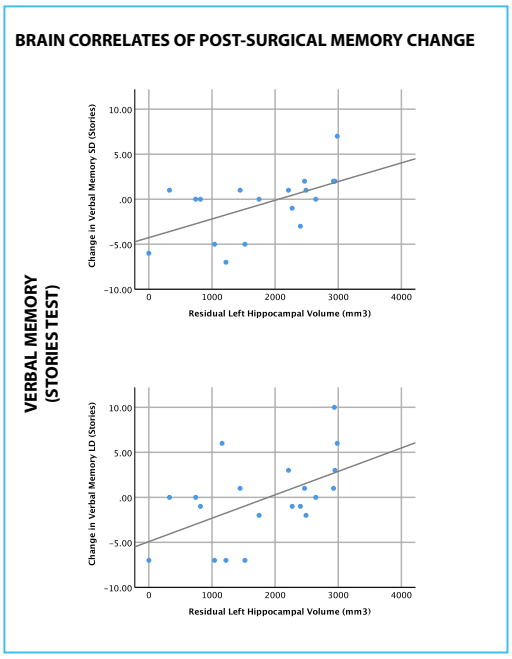


Figure 7. Association between left residual hippocampal volume and post-surgical verbal memory change. Scatterplots of left residucal hippocampal volume (ICV corrected, mm^3) and post-surgical change in verbal memory scores (Stories test, short delay, top row; long delay, bottom row) in Left Temporal epilepsy patients.

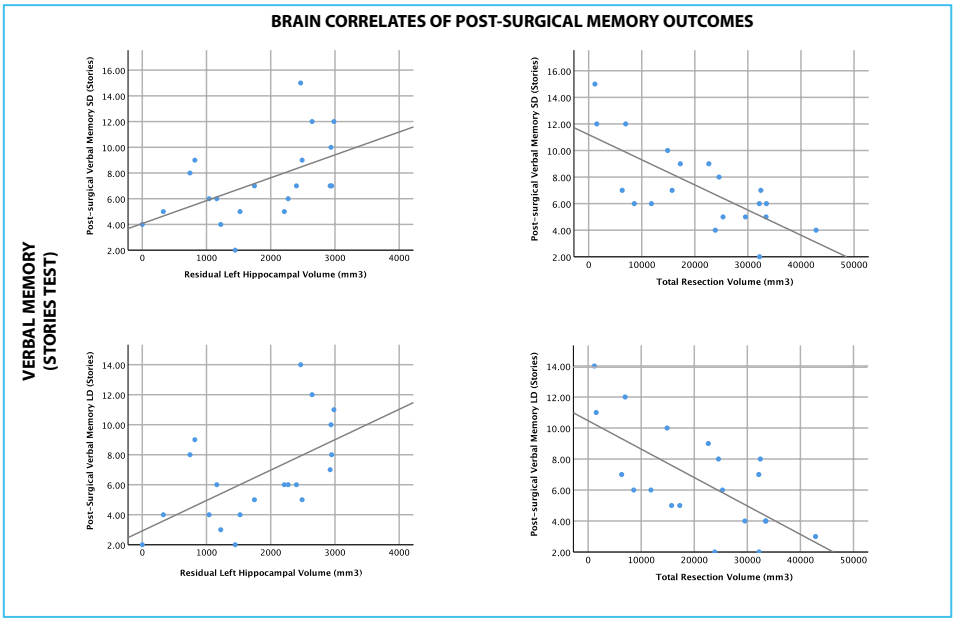


Figure 8. Brain correlates of post-surgical outcomes. Left column: Scatterplots of residual left hippocampal volume (ICV corrected, mm^3) and post-surgical memory scores (Stories test, short delay, top row; long delay, bottom row) in Left Temporal epilepsy patients. Right column: Scatterplots of total surgical resection volume (ICV corrected, mm^3) and post-surgical memory scores (Stories test, short delay, top row; long delay, bottom row) in Left Temporal epilepsy patients.

Figure 7. Association between left residual hippocampal volume and post-surgical memory change

Figure 8. Brain correlates of post-surgical outcomes

Discussion

This section will provide a summary of the main findings of this study and a discussion of their interpretation in the context of previous literature. It will close by outlining the study's main strengths and limitations and overall conclusions.

Pre-surgical hippocampal volumes

Here we report that paediatric temporal lobe patients have smaller presurgical hippocampal volumes, ipsilateral to lesion site, than age and gender matched healthy control participants.

Hippocampal atrophy has been reported in the context of adult TLE since the early 1990s (for a review see Bonilha & Keller, 2015) and quantitative MRI techniques are sometimes employed in the pre-surgical assessment of both adult and paediatric TLE patients (e.g., Guzmán Pérez-Carrillo et al., 2017). Fewer studies have reported hippocampal volumetric assessments in paediatric epilepsy populations, but these confirm that hippocampal pathology is present in paediatric TLE (Guimarães et al., 2007; Mohamed et al., 2001).
Overall, our results are compatible with a growing literature showing hippocampal atrophy in paediatric TLE.

The role of aetiology in hippocampal atrophy

Ipsilesional presurgical hippocampal volumes display a large variability within both the Left and Right Temporal patient populations in this study (Figure 1A). A large part of this variability

is to be imputed to the heterogeneity in epilepsy aetiologies across the dataset (Table 1). These included Focal Cortical Dysplasia, Hippocampal Sclerosis, Tumours and Other aetiologies (mainly comprising vascular malformations and cysts). Focal Cortical Dysplasia (FCD) refers to malformations of cortical tissue, arising due to pathological developmental processes. Importantly for this study, a FCD diagnosis does not exclude hippocampal pathological involvement. Indeed, one of the pathological categories of FCD (FCD type III) is defined by the presence of associated hippocampal sclerosis (Blümcke et al., 2011). The Tumour aetiological category includes low-grade tumours, which are often associated with epilepsy in paediatric and young adult populations (Blümcke et al., 2016). Tumour category includes patients with hippocampal pathological involvement (as also evidenced by pre-surgical hippocampal variability in this aetiological category, see Figure 1B).

Hippocampal Sclerosis (HS) is the most prevalent lesion giving rise to medically refractory epilepsy, especially in adult populations (Blumcke et al., 2012; Blumcke et al., 2013) with sometimes similar rates of FCD and HS reported in paediatric epilepsy surgical candidates (Cloppenborg et al., 2019). HS is characterised by cell loss, gliosis, and axonal reorganisation in the hippocampal formation, and it is often associated with cortical malformations of developmental origin (Blumke et al, 2012).

Our results confirm that within the TLE patient group, presurgical ipsilesional hippocampal volumes were significantly smaller in the HS aetiological category (Figure 1B). However, given the considerations above, it is important to stress that hippocampal pathology cannot be excluded in any of the aetiological groups included in this study. This consideration, coupled with power limitations (the HS patient category only includes N=17 Left Temporal, and N =14 Right Temporal patients) we decided to explore the association between hippocampal volume

and epilepsy/cognitive variables in the whole cohort of TLE patients, collapsing across the aetiology category.

Association between epilepsy factors and hippocampal pathology

There is considerable uncertainty around the pathogenesis of hippocampal atrophy in TLE, with a host of factors likely contributing to progressive injury of hippocampal tissue (including initial precipitating factors – e.g., febrile convulsion, genetic predisposition etc., Thom, 2014). Even the direction of causation between seizures and hippocampal sclerosis is still unclear (Bocti et al., 2003; Theodore & Gaillard, 2002).

In adult populations, duration of epilepsy has been associated with structural hippocampal (and extra-hippocampal) volume loss (reviewed in Bonilha and Keller, 2015), with recent studies (Bernhardt et al., 2016; Kim et al., 2015) showing that duration of seizures on the order of 2 decades is associated with decreased hippocampal neuron density. Comparable paediatric data are lacking.

In our paediatric TLE cohort (which includes children aged between 3 and 17 years; mean = 11.3, SD = 3.6) age at onset was the only significant predictor of presurgical hippocampal volumes, with younger age at onset being associated with smaller hippocampal volumes. This finding could imply enhanced hippocampal vulnerability to excitotoxic insult during early to mid- childhood. However, as age at onset and duration of epilepsy are highly correlated in our dataset, their respective contributions to hippocampal volume variability are difficult to disentangle. Our results are broadly compatible with those reported in the adult TLE literature

which has shown a link between longer seizure duration and progressive hippocampal volume loss.

Pre-surgical cognitive function

Here we report that both Right and Left Temporal lobe epilepsy patients present widespread cognitive impairments before surgery. Full Scale IQ and Verbal Comprehension was lower in Temporal lobe epilepsy patients when compared to Healthy controls (Figure 2A-C). Working Memory and Processing Speed indices were below age expected normative values (Figure D-E) in both groups of TLE patients.

Perceptual reasoning, an index of visual and abstract reasoning ability, was selectively lower in the Right Temporal epilepsy patients, indicating that right hemisphere pathology in early childhood results in visuo-spatial impairments in this paediatric cohort.

Overall, our results are consistent with accumulating evidence that neuropsychological impairments associated with TLE (both in adults and children) are not limited to cognitive functions subserved by the temporal lobes (e.g., declarative memory/verbal function) but encompass cognitive domains well beyond what would be expected on the basis of the location of the lesion (adults: Hwang et al., 2019; children: Guimarães et al., 2007; Rzezak et al., 2007; Smith, 2016). These results are therefore broadly supportive of the emerging paradigm proposing that cognitive dysfunction in TLE is best accounted for by a network-based view of epilepsy (Hermann et al., 2021).

The degree of impairment we observed in our paediatric TLE cohort may appear relatively mild (with average standard scores across domains generally lying within 1 SD of the age

expected normative value). However, it is important to stress that our dataset only included patients with IQ > 70 (see inclusion criteria, Methods section). Cormack et al., 2007 reviewed a large paediatric sample of TLE patients and showed that 57% had an IQ lower than 79 and that those with IQ within the normal range, 19% had low average intelligence. The impact of TLE on general intellectual function is therefore likely underestimated in our sample.

The degree to which general intellectual ability should be considered to be a confounding factor in the analysis of memory impairment in TLE has been the topic of extensive debate with some studies controlling for the impact of FSIQ on memory function using analyses of covariance methods (Skirrow et al., 2015; Skirrow et al., 2019) and others not doing so (e.g., Smith & Lah, 2011). Here we decided not to treat FSIQ as a covariate, as a recent study focusing on childhood TLE showed that memory impairments are robust to "controlling" for FSIQ (Rzezak et al., 2017). More specifically, we ascribe to the theoretical position exposed in Dennis et al., 2009, according to which correcting for IQ differences in the context of neurodevelopmental conditions can lead to misguided conclusions, as IQ changes are as much consequences of the condition as any other cognitive impairments and their respective effects cannot be easily "partialled out" or disentangled.

Pre-surgical memory function

Verbal memory

We observed a specific pattern of verbal memory impairment in our paediatric cohort of unilateral TLE patients. The Left Temporal patient group was selectively impaired on the short delay condition of the paired associate test (when compared to Healthy controls; Figure 2F).

Both patient groups had pre-surgical short delay paired associate test scores lying below age-expected normative values (Figure 5H). Interestingly, this was not the case for either patient group for the long delay paired associate condition (Figure 5I)

As the paired associate test, and in particular its long-delay condition, is thought to be especially sensitive to hippocampal dysfunction, these results are suggestive of relatively intact hippocampal processing in both patient groups before surgery.

Both Right and Left temporal patient groups had lower pre-surgical scores than age expected normative data for both the short and long delay conditions of the Stories verbal memory test (Figure 5 F-G). As this test consists in recalling a short narrative – execution is reliant on general verbal processes (vocabulary, comprehension, etc). As both patient groups demonstrate impaired verbal abilities (lower verbal comprehension indices than age normative and Healthy Control group, see Figure 2B), it is possible that the impairment observed on the Stories test is at least partly attributable to general verbal deficits rather than specific memory impairment.

Taken together, the pattern of verbal memory impairment observed in our paediatric TLE cohort at baseline (before surgery) is consistent with a semantic memory impairment (more reliant on lateral temporal cortical brain areas) as opposed to episodic-like memory impairment (more reliant on mesial temporal lobe areas – including the hippocampus) and is consistent with previous findings (Rzezak et al., 2014; Smith & Lah, 2011).

Visual memory

Here we report that children with Right Temporal lobe epilepsy are selectively impaired on a measure of visuospatial memory ability (Dot location) at longer delays, when compared to the

Left Temporal lobe epilepsy patients and Healthy control groups. These results indicate a degree of material specificity of memory function in this paediatric TLE cohort, akin to what has been observed by some authors in adult TLE populations.

Moreover, on a test of face recognition (configural memory) both patient groups were impaired at short delays, whilst only the Left Temporal patient group showed an impairment with respect to age expected norms in the long delay condition (Figure 5L-M). These results are consistent with an extensive literature implicating both mesial and lateral temporal brain areas in facial recognition both in children and adults (for reviews, see Behrmann et al., 2016; Simons & Spiers, 2003).

Brain correlates of pre-surgical cognitive and memory function

Presurgical right hippocampal volumes in Right Temporal patients correlated with FSIQ, verbal comprehension (Figure 3) and verbal memory at short delays (SD Paired associates; Figure 4). These results, whilst superficially puzzling, can be interpreted as reflecting the well-established bilateral contributions to verbal processing in paediatric populations (Weiss-Croft & Baldeweg, 2015).

Post-surgical intellectual and memory outcomes

Here we report very modest overall changes to both cognitive and memory function 1-year after resective TLE surgery.

Intellectual functioning (FSIQ), non-verbal reasoning (PRI), short term memory (WMI) and general processing speed (PSI) did not change significantly following resective surgery. The overall picture is one of substantial inter-individual variability, consistent with previous reports in the literature (e.g., Kaur et al., 2022; Moosa & Wyllie, 2017; Sherman et al., 2011; Skirrow et al., 2019).

General verbal functioning (indexed by the verbal comprehension scores) and narrative verbal memory (story recollection at both short and long delays) showed a small decline in both Left and Right Temporal patient groups. These results are consistent with previous literature indicating that paediatric TLE surgery carries substantially less long-term risk to verbal memory function than resective surgery in adult populations (Gleissner et al., 2005).

The short follow up duration of this study is likely to have contributed to the observation of small verbal memory declines. Verbal memory loss is observed at short term intervals after TL resection in children, and generally normalises 2 or more years after surgery (for a review see Baldeweg, 2015). In line with this, Skirrow et al., 2015 found long-term improvement in verbal memory following an average follow up duration of 9 years in a paediatric TLE surgical cohort. It is therefore likely that here we captured the short-lasting verbal decline observed after TLE surgery in paediatric populations at (relatively) short intervals following surgery.

Visual configural memory (facial recognition, at both short and long delay) was the only domain for which post-surgical improvements were observed in the current study. This result is consistent with previous reports of selective post-surgical improvements in facial recognition following paediatric TL resective surgery (Beardsworth & Zaidel, 1994; Mabbott & Smith, 2003).

Overall, the findings of decline of verbal memory in the Left Temporal patient group and either unchanged or improved visual memory scores following Temporal Lobe resection are consistent with those reported in a recent quantitative meta-analysis of lateralisation of memory functions in paediatric epilepsy patients (pre- and post-surgery; Kahana Levy et al., 2021). Levy et al., 2021 reviewed 25 studies which reported a mild effect size for post-surgical decline in verbal memory in children with Left Temporal epilepsy (and stability in verbal memory for children with Right Temporal epilepsy). Non-verbal memory was not affected by surgery in children with Right TLE in the studies reviewed.

