

Emerging surgical therapies in the treatment of pediatric epilepsy

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Abstract: In the approximately 1% of children affected by epilepsy, pharmacoresistance and early age of seizure onset are strongly correlated with poor cognitive outcomes, depression, anxiety, developmental delay, and impaired activities of daily living. These children often require multiple surgical procedures, including invasive diagnostic procedures with intracranial electrodes to identify the seizure-onset zone. The recent development of minimally invasive surgical techniques, including stereotactic electroencephalography (SEEG) and MRI-guided laser interstitial thermal therapy (MRgLITT), and new applications of neurostimulation, such as responsive neurostimulation (RNS), are quickly changing the landscape of the surgical management of pediatric epilepsy. In this review, the authors discuss these various technologies, their current applications, and limitations in the treatment of pediatric drug-resistant epilepsy, as well as areas for future research. The development of minimally invasive diagnostic and ablative surgical techniques together with new paradigms in neurostimulation hold vast potential to improve the efficacy and reduce the morbidity of the surgical management of children with drug-resistant epilepsy.

Keywords: Epilepsy; laser ablation; MRI-guided laser interstitial thermal therapy (MRgLITT); NeuroPace; responsive neurostimulation (RNS); stereotactic electroencephalography (SEEG)

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Introduction

Pediatric epilepsy is a relatively common disorder afflicting 1 of every 100 children, and up to one third of these patients demonstrate drug-resistant epilepsy (DRE) (1,2). In a 2009 statement, the International League Against Epilepsy defined DRE as the “failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom” (1). DRE represents a major therapeutic challenge and can be associated with significant comorbidities, including cognitive impairment, depression, anxiety, developmental delay, and impaired activities of daily living (3,4). Although it was initially perceived as a therapeutic option only after all other options

were exhausted, surgical treatment of properly selected patients can provide long-term seizure control rates of 50–70% (5). In fact, surgical intervention remains grossly underutilized, with approximately 100,000–500,000 surgical candidates in the U.S. but less than one percent of eligible patients undergoing epilepsy surgery each year (6). In light of improved seizure-control rates and reduced morbidity of modern epilepsy treatments, the American Academy of Neurology published a practice parameter recommending surgery as a treatment of choice for certain patients with DRE, as earlier referral can help avoid the adverse developmental and social effects of uncontrolled seizures (7). Despite this recommendation, several studies have shown that there has been no improvement in the delay from diagnosis to surgical referral for patients with DRE (8,9).



Figure 1 NeuroPace System. The NeuroPace device is shown with a depth electrode (top lead) and cortical surface electrode (bottom lead) attached to the device, which is implanted in the skull. Reproduced with permission from NeuroPace, Inc. (Mountain View, CA).

The reluctance to refer patients for evaluation at an epilepsy center is multifactorial, with reasons for delay including fear of surgical comorbidity, expense, and limited experience with modern, multidisciplinary treatment options (6). The recent emergence of novel surgical diagnostic and therapeutic strategies has the potential to increase the number of children who can benefit from surgical therapy, improve its efficacy, and decrease morbidity. This may turn the tide of misperception among families and community physicians regarding the surgical treatment of DRE in children. This review will discuss the application of several emerging diagnostic and therapeutic surgical techniques in pediatric epilepsy, including stereotactic electroencephalography (SEEG), MRI-guided laser interstitial thermal therapy (MRgLITT), and responsive neurostimulation (RNS).

