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FULL-LENGTH ORIGINAL RESEARCH

The UK experience of stereoelectroencephalography in children: An analysis of factors predicting the identification of a seizure-onset zone and subsequent seizure freedom

UK Children's Epilepsy Surgery Collaboration

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Abstract

Objective: Stereoelectroencephalography (SEEG) is being used more frequently in the pre-surgical evaluation of children with focal epilepsy. It has been shown to be safe in children, but there are no multicenter studies assessing the rates and factors associated with the identification of a putative seizure-onset zone (SOZ) and subsequent seizure freedom following SEEG-guided epilepsy surgery.

Methods: Multicenter retrospective cohort study of all children undergoing SEEG at six of seven UK Children's Epilepsy Surgery Service centers from 2014 to 2019. Demographics, noninvasive evaluation, SEEG, and operative factors were analyzed to identify variables associated with the identification of a putative SOZ and subsequent seizure freedom following SEEG-guided epilepsy surgery.

Results: One hundred thirty-five patients underwent 139 SEEG explorations using a total of 1767 electrodes. A putative SOZ was identified in 117 patients (85.7%); odds of successfully finding an SOZ were 6.4 times greater for non-motor seizures compared to motor seizures ($p = 0.02$) and 3.6 times more if four or more seizures were recorded during SEEG ($p = 0.03$). Of 100 patients undergoing surgical treatment, 47 (47.0%) had an Engel class I outcome at a median follow-up of 1.3 years; the only factor associated with outcome was indication for SEEG ($p = 0.03$); an indication of "recurrence following surgery/treatment" had a 5.9 times lower odds of achieving seizure freedom ($p = 0.002$) compared to the "lesion negative" cohort, whereas other indications ("lesion positive, define extent," "lesion positive, discordant noninvasive investigations" and "multiple lesions") were not statistically significantly different.

Significance: This large nationally representative cohort illustrates that SEEG-guided surgery can still achieve high rates of seizure freedom. Seizure semiology and the number of seizures recorded during SEEG are important factors in the identification of a putative SOZ, and the indication for SEEG is an important factor in postoperative outcomes.

KEYWORDS

epilepsy surgery, SEEG, pediatric epilepsy surgery, intracranial EEG

UK Children's Epilepsy Surgery Collaboration are listed in Appendix S5.

1 | INTRODUCTION

Surgery for refractory focal epilepsy in children is effective, with ~70% becoming seizure-free (Engel class I) following resective surgery in carefully selected candidates.[1] Seizure freedom improves quality of life; therefore, increasing numbers of children now undergo presurgical evaluation. More complex cases are being considered, including those without clear radiological abnormalities or for whom there is uncertain localization on noninvasive studies.[1,2] The increased complexity has resulted in more frequent use of invasive electroencephalography (EEG), particularly stereoelectroencephalography (SEEG), as it provides better topographic accuracy, the ability to explore spatially distant and deep areas (including bilateral and insular implantations), and better therapeutic options during the monitoring such as radiofrequency thermocoagulation.[1,3]

Recent studies have shown that advances in imaging, planning, and robotic-assisted surgery have made SEEG a safe tool in children, with low rates of adverse events such as hemorrhage and infection.[3-13] Despite these advances, the rate of seizure-free outcomes following SEEG-guided resective surgery stands at 50%-67%.[4,9,13-15] This may be attributable, at least in part, to the selection of more complex candidates who may not have been considered for surgery in the past. In the context of SEEG, the definition of "success" is in itself a complex consideration, as it may be variably interpreted as identification of the seizure-onset zone (SOZ), offering subsequent surgery or via the more traditional surgical outcomes of seizure freedom or improved quality of life. The rates of each of these measures may vary because they are dependent on a number of factors including the selection of candidates for SEEG, the implantation plan, subsequent interpretation of the SEEG recordings to devise a surgical strategy, and the adequacy of the operation itself (Figure 1). All of these may be influenced by institutional ethos and the biases of the multidisciplinary presurgical evaluation teams.

To explore these factors in a real-world setting, we undertook a nationwide multicenter study of the United Kingdom (UK) experience of pediatric SEEG. The two specific aims were to analyze preoperative and SEEG factors that predicted (a) whether or not a putative SOZ was identified on SEEG and (b) subsequent seizure freedom following surgical intervention.