In line with previous reports, this study shows that the greatest post-surgical improvements in verbal processing, and in verbal and visual memory function were observed in patients who had lower pre-surgical scores (Figure 6; e.g., Flint et al., 2017; Helmstaedter et al., 2011; Skirrow et al., 2011; Skirrow et al., 2015). These results underscore the possibility that pre-surgical function rests on residual functionality of ipsilesional brain tissue. According to this hypothesis, it is the removal of such functional brain tissue in the ipsilesional hemisphere during surgery that is responsible for the decline in memory function observed in some TLE patients following resective surgery.

Brain correlates of post-surgical memory outcomes

In keeping with the hypothesis that pre-surgical cognitive and memory function rests on the presence of functional tissue in the ipsilesional hemisphere, we found that residual hippocampal volumes in Left Temporal patients were correlated with post-surgical change in (narrative) verbal memory (Stories test). Larger residual hippocampal volumes were associated with larger verbal memory improvements following surgery (Figure 7). These results are

consistent with previous findings in the paediatric (Clusmann, 2008; Gleissner et al., 2002; Law et al., 2017; Skirrow et al., 2015; for a review see Flint et al., 2017) and adult literature (Bauman et al., 2019; Christoph Helmstaedter et al., 2011).

Larger resection volumes correlated with both post-surgical verbal memory change and post-surgical memory outcome, exclusively in the Left Temporal epilepsy patient group. More extensive resections were associated with larger post-surgical decline and lower post-surgical memory scores. These results are consistent with previous findings indicating that larger left temporal lobe resections result in larger post-surgical verbal memory decline both in adults (Helmstaedter et al., 2011; Helmstaedter et al., 2011; Liu et al., 2017; Sone et al., 2022) and children (Skirrow et al, 2015).

Clinical predictors of surgical memory outcomes

In Right Temporal patients, pre-surgical FSIQ was the only predictor of post-surgical verbal memory emphasizing the importance of pre-surgical variables in influencing post-operative outcome.

The only statistically significant predictor of post-surgical verbal memory outcomes in the Left Temporal patient group was resection extent. These results are in agreement with previous findings in the adult and paediatric literature showing better cognitive outcome after more limited resections (Law et al., 2017; Morino et al., 2006; Skirrow et al., 2015; Sone et al., 2022). However, the degree to which resection volume extent is associated with seizure freedom in paediatric populations is still debated (e.g., Benifla et al., 2017; Clusmann et al., 2004; Lopez-Gonzalez et al., 2012).

Strengths and limitations of the study

The main strength of this study lies in the relatively large sample size in comparison with previous studies of paediatric TLE surgery. This allowed separate analysis of Left and Right temporal lobe patient groups.

However, it is important to highlight that the sample size is still small in relationship to the large number of variables under consideration. Moreover, the sample was heterogeneous with respect to several, critical epilepsy-related variables including age at onset, duration of epilepsy and, more importantly, aetiology. For instance, while we have identified that pre-surgical hippocampal volumes differed across aetiology groups (with lower hippocampal volumes in children with hippocampal sclerosis), due to statistical power constraints, it was not possible to analyse effect of surgical variables on neuropsychological outcome separately in the different aetiology groups.

Another limitation of the current study is that we did not have access to a non-surgical epilepsy group, thus we could not draw any conclusions regarding the specific effect of surgery on neuropsychological outcome (as opposed to seizure freedom/cessation of medication, for instance).

The dataset included neuropsychological data collected across 20 years of clinical practice and therefore different versions of tests were used across and within participants, potentially introducing uncontrolled biases.

Although one of the aims of the study was to characterise surgical outcomes separately for Right and Left Temporal epilepsy patients, we did not have access to data related to language

lateralisation (fMRI) and therefore could not take this important variable into consideration when interpreting lateralisation effects.

Follow up time was variable across participants, but overall short – thus precluding exploration of long-term cognitive trajectories.

Data on surgical outcome in terms of seizure freedom was only available for a very limited set of the data, and this precluded meaningful analysis of this crucial variable.

Finally, volumetric assessments could only be performed by a single rater so no objective measure of bias could be computed.

Clinical implications

Here we will discuss some of the clinical implications resulting from the study conclusions. These should be considered in the context of the study limitations outlined above.

This study showed that age at epilepsy onset was the only parameter that correlated with pre-surgical hippocampal volumes, with earlier age at onset being associated with smaller hippocampal volumes. This result suggests that the hippocampus may be more vulnerable during a critical time window spanning early to mid-childhood. It is important therefore to recognise that children in these age ranges may be at enhanced risk of brain dysfunction due to epilepsy. From a clinical point of view, this implies that early pharmacological and surgical intervention have the best chance to halt the progression of hippocampal and cortical damage. In general, there is growing recognition that early surgery, before the onset of clinically detectable cognitive difficulties is advisable in paediatric pharmacologically resistant epilepsy (e.g. Braun and Cross, 2018). This recognition is often tempered by the reluctance of both surgical teams and families/patients to proceed with surgical intervention too early, as surgery, inevitably, implies damage and removal of healthy brain tissue. There is also a potential over-

reliance on the degree to which plasticity in the young brain can compensate for the damage inflicted to brain circuits by epilepsy. Although historically a great deal has been made of developmental plasticity, there is growing evidence pointing at the limits to this plasticity (e.g. Cacucci and Vargha-Khadem, 2019). The choice to proceed with early surgery should therefore be informed by the understanding that cognitive dysfunction is nearly always irreversible, with children affected by epilepsy continuing to develop capabilities as development progresses, following developmental curves that are shifted downwards with respect to healthy peers. The crucial consideration is that the extent of this downward shift is, in general, related to the extent of pre-surgical cognitive function.

From a clinical psychology point of view, early identification of neuropsychological vulnerabilities brought about by hippocampal and cortical damage should be implemented, as well as the design of neuropsychological interventions aimed at strengthening compensatory strategies. Clinical and educational psychologist should also communicate with schools, to increase awareness of the enhanced vulnerability to epilepsy in early to mid-childhood, such that any learning difficulties will not go unnoticed. Ideally, children and families should have access to integrated, community based care, including neuropsychological, psychological, educational and social work input.

The results presented here show that, at the point of engagement in the surgical pathway, children with medically TLE already display general cognitive problems – spanning domains beyond those traditionally thought to be supported by temporal lobe function.

The most robust finding in this study is the presence of pre-surgical verbal processing dysfunction, regardless of side of origin of temporal lobe epilepsy (right or left hemisphere). Our results specifically point to verbal semantic (as opposed to episodic) difficulties. From a

clinical point of view then, two principles must be kept in mind: 1) The diffuse nature of the cognitive difficulties (including processing speed, executive and attentional processes). This implies that neuropsychological, educational and social interventions need to be holistic, rather than focused on verbal memory alone; 2) The nature of the verbal memory dysfunction is more likely due to an underlying verbal semantic store impoverishment (i.e. children may struggle with learning as their semantic, verbally based conceptual foundations are weaker) rather than a purer episodic memory dysfunction (i.e. inability to remember events and material presented). In this context, strengthening verbal comprehension, becomes a priority.

Overall, children and families should receive support beyond the academic domain. Schools and all professionals involved in the care of children with epilepsy should be empowered to recognise that epilepsy-related cognitive dysfunction can and does have consequences on children's overall wellbeing, with children often complaining about social isolation (e.g. slower processing speed/lower verbal function interferes with the ability to keep up with day-to-day conversations, understanding of jokes, etc.).

Post-surgically we observed a (small) decline in verbal function and verbal memory, regardless of lesion laterality in children suffering from TLE, around one year following resective surgery (with large inter-individual differences). We also observed that children with higher pre-operative scores are most vulnerable to post-operative decline in performance across all the cognitive domains we explored. Families and children (especially those with higher pre-surgical function) must be counselled regarding the likelihood that some loss of function may ensue during the post-surgical period, whilst keeping in mind that this generally resolves several years after surgery. Schools should also be informed about this dip in performance, so that children could benefit from adaptations to their curricula in the years immediately following epilepsy surgery.

Lastly, our results suggest that pre-operative verbal memory ability is supported by functional tissue in the ipsilesional hemisphere. Moreover, in the left temporal patient group, extent of surgical resection was the only significant predictor of post-surgical verbal memory function. These results suggest that preservation of hippocampal and cortical tissue should remain a priority in epilepsy surgery and that amount of resected tissue can be used as a proxy to infer magnitude of likely post-surgical cognitive impairments.

Conclusions

Our findings confirm that paediatric TLE is characterised by a variable degree of hippocampal atrophy. In our cohort, extent of hippocampal atrophy was selectively associated with age at onset (with younger age at onset correlating with smaller ipsilesional pre-surgical hippocampal volumes).

In line with previous literature, we observed that general intellectual function (FSIQ) and verbal reasoning are affected in paediatric TLE, regardless of whether epilepsy originates in the left or the right hemisphere. Visuo-spatial impairments were instead limited to right temporal pathology in our paediatric TLE cohort. Taken together, these results suggest that verbal function is supported by bilateral brain networks in children with TLE, whilst visuo-spatial function rests on the integrity of the right hemisphere.

We observed a (small) decline in verbal function and verbal memory, regardless of lesion laterality in children suffering from TLE, around one year following resective surgery. Importantly, this overall decline in verbal memory and function masks large inter-individual

differences. We observed, in agreement with previous literature, that children with higher pre-operative scores are most vulnerable to post-operative decline in performance across all the cognitive domains we explored.

We observed significant associations between residual left hippocampal volumes and verbal memory following surgery, only in patients with lesions in the left hemisphere.
Taken together, these results suggest that pre-operative verbal memory ability is supported by functional tissue in the ipsilesional hemisphere.

Finally, in the left temporal patient group, we found that extent of surgical resection was the only significant predictor of post-surgical verbal memory function, whilst pre-surgical FSIQ was the only significant predictor of post-surgical verbal memory outcome in the right temporal patient group.

Bibliography

Aaberg, K. M., Suren, P., Soraas, C. L., Bakken, I. J., Lossius, M. I., Stoltenberg, C., & Chin, R. (2017). Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort. *Epilepsia*, *58*(11), 1880-1891. https://doi.org/10.1111/epi.13913

Adler, S., Blackwood, M., Northam, G. B., Gunny, R., Hong, S.-J., Bernhardt, B. C., Bernasconi, A., Bernasconi, N., Jacques, T., Tisdall, M., Carmichael, D. W., Cross, J. H., & Baldeweg, T. (2018). Multimodal computational neocortical anatomy in pediatric hippocampal sclerosis. *Annals of Clinical and Translational Neurology*, *5*(10), 1200-1210. https://doi.org/https://doi.org/10.1002/acn3.634

Alpherts, W. C., Vermeulen, J., van Rijen, P. C., da Silva, F. H., & van Veelen, C. W. (2006). Verbal memory decline after temporal epilepsy surgery?: A 6-year multiple assessments follow-up study. *Neurology*, *67*(4), 626-631. https://doi.org/10.1212/01.wnl.0000230139.45304.eb

Andersson-Roswall, L., Engman, E., Samuelsson, H., & Malmgren, K. (2010). Cognitive outcome 10 years after temporal lobe epilepsy surgery: a prospective controlled study. *Neurology*, *74*(24), 1977-1985. https://doi.org/10.1212/WNL.0b013e3181e39684

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), e1532-1543. https://doi.org/10.1542/peds.2011-0245

Baker, G. A., Hargis, E., Hsih, M. M., Mounfield, H., Arzimanoglou, A., Glauser, T., Pellock, J., & Lund, S. (2008). Perceived impact of epilepsy in teenagers and young adults: an international survey. *Epilepsy Behav*, *12*(3), 395-401. https://doi.org/10.1016/j.yebeh.2007.11.001

Baldeweg, T. a. S., C. (2015). *Long-term cognitive outcomes after epilepsy surgery in children*. Springer International Publishing.

Baldeweg, T. S., C. (2015). Long-Term Cognitive Outcomes after Epilepsy Surgery in Children. In S. I. Publishing (Ed.), *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 85-101).

Baum, K. T., Byars, A. W., deGrauw, T. J., Johnson, C. S., Perkins, S. M., Dunn, D. W., Bates, J. E., & Austin, J. K. (2007). Temperament, family environment, and behavior problems in children with new-onset seizures. *Epilepsy Behav*, *10*(2), 319-327. https://doi.org/10.1016/j.yebeh.2006.12.007

Bauman, K., Devinsky, O., & Liu, A. A. (2019). Temporal lobe surgery and memory: Lessons, risks, and opportunities. *Epilepsy Behav*, *101*(Pt A), 106596. https://doi.org/10.1016/j.yebeh.2019.106596

Baxendale, S. A., Thompson, P. J., & Kitchen, N. D. (2000). Postoperative hippocampal remnant shrinkage and memory decline: a dynamic process. *Neurology*, *55*(2), 243-249. https://doi.org/10.1212/wnl.55.2.243

Beardsworth, E. D., & Zaidel, D. W. (1994). Memory for faces in epileptic children before and after brain surgery. *Journal of Clinical and Experimental Neuropsychology*, *16*(4), 589-596. https://doi.org/10.1080/01688639408402670

Behrmann, M., Scherf, K. S., & Avidan, G. (2016). Neural mechanisms of face perception, their emergence over development, and their breakdown. *Wiley Interdiscip Rev Cogn Sci*, *7*(4), 247-263. https://doi.org/10.1002/wcs.1388

Bell, B., Lin, J. J., Seidenberg, M., & Hermann, B. (2011). The neurobiology of cognitive disorders in temporal lobe epilepsy. *Nat Rev Neurol*, *7*(3), 154-164. https://doi.org/10.1038/nrneurol.2011.3

Benifla, M., Bennet-Back, O., Shorer, Z., Noyman, I., Bar-Yosef, R., & Ekstein, D. (2017). Temporal lobe surgery for intractable epilepsy in children: What to do with the hippocampus? *Seizure*, *52*, 81-88. https://doi.org/10.1016/j.seizure.2017.09.020

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*(1), 289-300. https://doi.org/https://doi.org/10.1111/j.2517-6161.1995.tb02031.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/https://doi.org/10.1111/j.1528-1167.2007.01461.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., Zelko, F. A., Levy, S. R., & Testa, F. M. (2012). Age at onset of epilepsy, pharmacoresistance, and cognitive outcomes. *A prospective cohort study*, *79*(13), 1384-1391. https://doi.org/10.1212/WNL.0b013e31826c1b55

Bernhardt, B. C., Bernasconi, A., Liu, M., Hong, S.-J., Caldairou, B., Goubran, M., Guiot, M. C., Hall, J., & Bernasconi, N. (2016). The spectrum of structural and functional imaging abnormalities in temporal lobe epilepsy. *Annals of Neurology*, *80*(1), 142-153. https://doi.org/https://doi.org/10.1002/ana.24691

Bernhardt, B. C., Bernasconi, N., Concha, L., & Bernasconi, A. (2010). Cortical thickness analysis in temporal lobe epilepsy: reproducibility and relation to outcome. *Neurology*, *74*(22), 1776-1784. https://doi.org/10.1212/WNL.0b013e3181e0f80a

Besag, F., Aldenkamp, A., Caplan, R., Dunn, D. W., Gobbi, G., & Sillanpää, M. (2016). Psychiatric and Behavioural Disorders in Children with Epilepsy: an ILAE Task Force Report. *Epileptic Disord*, *18 Suppl 1*, 1-86. https://doi.org/10.1684/epd.2016.0809 (Psychiatric and Behavioural Disorders in Children with Epilepsy: an ILAE Task Force Report.)

Bilgiç, A., Işık, Ü., Çolak, R. S., Derin, H., & Çaksen, H. (2018). Psychiatric symptoms and health-related quality of life in children with epilepsy and their mothers. *Epilepsy & Behavior*, *80*, 114-121.

