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REVIEW ARTICLE

Epilepsy surgery in childhood: What challenges now need to be brought to the foreground?

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Abstract

Background: Over recent years, epilepsy surgery has gained its place as the standard of care for many cases of drug-resistant focal epilepsy. Our paper aims to briefly summarize major achievements in epilepsy surgery in children and discuss emerging aspects. **Methods:** Our review has a narrative and a systematic part. Articles included in the systematic part were original studies conducted over the last ten years in paediatric populations with epilepsy. The quality of the studies was assessed using appropriate bias assessment tools. **Results:** The vast majority of articles identified were retrospective studies. Although the efficacy and safety of epilepsy surgery have been proven, it is still underused in many healthcare systems, and a balance between thorough pre-surgical investigations and early intervention needs to be achieved. Cognitive function is stabilized and preserved after different types of epilepsy surgery, and in the longer term, clear benefits are demonstrated related to seizure freedom and weaning from antiseizure medications. Minimally invasive surgical methods are emerging as efficient and safe alternative options in many cases of patients with specific underlying conditions, but larger group data are needed. Finally, emerging genetic findings lead to a discussion about the utility of epilepsy surgery in specific genetic conditions, while social and national inequalities remind the need for more flexible approaches. **Conclusions:** Early referral and mindful selection of likely candidates, refinement of minimally invasive surgical methods, ways to benefit cognitive function, and early antiseizure medication withdrawal are the current challenges for epilepsy surgery in children.

Keywords: epilepsy surgery, children, minimally invasive methods, neurodevelopment, cognition, epilepsy challenges.

Introduction

Epilepsy is considered the most prevalent chronic neurological condition in childhood, affecting 1-2% of the paediatric population. It is a disorder with many etiologies and marked phenotypic variability. It exhibits significant resistance rates to first-line treatments (i.e., anti-seizure medications) and affects multiple aspects of cognition and quality of life. This complexity is a hallmark of epilepsy and inevitably affects treatment options. Management strategies aim not only at reducing seizure burden but also at minimizing cognitive impairment and helping these children reach their optimal neurodevelopmental potential [1].

Epilepsy surgery involves localization of the epileptogenic focus and its removal through resection, disconnection, or stimulation, aiming at reducing or eliminating seizures and improving quality of life without inducing any neurological impairment [2]. From an alternative or a last resort therapy at the beginning of the 20^{th} century, epilepsy surgery has now gained its place as the standard of care for many cases of drug-resistant focal epilepsy, and the number of patients who have benefited has escalated. A benefit of surgery over continued medical treatment has also been shown in selected patients [3]. The two factors that primarily contributed to the boost in the global interest in the surgical management of epilepsy were the development of the electroencephalogram (EEG) and the perfection of neuroimaging techniques (functional and structural) [4, 5]. Imaging has had a significant impact on increasing numbers of children who have come to surgery over the last decade [6]. The types of resections undertaken in children may be similar to adults, although multilobar resections and hemi-disconnections are more common [7].

Our review aims to briefly present the progress of paediatric epilepsy surgery over recent years, analyze current emerging aspects, and discuss missing points and future challenges, always in light of the differences to the adult population.

Methods of literature search

Structure of the manuscript

In general, our review paper has a narrative and a systematic part and is structured on:

i) what is already known in the field of paediatric epilepsy surgery (we briefly summarize the main points, narrative review)
ii) what new information is being added and what the arising dilemmas are which need to be addressed in the future (systematic review, studies with homogeneous endpoints are presented in tables)

Special emphasis is given to various unique features in the paediatric age.

Eligibility criteria

Studies fulfilling the following criteria were selected: (1) original papers, (2) published in the last ten years, (3) studies conducted in paediatric patients (<18 years) with epilepsy, (4) studies with outcomes relevant to epilepsy surgery

Search strategy and study selection

A comprehensive search by thesaurus was undertaken using health-related databases: Pubmed, Embase, Scopus, Web of Science, and Cochrane.

The terms that were used were: "epilepsy surgery" AND ["children" OR "paediatric" OR "childhood"] AND ["neurodevelopment" OR "cognitive function" OR "behavior" OR "language development" OR "language disorders" OR "language problems" OR "speech development" OR "school performance" OR "memory" OR "plasticity" OR "outcomes" OR "laser" OR "minimally invasive methods" OR "neuromodulatory" OR "brain stimulation" OR "vagus nerve stimulation" OR "antiepileptic drugs withdrawal" OR "antiepileptic drugs stop" OR "antiseizure medication withdrawal" OR "antiseizure medication stop" OR "genetic" OR "genotype" OR "underutilization" OR "challenges"].

Additional records were identified after considering references cited in initially identified papers.

After searching the literature, data were abstracted, and selected articles were scanned to eliminate studies on irrelevant topics, inappropriate methodology, or duplicate records. (Figure 1) Studies with interesting findings conducted in adult populations or in mixed populations without a separate analysis for paediatric/adolescent patients and some relevant review papers have been commented on but not included in the results of our literature search.

Quality assessment

The quality of the original studies included in our review was assessed using the Cochrane Risk of Bias Assessment Tool for the randomized trials and the ROBINS-I tool for other types of studies. Authors have selected these tools as they are widely used in systematic reviews and recommended by the Cochrane Collaboration. Both tools include i) pre-intervention (selection, confounding), ii) intervention (blinding, classification, deviation) and iii) post-intervention (measurement, reporting data, incomplete data) domains.

Evaluation of risk is based on the authors' judgment. The risk of bias was expressed as *low*, *high*, or *unclear* in the Cochrane tool and as *low*, *moderate*, or *serious* in the ROBINS-I tool [8, 9].

Studies on relevant topics but exclusively in adult populations have been referred to but not included in our primary results.

What makes children with epilepsy different?

The well-known cliché that "children are not young adults" is perfectly illustrated in the surgical treatment of epilepsy. A number of differences represent sources of potential challenges in this age group.

More specifically, the protection of the developing brain and the potential for plasticity is a greater issue than in adult patients. Apart from improving seizure control, pre-existing brain function needs to be preserved. However, there is further potential for developing language, cognition, social competence, and behavioral skills as individuals move through childhood and adolescence. These in paediatric patients are equally important as seizure frequency, as their development will determine the level of global functioning. Many children coming to epilepsy surgery have pre-existent cognitive and behavior deficits; it may be presumed that optimal development would be achieved with alleviation of seizures. On the other hand, additional co-morbidities frequently encountered in childhood and of high prevalence amongst epilepsy surgery candidates (e.g., autism spectrum disorder, attention deficit hyperactivity disorder or other psychiatric comorbidities) may interfere with surgical management and influence the final outcome [10, 11].

At the same time, parents are responsible for a child's care over decisions about management and therapies applied. This can significantly impact the degree of utilization of an offered treatment in paediatric groups of patients without appropriate counseling. The unique features of this three-part interaction should be taken into account.

Major achievements in the field of paediatric epilepsy surgery: what is known

Over the last decades, there has been a remarkable increase in the number of paediatric epilepsy surgeries performed, the complexity of the procedures undertaken, and stability in the proportion of Engel I class outcomes [12]. Progress in paediatric epilepsy surgery could be summarized by assessing its *safety*, *efficacy*, and *flexibility* of referral indications.

Epilepsy is a complex disease that encompasses many etiologies and rare syndromes. The etiology and specific epilepsy syndrome are important determinants of the outcome and key fac-

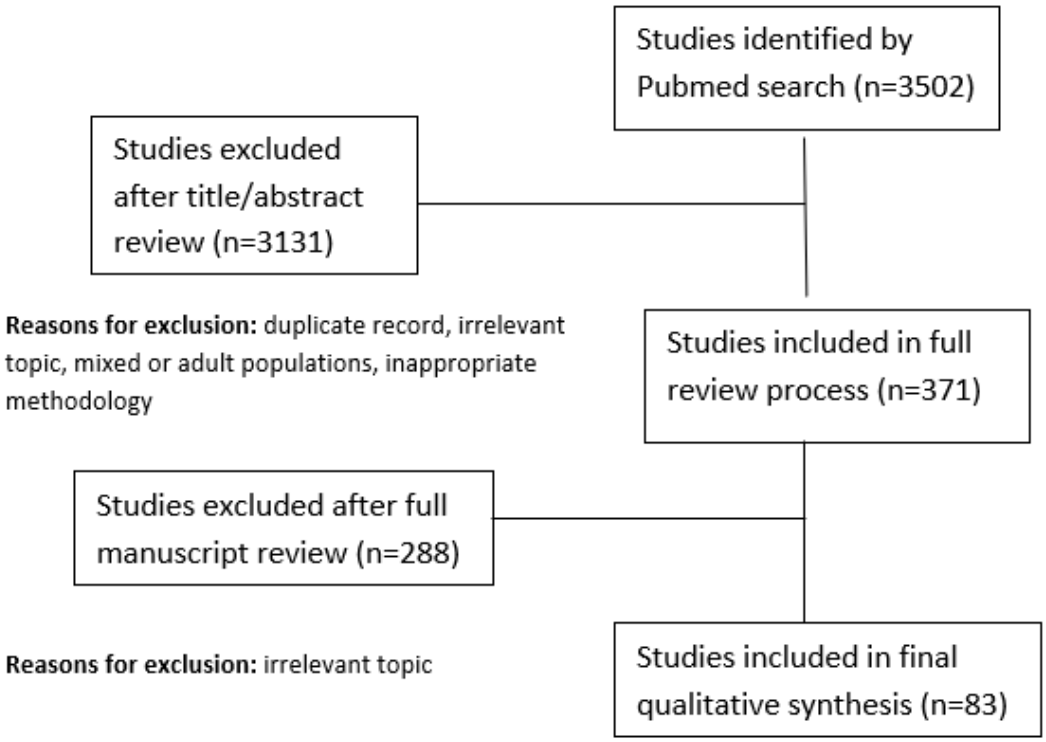

Figure 1. Flowchart for study selection according to PRISMA guidelines

tors in treatment selection [13]. The Paediatric Epilepsy Surgery Sub-commission of the International League Against Epilepsy (ILAE) developed recommendations for when referral should be made for consideration of assessment for surgery [14]. Although traditionally drug-resistant epilepsy, as defined in ILAE 2010 criteria, is a key factor, more specifically, children with uncontrolled or disabling seizures, as well as children with continuing presumed focal onset seizures from a localized pathology that cannot be classified as a clearly defined electroclinical entity are potential surgical candidates and warrant further evaluation in a specialist centre [15]. Further, in children with seizures, the likely result of a clearly defined localized lesion of low risk for removal may warrant evaluation even in the absence of continuing seizures [16]. Over the years, it has been widely recognized that a multidisciplinary approach is required for these patients. Indications for pre-surgical evaluation are now widely available, and evaluation protocols have been developed; preliminary baseline investigations include high-resolution Magnetic Resonance Imaging (MRI), video-EEG monitoring (ictal and interictal), and neuropsychological assessment. Additional investigations may offer additional information dependent on the underlying etiology [14, 17] (Figure 2).

These complementary investigations are suggested to localize the epileptogenic zone better (e.g., magnetoencephalography, single-photon emission computerized tomography, positron emission tomography, 3D source localization) or to assess the risk of postoperative deficits more precisely (e.g.fMRI, tractography of pyramidal tract and Meyer's loop) [18, 19, 20, 21]. In general, the purpose of all the aforementioned investigational options is to offer the opportunity to carefully select surgical candidates, maximize individual benefit and achieve some kind of precision medicine in the field of epilepsy surgery [22] (Figure 2).

Despite this range of supplementary noninvasive investigations, in some children, the seizure onset zone may not be completely clear or proximity to the eloquent cortex. In such individuals, invasive EEG recording may be justified. Traditionally, subdural grids were thought to be advantageous in children in view of the presumed cortical generation of seizures. However, stereoencephalography (SEEG) is now more widely used in view of the range of individuals who can be evaluated and relative lower morbidity. Although a long-established technique in presurgical evaluation, the number of studies about the use of SEEG in children has significantly increased over the last five years (Table 1). Most of these studies focus on the safety of this method and its efficacy in terms of localization of the epileptic zone. However, in clinical practice, SEEG is often combined with one of the later mentioned minimally invasive techniques (e.g., radioablation). According to the results of these studies, SEEG is generally well tolerated, although complications may arise and need to be considered by clinicians. In parallel, in most cases, SEEG provides clinically useful data allowing a targeted resective procedure, with robot-assisted and optic navigation methods seeming to be equivalent [23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35].

