Chapter

Advances in Pediatric Epilepsy Surgery

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Abstract

Epilepsy effects over 50 million people worldwide. Of those, 20–40% of children with epilepsy are considered medically refractory. When pharmacotherapy fails, surgical intervention remains an option to achieve seizure freedom or reduce seizure burden. In this chapter, we review the relevant presurgical evaluation patients undergo, the role of invasive monitoring, and the various types of epilepsy surgery that may help treat children with refractory epilepsy. We discuss in detail various types of surgery, including conventional resection, lobectomy, and disconnection surgeries, as well as innovations in the field including neuromodulation and LITT. We provide a comprehensive review of the current status of the field and highlight future directions.

Keywords: epilepsy, refractory epilepsy, epilepsy surgery, neuromodulation, pediatric neurosurgery

1. Introduction

Epilepsy is a heterogeneous neurological condition hallmarked by recurrent seizures affecting either part of or the whole body with or without impaired consciousness. It is thought that over 50 million people around the world live with epilepsy, with a cumulative incidence of 67.77 per 100,000 persons [1]. It has long been recognized that epilepsy affects pediatric patients at greater rates compared to their adult counterparts, with an estimated 10.5 million children affected worldwide with incidences of 85.29 per 100,000 persons in patients under 18 years of age, compared to 64.81 per 100,000 persons in patients over 19 years of age [1, 2]. In a separate study, it was found that the incidence of pediatric epilepsy was highest during the first year of life at 144 per 100,000 persons and decreases throughout the first decade [3].

It is imperative that pediatric patients with frequent seizures achieve disease freedom as continued epileptogenic activity can cause regression of or arrest cerebral maturation, possibly delaying cognitive development [4, 5]. In addition, mortality in those living with continued seizure is higher than those in age-matched populations [6–9]. In order to reduce the frequency and intensity of seizures, patients are placed on various antiseizure medications (ASM) that alter neurotransmitter action and electrical propagation throughout the brain. These medications can be associated with varying adverse effects with some patients being placed on multiple medications despite poor seizure control. Regardless of medications, approximately 20–40%

of pediatric patients will develop drug-resistant epilepsy (DRE), which represents persistent seizures despite adequate trials of at least two different ASMs [10]. Patients with this pharmaco-resistant form of epilepsy are more susceptible to cognitive problems, mood and personality changes, educational and social consequences, persistent seizures, increased risk of mortality, and comorbidities that greatly reduce the patient's and family's quality of life [11, 12]. In a study defining long-term survival of pediatric patients with drug-resistant epilepsy by treatment type, those with cranial epilepsy surgery had a 98% chance of being alive at 10 years, while those with vagus nerve stimulation had a 92% chance of being alive at 10 years, and those on medical treatment only had an 89% chance of being alive at 10 years [13].

When pharmacotherapy fails, surgical intervention is recommended to achieve seizure freedom or reduce seizure burden. Traditionally centered on open surgery, either for resection of the epileptogenic focus or disconnection of neural pathways involved in epilepsy networks, epilepsy surgery has grown significantly since its inception to include neuromodulation and more minimally invasive approaches [9, 14]. In this chapter, we discuss the evolution of epilepsy surgery over time, focusing on the traditional approaches as well as current advances in the field of pediatric epilepsy surgery.

With the development of improved pharmaceutical options and more advanced operative techniques, the indications for epilepsy surgery has evolved over the past several decades. In 2009, the International League Against Epilepsy (ILAE) defined DRE and recommended surgical resection, if possible [15]. Additional conditions that can benefit from surgical intervention include certain pathologies such as cortical dysplasia, Sturge–Weber Syndrome, Rasmussen syndrome, and/or seizure semiology that can be localized to a specific location or lesion [16, 17]. While the role of surgery has expanded to include those with nonlesional epilepsy, some patients such as those with active psychiatric illnesses, severe medical co-morbidities, or no discernable epileptogenic focus or network are less likely to benefit from surgical treatment [16]. Jehi et al. in an international panel and modified Delphi methodology presented expert consensus defining recommendations for timely referral of patients who could benefit from evaluation for epilepsy surgery, which included: (1) every patient <70 years of age as soon as they meet criteria for drug-resistant epilepsy; (2) patients >70 years of age with drug-resistant epilepsy with no surgical contraindication; (3) patients of any age who are seizure-free on 1–2 antiseizure medications with a brain lesion in non-eloquent cortex. Jehi et al. recommended against referral for epilepsy surgery for those with active substance abuse problems not cooperative with management [18]. In appropriately selected patients who undergo epilepsy surgery, long-term seizure control rates can range from 50 to 70% [19]. However, despite improved patient selection and operative techniques, surgical intervention remains underutilized with approximately 1% of the 100,000–500,000 eligible patients undergoing surgery annually [20].

2. Presurgical evaluation and workup

The goal of surgery is to minimize damaging effects of epilepsy on the developing brain caused by recurrent seizures and antiseizure medications. This is increasingly important in children due to the neuroplasticity of the young, developing brain and the need to prevent damage and allow proper development to occur. While surgery has become an invaluable resource for many patients with DRE, there are a number of significant steps that must be undertaken by the patient and healthcare providers prior to intervention.

2.1 Phase I evaluation

The typical workup for epilepsy can be divided into several stepwise phases to ensure optimal patient selection and treatment modality. Phase I consists of understanding the seizure semiology and obtaining neuroimaging to look for pathologic areas that might correlate with seizure focus (**Table 1**). All initial evaluations should begin with a detailed clinical history to determine the semiology, triggers, and frequency of seizures as well as a physical exam to evaluate for neurological deficits or abnormalities. Intracranial imaging with a magnetic resonance imaging (MRI) should be completed to rule out any structural etiology (i.e. hippocampal sclerosis, neoplasm, or cortical dysplasia) as the source of the patient's seizures. The next step in the work-up is to characterize the seizure using an interictal scalp electroencephalography (EEG) via long-term video monitoring. Patients should be evaluated by neuropsychology/neuropsychiatry to determine any subtle neurological deficits as well as baseline cognitive ability and reserve. Additional testing with magnetoencephalogram (MEG) and functional MRI (fMRI) can be used to localize eloquent cortical structures while interictal positron emission tomography (PET) and ictal photon emission computed tomography can demonstrate hypometabolism and increased cerebral blood flow within the epileptic foci helping to better localize it [10].

2.2 Phase II evaluation

In situations where the seizure focus is difficult to localize or where results are discordant, Phase II testing via intracranial EEG monitoring is recommended. This can be accomplished by either stereotactic electrocorticography (sEEG) depth electrode placement or subdural electrocorticography (sdEEG) grid placement for cortical monitoring. While intracranial monitoring implantation has been used since the 1960's, implant technology, as well as their indications, have significantly evolved over the past several decades.

The type of Phase II monitoring used and surgical plan vary by indications, patient specific factors, area of interest to be targeted, and practice pattern. There are several benefits of sEEG when compared to subdural grid/strip placement, the most significant one being the ability to sample large bilateral cortical/subcortical regions without the need for a large craniotomy [21–23]. A representative case of a patient with left temporo-occipital epilepsy, and a history of prior resection, who underwent sEEG placement for seizure localization is depicted in **Figure 1**. The minimally invasive nature of depth electrode placement, anchored in the calvarial bone, querying the areas of interest to better localize seizure onset zone can be appreciated. The large craniotomies used for sdEEG placement can add to morbidity, especially in instances requiring extensive bihemispheric mapping. Another advantage of sEEG placement is the relative ease of placement and removal, as these are typically placed percutaneously via a small burr hole and can be removed percutaneously. The stepwise approach of this evaluation allows the epilepsy team time to review the data to better localize the epileptic foci without maintaining the hardware in place for extended periods of time [22, 23]. This contrasts with sdEEG where explantation of the electrodes requires an additional craniotomy and operation, typically followed by resection of the epileptic region at that time. This can prove difficult in complex cases as it may limit the time allowed for the epilepsy and neurosurgical team to review the data and formulate a plan for resection.