Stereotactic electroencephalography (SEEG)

SEEG, the stereotactic placement of multiple depth electrodes for intracranial EEG recording, which was originally described more than 50 years ago by Talairach and Bancaud (10,11), has enjoyed a renaissance over the past decade in the context of improved stereotaxis, imaging, and seizure monitoring technologies (Figure 1). Diagnostic intracranial EEG evaluation of pediatric DRE is critical when seizure foci are poorly localized by noninvasive means and after interdisciplinary evaluation (12). SEEG particularly

facilitates a three-dimensional spatiotemporal understanding of seizure onset and progression. Targets are individualized based on hypothesized ictal foci using clinical semiology, scalp video EEG monitoring, structural and metabolic imaging, and interdisciplinary evaluation. Patients for whom SEEG is commonly indicated are those children with DRE whose magnetic resonance imaging scans are normal and those with multifocal lesions, nonlateralized seizure onset on scalp video EEG, proximity of ictal onset to putative functionally eloquent cortex, or discordant noninvasive data (Table 1). In comparison to surface electrode monitoring with subdural electrodes, SEEG may be particularly useful in the evaluation of children with multiple lesions including tuberous sclerosis complex, as well as for sampling deep targets such as insular cortex, the cingulate gyrus, and mesial temporal structures. In addition, placement does not require craniotomy (67). Furthermore, SEEG can be useful during the investigation of epileptic networks, such as limbic circuitry (67). Robotic assistance in depth electrode placement has demonstrated benefits in planning safe trajectories and reducing operating time and is associated with excellent target accuracy of 1–3 mm (35,68).

SEEG successfully identified the ictal onset zone in 90% of children in one large series (69), and these results have been confirmed by multiple reports (Tables 1 and 2). The first consecutive study of SEEG in the pediatric population reported 15 children (mean age 34.1 months), with 14 undergoing subsequent surgical resection (22). Ten of 14 children had at least 12-month follow-up: six patients were seizure free (Engel I), 2 had rare seizures (Engel II), and 2 patients had no meaningful improvement (Engel IV) (70). Cortical dysplasia (10 children) was the most frequent underlying ictal substrate. One patient died after electrode placement because of severe cerebral edema in the setting of hyponatremia of unclear etiology. A large retrospective cohort study of 200 patients, including children and adults, with 2663 SEEG electrode implantations, reported successful identification of the ictal onset zone in 154 patients (77%) (67). In this cohort, 134 patients underwent subsequent resection and 61 patients (68%) were seizure-free at 12 months. Again, the most common underlying etiology was cortical dysplasia. Minimal morbidity occurred after SEEG, with an extremely low incidence of surgical site infection (0.08%), intracranial hemorrhage (0.08%), or new focal neurologic deficit (0.04%). Results demonstrating low morbidity and mortality with SEEG have been confirmed by multiple reports from different centers in both adult and pediatric cohorts. Some studies have reported a higher rate of

Table 1 Summary of various emerging technologies in the surgical management of epilepsy