Although the presurgical evaluation was initially confined to specialist epilepsy centres, especially in countries with centralized healthcare services, the ILAE has now developed criteria

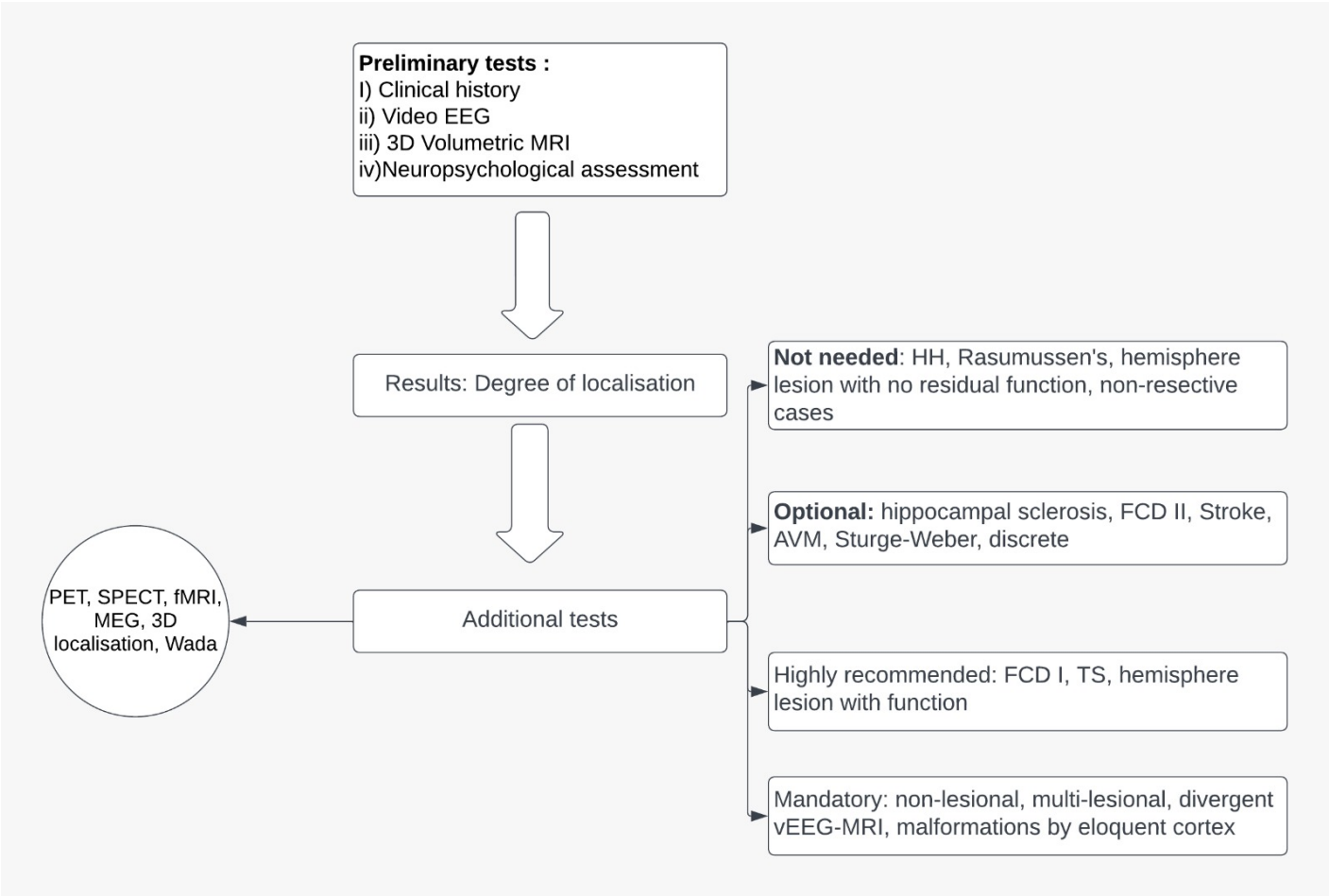

Figure 2. Proposed algorithm for pre-surgical evaluation in children with epilepsy (adapted from Jayakar et al., 2014; AVM: arteriovenous malformation, EEG: electroencephalogram, FCD: focal cortical dysplasia, (f)MRI: (functional) magnetic resonance imaging, HH: hypothalamic hamartomas, MEG: magnetoencephalography, PET: positron emission tomography, SPECT: single-photon emission computerized tomography, TS: tuberous sclerosis).

for Level 1 and Level 2 centres according to facilities and competencies [36]. Level 1 centres provide care for children age ≥ 9 years with discrete lesions including hippocampal sclerosis, undergoing lobectomy or lesionectomy, not close to the eloquent cortex. The team includes a paediatric epileptologist, paediatric neurosurgeon, and paediatric neuroradiologist, while access to video-EEG and 1.5T MRI is needed. *Level 2* centres can provide care across the whole age span and for a broad spectrum of etiologies, even for patients with normal MRI, ill-defined MRI lesions, or foci in the eloquent cortex. A wider range of diagnostic technologies must be available, and the multi-disciplinary team needs to be supported by neurophysiology, neuroradiology, epilepsy neurosurgery, neuropsychology, neuro-anesthesia, neurocritical care, and psychiatry services [36].

According to the literature, epilepsy surgery has an acceptable safety profile for all ages when conducted in a specialist paediatric centre. However, data suggest that children are less likely to present perioperative complications (especially intracranial hemorrhage) than adults [37]. The efficacy of a number of surgical techniques has now been well-established for a series of anatomical disorders, according to their size: hemimegalencephaly, hemidysplasia and Rasmussen's syndrome (hemispherectomy), focal cortical dysplasia, tuberous sclerosis, Sturge-Weber syndrome, developmental tumors, polymicrogyria, as well as cases of hippocampal sclerosis [14]. Hemi-disconnection has higher rates of success than lobectomy, while seizure freedom rates are higher for patients with underlying developmental tumors or vascular abnormalities compared to children with malformations of cortical development. Almost 75% of children undergoing temporal lobectomy achieve seizure freedom, with abnormal MRI and with lack of generalized seizures as positive predictors. On the other hand, seizure freedom rates are lower for children undergoing extra-temporal resection. Early age of intervention plays a positive role in this patient group [38, 39, 40, 41].

Vagus Nerve Stimulation (VNS) is considered a relatively established minimal surgical approach in children, particularly for those patients who are not eligible for a resective/disconnective surgical method or have already had a previous failed epilepsy surgery. Many studies and cohorts in the literature have shown that VNS is quite tolerable and safe with mainly transient adverse effects (e.g., voice changes, cough, skin irritation, focal infections). In parallel, VNS can demonstrate benefit in children

with various types of epilepsy, especially for multifocal structural epilepsies or generalized seizures in patients with genetic epilepsy (e.g., Dravet, Lennox-Gastaut) [42, 43, 44, 45, 46]. That aside, seizure freedom, the result of VNS, is rare. Finally, there is very recent evidence in the literature (i.e., retrospective review of patient chart reviews) about the use of responsive VNS among children with refractory epilepsy. Data is encouraging, showing safety and utility, but more detailed research is required to support any sustained impact [47, 48].

Increasing data about aspects of paediatric epilepsy surgery

Minimally invasive methods: from the resection of an apparent abnormality to the treatment of presumed lesions

Minimally invasive surgical methods, including stereotactic thermoablation, stereotactic laser ablation, and radiosurgery, promise to be beneficial to selected patients with particularly small lesions (e.g., nodular heterotopias), small hypothalamic hamartomas, restricted hippocampal sclerosis) [49].

Regarding the rest of the methods, in the literature, there is emerging data about the efficacy of these methods in the paediatric age group, and we were able to identify seven original papers, all of which represent retrospective studies [50, 51, 52, 53, 54, 55, 56]. The surgical techniques used were MR-guided laser ablation, thermal therapy, and endoscopic disconnection, and the etiological background mainly included cases of focal cortical dysplasia and hypothalamic hamartomas. (Table 2) Results are encouraging, as most children are seizure-free (with or without antiseizure medications), and no long-lasting complications have been described. There are no available data about the impact of minimally invasive surgical methods on these children's long-term neurodevelopment and cognitive function.

On the other hand, it would be useful to highlight that many of the aforementioned studies have a moderate-high risk of bias, mainly due to the inadequate description of the outcomes and sample size calculation. In some, the number of participants is quite small (<10), and the short follow-up period inevitably decreases the level of evidence provided. (Table 2).

TABLE 2 HERE

With regard to neuromodulatory methods, brain stimulation is increasingly adopted as a potentially curative, minimally invasive method of epilepsy by modulating cortical excitability and remedying dysfunctional neuronal networks. There has been an increasing body of evidence about its effectiveness in adult patients with drug-resistant epilepsy, especially when resective surgical procedures have failed to achieve seizure control. Outcomes are particularly favorable with stimulation of the centromedian nucleus of the thalamus and the anterior thalamic nucleus. In some studies, seizure freedom rates or seizure reduction often exceed 80%. However, it is noteworthy that in the vast majority of these studies, seizure recording was self-reported and not based on any kind of seizure diaries [57, 58, 59, 60].

Regarding childhood, we identified only three studies conducted over the last ten years in paediatric patients with pharmacoresistant epilepsy undergoing deep brain stimulation as an adjunctive therapy [61, 62, 63]. (Table 3) Results are encouraging and the procedure well-tolerated, but the small number of participants and the retrospective design do not permit us to draw safe conclusions. Methods of evaluation of stimulation efficacy included visually counting interictal discharges and seizures records during the pre-stimulation, stimulation, and post-stimulation period. Prospective registries are essential to identify the optimal target of brain stimulation and prognostic factors.

TABLE 3 HERE

Although minimally invasive epilepsy surgery has a significant potential to efficiently replace a number of conventional surgical methods in selected cases, the full spectrum of possibilities of these methods and their long-term impact compared to the conventional ones need more thorough investigation.

Cognitive outcomes

Since the efficacy of resective or disconnective surgery with regard to seizure control has been proven, it is plausible that the interest is now being shifted to more long-term aspects of the well-being of these children, and mainly to their neurodevelopment and long term cognitive outcome. The premise on which we have advocated early surgery has always been to give children optimal neurodevelopmental and psychosocial outcomes.

Indeed, there are multiple pathophysiological pathways that are presumed to negatively affect cognitive function in children with epilepsy and include the underlying epileptogenesis-related neuronal dysfunction, the burden of uncontrolled seizures, the adverse effects of antiseizure medications, as well as additional genetic factors and environmental inputs [64, 65].

Epilepsy surgery would, therefore, theoretically be seen to exert a beneficial effect on cognition both directly (removal of a brain lesion) and indirectly (better seizure control, withdrawal of antiseizure medications).

Our literature search identified 48 original studies (45 retrospective and three prospective) over the last ten years about cognitive outcomes in children after epilepsy surgery [3, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112] (Table 4). There are two main types of study: i) those comparing pre- and post-surgical cognitive outcomes and ii) those comparing cognitive outcomes between children undergoing and children not undergoing epilepsy surgery (Table 4). Studies of the first type have shown encouraging results, mainly in the stabilization of cognitive function and improvement in some aspects of behavior and neurodevelopment, which, however, are not consistent between studies. On the other hand, most of the studies of the second type have not identified a real difference in cognitive performances between the surgical and non-surgical treatment of epilepsy after a follow-up period of 1-7 years [81, 82, 83, 84, 85, 86, 87, 88, 89]. Only the single-

center randomized trial by Dwivedi (2017) significantly favored epilepsy surgery against antiseizure medications with regard to behavioral aspects, although the intelligence quotient did not show any significant difference [3]. However, it should also be highlighted that the follow-up period was only 12 months in this study.

TABLE 4 HERE

The multivariate regression analysis revealed that cognitive development after surgery strongly depends on the duration of epilepsy (shorter duration associated with better cognitive outcome), pre-surgical developmental status, and is also associated with underlying etiology [67, 70, 71, 72, 76, 79, 81]. Nevertheless, in some studies, better cognitive outcomes are correlated with lesser antiseizure medication load [71, 109], a finding implying that epilepsy surgery can positively influence by decreasing the burden of antiseizure medications, but this is discussed in more detail below.

We identified 14 studies focusing on language function among patients undergoing epilepsy surgery [69, 74, 75, 82, 83, 84, 86, 87, 88, 91, 92, 93, 94, 95]. According to their findings, language aspects (e.g., lexical breadth and depth) did not show significant deterioration after epilepsy surgery, and even some improvement could be noticed with the baseline language scores, the baseline IQ, and older age at epilepsy onset representing positive prognostic factors [86, 94]. The results were also encouraging for children with ESES and language impairment undergoing surgery [83]. It is interesting to mention that the drop in verbal memory scores among patients undergoing temporal resection appeared to depend on the side of the resection (right VS left) and the pattern of language representation (typical VS atypical) [74, 82].

In terms of methodology, 3 basic concepts need to be highlighted: duration of follow-up, age of cohorts, and *differences between individual and group data*. More specifically, Skirrow et al. (2011) were able to identify a significant increase in IQ scores in children undergoing epilepsy surgery after a minimum period of follow-up of 5 years, while in the same study anon-surgical group did not demonstrate significant improvement; as IQ changes were only seen $\geq$ 6 years after surgery, authors discuss whether a prolonged period of post-surgical follow-up may sometimes be needed to see a real improvement in cognitive skills [109]. However, according to the results of our review, this is not always true, as other studies with long follow-up periods, such as those by Lee et al. (mean follow-up7 years) and Puka et al. (mean follow-up12.7 years), do not necessarily identify significant improvement in cognitive outcomes [81, 99].

In parallel, it has been shown by Helmstaedter et al. (2019) that a younger age of patients is associated with better outcomes, including IQ score, memory, and language skills; this finding is quite plausible since younger age often implies shorter seizure duration [71]. Nevertheless, this difference is not always confirmed by studies based on young age cohorts [90]. At the same time, the issue of individual versus group data needs to be considered. Although significant improvement in cognitive skills after surgery may be present on a group level, individual losses often co-exist and should be evaluated, and their potential causes thoroughly investigated [97, 98].

In any case, it would be an omission if we did not comment on the significant heterogeneity among all these studies with regard to the size of the sample, underlying pathology, surgical techniques, how cognitive outcomes are reported (e.g., absolute scores, change from baseline, non deterioration, degree of parental satisfaction), as well as the tools used to measure cognitive outcomes. In this way, considerable bias is introduced in the interpretation of their findings, and the comparison of different studies becomes tricky. Furthermore, 30 out of 32 papers represent retrospective studies where cognitive outcomes are not the primary outcomes in most. These two facts inevitably reduce the level of evidence provided.

The well-known Hippocratic principle "first, do no harm" is fulfilled when we consider the relationship between paediatric epilepsy surgery and cognitive outcomes; however, a clear benefit on future neurodevelopment of these children or any superiority compared to other treatments has not yet, been proven.

At the same time, as the number of studies evaluating co gnitive outcomes after epilepsy surgery increases, the concept of what we call "safety profile" is broadened; safety evaluation now focuses on major perioperative adverse events and includes the long-term neurodevelopmental potential of these children.

Although no study can address all methodological issues, analysis of findings by age and longer follow-up periods might be prioritized by researchers in the future.

Neurobehavioural Co-morbidities

A series of neurobehavioural co-morbidities (e.g., autism spectrum disorder, attention/deficit hyperactivity disorder) are present in children with epilepsy at higher rates compared to the general paediatric population and exert an accumulative negative effect on their psychosocial outcome. Their prevalence is particularly high in children referred for epilepsy surgery [113]. Results from cross-sectional analyses show that the co-existence of autism or cognitive disabilities in these patients is associated with poorer long-term seizure outcomes after resective surgery. However, this does not mean that a worthwhile improvement cannot be achieved. It should be highlighted that deterioration in some cases noticed one year after the initial surgery may have been related to the emergence of a child's personality following seizure control and weaning of medication [114].