Key Points

- First multicenter nationally representative study of pediatric stereoelectroencephalography (SEEG)
- Systematically examine factors associated with finding a putative seizure-onset zone (SOZ) and subsequent surgical outcome following SEEG-guided treatment
- In a series of 135 patients undergoing SEEG, a total of 117 (85.7%) had a putative SOZ
- Of 100 patients undergoing surgical treatment, 47 (47.0%) had an Engel class I outcome at median follow-up of 1.3 years
- The main factor associated with postoperative outcome was indication for SEEG

2 | METHODS

2.1 | Design

Multicenter retrospective cohort observational study. This study has been reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines (available in the Supplementary Material).[16]

2.2 | Centers

All centers performing pediatric epilepsy surgery and SEEG in England are part of a centrally commissioned National Health Service (NHS) England Children's Epilepsy Surgery Service (CESS). All of these centers and the single center performing pediatric SEEG in Scotland were invited to participate in this retrospective cohort study, encompassing all centers performing pediatric SEEG in the UK. Six of the seven centers agreed to participate (Supplementary Box 1). Each center registered the study as a retrospective service evaluation with their local research and development office.

2.3 | Case selection

All children who underwent SEEG at these pediatric centers between 2014 and the end of March 2019 were eligible for inclusion. There were no exclusion criteria. Patients were selected for SEEG based on local epilepsy multidisciplinary team (MDT) decision following noninvasive evaluation that included at least an epilepsy-protocol magnetic resonance imaging (MRI) scan (defined locally at each institution), EEG video-telemetry, and neurodevelopmental/neuropsychological evaluation. Other adjunctive investigations may have included positron emission tomography (PET), magnetoencephalography (MEG), functional MRI (fMRI), and ictal single-photon emission computed tomography (SPECT) scans, at the discretion of the local MDT. Decisions during the SEEG process (implantation strategy, duration of recording,

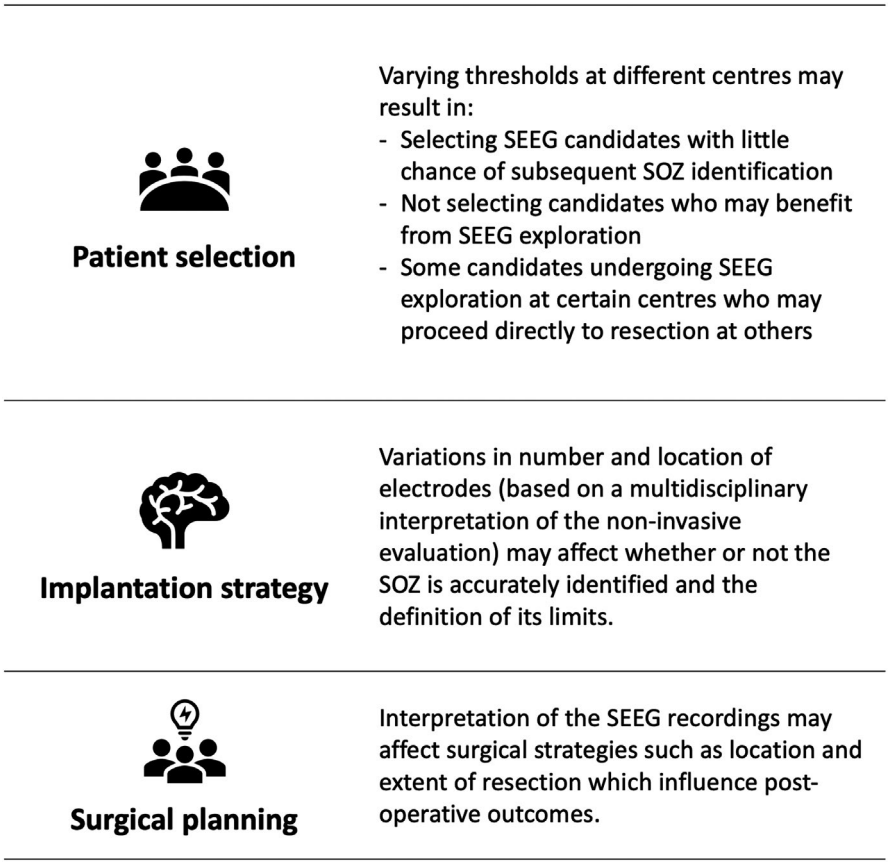

FIGURE 1 Schematic illustration of the factors affecting surgical success in an SEEG program. SEEG = stereoelectroencephalography, SOZ = seizure-onset zone