Technique	Indications	References
Stereotactic electroencephalography (SEEG)	<ul style="list-style-type: none"> • Drug-resistant epilepsy[†] • MRI-negative seizure zone identification • Anatomico-electro-clinical and MRI data discordance • Multiple discordant lesions (e.g., tuberous sclerosis) • Overlap with eloquent cortex • Need for bilateral explorations • After subdural grid failure • Hypothesized involvement of widespread epileptogenic networks 	Smith <i>et al.</i> 1992 (13); Munari <i>et al.</i> 1994 (14); Behrens <i>et al.</i> 1994, 1997 (15,16); Kramer <i>et al.</i> 1994 (17); Wiggins <i>et al.</i> 1999 (18); Lee <i>et al.</i> 2000 (19); Guenot <i>et al.</i> 2001 (20); Rydenhag and Silander 2001 (21); Cossu <i>et al.</i> 2005, 2012, 2014, 2015 (22-25); De Almeida <i>et al.</i> 2006 (26); Burneo <i>et al.</i> 2006 (27); Johnston <i>et al.</i> 2006 (28); McGonigal <i>et al.</i> 2007 (29); Tanriverdi <i>et al.</i> 2009 (30); MacDougall <i>et al.</i> 2009 (31); Ozlen <i>et al.</i> 2010 (32); Blauwblomme <i>et al.</i> 2011 (33); Derrey <i>et al.</i> 2012 (34); Cardinale <i>et al.</i> 2013 (35); Gonzalez-Martinez <i>et al.</i> 2013, 2014a, 2014b (36-38); Van Roojen <i>et al.</i> 2013 (39); Nowell <i>et al.</i> 2014 (40); Taussig <i>et al.</i> 2014 (41); Serletis <i>et al.</i> 2014 (42); Liava <i>et al.</i> 2014 (43); Dylgjeri <i>et al.</i> 2014 (44); Dorfmueller <i>et al.</i> 2014 (45); Enatsu <i>et al.</i> 2015 (46); Suresh <i>et al.</i> 2015 (47); Ciurea <i>et al.</i> 2015 (48); Craiu <i>et al.</i> 2015 (49); Oderiz <i>et al.</i> 2015 (50); Mathon <i>et al.</i> 2015 (51); Catenoix <i>et al.</i> 2015 (52)
Laser interstitial thermal therapy (LITT)	<ul style="list-style-type: none"> • Drug-resistant epilepsy[†] • Deep-seated epileptogenic lesions (e.g., mesial temporal sclerosis, hypothalamic hamartoma, deep tumors) 	Curry <i>et al.</i> 2012 (53); Esquenazi <i>et al.</i> 2014 (54); Hawasli <i>et al.</i> 2014 (55); Willie <i>et al.</i> 2014 (56); Drane <i>et al.</i> 2015 (57); Kang <i>et al.</i> 2015 (58); Lewis <i>et al.</i> 2015 (59); Waseem <i>et al.</i> 2015 (60)
Responsive neurostimulation (RNS), NeuroPace	<ul style="list-style-type: none"> • ≥18 years of age • Drug-resistant epilepsy[†] • Partial-onset seizures • ≤2 epileptogenic foci • Average of ≥3 seizures per 3 months average 	Morrell 2011, 2014 (61,62); Heck <i>et al.</i> 2014 (63); King-Stephens <i>et al.</i> 2015 (64); Loring <i>et al.</i> 2015 (65); Meador <i>et al.</i> 2015 (66)

[†], failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom (1). LITT, laser interstitial thermal therapy; MRI, magnetic resonance imaging; RNS, responsive neurostimulation; SEEG, stereotactic electroencephalography.

permanent morbidity after evaluation with surface electrodes (3–6%) compared with the use of SEEG electrodes (0–3%) because of the need for craniotomy and invasive grid placement in both adult and pediatric patients (34–37,42); however, comparisons of surface electrodes and SEEG as well as complication rates have been limited because of differing study indications, methodology, and techniques.

Larger studies of SEEG monitoring in pediatric patients have reported that efficacy of seizure foci identification and safety are similar to those reported in studies of adults (22,41,43,44). A study of 15 patients (mean age seizure onset 6.4 months, SEEG placement 34.1 months) showed Engel I seizure freedom in 60% of patients (22). Liava *et al.* (43) evaluated 62 children (mean age epilepsy onset 3.2 years, surgery 7.9 years) with SEEG used in 39% of patients. The preoperative MRI demonstrated one or more structural lesions in over 90% of patients, including focal cortical dysplasia (50%), tumor (24%), and gliosis (14.5%). After surgery, 85.5% of patients achieved Engel I seizure freedom.

In a study of ten children (mean age at epilepsy onset 1.3 years, SEEG placement 6.4 years, surgery 6.6 years), Dylgjeri *et al.* (44) reported Engel I seizure freedom in 70% of cases. No patient complications from SEEG placement were reported in this study. Taussig *et al.* (41) evaluated 65 pediatric patients (mean age at epilepsy onset 29.8 months, SEEG placement 98.6 months) who underwent SEEG placement. MRI results were normal or unremarkable in 20% of cases and 78% of patients underwent eventual surgery, with focal cortical dysplasia the most common diagnosis (51%). With a mean follow-up of 24 months, Engel I seizure freedom was achieved in 67% of patients. Overall Engel I seizure freedom outcomes are 60–80% in pediatric patients, a rate achieved with low morbidity and mortality from SEEG placement.

