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SHORT RESEARCH ARTICLE

Pediatric neuromodulation for drug-resistant epilepsy: Survey of current practices, techniques, and outcomes across US epilepsy centers

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Abstract

Neuromodulation via Responsive Neurostimulation (RNS) or Deep Brain Stimulation (DBS) is an emerging treatment strategy for pediatric drug-resistant epilepsy (DRE). Knowledge gaps exist in patient selection, surgical technique, and perioperative care. Here, we use an expert survey to clarify practices. Thirty-two members of the Pediatric Epilepsy Research Consortium were surveyed using REDCap. Respondents were from 17 pediatric epilepsy centers (missing data in one): Four centers implant RNS only while 13 implant both RNS and DBS. Thirteen RNS programs commenced in or before 2020, and 10 of 12 DBS programs began thereafter. The busiest six centers implant 6–10 new RNS devices per year; all DBS programs implant <5 annually. The youngest RNS patient was 3 years old. Most centers (11/12) utilize MP2RAGE and/or FGATIR sequences for planning. Centromedian thalamic nuclei were the unanimous target for Lennox–Gastaut syndrome. Surgeon exposure to neuromodulation occurred mostly in clinical practice (14/17). Clinically significant hemorrhage ($n = 2$) or infection ($n = 3$) were rare. Meaningful seizure reduction (>50%) was reported by 81% (13/16) of centers. RNS and DBS are rapidly evolving treatment modalities for safe and effective treatment of pediatric DRE. There is increasing interest in multicenter collaboration to gain knowledge and facilitate dialogue.

Charuta N Joshi and Cemal Karakas contributed equally to the authorship.

For Affiliation refer page on 790

Plain language summary: We surveyed 32 pediatric epilepsy centers in USA to highlight current practices of intracranial neuromodulation. Of the 17 that replied, we found that most centers are implanting thalamic targets in pediatric drug-resistant epilepsy using the RNS device. DBS device is starting to be used in pediatric epilepsy, especially after 2020. Different strategies for target identification are enumerated. This study serves as a starting point for future collaborative research.

KEYWORDS

DBS, neuromodulation, outcomes, practices, RNS

1 | INTRODUCTION

Epilepsy is a common chronic neurological disorder in children, impacting 1% of the global pediatric population.[1] Thirty to 40% of these children will experience drug-resistant epilepsy (DRE), becoming surgical candidates.[2,3] Surgical treatments include resection, disconnection, ablation, or electrical modulation of the epileptogenic network.[4,5] Neuromodulation surgery using deep brain stimulation (DBS) or responsive neurostimulation (RNS) is utilized when resection or ablation of the epileptogenic network may have an unacceptable side-effect profile.[6,7] DBS and RNS are only approved by the Food and Drug Administration (FDA) for adults (>18 years old) but off-label use in children has increased recently.[6,8–12] Despite this increase, data on patient selection criteria, surgical methodologies, postoperative care protocols, and strategies for mitigating or managing complications in the pediatric population is limited. This presents a barrier to optimal patient outcomes.

Individual centers have institutional protocols for the deployment of neuromodulatory therapies in pediatric patients as well as cortical/subcortical thalamic nuclei targeting with or without stereo-electroencephalography (sEEG).[13,14] In the absence of high-quality evidence in pediatric DRE, survey data exploring current practices can help clarify a starting point for patient selection, surgical techniques, and post-operative care.

The objective of the Pediatric Epilepsy Research Consortium (PERC) is to build a network to support collaborative research to enhance the care of children with epilepsy. In 2022, the Neuromodulation sub-Special Interest Group (sub-SIG) was established within the PERC Epilepsy Surgery SIG to better understand current practices in pediatric neuromodulation. In this study, we aimed to clarify current practices, techniques, and outcomes with neuromodulation using DBS or RNS for pediatric DRE through a survey among experts in the United States.

2 | METHODS

A REDCap[15] survey was sent to 32 centers that form the Neuromodulation PERC sub-SIG. This study was approved by the University of Texas Southwestern (UTSW) Institutional Review Board. Each center returned only one survey between June 5 and October 8, 2023 (Appendix S1). Data for primary analysis included: general practice; surgical considerations; post-operative care; surgeon experience; and seizure outcomes (Table 1).

Secondary analysis was conducted on a separately administered survey (Figure 1) which aimed to clarify key drivers influencing the choice of DBS versus RNS. This 5-point Likert survey explored surgeon/neurologist preferences; the role of published literature, patient comorbidities and preferences, geographic distance from the hospital, and insurance coverage in choices made. Other key drivers explored included the potential for future surgery and the need for battery replacement.