On the other hand, data from cohorts of children with epilepsy and autism undergoing surgery has shown that surgery can also improve many behavioral aspects, including aggression and aberrant behavioral patterns. This finding implies that some behavioral problems often encountered in these children could be attributed to their underlying refractory epilepsy [115]. Similarly, according to Reilly et al. (2019), parent-rated symptoms of attention deficit and hyperactivity improved at 2-year follow-up after epilepsy surgery [116]. (Table 5)

TABLE 5 HERE

All the aforementioned findings highlight the need for further investigation of the pathophysiological relationship between epilepsy and co-morbidities, as they are part of the same disorder. A child with a specific genetic background may have a widely

abnormal neuronal network, which is difficult to completely localize, or may also be prone to developing an alternative epileptogenic area [117]. Appropriate identification of such prognostic factors could provide useful information for more targeted counseling of families considering epilepsy surgery. Furthermore, better training for clinicians involved in paediatric epilepsy care about co-morbidities would be of paramount clinical importance [118].

Timing of antiseizure medication withdrawal

We identified in the literature a total of 3 studies over the last ten years about the timing of antiseizure medication withdrawal in children after surgery and seizure outcomes [119, 120, 121]. The time of starting the withdrawal ranged from 6 months to 2.7 years. (Table 6) TABLE 6 HERE

The TimeToStop study, a pan-European study based on a paediatric epilepsy surgery cohort, aimed at investigating how various potential determinants of seizure recurrence related to time to relapse after surgery [120]. This study showed that the time interval to antiseizure medication reduction was the only independent prognostic factor of seizure relapse. This fact implies that an early withdrawal of antiseizure medications does not actually affect the final seizure outcome but just unmasks an unsuccessful surgical procedure [120, 121]. Multivariate analysis in the study by Choi et al. (2019) has shown that incomplete resection and epileptic discharges on postoperative EEGs are significant predictors of seizure recurrence [119]. Data from retrospective studies also imply that antiseizure medication withdrawal after surgery is associated with an improvement in intelligence quotient and psychomotor development in paediatric patients [122, 123]. (Table 7)

TABLE 7 HERE

A randomized trial aimed at comparing cognitive function between children with early and children with late drugs withdrawal after surgery, however, could not be undertaken; in practice, the vast majority of the parents strongly preferred an early withdrawal and, subsequently, the "time to stop" was "now" [124]. Data, therefore, suggest that antiseizure medication withdrawal should be an aim of epilepsy surgery and should be considered earlier rather than later.

Dilemmas arising

Is the best the enemy of the good?

Current trends in paediatric epilepsy favor early interventions. The belief is, "time is brain". Indeed, early surgical treatment of drug-resistant epilepsy is presumed to preserve neuronal networks and protect the brain from prolonged exposure to seizure burden, permitting earlier discontinuation of antiseizure medications and improving cognition and psychosocial outcomes [125]. However, how feasible is an early intervention given the extensive pre-surgical investigations and the coordination of many different medical and non-medical specialties that may be required? At the same time, the underuse of epilepsy surgery in many healthcare systems is highlighted in the literature and should also be taken into account. Prideaux et al. recently studied children with drug-resistant epilepsy and reported remarkable delays between seeing a neurologist and being evaluated in an epilepsy surgery clinic, as well as between potential indications for a surgical evaluation to agreed surgical candidacy [126]. A number of studies have also revealed that a significant proportion (up to 25%) of caregivers of children with active epilepsy, even with poor seizure control, may be reluctant or skeptical about surgical treatment (Table 8). This attitude is significantly correlated with specific traits of a patient's social profile [127, 128, 129]. Shen et al. (2018) have shown that most parents whose children have undergone epilepsy surgery believe that benefits would be greater if this had happened earlier. Furthermore, they are more likely to accept a lower likelihood of seizure freedom and deficits after surgery than their physicians [130]. Whether underutilization of epilepsy surgery services reflects only parental wish or clinicians' uncertainty also plays a role is open to discussion [131].

TABLE 8 HERE

From this point of view, a potential delay in referring children to epilepsy surgery centers can negatively impact the wide utilization of this treatment.

Nevertheless, the same studies have also shown that cautious guidance and sensitive counseling of caregivers along with appropriate education of neurologists can dramatically alter parental views about the surgical management of epilepsy, while the potential contribution of centralization of some children's epilepsy services also needs to be explored (Figure 3) [132].

How early is too early?

As most epilepsy experts agree that "the earlier, the better" and since surgery can provide the possibility of a cure in many cases, one might consider that children with well-controlled seizures, the result of circumscribed lesions could also be eligible for surgical management of their epilepsy to avoid the burden of antiseizure medications. No studies balancing the benefits and risks of surgery in this population are available, as plausible ethical issues slow the conduction of clinical trials in this field. However, according to Braun et al. (2018), surgery in children with non-eloquent well-defined lesions could be an option, even if seizure control is still good, given that the risk of complications remains relatively low [16] (Figure 3).

It has already been discussed in previous sections of this review that epilepsy surgery can be associated with beneficial neurodevelopmental outcomes, and shorter seizure duration predisposes to this. In addition, there are specific pathological entities common in childhood (e.g., glioneuronal tumors, vascular and cortical malformations) that are associated with excellent rates of postsurgical seizure freedom. In contrast, spontaneous seizure remission in these cases is relatively rare. It should also be mentioned that, particularly for children with suspected low-grade tumors, diagnosis and classification on a molecular level could permit more targeted approaches in the future [16].

The interplay between genotype and phenotype

The relationship between genetic findings and surgical outcomes in patients with epilepsy is complex. Studies investigating the correlation of the genotype of specific brain lesions with the outcome of epilepsy surgery are extremely few, with quite heterogeneous endpoints and subsequently emerging questions that outweigh available answers. A significant part of their molecular genetic findings converge on various levels of PI3K/AKT/mTORpathway [133]. Although the genetic background does not always reliably predict the phenotypic manifestations, it seems that surgery in children with pathologic variants affecting the mTOR pathway is associated with a better prognosis considering their likely association with a structural brain abnormality compared to variants affecting ion channel function, synaptic transmission or cell-cell adhesion [133].

Children with focal malformations of cortical development are usually very good candidates for surgical management of epilepsy. It is also suggested in the literature that an underlying genetic cause leading to a specific morphological abnormality and discrete histopathological findings could potentially affect the likelihood of seizure freedom after surgery and the risk of recurrence [134, 135]. In these cases, it is essential that the possibility of dual pathology be considered, especially for relatively common entities. A recent retrospective multicentre analysis of patients carrying *SCN1A* variants who underwent epilepsy surgery showed that a clear electroclinical phenotype of Dravet is not associated with good surgical outcomes, even in cases with well-defined lesions. However, when the Dravet phenotype is not predominant, patients with an isolated epileptogenic focus in association with an SCN1A variant could benefit from a surgical approach [136]. In other words, in the presence of genetic variants, the phenotypic expression most often guides appropriate management.

At the same time, focal cortical dysplasias comprise a broad spectrum of disorders, and it is often hard to identify significant clinical factors suggestive of the outcome of surgical treatment [137, 138]. Therefore, molecular findings in children with focal brain malformations should be systematically investigated, as they could contribute to a better stratification of these patients, which may prove to be of crucial importance in terms of accurate diagnosis and individualized approach (Figure 3).

Epilepsy surgery and social inequalities

Although, in many cases, epilepsy diagnosis and management are simple and straightforward, in some others, definite diagnosis, classification, and therapeutic approach are the source of significant controversy [139]. An accurate diagnosis often needs advanced investigations not easily available in all healthcare systems, and subsequently, the approach to a patient with epilepsy may reflect the resources and the socioeconomical status of a country. These discrepancies are also reflected in the field of epilepsy surgery.

It is noteworthy that access to antiseizure medications remains inadequate in some limited-resources countries. More specifically, although the availability of antiseizure medications has increased over the last years alongside a decrease in their cost [140], the resource burden of epilepsy surgery and pre-surgical screening procedures is still heavy in many parts of the world. This fact inevitably exacerbates disparities between different nations [141, 142]. This can be to the extent that assessment of whether drug-resistant epilepsy is present cannot be confirmed [143]. From this point of view, in the setting of well-defined lesional cases based on ictal EEG and neuroimaging, epilepsy surgery could be considered a more viable and definitive intervention.

In general, strategies to reduce the cost of epilepsy surgery for low-income populations need to be discussed [144]. Some research groups have suggested selection criteria for specific types of epilepsy surgery (extra-temporal, anterior temporal lobectomy, hemispherectomy, focal lesionectomy), which are mainly based on EEG and MRI findings and could be applied in poor-resources settings, especially in those lacking Level 2 centres [25, 145, 146]. In addition, "when to stop" criteria could be helpful in terms of avoiding prolonged investigations in non-eligible children. This is particularly significant, as even minimally invasive diagnostic procedures (e.g., SEEG) may be associated with complications.

Although none of the aforementioned studies were conducted in a pure paediatric population, their findings and suggestions could also be applied to paediatric patients. Although the focus on individualized treatments has been the hallmark of medical research over the past decades, emerging public health challenges and social turmoil underscore the need for flexible healthcare services responding to changing needs, and epilepsy surgery has also to be in line with the trends of the time [146].

What can we learn from the evolution of paediatric epilepsy surgery?

Having a closer look at the milestones in epilepsy surgery history and the challenges we have encountered, one realizes that a series of valuable lessons could be learnt. First of all, the advent and wide implementation of epilepsy surgery in children have had a remarkable effect on how these patients are treated. The requirement for an extensive pre-surgical work-up has significantly improved and broadened the way paediatric patients with epilepsy are approached and evaluated, upgrading the quality of care provided. New complex needs and problems of this population have been identified, and this fact has contributed to a deeper understanding of additional aspects of this disorder. At the same time, thorough pre-surgical investigations remind us of the need for multidisciplinary assessment of patients with complex health needs before applying any kind of treatment. In parallel, the advances in the pre-surgical investigational tools permit an individualized approach to these children and introduce a different type of precision medicine, which does not necessarily require genetic testing.

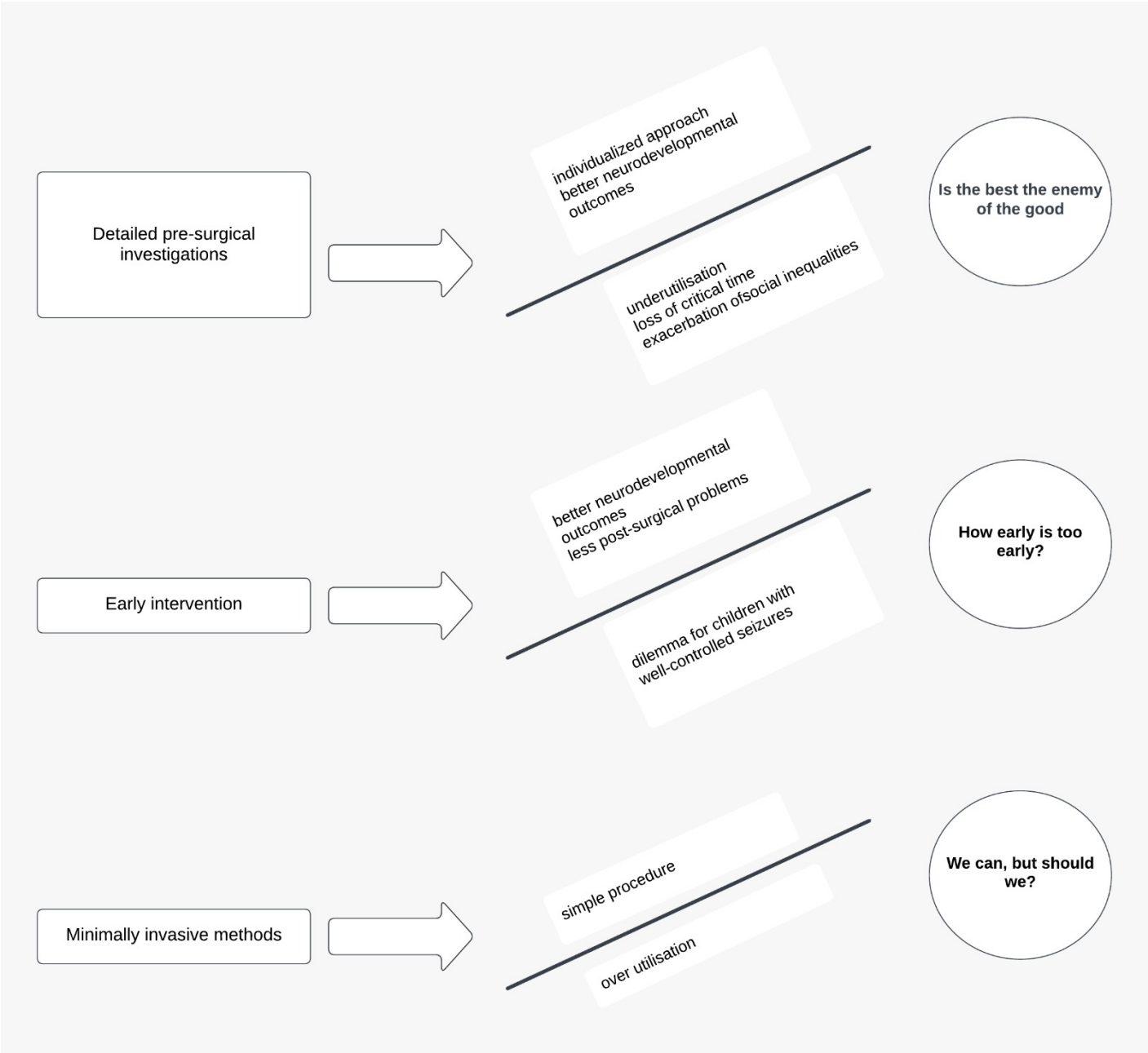

Figure 3. Major steps in the field of paediatric epilepsy surgery and arising challenges.

As new therapies are added, and existing therapies are refined, it is obvious that comparing various aspects of different treatment options will be a routine practice. Clinicians should also be familiar that decisions about any management strategies need to be based on validated evidence.

In general, the development of epilepsy surgery has paved the way for future innovations in paediatric epilepsy and provided an essential framework for how these children should be approached and investigated.