SEEG has enabled the development of quantitative algorithms to aid in seizure localization. A recent study used an algorithm-derived SEEG pattern to successfully identify the ictal onset zone using interictal fast activity

Table 2 Meta-analysis of studies evaluating stereotactic electroencephalography (SEEG) for epilepsy evaluation

Reference	Number of patients	Number and type of electrode	Patient age groups
Smith <i>et al.</i> 1992 (13)	164	171 depth	
Munari <i>et al.</i> 1994 (14)	70	714 SEEG	Adult and pediatric
Behrens <i>et al.</i> 1994 (16)	160	26 depth	
Kramer <i>et al.</i> 1994 (17)	56	16 depth	Adult and pediatric
Behrens <i>et al.</i> 1997 (15)	429	279 strip, grid and depth	
Wiggins <i>et al.</i> 1999 (18)	38	Strip, grid and depth	
Lee <i>et al.</i> 2000 (19)	49	Strip, grid and depth	
Rydenhag and Silander 2001 (21)	182	205 strip, grid and depth	Adult and pediatric
Guenot <i>et al.</i> 2001 (20)	100	1,118 SEEG electrodes	
Cossu <i>et al.</i> 2005 (23)	211	215 SEEG	
De Almeida <i>et al.</i> 2006 (26)	217	3,022 SEEG	Adult
Burneo <i>et al.</i> 2006 (27)	116	Strip, grid and depth	
Johnston <i>et al.</i> 2006 (28)	112	Strip, grid and depth	Adult and pediatric
McGonigal <i>et al.</i> 2007 (29)	100	SEEG	Adult and pediatric
Tanriverdi <i>et al.</i> 2009 (30)	491	6,415 SEEG	Adult and pediatric
MacDougall <i>et al.</i> 2009 (31)	172	177 strip, grid and depth	Adult
Ozlen <i>et al.</i> 2010 (32)	70	276 strip, grid and depth	Adult and pediatric
Blauwblomme <i>et al.</i> 2011 (33)	95	Strip, grid and depth	Pediatric
Cossu <i>et al.</i> 2012 (22)	15	SEEG	Pediatric
Derrey <i>et al.</i> 2012 (34)	1	14 SEEG	Pediatric
Cardinale <i>et al.</i> 2013 (35)	500	6,496 SEEG	Adult and pediatric
Gonzalez-Martinez <i>et al.</i> 2013 (36)	100	1,310 SEEG	Adult and pediatric
Van Roojen <i>et al.</i> 2013 (39)	14	SEEG	
Gonzalez-Martinez <i>et al.</i> 2014 (37)	122	1,586 SEEG	Adult and pediatric
Cossu <i>et al.</i> 2014 (24)	5	SEEG and radiofrequency thermal ablation	
Nowell <i>et al.</i> 2014 (40)	22	187 SEEG	Adult
Taussig <i>et al.</i> 2014 (41)	65	SEEG	Pediatric
Serletis <i>et al.</i> 2014 (42)	200	2,663 SEEG	Adult and pediatric
Liava <i>et al.</i> 2014 (43)	62	SEEG	Pediatric
Dylgjeri <i>et al.</i> 2014 (44)	10	SEEG	Pediatric
Cossu <i>et al.</i> 2015 (25)	89	SEEG and thermal ablation	Adult and pediatric
Enatsu <i>et al.</i> 2015 (46)	18	SEEG	Adult and pediatric
Suresh <i>et al.</i> 2015 (47)	18	SEEG	Adult
Ciurea <i>et al.</i> 2015 (48)	1	SEEG	Adult
Craiu <i>et al.</i> 2015 (49)	1	SEEG	Adult
Oderiz <i>et al.</i> 2015 (50)	3	SEEG	Adult and pediatric
Mathon <i>et al.</i> 2015 (51)	163	163 strip, grid and depth	Adult
Catenoix <i>et al.</i> 2015 (52)	14	SEEG and thermal ablation	Adult

Medline literature search using MeSH search term "SEEG" or "stereoelectroencephalography" since 1990 for English-language manuscripts involving clinical use of SEEG. SEEG, stereotactic electroencephalography.