whether to perform stimulation and, if so, stimulation locating and settings, and interpretation of SEEG findings) were also made at the local team level. The CESS network also conducts a national MDT meeting that allows complex cases to be discussed; although this ensures some alignment of decision-making, the decision to offer SEEG, implantation strategies, and interpretation of SEEG findings remain at the discretion of the local MDT.

2.4 | Data collection

Data were collected from patient records via a piloted proforma between September 2019 and December 2020. Data were collected in a number of domains (Table S1). To reduce bias, the majority of the data were designed to be readily available in the presurgical MDT proforma, which is largely similar across the centers. The two outcome measures of interest were (a) a binary outcome of whether or not a putative SOZ was identified following the SEEG exploration and (b) the postoperative Engel class at last follow-up that was dichotomized into class I (seizure free) and class II-IV (not seizure-free). The putative SOZ, defined as the contacts at which ictal onset was observed, was defined individually by each. If there were multifocal areas of ictal onset or if the electrophysiological onset was after the clinical onset, it was considered that no putative SOZ could be identified.

2.5 | Statistical analysis

The statistical analysis was conducted according to a pre-specified analysis plan incorporating demographic, pre-surgical evaluation, and SEEG (and, for the two analyses, resective operation) factors into a stepwise binary logistic regression model to identify factors that predicted (a) the identification of a SOZ on SEEG and (b) subsequent seizure freedom following resection. For both analyses, only the second exploration was taken into consideration for patients who had undergone two explorations. Cases with missing data would have been excluded but all records were complete. In addition, three descriptive analyses were performed, which were explored as they were thought to be of clinical interest or were deemed to warrant further exploration given the results of the pre-specified statistical analyses.

All statistical analyses were performed on Microsoft Excel v16 (Microsoft Inc), SPSS v24 (IBM Inc), and Matlab R2018b (The Mathworks Inc). p-values <0.05 were considered statistically significant.

3 | RESULTS

3.1 | Demographics

A total of 139 SEEG explorations were conducted in 135 patients across the six centers during the inclusion period

(Figure S1a). The median age at SEEG was 11 years (range 3-19) with a bimodal distribution (peaks at around ages 9 and 16), and the median duration of epilepsy at SEEG implantation was 7 years (range 0-19) (Figure S1b). The most common indications for SEEG (classified in Table S1) were "lesion positive, define extent" (29.5%) and "lesion negative" (28.1%) (Figure S1c); of the four repeat explorations, three were "lesion negative."

3.2 | Noninvasive evaluation

Prior to invasive evaluation, all patients underwent detailed clinical evaluation, MRI scans, and scalp EEG video-telemetry (Table S2, seizure semiology in Figure S1d). Seventeen percent had pre-existing focal neurologic deficit on examination, 31.1% had significant neuropsychological impairment (FSIQ <70), and 14.8% had a neuropsychiatric diagnosis (eg, autism, anxiety, depression). At the discretion of the local team, a proportion of patients underwent additional investigations: interictal PET (57.8%), MEG (18.5%), ictal SPECT (17.8%), and language fMRI (22.2%).

3.3 | SEEG implantation and surgical safety

Apart from the first six at Great Ormond Street Hospital, the first in Edinburgh (frameless neuronavigated procedures) and the first two at King's Health Partners (frame-based arc procedures), all cases were performed using a frame-based robotic-assisted technique (Renishaw Neuromate system), detailed elsewhere.[8] A total of 1767 electrodes were implanted across the 139 explorations, with a median (interquartile range (IQR) of 12 (10-15) electrodes per implantation (Figure 2a). Dividing the brain into 10 lobes, a median [IQR] of 4 [3-4] lobes were explored (Figure 2a). A ratio of electrodes/lobe was calculated as a surrogate marker of confidence in the implantation hypothesis, with high ratios indicating increased confidence (Figure 2b). There were significant differences between the ratios for each indication (Kruskal-Wallis test, $p = 9.3\text{x}10^{-6}$, Figure 2d). There were 98 unilateral (70.5%) and 41 bilateral (29.5%) explorations; left hemisphere lobes were explored more frequently than the right (Figure 2c).