Blümcke, I., Aronica, E., Becker, A., Capper, D., Coras, R., Honavar, M., Jacques, T. S., Kobow, K., Miyata, H., Mühlebner, A., Pimentel, J., Söylemezoğlu, F., & Thom, M. (2016). Low-grade epilepsy-associated neuroepithelial tumours - the 2016 WHO classification. *Nat Rev Neurol*, *12*(12), 732-740. https://doi.org/10.1038/nrneurol.2016.173

Blumcke, I., Coras, R., Miyata, H., & Ozkara, C. (2012). Defining clinico-neuropathological subtypes of mesial temporal lobe epilepsy with hippocampal sclerosis. *Brain Pathol*, *22*(3), 402-411. https://doi.org/10.1111/j.1750-3639.2012.00583.x

Blümcke, I., Coras, R., Miyata, H., & Özkara, C. (2012). Defining Clinico-Neuropathological Subtypes of Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis. *Brain*

Pathology, *22*(3), 402-411. https://doi.org/https://doi.org/10.1111/j.1750-3639.2012.00583.x

Blumcke, I., Thom, M., Aronica, E., Armstrong, D. D., Bartolomei, F., Bernasconi, A., Bernasconi, N., Bien, C. G., Cendes, F., Coras, R., Cross, J. H., Jacques, T. S., Kahane, P., Mathern, G. W., Miyata, H., Moshe, S. L., Oz, B., Ozkara, C., Perucca, E., . . . Spreafico, R. (2013). International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia*, *54*(7), 1315-1329. https://doi.org/10.1111/epi.12220

Blümcke, I., Thom, M., Aronica, E., Armstrong, D. D., Vinters, H. V., Palmini, A., Jacques, T. S., Avanzini, G., Barkovich, A. J., Battaglia, G., Becker, A., Cepeda, C., Cendes, F., Colombo, N., Crino, P., Cross, J. H., Delalande, O., Dubeau, F., Duncan, J., . . . Spreafico, R. (2011). The clinicopathologic spectrum of focal cortical dysplasias: a consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission. *Epilepsia*, *52*(1), 158-174. https://doi.org/10.1111/j.1528-1167.2010.02777.x

Bocti, C., Robitaille, Y., Diadori, P., Lortie, A., Mercier, C., Bouthillier, A., & Carmant, L. (2003). The pathological basis of temporal lobe epilepsy in childhood. *Neurology*, *60*(2), 191-195. https://doi.org/10.1212/01.wnl.0000044055.73747.9f

Bonilha, L., Jensen, J. H., Baker, N., Breedlove, J., Nesland, T., Lin, J. J., Drane, D. L., Saindane, A. M., Binder, J. R., & Kuzniecky, R. I. (2015). The brain connectome as a personalized biomarker of seizure outcomes after temporal lobectomy. *Neurology*, *84*(18), 1846-1853. https://doi.org/10.1212/wnl.0000000000001548

Bonilha, L., & Keller, S. S. (2015). Quantitative MRI in refractory temporal lobe epilepsy: relationship with surgical outcomes. *Quant Imaging Med Surg*, *5*(2), 204-224. https://doi.org/10.3978/j.issn.2223-4292.2015.01.01

Boshuisen, K., van Schooneveld, M. M., Uiterwaal, C. S., Cross, J. H., Harrison, S., Polster, T., Daehn, M., Djimjadi, S., Yalnizoglu, D., Turanli, G., Sassen, R., Hoppe, C., Kuczaty, S., Barba, C., Kahane, P., Schubert-Bast, S., Reuner, G., Bast, T., Strobl, K., . . . Braun, K. P. (2015). Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. *Ann Neurol*, *78*(1), 104-114. https://doi.org/10.1002/ana.24427

Braun, K. P. S., & Cross, H. J. (2018) Pediatric epilepsy surgery: the earlier the better. Expert Review of Neurotherapeutics, 18(4), 261-263. https://doi.org/10.1080/14737175.2018.1455503

Brodie, M. J., Barry, S. J., 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

Bruce, P. H., Jana, E. J., Daren, C. J., & Michael, S. (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

Buck, S., Bastos, F., Baldeweg, T., & Vargha-Khadem, F. (2021). The Pair Test: A computerised measure of learning and memory. *Behav Res Methods*, *53*(2), 928-942. https://doi.org/10.3758/s13428-020-01470-9

Burgess, N., Maguire, E. A., & O'Keefe, J. (2002). The human hippocampus and spatial and episodic memory. *Neuron*, *35*(4), 625-641. https://doi.org/10.1016/s0896-6273(02)00830-9

Camfield, C., Camfield, P., Gordon, K., Smith, B., & Dooley, J. (1993). Outcome of childhood epilepsy: A population-based study with a simple predictive scoring system for those

treated with medication. *The Journal of Pediatrics*, *122*(6), 861-868. https://doi.org/https://doi.org/10.1016/S0022-3476(09)90008-7

Cardoso, M. J., Leung, K., Modat, M., Keihaninejad, S., Cash, D., Barnes, J., Fox, N. C., & Ourselin, S. (2013). STEPS: Similarity and Truth Estimation for Propagated Segmentations and its application to hippocampal segmentation and brain parcelation. *Med Image Anal*, *17*(6), 671-684. https://doi.org/10.1016/j.media.2013.02.006

Chadwick D, B. E., Callaghan N, et al. (1998). Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia*, *39*(7), 799-803. https://doi.org/10.1111/j.1528-1157.1998.tb01167.x

Chen, H. H., Chen, C., Hung, S. C., Liang, S. Y., Lin, S. C., Hsu, T. R., Yeh, T. C., Yu, H. Y., Lin, C. F., Hsu, S. P., Liang, M. L., Yang, T. F., Chu, L. S., Lin, Y. Y., Chang, K. P., Kwan, S. Y., Ho, D. M., Wong, T. T., & Shih, Y. H. (2014). Cognitive and epilepsy outcomes after epilepsy surgery caused by focal cortical dysplasia in children: early intervention maybe better. *Childs Nerv Syst*, *30*(11), 1885-1895. https://doi.org/10.1007/s00381-014-2463-y

Chen, S., Zhang, J., Ruan, X., Deng, K., Zhang, J., Zou, D., He, X., Li, F., Bin, G., Zeng, H., & Huang, B. (2020). Voxel-based morphometry analysis and machine learning based classification in pediatric mesial temporal lobe epilepsy with hippocampal sclerosis. *Brain Imaging Behav*, *14*(5), 1945-1954. https://doi.org/10.1007/s11682-019-00138-z

Cloppenborg, T., May, T. W., Blümcke, I., Fauser, S., Grewe, P., Hopf, J. L., Kalbhenn, T., Polster, T., Schulz, R., Woermann, F. G., & Bien, C. G. (2019). Differences in pediatric and adult epilepsy surgery: A comparison at one center from 1990 to 2014. *Epilepsia*, *60*(2), 233-245. https://doi.org/https://doi.org/10.1111/epi.14627

Clusmann, H. (2008). Predictors, procedures, and perspective for temporal lobe epilepsy surgery. *Semin Ultrasound CT MR*, *29*(1), 60-70. https://doi.org/10.1053/j.sult.2007.11.004

Clusmann, H., Kral, T., Gleissner, U., Sassen, R., Urbach, H., Blümcke, I., Bogucki, J., & Schramm, J. (2004). Analysis of different types of resection for pediatric patients with temporal lobe epilepsy. *Neurosurgery*, *54*(4), 847-859; discussion 859-860. https://doi.org/10.1227/01.neu.0000114141.37640.37

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

Coleman, H., McIntosh, A., Rayner, G., & Wilson, S. J. (2021). Understanding long-term changes in patient identity 15-20 years after surgery for temporal lobe epilepsy. *Epilepsia*, *62*(10), 2451-2462. https://doi.org/10.1111/epi.17027

Conway, L., Widjaja, E., & Smith, M. L. (2018). Impact of resective epilepsy surgery on health-related quality of life in children with and without low intellectual ability. *Epilepsy Behav*, *83*, 131-136. https://doi.org/10.1016/j.yebeh.2018.03.036

Cormack, F., Gadian, D. G., Vargha-Khadem, F., Cross, J. H., Connelly, A., & Baldeweg, T. (2005). Extra-hippocampal grey matter density abnormalities in paediatric mesial temporal sclerosis. *Neuroimage*, *27*(3), 635-643. https://doi.org/10.1016/j.neuroimage.2005.05.023

Cormack, F., Helen Cross, J., 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/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), 255-259. https://doi.org/https://doi.org/10.1016/j.eplepsyres.2011.09.004

Crudgington, H., Collingwood, A., Bray, L., Lyle, S., Martin, R., Gringras, P., Pal, D. K., & Morris, C. (2020). Mapping epilepsy-specific patient-reported outcome measures for children to a proposed core outcome set for childhood epilepsy. *Epilepsy Behav*, *112*, 107372. https://doi.org/10.1016/j.yebeh.2020.107372

Crudgington, H., Rogers, M., Bray, L., Carter, B., Currier, J., Dunkley, C., Gibbon, F. M., Hughes, D., Lyle, S., Roberts, D., Tudur Smith, C., Gringras, P., Pal, D. K., & Morris, C. (2019). Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core outcome set using systematic review methods and a Delphi survey consensus. *Epilepsia*, *60*(5), 857-871. https://doi.org/10.1111/epi.14735

Crudgington, H., Rogers, M., Morris, H., Gringras, P., Pal, D. K., & Morris, C. (2020). Epilepsy-specific patient-reported outcome measures of children's health-related quality of life: A systematic review of measurement properties. *Epilepsia*, *61*(2), 230-248. https://doi.org/10.1111/epi.16430

Dagar, A., Chandra, P. S., Chaudhary, K., Avnish, C., Bal, C. S., Gaikwad, S., Garg, A., Sarkar, C., Srivastava, A., Padma, M. V., Rekha, D., Gulati, S., Paul, V., Prasad, K., Singh, M. B., & Tripathi, M. (2011). Epilepsy surgery in a pediatric population: a retrospective study of 129 children from a tertiary care hospital in a developing country along with assessment of quality of life. *Pediatr Neurosurg*, *47*(3), 186-193. https://doi.org/10.1159/000334257

Danguecan, A. N., & Smith, M. L. (2019). Verbal associative memory outcomes in pediatric surgical temporal lobe epilepsy: Exploring the impact of mesial structures. *Epilepsy Behav*, *101*(Pt A), 106529. https://doi.org/10.1016/j.yebeh.2019.106529

Dennis, M., Francis, D. J., Cirino, P. T., Schachar, R., Barnes, M. A., & Fletcher, J. M. (2009). Why IQ is not a covariate in cognitive studies of neurodevelopmental disorders. *J Int Neuropsychol Soc*, *15*(3), 331-343. https://doi.org/10.1017/s1355617709090481

Derry, P. A., & Wiebe, S. (2000). Psychological adjustment to success and to failure following epilepsy surgery. *Canadian journal of neurological sciences*, *27*(S1), S116-S120.

Ding, P., Liang, S., Zhang, S., Zhang, J., Hu, X., & Yu, X. (2016). Resective surgery combined with corpus callosotomy for children with non-focal lesional Lennox-Gastaut syndrome. *Acta Neurochir (Wien)*, *158*(11), 2177-2184. https://doi.org/10.1007/s00701-016-2947-5

Downes, M., Greenaway, R., Clark, M., Helen Cross, J., Jolleff, N., Harkness, W., Kaliakatsos, M., Boyd, S., White, S., & Neville, B. G. (2015). Outcome following multiple subpial transection in Landau-Kleffner syndrome and related regression. *Epilepsia*, *56*(11), 1760-1766. https://doi.org/10.1111/epi.13132

Dupont, S., Tanguy, M.-L., Clemenceau, S., Adam, C., Hazemann, P., & Baulac, M. (2006). Long-term Prognosis and Psychosocial Outcomes after Surgery for MTLE. *Epilepsia*, *47*(12), 2115-2124. https://doi.org/https://doi.org/10.1111/j.1528-1167.2006.00852.x

Dwivedi, R., Ramanujam, B., Chandra, P. S., Sapra, S., Gulati, S., Kalaivani, M., Garg, A., Bal, C. S., Tripathi, M., Dwivedi, S. N., Sagar, R., Sarkar, C., & 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

Dwivedi, R., Ramanujam, B., Chandra, P. S., Sapra, S., Gulati, S., Kalaivani, M., Garg, A., Bal, C. S., Tripathi, M., Dwivedi, S. N., Sagar, R., Sarkar, C., & Tripathi, M. (2017). Surgery for Drug-Resistant Epilepsy in Children. *N Engl J Med*, *377*(17), 1639-1647. https://doi.org/10.1056/NEJMoa1615335

Elliott, I., Kadis, D. S., Lach, L., Olds, J., McCleary, L., Whiting, S., Snyder, T., & Smith, M. L. (2012). Quality of life in young adults who underwent resective surgery for epilepsy in childhood. *Epilepsia*, *53*(9), 1577-1586. https://doi.org/10.1111/j.1528-1167.2012.03594.x

Elliott, I. M., Lach, L., & Smith, M. L. (2005). I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. *Epilepsy Behav*, *7*(4), 664-678. https://doi.org/10.1016/j.yebeh.2005.07.004

Engel, J. (1993). *Surgical Treatment of the Epilepsies, 2nd ed.* Raven Press.

Engel, J. (2001). Mesial Temporal Lobe Epilepsy: What Have We Learned? *The Neuroscientist*, *7*(4), 340-352. https://doi.org/10.1177/107385840100700410

Engel, J., Jr. (1993). Update on surgical treatment of the epilepsies. Summary of the Second International Palm Desert Conference on the Surgical Treatment of the Epilepsies (1992). *Neurology*, *43*(8), 1612-1617. https://doi.org/10.1212/wnl.43.8.1612

Engel, J., Jr. (2016). What can we do for people with drug-resistant epilepsy? The 2016 Wartenberg Lecture. *Neurology*, *87*(23), 2483-2489. https://doi.org/10.1212/wnl.0000000000003407

Engle, J. A., & Smith, M. L. (2010). Attention and material-specific memory in children with lateralized epilepsy. *Neuropsychologia*, *48*(1), 38-42. https://doi.org/10.1016/j.neuropsychologia.2009.08.005

Excellence, N. I. f. H. a. C. (2022). *NG 217 Epilepsies in children, young people and adults*.

Fastenau, P. S., Jianzhao, S., Dunn, D. W., & Austin, J. K. (2008). Academic underachievement among children with epilepsy: proportion exceeding psychometric criteria for learning disability and associated risk factors. *J Learn Disabil*, *41*(3), 195-207. https://doi.org/10.1177/0022219408317548

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

Fastenau, P. S., Johnson, C. S., Perkins, S. M., Byars, A. W., deGrauw, T. J., Austin, J. K., & Dunn, D. W. (2009b). 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

Ferro, M. A., Avery, L., Fayed, N., Streiner, D. L., Cunningham, C. E., Boyle, M. H., Lach, L., Glidden, G., Rosenbaum, P. L., Ronen, G. M., & group, Q. (2017). Child- and parent-reported quality of life trajectories in children with epilepsy: A prospective cohort study. *Epilepsia*, *58*(7), 1277-1286. https://doi.org/10.1111/epi.13774

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

Follansbee-Junger, K. W., Mann, K. A., Guilfoyle, S. M., Morita, D. A., Varni, J. W., & Modi, A. C. (2016). Development of the PedsQL™ Epilepsy Module: Focus group and cognitive

interviews. *Epilepsy Behav*, *62*, 115-120. https://doi.org/10.1016/j.yebeh.2016.06.011

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 Res*, *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*(Pt 12), 2822-2829. https://doi.org/10.1093/brain/awh597

Gonzalez, L. M., Anderson, V. A., Wood, S. J., Mitchell, L. A., & Harvey, A. S. (2007). The Localization and Lateralization of Memory Deficits in Children with Temporal Lobe Epilepsy. *Epilepsia*, *48*(1), 124-132. https://doi.org/https://doi.org/10.1111/j.1528-1167.2006.00907.x

Gonzalez, L. M., Mahdavi, N., Anderson, V. A., & Harvey, A. S. (2012). Changes in memory function in children and young adults with temporal lobe epilepsy: a follow-up study. *Epilepsy & Behavior*, *23*(3), 213-219.