While there are several advantages in favor of sEEG, it is not always the most optimal invasive monitoring strategy. In patients who are less than 3 years of age, the

	Evaluation	Function	Strength/Weakness
Phase I			
	Clinical exam	Describe semiology, triggers, and frequency of seizures. Evaluate for neurological deficits	Clinician dependent. Can be difficult to localize lesions.
	Neuropsychology/ neuropsychiatry	Determine subtle neurological/psychological deficits and determine cognitive reserve	Evaluation can be clinician dependent. Standardized forms and help reduce bias and improve interpretability.
	MRI	High-resolution images that can aid in the localization of epileptic pathologies	Able to detect various cerebral pathologies. Can be difficult to interpret subtle abnormalities. Long sequences can require general sedation in the pediatric population.
	fMRI	Determine regions of eloquent cortex	Can help map language, motor, and memory function. Similar reliability to WADA testing. Dependent on patient cooperation.
	MEG	Able to localize epileptic regions based on induction of magnetic fields	Increased sensitivity to cortical epileptic areas. Skull attenuation can limit detection fo deeper lesions.
	Interictal positron emission tomography (PET)	Detection of epileptic foci glucose hypometabolism	Able to detec MRI-negative lesions Glucose hypometabolism is wider than epileptic focus.
	Ictal photon emission CT	Detection of increased cerebral blood flow in the epileptic region	Efficacy depends on timing of tracer injection and seizure frequency.
	Scalp/video EEG	Detection of interictal cortical electrical activity with associated semiology	Inexpensive. Effective in detecting cortical epileptic discharges. Low spatial resolution, skull can cause attenuation of signal.
Phase II			
	Stereo-EEG	Localization of deep cortical epileptic zones when unable to be adequately identified on imaging or scalp EEG	Able to sample bi-hemispheric cortical and subcortical regions simultaneously. Percutaneous placement in the OR and can be removed without the need of additional surgery. No optimal for patients with thin skulls. Lack fidelity with functional cortical mapping.
	Subdural-EEG	Subdural electrode grids/stripes are placed to map cortical function and epileptic regions	High number of electrodes allow for good spatial resolution and functional mapping. Craniotomy needed for placement and removal.

Table 1.
Epilepsy surgery preoperative evaluations.

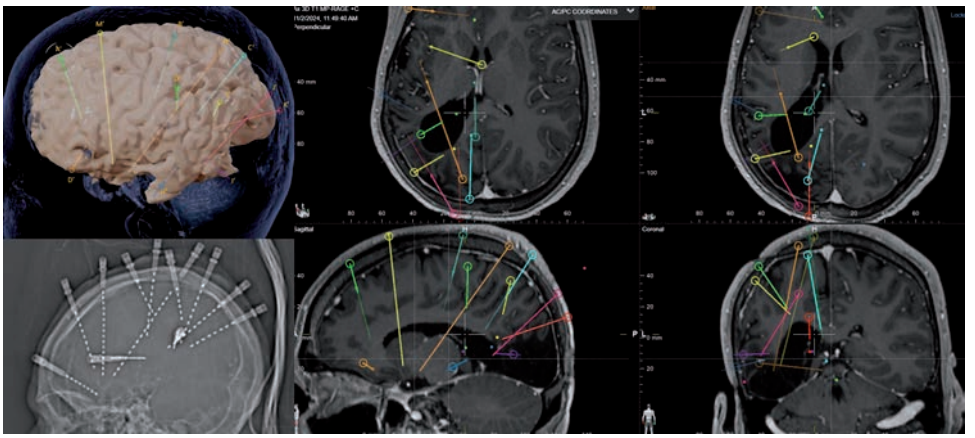

Figure 1.
Stereotactic electroencephalography demonstrative case. The figure above depicts a representative case of a 20-year-old with drug resistant epilepsy, previously treated with a left craniotomy for resection of the temporo-occipital lobes. The patient's phase I data suggested left sided lateralization. sEEG was planned using the patient's preoperative MRI, CT angiogram, and stereotactic planning software completed. On the day of surgery, sEEG was completed using robot assisted techniques and intraoperative CT, querying the left side around the margins of the prior resection as well as the orbitofrontal region, insula, cingulate, and parietal lobe to better localize seizures to the mesial posterior cingulate cortex and gliotic area around the prior resection to guide next steps with therapeutic resective surgery.

thickness of the skull limits the feasibility of percutaneous electrode placement, while sdEEG electrodes can be placed with relatively low complications [24, 25]. Subdural grids and strips are also more favorable in cases where functional mapping is needed as sdEEG have a higher density of cortical contacts compared to sEEG allowing for better spatial resolution [21]. Additionally, the contiguous nature of the sdEEG electrodes allow for improved delineation of the epileptic region compared to normal cerebrum, potentially improving cortical resection without the need interpolation methods used in cases of sEEG placement [22].

Complications following intracranial EEG monitoring are relatively rare, with several meta-analyzes looking at both sEEG and sdEEG electrode placement and the prevalence postoperative hematomas, cerebrospinal fluid (CSF) leak, and infection. In one study assessing sEEG, overall pooled complications were low at 1.3%, with the most common complications being hemorrhage (prevalence of 1.0%) and infection (prevalence of 0.8%) [26]. In sdEEG placement, pooled complications were significantly greater including those for hemorrhage (prevalence 4.0%) and infection (prevalence 3.0%) [25, 27]. Within both groups, rates of morbidity, including permanent neurological deficit, and mortality were similar accounting for only ~0.5% of cases, most of which were related to intracranial hemorrhage [25, 26, 28, 29].

3. Epilepsy surgery

Once the Phase I and/or Phase II workup has been completed and the epileptogenic foci or generalized network is localized, surgical planning can begin, encompassing a wide array of operative techniques and approaches. The therapeutic surgery selected depends greatly on the etiology of the seizures as well as the location of the epileptic zone, so appropriate patient selection is paramount to achieving operative

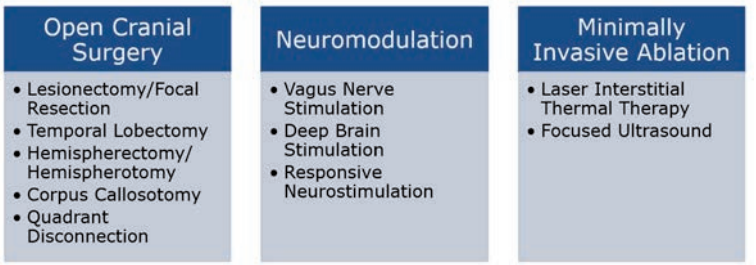

Figure 2.
Types of epilepsy surgery. The figure above depicts the broad categories of epilepsy surgery, including open cranial surgery, neuromodulation, and minimally invasive surgery.

success. Surgery includes open cranial approaches, neuromodulation, and minimally invasive ablation approaches (**Figure 2**). **Table 2** represents a summary of surgical approaches and considerations in the management of epilepsy.

For many of these surgical interventions, surgical adjuncts are paramount. Stereotactic neuronavigation can be used to register the patient's face to their pre-operative magnetic resonance imaging to guide surgical approach and/or resection. Intraoperative ultrasound can be used for real-time dynamic evaluation of neuro-anatomy. Intraoperative CT scan can be used to register surgical robots for stereotactic depth electrode placement. Intraoperative MRI, in centers where it is available, can be used to evaluate extent of resection or provide real-time thermography in cases of laser ablation. These surgical imaging adjuncts, when paired with innovative tools, such as endoscopy, neuromodulation, and ablative procedures, can provide adaptive, state-of-the-art approaches to surgical treatment.