At the same time, challenges in paediatric epilepsy surgery reflect general challenges in epilepsy management. Whereas the clinical approach to some patients is clear and indisputable, some other cases may be associated with controversy in terms of the extent of the surgical procedure or even its necessity and, therefore, require a reasonable balance of benefits and risks and management in a high-level specialist epilepsy centre with accumulated experience. In other words, epilepsy surgery development is a gentle reminder of two innate features of epilepsy, which are complexity and heterogeneity. It is an imperative reminder of a fundamental principle of paediatric care. The wide availability of antiseizure medications often makes us forget; that the aim is to address children's needs, improve their lives, and not just achieve symptom control. In summary, the history, the progress, and the challenges associated with epilepsy surgery in children are teaching us basic lessons about the medical approach to child health promotion.

Limitations

Our review presents some limitations. First of all, due to the increasingly emerging number of papers about epilepsy surgery in childhood, we had to restrict our search and focus on studies published over the last ten years and on those having specific and well-defined outcomes. Studies fulfilling our selection criteria exhibited heterogeneity with regard to the selection of the population, sample size, type of epilepsy, and underlying etiology, as well as definition and measurement of the main outcomes. This variability inevitably limits the comparability of the results between different studies. The vast majority of the articles selected represented retrospective studies and only one randomized trial was identified, which decreases the evidence level. The assessment of risk bias in the selected papers was based on the authors' judgment. Similarly, the areas highlighted in our manuscript as the current challenges in paediatric epilepsy surgery were selected according to the personal judgment of the authors. In this way, some degree of bias might have been introduced in presenting current literature data.

Conclusion

Epilepsy surgery has a definite role in managing children with drug-resistant focal onset epilepsy allowing seizure freedom and an early reduction of the antiseizure medications. The long-term effect on multiple aspects of neurodevelopment needs to be more thoroughly investigated. At the same time, efforts should also be made to increase its utilization. The protection of cognitive function must always be a priority, and the use of additional endpoints when designing studies could permit a more global evaluation of epilepsy surgery outcomes. Minimally invasive methods promise to minimize the risks and multiply the benefits for the patients and undoubtedly represent a featured goal for future research. At the same time, the embodiment of data about genotype into clinical practice paves the way for more targeted approaches. In addition, rendering surgical treatment of epilepsy more accessible for patients in healthcare systems with low resources is still an open challenge, given that new technologies mainly drive its most emerging advents. It is precisely this attempt for generalization of the use of epilepsy surgery, but in carefully selected children and with the least invasive methods, that makes future clinical research in this field more than a challenge.

Finally, aspects of epilepsy surgery in childhood have long been investigated; its possibilities to benefit paediatric patients in all fields of their lives are yet to be fully explored. The balance between potential and limitations needs to be always considered. Like most medical breakthroughs, so does epilepsy surgery have the traits of "Lernaean Hydra": for every problem that is "chopped off", new and more complex challenges and dilemmas arise...

Abbreviations

EEG:	Electroencephalogram
ILAE:	International League Against Epilepsy
MRI:	Magnetic Resonance Imaging
SEEG:	Stereoencephalography
VNS:	Vagus Nerve Stimulation

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Competing interests

None.

Author contributions

JHC conceived and designed the study, interpreted data, and critically revised the manuscript for important intellectual content. MG acquired and analysed data and wrote the manuscript. JHC and MG have given final approval of the version to be published.

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References

[1] Wilmshurst JM, Berg AT, Lagae L, Newton CR, Cross JH. The challenges and innovations for therapy in children with epilepsy. Nature Reviews Neurology. 2014;10(5):249-60. **PubMed**.

[2] West S, Nevitt SJ, Cotton J, Gandhi S, Weston J, Sudan A, et al. Surgery for epilepsy. Cochrane Database of Systematic Reviews. 2019. **PubMed**.

[3] Dwivedi R, Ramanujam B, Chandra PS, Sapra S, Gulati S, Kalaivani M, et al. Surgery for Drug-Resistant Epilepsy in Children. New England Journal of Medicine. 2017;377(17):1639-47. **PubMed**.

[4] Jr JE. Evolution of concepts in epilepsy surgery. Epileptic Disord. 2019;21(5):391-409. **PubMed**.

[5] Lüders H, Najm I, Nair D, Widdess-Walsh P, Bingman W. The epileptogenic zone: general principles. Epileptic Disord. 2006;10(2):1-4. **PubMed**.

[6] Baud MO, Perneger T, Rácz A, Pensel MC, Elger C, Rydenhag B, et al. European trends in epilepsy surgery. Neurology. 2018;91(2):e96-e106. **PubMed**.

[7] Harvey AS, Cross JH, Shinnar S, and GWM. Defining the spectrum of international practice in pediatric epilepsy surgery patients. Epilepsia. 2008;49(1):146-55. **PubMed**.

[8] Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343(oct18 2):d5928-8. **PubMed**.

[9] Hinneburg I. ROBINS-1: A tool for asssessing risk of bias in non-randomised studies of interventions. Med Monatsschr Pharm. 2017;40(4):175-7. **PubMed**.

[10] McLellan A, Davies S, Heyman I, Harding B, Harkness W, Taylor D, et al. Psychopathology in children with epilepsy before and after temporal lobe resection. Developmental Medicine and Child Neurology. 2005;47(10):666-72. **PubMed**.

[11] Colonnelli MC, Cross JH, Davies S, D'argenzio L, Scott RC, Pickles A, et al. Psychopathology in children before and after surgery for extratemporal lobe epilepsy. Developmental Medicine & Child Neurology. 2012;54(6):521-6. **PubMed**.

[12] Barba C, Cross JH, Braun K, Cossu M, Klotz KA, Masi SD, et al. Trends in pediatric epilepsy surgery in Europe between 2008 and 2015: Country-, center-, and age-specific variation. Epilepsia. 2019;61(2):216-27. **PubMed**.

[13] Sokka A, Olsen P, Kirjavainen J, Harju M, Keski-Nisula L, Räisänen S, et al. Etiology, syndrome diagnosis, and cognition in childhood-onset epilepsy: A population-based study. Epilepsia Open. 2017;2(1):76-83. **PubMed**.

[14] Cross JH, Jayakar P, Nordli D, Delalande O, Duchowny M, Wieser HG, et al. Proposed Criteria for Referral and Evaluation of Children for Epilepsy Surgery: Recommendations of the Subcommission for Pediatric Epilepsy Surgery. Epilepsia. 2006;47(6):952-9. **PubMed**.

[15] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2009;51(6):1069-77. **PubMed**.

[16] Braun KPJ, Cross JH. Pediatric epilepsy surgery: the earlier the better. Expert Review of Neurotherapeutics. 2018 Mar;18(4):261-3. **PubMed**. Available from: https://doi.org/10.1080/14737175.2018.1455503.

[17] Jayakar P, Gaillard WD, Tripathi M, Libenson MH, Mathern GW, and JHC. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014;55(4):507-18. **PubMed**.

[18] Burch J, Hinde S, Palmer S, Beyer F, Minton J, Marson A, et al. The clinical effectiveness and cost-effectiveness of technologies used to visualise the seizure focus in people with refractory epilepsy being considered for surgery: a systematic review and decision-analytical model. Health Technology Assessment. 2012;16(34). **PubMed**.

[19] Mellerio C, Labeyrie MA, Chassoux F, Roca P, Alami O, Plat M, et al. 3T MRI improves the detection of transmantle sign in type 2 focal cortical dysplasia. Epilepsia. 2013;55(1):117-22. **PubMed**.

[20] Wagner J, Weber B, Urbach H, Elger CE, Huppertz HJ. Morphometric MRI analysis improves detection of focal cortical dysplasia type II. Brain. 2011 Sep;134(10):2844-54. **PubMed**. Available from: https://doi.org/10.1093/brain/awr204.

[21] Winston GP, Daga P, Stretton J, Modat M, Symms MR, McEvoy AW, et al. Optic radiation tractography and vision in anterior temporal lobe resection. Annals of Neurology. 2012;71(3):334-41. **PubMed**.

[22] Jin P, Wu D, Li X, Ren L, Wang Y. Towards precision medicine in epilepsy surgery. Annals of translational medicine. 2016 02;4:24. **PubMed**.

[23] Zhao R, Xue P, Zhou Y, Yang H, Zhou S, Wang Y, et al. Application of Robot-Assisted Frameless Stereoelectroencephalography Based on Multimodal Image Guidance in Pediatric Refractory Epilepsy: Experience of a Pediatric Center in a Developing Country. World Neurosurgery. 2020;140:e161-8. **PubMed**.

[24] Kim LH, Parker JJ, Ho AL, Pendharkar AV, Sussman ES, Halpern CH, et al. Postoperative outcomes following pediatric intracranial electrode monitoring: A case for stereoelectroencephalography (SEEG). Epilepsy & Behavior. 2020;104:106905. **PubMed**.

[25] Sharma JD, Seunarine KK, Tahir MZ, Tisdall MM. Accuracy of robot-assisted versus optical frameless navigated stereoelectroencephalography electrode placement in children. Journal of Neurosurgery: Pediatrics. 2019;23(3):297-302. **PubMed**.

[26] McGovern RA, Knight EP, Gupta A, Moosa ANV, Wyllie E, Bingaman WE, et al. Robot-assisted stereoelectroencephalography in children. Journal of Neurosurgery: Pediatrics. 2019;23(3):288-96. **PubMed**.

[27] Candela-Cantó S, Aparicio J, López JM, Baños-Carrasco P, Ramírez-Camacho A, Climent A, et al. Frameless robot-assisted stereoelectroencephalography for refractory epilepsy in pediatric patients: accuracy, usefulness, and technical issues. Acta Neurochirurgica. 2018;160(12):2489-500. **PubMed**.

[28] Ho AL, Muftuoglu Y, Pendharkar AV, Sussman ES, Porter BE, Halpern CH, et al. Robot-guided pediatric stereoelectroencephalography: single-institution experience. Journal of Neurosurgery: Pediatrics. 2018;22(5):489-96. **PubMed**.

[29] Goldstein HE, Youngerman BE, Shao B, Akman CI, Mandel AM, McBrian DK, et al. Safety and efficacy of stereoelectroencephalography in pediatric focal epilepsy: a single-center experience. Journal of Neurosurgery: Pediatrics. 2018;22(4):444-52. **PubMed**.

[30] Abel TJ, Osorio RV, Amorim-Leite R, Mathieu F, Kahane P, Minotti L, et al. Frameless robot-assisted stereoelectroencephalography in children: technical aspects and comparison with Talairach frame technique. Journal of Neurosurgery: Pediatrics. 2018;22(1):37-46. **PubMed**.

[31] Taussig D, Lebas A, Chipaux M, Jan M, Fohlen M, Bulteau C, et al. Stereo-electroencephalography (SEEG) in children surgically cured of their epilepsy. Neurophysiologie Clinique/Clinical Neurophysiology. 2016;46(1):3-15. **PubMed**.

[32] Dorfmüller G, Ferrand-Sorbets S, Fohlen M, Bulteau C, Archambaud F, Delalande O, et al. Outcome of surgery in children with focal cortical dysplasia younger than 5 years explored by stereo-electroencephalography. Child's Nervous System. 2014;30(11):1875-83. **PubMed**.

[33] Taussig D, Chipaux M, Lebas A, Fohlen M, Bulteau C, Ternier J, et al. Stereo-electroencephalography (SEEG) in 65 children: an effective and safe diagnostic method for pre-surgical diagnosis, independent of age. Epileptic Disorders. 2014;16(3):280-95. **PubMed**.

[34] Gonzalez-Martinez J, Mullin J, Bulacio J, Gupta A, Enatsu R, Najm I, et al. Stereoelectroencephalography in Children and Adolescents With Difficult-to-Localize Refractory Focal Epilepsy. Neurosurgery. 2014;75(3):258-68. **PubMed**.

[35] Cossu M, Schiariti M, Francione S, Fuschillo D, Gozzo F, Nobili L, et al. Stereoelectroencephalography in the presurgical evaluation of focal epilepsy in infancy and early childhood. Journal of Neurosurgery: Pediatrics. 2012;9(3):290-300. **PubMed**.

[36] Gaillard N WD Jette, ST A, Arzimanoglou A, Braun K, Cukiert A, Dick A, et al. Task Force for Paediatric Epilepsy Surgery, Commission for Paediatrics, and the Surgical Commission of the International League Against Epilepsy. Epilepsia submitted. nd.

[37] d'Orio P, Rizzi M, Mariani V, Pelliccia V, Russo GL, Cardinale F, et al. Surgery in patients with childhood-onset epilepsy: analysis of complications and predictive risk factors for a severely complicated course. Journal of Neurology, Neurosurgery & Psychiatry. 2018;90(1):84-9. **PubMed**.

[38] Widjaja E, Jain P, Demoe L, Guttmann A, Tomlinson G, Sander B. Seizure outcome of pediatric epilepsy surgery. Neurology. 2020;94(7):311-21. **PubMed**.

[39] Englot DJ, Rolston JD, Wang DD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after temporal lobectomy in pediatric patients. Journal of Neurosurgery: Pediatrics. 2013;12(2):134-41. **PubMed**.

[40] Englot DJ, Breshears JD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after resective surgery for extra–temporal lobe epilepsy in pediatric patients. Journal of Neurosurgery: Pediatrics. 2013;12(2):126-33. **PubMed**.

[41] Harris WB, Phillips HW, Chen JS, Weil AG, Ibrahim GM, Fallah A. Seizure outcomes in children with Rasmussen's encephalitis undergoing resective or hemispheric epilepsy surgery: an individual participant data meta-analysis. Journal of Neurosurgery: Pediatrics. 2020;25(3):274-83. **PubMed**.

[42] Orosz I, McCormick D, Zamponi N, Varadkar S, Feucht M, Parain D, et al. Vagus nerve stimulation for drug-resistant epilepsy: A European long-term study up to 24 months in 347 children. Epilepsia. 2014;55(10):1576-84. **PubMed**.

[43] Elliott RE, Rodgers SD, Bassani L, Morsi A, Geller EB, Carlson C, et al. Vagus nerve stimulation for children with treatment-resistant epilepsy: a consecutive series of 141 cases. Journal of Neurosurgery: Pediatrics. 2011;7(5):491-500. **PubMed**.

[44] Tsai JD, Fan PC, Lee WT, Hung PL, Hung KL, Wang HS, et al. Vagus nerve stimulation in pediatric patients with failed epilepsy surgery. Acta Neurologica Belgica. 2020;121(5):1305-9. **PubMed**.

[45] Welch WP, Sitwat B, Sogawa Y. Use of Vagus Nerve Stimulator on Children With Primary Generalized Epilepsy. Journal of Child Neurology. 2018;33(7):449-52. **PubMed**.