Goodwin, S. W., Lambrinos, A. I., Ferro, M. A., Sabaz, M., & Speechley, K. N. (2015). Development and assessment of a shortened Quality of Life in Childhood Epilepsy Questionnaire (QOLCE-55). *Epilepsia*, *56*(6), 864-872. https://doi.org/10.1111/epi.13000

Griffiths, S. Y., Sherman, E. M., Slick, D. J., Eyrl, K., Connolly, M. B., & Steinbok, P. (2007). Postsurgical health-related quality of life (HRQOL) in children following hemispherectomy for intractable epilepsy. *Epilepsia*, *48*(3), 564-570. https://doi.org/10.1111/j.1528-1167.2006.00966.x

Guimarães, C. A., Bonilha, L., Franzon, R. C., Li, L. M., Cendes, F., & Guerreiro, M. M. (2007). Distribution of regional gray matter abnormalities in a pediatric population with temporal lobe epilepsy and correlation with neuropsychological performance. *Epilepsy Behav*, *11*(4), 558-566. https://doi.org/10.1016/j.yebeh.2007.07.005

Guzmán Pérez-Carrillo, G. J., Owen, C., Schwetye, K. E., McFarlane, S., Vellimana, A. K., Mar, S., Miller-Thomas, M. M., Shimony, J. S., Smyth, M. D., & Benzinger, T. L. S. (2017). The use of hippocampal volumetric measurements to improve diagnostic accuracy in pediatric patients with mesial temporal sclerosis. *Journal of Neurosurgery: Pediatrics PED*, *19*(6), 720-728. https://doi.org/10.3171/2016.12.PEDS16335

Helmstaedter, C., Beeres, K., Elger, C., Kuczaty, S., Schramm, J., & Hoppe, C. (2020). Cognitive outcome of pediatric epilepsy surgery across ages and different types of surgeries: a monocentric 1-year follow-up study in 306 patients of school age. *Seizure*, *77*, 86-92.

Helmstaedter, C., Elger, C. E., & Witt, J. A. (2016). The effect of quantitative and qualitative antiepileptic drug changes on cognitive recovery after epilepsy surgery. *Seizure*, *36*, 63-69. https://doi.org/10.1016/j.seizure.2016.02.001

Helmstaedter, C., & Kockelmann, E. (2006). Cognitive Outcomes in Patients with Chronic Temporal Lobe Epilepsy. *Epilepsia*, *47*(s2), 96-98. https://doi.org/https://doi.org/10.1111/j.1528-1167.2006.00702.x

Helmstaedter, C., Petzold, I., & Bien, C. G. (2011). The cognitive consequence of resecting nonlesional tissues in epilepsy surgery—Results from MRI- and histopathology-negative patients with temporal lobe epilepsy. *Epilepsia*, *52*(8), 1402-1408. https://doi.org/https://doi.org/10.1111/j.1528-1167.2011.03157.x

Helmstaedter, C., Reuber, M., & Elger, C. C. (2002). Interaction of cognitive aging and memory deficits related to epilepsy surgery. *Ann Neurol*, *52*(1), 89-94. https://doi.org/10.1002/ana.10260

Helmstaedter, C., Roeske, S., Kaaden, S., Elger, C. E., & Schramm, J. (2011). Hippocampal resection length and memory outcome in selective epilepsy surgery. *J Neurol Neurosurg Psychiatry*, *82*(12), 1375-1381. https://doi.org/10.1136/jnnp.2010.240176

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. *Prog Brain Res*, *135*, 429-438. https://doi.org/10.1016/s0079-6123(02)35040-4

Hermann, B. P., Struck, A. F., Busch, R. M., Reyes, A., Kaestner, E., & McDonald, C. R. (2021). Neurobehavioural comorbidities of epilepsy: towards a network-based precision taxonomy. *Nature Reviews Neurology*, *17*(12), 731-746. https://doi.org/10.1038/s41582-021-00555-z

Hermann, B. P., Wyler, A. R., Somes, G., Berry, A. D., 3rd, & Dohan, F. C., Jr. (1992). Pathological status of the mesial temporal lobe predicts memory outcome from left anterior temporal lobectomy. *Neurosurgery*, *31*(4), 652-656; discussion 656-657. https://doi.org/10.1227/00006123-199210000-00006

Hum, K. M., Smith, M. L., Lach, L., & Elliott, I. M. (2010). Self-perceptions of social function 2years after pediatric epilepsy surgery. *Epilepsy & Behavior*, *17*(3), 354-359. https://doi.org/https://doi.org/10.1016/j.yebeh.2009.11.022

Hwang, G., Dabbs, K., Conant, L., Nair, V. A., Mathis, J., Almane, D. N., Nencka, A., Birn, R., Humphries, C., Raghavan, M., DeYoe, E. A., Struck, A. F., Maganti, R., Binder, J. R., Meyerand, E., Prabhakaran, V., & Hermann, B. (2019). Cognitive slowing and its

underlying neurobiology in temporal lobe epilepsy. *Cortex*, *117*, 41-52. https://doi.org/10.1016/j.cortex.2019.02.022

Igarashi, K., Oguni, H., Osawa, M., Awaya, Y., Kato, M., Mimura, M., & Kashima, H. (2002). Wisconsin card sorting test in children with temporal lobe epilepsy. *Brain and Development*, *24*(3), 174-178. https://doi.org/https://doi.org/10.1016/S0387-7604(02)00024-4

Ireland, J. E. C. o. t. U. a. (2011). *Epilepsy prevalence, incidence and other statistics*.

Jain, P., Smith, M. L., Speechley, K., Ferro, M., Connolly, M., Ramachandrannair, R., Almubarak, S., Andrade, A., Widjaja, E., & Pepsqol Study, T. (2020). Seizure freedom improves health-related quality of life after epilepsy surgery in children. *Dev Med Child Neurol*, *62*(5), 600-608. https://doi.org/10.1111/dmcn.14390

Jalava, M., Sillanpää, M., Camfield, C., & Camfield, P. (1997). Social adjustment and competence 35 years after onset of childhood epilepsy: a prospective controlled study. *Epilepsia*, *38*(6), 708-715. https://doi.org/10.1111/j.1528-1157.1997.tb01241.x

Jambaqué, I., Dellatolas, G., Fohlen, M., Bulteau, C., Watier, L., Dorfmuller, G., Chiron, C., & 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

Jenkinson, M., Beckmann, C. F., Behrens, T. E., Woolrich, M. W., & Smith, S. M. (2012). FSL. *Neuroimage*, *62*(2), 782-790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Jennum, P., Christensen, J., Ibsen, R., & Kjellberg, J. (2016). Long-term socioeconomic consequences and health care costs of childhood and adolescent-onset epilepsy. *Epilepsia*, *57*(7), 1078-1085. https://doi.org/10.1111/epi.13421

Jones, C., & Reilly, C. (2016). Parental anxiety in childhood epilepsy: A systematic review. *Epilepsia*, *57*(4), 529-537. https://doi.org/10.1111/epi.13326

Jones, J. H., M. (2015). *Quality-of-life outcomes in adults following epilepsy surgery*. Springer International Publishing.

Kahana Levy, N., Segalovsky, J., Benifla, M., & Elkana, O. (2021). Quantitative Meta-Analyses: Lateralization of Memory Functions Before and After Surgery in Children with Temporal Lobe Epilepsy. *Neuropsychol Rev*, *31*(4), 535-568. https://doi.org/10.1007/s11065-020-09470-4

Kaur, N., Nowacki, A. S., Haut, J. S., Klaas, P., Ferguson, L., Lachhwani, D., Bingaman, W., Lineweaver, T. T., & Busch, R. M. (2022). Cognitive outcomes following pediatric epilepsy surgery. *Epilepsy Research*, *180*, 106859. https://doi.org/https://doi.org/10.1016/j.eplepsyres.2022.106859

Keene, D. L., Higgins, M. J., & Ventureyra, E. C. (1997). Outcome and life prospects after surgical management of medically intractable epilepsy in patients under 18 years of age. *Childs Nerv Syst*, *13*(10), 530-535. https://doi.org/10.1007/s003810050132

Kemp, S., Garlovsky, J., Reynders, H., Caswell, H., Baker, G., & Shah, E. (2016). Predicting the psychosocial outcome of epilepsy surgery: A longitudinal perspective on the 'burden of normality'. *Epilepsy & Behavior*, *60*, 149-152. https://doi.org/https://doi.org/10.1016/j.yebeh.2016.04.029

Kennepohl, S., Sziklas, V., Garver, K. E., Wagner, D. D., & Jones-Gotman, M. (2007). Memory and the medial temporal lobe: hemispheric specialization reconsidered. *Neuroimage*, *36*(3), 969-978. https://doi.org/10.1016/j.neuroimage.2007.03.049

Khan, M., Paktiawal, J., Piper, R. J., Chari, A., & Tisdall, M. M. (2021). Intracranial neuromodulation with deep brain stimulation and responsive neurostimulation in

children with drug-resistant epilepsy: a systematic review. *Journal of Neurosurgery: Pediatrics*, 1-10. https://doi.org/10.3171/2021.8.Peds21201

Kim, J. B., Suh, S.-i., & Kim, J. H. (2015). Volumetric and shape analysis of hippocampal subfields in unilateral mesial temporal lobe epilepsy with hippocampal atrophy. *Epilepsy Research*, *117*, 74-81. https://doi.org/https://doi.org/10.1016/j.eplepsyres.2015.09.004

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

Kuehn, S. M., Keene, D. L., Richards, P. M., & Ventureyra, E. C. (2002). Are there changes in intelligence and memory functioning following surgery for the treatment of refractory epilepsy in childhood? *Childs Nerv Syst*, *18*(6-7), 306-310. https://doi.org/10.1007/s00381-002-0599-7

Kwan, P., & Brodie, M. J. (2000). Early identification of refractory epilepsy. *N Engl J Med*, *342*(5), 314-319. https://doi.org/10.1056/nejm200002033420503

Kwon, C.-S., Jacoby, A., Ali, A., Austin, J., Birbeck, G. L., Braga, P., Cross, J. H., de Boer, H., Dua, T., Fernandes, P. T., Fiest, K. M., Goldstein, J., Haut, S., Lorenzetti, D., Mifsud, J., Moshe, S., Parko, K. L., Tripathi, M., Wiebe, S., & Jette, N. (2022). Systematic review of frequency of felt and enacted stigma in epilepsy and determining factors and attitudes toward persons living with epilepsy—Report from the International League Against Epilepsy Task Force on Stigma in Epilepsy [https://doi.org/10.1111/epi.17135]. *Epilepsia*, *63*(3), 573-597. https://doi.org/https://doi.org/10.1111/epi.17135

Lah, S. (2004). Neuropsychological outcome following focal cortical removal for intractable epilepsy in children. *Epilepsy Behav*, *5*(6), 804-817. https://doi.org/10.1016/j.yebeh.2004.08.005

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

Law, N., Benifla, M., Rutka, J., & Smith, M. L. (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

Leal, S. T. F., Santos, M. V., Thome, U., Machado, H. R., Escorsi-Rosset, S., Dos Santos, A. C., Wichert-Ana, L., Leite, J. P., Fernandes, R. M. F., Sakamoto, A. C., & Hamad, A. P. A. (2020). Impact of epilepsy surgery on quality of life and burden of caregivers in children and adolescents. *Epilepsy Behav*, *106*, 106961. https://doi.org/10.1016/j.yebeh.2020.106961

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

Lenck-Santini, P. P., & Scott, R. C. (2015). Mechanisms Responsible for Cognitive Impairment in Epilepsy. *Cold Spring Harb Perspect Med*, *5*(10). https://doi.org/10.1101/cshperspect.a022772

Liang, S., Wang, S., Zhang, J., Ding, C., Zhang, Z., Fu, X., Hu, X., Meng, X., Jiang, H., & Zhang, S. (2012). Long-term outcomes of epilepsy surgery in school-aged children with partial epilepsy. *Pediatr Neurol*, *47*(4), 284-290. https://doi.org/10.1016/j.pediatrneurol.2012.06.014

Liang, S., Zhang, S., Hu, X., Zhang, Z., Fu, X., Jiang, H., & Xiaoman, Y. (2014). Anterior corpus callosotomy in school-aged children with Lennox-Gastaut syndrome: a prospective study. *Eur J Paediatr Neurol*, *18*(6), 670-676. https://doi.org/10.1016/j.ejpn.2014.05.004

Lindsay, J., Ounsted, C., & Richards, P. (1987). Hemispherectomy for childhood epilepsy: a 36-year study. *Dev Med Child Neurol*, *29*(5), 592-600. https://doi.org/10.1111/j.1469-8749.1987.tb08501.x

Liu, A., Thesen, T., Barr, W., Morrison, C., Dugan, P., Wang, X., Meager, M., Doyle, W., Kuzniecky, R., Devinsky, O., & Blackmon, K. (2017). Parahippocampal and Entorhinal Resection Extent Predicts Verbal Memory Decline in an Epilepsy Surgery Cohort. *J Cogn Neurosci*, *29*(5), 869-880. https://doi.org/10.1162/jocn_a_01089

Liu, S., Yu, T., Guan, Y., Zhang, K., Ding, P., Chen, L., Shan, Y., Guo, Q., Liu, Q., Yao, Y., Yang, M., Zhang, S., Lin, Y., Zhao, R., Mao, Z., Zhang, J., Zhang, C., Zhang, R., Yang, Z., . . . Liang, S. (2020). Resective epilepsy surgery in tuberous sclerosis complex: a nationwide multicentre retrospective study from China. *Brain*, *143*(2), 570-581. https://doi.org/10.1093/brain/awz411

Lopez-Gonzalez, M. A., Gonzalez-Martinez, J. A., Jehi, L., Kotagal, P., Warbel, A., & Bingaman, W. (2012). Epilepsy surgery of the temporal lobe in pediatric population: a retrospective analysis. *Neurosurgery*, *70*(3), 684-692. https://doi.org/10.1227/NEU.0b013e318235183d

Loring, D. W., Lowenstein, D. H., Barbaro, N. M., Fureman, B. E., Odenkirchen, J., Jacobs, M. P., Austin, J. K., Dlugos, D. J., French, J. A., Gaillard, W. D., Hermann, B. P., Hesdorffer, D. C., Roper, S. N., Van Cott, A. C., Grinnon, S., & Stout, A. (2011). Common data elements in epilepsy research: development and implementation of the NINDS

epilepsy CDE project. *Epilepsia*, *52*(6), 1186-1191. https://doi.org/10.1111/j.1528-1167.2011.03018.x

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

MacAllister, W. S., & Schaffer, S. G. (2007). Neuropsychological deficits in childhood epilepsy syndromes. *Neuropsychol Rev*, *17*(4), 427-444. https://doi.org/10.1007/s11065-007-9048-4

Maizuliana, H., Usui, N., Terada, K., Kondo, A., & Inoue, Y. (2020). Clinical, semiological, electroencephalographic, and neuropsychological features of "pure" neocortical temporal lobe epilepsy. *Epileptic Disord*, *22*(1), 55-65. https://doi.org/10.1684/epd.2020.1132

Maragkos, G. A., Geropoulos, G., Kechagias, K., Ziogas, I. A., & Mylonas, K. S. (2019). Quality of Life After Epilepsy Surgery in Children: A Systematic Review and Meta-Analysis. *Neurosurgery*, *85*(6), 741-749. https://doi.org/10.1093/neuros/nyy471

Markand, O. N., Salanova, V., Whelihan, E., & Emsley, C. L. (2000). Health-related quality of life outcome in medically refractory epilepsy treated with anterior temporal lobectomy. *Epilepsia*, *41*(6), 749-759. https://doi.org/10.1111/j.1528-1157.2000.tb00238.x

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 & Behavior*, *62*, 189-196. https://doi.org/https://doi.org/10.1016/j.yebeh.2016.06.028

McEwan, M. J., Espie, C. A., Metcalfe, J., Brodie, M. J., & Wilson, M. T. (2004). Quality of life and psychosocial development in adolescents with epilepsy: a qualitative investigation using focus group methods. *Seizure*, *13*(1), 15-31. https://doi.org/https://doi.org/10.1016/S1059-1311(03)00080-3

McLaughlin, R. M., Schraegle, W. A., Nussbaum, N. L., & Titus, J. B. (2018). Parental coping and its role in predicting health-related quality of life in pediatric epilepsy. *Epilepsy Behav*, *87*, 1-6. https://doi.org/10.1016/j.yebeh.2018.08.009

McLellan, A. (2015). *Long-term psychiatric and behavior outcomes in children following epilepsy surgery*. Springer International Publishing.