3 | RESULTS

Of the 17 responding centers, 16 completed all questions (53% response rate). The total number of responses obtained varied by question, depending on whether every center answered that question.

3.1 | Primary analysis

3.1.1 | General practices

Thirteen centers performed both RNS and DBS procedures while four centers offered solely RNS in pediatric DRE. Only 16 respondents reported the year in which their programs started. Two centers-initiated DBS prior to 2020, and the remaining 10 centers began implanting DBS during or after 2020. One center reported offering

TABLE 1 Summary of survey results across 17 academic epilepsy centers.

Aspect		Response/findings
General practice	Centers performing procedures	13 (RNS and DBS) 4 (solely RNS)
	RNS and DBS adoption	DBS (two prior to 2020, remainder [10/12] during or after 2020) RNS (one center as early as 2007, the majority [8/15] started pre-2020)
	Annual new RNS procedures	Total of 6–10 procedures (6/16 centers)
	Annual new DBS procedures	Less than five procedures (12/12 centers)
	Minimum age guideline	Divided across centers Youngest age: 2–16 years
Surgical techniques	Thalamic electrode placement	0–5 patients (10/16 centers)
	Neuroimaging modalities	Most use MP2RAGE and FGATIR techniques
	Thalamic nuclei targeting	MRI guided direct stereotactic targeting One center uses an atlas with AC-PC coordinates All centers place electrodes in thalamic CMN in patients with LGS
Invasive monitoring	sEEG electrode utilization	All centers, case by case basis
	Electrode placement	15 centers use robot-assisted guidance,2 report frameless stereotaxy 4/16 centers also use frame-based stereotaxy
Postoperative care	Antibiotic usage	87% (14/16 centers) use systemic antibiotics 7/14 use antibiotics perioperatively <24 h
	Return to school	Majority (10/16 centers) after 2 weeks 4/16 restrict school activities longer 2/16 centers restrict school activity for ≤1 week
Complications	Significant complications	2 hemorrhages, 3 infections 6 centers reported reoperations with a range of 1–10% for complications
Surgeon experience	Exposure to neuromodulation	Almost half (8/17) during residency/fellowship 5/17 did an observership Majority (14/17) enriched skills in practice
	Adult vs pediatric practice	10/16 reported <5 per year in their pediatric practice
Outcomes	>50% seizure reduction	9/16 centers reported 50%–75% reduction 1/16 reported >90% 3/16 reported 76%–90% 3/16 reported <50%

Abbreviations: AC-PC, anterior commissure–posterior commissure; CMN, centromedian nuclei; DBS, deep brain stimulation; FGATIR, fast gray matter T1 inversion recovery; LGS, Lennox–Gastaut Syndrome; MP2RAGE, magnetization-prepared rapid gradient-echo sequence; MRI, magnetic resonance imaging; RNS, responsive neurostimulation; sEEG, stereo-electroencephalography.

RNS as early as 2007; eight started RNS implantation in 2020; the remaining seven started between 2007 and 2020, excluding 2020. Since starting RNS implants, six of 16 centers have performed 6–10 novel implantations per year. Since starting DBS all 13 centers have performed less than five novel implantations per year. Twelve centers (12/16) are implanting thalamic targets using RNS in pediatric DRE and 11/16; using RNS; have implanted >2 electrodes. Half of the respondents had a minimum age for pediatric neuromodulation, with the reported youngest acceptable age for implantation varying from 2 years to 16 years. The youngest patient implanted with RNS in surveyed centers was 3 years old. One respondent restricted implantation to patients weighing at least or more than 40 kg.

3.1.2 | Surgical considerations

Sixteen answered most questions. All centers except one have placed thalamic electrodes (using either RNS/DBS); 10 of 16 centers have placed thalamic electrodes in less than five patients. Ten centers use MRI with magnetization-prepared rapid gradient-echo sequence (MP2RAGE) while 11 use fast gray matter T1 inversion recovery (FGATIR) sequences to identify thalamic targets. Fifteen centers implanting thalamic leads do so using direct stereotactic targeting using radiographic information. One center uses a stereotactic atlas with anterior commissure (AC)-posterior commissure (PC) coordinates. All 16 centers reported using neuromodulation after noninvasive/invasive monitoring on a case-by-case basis