3.1 Lesional resection

In patients who have extra-temporal epileptic lesions, originating from focal cortical dysplasia, tumors, or vascular malformation, most can achieve favorable seizure control upon resection of the offending lesion. Tumors, for example, have been shown to be responsible for 10–30% of DRE with the most common ones being low-grade astrocytomas and gangliogliomas [30]. **Figure 3** depicts focal resection of a tumor via craniotomy. Several studies have demonstrated the efficacy of lesionectomy for seizure control, however, the durability for seizure freedom following resection can vary widely depending on the type of cortical dysplasia, incomplete resection, and longer epilepsy duration, all associated with worse long-term outcomes following surgical intervention [31, 32]. One study demonstrated Engel class I seizure control in 63.2% of patient following surgical resection of non-mesial temporal sclerosis lesions at a mean of 2.9 ± 2.1 years post-operatively [33]. While another study assessing focal cortical dysplasia in pediatric patients demonstrated that 62% of patients achieved Engel class I seizure control at 2 years postoperatively before dropping down to 58% at 5 years [34]. In patients with posterior cortical epileptic foci, seizure freedom was found to be 73.1% within the first 6 months and 54.8% at 6 years demonstrating a lack of durability in some patients [35]. The location of the epileptic foci can also affect the response to surgery, with lesions located in the parietal cortex having worse seizure freedom at 5 years (52%) compared to lesions within the occipital (89%) and parieto-occipital (93%) lobes [35]. Surgical resection of these lesions can be augmented with cortical mapping and electrocorticography (ECoG) to improve resection of the

Advances in Pediatric Epilepsy Surgery
DOI: http://dx.doi.org/10.5772/intechopen.1012003

Surgery	Indications	Considerations	Outcomes
Lesional/focal resection	Identified structural lesion as the source of epileptic activity (i.e. focal cortical dysplasia, tumors, or vascular malformation)	Ideal for single lesion epilepsy that can be identified on MRI. Multifocal lesional epilepsy can be difficult to treat. Cortical mapping can improve gross total resection and limit damage to normal parenchyma.	Potentially curative if lesion is completely resected.
Temporal lobectomy/ amygdalohippocampectomy	Epileptic zone originating from the temporal lobe (i.e. mesial temporal sclerosis)	Resection of the dominant temporal lobe increases the chances of language, fluency, memory, and visual deficits. fMRI and neuropsychiatric testing can be helpful in preoperative risk assessment. ECoG can assist surgeons in determining the extent of hippocampal resection for prognostication postoperatively.	Have demonstrated seizure freedom between 58 and 81% in the pediatric population.
Hemispherectomy/ hemispherotomy	Epileptic activity that is related to diffuse hemispheric injury either from acquired (i.e. infarction or hemorrhage) or progressive sources (i.e. Rasmussen's encephalitis, Sturge–Weber syndrome)	Multiple surgical approaches may accomplish this disconnection, including vertical and lateral approaches. Anatomic hemispherectomy has fallen out of favor in most cases for functional disconnection surgery given adverse effects (hemosiderosis, hydrocephalus, blood loss). Minimal access or endoscopic techniques allow for smaller incisions and less removal of cortical tissue	Studies have demonstrated 65–90% rates of seizure-freedom on long-term follow-up.
Corpus callosotomy	Allows for hemispheric disconnection and improvement of seizures from infantile spasms/West syndrome, Lennox–Gastaut syndrome (LGS), drop attacks	Complete callosotomy can lead to increased rates of disconnection syndrome compared to anterior callosotomy alone, though complete callosotomy has higher rates of seizure freedom from drop attacks.	Seizure improvement can range from 39 to 90% depending on semiology.
Vagus nerve stimulation (VNS)	Vagal nerve afferent fibers release norepinephrine causing a reduction in seizure frequency via the forebrain, limibic system, and spinal cord	Side effects may include laryngeal motor dysfunction/ paresthesia, bradycardia/heart block, and gastrointestinal distress typically from vagal efferent fibers.	Generally cited as a ~ 50% in seizure reduction in 50% of patients.
Responsive neurostimulation (RNS)	A closed loop system that inhibits epileptic propagation in patients with medically refractory partial seizures and ≤ 2 epileptic foci, broadly being applied to thalamic targets for more generalized types of epilepsy	Currently not FDA approved for pediatric patients with epilepsy; often used off-label. Allows for cortical as well as deep subcortical targeting of multiple thalamic nuclei and the hippocampi involved in epilepsy networks. Expanding indications in diffuse and generalized epilepsy. May limit ability for MRI in the future.	Mostly palliative treatment of DRE with 50–75% seizure reduction and few patients demonstrating seizure freedom.

Surgery	Indications	Considerations	Outcomes
Deep brain stimulation (DBS)	An open loop system that inhibits epileptic propagation in patients with medically refractory seizures	Currently not FDA approved for pediatric patients with epilepsy; often used off-label. Allows for deep subcortical targeting of multiple thalamic nuclei involved in epilepsy networks. May limit ability for MRI in the future.	Mostly palliative treatment of DRE with ~50% in seizure reduction.
Laser interstitial thermal therapy (LITT)	Small/focal lesions (hypothalamic hamartoma, selective amygdalohippocampectomies, etc) that are amenable to thermal ablation. Also used in minimally invasive disconnection surgery via multiple lasers and trajectories.	Minimally invasive procedure that can reach deep subcortical lesions or be used to minimally invasively achieve disconnections. Repeat ablations in iterative strategies are well tolerated. Costs are per laser fiber, which are one-time use.	Seizure control rates between 40 and 60%. Considered to have less longevity than open approaches.
Focused ultrasound (FUS)	Uses high-frequency ultrasound to cause thermal ablation of epileptic lesions.	Currently not FDA approved for epilepsy. Targeting is currently not suitable for superficial lesions. Hair shaving is necessary.	Destructive procedure without surgical incision. Limited studies have demonstrated a reduction in seizure threshold in some but not all patients.

Table 2.
Epilepsy surgery types.

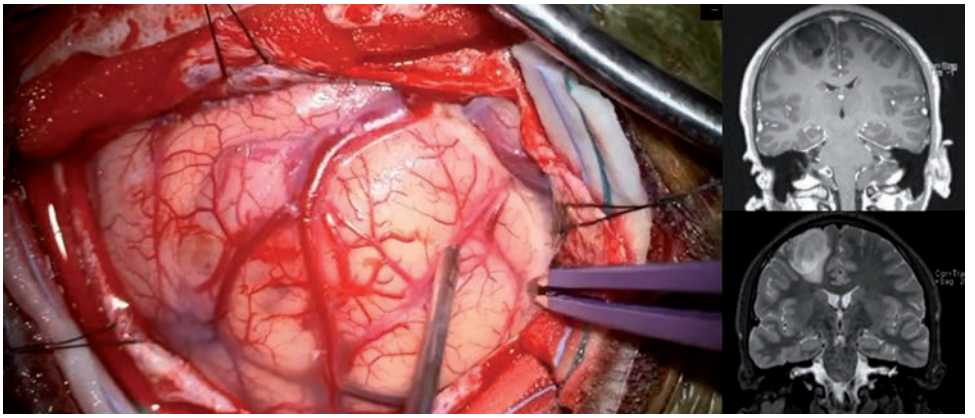

Figure 3.
Demonstrative case of a focal resection of a brain tumor. This 15-year-old patient presented with new onset seizures. They were started on antiseizure medications and MRI demonstrated a T1 hypointense and T2 hyperintense lesion in the right frontal lobe. They underwent gross total resection of the lesion which was tolerated well with resolution of seizure activity; the image depicted above demonstrates the pale, expanded gyrus of the involved lesion. A corticectomy around the lesion was made to dissect the planes of the lesion for resection. Pathology was consistent with astrocytoma WHO grade 3.

epileptic foci and surrounding pathologic tissue while sparing healthy parenchyma thus minimizing neurological impairment [33].

There are risks to every surgery, with open resection, the risks include bleeding, infection, CSF leak, wound healing issues, neurological deficit which varies depending on the location of the craniotomy and region of brain involved, seizure, stroke, coma, and death. While these risks are rare, they are important to discuss with patients in the process of obtaining informed consent to proceed with surgery.