[46] Gedela S, Sitwat B, Welch WP, Krafty RT, Sogawa Y. The effect of vagus nerve stimulator in controlling status epilepticus in children. Seizure. 2018;55:66-9. **PubMed**.

[47] Santhumayor B, Karkare S, Kothare S, Rodgers S. Evaluating vagus nerve stimulation treatment with heart rate monitoring in pediatric patients with intractable epilepsy. Child's Nervous System. 2021;38(3):547-56. **PubMed**.

[48] Lo WB, Chevill B, Philip S, Agrawal S, Walsh AR. Seizure improvement following vagus nerve stimulator (VNS) battery change with cardiac-based seizure detection automatic stimulation (AutoStim): early experience in a regional paediatric unit. Child's Nervous System. 2020;37(4):1237-41. **PubMed**.

[49] Pearce K, Dixon L, D'Arco F, Pujar S, Das K, Tahir Z, et al. Epilepsy surgery in children: what the radiologist needs to know. Neuroradiology. 2020;62(9):1061-78. **PubMed**.

[50] Tovar-Spinoza Z, Ziechmann R, Zyck S. Single and staged laser interstitial thermal therapy ablation for cortical tubers causing refractory epilepsy in pediatric patients. Neurosurgical Focus. 2018;45(3):E9. **PubMed**.

[51] Fayed I, Sacino MF, Gaillard WD, Keating RF, Oluigbo CO. MR-Guided Laser Interstitial Thermal Therapy for Medically Refractory Lesional Epilepsy in Pediatric Patients: Experience and Outcomes. Pediatric Neurosurgery. 2018;53(5):322-9. **PubMed**.

[52] Curry DJ, Raskin J, Ali I, Wilfong AA. MR-guided laser ablation for the treatment of hypothalamic hamartomas. Epilepsy Research. 2018;142:131-4. **PubMed**.

[53] Southwell DG, Birk HS, Larson PS, Starr PA, Sugrue LP, Auguste KI. Laser ablative therapy of sessile hypothalamic hamartomas in children using interventional MRI: report of 5 cases. Journal of Neurosurgery: Pediatrics. 2018;21(5):460-5. **PubMed**.

[54] Lewis EC, Weil AG, Duchowny M, Bhatia S, Ragheb J, Miller I. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. Epilepsia. 2015;56(10):1590-8. **PubMed**.

[55] Calisto A, Dorfmüller G, Fohlen M, Bulteau C, Conti A, Delalande O. Endoscopic disconnection of hypothalamic hamartomas: safety and feasibility of robot-assisted, thulium laser–based procedures. Journal of Neurosurgery: Pediatrics. 2014;14(6):563-72. **PubMed**.

[56] Curry DJ, Gowda A, McNichols RJ, Wilfong AA. MR-guided stereotactic laser ablation of epileptogenic foci in children. Epilepsy & Behavior. 2012;24(4):408-14. **PubMed**.

[57] Anderson DG, Németh AH, Fawcett KA, Sims D, Miller J, Krause A. Deep Brain Stimulation in Three Related Cases of North Sea Progressive Myoclonic Epilepsy from South Africa. Movement Disorders Clinical Practice. 2016 Jun;4(2):249-53. **PubMed**. Available from: https://doi.org/10.1002/mdc3.12372.

[58] Benedetti-Isaac JC, Torres-Zambrano M, Vargas-Toscano A, Perea-Castro E, Alcalá-Cerra G, Furlanetti LL, et al. Seizure frequency reduction after posteromedial hypothalamus deep brain stimulation in drug-resistant epilepsy associated with intractable aggressive behavior. Epilepsia. 2015;56(7):1152-61. **PubMed**.

[59] Cukiert A, Cukiert CM, Burattini JA, Mariani PP, Bezerra DF. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. Epilepsia. 2017;58(10):1728-33. **PubMed**.

[60] Yan H, Toyota E, Anderson M, Abel TJ, Donner E, Kalia SK, et al. A systematic review of deep brain stimulation for the treatment of drug-resistant epilepsy in childhood. Journal of Neurosurgery: Pediatrics. 2019;23(3):274-84. **PubMed**.

[61] Sa M, Singh R, Pujar S, D'Arco F, Desai N, Eltze C, et al. Centromedian thalamic nuclei deep brain stimulation and Anakinra treatment for FIRES – Two different outcomes. European Journal of Paediatric Neurology. 2019;23(5):749-54. **PubMed**.

[62] Kokoszka MA, Panov F, Vega-Talbott ML, McGoldrick PE, Wolf SM, Ghatan S. Treatment of medically refractory seizures with responsive neurostimulation: 2 pediatric cases. Journal of Neurosurgery: Pediatrics. 2018;21(4):421-7. **PubMed**.

[63] Valentín A, Selway RP, Amarouche M, Mundil N, Ughratdar I, Ayoubian L, et al. Intracranial stimulation for children with epilepsy. European Journal of Paediatric Neurology. 2017;21(1):223-31. **PubMed**.

[64] Hamed SA. The Aspects and Mechanisms of Cognitive Alterations in Epilepsy: The Role of Antiepileptic Medications. CNS Neuroscience & Therapeutics. 2009;15(2):134-56. **PubMed**.

[65] Moavero R, Santarone ME, Galasso C, Curatolo P. Cognitive and behavioral effects of new antiepileptic drugs in pediatric epilepsy. Brain and Development. 2017;39(6):464-9. **PubMed**.

[66] Leal STF, Santos MV, Thomé U, Machado HR, Escorsi-Rosset S, dos Santos AC, et al. Impact of epilepsy surgery on quality of life and burden of caregivers in children and adolescents. Epilepsy & Behavior. 2020;106:106961. **PubMed**.

[67] Ko A, Lee JS. Factors associated with seizure and cognitive outcomes after epilepsy surgery for low-grade epilepsy-associated neuroepithelial tumors in children. Clinical and Experimental Pediatrics. 2020;63(5):171-7. **PubMed**.

[68] Marashly A, Koop J, Loman M, Lee YW, Lew SM. Examining the Utility of Resective Epilepsy Surgery in Children With Electrical Status Epilepticus in Sleep: Long Term Clinical and Electrophysiological Outcomes. Frontiers in Neurology. 2020;10. **PubMed**.

[69] Grayson LE, Peters JM, McPherson T, Krueger DA, Sahin M, Wu JY, et al. Pilot Study of Neurodevelopmental Impact of Early Epilepsy Surgery in Tuberous Sclerosis Complex. Pediatric Neurology. 2020;109:39-46. **PubMed**.

[70] Skirrow C, Cross JH, Owens R, Weiss-Croft L, Martin-Sanfilippo P, Banks T, et al. Determinants of IQ outcome after focal epilepsy surgery in childhood: A longitudinal case-control neuroimaging study. Epilepsia. 2019;60(5):872-84. **PubMed**.

[71] Helmstaedter C, Beeres K, Elger CE, Kuczaty S, Schramm J, Hoppe C. 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. 2020;77:86-92. **PubMed**.

[72] Benova B, Belohlavkova A, Jezdik P, Jahodová A, Kudr M, Komarek V, et al. Cognitive performance in distinct groups of children undergoing epilepsy surgery—a single-centre experience. PeerJ. 2019;7:e7790. **PubMed**.

[73] Wang Y, Zhang C, Wang X, Sang L, Zhou F, Zhang JG, et al. Seizure and cognitive outcomes of posterior quadrantic disconnection: a series of 12 pediatric patients. British Journal of Neurosurgery. 2019;34(6):677-82. **PubMed**.

[74] Danguecan AN, Smith ML. Verbal associative memory outcomes in pediatric surgical temporal lobe epilepsy: Exploring the impact of mesial structures. Epilepsy & Behavior. 2019;101:106529. **PubMed**.

[75] Hoppe C, Porębska I, Beeres K, Sassen R, Kuczaty S, Gleissner U, et al. Parents' view of the cognitive outcome one year after pediatric epilepsy surgery. Epilepsy & Behavior. 2019;101:106552. **PubMed**.

[76] Kadish NE, Bast T, Reuner G, Wagner K, Mayer H, Schubert-Bast S, et al. Epilepsy Surgery in the First 3 Years of Life: Predictors of Seizure Freedom and Cognitive Development. Neurosurgery. 2018;84(6):E368-77. **PubMed**.

[77] Baba H, Toda K, Ono T, Honda R, Baba S. Surgical and developmental outcomes of corpus callosotomy for West syndrome in patients without MRI lesions. Epilepsia. 2018;59(12):2231-9. **PubMed**.

[78] Faramand AM, Barnes N, Harrison S, Gunny R, Jacques T, Tahir MZ, et al. Seizure and cognitive outcomes after resection of glioneuronal tumors in children. Epilepsia. 2017;59(1):170-8. **PubMed**.

[79] Ramantani G, Kadish NE, Mayer H, Anastasopoulos C, Wagner K, Reuner G, et al. Frontal Lobe Epilepsy Surgery in Childhood and Adolescence: Predictors of Long-Term Seizure Freedom, Overall Cognitive and Adaptive Functioning. Neurosurgery. 2017;83(1):93-103. **PubMed**.

[80] Sierra-Marcos A, del Castillo MCF, Álvarez-Linera J, Budke M, García-Fernández M, Pérez-Jiménez MA. Functional surgery in pediatric drug-resistant posterior cortex epilepsy: Electro-clinical findings, cognitive and seizure outcome. Seizure. 2017;52:46-52. **PubMed**.

[81] Puka K, Tavares TP, Smith ML. Development of intelligence 4 to 11 years after paediatric epilepsy surgery. Journal of Neuropsychology. 2015;11(2):161-73. **PubMed**.

[82] Law N, Benifla M, Rutka J, Smith ML. Verbal memory after temporal lobe epilepsy surgery in children: Do only mesial structures matter? Epilepsia. 2016;58(2):291-9. **PubMed**.

[83] Gröppel G, Dorfer C, Dressler A, Mühlebner A, Porsche B, Hainfellner JA, et al. Immediate termination of electrical status epilepticus in sleep after hemispherotomy is associated with significant progress in language development. Developmental Medicine & Child Neurology. 2016;59(1):89-97. **PubMed**.

[84] Sibilia V, Barba C, Metitieri T, Michelini G, Giordano F, Genitori L, et al. Cognitive outcome after epilepsy surgery in children: A controlled longitudinal study. Epilepsy & Behavior. 2017;73:23-30. **PubMed**.

[85] Puka K, Smith ML. Remembrance and time passed: Memory outcomes 4-11 years after pediatric epilepsy surgery. Epilepsia. 2016;57(11):1798-807. **PubMed**.

[86] Puka K, Smith ML. Predictors of language skills in the long term after pediatric epilepsy surgery. Epilepsy & Behavior. 2016 Oct;63:1-8. **PubMed**.

[87] Puka K, Smith ML. Academic skills in the long term after epilepsy surgery in childhood. Epilepsy & Behavior. 2016;62:97-103. **PubMed**.

[88] Meekes J, Chanturidze M, Braams OB, Braun KPJ, van Rijen PC, Hendriks MPH, et al. Lexicon before and after epilepsy surgery in adolescents. Neuropsychology. 2016;30(4):416-24. **PubMed**.

[89] Law N, Kerr E, Smith ML. Evaluation of behavioral outcomes in children 1 year after epilepsy surgery. Epilepsia. 2015 Aug;56(10):1605-14. **PubMed**. Available from: https://doi.org/10.1111/epi.13126.

[90] Shurtleff HA, Barry D, Firman T, Warner MH, Aguilar-Estrada RL, Saneto RP, et al. Impact of epilepsy surgery on development of preschool children: identification of a cohort likely to benefit from early intervention. Journal of Neurosurgery: Pediatrics. 2015;16(4):383-92. **PubMed**.

[91] Skirrow C, Cross JH, Harrison S, Cormack F, Harkness W, Coleman R, et al. Temporal lobe surgery in childhood and neuroanatomical predictors of long-term declarative memory outcome. Brain. 2015;138(1):80-93. **PubMed**.

[92] Bulteau C, Grosmaitre C, Save-Pédebos J, Leunen D, Delalande O, Dorfmüller G, et al. Language recovery after left hemispherotomy for Rasmussen encephalitis. Epilepsy & Behavior. 2015;53:51-7. **PubMed**.

[93] de Bode S, Smets L, Mathern GW, Dubinsky S. Complex syntax in the isolated right hemisphere: Receptive grammatical abilities after cerebral hemispherectomy. Epilepsy & Behavior. 2015;51:33-9. **PubMed**.

[94] Gröppel G, Dorfer C, Mühlebner-Fahrngruber A, Dressler A, Porsche B, Czech T, et al. Improvement of language development after successful hemispherotomy. Seizure. 2015;30:70-5. **PubMed**.

[95] Downes M, Greenaway R, Clark M, Cross JH, Jolleff N, Harkness W, et al. Outcome following multiple subpial transection in Landau-Kleffner syndrome and related regression. Epilepsia. 2015;56(11):1760-6. **PubMed**.

[96] Chen HH, Chen C, Hung SC, Liang SY, Lin SC, Hsu TR, et al. Cognitive and epilepsy outcomes after epilepsy surgery caused by focal cortical dysplasia in children: early intervention maybe better. Child's Nervous System. 2014;30(11):1885-95. **PubMed**.

[97] Ramantani G, Kadish NE, Anastasopoulos C, Brandt A, Wagner K, Strobl K, et al. Epilepsy Surgery for Glioneuronal Tumors in Childhood. Neurosurgery. 2014;74(6):648-57. **PubMed**.

[98] Lee YJ, Lee JS, Kang HC, Kim DS, Shim KW, Eom S, et al. Outcomes of epilepsy surgery in childhood-onset epileptic encephalopathy. Brain and Development. 2014;36(6):496-504. **PubMed**.

[99] Lee YJ, Kim EH, Yum MS, Lee JK, Hong S, Ko TS. Long-Term Outcomes of Hemispheric Disconnection in Pediatric Patients with Intractable Epilepsy. Journal of Clinical Neurology. 2014;10(2):101. **PubMed**.

[100] Park SY, Kwon HE, Kang HC, Lee JS, Kim DS, Kim HD. Epilepsy Surgery in Pediatric Intractable Epilepsy with Destructive Encephalopathy. Journal of Epilepsy Research. 2013;3(2):48-53. **PubMed**.