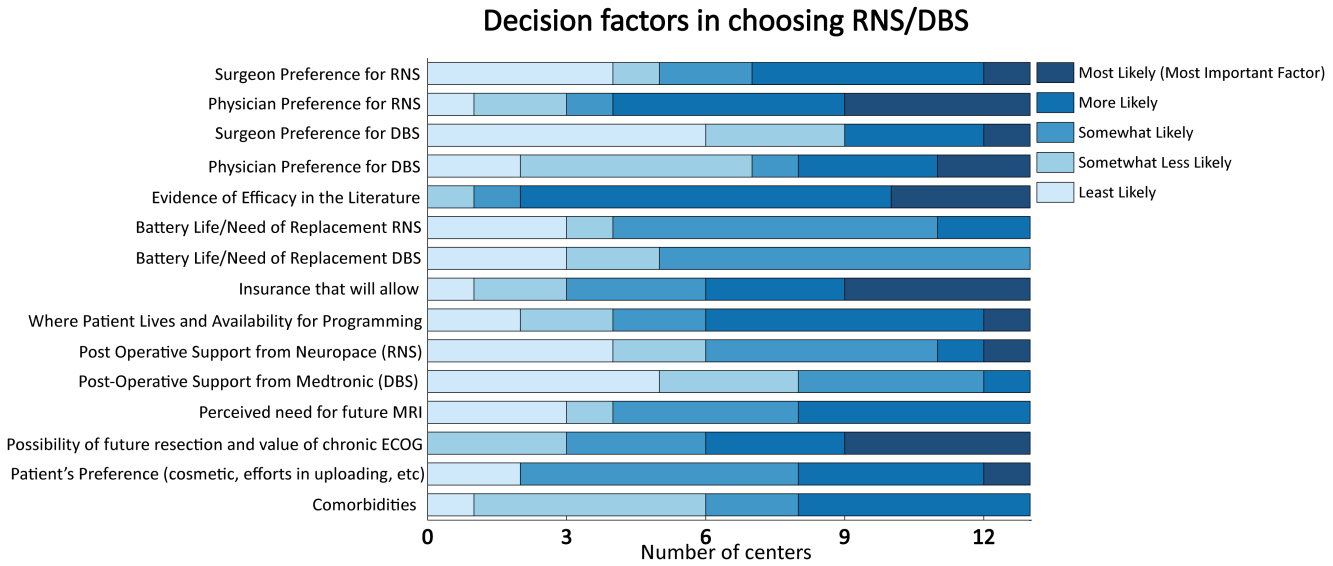

FIGURE 1 Likert Scale for key drivers of clinical practice pertaining to neuromodulation. DBS, Deep Brain Stimulation; ECOG, electrocorticography; MRI, Magnetic resonance imaging; RNS, Responsive neurostimulation.

to rule out a resectable focus. When asked to specify a target in patients with Lennox–Gastaut syndrome (LGS), all respondents targeted bilateral centromedian nuclei (CMN). All centers indicated that in patients with MRI-positive epilepsy, neuromodulation was selected only if the functional consequences of a resection or disconnection were unacceptable. Fifteen surgeons reported using robot-assisted guidance for placement of DBS/RNS/sEEG electrodes, while a minority (4/16) have also used frame-based stereotaxy. Two have used frameless stereotaxy. Eleven centers have placed more than two electrodes per RNS generator while none have placed more than two electrodes using DBS for pediatric DRE. One center has placed > two electrodes in a patient with movement disorders. Three centers routinely place more than two electrodes per generator in all their RNS patients. Despite the ubiquity of extra electrodes, 13 of 15 responding centers report a total of less than five patients needing to change out active electrodes during follow-up. Only two centers report a subsequent resection following the implantation of a neuromodulation device.

3.1.3 | Post-operative course

Fourteen of 16 centers (87%) use post-operative antibiotics; seven for <24 h; four for up to 48 h and two for >48 h. Ten centers recommend returning to school after 2 weeks: and four centers for longer than 2 weeks. Two centers restricted school activity for 1 week or less. Only two centers reported clinically significant hemorrhage; three reported infections; six centers reported reoperations with a range of 1%–10% for complications in their experience.

3.1.4 | Surgeon experience

Surgeons at eight of 17 centers had some exposure to neuromodulation techniques during their neurosurgery residency or fellowship, while five surgeons did an observership after completing the fellowship. Fourteen of 17 surgeons reported having enriched their skills in practice. Surgeon practice often includes adults, with one center reporting their surgeon doing more than 10 surgeries per year in adult patients. Five centers report less than five RNS/DBS per year in their pediatric practice. There is also a variability in the minimum age that surgeons would accept for RNS/DBS: the minimum age for the 16 centers varied from 2 to 16 years; the youngest patient implanted at all 17 centers was 3 years old.