3.2 Temporal lobectomy

The prevalence of temporal lobe epilepsy (TLE) can range from 4 to 10 cases per 1000 in the developed world, frequently caused by mesial temporal sclerosis or imaging negative syndromes such as autosomal dominant TLE, familial (polygenic) TLE, and idiopathic partial epilepsy [36, 37]. Historically there have been two dominant surgical approaches to address temporal epilepsy; anterior temporal lobectomy (ATL) and selective amygdalohippocampectomy (SAH). Typically, ATL is performed by resecting 4–6 cm of the temporal lobe on the non-dominant side and 3.5–4 cm on the dominant side to preserve language and memory function. Selective amygdalohippocampectomy allows for sparing of the lateral temporal lobe and neocortex while removal of the mesial temporal structures and seizure foci is performed (**Figure 4**) [37].

Several studies have demonstrated the advantage of ATL compared to medical management in pediatric patients with DRE related to TLE. Radhakrishnan et al. found that 80.6% of patients were seizure-free at a mean follow-up of 8.1 years, while a randomized trial by Wiebe et al. found that 58% of patients were seizure-free at one-year follow-up [38, 39]. Depending on the pathology and location of epileptic activity, either of the two surgical approaches can be employed by the surgeon, however, there have been several studies that have demonstrated improved seizure control following ATL compared to SAH in the pediatric population, likely related the

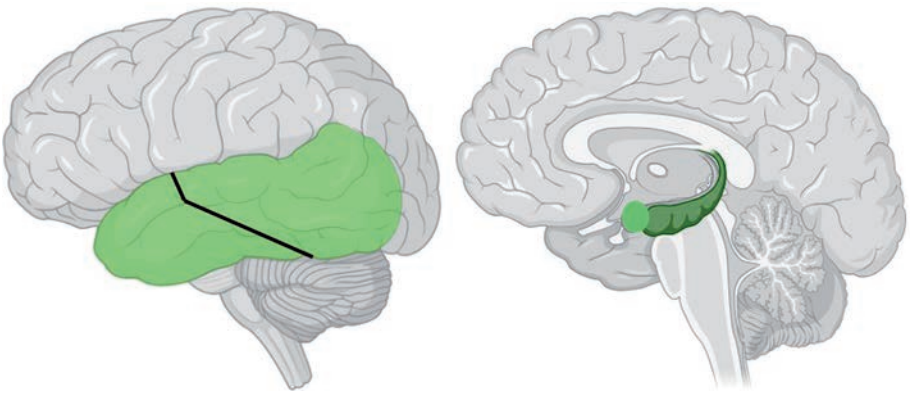

Figure 4.
Anterior temporal lobectomy lateral resection and mesial temporal structures. The figure above shows the lateral resection and mesial structures resected in a standard anterior temporal lobectomy.

increased frequency of pathologies occurring outside of the hippocampus [40, 41]. While intraoperative ECoG can assist surgeons in determining the extent of posterior resection of the hippocampus, possibly sparing functional components, it does not necessarily improve seizure free outcomes compared to anatomical resection [42, 43]. Temporal lobe resection, especially of the dominant lobe, can lead to a number of impairments in language, fluency, memory, and visual deficits [44, 45]. Extensive neuropsychiatric testing and functional MRI can be used to understand the patient's baseline cognitive, language, memory, and functional speech to help optimize safety of resection and perioperative risk stratification. It is not uncommon for speech therapy and/or occupational therapy to be recommended for enhanced postoperative recovery in the weeks to months after surgery for patients with dominant temporal lobe epilepsy who undergo ATL.

3.3 Hemispherectomy

Conditions characterized by diffuse unihemispheric cerebral injury either from an acquired (perinatal infarction, cerebral hemorrhage, hemiconvulsion-hemiplegia epilepsy syndrome, or hemispheric cortical dysplasia) or progressive (Rasmussen's encephalitis, Sturge–Weber syndrome) etiology require a more extensive disconnection of epileptic network [46]. The goal of hemispherectomy or hemispherotomy is to isolate the involved epileptic hemisphere from the rest of the cerebrum, thus preventing the abnormal discharges from propagating throughout the brain. The first anatomical hemispherectomies were conducted by Walter Dandy during resection of large gliomas, involving ligation of the anterior and middle cerebral arteries followed by en bloc resection of the hemisphere [47]. It's uses in epilepsy surgery became popularized in the 1950s to treat infantile hemiplegia [47]. However, by the mid-1960s, significant delayed postoperative complications following anatomical hemispherectomies such as hydrocephalus, subdural fluid collections, and superficial cortical hemosiderosis were noted [48]. Given the morbidity associated with anatomical hemispherectomies, variations began to develop with less emphasis on resection and more on disconnecting the epileptic hemisphere from the healthy one [49–51]. The goals of these functional hemispherectomies were the same as in an anatomical disconnection: disconnection of the cortico-thalamic tract, resection of the mesial

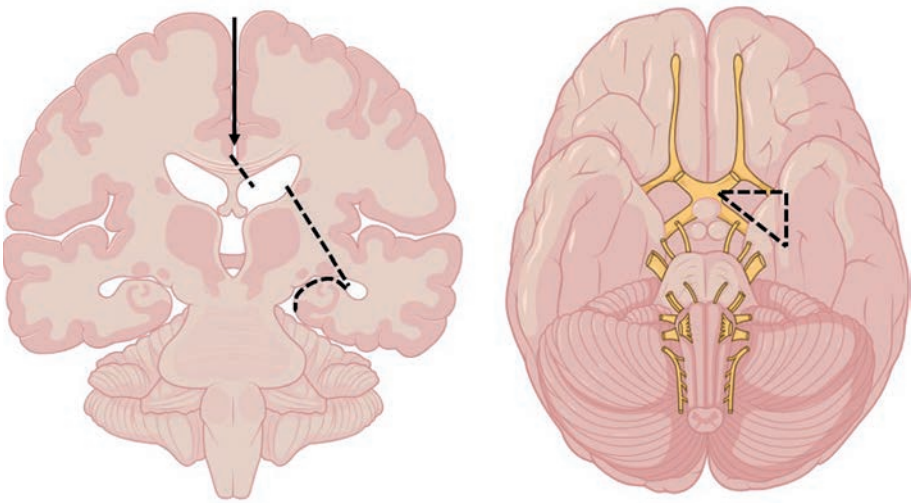

Figure 5.
Hemispheric disconnections via a vertical hemispherotomy. The figure demonstrates the cuts for a vertical hemispherectomy, starting with an interhemispheric approach to a corpus callosotomy, insular disconnection from the lateral aspect of the caudate to the temporal horn for disconnection of the corticothalamic tracts, and mesial temporal disconnection (coronal view). The figure additionally demonstrates the frontobasal disconnection (axial view), depicted with the traditional disconnection using anatomical landmarks of the ACAs, to the ICAs, to the MCA, to the temporal horn (right angle dashed line), vs. the Kawai modification along the optic radiations (oblique dashed line).

temporal structures, corpus callosotomy, and disconnection of the orbito-fronto-hypothalamic tract, all while leaving the diseased brain vascularized and intact (**Figure 5**) [52].