Recording occurred for a median (IQR) of 7 (5-7) days. Stimulation testing was performed in 111 cases (79.9%) with a mixture of 1 Hz and 50 Hz stimulation to encompass both seizure and functional stimulation; 68 (61.3%) had seizures stimulated, in whom 59 (86.8%) were thought consistent with their habitual seizures. Functional areas including primary and supplementary motor, somatosensory, language, primary visual, and auditory cortices were identified in 75 (54.0%).

In terms of safety, only one case (0.7%) had significant bleeding requiring surgical evacuation, three (2.2%) had minor asymptomatic bleeding identified on the routine post-operative computed tomography (CT) scan, and five (3.6%) had one or more electrodes either malpositioned (extradural) or pulled out. In two cases, complications resulted in no recordings being gathered. Overall, no long-term neurologic deficits were attributable to the SEEG procedures.

3.4 | Identification of a putative SOZ

To identify factors that predicted the identification of a putative SOZ, we considered only the second exploration in those that were implanted twice (n = 4) and excluded those with no recordings (n = 2), giving a total of 133 patients. An SOZ was identified in 117 of these (88.0%). Pre-operative and operative variables were assessed for differences between the patients in whom a SOZ was or was not identified (Table 1). In the univariate analysis, an MEG scan was less commonly performed ($p = 0.04$), ≥4 seizures were more commonly recorded during SEEG ($p = 0.04$), and a habitual seizure was more commonly stimulated ($p = 0.03$) when an SOZ was identified.

A binomial logistic regression model was created using the variables in Table 1 that had a p-value of <=0.25. Backwards elimination resulted in a statistically significant model ($p = 0.003$) with two significant variables, namely semiology type ($p = 0.02$) and the number of seizures recorded during SEEG ($p = 0.03$). The odds of successfully finding a SOZ were 6.4-fold (95% confidence interval [CI] 1.3–30.2) higher for non-motor seizures (compared to motor seizures) and 3.6-fold (95% CI 1.1–11.1) higher if ≥4 seizures were recorded during SEEG.

3.5 | Surgical resection and subsequent seizure freedom

Overall, 105 patients (78.9% of all patients, 89.7% of those in whom a SOZ was identified) were offered further surgical intervention for their epilepsy (excluding vagal nerve stimulator implantation). Twelve patients were not offered surgical treatment despite identification of a putative SOZ due to a high risk of deficit due to overlap with functional motor or language areas (six patients), a widespread SOZ (five patients), and low seizure burden in the period following SEEG (one patient). A further five patients who were offered surgery did not undergo surgical intervention—two transferred to the adult services for their surgery and three opted against proceeding with surgery due to either low seizure burden or high risk of deficit.