McNair, D., Lorr, M., & Droppleman, L. (1989). Profile of mood states (POMS).

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

Mendes, T. P., Crespo, C. A., & Austin, J. K. (2017). Family Cohesion, Stigma, and Quality of Life in Dyads of Children With Epilepsy and Their Parents. *J Pediatr Psychol*, *42*(6), 689-699. https://doi.org/10.1093/jpepsy/jsw105

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

Mikati, M. A., Ataya, N., Ferzli, J., Kurdi, R., El-Banna, D., Rahi, A., Shamseddine, A., Sinno, D., & Comair, Y. (2010). Quality of life after surgery for intractable partial epilepsy in children: a cohort study with controls. *Epilepsy Res*, *90*(3), 207-213. https://doi.org/10.1016/j.eplepsyres.2010.05.002

Modi, A. C., King, A. S., Monahan, S. R., Koumoutsos, J. E., Morita, D. A., & Glauser, T. A. (2009). Even a single seizure negatively impacts pediatric health-related quality of life. *Epilepsia*, *50*(9), 2110-2116. https://doi.org/10.1111/j.1528-1167.2009.02149.x

Modi, A. C., Wagner, J., Smith, A. W., Kellermann, T. S., & Michaelis, R. (2017). Implementation of psychological clinical trials in epilepsy: Review and guide. *Epilepsy & Behavior*, *74*, 104-113. https://doi.org/https://doi.org/10.1016/j.yebeh.2017.06.016

Moffat, C., Dorris, L., Connor, L., & Espie, C. A. (2009). The impact of childhood epilepsy on quality of life: A qualitative investigation using focus group methods to obtain children's perspectives on living with epilepsy. *Epilepsy & Behavior*, *14*(1), 179-189. https://doi.org/https://doi.org/10.1016/j.yebeh.2008.09.025

Mohamed, A., Wyllie, E., Ruggieri, P., Kotagal, P., Babb, T., Hilbig, A., Wylie, C., Ying, Z., Staugaitis, S., Najm, I., Bulacio, J., Foldvary, N., Lüders, H., & Bingaman, W. (2001). Temporal lobe epilepsy due to hippocampal sclerosis in pediatric candidates for epilepsy surgery. *Neurology*, *56*(12), 1643-1649. https://doi.org/10.1212/wnl.56.12.1643

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

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/https://doi.org/10.1016/j.spen.2017.10.010

Moreira, H., Carona, C., Silva, N., Frontini, R., Bullinger, M., & Canavarro, M. C. (2013). Psychological and quality of life outcomes in pediatric populations: a parent-child perspective. *J Pediatr*, *163*(5), 1471-1478. https://doi.org/10.1016/j.jpeds.2013.06.028

Morino, M., Uda, T., Naito, K., Yoshimura, M., Ishibashi, K., Goto, T., Ohata, K., & Hara, M. (2006). Comparison of neuropsychological outcomes after selective amygdalohippocampectomy versus anterior temporal lobectomy. *Epilepsy Behav*, *9*(1), 95-100. https://doi.org/10.1016/j.yebeh.2006.04.017

Nickels, K. C., Wong-Kisiel, L. C., Moseley, B. D., & Wirrell, E. C. (2012). Temporal Lobe Epilepsy in Children. *Epilepsy Research and Treatment*, *2012*, 849540. https://doi.org/10.1155/2012/849540

O'Brien, J., Gray, V., & Woolfall, K. (2020). Child and parent experiences of childhood epilepsy surgery and adjustment to life following surgery: A qualitative study. *Seizure*, *83*, 83-88. https://doi.org/10.1016/j.seizure.2020.10.006

Oitment, C., Vriezen, E., & Smith, M. L. (2013). Everyday memory in children after resective epilepsy surgery. *Epilepsy Behav*, *28*(2), 141-146. https://doi.org/10.1016/j.yebeh.2013.04.013

Pérez-García, F., Dorent, R., Rizzi, M., Cardinale, F., Frazzini, V., Navarro, V., Essert, C., Ollivier, I., Vercauteren, T., Sparks, R., Duncan, J. S., & Ourselin, S. (2021). A self-supervised learning strategy for postoperative brain cavity segmentation simulating resections. *International Journal of Computer Assisted Radiology and Surgery*, *16*(10), 1653-1661. https://doi.org/10.1007/s11548-021-02420-2

Pérez-García F., R. R., Alim-Marvasti A., Sparks R., Duncan J.S., Ourselin S. . (2020). EPISURG: MRI dataset for quantitative analysis of resective neurosurgery for refractory epilepsy. University College London. DOI 10.5522/04/9996158.v1

Perry, M. S., & Duchowny, M. (2013). Surgical versus medical treatment for refractory epilepsy: outcomes beyond seizure control. *Epilepsia*, *54*(12), 2060-2070. https://doi.org/10.1111/epi.12427

Phillips, N. L., Widjaja, E., & Smith, M. L. (2019). Impact of resective surgery for pediatric drug-resistant epilepsy on emotional functioning. *Epilepsy Behav*, *101*(Pt A), 106508. https://doi.org/10.1016/j.yebeh.2019.106508

Prados, F. M., Cardoso, J., Burgos, N., Wheeler-Kingshott, C.A.M., Ourselin, S. . (2016). *NiftyWeb: web based platform for image processing on the cloud.* International Society for Magnetic Resonance in Medicine (ISMRM) 24th Scientific Meeting and Exhibition, Singapore.

Puka, K., & Smith, M. L. (2015). Predictors of long-term quality of life after pediatric epilepsy surgery. *Epilepsia*, *56*(6), 873-881. https://doi.org/10.1111/epi.13004

Puka, K., Tavares, T. P., Anderson, K. K., Ferro, M. A., & Speechley, K. N. (2018). A systematic review of quality of life in parents of children with epilepsy. *Epilepsy & Behavior*, *82*, 38-45.

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

Puka, K., Widjaja, E., & Smith, M. L. (2017). The influence of patient, caregiver, and family factors on symptoms of anxiety and depression in children and adolescents with intractable epilepsy. *Epilepsy Behav*, *67*, 45-50. https://doi.org/10.1016/j.yebeh.2016.12.011

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & Neville, B. G. (2014). Neurobehavioral comorbidities in children with active epilepsy: a population-based study. *Pediatrics*, *133*(6), e1586-1593. https://doi.org/10.1542/peds.2013-3787

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & Neville, B. G. (2015). Factors associated with quality of life in active childhood epilepsy: a population-based study. *Eur J Paediatr Neurol*, *19*(3), 308-313. https://doi.org/10.1016/j.ejpn.2014.12.022

Reilly, C., Atkinson, P., Das, K. B., Chin, R. F. C., Aylett, S. E., Burch, V., Gillberg, C., Scott, R. C., & 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/https://doi.org/10.1111/epi.12826

Reilly, C., Baldeweg, T., Stewart, N., Wadhwani, S., Jones, C., Helen Cross, J., & Heyman, I. (2019). Do behavior and emotions improve after pediatric epilepsy surgery? A systematic review. *Epilepsia*, *60*(5), 885-897. https://doi.org/10.1111/epi.14737

Ronen, G. M., Streiner, D. L., & Rosenbaum, P. (2003). Health-related quality of life in childhood epilepsy: Moving beyond 'seizure control with minimal adverse effects'. *Health and Quality of Life Outcomes*, *1*(1), 36. https://doi.org/10.1186/1477-7525-1-36

Roth, J., Olasunkanmi, A., MacAllister, W. S., Weil, E., Uy, C. C., Devinsky, O., & Weiner, H. L. (2011). Quality of life following epilepsy surgery for children with tuberous sclerosis complex. *Epilepsy Behav*, *20*(3), 561-565. https://doi.org/10.1016/j.yebeh.2010.11.003

Rzezak, P., Fuentes, D., Guimarães, C. A., Thome-Souza, S., Kuczynski, E., Li, L. M., Franzon, R. C., Leite, C. C., Guerreiro, M., & Valente, K. D. (2007). Frontal lobe dysfunction in children with temporal lobe epilepsy. *Pediatr Neurol*, *37*(3), 176-185. https://doi.org/10.1016/j.pediatrneurol.2007.05.009

Rzezak, P., Guimarães, C. A., Guerreiro, M. M., & Valente, K. D. (2017). The impact of intelligence on memory and executive functions of children with temporal lobe epilepsy: Methodological concerns with clinical relevance. *Eur J Paediatr Neurol*, *21*(3), 500-506. https://doi.org/10.1016/j.ejpn.2016.12.010

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

Sabaz, M., Cairns, D. R., Lawson, J. A., Bleasel, A. F., & Bye, A. M. (2001). The health-related quality of life of children with refractory epilepsy: a comparison of those with and without intellectual disability. *Epilepsia*, *42*(5), 621-628. https://doi.org/10.1046/j.1528-1157.2001.25200.x

Sabaz, M., Lawson, J. A., Cairns, D. R., Duchowny, M. S., Resnick, T. J., Dean, P. M., Bleasel, A. F., & Bye, A. M. (2006). The impact of epilepsy surgery on quality of life in children. *Neurology*, *66*(4), 557-561. https://doi.org/10.1212/01.wnl.0000197788.38783.09

Saghafi, S., Ferguson, L., Hogue, O., Gales, J. M., Prayson, R., & Busch, R. M. (2018). Histopathologic subtype of hippocampal sclerosis and episodic memory performance before and after temporal lobectomy for epilepsy. *Epilepsia*, *59*(4), 825-833. https://doi.org/10.1111/epi.14036

Saling, M. M. (2009). Verbal memory in mesial temporal lobe epilepsy: beyond material specificity. *Brain*, *132*(Pt 3), 570-582. https://doi.org/10.1093/brain/awp012

Schouten, A., Oostrom, K. J., Pestman, W. R., Peters, A. C., & Jennekens-Schinkel, A. (2002). Learning and memory of school children with epilepsy: a prospective controlled longitudinal study. *Dev Med Child Neurol*, *44*(12), 803-811. https://doi.org/10.1017/s0012162201002973

Scott, A. J., Sharpe, L., Loomes, M., & Gandy, M. (2020). Systematic Review and Meta-Analysis of Anxiety and Depression in Youth With Epilepsy. *J Pediatr Psychol*, *45*(2), 133-144. https://doi.org/10.1093/jpepsy/jsz099

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

Sillanpää, M., Haataja, L., & Shinnar, S. (2004). Perceived impact of childhood-onset epilepsy on quality of life as an adult. *Epilepsia*, *45*(8), 971-977. https://doi.org/10.1111/j.0013-9580.2004.44203.x

Sillanpää, M., Jalava, M., Kaleva, O., & Shinnar, S. (1998). Long-term prognosis of seizures with onset in childhood. *N Engl J Med*, *338*(24), 1715-1722. https://doi.org/10.1056/nejm199806113382402

Sillanpää, M., & Schmidt, D. (2006). Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. *Brain*, *129*(3), 617-624. https://doi.org/10.1093/brain/awh726

Simons, J. S., & Spiers, H. J. (2003). Prefrontal and medial temporal lobe interactions in long-term memory. *Nat Rev Neurosci*, *4*(8), 637-648. https://doi.org/10.1038/nrn1178

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., Meierotto, E., Gaiottino, J., Vargha-Khadem, F., & Baldeweg, T. (2015). Temporal lobe surgery in

childhood and neuroanatomical predictors of long-term declarative memory outcome. *Brain*, *138*(Pt 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., Shah, E., Harkness, W., Vargha-Khadem, F., & 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

Skirrow, C. B., T. (2015). *Educational and employment outcomes following epilepsy surgery in children*. Springer International Publishing.

Smith, M. L. (2016). Rethinking cognition and behavior in the new classification for childhood epilepsy: Examples from frontal lobe and temporal lobe epilepsies. *Epilepsy Behav*, *64*(Pt B), 313-317. https://doi.org/10.1016/j.yebeh.2016.04.050

Smith, M. L., Elliott, I. M., & 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

Smith, M. L., & Lah, S. (2011). One declarative memory system or two? The relationship between episodic and semantic memory in children with temporal lobe epilepsy. *Neuropsychology*, *25*(5), 634-644. https://doi.org/10.1037/a0023770

Sone, D., Ahmad, M., Thompson, P. J., Baxendale, S., Vos, S. B., Xiao, F., de Tisi, J., McEvoy, A. W., Miserocchi, A., Duncan, J. S., Koepp, M. J., & Galovic, M. (2022). Optimal Surgical Extent for Memory and Seizure Outcome in Temporal Lobe Epilepsy. *Annals of Neurology*, *91*(1), 131-144. https://doi.org/https://doi.org/10.1002/ana.26266

Speechley, K. (2013). *What if quality of life better expressed outcomes for epilepsy?* . John Libbey Eurotext.

Speechley, K. N., Ferro, M. A., Camfield, C. S., Huang, W., Levin, S. D., Smith, M. L., Wiebe, S., & Zou, G. (2012). Quality of life in children with new-onset epilepsy: a 2-year prospective cohort study. *Neurology*, *79*(15), 1548-1555. https://doi.org/10.1212/WNL.0b013e31826e25aa

Spencer, S. S., Berg, A. T., Vickrey, B. G., Sperling, M. R., Bazil, C. W., Haut, S., Langfitt, J. T., Walczak, T. S., & Devinsky, O. (2007). Health-related quality of life over time since resective epilepsy surgery. *Ann Neurol*, *62*(4), 327-334. https://doi.org/10.1002/ana.21131

Stewart, E., & Smith, M. L. (2019). Visuospatial learning and memory in children pre- and posttemporal lobe resection: Patterns of localization and lateralization. *Epilepsy Behav*, *94*, 189-194. https://doi.org/10.1016/j.yebeh.2019.03.031

Stomberg, M., Bien, C. G., Kalbhenn, T., Polster, T., & May, T. W. (2021). Epilepsy associated with tuberous sclerosis complex in childhood: Long-term outcome in children after epilepsy surgery and children non-eligible for epilepsy surgery. *Epilepsy Behav*, *122*, 108210. https://doi.org/10.1016/j.yebeh.2021.108210

Téllez-Zenteno, J. F., Dhar, R., & Wiebe, S. (2005). Long-term seizure outcomes following epilepsy surgery: a systematic review and meta-analysis. *Brain*, *128*(Pt 5), 1188-1198. https://doi.org/10.1093/brain/awh449

Theodore, W. H., & Gaillard, W. D. (2002). Neuroimaging and the progression of epilepsy. *Prog Brain Res*, *135*, 305-313. https://doi.org/10.1016/s0079-6123(02)35028-3

Titus, J. B., Lee, A., Kasasbeh, A., Thio, L. L., Stephenson, J., Steger-May, K., Limbrick, D. D., Jr., & Smyth, M. D. (2013). Health-related quality of life before and after pediatric epilepsy surgery: the influence of seizure outcome on changes in physical functioning and

social functioning. *Epilepsy Behav*, *27*(3), 477-483. https://doi.org/10.1016/j.yebeh.2013.03.003

Tulving, E., & Markowitsch, H. J. (1998). Episodic and declarative memory: role of the hippocampus. *Hippocampus*, *8*(3), 198-204. https://doi.org/10.1002/(sici)1098-1063(1998)8:3<198::Aid-hipo2>3.0.Co;2-g

Ulate-Campos, A., & Fernández, I. S. (2017). Cognitive and Behavioral Comorbidities: An Unwanted Effect of Antiepileptic Drugs in Children. *Semin Pediatr Neurol*, *24*(4), 320-330. https://doi.org/10.1016/j.spen.2017.10.011

van Empelen, R., Jennekens-Schinkel, A., van Rijen, P. C., Helders, P. J., & van Nieuwenhuizen, O. (2005). Health-related quality of life and self-perceived competence of children assessed before and up to two years after epilepsy surgery. *Epilepsia*, *46*(2), 258-271. https://doi.org/10.1111/j.0013-9580.2005.27304.x

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

Vaz, S. A. (2004). Nonverbal memory functioning following right anterior temporal lobectomy: a meta-analytic review. *Seizure*, *13*(7), 446-452. https://doi.org/10.1016/j.seizure.2003.12.004

Weiss-Croft, L. J., & Baldeweg, T. (2015). Maturation of language networks in children: A systematic review of 22years of functional MRI. *Neuroimage*, *123*, 269-281. https://doi.org/10.1016/j.neuroimage.2015.07.046

Weschler, D. (1991). *Wechsler Intelligence Scale for Children- Third Edition (WISC-III).* Pearson Assessment.