3.4 Hemispherotomy

Hemispherotomy represents progression of the functional hemispherectomy with the major difference being less removal of cortical tissue, however, major disconnection goals remain the same. There are a variety of hemispherotomies that have been described over the years based on surgical approach and order of operations. The peri-insular hemispherotomy consists of several disconnections made through a lateral approach, centered around the circular sulcus, that include transection of the corona radiata, intraventricular callosotomy, posterior hippocampotomy, fronto-basal disconnection, temporal lobe resection, and insular disconnection [53]. This allows for unihemispheric disconnection of epileptic regions from transmitting signals to the contralateral hemisphere, reducing seizure potential. The vertical parasagittal hemispherotomy is another approach allowing for disconnection through an interhemispheric window [49, 54], beginning with an interhemispheric corpus callosotomy, entering the ventricle, allowing for the corona radiata disconnection via the internal capsule before progressing to the trigone of the temporal horn, allowing for disconnection of the temporal lobe, and finally the fronto-basal region is disconnected just anterior to the basal ganglia [49]. Different modifications to these techniques have allowed surgeons to access the various white matter tracts through different approaches based on the specific needs of the surgeon and patient. Another adaptation includes the transsylvian transventricular approach, sought to improve operative times and blood loss [55]. This approach starts with a small craniotomy over the

sylvian fissure and transcortical exposure of the lateral ventricle exposing the frontal to the temporal horns encircling the insular cortex. The frontobasal and mesial white matter tracts are disconnected via corpus callosotomy while an amygdalohippocampectomy completes the temporal disconnection. At 46 months postoperatively, 88% of patients achieved Engel Class I outcomes while, 6% had Engel Class III and Class IV outcomes [55].

3.4.1 Endoscopic approaches

As technology continues to progress, more minimally invasive disconnection techniques have emerged that utilize smaller operating corridors while reducing complications. The use of the endoscope in a transventricular disconnection surgery was introduced by Bahuleyan et al. in 2010 [56]. This technique involved placing burr holes at Kocher's and Frazier's point to allow access to the frontal and occipital horns of the lateral ventricle respectively. Rigid endoscopes are then inserted through the burr holes and incised dura with the steps for disconnection accomplished through both openings. The anterior burr hole allows for disconnection of the frontbasal tracts, anterior callosotomy, and unroofing of the anterior temporal horn; while the posterior burr hole provides disconnections to the fornix, posterior callosotomy, and unroofing of the posterior temporal horn [56]. Lam et al. adapted this endoscopic approach in children [57]; their approach used a small paramedian craniotomy in a similar fashion to an interhermispheric approach with a backup temporal incision marked in case the surgery required additional views to complete the frontobasal and insular disconnections. Once the endoscope was inserted and relevant anatomical landmarks identified, the steps toward complete disconnection were performed. Specifically, the corpus callosum was disconnected from rostrum to splenium, the corona radiata (including internal capsule) and frontobasal fibers (uncinate, occipitofrontal fasciculi) were subsequently disconnected via the temporal horn, followed by disconnection of the mesial temporal structures (hippocampus and fornix) to complete the hemispherotomy. A recent case report by LoPresti et al. also describes the use of an endoscopic-assisted posterior quadrantectomy technique in a 17-year-old patient with intractable epilepsy and right hemiparesis secondary to prior CNS lymphoma and treatment [58]. Examining the evolution of endoscopic techniques, appropriate patient selection was paramount in allowing for efficacy and safety of the operation with several authors suggesting that patients with ventriculomegaly and cortical atrophy being optimal candidates to visualize the ventricles and surrounding structures. Additionally, many authors have noted the steep learning curve for these procedures given the novel equipment and surgical approach necessary to perform a successful surgery. Benefits of these procedure may involve decreased intraoperative blood loss, decreased risk of hydrocephalus, improved pain control, and shorter operative times thus improving patient satisfaction and outcomes. Risks may include the standard risks of a craniotomy and the potential risk of recurrent seizures should complete disconnection not be accomplished.

3.5 Corpus callosotomy

Corpus callosotomy is a useful tool for the treatment of a number of pediatric epileptic disorders including infantile spasms/West syndrome, Lennox–Gastaut syndrome (LGS), drop attacks, and severe epilepsy with multiple independent spike foci (SE-MISF) [59, 60]. The procedure essentially disconnects the epileptogenic hemisphere from the normal hemisphere to mitigate seizure propagation. The first corpus

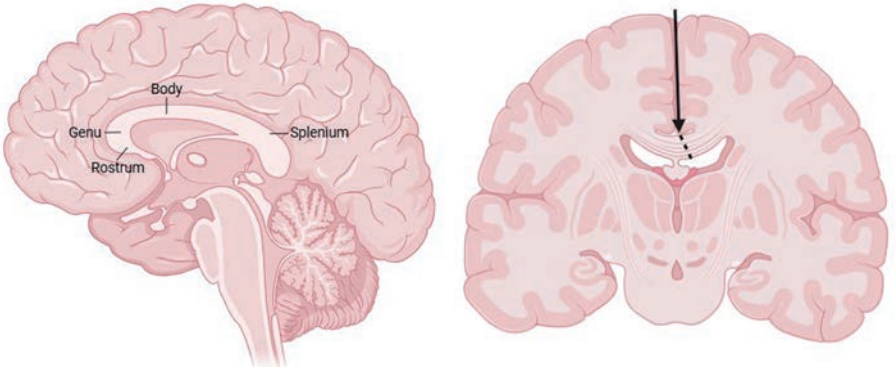

Figure 6.
Corpus callostomy. A corpus callosotomy entails sectioning the corpus callosum along its width, from the rostrum ventrally and anteriorly, to the genu, through the body, to the posterior one third, for an anterior 2/3 corpus callosotomy. For a complete callosotomy, this is extended through the splenium for a complete disconnection.

callosotomy was performed by William P. Van Wagenen in 1939 at the University of Rochester [61]. The procedure was largely abandoned until Roger Sperry published the role of the corpus callosum in interhemispheric connectivity in split-brain studies in the 1950s and 60s [60]. As corpus callosotomies became more widely used to treat intractable epilepsy, studies described disconnection syndrome with a complete callosotomy, thus limitations of the callosotomy to the anterior two-thirds of the corpus callosum were favored for the improved side effect profile. At present, corpus callosotomy represents an effective and well tolerated intervention in pediatric patients with DRE. Both Rathore et al. and Shimuzu demonstrated an improvement in generalized seizure outcomes following both complete and anterior callosotomy, with a ≥ 90% and ~ 87% reduction respectively in each study [62, 63]. Drop attacks specifically were found to benefit from callosal lesioning, with two separate studies demonstrating a ≥ 90% reduction in the severity and frequency of these seizure events [64, 65]. A systemic review conducted by Graham et al. further demonstrated the efficacy of corpus callosotomy in the reduction of drop attacks (67.4%) compared to generalized seizures (39.5%) [66]. Regarding risks of surgery, rates of disconnection syndrome were greater in the complete callosotomy group (12.5%) compared to the anterior callosotomy group (0%), however, there were no differences between surgical or other neurological complications [66]. Disconnection syndrome may result in aphasia and apraxia, with difficulty coordinating movement, and impairment of language and motor function. Thus, patient selection is key to ensure tolerable risk profile and treatment of the seizure types most commonly improved with callosotomy. As such, the use of corpus callostomy remains an integral part in the surgical treatment of DRE and it has become especially useful in the treatment of drop attacks and hemispheric disconnection surgeries (**Figure 6**).

3.6 Laser interstitial thermal therapy

MRI-guided laser interstitial thermal therapy (MRgLITT) has emerged as an exciting tool for the treatment of DRE, especially within the pediatric population. MRgLITT utilizes an optical fiber that is heated by an insulated diode laser, while the catheter is cooled with either saline or CO2 [67]. This laser produces an intense heat that dissipates around the catheter tip, heating the surrounding tissue resulting in

thermal denaturation of cellular enzymes and eventually apoptosis. The diode and catheter are advanced into the brain via a stereotactic frame or robot with the target preset by the surgeon. The main advantage to MRgLITT is that it a minimally invasive way to reach deep subcortical regions, making it an ideal tool for patients with lesional (i.e. hypothalamic hamartomas) epilepsy in deep, harder to access locations by conventional approaches. However, it has also been shown to be efficacious for minimally invasive disconnection surgeries as well, applied via multiple laser fibers and trajectories to accomplish MRgLITT corpus callosotomies and hemispherotomies.