3.1.5 | Seizure outcomes

Of 16 responding centers that reported on >50% improvement in seizures, 13 reported >50% of patients had at least a 50% seizure reduction. One center reported >90% of patients; three reported <50% of patients; three reported 76%–90% of patients; nine reported 50%–75% of patients had at least 50% seizure reduction.

3.2 | Secondary analysis

A Likert scale with scores of likelihood was presented. Surgeons and neurologists displayed divergent tendencies towards RNS and DBS (Figure 1), with a significant number basing their choices on personal comfort with the

procedures and seizure semiology. Perceived effectiveness was a major determinant, endorsed by most of the respondents. Considerations of battery life, the need for MRI, and the possibility of future surgery affected decision-making comparably for both RNS and DBS. Insurance coverage, geographic accessibility, and post-operative support from device companies variably influenced clinical choices. Patient preferences and comorbidities were important, with nearly half of the respondents considering these factors.

4 | DISCUSSION

This survey, involving 17 academic epilepsy centers in the US with complete answer sets for 16, offers an insight into current intracranial neuromodulation practices in pediatric DRE. The survey highlights significant growth in the adoption of DBS for DRE after 2020. While the FDA approved DBS in adult epilepsy in 2018,[16] RNS has been approved in the USA since 2013.[17] A large RNS case series involving a total of 56 patients from 22 PERC centers, underscores its popularity in pediatric DRE.[6] In addition to the delayed adoption of DBS, most responding centers perform fewer than five cases annually, whereas six centers perform at least 10 new RNS procedures per year. This could be related to the lag time between FDA approval and local adoption practices and comfort level. We presume that the ability to review electrocorticograms and deliver closed-loop stimulation; the possibility of utilizing both cortical and subcortical approaches, is intriguing and attractive with RNS compared to the scheduled thalamic stimulation of DBS. One might argue that DBS seems less invasive. Further head-to-head comparisons between RNS and DBS are required for pediatric DRE. Our findings of thalamic RNS implantation in pediatric DRE in most centers and implantation of greater than two electrodes in RNS devices are important and representative of increasing expertise and rapid adoption of open-label practices. However, the number of patients who needed a change in the active electrode is small. In the absence of individual patient data, this could reflect a shorter follow-up in the overall sample.

In the survey, all experts recommend targeting bilateral CMN in LGS patients, reflecting the efficacy demonstrated by a randomized clinical trial (RCT) of CMN DBS.[18] Pioneering observations by a study in 1987[19] regarding the benefits of electrical stimulation of the CMN were further validated by the double-blind, RCT (ESTEL), published in 2022.[18] This study demonstrated the effectiveness of CMN DBS in patients, involving 20 participants with LGS, with 89% of patients in the stimulation group experiencing a ≥50% reduction in 24-h EEG-recorded seizures, compared to none in the control group.[18]

The survey reveals that 81% of centers have experienced meaningful seizure reduction with neuromodulation (>50%), with rare side effects. Minor variations in seizure reduction outcomes among centers suggest that optimizing factors such as target selection, the use of intracranial monitoring before neuromodulation, and surgical experience, may be material to outcomes. Most centers use MRI with MP2RAGE and/or FGATIR sequences. The increasing use of intracranial monitoring with sEEG electrodes for target identification indicates a growing sophistication in signal analysis and the relative safety of the technique.[20] Questions meant to explore real-world decision making regarding choices of neuromodulation indicated balance between literature support and personalized nature of decisions made in planning DBS/ RNS in pediatric DRE.[16]

Only half of responding surgeons had exposure to neuromodulation techniques during their training; a significant majority have refined their skills during their practice. Previous studies have explored the factors contributing to this knowledge gap among neurosurgeons. These include relatively smaller exposure to epilepsy surgery cases in neurosurgery resident case logs, a small number of dedicated fellowship training programs specifically focused on epilepsy surgery and lower self-assessment exam scores among neurosurgery residents in epilepsy-related questions highlighting relative weakness in curricular attention to epilepsy during training.[21] This emphasizes the need for contemporary neurosurgeons to adapt to and embrace newer neuromodulation technology in their epilepsy surgery practice.