Table 3 Meta-analysis of patients undergoing laser interstitial thermal therapy (LITT) for epilepsy treatment

Reference	Population	Sample size
Curry <i>et al.</i> 2012 (53)	Mixed	5
Kang <i>et al.</i> 2015 (58)	MTS	20
Willie <i>et al.</i> 2014 (56)	MTS	13
Drane <i>et al.</i> 2015 (57)	TLE	19
Waseem <i>et al.</i> 2015 (60)	TLE	7
Hawasli <i>et al.</i> 2014 (55)	Insular	1
Esquenazi <i>et al.</i> 2014 (54)	Periventricular nodular heterotopia	2
Gonzalez-Martinez <i>et al.</i> 2014 (77)	Periventricular nodular heterotopia	1
Cossu <i>et al.</i> 2014 (24)	Periventricular nodular heterotopia	5
Cossu <i>et al.</i> 2015 (25)	Hippocampal sclerosis, periventricular nodular heterotopia, focal cortical dysplasia, other	89
Catenoix <i>et al.</i> 2015 (52)	Periventricular nodular heterotopia, focal cortical dysplasia	14

Medline literature search using Mesh search term “LITT” or “laser” and “epilepsy” or “seizure” since 1990 for English-language manuscripts involving clinical use of MRgLITT. MTS, mesial temporal sclerosis; TLE, temporal lobe epilepsy.

(80–120 Hz) associated with slow transient polarizing shifts and voltage depression (71). A three-dimensional model of seizure activity was created from the position of the SEEG electrodes. This method was validated using a separate cohort of 14 patients, with complete correlation with clinician-identified seizure onset in 13 cases and partial correlation in 1 case. Single-pulse electrical stimulation (SPES) has also been used to improve detection of epileptic sites (72). Electrodes may act as either activators or bidirectional activator/detectors, and stimulation was able to generate three-dimensional reconstructed networks. Other studies have used various SEEG data measurements to model the epileptogenic zone, including absolute signal slope (e.g., change in signal strength/time), ordinal patterns of EEG activity, multivariate cross-correlation matrices of EEG activity, and multivariate model-free information theory (73). Other methods of EEG quantitation include the joint sign periodogram event characterization transformation algorithm (74), epilepticity index (75), and high-frequency oscillations (76). As quantitative algorithms analyzing specific interictal and ictal features of intracranial EEG recordings become more clinically informative, SEEG is playing a rapidly expanding role in modeling the epileptogenic zone in appropriately selected children.

MRI-guided laser interstitial thermal therapy (MRgLITT)

In parallel with the development of robot-assisted,

minimally invasive intracranial EEG recordings and quantitative algorithms to model the epileptogenic zone, novel minimally invasive surgical treatment strategies have emerged. Specifically, MRgLITT has been an exciting new minimally invasive tool in the management of a variety of neurosurgical lesions, especially DRE in children (*Tables 1 and 3*). MRgLITT utilizes an optical fiber with a diffusing tip heated by a diode laser insulated in an outer cannula that cools the laser with either saline or carbon dioxide (78). The probe is delivered by frame-based stereotaxis, robotic stereotaxis, or MRI-based frameless stereotactic techniques to a defined target. After placement, heat diffused from the probe is monitored in real-time using MR thermography. Heating of tissue results in time- and temperature-dependent thermal denaturation of critical enzymes and eventually cell death.