[101] Hallböök T, Tideman P, Rosén I, Lundgren J, Tideman E. Epilepsy surgery in children with drug-resistant epilepsy, a long-term follow-up. Acta Neurologica Scandinavica. 2013 Jun;128(6):414-21. **PubMed**.

[102] Ramantani G, Kadish NE, Strobl K, Brandt A, Stathi A, Mayer H, et al. Seizure and cognitive outcomes of epilepsy surgery in infancy and early childhood. European Journal of Paediatric Neurology. 2013;17(5):498-506. **PubMed**.

[103] Villarejo-Ortega F, García-Fernández M, Castillo CFD, Fabregate-Fuente M, Álvarez-Linera J, Prada-Vicente ID, et al. Seizure and developmental outcomes after hemispherectomy in children and adolescents with intractable epilepsy. Child's Nervous System. 2012;29(3):475-88. **PubMed**.

[104] Beaton AE, Durnford A, Heffer-Rahn PE, Kirkham F, Griffin A, Gray WLS. Transsylvian selective amygdalohippocampectomy in children with hippocampal sclerosis: Seizure, intellectual and memory outcome. Seizure. 2012;21(9):699-705. **PubMed**.

[105] Iwatani Y, Kagitani-Shimono K, Tominaga K, Okinaga T, Mohri I, Kishima H, et al. Long-term developmental outcome in patients with West syndrome after epilepsy surgery. Brain and Development. 2012;34(9):731-8. **PubMed**.

[106] Liu SY, An N, Yang MH, Hou Z, Liu Y, Liao W, et al. Surgical treatment for epilepsy in 17 children with tuberous sclerosis-related West syndrome. Epilepsy Research. 2012;101(1-2):36-45. **PubMed**.

[107] Aaberg K, Eriksson AS, Ramm-Pettersen J, Nakken K. Long-term outcome of resective epilepsy surgery in Norwegian children. Acta Paediatrica. 2012;101(12):e557-60. **PubMed**.

[108] García-Fernández M, Castillo CFD, Ugalde-Canitrot A, Pérez-Jiménez Á, Álvarez-Linera J, Prada-Vicente ID, et al. Epilepsy surgery in children with developmental tumours. Seizure. 2011;20(8):616-27. **PubMed**.

[109] Skirrow C, Cross JH, Cormack F, Harkness W, Vargha-Khadem F, Baldeweg T. Long-term intellectual outcome after temporal lobe surgery in childhood. Neurology. 2011;76(15):1330-7. **PubMed**.

[110] Dunkley C, Kung J, Scott RC, Nicolaides P, Neville B, Aylett SE, et al. Epilepsy surgery in children under 3 years. Epilepsy Research. 2011;93(2-3):96-106. **PubMed**.

[111] Peltola ME, Liukkonen E, Granström ML, Paetau R, Kantola-Sorsa E, Valanne L, et al. The effect of surgery in encephalopathy with electrical status epilepticus during sleep. Epilepsia. 2010;52(3):602-9. **PubMed**.

[112] Lippé S, Bulteau C, Dorfmuller G, Audren F, Delalande O, Jambaqué I. Cognitive outcome of parietooccipital resection in children with epilepsy. Epilepsia. 2010;51(10):2047-57. **PubMed**.

[113] McLellan A, Davies S, Heyman I, Harding B, Harkness W, Taylor D, et al. Psychopathology in children with epilepsy before and after temporal lobe resection. Developmental Medicine and Child Neurology. 2005;47(10):666. **PubMed**.

[114] Qualmann KJ, Spaeth CG, Myers MF, Horn PS, Holland K, Mangano FT, et al. Pediatric Epilepsy Surgery. Journal of Child Neurology. 2017;32(5):467-74. **PubMed**.

[115] Kokoszka MA, McGoldrick PE, Vega-Talbott ML, Raynes H, Palmese CA, Wolf SM, et al. Epilepsy surgery in patients with autism. Journal of Neurosurgery: Pediatrics. 2017;19(2):196-207. **PubMed**.

[116] Reilly C, Hallböök T, Viggedal G, Rydenhag B, Uvebrant P, Olsson I. Parent-reported symptoms of ADHD in young people with epilepsy before and two years after epilepsy surgery. Epilepsy & Behavior. 2019 May;94:29-34. **PubMed**. Available from: https://doi.org/10.1016/j.yebeh.2019.02.003.

[117] Vale FL, Pollock G, Benbadis SR. Failed epilepsy surgery for mesial temporal lobe sclerosis: a review of the pathophysiology. Neurosurgical Focus. 2012;32(3):E9. **PubMed**.

[118] Mula M, Cavalheiro E, Guekht A, Kanner AM, Lee HW, Özkara Ç, et al. Educational needs of epileptologists regarding psychiatric comorbidities of the epilepsies: a descriptive quantitative survey. Epileptic Disorders. 2017;19(2):178-85. **PubMed**.

[119] Choi SA, Kim SY, Kim WJ, Shim YK, Kim H, Hwang H, et al. Antiepileptic Drug Withdrawal after Surgery in Children with Focal Cortical Dysplasia: Seizure Recurrence and Its Predictors. Journal of Clinical Neurology. 2019;15(1):84. **PubMed**.

[120] Boshuisen K, Schmidt D, Uiterwaal CSPM, Arzimanoglou A, Braun KPJ, Group TS. Time to relapse after epilepsy surgery in children: AED withdrawal policies are a contributing factor. Epileptic Disorders. 2014;16(3):305-11. **PubMed**.

[121] Boshuisen K, Arzimanoglou A, Cross JH, Uiterwaal CS, Polster T, van Nieuwenhuizen O, et al. Timing of antiepileptic drug withdrawal and long-term seizure outcome after paediatric epilepsy surgery (TimeToStop): a retrospective observational study. The Lancet Neurology. 2012;11(9):784-91. **PubMed**.

[122] Boshuisen K, van Schooneveld MMJ, Uiterwaal CSPM, Cross JH, Harrison S, Polster T, et al. Intelligence quotient improves after antiepileptic drug withdrawal following pediatric epilepsy surgery. Annals of Neurology. 2015;78(1):104-14. **PubMed**.

[123] van Schooneveld MMJ, van Erp N, Boshuisen K, Meekes J, Braun KPJ. Withdrawal of antiepileptic drugs improves psychomotor speed after childhood epilepsy surgery. Epilepsy Research. 2013;107(1-2):200-3. **PubMed**.

[124] Lamberink HJ, Geleijns K, Otte WM, Arzimanoglou A, Cross JH, Korff CM, et al. Why the TimeToStop trial failed to recruit: a survey on antiepileptic drug withdrawal after paediatric epilepsy surgery. Epileptic Disorders. 2018;20(5):374-85. **PubMed**.

[125] Braun K, van Eijsden P. Paediatric epilepsy surgery; the earlier, the better. Ned TijdschrGeneeskd. 2018;162(2587). **PubMed**.

[126] Prideaux L, Barton S, Maixner W, Harvey AS. Potential delays in referral and assessment for epilepsy surgery in children with drug-resistant, early-onset epilepsy. Epilepsy Research. 2018;143:20-6. **PubMed**.

[127] Ladino LD, Benjumea-Cuartas V, Vargas-Osorio J, Villamil-Osorio L, Hernández-Vanegas L, Martínez-Juárez I, et al. Barriers impeding access to epilepsy surgery: A review of the literature. Revista de Neurologia. 2017 09;65:268-79. **PubMed**.

[128] Knight EMP, Schiltz NK, Bakaki PM, Koroukian SM, Lhatoo SD, Kaiboriboon K. Increasing utilization of pediatric epilepsy surgery in the United States between 1997 and 2009. Epilepsia. 2015;56(3):375-81. **PubMed**.

[129] Erba G, Messina P, Pupillo E, Beghi E. Acceptance of epilepsy surgery in the pediatric age — What the parents think and what the doctors can do. Epilepsy & Behavior. 2013;29(1):112-20. **PubMed**.

[130] Shen A, Quaid KT, Porter BE. Delay in pediatric epilepsy surgery: A caregiver's perspective. Epilepsy & Behavior. 2018;78:175-8. **PubMed**.

[131] Kumlien E, Mattsson P. Attitudes towards epilepsy surgery: A nationwide survey among Swedish neurologists. Seizure. 2010;19(4):253-5. **PubMed**.

[132] Zuccato JA, Milburn C, Valiante TA. Balancing health literacy about epilepsy surgery in the community. Epilepsia. 2014;55(11):1754-62. **PubMed**.

[133] Sanders MWCB, Lemmens CMC, Jansen FE, Brilstra EH, Koeleman BPC, and KPJB. Implications of genetic diagnostics in epilepsy surgery candidates: A single-center cohort study. Epilepsia Open. 2019;4(4):609-17. **PubMed**.

[134] Benova B, Jacques TS. Genotype-phenotype correlations in focal malformations of cortical development: a pathway to integrated pathological diagnosis in epilepsy surgery. Brain Pathology. 2019;29(4):473-84. **PubMed**.

[135] Skjei KL, Church EW, Harding BN, Santi M, Holland-Bouley KD, Clancy RR, et al. Clinical and histopathological outcomes in patients with SCN1A mutations undergoing surgery for epilepsy. Journal of Neurosurgery: Pediatrics. 2015;16(6):668-74. **PubMed**.

[136] Vezyroglou A, Varadkar S, Bast T, Hirsch E, Strobl K, Harvey AS, et al. Focal epilepsy in SCN1A-mutation carrying patients: is there a role for epilepsy surgery? Developmental Medicine &Child Neurology. 2020;62(11):1331-5. **PubMed**.

[137] Wang TS, Liu QZ, Liu M, Zhang Q, Wang RF, Wu CW, et al. Clinical features and surgical outcomes in young children with focal cortical dysplasia type II. CNS Neuroscience & Therapeutics. 2019;26(2):270-7. **PubMed**.

[138] Alexandre V, Walz R, Bianchin MM, Velasco TR, Terra-Bustamante VC, Wichert-Ana L, et al. Seizure outcome after surgery for epilepsy due to focal cortical dysplastic lesions. Seizure. 2006;15(6):420-7. **PubMed**.

[139] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58(4):512-21. **PubMed**.

[140] Wilmshurst JM, Burman R, Gaillard WD, Cross JH. Treatment of infants with epilepsy: Common practices around the world. Epilepsia. 2015;56(7):1033-46. **PubMed**.

[141] Burneo JG, Jette N, Theodore W, Begley C, Parko K, Thurman DJ, et al. Disparities in epilepsy: Report of a systematic review by the North American Commission of the International League Against Epilepsy. Epilepsia. 2009;50(10):2285-95. **PubMed**.

[142] Hong Z, Qu B, Wu XT, Yang TH, Zhang Q, Zhou D. Economic burden of epilepsy in a developing country: A retrospective cost analysis in China. Epilepsia. 2009;50(10):2192-8. **PubMed**.

[143] Trinka E, Kwan P, Lee B, Dash A. Epilepsy in Asia: Disease burden, management barriers, and challenges. Epilepsia. 2018;60:7-21. **PubMed**.

[144] Wu XT, Li L, Yan B, Stefan H, Lei D, Zhou D. How to effectively constraint the cost of presurgical evaluation for resective surgery in low-income population: Clinically oriented opinions. Seizure. 2011;20(5):425-7. **PubMed**.

[145] Dash GK, Radhakrishnan A, Kesavadas C, Abraham M, Sarma PS, Radhakrishnan K. An audit of the presurgical evaluation and patient selection for extratemporal resective epilepsy surgery in a resource-poor country. Seizure. 2012;21(5):361-6. **PubMed**.

[146] Wolfe I, Thompson M, Gill P, Tamburlini G, Blair M, van den Bruel A, et al. Health services for children in western Europe. The Lancet. 2013;381(9873):1224-34. **PubMed**.

Table 1. Studies about the use of stereoencephalography in children with drug-resistant epilepsy (FCD: focal cortical dysplasia, m: months, ON: optic navigation, RA: robot-assisted, SEEG: stereoencephalography, SOZ: seizure onset zone). The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Study type	Findings	Risk of bias
Zhao [23]	2020	20 children with drug-resistant epilepsy (16 unilateral, 4 bilateral, 189 electrodes in total)	Retrospective	• 13: tail resection, 7: radiofrequency thermocoagulation • After a mean follow-up of 2.65 y: 13 ILAE class 1, 2 class 2, 3 class 3, 1 class 4, 1 class 5 • 1 patient : electrodes displacement, 2 patients : pneumocephalus	Low
Kim [24]	2020	38 children with drug-resistant epilepsy (22 SEEG, 16 SDE)	Retrospective	SEEG patients (compared to SDE): • ↓ operative time, ↓ length of stay, ↓ days in ICU • similar seizure outcomes • ↓ pain scores No complications in both	Low
Sharma [25]	2019	26 children with drug-resistant epilepsy (14 RA SEEG, 6 ON SEEG), 8-17 electrodes/patient	Retrospective	• No complications • ON: significantly ↑ median target point & median entry point localisation error	Low
McGovern [26]	2018	57 children with drug-resistant epilepsy underwent 64 SEEG procedures, 12.4 electrodes placed per implantation	Retrospective	• SEEG analysis: definable epileptogenic zone in 51 (89%) patients • 74% underwent surgery, and 50% of them were seizure-free 19.6 m later • 1 patient: symptomatic haemorrhage with permanent neurological deficit	Low-Moderate
Candela-Cantó [27]	2018	14 children with drug-resistant epilepsy underwent SEEG (164 electrodes implanted in total)	Prospective	• Median entry point localization error 1.57 mm & median target point localization error 1.77 mm • intraoperative technical issues in 7, aseptic meningitis in 1, right frontal hematoma in 1 • Preimplantation enquiries were answered in 12/14 patients • 10 underwent surgery (resection or disconnection),1 thermocoagulation	Moderate