Weschler, D. (1997a). *Weschler Adult Intelligence Scale (3rd ed.)*. The Psychological Corporation.

Weschler, D. (1997b). *Weschler Memory Scale-Third Edition (WMS-III).* Pearson Assessment.

Weschler, D. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI).* Pearson Assessment.

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

Weschler, D. (2003). *Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV).* Pearson Assessment.

Weschler, D. (2008). *Wechsler Adult Intelligence Scale (4th ed.)*. Pearson Assessment.

Weschler, D. (2009). *Wechsler Memory Scale-Fourth edition (WMS-IV)*. Pearson Assessment.

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

Weschler, D. (2014). *Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V).* Pearson Assessment.

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*(6). https://doi.org/10.1002/14651858.CD010541.pub3

Whelan, C. D., Altmann, A., Botía, J. A., Jahanshad, N., Hibar, D. P., Absil, J., Alhusaini, S., Alvim, M. K. M., Auvinen, P., Bartolini, E., Bergo, F. P. G., Bernardes, T., Blackmon, K., Braga, B., Caligiuri, M. E., Calvo, A., Carr, S. J., Chen, J., Chen, S., . . . Sisodiya, S. M. (2018). Structural brain abnormalities in the common epilepsies assessed in a worldwide ENIGMA study. *Brain*, *141*(2), 391-408. https://doi.org/10.1093/brain/awx341

Wieser, H. G., Blume, W. T., Fish, D., Goldensohn, E., Hufnagel, A., King, D., Sperling, M. R., Lüders, H., & Pedley, T. A. (2001). ILAE Commission Report. Proposal for a new classification of outcome with respect to epileptic seizures following epilepsy surgery. *Epilepsia*, *42*(2), 282-286.

Willment, K., & Golby, A. (2013). Hemispheric Lateralization Interrupted: Material-Specific Memory Deficits in Temporal Lobe Epilepsy [Mini Review]. *Frontiers in Human Neuroscience*, *7*. https://doi.org/10.3389/fnhum.2013.00546

Wilson, S. J., Bladin, P. F., Saling, M. M., McIntosh, A. M., & Lawrence, J. A. (2001). The longitudinal course of adjustment after seizure surgery. *Seizure*, *10*(3), 165-172. https://doi.org/10.1053/seiz.2000.0491

Wirrell, E. C. (2013). Predicting pharmacoresistance in pediatric epilepsy. *Epilepsia*, *54*(s2), 19-22. https://doi.org/https://doi.org/10.1111/epi.12179

Wirrell, E. C., Grossardt, B. R., Wong-Kisiel, L. C., & Nickels, K. C. (2011). Incidence and classification of new-onset epilepsy and epilepsy syndromes in children in Olmsted County, Minnesota from 1980 to 2004: a population-based study. *Epilepsy Res*, *95*(1-2), 110-118. https://doi.org/10.1016/j.eplepsyres.2011.03.009

Witt, J. A., Coras, R., Becker, A. J., Elger, C. E., Blümcke, I., & Helmstaedter, C. (2019). When does conscious memory become dependent on the hippocampus? The role of memory load and the differential relevance of left hippocampal integrity for short- and long-term aspects of verbal memory performance. *Brain Struct Funct*, *224*(4), 1599-1607. https://doi.org/10.1007/s00429-019-01857-1

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

World Health Organization (2012) The World Health Organization Quality of life (WHOQOL) , Retrieved 3rd of June from https://www.who.int/publications/i/item/WHO-HIS-HSI-Rev.2012.03

Yang, T. F., Wong, T. T., Kwan, S. Y., Chang, K. P., Lee, Y. C., & Hsu, T. C. (1996). Quality of life and life satisfaction in families after a child has undergone corpus callostomy. *Epilepsia*, *37*(1), 76-80. https://doi.org/10.1111/j.1528-1157.1996.tb00515.x

Yushkevich, P. A., Piven, J., Hazlett, H. C., Smith, R. G., Ho, S., Gee, J. C., & Gerig, G. (2006). User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage*, *31*(3), 1116-1128. https://doi.org/10.1016/j.neuroimage.2006.01.015

Zupanc, M. L., Rubio, E. J., Werner, R. R., Schwabe, M. J., Mueller, W. M., Lew, S. M., Marcuccilli, C. J., O'Connor, S. E., Chico, M. S., Eggener, K. A., & Hecox, K. E. (2010). Epilepsy surgery outcomes: quality of life and seizure control. *Pediatr Neurol*, *42*(1), 12-20. https://doi.org/10.1016/j.pediatrneurol.2009.07.018

Part 3: Critical appraisal

Critical appraisal

This appraisal summarises the learning journey that culminated with the drafting of the current thesis, outlining the main challenges I encountered during this process and dwelling on cultural considerations borne out of my personal experience of having to "re-train" from basic circuit neuroscientist to clinical paediatric neuropsychological researcher, in a short span of time (as per doctoral constraints). As such, the critical appraisal will cover, but will not be limited to, the discussion of issues that that are linked to the drafting of the systematic review and empirical papers and which have arisen directly prior to and during the data gathering, analysis and interpretation processes. The appraisal will also include personal reflections of my experiences during the one-year paediatric neuropsychology placement which constituted one third of my DClinPsy training experience, and which has been critical in facilitating the development of the clinical and conceptual skills required to conduct the research reported in the empirical paper.

The structure of this appraisal is somewhat chronological, outlining, at first, "the baseline" – the starting point, in terms of my knowledge and skills at the point of engagement with paediatric neuropsychology – it will then move onto the discovery of clinical neuropsychology practises in a large tertiary NHS centre, and lastly, will describe the processes which resulted in the experimental work that I conducted and whose results have been reported in the empirical paper section of this thesis.

The "baseline"

I am a biologist by training, who has a long-standing interest in the emergence of structure and order via self-organising processes. This early focus naturally led me to the study of developmental biology, with a specific emphasis on the molecular and structural processes responsible for the embryonic development of the mammalian nervous system. A chance and transformational encounter with the phenomenon of "place cells" at the beginning of my doctorate studies in neuroscience at UCL, "side-tracked" me and led to many years of study of this baffling phenomenon. The existence of single neurons in the mammalian (and non-mammalian) hippocampus which seem to encode the current location of the organism is still largely mysterious. My ingrained bias towards the study of origins and development resulted in me pursuing the question of how place signals arise via the study of their emergence during post-natal life. All this work has been and continues to be conducted in rodents. As a circuit neuroscientist, I have had many years of experience in conducting in vivo neural recordings of the hippocampus and neighbouring brain areas, with the aim to better understand the neural mechanisms underpinning its role in spatial navigation and declarative memory.

Before starting the DClinPsy I had, of course, kept abreast of the main themes in the cognitive neuroscience of spatial navigation and memory and in particular its developmental aspects – themes largely confined to the study of healthy children and adults. I was, however, largely ignorant of clinical paediatric neuropsychology practice and research. This all had to change (and rather quickly!) when I started my one-year long placement in the paediatric neuropsychology department of a large tertiary hospital.

The steepest of learning curves – paediatric neuropsychology training

I started my year-long placement in a paediatric neuropsychology service in a large tertiary hospital in March 2021. At the time the UK was just coming out of the second Covid-19 wave and associated national lockdown (the "alpha" wave). The paediatric neuropsychology service was largely working remotely, conducting tele-neuropsychological assessments – something which inevitably complicated my neuropsychology training. It was only progressively that we were allowed to conduct in person appointments.

The neuropsychology team I joined includes a dedicated epilepsy surgery pathway and therefore I had plenty of opportunities to meet and assess young patients both before and after they received resective epilepsy surgery. I had the opportunity to observe and contribute to MDT discussions during which decisions for suitability to surgery are taken.

Resective surgery for paediatric medically resistant epilepsy

The first impact with clinical paediatric epilepsy, and in particular surgical treatment, has been rather disconcerting. When I started the placement, I was not aware of what, to me, sounded like rather radical surgical approaches (hemispherectomies, lobectomies, etc) where large brain areas (up to a whole hemisphere!) would be functionally disconnected (or wholly resected), in order to provide the best chance of obtaining post-surgical seizure freedom.

It is very likely that what I felt when confronted with the knowledge that, inevitably, healthy brain tissue would be removed during the surgical procedure - bears some similarities with the shock that some families will experience when first counselled about epilepsy surgery. It is indeed still the case that, notwithstanding its excellent safety record and very high success rate

(measured in terms of seizure outcome), resective surgery for epilepsy counts amongst the most under-utilised medical procedures (Engel, 2013).

It became quickly clear to me that research in surgical outcomes in paediatric epilepsy populations carries special value in informing clinical and personal decisions around the suitability of resective surgery in the treatment of medically resistant epilepsy. It is for this reason that I chose to become involved in the research project which ultimately culminated in the drafting of both the systematic review paper and the empirical paper in this thesis.

What kind of outcome?

Surgical success has mainly been thought of in terms of its ability to confer seizure freedom. This appears to be quite appropriate in terms of medical management of epilepsy – as seizure status is easily quantifiable and continuing seizures can be life threatening (Shankar et al., 2017), and have been associated with both cognitive and academic underachievement, and lower quality of life (Baldeweg, 2015; Elliott et al., 2005; Fastenau et al., 2008).

However, an emerging literature on surgical outcomes in terms of overall quality of life (see, e.g. systematic review, this thesis) paints a complex picture as to whether seizure freedom should be the main (or only) parameter against which to measure surgical success.

The choice of which outcome measures should be used to measure epilepsy surgery success, and therefore inform clinical decision making is particularly fraught with complexity in the context of paediatric interventions. Clinical assessment of children who are candidates for

resective epilepsy surgery has made me acutely aware of how difficult clinical decision making can be in this area.

There are several factors contributing to the complexity of assessing epilepsy surgery outcomes in children which I will summarise here under two broad categories:

- uncertainty related to the complex nature of developmental processes.
- difficulties in identifying who is the target of the intervention and who is affected by it (who speaks on behalf of whom? Is the outcome to be thought of in relation to the child/their family?).

Complex nature of developmental processes

It has taken several decades to start thinking of developing organisms as quite distinct from small adults – this is particularly true of clinical neuropsychology – where the main assessment tools have their origins in modification of measures used to assess adults.

Incontrovertible clinical evidence demonstrates that early brain damage (from infancy to childhood) results in patterns of cognitive impairments that are qualitatively different from those resulting from focal lesions in the adult brain. Focal damage to brain circuits in adulthood results in selective cognitive impairments (e.g., amnesia, aphasia, agnosia). The same damage, when occurred during development, often results in less selective cognitive impairments (e.g., dysphasia, dyscalculia, and dyslexia). The earlier the damage, the most likely this will result in pervasive cognitive impairments affecting many if not all cognitive domains (leading to learning disability).

This evidence has shaped our views of how cognition emerges during development in humans. Early theories of the emergence of brain organisation and function during development can be split in two main classes: those advocating early specialisation (e.g., Witelson & Pallie, 1973) and those instead highlighting equipotentiality and plasticity of developing circuits (Cacucci & Vargha-Khadem, 2019). A "middle ground" view gradually emerged (and is still evolving). This view emphases the interplay between relatively fixed genetic processes and circuit plasticity ultimately resulting in progressive cognitive specialisation. According to this view, brain specialisation and lateralisation of function occur progressively during development (e.g., language is supported by a largely bilateral network which progressively is refined and localises to the dominant hemisphere in adulthood – (Olulade et al., 2020). If damage is sustained during late developmental phases (e.g., adolescence) the resulting pattern of cognitive impairments is similar to that observed in adults. If damage instead occurs during early development (infancy, childhood) compensatory mechanisms are thought to be set in train, such that reorganisation of function can be accommodated by circuits that have not been affected by the damage. Whilst mechanistic knowledge of reorganisation processes is largely unknown, as are the opportunities and constraints that govern it, some broad principles have been derived from clinical and experimental observations.

Clinical evidence shows that reorganisation can carry a price. Visuo-spatial function in children who have reorganised language to the originally non-dominant hemisphere is often less efficient than in healthy children. Lower visuo-spatial function is thought to result from language processing "crowding out" functions that would be normally subserved by non-dominant hemisphere circuits. Another well described and established phenomenon is the one referred to as "growing into deficits". Even in the case of static damage (damage which is not thought to evolve during time), cognitive impairments in children can often become manifest years after the original insult, as the timing of emergence of deficits depends also on the timing

of emergence of cognitive skills (e.g., commonly executive function deficits become evident around adolescence, and damage to frontal brain areas is often silent until these functions would naturally emerge at around this age).

The picture is even more complex when pathology, as in the case of epilepsy, is not easily localisable in space or time. Even when overt pathology is confined to discrete brain areas, epilepsy is best thought of as network disorder, with often bilateral circuit dysfunction being observed (e.g., via functional imaging analyses; Cormack et al., 2005; Hermann et al., 2021). It is also clear that epilepsy evolves during time, as demonstrated, for example, by evolution in semiology and physiological alterations observed (via EEG monitoring).

The use of anti-epileptic medication is an added factor thought to have an impact on brain development (Boshuisen et al., 2015; Ijff & Aldenkamp, 2013).

Taken together age at onset, duration of epilepsy, aetiology, use of anti-epileptic medication, and many other factors are thought to contribute (non-linearly) to cognitive outcome in paediatric epilepsy. If one adds to these sources of variability: the existence of several surgical approaches, the effect of locus of original epileptogenic focus, psycho-social factors - the complexity of the task of trying to predict paediatric epilepsy surgical outcomes appears staggering.

It is this complexity that I have most struggled with, in my transition from basic circuit neuroscience, where experimental design is prospective and the experimenter has (relative) control on the variables of interest, to clinical neuroscience, where, for this project, I was constrained to work within a retrospective design – with clinical data that can never be, for practical reasons, complete, and where sample sizes are often too small in comparison to the number of variables one needs to take into account.

The process of becoming “encultured” into the traditions and modus operandi of clinical neuropsychology research was facilitated by my frequent discussions with the rest of the team

including neuropsychology clinicians, paediatric cognitive scientists, neurologists, neurosurgeons, radiologists, etc.