The expanding literature on MRgLITT has shown that it can be a vital intervention in the correct patient population, and that it is both safe and efficacious. In a case series of 17 patients (mean age 15.3 years) with DRE and primarily lesional type epilepsy treated with MRgLITT, 41% and 6% of patients achieved Engle I and Engle II outcomes respectively at a mean follow-up of 16.1 months [68]. Four complications were encountered in this series related to inaccurate probe placement, system malfunction, or postoperative dexamethasone induced gastritis. Another small case series of five pediatric patients demonstrated similar results with Engle I outcomes seen in three of the five patients at a maximum of 13 months post-intervention with no complications encountered [69]. To date, medial temporal sclerosis remains the best studied epileptic pathology in MRgLITT (**Figure 7**). While the majority of these studies are in the adult literature, this procedure is applied in children can improve epilepsy outcomes in the pediatric population. Drane et al. assessed the differences in facial recognition and seizure outcomes of MRgLITT and traditional temporal lobectomy in adults with temporal lobe epilepsy [70]. They demonstrated that patients undergoing MRgLITT had improved accuracy on facial recognition with similar rates of seizure control between the two cohhorts, 57.9% treated with MRgLITT and 61.5% who underwent craniotomy. While the use of MRgLITT has some significant benefits in the treatment of select pathologies and patients, gaps still remain in our understanding of this technology and how to best apply it in a clinical setting. Additionally, the long-term outcomes in relation to the treatment of DRE and its durability remain to be seen and will help clinicians and patients to choose the most appropriate therapy for them.

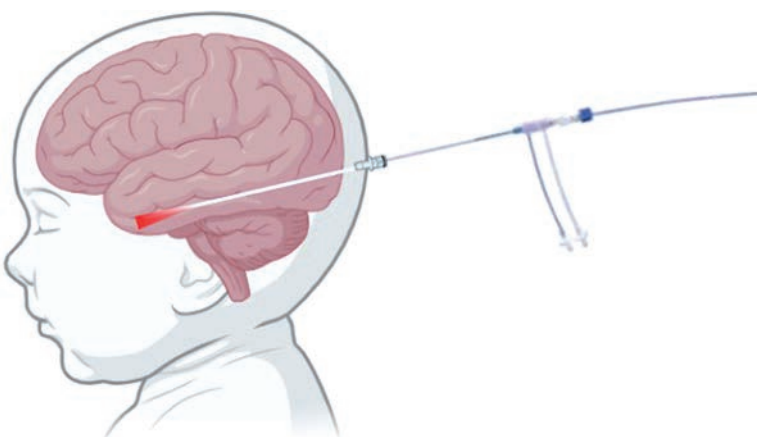

Figure 7.
MRI-guided laser interstitial thermal therapy. This diagram depicts the surgical procedure of MRgLITT, entailing a small burr hole through which an anchor bolt is placed and a laser fiber is passed to the targeted depth stereotactically. This laser fiber is then used to ablate tissue at the target. Its position can be advanced or withdraw along the stereotactic trajectory, which is often targeted along the long-axis of the desired ablation zone.

3.7 Neuromodulation

While DRE only represents a small subset of epileptic pediatric patients, there can be several factors that can preclude their consideration from resective intervention. Patients without a lesional focus as a clear anatomical cause of their seizures can be difficult to manage even with disconnective surgeries as the epileptic zone might not localize to one hemisphere or location, unfavorable anatomy can limit the operative corridors, or the surgical risk might outweigh the perceived benefits from a larger intervention [19]. In these scenarios, electrical neuromodulation can play a pivotal role in reducing seizure frequency and improving the quality of life in these patients. In 1886, Victor Horsley first utilized electrical cortical stimulation to aid in the resection epileptic foci; while Wilder Penfield expanded this work by mapping our cortical networks to better explain the role of neuroanatomy in seizure development [71], it was not until the 1970s when therapeutic interventions with electrical stimulation began to be used for treatment of epilepsy [72, 73].

3.7.1 Vagus nerve stimulation

In 1990, Penry et al. published results on intermittent vagus nerve stimulation (VNS) for the treatment of intractable seizures [74]. The VNS device consists of an implantable impulse generator that connects to a platinum coated electrode wrapped around the left vagus nerve, delivering an electrical signal in a fashion similar to a cardiac pacemaker (**Figure 8**). While the mechanism of action of vagus nerve stimulators (VNS) on seizure reduction was initially difficult to explain, over the past several decades the interactions between various subcortical areas and the neurotransmitters released by them have shed light on this complex system. At present,

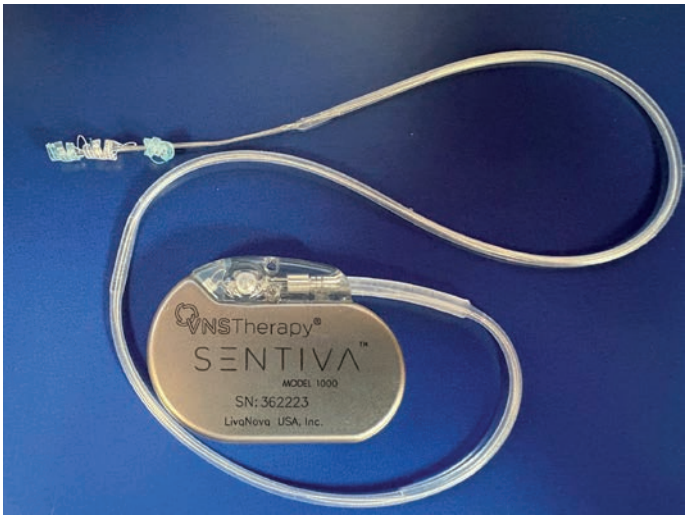

Figure 8.
Vagus nerve stimulator. The vagus nerve stimulator (VNS) consists of an internal pulse generator (IPG) which is placed in a subcutaneous pocket beneath the clavicle and a lead which is connected to the IPG and tunneled to the neck where its three coils, including an anode, anchor, and cathode, are implanted around the vagus nerve, within the carotid sheath. These are performed on the left side to minimize risk of cardiac arrhythmia, associated with vagus nerve function on the right side. Other risks of surgery include bleeding, infection, hoarseness of voice, dysphagia, pain, vocal fold paralysis, risk of damage to surrounding structures, and failure to control seizures.

the hypothesis is that vagal nerve afferents synapsing on the nucleus of the solitary tract (NST), with projections to the locus coeruleus (LC) and dorsa raphe, increase noradrenergic tone in the CNS via norepinephrine release into the forebrain, limbic system, and spinal cord thus reducing seizure activation and propagation [75]. While these afferent fibers are thought to mediate the antiseizure benefits of VNS placement, vagus nerve efferents cause many of the side effects associated with their use including laryngeal motor dysfunction/paresthesia, bradycardia/heart block, and gastrointestinal distress [75].

In 1997, the FDA approved VNS implantation in children >12 years of age with medically intractable partial seizures who are not candidates for surgical resection. Twenty years later, the FDA modified its approval to include pediatric patients ≥4 years of age, thus expanding its application to many more individuals. Since its introduction, there have been a number of studies delineating the efficacy and optimal patient selection for this form of intervention. In 2013, the American Association of Neurology (AAN) issued an update on their guidelines for VNS placement citing several studies demonstrating a > 50% in seizure reduction in 55% of pediatric patients survey across 13 different studies, with a pooled seizure freedom rate of 7% [76]. Patients with Lennox–Gastaut syndrome can be particularly difficult to treat, but also demonstrated a similar responder rate of 55% and a > 50% reduction in seizure frequency [76]. A more recent systemic review by Hajtovic et al. attempted to better isolate genetic conditions that had more robust benefits following VNS implantation. Their study found that patients with tuberous sclerosis had a pooled seizure freedom rate of 40%, with 31% of patients experiencing a ≥ 90% seizure reduction rate, and 68% of patient with a ≥ 50% reduction. Other etiologies such as Dravet syndrome, Rett syndrome, and various epileptic genetic disorders had limited efficacy based their small sample sizes and limited studies available for interpretation [77]. Given the heterogeneity in response rates and seizure freedom following VNS implantation, more research is needed to better identify patients who will have greater benefits following treatment. In light of this, institutions both in the US and Canada are collaborating with the Connectomic Profiling and Vagus Nerve Stimulation Outcomes Study (CONNECTiVOS) to identify patient biomarkers that can be used to select the ideal patient for VNS intervention [78].