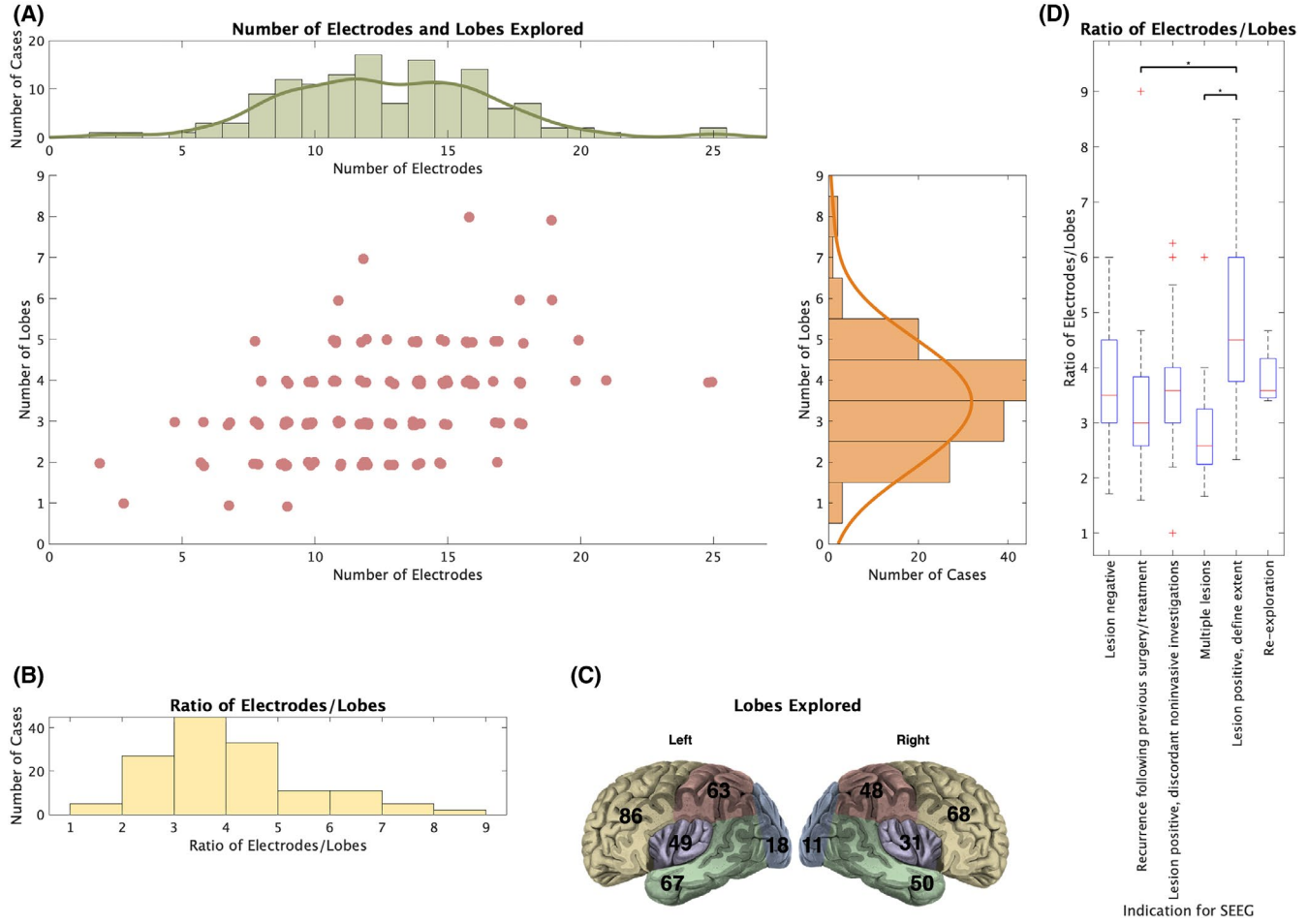

FIGURE 2 SEEG exploration factors in 139 explorations. (A) Scatter plot of number of electrodes and lobes explored with histograms for each shown separately at the ends of the axes, indicating a range in both domains. The moderate correlation between the two (Spearman correlation r = 0.46, $p = 1 \times 10^{-8}$) indicates that it is not necessarily that more lobes equate to more electrodes. (B) Ratio of electrodes/lobes, a novel surrogate indicator of "confidence" in the pre-implantation hypothesis as a more limited spatial exploration (higher ratio) is likely to indicate more confidence from the noninvasive investigations. (C) Visual representation of the lobes explored, showing more exploration of the left-sided lobes. (D) Box plots showing the ratio of electrodes/lobes by indication for SEEG. Kruskal-Wallis testing revealed significant differences between the groups ($p = 9 \times 10^{-6}$) with post hoc pairwise comparisons showing significant differences between the "lesion positive, discordant noninvasive investigations" group, and "recurrence following previous surgery/treatment" ($p = 3 \times 10^{-4}$) and "multiple lesions" ($p = 6 \times 10^{-5}$) groups following correction for multiple comparisons using the Tukey method

The interventions received by the 100 patients and outcomes at last follow-up (median 1.3 years from the last surgical procedure, IQR 1.0–1.9 years, 85.0% with at least 1 year follow-up) are shown in Figure 3a. Overall, 47 patients (47.0% of those undergoing SEEG-guided treatment or 34.8% of all patients in this series) had an Engel class I outcome.