Choice of outcome measures

Another important set of considerations that arose during the process of choosing the research focus for both the systematic review and the empirical papers relates to the issue of choice of outcome variables.

The main outcome measure used in the literature of paediatric epilepsy surgery is seizure freedom, the second most common set of outcome measures are those indexing cognitive function (mainly IQ) and academic achievement. Historically, it is clear that the use of mainly quantitative approaches to the study of surgical epilepsy outcomes has privileged the choice of easily operationalised variables.

It is only recently that a more "holistic" approach to the conceptualisation of surgical outcomes is emerging, with the inclusion of outcome measures that consider psycho-social variables and measures which attempt to capture overall well-being (e.g., quality of life measures).

The historical emphasis on seizure outcome is clearly informed by the medical context within which surgical interventions are performed, and by the risk to life that seizures carry. The emphasis on cognitive and academic outcomes reflects both deeply ingrained western biases attributing great value to intellectual function and the consequent emphasis that neuroscience has placed on the study of cognitive functions (as opposed to, for instance, affective functions). The focus on cognitive outcomes also reflects the expectations of medical professionals that, in paediatric populations, cognitive impairments could be rescued upon cessation of seizure

activity – expectations resting on the assumption that developing brains have enhanced plasticity potential (see above). Accumulating evidence, however, seems to suggest that, overall, post-surgical cognitive recovery, even when present, is, overall, relatively modest. It is for this reason that I feel a shift of emphasis from cognitive to quality of life/wellbeing outcomes has the potential to improve clinical decision making and the experience of families and children affected by paediatric epilepsy.

It is also important to consider that epilepsy surgery is gradually being recommended at earlier ages (e.g., Engel, 2019), on the basis of an emerging literature demonstrating that longer epilepsy duration before surgery is associated with worse long-term cognitive outcomes (Kadish et al., 2019; Ramantani & Reuner, 2018) and prospects of achieving seizure freedom (Bjellvi et al., 2019).

It is therefore more often the families of the young patient rather than the patient themselves, who are tasked with making the final decision about epilepsy surgery. Moreover, whilst most patients will be formally assessed on selective cognitive domains, (via the use of specific neuropsychological testing), parents/carers and teachers are those who will more often report on broader behavioural/cognitive and quality of life of the young patients. It is therefore important to note which voice is being heard when measuring surgical outcomes.

There is a growing appreciation of these issues in the field of paediatric neuropsychology, with more and more quantitative research studies on paediatric epilepsy surgical outcomes offering, for example, analyses of agreement between parental and children's ratings. In this context it is notable that recent initiatives aimed at designing new instruments to evaluate epilepsy surgery outcomes have included the active involvement of children and families (e.g. Crudgington et al., 2019).

Conclusions

Coming to clinical neuropsychology as a total outsider has perhaps made it easier for me to notice some of the biases which have crept in the choice of clinical outcomes in paediatric epilepsy surgery. However, my basic (quantitative) scientist training has hampered my efforts to grapple with the extra complexity of "holistic" and qualitative approaches. It is for these reasons, perhaps, that I decided to focus my systematic review paper on studying surgical outcomes from the perspective of quality of life (a more "holistic" construct) whilst retreating in the (relatively) safer quantitative approach of studying brain-to-cognition relationships for the empirical paper.

This journey has been full of surprises and, at times, rather treacherous. The main lesson I learned is that resilience, determination, humility, and cooperation are the values we should strive for in both scientific and clinical practice.

Bibliography

Baldeweg, T. S., C. (2015). Long-Term Cognitive Outcomes after Epilepsy Surgery in Children. In S. I. Publishing (Ed.), *Long-Term Outcomes of Epilepsy Surgery in Adults and Children* (pp. 85-101).

Bjellvi, J., Olsson, I., Malmgren, K., & Wilbe Ramsay, K. (2019). Epilepsy duration and seizure outcome in epilepsy surgery. *Neurology*, *93*(2), e159. https://doi.org/10.1212/WNL.0000000000007753

Boshuisen, K., van Schooneveld, M. M., Uiterwaal, C. S., Cross, J. H., Harrison, S., Polster, T., Daehn, M., Djimjadi, S., Yalnizoglu, D., Turanli, G., Sassen, R., Hoppe, C., Kuczaty, S., Barba, C., Kahane, P., Schubert-Bast, S., Reuner, G., Bast, T., Strobl, K., . . . Braun, K. P. (2015). Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. *Ann Neurol*, *78*(1), 104-114. https://doi.org/10.1002/ana.24427

Cacucci, F., & Vargha-Khadem, F. (2019). Contributions of nonhuman primate research to understanding the consequences of human brain injury during development. *Proc Natl Acad Sci U S A*, *116*(52), 26204-26209. https://doi.org/10.1073/pnas.1912952116

Cormack, F., Gadian, D. G., Vargha-Khadem, F., Cross, J. H., Connelly, A., & Baldeweg, T. (2005). Extra-hippocampal grey matter density abnormalities in paediatric mesial temporal sclerosis. *Neuroimage*, *27*(3), 635-643. https://doi.org/10.1016/j.neuroimage.2005.05.023

Crudgington, H., Rogers, M., Bray, L., Carter, B., Currier, J., Dunkley, C., Gibbon, F. M., Hughes, D., Lyle, S., Roberts, D., Tudur Smith, C., Gringras, P., Pal, D. K., & Morris, C. (2019). Core Health Outcomes in Childhood Epilepsy (CHOICE): Development of a core

outcome set using systematic review methods and a Delphi survey consensus. *Epilepsia*, *60*(5), 857-871. https://doi.org/https://doi.org/10.1111/epi.14735

Elliott, I. M., Lach, L., & Smith, M. L. (2005). I just want to be normal: a qualitative study exploring how children and adolescents view the impact of intractable epilepsy on their quality of life. *Epilepsy Behav*, *7*(4), 664-678. https://doi.org/10.1016/j.yebeh.2005.07.004

Engel, J. (2013). Why is There Still Doubt to Cut it Out?: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., Jr. (2019). Evolution of concepts in epilepsy surgery. *Epileptic Disord*, *21*(5), 391-409. https://doi.org/10.1684/epd.2019.1091

Fastenau, P. S., Jianzhao, S., Dunn, D. W., & Austin, J. K. (2008). Academic underachievement among children with epilepsy: proportion exceeding psychometric criteria for learning disability and associated risk factors. *J Learn Disabil*, *41*(3), 195-207. https://doi.org/10.1177/0022219408317548

Hermann, B. P., Struck, A. F., Busch, R. M., Reyes, A., Kaestner, E., & McDonald, C. R. (2021). Neurobehavioural comorbidities of epilepsy: towards a network-based precision taxonomy. *Nature Reviews Neurology*, *17*(12), 731-746. https://doi.org/10.1038/s41582-021-00555-z

Ijff, D. M., & Aldenkamp, A. P. (2013). Chapter 73 - Cognitive side-effects of antiepileptic drugs in children. In O. Dulac, M. Lassonde, & H. B. Sarnat (Eds.), *Handbook of Clinical Neurology* (Vol. 111, pp. 707-718). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-444-52891-9.00073-7

Kadish, N. E., Bast, T., Reuner, G., Wagner, K., Mayer, H., Schubert-Bast, S., Wiegand, G., Strobl, K., Brandt, A., Korinthenberg, R., van Velthoven, V., Schulze-Bonhage, A.,

Zentner, J., & Ramantani, G. (2019). Epilepsy Surgery in the First 3 Years of Life: Predictors of Seizure Freedom and Cognitive Development. *Neurosurgery*, *84*(6), E368-E377. https://doi.org/10.1093/neuros/nyy376

Olulade, O. A., Seydell-Greenwald, A., Chambers, C. E., Turkeltaub, P. E., Dromerick, A. W., Berl, M. M., Gaillard, W. D., & Newport, E. L. (2020). The neural basis of language development: Changes in lateralization over age. *Proceedings of the National Academy of Sciences*, *117*(38), 23477-23483. https://doi.org/doi:10.1073/pnas.1905590117

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

Shankar, R., Donner, E. J., McLean, B., Nashef, L., & Tomson, T. (2017). Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know. *Epileptic Disord*, *19*(1), 1-9. https://doi.org/10.1684/epd.2017.0891

Witelson, S. F., & Pallie, W. (1973). Left hemisphere specialization for language in the newborn. Neuroanatomical evidence of asymmetry. *Brain*, *96*(3), 641-646. https://doi.org/10.1093/brain/96.3.641

Appendix

Table 1. List of studies included in literature review paper.

Authors	Study design	Where	N participants (active group)	Inclusion of pharmacologically treated control	Follow up duration (mean/range or SD)	Surgery type/etiology	QOL and other measures	Rater	Seizure outcome (% participants Engel I outcome)	Main findings*	Factors significantly associated with outcome	Factors not significantly associated with outcome
Gilliam et al 1997	retrospective, cross-sectional	University of Alabama at Birmingham or Cleveland Clinic Epilepsy centers, Alabama, US.	33	no	2.7 years (7months-6years)	TE + ExTE (CC excluded)	CHQ	P	67	6 of 12 subscales lower in surgical than in age matched control participants in the domains of physical function, general health and self-esteem		
Ciliberto et al 2012	retrospective, cross-sectional	Washington University St Louis	7	no	3.64 years (2–5.3 years)	HE	QOLCE, IQ	P	71	All patients enjoyed decrease in seizure frequency and subjective increase in QOL after surgery. 2 out of 7 individuals had increased adaptive and social functioning.		
Keene et al 1997	retrospective, cross-sectional	Children's Hospital of Eastern Ontario, Canada	64	no	>2 years (7.6+3.8 years)	TE + ExTE +HE	QOLIE-31	P	55	Quality-of-life measures paralleled the improvements in seizures control, being highest in Engel I, outcome group and lowest in Engel IV outcome groups	Seizure freedom	
Elliott et al 2012	retrospective, cross-sectional	Hospital for Sick Children (Toronto) or the Children's Hospital of Eastern Ontario (Ottawa)	69	no	2 to 22 years (mean 8.83 years, standard deviation [SD] 4.99)	TE+ExTE	QOLIE-31, SHE, POMS	P	55.1	After accounting for mood, sex, and number of antiepileptic drugs, the seizure-free group reported better cognitive and physical function and overall QOL, experienced less seizure worry, and had better self-perception. Mood was the most consistently predictive covariate, and was independently predictive of many aspects of QOL	Seizure Freedom, mood	
Moritake et al 2009	retrospective, cross-sectional	Kyoto University	47	no	12.4 (SD 3.7) years	Lesionectomy	Unstandardised Questionnaire	C	n/a	The mean increases in QOL score points were significantly higher in the late childhood onset group than those in the early childhood onset group and were also significantly higherin the temporal resection group and extratemporal resection of non-dysplastic cortical pathology group than in the extratemporal resection of dysplastic cortical pathology group. Postoperative QOL improvement and occupational status of patients depended on the completeness of seizure control.	Location of lesion and nature of pathology. Age of onset of epilepsy. Seizure outcome.	
Roth et al 2011	retrospective, cross-sectional	The Comprehensive Epilepsy Center, NYU Langone Medical Center, New York University School of Medicine, New York, NY, USA	39	no	3.9 years	Multistage resections (tuberous sclerosis)	Unstandardised semi-structured interview	P	77	46-85% had at least moderate improvement in QOL.	Significant correlation between QOL and Engel outcome class.	
Hum et al 2010	qualitative study, retrospective, cross-sectional	Hospital for Sick Children, Toronto, Canada	27	no	2 years	Mixed	Semi-structured open-ended interview	C	48	Many of the seizure-free participants reported greater independence following surgery. However, most participants, irrespective of seizure status, continued to report some problems with peer relations and isolation.	Seizure freedom	
Chen et al 2014	retrospective, longitudinal	Taipei Veterans General Hospital	30	no	mean duration of their follow-up was 21.5 months (range, 4 to 97)	Mixed	CHQ-PF50, ABAS-II, IQ/DQ	P	70	The best QOL outcomes were observed in patients who had early seizure onset, no significant cognitive function deficit and early surgical intervention with complete resection and less than 2-year seizure duration. (Note: these conclusions are descriptive - no statistical analyses performed).	Seizure onset, age at surgery, extent of resection, IQ	

Reilly et al 2020	retrospective, longitudinal	Sahlgrenska University Hospital, Gotheburg, Germany	107	no	2 years	Mixed	ELDQOL/ unstandardised questionnaire behaviour and emotional functioning	P	48	Significant improvement in QOL at follow up. This was also true in children with multiple disabilities. Seizure freedom associated with both improvements in QOL and behaviour. Reduction in AED contributed to reduced behavioural difficulties.	Lower baseline QOL scores, seizure free status, improvement in behaviour	AED load (this only contributed to behaviour improvement - not QOL change), Demographic variables: gender; epilepsy variables: age at surgery, age at onset,change in IQ, baseline IQ, surgery type/location
van Empelen et al 2005	prospective, longitudinal	Wilhelmina Children's Hospital, Utrecht, Netherlands	21	no	6 months, 1-2 years	Mixed	HAY, SSP-C/SSP-A	P&C	72 (at 2-year FU)	At 6 months improvement in the frequency of activities, more frequent positive emotions.2 years after surgery children perceived themselves as being socially more competent and greater self-worth. In the adolescent group several aspects of self-perceived competence improved shortly after surgery, at 2 years athletic competence and romance improved.	Duration of follow up	
Dagar et al 2011	retrospective, longitudinal data available for subset of participants	Department of Neurosurgery and Neurology (Unit I), All India Institute of Medical Sciences	40	no	>1year (47.3 sd22.9 months) range 14-112 months	Mixed	QOLCE, CBCL, SSQ	P	79.5	QOL correlated with duration of seizures, epileptic encephalopathy and outcome of surgery, but not with side of surgery, age and sex.	Duration of seizures, epileptic encephalopathy and outcome of surgery	Side of surgery, age and sex
Sabaz et al 2006	prospective, longitudinal	3 centres: two hospitals in the Sydney metropolitan area, Australia (Sydney Children's Hospital; Children's Hospital at Westmead), and one in the United States (Miami Children's Hospital, FL)	35	no	6, 18 months	Mixed	QOLCE	P	n/a	Greater improvement in QOL for seizure free vs persistent seizures children. This was significant for overall QOL and for the following subscales: cognitive, social, emotional, behavioural and physical domains of life. Main effects of surgery were only observed for: language, stigma, energy/fatigue, and behavior QOLCE subscale scores.	Seizure freedom	
Titus et al 2013	retrospective, longitudinal	St. Louis Children's Hospital, MO USA	28	no	6 to 14 months (mean = 12; SD = 3.6)	Mixed (includes HE and CC)	QOLCE, BASC-2	P	n/a	Significant improvements in overall QOL after surgery, especially physical and social activities (despite unchanged IQ and psychological functioning). Better seizure outcome corelated with improvement in QOL - but no significant difference between QOL improvement and Engel class.	Seizure outcome	IQ, psychological functioning