3.7.2 Responsive neurostimulation

The role of neuromodulation in epilepsy was further expanded in 2013 with the introduction of responsive neurostimulation (RNS), a closed-loop implantable pulse generator with two electrodes that detect a seizure and deliver targeted therapy to the epileptic source [75]. The RNS system exerts is antiseizure effects through electrical disruption of the seizure focus and inhibits the propagation of electrical signals to distal cortical regions [75]. Additional underlying mechanisms could also include disruption of axonal conduction from high-frequency stimulation and as well as changes in synaptic plasticity and neurogenesis from chronic stimulation [75]. In RNS, an implanted device sits within the skull and is connected to two electrodes, targeted either subcortically or cortically, to sense and stimulate in response to seizures (**Figure 9B**). A demonstrative case treated with RNS is depicted in **Figure 10**.

At present, RNS is approved for patients ≥18 years of age with medically refractory partial seizures and ≤ 2 epileptic foci [11]. While not currently FDA approved in the pediatric population, there are ongoing efforts to expand its application and off-label use to include pediatric patients who suffer from DRE, focusing increasing

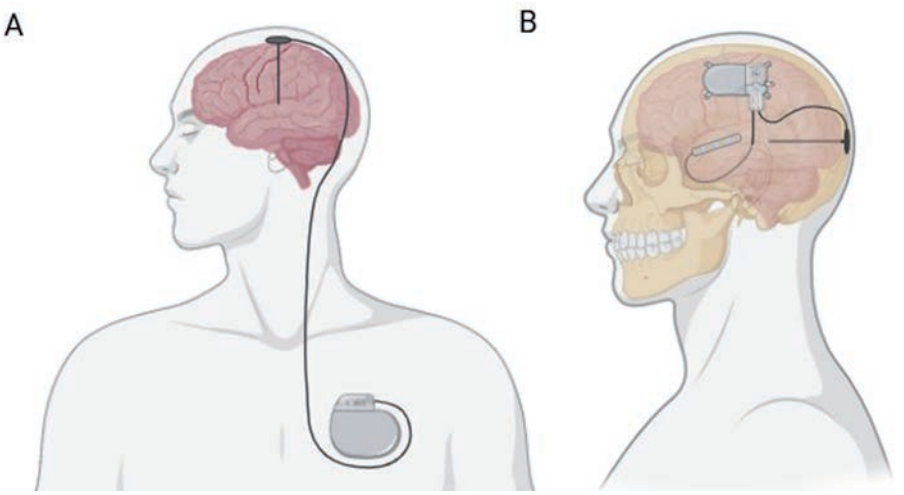

Figure 9.
Deep brain stimulation and responsive neurostimulation. Diagram A depicts the surgical approach to deep brain stimulation (DBS) where one to two depth electrodes are placed stereotactically, through burr holes, anchored to the skull, and tunneled with lead extenders to an internal pulse generator (IPG) subcutaneously on the chest wall which stimulates networks involved in seizures to interrupt seizure activity. Diagram B depicts the surgical approach to responsive neurostimulation (RNS) where an implanted device sits within the skull and is connected to two electrodes, targeted either subcortically or cortically, to sense and stimulate in response to seizures.

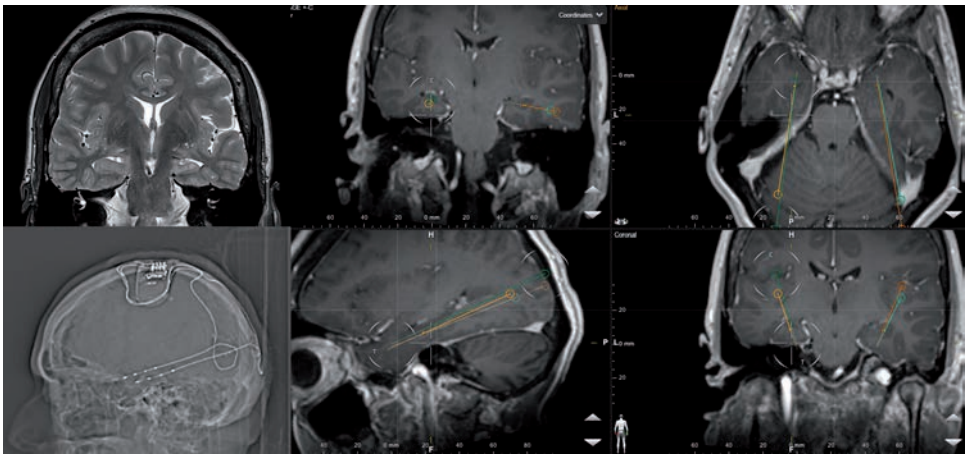

Figure 10.
Demonstrative case of a RNS for bitemporal epilepsy. The patient had a history of bitemporal epilepsy. MRI demonstrated T2/FLAIR signal in the left hippocampus, consistent with mesial temporal sclerosis. Phase I evaluation was consistent with bitemporal epilepsy. They underwent bihippocampal RNS placement for treatment of epilepsy with reduction in seizure burden and frequency.

efforts on generalized or diffuse etiologies via thalamic stimulation. A recent pediatric case study demonstrated that RNS implantation can be a safe and effective treatment with improvement of seizure control in a 16-year-old female with incomplete resection of focal cortical dysplasia and continued debilitating seizures despite antiseizure medication management [79]. A separate study assessed the safety of RNS implantation in an off-label study of 27 pediatric patients (ages 7–17 years) demonstrating an overall reduction in seizure frequency with >50% of the patients have an

improvement of 75% or more in seizure frequency at an average follow-up period of 22 months [80]. A recent literature review and case series also demonstrated improvement in seizure reduction following centromedian nucleus of the thalamus (CMT) RNS implantation in 21 adult patients and three pediatric cases [81]. The authors demonstrated an average seizure reduction of 77% with 95% and 55% of adult patients experiencing a > 50% and ≥ 90% reduction in seizure frequency respectively. In their pediatric subset, all patients experienced between a 70–100% improvement in their seizure burden.

There are several limitations that make placement of an RNS system more challenging in the pediatric population compared to their adult counterparts. For one, the pulse generator is designed to be placed in full-thickness calvariums which can limit their placement in patients with thinner and/or growing skulls. Additionally, for small, deep thalamic nuclei with precise targeting, it is unknown how the growing pediatric skull may impact depth electrode placement over time as the patient ages and continues to develop. Furthermore, MRI is currently contraindicated in patients with RNS implantation which will limit future neuroimaging in pediatric patients. Lastly, the RNS system has demonstrated mostly palliative seizure control with few patients become completely seizure-free over time, impacting seizure frequency and severity and significant rates, but not often providing cure [79]. Risks of RNS placement include bleeding, infection, failure to control seizures, damage to surrounding structures, neurological deficits, seizure, stroke, coma, and death. Despite this, a preeminent open-label prospective clinical trial (RESPONSE study) is currently under investigation assessing the safety and efficacy of RNS implantation for patients between the ages of 12–17 years old with the first patient treated in May of 2022 [82, 83].

3.7.3 Deep brain stimulation

The application of electrical stimulation to cortical and subcortical regions for the treatment of neurological disorders has existed for over 70 years [84]. These electrical impulses are thought to inactivate the implanted structure via high-frequency stimulation causing time locking of the natural axonal activity [75]. Initially used in the treatment of movement disorders [84, 85], DBS has been well documented as an effective and safe surgery, with its application in the treatment of epilepsy is evolving. In the 1980s, the Irving Cooper placed electrodes within the anterior nucleus of the thalamus (ANT) and cerebellum for the treatment of intractable partial seizures with clinical and pharmacologic improvement in the patient's semiology [86]. Since then, a number of targets have been proposed as potential targets in the treatment of epilepsy including the cerebellum, thalamus, hippocampus, caudate, nucleus accumbens, and subthalamic nucleus, among others [87].