Selected SEEG and operative variables were assessed for differences between those who did and did not achieve an Engel class I outcome following resective surgery (n = 92; cases undergoing thermocoagulation only were excluded as this is primarily used as a prognostic test rather than definitive treatment across the CESS centers). Overall, 44 patients (47.8%) had an Engel class I outcome. Significant variables on univariate analysis included the indication for SEEG ($p = 0.01$) and the postoperative histology ($p = 0.006$) (Table 2).

A binomial logistic regression model was created using the variables in Table 2 that had a p-value of <=0.25. Backwards elimination resulted in a statistically significant model ($p = 2 \times 10^{-5}$) with two variables, one of which was statistically significant (indication for SEEG, $p = 0.03$) and one not (histology, $p = 0.10$). Within the indication for SEEG, "recurrence following surgery/treatment" had a 5.9-fold lower odds of achieving seizure freedom ($p = 0.002$) compared to the "lesion negative" cohort. Those with focal cortical dysplasia (FCD) type 2a and 2b on histopathological examination had a 8.9-fold and a 10.4-fold higher odds of seizure freedom ($p = 0.02$ and $p = 0.01$, respectively) compared to nondiagnostic/other histology.

TABLE 1 Factors associated with whether or not an SOZ was identified on SEEG in 133 patients undergoing SEEG

	SOZ Identified		SOZ Not Identified		*p*-value
	n = 117		n = 16		
Demographics					
Age (years, median [IQR])	11 [8-16]		11 [7.5-14.5]		.56
Duration of epilepsy (years, median [IQR])	7 [4.5-10]		8 [5-10]		.45
Center					.48
Semiology					
Number of semiologies (median)	2		2		.76
Predominant semiology awareness					
Aware	51	43.6%	7	43.8%	.99
Not aware	66	56.4%	9	56.3%	
Predominant semiology type					
Motor	65	55.6%	14	87.5%	**.15**
Non-motor	52	44.4%	2	12.5%	
Predominant semiology lateralized?	74	63.2%	13	81.3%	**.16**
MRI Scan					
Location of abnormality					
None	23	19.7%	3	18.8%	.93
Unilateral	83	70.9%	11	68.8%	
Bilateral	11	9.4%	2	12.5%	
Type of abnormality					
Focal cortical dysplasia	43	36.8%	4	25.0%	0.68
Normal	23	19.7%	3	18.8%	
Tubers (TSC)	11	9.4%	2	12.5%	
Ischemia/atrophy	6	5.1%	1	6.3%	
Mesial temporal sclerosis	6	5.1%	0	0.0%	
Nonspecific abnormality	6	5.1%	2	12.5%	
Other	6	5.1%	0	0.0%	
Previous resection/treatment	16	13.7%	4	25.0%	
EEG Video-telemetry					
Ictal EEG summary					
Unilobar	77	65.8%	6	37.5%	**.13**
Multilobar	9	7.7%	1	6.3%	
Lateralizing but not localizing	8	6.8%	4	25.0%	
Bilateral	7	6.0%	1	6.3%	
Nonlocalizing, nonlateralizing	15	12.8%	4	25.0%	
Interictal EEG summary					
Unilobar	66	56.4%	5	31.3%	.28
Multilobar	12	10.3%	4	25.0%	
Lateralizing but not localizing	7	6.0%	2	12.5%	
Bilateral	12	10.3%	3	18.8%	
Nonlocalizing, nonlateralizing	19	16.2%	2	12.5%	

(Continues)

TABLE 1 (Continued)