Conway et al 2018	retrospective, longitudinal	Hospital for Sick Children in Toronto, Ontario	111	no	1 year	Mixed (excludes HE and CC)	QOLCE-76	P	66.7 (low pre-op IQ), 72.4 (normal intelligence)	Children with epilepsy and low intellectual ability had lower overall HRQL compared with those with normal intelligence (b=-10.45, SE=4.89, p=.035). No differences in change in HRQL related to intellectual level were found. In the broader sample, significant postoperative improvements were found for HRQL related to physical activity (b=8.28, SE=1.79, p<.001), social activity (b=15.81, SE=2.76, p<.001), and behavior (b=4.34, SE=1.35, p=.001). Postoperative improvements in physical and social HRQL were associated with better seizure control (p=.011). Conversely, cognitive and emotional domains of HRQL did not improve one year postoperatively, even in the presence of improved seizure control.	Seizure outcome	Pre-surgical IQ, no differences were observed among children with and without low intellectual ability in terms of postsurgical change in HRQL at the group level.
Leal et al 2020	retrospective, longitudinal	Center for Epilepsy Surgery (CIREP), Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil	50	no	6 months, 2 years	Mixed (includes HE and CC)	QVCE-50, AUQUEI, QOLIE-AD-48, semi structured interview caregiver burden (ZARIT scale)	P&C but childrenn data could not be reported	70	Preoperatively, 21 (42%) presented with moderate or severe intellectual disability. Postoperative cognitive evaluations at the two-year follow-up showed 18 (36%) maintained similar deficits. The QVCE-50 showed postoperative improvement in the two-year follow-up period, but not at six months after surgery. Postoperative improvements were associated mainly with better seizure outcome. Auto perception evaluations were limited because of the clinical and cognitive severity of patients. The burden of caregivers was quoted as mild to moderate and remained unchanged postoperatively.	Seizure outcome, parental education, school attendance, use of psychiatric medication, behavioural disorder, follow up duration (2 years vs 6 months)	Family income, age at surgery
Liang et al 2012	retrospective, longitudinal	4 centres china (beijing and shijiazhuang)	206	no	1,2,5 years	Mixed (includes CC)	QOLIE-31	P	67.5 (at 5 years)	Patients with low IQ preoperative and who became seizure free postoperatively achieved improvements in Memory quotients, IQ and overall QOL at 2 years. Overall QOL increased significantly in children who were seizure free and in the patients with preoperative low IQ and received corpus callosotomies.	Seizure freedom, pre-operative IQ, type of seizure	
Liu et al 2020	retrospective, longitudinal	Nationwide survey of epilepsy in Tuberous-sclerosis, (26 centres), China	262	no	1 year	Mixed resective and CCT (tuberous sclerosis)	QOLIE-31/QOLCE	P		Quality of life and intelligence quotient improvements were frequently observed in patients with postoperative seizure freedom and preoperative low intelligence quotient.	Seizure freedom, preoperative IQ < 70	
Panigrahi et al 2016	retrospective, longitudinal	Krishna Institute of Medical Sciences, Minister Road, Secunderabad, 03 Telangana, India	21	no	>2 years, (mean 25.4 ± 1.5 months)	HE	QOLIE	P	90.5	Improved quality of life in epilepsy scores was observed in 80.0% of the lateral peri-insular functional hemispherotomy group and 87.5% children in VPH group at the last follow-up.		Surgery type (2 Hemispherotomy approaches)
Yang et al 1996	retrospective, longitudinal	Taipei Veterans General Hospital, Taiwan	25	no	19.3 months	CC	Unstandardised Questionnaire	P	64	72% parents described a good level of satisfaction with their families QOL after callosotomy. Reduction in seizure severity significantly correlated with QOL satisfaction.	Seizure severity	Cognitive function
Gagliardi et al 2011	retrospective, longitudinal	Hospital de clinicas UNICAMP, Campinas, Brazil	13	no	3.8 y (7months-10years)	TE	Unstandardised Semi-structured interview	P	100	General improvement in QOL postoperatively. Statistically significant post-operative improvement in general health issues, adverse effect of AEDs, relationship with parents.		
O'Brien et al 2020	retrospective, qualitative	Two hospitals, Liverpool, UK	16	no	6 months-3 years	Mixed (no detailed information)	Semi-structured interviews	P&C		Epilepsy surgery had a positive impact on participants' lives, but families described difficulties in adjusting to postsurgical changes and leading a 'normal' life.		

Zupanc et al 2010	retrospective, cross-sectional	Children's Hospital of Wisconsin, US	83	no	1.6 ± 0.8 years	TE + ExTE +HE	QOLIE-C/QOLIE-A	P&C	68.7	Quality of life outcomes paralleled seizure outcomes. Statistical analysis of the Quality of Life in Childhood Epilepsy survey demonstrated that physical activity, cognition, social activity, general health, quality of life, and overall quality of life were significantly better in children with seizure-free outcomes than in children who were not seizure-free. The subscale of well-being indicated that seizure-free children manifested significantly less depression and felt significantly more in control. The subscale of social activity indicated that seizure-free children were significantly more socially active than children who were not seizure-free. However, well-being, anxiety, self-esteem, social interaction, stigma, and behavior did not reach statistical significance.	Seizure outcome (for children, not for adolescents - but these were almost all seizure free)	
Skirrow et al 2011	retrospective, longitudinal	GOSH, London, UK	42	yes	>5years	TE	QOLIE-36 UK, SDQ	P	86	Surgical group reported increased quality of life strongly associated with seizure freedom (but independent of surgery per se). Increase in IQ >5 years post-surgery in surgical group only.	Seizure freedom	Surgery, post-operative IQ, AED load
Fletcher et al 2015	retrospective, cross-sectional	Cure Children's Hospital Uganda	19	yes	8 years	TE	QOLIE-31/Child and parent stigma scale/ Rosenberg Self-esteem scale/Liverpool seizure severity scale	P&C	70	QOL was significantly higher in the surgical vs nonsurgical patients. Self-esteem (parent and child) did not differ across surgical and non-surgical groups. The surgical group had lower perceived stigma compared with the nonsurgical patients.	Inverse relationship between seizure severity and QOL. Stigma of epilepsy correlated with seizure severity (positive correlation).	
Stomberg et al 2021	retrospective, cross-sectional	Bethel Epilepsy Centre, Bielefeld, Germany	34 S	yes	> 1 year	Mixed (tuberous sclerosis)	VABS II, DISABKIDS, IOFS (Impact on Family Scale), SDQ-D, GEOS-43G (Glasgow Epilepsy Scale)	P	53	In children with TSC-related epilepsy, quality of life, social adaptation, and impact on family were related togeneral developmental level, which in turn was significantly related to seizure freedom.	Higher developmental level at follow up associated with improved quality of life, social adaptation, impact on family and parental concerns. Parental concerns associated with seizure freedom.	Seizure freedom had no significant direct impact on quality of life and social adaptation.
Griffiths et al 2007	retrospective, cross-sectional	British columbia Children's hospital, Canada	26	yes	n/a	HE	ICI, HARCES	P	n/a	Hemispherectomy is not associated with lower QOL	Residual seizure frequency negatively correlated with QOL; Female gender, higher AED load and lower functional independence predicted worse QOL	Surgery type
Downes et al 2015	retrospective, cross-sectional	Great Ormond Street Hospital NHS Foundation Trust	14	yes	18 months - 5 years	Multiple subpial transection of the posterior temporal lobe	PedsQL, IQ/DQ	P&C	71.4 (seizures), 50 (ESES)	There were no statistically significant differences between the groups in language, nonverbal ability, adaptive behavior, or quality of life at follow-up. Continuing seizures and an earlier age of onset were most predictive of poorer quality of life at long-term follow-up.	Seizure severity, younger age of epilepsy onset	
Mikati et al 2008	retrospective, cross-sectional	American University of Beirut Medical Center, Beirut, Lebanon	17	yes	2.4 years	Focal resection	QOLCE-91	P	n/a	Overall QOL better in surgical than nonsurgical group, general health, physical activities, well-being were also higher in surgical than non-surgical participants; cognitive, social and behavioural functioning did not differ across groups.		

Puka et al 2015	retrospective, cross-sectional	Hospital for Sick Children in Toronto, Ontario	71	yes	4-11 years	Mixed	QOLCE, QOLIE-31-P, QOLIE-48-A; ABCL/CBCL; STAIC/STAI	P&C - C only administered anxiety		In terms of QOL, the only differences related to surgical status were greater concerns by nonsurgical patients on the seizure worry and medication effects subscales. Almost all QOL ratings were enhanced in seizure-free patients. Internalizing behavior (anxiety/depression) mediated the relationship between seizure freedom and better QOL, where seizure freedom led to better ratings of anxiety/depression, which in turn led to better ratings of QOL. AED use was found to be associated with social functioning, medication effects, and seizure worry. IQ and duration of follow-up were not found to independently influence HRQOL.	Internalising behaviour (anxiety/depression), seizure freedom, AED load.	No significant effect of IQ, surgical status or length of follow up on QOL.
Jain et al 2020	prospective, longitudinal	The Hospital for Sick Children, Toronto Ontario, Canada; BLK Speciality Hospital, New Delhi, India; Danat Al Emarat Hospital for women and Children, Abu Dhabi, UAE	147	yes	1 year	Mixed (includes HE)	QOLCE-76	P	n/a	Surgery had no direct effect on total QOLCE score at 1-year (beta=0.24 [95% CI -2.04 to 2.51], p=0.839) compared to pharmacological management, but had an indirect effect on total QOLCE that was mediated by seizure freedom (beta=0.92 [95% CI 0.19-1.65], p=0.013), adjusting for baseline total QOLCE score. Surgery had a direct effect on improving social function (p=0.043), and an indirect effect on improving physical function (p=0.016), cognition (p=0.042), social function (p=0.012) and behavior (p=0.032), mediated by seizure freedom. INTERPRETATION: Greater seizure freedom achieved through epilepsy surgery mediated the improvement in HRQoL compared to pharmacological management in children with DRE.	Seizure freedom	SES, sex, number of household members, seizure freedom
Philips et al 2020b	prospective, longitudinal	nine hospitals across Canada: The Hospital for Sick Children, Toronto; McMaster Children's Hospital, Hamilton; London Health Sciences Centre, London; Alberta Children's Hospital, Calgary; British Columbia Children's Hospital, Vancouver; The Children's Hospital of Winnipeg, Winnipeg; CHU *Sainte-Justine* , Montreal; Royal University Hospital, Saskatoon; IWK Children's Hospital, Halifax.	48	yes	1 year	Mixed	QOLCE/family resources QIDS-SR16/GAD-7; family functioning at baseline. The family Adaptability, Partnership, Growth, Affective, and Resolve (APGAR), Family Inventory of Resources for Management (FIRM)	P	68	Treatment (surgery vs medical), was not independently associated with improved QOL. Seizure freedom rather than type of treatment was associated with better QOL. Caregiver and family factors were not associated with higher child HRQOL at follow-up after accounting for epilepsy characteristics, treatment, seizure outcome, and baseline child HRQOL. Family resources moderated the association between seizure outcome and child HRQOL at follow-up, seizure freedom was strongly associated with higher HRQOL when family resources were high (b = 13.50, 95% CI = 8.35-18.54, P < .001), relative to when family resources were low. Family relationships and demands did not moderate the relationship between seizure outcome and HRQOL.	Family resources, seizure freedom	
Ding et al 2016	prospective, RCT	PLA General Hospital, Beijing, China	43	yes	3-5 years	CC	QOLIE-31	P	73.9 (CCT+resection), 65 (resection only)	Significant changes were observed in QOL and FSIQ between the medicine and surgery groups. Children with combined CCT surgery demonstrated more postoperative improvement than the children with resective surgery alone based on the mean QOL score (10.78 vs. 5.75, p = 0.0152) and full-scale IQ (7.91 vs. 4.55, p = 0.0446). There was a trend of better seizure outcome in combined CCT surgical subgroup, but this did not reach statistical significance.	surgery type	

Liang et al 2014	prospective, longitudinal	Capital Epilepsy Therapy Center in Beijing	23	yes	1,2,5 years	ant CC	QOLIE-31	P	87 at 5 years follow up)	Significant differences were found in mean changes of IQ and overall QOL between the medicine and surgery groups at the 2-year follow-up, showing positive results for the surgery group, but these changes were not related to postoperative outcomes of seizure control.		In the surgery group, preop IQ, post-op seizure control, age at enrollment no effects on mean changes in IQ and QOL.
Markand et al 2000	prospective, longitudinal	Indiana university epilepsy surgery program, Indiana, US	53	yes	1,2 years	ATL	QOLIE-89	P	n/a	Improvement in 10 out of 17 subscales: overall, emotional well-being, attention/concentration, language, social isolation, health perception, role limitations, health discouragement, and seizure worry - for the first 5 scales the improvement was more at 2 years than 1 year follow up. QOL improvement was related to achieving an entirely seizure-free status (Engel class I).	Seizure freedom, follow up duration	
Dwivedi et al 2017	prospective, RCT	All India Institute of Medical Sciences in New Delhi	57	yes	1 year	Mixed	PedsQL, CBCL, Vineland Social maturity scale - Binet Kamat IQ, Hague seizure severity scale, seizure freedom	P	77	Between-group differences in the change from baseline to 12 months significantly favored surgery with respect to QOL but not on IQ.		
Mikati et al 2010	retrospective, cross-sectional	American University of Beirut Medical Center, Beirut, Lebanon	19	yes (three groups: surgical, medical, healthy controls)	3 years	Focal resection	QOLCE-91	P	78.9	There were no significant differences between healthy and surgery groups in the total QOL score ($p = 0.101$) nor in any of the QOL domains (general health $p = 0.089$, social $p = 0.439$, cognitive $p = 0.151$, emotional $p = 0.096$, physical $p = 0.123$, overall QOL $p = 0.766$). Surgery patients similar to healthy subjects in social emotional cognitive behavioural and overall QOL, but had lower scores in total QOL, physical and health domains. Surgery patients scored better than non- surgery patients in the behavioural domain and the side effects scale score. Non surgery patients scored worse than healthy in total QOL, physical, behavioral, health and overall QOL. Seizure severity and IQ was associated with total QOL scores.	Seizure severity and IQ. In the surgery group, HASES score was positively associated with total QOL scores. In the non-surgery group, IQ was positively associated with total QOL scores.	Age at epilepsy onset, age at surgery, age at QOL interview, seizure frequency before surgery, SES, sex, Number of household members, seizure freedom, time to evaluation and number of AEDs before and after surgery were not found to be significantly associated with total QOL in the surgery and non-surgery groups.

*Please note that text in Main finding section of table includes direct quotations from research articles.

Table 1 Key

Etiology:

TE	Temporal lobe excision
ExTE	Extra-temporal lobe excision
CC	Corpus Callosectomy
HE	Hemispherectomy

QOL and other measures:

ABAS-II	Adaptive Behavior Assessment System, 2nd edition
ABCL	Adult Behaviour Checklist
APGAR	Adaptability, Parnertship, Growth, Affective and Resolve
AUQUEI	Pictured Child's Quality of Life Self Questionnaire
BASC-2	The Behavior Assessment System for Children 2nd edition
CBCL	Child Behaviour Checklist
CHQ	Child Health Questionnaire
DISABKIDS	Quality of life questionnaires for children with chronic conditions
DQ	Developmental Quotient
ELDQOL	Epilepsy and Learning Disabilities Quality of Life Scale)
FIRM	Family Inventory of Resources for Management
GAD-7	Generalised Anxiety Disorder
GEOS-43G	Glasgow Epilepsy Scale
HARCES	Hague Restrictions in Chldhood Epilepsy Scale
HAY	How Are You questionnaire
ICI	Impact of Childhood Illness Scale
IOFS	Impact on Family Scale
IQ	Intellectual Quotient
PedsQL	Pediatric Quality of Life Inventory
POMS	Profile of Mood States
QOLCE	Quality of Life in Childhood Epilepsy Questionnaire
QOLIE-31	Quality of Life in Epilepsy Inventory
QVCE-50	Qualidade de Vida da Crianca com Epilepsia/Quality of Life of Children with Epilepsy
SDQ	Strenghts and Difficulties Questionnaire
SHE	Subjective Handicap of Epilepsy Scale
SSP	Self Perception Profile
SSQ	Seizure Severity Questionnaire
STAIC/STAI	State Trait Inventory for Children
VABS-II	Vineland Adaptive Behavior Scale

Rater:

P	Parent/Carer
C	Child/Patient