Thalamic DBS for DRE has been FDA approved since 2018. Surgery entails the placement of two depth electrodes stereotactically, through burr holes, anchored to the skull, and tunneled with lead extenders to an internal pulse generator (IPG) subcutaneously on the chest wall which stimulates networks involved in seizures to interrupt seizure activity (**Figure 9A**). Risks of DBS include bleeding, infection, failure to control seizures, damage to surrounding structures, neurological deficits, seizure, stroke, coma, and death.

The best reported and most efficacious DBS targets for epilepsy are in the thalamus, specifically the anterior nucleus of the thalamus (ANT), centromedian nucleus of the thalamus (CMT), dorsalis medialis (DM) nucleus, and pulvinar nucleus [87]. The ANT has significant connectivity throughout the mesial/anterior frontal lobe and

temporal lobes, areas often associated with epileptic foci [54, 88]. In 2010, a multicenter study assessing bilateral ANT DBS lead placement demonstrated a seizure reduction of at least 50% in 56% of adult patients treated at 2 years compared to the control group with 14 patients being seizure free at 6-months [89]. The Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy (SANTÉ) study published seven-year follow-up data demonstrating robust long-term seizure control with a median seizure reduction of 75% and an overall patient mortality of 6.9 deaths per 1000 person-years [90].

While the ANT has demonstrated the best efficacy for focal seizures, CMT has emerged as a target of interest for generalized and multifocal seizures [87]. In epilepsy patients, activation of the CMT exhibits diffuse ipsilateral cortio-cortical evoked potentials, with projections to a number of nuclei including the caudate, lentiform nucleus, sensorimotor/premotor corticies, and subthalamic nucleus among others [91, 92]. The use of the CMT in epilepsy targeting was popularized by Velasco et al. in 1987 in five patients with multifocal/generalized epilepsy [93]. A recent prospective open-label study of 20 patients (median age 15.5 years of age) demonstrated a > 50% in seizure reduction in 90% of their patients with one patient being seizure free at 2 years [94] . In 2022, Dalic et al. reported their results of 20 patients with Lennox–Gastaut syndrome and CMT DBS implantation, demonstrating a 53.8% reduction in seizure frequency compared to the control group, however, this was not statistically significant [95].

As with the prior two thalamic nuclei, both the DM and pulvinar remain areas of investigation for DRE treatment. Stimulation of the DM shows activation of the ipsilateral orbitofrontal, mesial/lateral frontal area, along with some activation of the mesial temporal region [91]. The pulvinar represents the largest thalamic nucleus with a number of connections to both cortical and subcortical regions. The medial pulvinar specifically has projections to typical epileptic areas including the amygdala, hippocampus, temporal neocortex, cingulate and orbitofrontal cortex [96]. There remain limited clinical studies related to seizure control and the DM and pulvinar, with the majority of studies existing in animal models or small cases series. In a study of eight patients with DRE originating from the temporal lobe and pulvinar DBS, five of the eight patients experiencing less severe seizures with improved levels of consciousness compared to those patients with non-pulvinar stimulation [97].

While much of the DBS literature has examined adults. Several case reports and retrospective series detail safety and efficacy in children with epilepsy. There are ongoing clinical trials in North America examining the role of DBS in pediatric epilepsy.

4. Future directions

The treatment of DRE remains a challenging and often multi-factorial discussion between the patient and the treating clinicians, including epileptologists, neuropsychologists, and neurosurgeons. This pathology can prove to be even more complicated in pediatric patients given their growing anatomy, limited working space, diverse pathologies, and developing brain impacted by the side effects of sedating seizure medication and unrelenting seizures. It is therefore imperative that a thorough workup be conducted for all patients presenting for seizure evaluation so that the semiology can be described and etiologies localized. The use of both Phase I and Phase II testing allows the clinical team to proceed in an organized fashion so that a

complete evaluation is conducted for each evaluation. Based on this workup, referral for epilepsy surgery is recommended. As our understanding of epilepsy continues to evolve and the treatment options become more diverse, the goal is for future interventions to be tailored to individuals based on their seizures and pathology. At the heart of the presurgical evaluation is the multidisciplinary care coordination between the epilepsy neurology and neurosurgical team.

At present, surgical resection remains a mainstay in the treatment of DRE, especially in patients with localizable disease during testing. However, neuromodulation allow neurosurgeons to operate on previously untreatable patients and minimally invasive approaches to surgery allow neurosurgeons to provide surgical treatment with fewer adverse effects while improving seizure outcomes. In patients who are not candidates for either resection or disconnection surgeries, newer palliative options such as MRgLITT, VNS, RNS, and DBS are becoming more accessible and expanding the indications for intervention. Furthermore, adaptation of existing technologies, like stereotactic radiosurgery, which are not commonly used for the treatment of epilepsy, have a role in the treatment of epilepsy related to deep, hard to reach lesions such as hypothalamic hamartomas. While these interventions are further defining their place in the treatment paradigm for DRE, new technologies are already in development offering less invasive approaches.

4.1 Focused ultrasound

Focused ultrasound (FUS) is a promising new therapy that already has FDA approval for the treatment of essential tremor and Parkinson's disease. FUS entails a high-frequency ultrasound beam amplified and localized to a focal target within the brain, typically with the assistance of MR imaging, causing acoustic ablation of the target [98]. The application of FUS in epilepsy remains limited and an area of future interest given its non-invasive nature and ease of operation. Several case series out of Asia have demonstrated its efficacy in lowering seizure thresholds in some but not all patients with limited adverse effects [99–101]. However, in these studies, the sample sizes are small with minimal long-term follow-up over 12 months, making their generalizability limited.

While there is still significant research needed to address the current shortcomings of these newer technologies, they remain viable options for many patients. Larger clinical trials with a more pediatric focus are also needed to help refine the selection criteria and report the outcomes for this under-researched population. Additionally, long-term follow-up comparing approaches and outcomes will help elucidate who may benefit most from which procedure going forward when there is overlap in what may be offered.

5. Conclusion

Epilepsy is a common, life-changing condition. When medical management fails, surgical treatment is recommended to, where able provide seizure freedom, and improve seizure burden, reduce seizure frequency, improve quality of life, and improve changes of long-term survival. We summarize updates in epilepsy surgery evaluation and provide a comprehensive review of the current status of pediatric epilepsy surgery, including advances and innovations in the field. Pediatric DRE is a highly complex pathology that continue to push the boundaries of both neurology

and neurosurgery; ongoing innovations in technology and diagnostic and/or therapeutic approaches continue to advance the field.

Conflicts of interest

Sandi Lam discloses research funding from:
PCORI: Comparative effectiveness of palliative surgery versus additional antiseizure medications for Lennox–Gastaut Syndrome.
PCORI supplement: Indirect costs of care for families of patients with Lennox–Gastaut Syndrome.
NIH/NINDS SBIR: Assessment of CSF Shunt Flow with Thermal Anisotropy Measurement Device.
NSF SBIR II: Development of a Noninvasive, Wireless Telemedicine Flow Sensor for Patients with Hydrocephalus.
Northwestern Institute of Global Health: Building Capacity for Treatment of Surgical Epilepsy in Uganda.
Sandi Lam discloses Industry and No- Profit COI:
Livanova: Advisory Board.
Synergia: Advisory Board.
BrainLab: Consultant.
Encoded Therapeutics: Consultant.
Jaguar Therapeutics: Consultant and Chair of DSMB.
Ovid Therapeutics: Consultant.
Brain Recovery Project/Pediatric Epilepsy Surgery Alliance: Board Member.
CURE Epilepsy: Scientific Board Member.

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