	SOZ Identified		SOZ Not Identified		*p*-value
	n = 117		n = 16		
Adjunctive investigations performed					
PET	65	56.0%	12	75.0%	**.14**
MEG	19	16.4%	6	37.5%	**.04**
Ictal SPECT	20	17.2%	2	12.5%	.64
fMRI	28	24.1%	2	12.5%	.30
Indication for SEEG					
Lesion negative	32	27.6%	5	31.3%	.68
Lesion positive, define extent	38	32.8%	3	18.8%	
Lesion positive, discordant investigations	19	16.4%	2	12.5%	
Multiple lesions	12	10.3%	2	12.5%	
Recurrence following previous surgery/ treatment	16	13.8%	4	25.0%	
SEEG factors					
Total electrodes (median [IQR])	14 [11-18]		15.5 [12-19.5]		.33
Number of lobes (median [IQR])	3 [3-4]		4 [3-4.5]		**.23**
Electrodes/lobes ratio (median [IQR])	4 [3.4-5]		4 [3.4-5]		.71
Laterality					
Unilateral	85	73.3%	8	50.0%	**.06**
Bilateral	32	27.6%	8	50.0%	
Days recording					
<7	58	50.0%	8	50.0%	.97
7+	59	50.9%	8	50.0%	
Number of seizures recorded					
<4	24	20.7%	7	43.8%	**.04**
≥4	93	80.2%	9	56.3%	
Stimulation factors					
Stimulation performed?	96	82.8%	11	68.8%	**.21**
Seizure stimulated?	62	53.4%	3	18.8%	**.01**
Was it a habitual seizure?	55	47.4%	2	12.5%	**.03**

Note: Comparisons were made using Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.
Bold indicates factors that had a *p*-value of <= 0.25 that were included in the binary logistic regression model.

3.6 | Exploratory analyses

In these post hoc exploratory analyses, numbers and percentages are reported but no statistical tests performed. The particular cohorts were selected because of clinical interest.

3.6.1 | SEEG in children with tuberous sclerosis complex

Thirteen patients underwent SEEG in the context of tuberous sclerosis complex (TSC), with a median age of 8 years (range 5-15). An SOZ was identified in 11 of these (84.6%) and all underwent resective surgery, which involved a single tuber (3 patients), multiple tubers (6 patients), or multiple tubers and mesial temporal structures (two patients). Engel class I was achieved in one patient (7.7% of all patients explored), class II in two (15.4%), class III in six (46.2%), and class IV in two (15.4%).

3.6.2 | Re-explorations following previous intervention

Of the 20 such cases, 16 underwent resections (with or without electrocorticography guidance), 3 had undergone disconnective procedures (2 temporo-parieto-occipital (TPO)