Two MRgLITT systems are currently approved by the Food and Drug Administration (FDA) for clinical use in the United States: Visualase (Medtronic, Minneapolis, MN) and NeuroBlate (Monteris Medical, Plymouth, NM). Although these systems are built around the same concept, there are differences between them, including computer-guided robotic catheter movement, directional manipulation of thermal energy, and low-temperature safety controls to protect critical structures from injury (78,79). Advantages of MRgLITT include the ability to target deep lesions (e.g., hypothalamic hamartomas, mesial temporal sclerosis) via a minimally invasive approach and monitoring of the treatment in real time. This contrasts with other minimally

invasive or noninvasive treatment methods, including gamma knife radiosurgery or radiofrequency ablation (80-82). Further, MRgLITT can easily reach deep lesions close to the skull base, in contrast with focused ultrasound (83).

Multiple studies have shown an expanding role for MRgLITT in the treatment of pediatric DRE. A recent report evaluated MRgLITT in the management of 17 pediatric (mean age 15.3 years) patients with DRE and a variety of epileptogenic substrates, including focal cortical dysplasia (n=12), tuberous sclerosis (n=5), hypothalamic hamartoma (n=1), mesial temporal sclerosis (n=1), Rasmussen encephalitis (n=1), and tumor (n=1) (59). Seizure control rates were promising, with 41% of patients achieving seizure freedom and 59% achieving an Engel I or Engel II outcome. Four complications were reported, namely inaccurate probe placement (n=2), probe system failure (n=1), and postoperative dexamethasone-induced gastritis (n=1). The use of MRgLITT in the treatment of hypothalamic hamartomas was evaluated in a study of 14 pediatric patients (median age 8 years); postoperative Engel I seizure freedom was achieved in 86% of patients with a mean followup of 9 months (84). Another study evaluated the role of MRgLITT in five pediatric patients (age 5–15 years) for a combination of tuberous sclerosis, mesial temporal lobe epilepsy, cortical dysplasia, and hypothalamic hamartoma (53). Engel I seizure freedom was achieved in three patients with limited follow-up ranging from 2 to 13 months. MRgLITT has also been reportedly used for treatment of various other conditions including periventricular nodular heterotopia (54,77), insular epileptic foci (55), glial neoplasms (85), brain metastases (86), and teratoma (87).

To date, the most well-studied application of MRgLITT in DRE is the minimally invasive treatment of mesial temporal sclerosis (MTS). Although randomized trials have clearly demonstrated the efficacy of craniotomy and temporal lobectomy in patients with DRE and MTS (88,89), this procedure is frequently associated with a decline in verbal memory when performed in the dominant hemisphere (90,91). Minimally invasive approaches including radiofrequency ablation have shown good outcomes (81), suggesting a role for MRgLITT. A recent report of 20 children and adults (age range 0.9–50 years) undergoing MRgLITT for MTS demonstrated seizure control rates of 53% at 6 months, with 4 patients requiring anterior temporal lobectomy after MRgLITT for definitive seizure control (58). Unfortunately, although a median follow-up of 13.4 months (range, 1.3–38.5 months) was

achieved, a large number of patients were lost to follow-up, limiting the available data on long-term seizure freedom. Another study of 13 adult patients from a single institution (9 with MTS) showed seizure control rates of 77% along with control of 67% in patients with MTS (n=6/9) (56). One prospective study of temporal lobe epilepsy compared 19 adult patients undergoing MRgLITT treatment with 39 adult patients undergoing standard temporal lobectomy for temporal lobe epilepsy in the dominant hemisphere. Patients undergoing craniotomy had a more significant decline in facial recognition and naming ($P<0.0001$) (57). Rates of seizure control were similar in both groups, with 57.9% of patients treated with MRgLITT and 61.5% who underwent craniotomy achieving seizure freedom. Although most of the data regarding MRgLITT in MTS treatment are from the adult literature, efficacy and safety in pediatric patients have been shown in several reports, suggesting an expanding role for MRgLITT in children in the future (58).