5 | LIMITATIONS

The retrospective data collected is self-reported and, therefore, subject to biases or inaccuracies. Respondents may not accurately recall past practices or outcomes. With 17 centers participating, the findings may not fully represent the broader community of epilepsy centers, potentially introducing a selection bias where centers with more favorable outcomes or established neuromodulation programs were more inclined to participate. The interpretation of open-ended questions and Likert scale responses may introduce subjectivity, potentially affecting the robustness of the conclusions drawn. These limitations underscore the need for further research.

6 | CONCLUSION

This survey across 17 academic epilepsy centers in the US has shed some light on the practice patterns of pediatric neuromodulation for DRE. RNS and DBS are rapidly emerging as reliable and effective methods for managing pediatric DRE. The variation in decision-making between RNS and DBS, patient selection, surgical methodologies, and postoperative care present opportunities for standardized protocols to enhance patient outcomes.

Future direction

Further research with retrospective and prospective, multicenter, longitudinal designs are planned within PERC and will provide more robust evidence and insights into pediatric neuromodulation practices for DRE.

Statistical methods

Since this was an observational study of survey sent to practitioners/centers STROBE guidelines are followed.

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Charuta Joshi: Concept, Design Questionnaire, Initial draft, Contribution to data, Editing final manuscript; Cemal Karakas: Initial draft, Contribution to data, Editing final manuscript; Krista Eschbach: Initial draft, Contribution to data, Editing final manuscript; Debopam Samanta: Initial draft, Contribution to data, Editing final manuscript; Kurtis Auguste: Design Questionnaire, Editing final manuscript; Virendra Desai: Contribution to data, Editing final manuscript; Rani Singh: Contribution to data, Editing final manuscript; Patricia McGoldrick: Design Questionnaire, Contribution to data, Editing final manuscript; Steven Wolf: Design Questionnaire, Contribution to data, Editing final manuscript; Taylor J. Abel: Contribution to data, Editing final manuscript; Edward Novotny: Contribution to data, Editing final manuscript; Chima Oluigbo: Design Questionnaire, Contribution to data, Editing final manuscript; Shilpa B. Reddy: Contribution to data, Editing final manuscript; Allyson Alexander: Contribution to data, Editing final manuscript; Angela Price: Contribution to data, Editing final manuscript; Puck Reeders: Initial draft, Contribution to data, Editing final manuscript; Nancy Mcnamara: Design Questionnaire, Contribution to data, Editing final manuscript; Erin Fedak Romanowski: Contribution to data, Editing final manuscript; Ian Mutchnick: Contribution to data, Editing final manuscript; Adam P.

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CONFLICT OF INTEREST STATEMENT

Charuta Joshi has no relevant disclosures to this manuscript – however served on medical advisory board of Zogenix, has been a paid consultant for Aquestives, is on the DSMB for Praxis, is a recipient of a grant from Jazz for studying EMAtS (contracts still being negotiated)- however none of this work above is related to these declared conflicts of interest, Cemal Karakas has no conflict of interest, Krista Eschbach has no conflict of interest, Debopam Samanta has no conflicts of interest, Kurtis Auguste has no conflict of interest, Virendra Desai has no conflict of interest, Rani Singh has no conflict of interest, Patricia McGoldrick gets research support from neuropace and is a livanova speaker, Steven Wolf gets research support from neuropace and is a livanova speaker, Taylor J. Abel a consultant for NeuroOne and Monteris Medical, Edward Novotny has no conflict of interest, Chima Oluigbo has no conflict of interest, Shilpa B. Reddy has no conflict of interest, Allyson Alexander is a paid consultant for NuXcel, Angela Price has no conflict of interest, Puck Reeders has no conflict of interest, Nancy Mcnamara has no conflict of interest, Erin Fedak Romanowski is a paid consultant for the Epilepsy Study Consortium, Ian Mutchnick has no conflict of interest, Adam P. Ostendorf has no conflict of interest, Ammar Shaikhouni has no conflict of interest, Andrew Knox has no conflict of interest, Gewalin Aungaroon has no conflict of interest, Joffre Olaya has no conflict of interest, Carrie R Muh is a Consultant for Livanova and Monteris NeuroBlate.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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ETHICS STATEMENT

We confirm that (a) all co-authors have been substantially involved in the study and/or the preparation of the manuscript; (b) no undisclosed groups or persons have had a primary role in the study and/or in manuscript preparation (i.e., there are no “ghost-writers”); and (c) all co-authors have seen and approved the submitted version of the paper and accept responsibility for its content.

DATA AVAILABILITY STATEMENT

Raw data can be made available upon request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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