(Table 1 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Ho [28]	2018	20 children with drug-resistant epilepsy who underwent RA SEEG (11.1 electrodes per patient)	Retrospective	• Mean radial error: 1.75 ± 0.94 mm • Mean operating time was 10.98 minutes/lead, with improvements in total (33.36 minutes/lead vs. 21.76 minutes/lead) & operative (13.84 minutes/lead vs. 7.06 minutes/lead) case times/lead over the course of the study • 95%: clinical useful data & surgery performed; 50% of them Engel class I 3 m later • No postoperative complications	Moderate
Goldstein [29]	2018	25 children with drug-resistant epilepsy underwent 30 SEEG procedures (342 electrodes implanted in total)	Retrospective	• SEEG localized the hypothetical SOZ in 23 of 25 patients (92%); 18 patients have undergone definitive surgical intervention (15 with ≥ 6m follow-up: 53% Engel I, 40% Engel II or III) • No major complications (1: electrode deflection, 2: electrode infection)	Low-Moderate
Abel [30]	2018	35 children with drug-resistant epilepsy undergoing SEEG (17 RA, 18 Talairach frame-based)	Retrospective	• No differences in complication rates, rates of resective epilepsy surgery, or seizure freedom rates between 2 groups • 1: transient paraesthesia with 2 subdural haematomas, 3: minor asymptomatic intracranial bleeding	Low-Moderate
Taussig [31]	2016	48 children with drug-resistant epilepsy undergoing SEEG Group 1: 17 children (<5 y) Group 2: 31 children (≥ 5 y)	Retrospective	• 1 patient: slight intracerebral haemorrhage • All underwent surgery • Group 1: significantly ↓ Interictal spikes and slow waves outside the resection zone • Group 1: no auras	Moderate
Dorfmüller [32]	2014	19 children with drug-resistant epilepsy and FCD	Retrospective	• No complications • Epileptogenic zone was identified in all children • All children underwent surgery • 845: seizure-free at a mean follow-up of 29 m	Moderate

(Table 1 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Taussig [33]	2014	65 children with drug-resistant epilepsy undergoing SEEG	Retrospective	• No complications	Low-Moderate
		Group 1: 21 children (<5 y)		• SEEG led to surgery in 78% of patients (90.5% in group 1; 73% in group 2), after a second invasive investigation in 9.2 % of patients	
		Group 2: 44 children (≥ 5 y)		• Engel class 1 was reported for 67% of patients (79% of patients in group 1 and 59% in group 2)	
Gonzalez-Martinez [34]	2014	60 children with drug-resistant epilepsy undergoing SEEG	Retrospective	• 60% underwent resection	Low
				• 13.3%: failure to localise	
				• 55.5% Engel class I 27.7% Engel class II or III) at the end of the follow-up period (mean, 25.9 m)	
				• 1 patient int caps infarct, 1 patient CSF leakage	
Cossu [35]	2012	15 children with drug-resistant epilepsy undergoing SEEG	Retrospective	• 1 patient died the day following electrode placement due to massive brain edema and profound hyponatremia of undetermined cause	Moderate
				• 13/14: received operations (microsurgical resections)	
				• Of the 10 patients with a postoperative follow-up of at least 12 m, 60%) Engel Class Ia, 20% Engel Class II, 20% Engel Class IV	

Table 2. The effect of minimally invasive methods on the outcomes of epilepsy surgery in children with drug-resistant epilepsy (ASM: antiseizure medications, FCD: focal cortical dysplasias, HH: hypothalamic hamartomas, MTS: mesial temporal sclerosis, PH: periventricular heterotopias, TS: tuberous sclerosis). The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Study type	Findings	Risk of bias
Tovar-Spinoza [50]	2018	7 children of mean age 6.6 y with cortical tubers undergoing magnetic resonance-guided laser interstitial thermal therapy	Retrospective	After a mean follow-up of 19.3 m: • 100%: reduction in seizure frequency • 71.4%: reduction in ASM • No perioperative complications	Moderate
Fayed [51]	2018	12 children of mean age 11.1 y with HH, FCD, PH, MTS, TS undergoing MR-guided laser interstitial thermal therapy	Retrospective	After a mean follow-up of 10 m: • 66.7%: seizure-free (Engel I) • 16.7%: significant improvement (Engel II) • 16.7%: worthwhile improvement (Engel III) • Left superior quadrantanopsia in 1 patient postoperatively	Low
Curry [52]	2018	46 males with HH undergoing MR-guided laser ablation	Retrospective	After an 1-y follow-up: • 93%: free of gelastic seizures • 12%: seizure-free & free of any ASM • Complications: worsening of diabetes insipidus (1), deficit in short-term memory from left-sided mammillary body injury (1), delayed wound healing (4), hyponatremia (3), temporary increase in non-gelastic seizures (9)	Moderate
Southwel [53]	2018	5 males of 9.8 y undergoing MR-guided laser ablation of HH	Retrospective	After a follow-up period varying from 7 to 45 m: • 3 patients: seizure-free (Engel I) • 2 patients: worthwhile improvement (Engel III) • Complications: precocious puberty in 1 patient	Serious

(Table 2 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Lewis [54]	2015	17 children of mean age 15.3 y with FCD, HH, TS undergoing MR-guided laser interstitial thermal therapy	Retrospective	After a follow-up period of 16.1 m: • 41%: Engel class I • 6%: Engel class II • 18%: Engel class III • 35%: Engel class IV • Complications in 8 patients (mainly technical errors)	Serious
Calisto [55]	2014	20 children (mean age 11.8 y with HH undergoing either conventional disconnection by monopolar coagulation (13) thulium 2-μm laser disconnection (7)	Retrospective	After a follow-up period of 12 m: • Monopolar coagulation: Engel class I or II in 61.5% • Laser disconnection: Engel class I or II in 85.7% • Immediate postoperative complications: 53.8%of patients who underwent monopolar coagulator disconnection & 28.6%of patients who underwent laser disconnection • No complications persisted at the 12-month follow-up	Serious
Curry [56]	2012	5 children of age 5-16 y with FCD, HH, TS undergoing MR-guided laser interstitial thermal therapy	Retrospective	After a follow-up period of 2-13 m: • All 5 seizure-free • 2/5: Engel I • No complications	Serious

Table 3. Studies about the effect of brain stimulation on children with drug-resistant epilepsy (d: day, DBS: deep brain stimulation, m: months, SCS: subacute cortical stimulation, y: years). The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Electrodes placement	Study type	Findings	Risk of bias
Sa [61]	2019	2 patients with FIRES after treatment with Anakinra: (i) 9-y boy with focal seizures and secondary generalisation, (ii) 5-y boy with generalized seizures	Centromedian thalamic nuclei	Retrospective	Reduction in generalized seizures (i) 15 m later: still on Anakinra, short focal seizures with an average of 2-5 per month, good motor & cognitive function (ii) 18 m later: vegetative state with frequent focal seizures	Low
Kokoszka [62]	2018	2 patients with drug-resistant epilepsy: (i) 14-y boy with cortical dysplasia, (ii) 9-y old girl with left watershed infarct	(i) Bil anterior thalamic nuclei (ii) epileptogenic zone in the left posterior frontal and parietal lobes	Retrospective	(i) after 19 m of follow-up: seizure frequency from 15-30/d to 3/d (ii) after 21 m of follow-up: seizure frequency from 12/m to 2/m	Low
Valentin [63]	2017	8 children with drug-resistant epilepsy 6- 15y	(i) 5 children: SCS (ii) 3 children: DBS (centromedian& anterior thalamic nucleus)	Retrospective	(i) SCS: 4 improvement in seizure frequency >50%, 1 no improvement (ii) DBS: 2 improvement in seizure frequency>60%, 1 no improvement	Moderate

Table 4. Original studies about cognitive outcomes in children with drug-resistant epilepsy after epilepsy surgery (DNT: dysembryoblasticneuroepithelial tumor, (G)DQ: (Global) Developmental Quotient, EEG: electroencephalogram, ESES: Electrical Status Epilepticus in Sleep, FCD: Focal Cortical Dysplasia, FSIQ: Full-scale Intelligence Quotient, IQ: Intelligence Quotient, GNT: Glioneuronal tumor, LEAT: Low-Grade Epilepsy-Associated Tumor, y: years). The risk of bias was calculated based on ROBINS-I tool and Cochrane Risk of Bias Assessment Tool (for Dwvivedi et al. study).

Study	Year	Population	Study type	Findings	Risk of bias
Leal [66]	2020	50 children (mean age 8.2 y) undergoing epilepsy surgery	Retrospective	• 42%: moderate or severe intellectual disability • At 2-year follow-up: 36% maintained similar deficits	Low
Ko [67]	2020	58 children with LEATs (mean age 10.2 y) undergoing epilepsy surgery	Retrospective	Postoperative cognitive abilities were significantly influenced by epilepsy duration	Low
Marashly [68]	2020	14 patients 3-14 y undergoing surgery for ESES (hemispherectomy, focal resection)	Retrospective	No significant change after surgery in intellectual functioning, adaptive functioning, attention problems	Moderate
Grayson [69]	2020	160 children with tuberous sclerosis-19 undergoing surgery (3-21 m)	Prospective	Vineland Adaptive Behavior Scales 2nd ed, Mullen Scales of Early Learning, Preschool Language Scales 5th ed after 12-24 m: • The surgical group scored the lowest. • Favorable surgical outcome was associated with increased Mullen Scales of Early Learning receptive and expressive language subscores.	Moderate
Skirrow [70]	2019	52 children (mean age 14 y) undergoing epilepsy surgery (focal resection)	Retrospective	• Applying a $\geq$ 10-point change threshold, 39% in IQ,10% decline in IQ after surgery • Clinical factors associated with IQ increase: lower preoperative IQ, longer follow-up duration	Low
Helmstaedter [71]	2020	306 children (mean age 5.5 $\pm$ 4.1undergoing epilepsy surgery (hemispherectomy, focal resection)	Retrospective	• Preoperatively 85% cognitive impairments, 71% behavioral problems • 1 year after surgery: 21-50% improvement in cognition (from impaired to unimpaired) • Seizure freedom, younger age at evaluation, later onset age, lower antiseizure medication load, less baseline damage: predicted better outcomes	Low
Benova [72]	2019	203 children (<19 y) undergoing epilepsy surgery (unilobar/multilobar/focal resection, hemispherotomy, Hemispherectomy)	Retrospective	Epilepsy surgery tends to improve post-surgical IQ/DQ, most significantly in patients with lower pre-surgical IQ/DQ	Low

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Wang [73]	2019	12 children 4.5-15 y undergoing posterior quadrantic disconnection	Retrospective	After a median of 28-month follow-up: significant linear relationship between improvement in IQ &operative age	Moderate-Serious
Danguecan [74]	2019	65 children (6-18 y) with LTLE or RTLE undergoing combined mesial/lateral resection VS only lateral resection	Retrospective	Verbal associative memory scores 12 m later: • post-surgical ↓ only in L resection (non-significant) • L resection: ↓ in lateral+mesial>lateral (non-significant) • Typical language group: ↓ in L lateral+ mesial (significant) • Atypical language group: ↓ in L lateral group (trend)	Low
Hoppe [75]	2019	96 children 5-17.5 y undergoing epilepsy surgery	Retrospective	Parental questionnaires about neuropsychological performance 12 m later: • Improvements: language, memory, executive functions, attention, school • Unchanged: Visuospatial abilities • 35%: decline in $\geq$ 1 domain • Later onset of epilepsy: better scores • Seizure-free, low ASM load: post-surgical improvement	Low
Kadish [76]	2019	48 children 1.1 $\pm$ 0.7 y undergoing epilepsy surgery (hemispherotomy, multilobar/intralobar resection)	Retrospective	• Cognitive & developmental impairment in 89% • Longer epilepsy duration &larger lesion extent determined the postsurgical developmental outcome	Moderate
Baba [77]	2018	56 patients (mean age 22.6 m) with West syndrome undergoing callosotomy	Retrospective	After a mean of 36-month follow-up: good seizure outcomes prevented declines in neurodevelopment	Low
Faramand [78]	2018	150 children with GNTs (mean age 9.2 y) undergoing resective surgery	Retrospective	• No significant difference between pre- & post-operative FSIQ	Moderate

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
				• After a median of 2-year follow-up: 61% gain in FSIQ, 36.5% decline & 2.5% no change	
Ramantani [79]	2018	75 children 10.0 ± 4.9 y with FCD/brain tumors undergoing frontal lobe resection	Retrospective	After a mean of 8-y follow-ups: • Cognitive outcomes remained stable in the majority of patients • Presurgical higher performance & tumors: better cognitive outcomes	
Dwivedi [3]	2017	116 children (0.8-17 y) with drug-resistant epilepsy (57 surgery, 59 non-surgery)	Prospective (randomized single-center trial)	After 12 months of follow-up: • 77% seizure-free in the surgery group VS 7% in the non-surgery (p<0.001) • Behavior & maturity scores: significantly better in the surgery group • Intelligent scores: no difference	Low
Sierra-Marcos [80]	2017	55 children 3-10 y with posterior complex epilepsy undergoing epilepsy surgery (lesionectomy, tailored resection)	Retrospective	After a mean of 3.5-y follow-up: • 65%: improvement of neuropsychological performances • 23.22%: improvement in verbal memory; this improvement was sustained at 5 years in 16% • decline in none	Low
Puka [81]	2017	97 children 5.5-16.5 y of whom 61 undergoing epilepsy surgery (lesionectomy, lobectomy, corticectomy)	Retrospective	After a mean of 7-y follow-ups: • Similar cognitive outcomes between surgical and non-surgical patients • Low pre-operative scores were predictive of improvement over time, whereas high pre-operative scores were predictive of high scores at follow-up	Low

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Law [82]	2017	23 children 5.5-18 y undergoing L or R TLE surgery sparing or not mesial structures	Retrospective	Verbal memory changes 12 m later using a list learning task: • ↓ only in the L, including mesial structures • Risk factors: typical language representation& intact preoperative verbal memory • Post-surgical seizure status: no effect	Low
Groppel [83]	2017	11 children with ESES VS 21 without ESES undergoing hemispherotomy (10 m-11.5 y)	Retrospective	Language quotients after 3 m & 12 m: • In remission of ESES after surgery, language improvement was bigger than seizure-free children without preoperative ESES	Low
Sibilia [84]	2017	31 children 17 m-15 y undergoing epilepsy surgery VS 14 controls surgical candidates	Retrospective	IQ & GDQ at 12 & 24 m of follow-up: • No difference in scores between surgical and non-surgical groups at 24 m • Surgical group: better outcomes at 12 m in digit span scores and Rey recall scores	Low
Puka [85]	2016	88 children 9-16 y of whom 53 underwent respective epilepsy surgery	Retrospective	After a mean of 7-y follow-ups: • Memory outcomes were affected by seizure control, not surgical status	Low
Meekes [88]	2016	16 children 12.6 –15.8 undergoing epilepsy surgery VS 32 healthy matched controls	Retrospective	Dutch version of the controlled oral word production task at 0, 6, 12, 24 m: • Lexical breadth and depth do not deteriorate after epilepsy surgery	Low-Moderate
Puka [86]	2016	97 patients 4-18 y of whom 61 underwent epilepsy surgery	Retrospective	After a mean follow-up of 7 y assessment with Boston Naming Test, vocabulary subtest of the Wechsler Intelligence scales & letter and semantic (animal) fluency: • Scores across language tasks were similar at baseline and follow-up. • Older age at epilepsy onset, higher IQ, higher baseline scores: ↑ follow-up scores on all language tasks	Low-Moderate