Responsive neurostimulation (RNS)

Initial evaluation of electrical stimulation in the study of epilepsy was performed by Penfield and Jasper in 1954 (92,93). Deep brain stimulation has been used successfully for treatment of epilepsy in small series targeting the cerebellum (94), centromedian thalamic nucleus (95,96), and anterior nucleus of the thalamus (97-99). Targeting of the hippocampus, subthalamic nucleus, and caudate have also been reported (100-108). These early studies of open-loop stimulation technology were important benchmarks in the use of neurostimulation to treat epilepsy and provided the foundation for RNS (109).

RNS is a novel treatment paradigm that is distinct from other types of neurostimulation because it employs continuous monitoring of a focal EEG signal via intracranial electrodes placed over an ictal onset zone, with cortical stimulation based on computer analysis of EEG signal input to abort seizure onset (*Table 1*). The first commercially available implantable system was introduced by NeuroPace, Inc. (Mountain View, CA, USA) and received FDA approval in the U.S. in 2013 for patients ≥ 18 years of age with medically refractory (appropriate selection and trial of ≥ 2 medications), partial-onset seizures, ≤ 2 epileptogenic foci, and an average of ≥ 3 seizures per 3-month average (*Figure 2*) (61,63). NeuroPace is compatible with both surface and depth electrodes that both detect epileptogenic activity and produce electrical stimulation to disrupt seizure onset. The device measures epileptic activity by the bandpass, line-

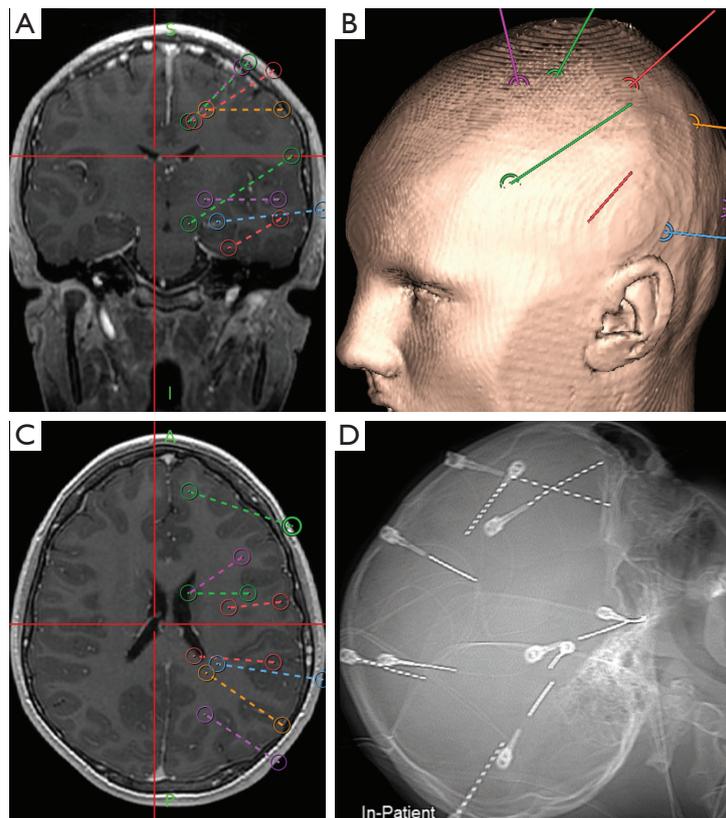


Figure 2 Case example of stereotactic electroencephalogram (SEEG) planning and electrode placement. This is a case of a 12-year-old boy presenting with medically refractory epilepsy described as complex, partial seizures with automatisms and confusion. Despite workup by video EEG and imaging, no definitive locus for the epileptic zone could be identified. The patient underwent placement of bilateral SEEG electrodes and, during video monitoring, a deep-seated epileptogenic zone on the right side was identified suggestive of a deep cortical dysplasia. Because of the location of the lesion and epileptogenic zone, traditional diagnostic methods could not delineate the area.

length, and area algorithms to delivery stimulation ranging from 1 to 333 Hz, amplitudes of 0.5 to 12 mA, and pulse-widths from 40 to 1,000 μ s, device settings familiar to most clinicians managing deep brain stimulation systems.

A landmark study leading to FDA approval of NeuroPace was conducted by the RNS System in Epilepsy Study Group (61). This study involved 191 adults (mean age 34.9 years) with refractory epilepsy undergoing subdural or depth electrode placement at 1 or 2 specified epileptogenic foci. Double-blind randomization to either stimulation or sham stimulation was performed, followed by a three-month evaluation period. Thereafter, the sham group was also stimulated. An initial reduction in seizure frequency was seen, as in prior trials evaluating surgical treatment for epilepsy; however, a sustained reduction in mean seizure frequency was seen in 37.9% of stimulated patients *vs.* 17.3% of sham patients ($P=0.012$). Overall, 46% of patients

showed a 50% reduction in mean seizure frequency as well as improvement in secondary outcomes, including quality-of-life assessment (63,66). Long-term reduction in median seizure frequency of 48–66% was observed over a mean follow-up of 5.4 years, with improvement in quality-of-life measures (110). No patient showed complete seizure freedom but 36.7% had 1 seizure-free period of >3 months, 23% had a seizure-free period of >6 months, and 12.9% had a seizure-free period of >12 months. Since follow-up, 11 deaths from the study group cohort were reported, with 7 due to sudden unexpected death in epilepsy (SUDEP), 2 from suicide in patients with histories of depression, 1 from status epilepticus, and 1 from lymphoma. Notably, rates of SUDEP were not decreased in patients treated via RNS compared with the overall epilepsy population. A follow-up secondary analysis of neuropsychological outcomes showed sustained improvements two years after implantation (65).

Moreover, a 32% improvement in naming scores among patients (n=76) with focal neocortical epilepsy and 8.5% improvement in verbal memory among patients (n=86) with mesial temporal onset seizures were also observed. Evaluation of device activity after implantation as well as stimulation data show that the device can drastically alter the severity and character of patient seizures (62); however, the relationship between these electroencephalographic changes and clinical seizure behavior remains unclear.

While currently only FDA approved for adults, the NeuroPace system may have a role in the treatment of children with DRE who are not candidates for or who have failed other surgical treatments. To date, there have been no reports of the use of NeuroPace to treat patients younger than 18 years of age; however, a number of features of NeuroPace may appeal for use in a pediatric population. One study explored the possibility of using the device as an outpatient chronic ambulatory electrocorticography (ECoG) device using the original trial data (64). Among 191 patients in the study cohort, 82 had received bilateral mesial temporal lobe implants with the NeuroPace device because clear lateralization was not present on preoperative evaluation. After analysis of the captured electrographic data in this subgroup, bilateral ictal onset was confirmed in 84% after a mean of 41.6 days (range, 0–376 days) after implantation; however, unilateral localization was apparent in 16% of patients, suggesting the possibility of resection. Conversely, among 11 patients with presumed unilateral onset, 64% demonstrated bilateral electrographic seizures. Therefore, the potential of the NeuroPace device to serve as an ambulatory ECoG may make it a useful tool in a pediatric setting where patients may not tolerate the stress and morbidity of intracranial monitoring as well as adult patients do. Overall, RNS promises to be a useful tool in the arsenal of epilepsy treatment for patients with epileptogenic foci not amenable for surgical resection. Multiple questions remain regarding the use of RNS, including further elucidation of the mechanism of action to improve future trials and patient selection. Evaluation in pediatric patients remains to be explored.

Conclusions

The combination of novel seizure modifying approaches, such as RNS, and minimally invasive methods of intracranial monitoring with SEEG, quantitative algorithms for modeling the epileptogenic zone, and minimally invasive treatment paradigms such as laser ablation has the power

to significantly change the surgical management of DRE in children in the future. The further development of these technologies in parallel may truly represent a disruptive innovation that significantly improves outcomes and decreases morbidity in children with disabling seizures.

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Footnote

Conflicts of Interest: The authors have no conflict of interest to declare.

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