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Puka [87]	2016	97 patients 4-18 y of whom 61 underwent epilepsy surgery	Retrospective	Wechsler Individual Achievement Test, Wechsler Fundamentals Academic Skills, Wide Range Achievement Test at baseline, 1y, 7y: • At 7y arithmetic scores lower in all groups, reading & spelling scores unchanged • No difference between surgical & non-surgical	Low-Moderate
Law [89]	2015	187 children 7.5-11.5 y of whom 147 underwent epilepsy surgery	Retrospective	After 1 y of follow up: • Behavioural outcomes were not affected by neither surgical or seizure outcome	Low
Shurtleff [90]	2015	15 cognitively intact children 2-6 y who underwent epilepsy surgery (focal resection)	Retrospective	After a mean follow-up of 55 m: • No group changes from baseline occurred in Full Scale, verbal, or nonverbal IQ.	Moderate
Bulteau [92]	2015	6 children 8.4 -14.6y underwent L hemispherotomy for Rasmussen encephalitis	Prospective	WISC-IV scale, Phonemic Discrimination Scale, Computerized Oral Speech Battery, complementary verbal tasks after 5.6 y: • 6/6: recovered sufficiently to attend a regular verbal comprehension index • 5/6: recovered normal or adapted school • 5/6: ↓ in performance reasoning index	Moderate-Serious
Skirrow [91]	2015	53 children with epilepsy-42 underwent L or R temporal lobe resection (mean age 13.8y)	Retrospective	Wechsler Intelligence scale, Children's Auditory Verbal Learning Test, Doors and People Test, British Picture Vocabulary Scale, Wechsler Memory Scale-Revisedafter a mean follow-up of 7y: • No significant post-surgical ↓ in memory • R resection: ↑ verbal episodic memory • L resection: ↑ visual episodic memory • Better verbal memory was linked to greater post-surgical residual hippocampal volumes • After left temporal surgery, better semantic memory was associated with smaller resection volumes and greater temporal pole integrity. • Results were independent of post-surgical intellectual function and language lateralization.	Low

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
De Bode [93]	2015	10 children 4-12y undergoing L cerebral hemispherectomy VS 9 matched controls (median age surgery 10y, median age assessment 14y)	Retrospective	Receptive portion of Curtiss and Yamada Clinical Language Evaluation consisting of sentence–picture matching tasks: • Same developmental sequence of syntactic development	Moderate-Serious
Groppel [94]	2015	28 children (median age 64.5m) undergoing vertical perithalamichemispherotomy	Retrospective	Denver Scales II & German versions of the Wechsler Intelligence Scales after a median follow-up of 3y: • 31%: significant gains in language quotients • Short disease duration prior to surgery, acquired pathology, lack of epileptiform EEG discharges in the contralateral hemisphere and/or normalization of EEG sleep patterns after surgery, successful ASM withdrawal were linked to favourable language outcomes.	Moderate-Serious
Downes [95]	2015	14 children with LKS or ESES undergoing multiple subpial transection of the posterior temporal lobe (mean age 6.23y) VS 21 children with LKS or ESES	Retrospective	Vineland Adaptive Behavior Scales-II (communication) &Paediatric Quality of Life Inventory after 1.5-5y: • No differences between the groups in language, nonverbal ability, adaptive behavior, or quality of life at follow-up • No difference in the proportion of patients showing improvement or deterioration in the language category over time for either group.	Moderate
Chen [96]	2014	30 children 1.7-17.6 y with FCD undergoing epilepsy surgery	Retrospective	After a mean follow-up of 21.5 m: • For 14 patients who received both preoperative and postoperative evaluation, only 2 mild reductions in DQ & IQ and 5 cases mild to moderate improvement	Moderate

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Ramantani [97]	2014	29 children 1.3-12.3 y with GNTs undergoing epilepsy surgery	Retrospective	12 months after surgery: • Improvements in verbal IQ, performance IQ, visual memory, as well as a trend toward improvement in full-scale IQ • Despite individual losses, no deterioration was noted in any cognitive variable on a group level	Moderate
Lee [98]	2014	42 children with LGS 8 m-17.3 y undergoing epilepsy surgery (lobar resection, hemispherotomy, and corpus callosotomy)	Retrospective	After 2 years: • At an individual level, an increase in FSIQ score was observed in 19 (70.4%, 19/27) patients, and a significant gain of at least 10 points were achieved in 12 (44.4%) patients	Moderate
Lee [99]	2014	12 children (mean age 6.5 y) with focal symptomatic epilepsy, West syndrome &Rasmussen's syndrome undergoing hemispheric disconnection	Retrospective	After a mean follow-up of 12.7 y: • The overall developmental severity category was unchanged. • 12/12: exacerbation of pre-surgical hemiparesis, but transient in 11	Moderate-Serious
Park [100]	2013	48 children with encephalopathy (median age 9 y) undergoing epilepsy surgery (respective or palliative)	Retrospective	After 1 year: • No significant changes in postoperative neuropsychological outcomes • 77.8 %of parents whose children were not seizure-free reported satisfaction with their children's improvement in cognitive and behavior issues.	Moderate-Serious

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Hallböök [101]	2013	45 children (median age 8 y) with epilepsy undergoing epilepsy surgery (hemispherectomy, focal/local resection, multilobar, disconnection)	Retrospective	After a follow-up of 5-21 y: • 34/45 preserved their category of cognitive level after surgery, 7/45 deteriorated & 4/45 improved • Cognitive improvements in accordance with seizure control and no antiseizure medications	Low
Ramantani [102]	2013	30 children (mean age 20 m) with focal epilepsy (cortical malformation, infarction, GNET) undergoing surgery (hemispherectomy, multilobar/intralobar resection)	Retrospective	After a follow-up of 1-11.6 y (mean 4 y): • 89%: pre-surgical developmental impairment • 21 children remained within the respective developmental category compared to the preoperative evaluation; 7 showed a decrease • Postoperative developmental status was negatively related to the extent of resection	Low
Villarejo-Ortega [103]	2013	17 children (median age 5.9 y) undergoing hemispherectomy for Rasmussen's encephalitis, cortical malformations, or vascular lesions	Retrospective	After a mean follow-up of 3 years: • Patients with cortical malformations & vascular lesions: pre-surgical developmental delay persists afterward • Vascular lesions group: A linear correlation was found between earlier age at surgery and better outcome in the personal-social, gross motor & adaptive domains	Low

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Beaton [104]	2012	10 children (mean age 13.8 y) with unilateral hippocampal sclerosis undergoing amygdalo-hippocampectomy	Prospective	After a follow-up of 24 m: • No significant improvement or decline at a group level for intellect or verbal or visual memory • Significant improvement found post-operatively for immediate &delayed facial memory	Moderate
Iwatani [105]	2012	6 children (mean age 1.4 y) with West syndrome undergoing epilepsy surgery	Retrospective	After a mean follow-up of 4.9 y: • Motor function & developmental age increased after surgery in 6 & 5, respectively • None showed developmental regression.	Moderate
Liu [106]	2012	17 patients with West syndrome secondary to tuberous sclerosis undergoing surgical resection with a combined palliative operative procedure (1.5-8y)	Retrospective	Intelligence Scale for children-Revised (WISC-R) for children 6-14y, Wechsler Preschool and Primary Scales of Intelligence (WPPSI) for children aged 4-6, Gesell Developmental Schedules for children <4 after a follow-up of 1.2-6y: • Significant improvement in the motor, adaptive, language & personal-social field	Moderate-Serious
Aaberg [107]	2012	54 children undergoing epilepsy surgery (mean age 8.6 y)	Retrospective	Patient/Carers questionnaires 2y later: • 71% better general functioning • 44-52% better motor, attention, behavior/mood, language	Moderate

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
García-Fernández [108]	2011	21 children (mean age 11.6 y) with developmental tumors & epilepsy undergoing surgery	Retrospective	After a mean follow-up of 4.68 y: • Significant improvements in perceptive-visual &auditory aspects, non-verbal abilities, linguistic performances, verbal learning, selective attention &executive functions • Greater improvements in: lesionectomy (VS extended resection), later-onset epilepsy & drug-resistant group	Moderate
Skirrow [109]	2011	42 children (mean age 13.3 y) with hippocampal sclerosis or DNT undergoing surgery VS matched non-surgical group of 11 children	Retrospective	After a follow-up of 9 y: • A significant increase in IQ in the surgical group after a follow-up period of >5 years • IQ increases associated with cessation of antiseizure medication	Low
Dunkley [110]	2011	22 children (mean age 20 m) with epilepsy of various etiologies (cortical malformation, hippocampal sclerosis, tuberous sclerosis, DNET, cerebral infarction, Sturge-Weber syndrome) undergoing surgery (hemispherectomy, multilobar/lobar/focal resection)	Retrospective	After a mean follow-up of 63.5 m: • 5 children decrease in DQ/IQ >15 , 3 children an increase DQ/IQ >15& 14 no change	Low-Moderate

(Table 4 continued)

Study	Year	Population	Study type	Findings	Risk of bias
Peltola [111]	2011	13 children 3.6-9 y with pharmacoresistant ESES undergoing surgery (hemispherotomy, callosotomy, focal resection)	Retrospective	After a follow-up of 2 y: • By 6 months after surgery, cognitive decline was arrested in all but 1 patient • Improved behavior in all 4resectionand 6/9 callosotomy patients • At 2 y, all except 1 patient had maintained or improved the cognitive level they had at 6 m postoperatively • Cognitive improvement by $\geq$ 10 points was observed in 3 patients.	Low-Moderate
Lippe [112]	2010	5 children 0.6-7 y with cortical dysplasia undergoing occipitoparietal respective surgery	Retrospective	After a follow-up of 3-7 y: • All children improved their intellectual abilities (visual perceptual cognition <verbal functions)	Serious

Table 5. The relationship between neurobehavioural co-morbidities and epilepsy surgery in childhood. The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Study type	Findings	Risk of bias
Reilly [116]	2019	107 childre undergoing epilepsy surgery	Retrospective	Parent-reported features of ADHD were significantly reduced 2 y after epilepsy surgery (Conners 10-item scale)	Moderate
Kokoszka [115]	2017	56 patients with autism undergoing epilepsy surgery	Retrospective	At a mean follow-up of 47 $\pm$ 30 months, aggression and aberrant behavioral patterns improved in 24 of 56 patients	Moderate
Qualmann [114]	2017	52 patients undergoing epilepsy surgery	Retrospective	Autism or cognitive disability was significantly associated with an ILAE >1 (no seizure-freedom after surgery)	Low

Table 6. Original studies about the relationship between ASM withdrawal after surgery and seizure recurrence in children (ASM: antiseizure medications, FCD: focal cortical dysplasia, m: months, y: years). The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Study type	Time interval to start ASM withdrawal	Mean duration of follow-up	Findings	Risk of bias
Choi [119]	2019	70 children and adolescents with FCD undergoing resective epilepsy surgery	Retrospective	0.5-2.7 y	mean: 4.5 y	• seizure recurrence in 35% of children during ASM reduction or after ASM withdrawal • incomplete resection & postoperative epileptic discharges: important predictors of seizure recurrence	Low
Boshuisen [120]	2014	95 children who underwent epilepsy surgery &presented seizure recurrence after ASM reduction/withdrawal	Retrospective	11.9± 12.3 m	up to 100 m	• 14% relapse within 6 m, 24% within 12 m & 48% within 24 m • a shorter interval to ASM reduction: the only independent predictor of a shorter time to relapse • incomplete resection: shorter time to recurrence • timing of recurrence: not related to the chance of regaining seizure freedom	Low
Boshuisen [121]	2012	766 children undergoing epilepsy surgery	Retrospective	11.9-13.2 m	61.6 ± 29.7 m	• 95 of 766 patients (12.5%) had seizure recurrence during or after ASM withdrawal • shorter time interval to ASM withdrawal predicted seizure recurrence	Low

Table 7. The effect of ASM withdrawal after epilepsy surgery on aspects of neurodevelopment The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Study type	Findings	Risk of bias
Boshuisen [122]	2015	301 children after epilepsy surgery	Retrospective	ASM reduction after surgery significantly improved IQ scores in neuropsychological tests	Low
van Schooneveld [123]	2013	57 seizure-free children after epilepsy surgery	Retrospective	At 24 months after surgery, the withdrawal group had improved significantly more than the no-withdrawal on psychomotor tests (reaction time to light/sound/tapping)	Low

Table 8. Original studies in the literature about the underutilization of epilepsy surgery in children. The risk of bias was calculated based on ROBINS-I tool.

Study	Year	Population	Study type	Findings	Risk of bias
Prideaux [125]	2018	Medical records of children undergoing epilepsy surgery	retrospective	Mean duration: • neurologist-epilepsy surgery program: 6.2 m • epilepsy surgery program-surgical candidacy: 6.1 m	Low
Shen [130]	2018	58 caregivers of children with epilepsy	retrospective	• 30/58 caregivers wished their child had undergone epilepsy surgery earlier • Caregivers were willing to accept a lower likelihood of seizure freedom than their physician reported was likely.	Moderate
Pestana [128]	2015	Children undergoing epilepsy surgery identified from serial cross-sectional analysis of paediatric hospital discharges	retrospective	The rate of the increase in paediatric epilepsy use was lowest in blacks and children with public insurance.	Low
Erba [129]	2013	• 138 parents of paediatric patients with epilepsy • 60 child neurologists	retrospective	• 25.2% were opposed to this treatment • after providing factual information, 50.4% of the responders stated that they had become more favorable • 60% of child neurologists did not fully comply with guidelines about epilepsy surgery	Low