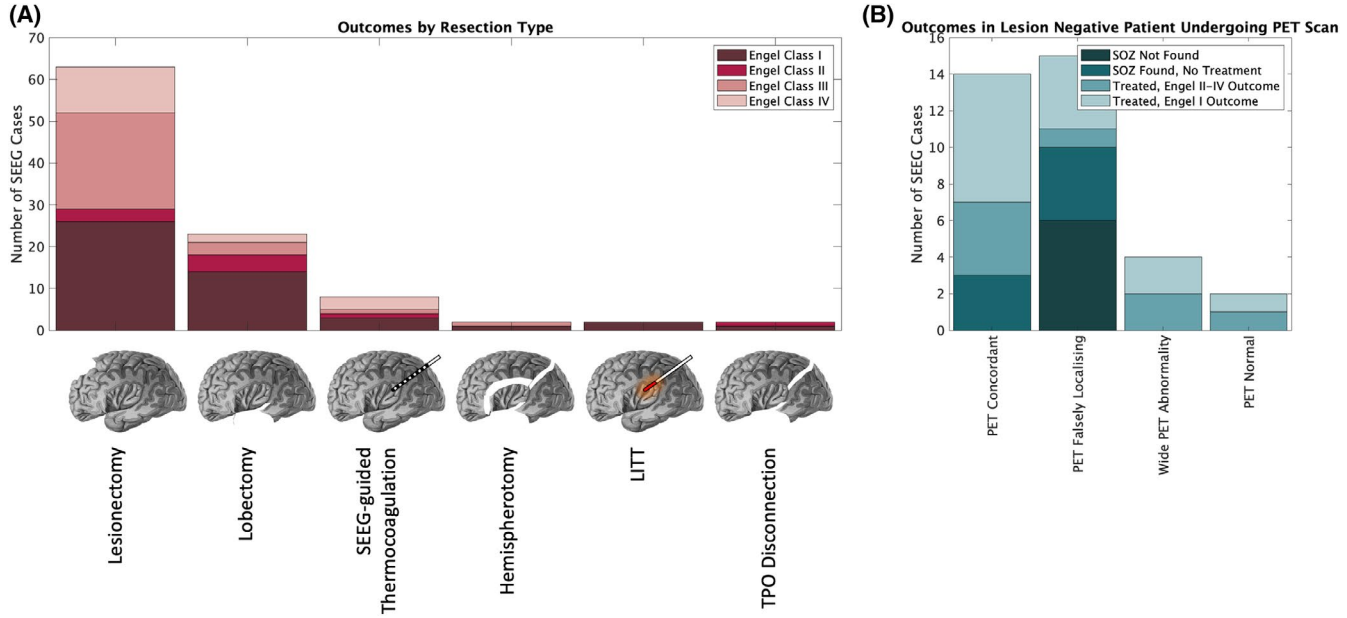

FIGURE 3 (A) Outcome by resection type. Three patients underwent two lesionectomy procedures. Four underwent thermocoagulation prior to other treatment (two lesionectomy, two LITT) and have been classified as their second (definitive) treatment. Lesionectomy involves an SEEG-tailored focal resection of the presumed epileptogenic zone, whereas lobectomy involves a larger resection of the lobe. LITT = laser interstitial thermal therapy, TPO disconnection = temporo-parieto-occipital disconnection. (B) Outcomes in lesion-negative SEEG cases stratified by finding on the pre-SEEG PET scan. Note that although a lower proportion of those with a falsely localizing PET scan went on to have an Engel class I outcome, the proportion of those with an Engel class I outcome as a function of those receiving treatment is similar across groups

disconnections and a corpus callosotomy) and 1 had undergone gamma knife radiosurgery (to a nodular heterotopia). Histologies from the resective/TPO procedures were FCD type IIa (5/18), FCD type IIb (4/18), nondiagnostic/other (8/18), and FCD type 1 (1/18). The median duration (range) from first operation to SEEG was 4 (1–13) years.

A SOZ was identified in 15 patients (75.0%), of whom 10 underwent subsequent further resective/disconnective surgery and two underwent radiofrequency thermocoagulation. Overall, Engel class I was achieved in two patients (10% of all patients explored), class II in three (15.0%), class III in six (30.0%), and class IV in one (5.0%). Of interest, of the eight patients who underwent a repeat lesionectomy, none achieved a class I outcome.

3.6.3 | The Utility of PET Scans

The earlier finding on univariate analysis of an increased proportion of PET scans being done in patients for whom an SOZ was not identified is perhaps an indicator that PET scans are reserved for the more complex cases. Because these are thought to be particularly useful in lesion-negative cases, we explored this group further.

Thirty-five lesion-negative cases underwent PET scans. A putative SOZ was identified through SEEG in 29 (82.9%). The localization of the PET scan hypometabolism was compared to the localization of the SOZ at the sublobar level from the text data on the data collection proforma. It was concordant in 14 (40.0%), falsely localizing in 15 (42.9%), had wide PET abnormalities in 4 (11.4%), and was normal in 2 (5.7%). Twenty-two went on to have surgical treatment, with 14 (63.6%) achieving an Engel class I outcome. The distribution by concordance is shown in Figure 3b.

3.6.4 | Lesion concordance with SEEG-defined SOZ in those with MRI lesions and discordant noninvasive investigations

Twenty-two patients had MRI-visible lesions but underwent SEEG due to discordant scalp EEG videotelemetry and/or semiology. Of those, 19 (86.4%) had an SOZ defined and 18 (81.8%) went on to have surgical treatment. Eleven (61.1%) of the SEEG-defined SOZs were concordant with the MRI lesion; 7 of 11 (63.6%) had an Engel class I outcome. Of the seven with nonconcordance between SEEG-defined SOZ and MRI, two had temporal lobectomies with confirmed hippocampal sclerosis, one had thermocoagulation only, and the other four underwent focal resections, all with nondiagnostic histology (including one who had the lesion and another independent area resected); five of seven (71.4) had an Engel class I outcome.

TABLE 2 Factors associated with favorable or unfavorable outcome in 92 patients undergoing SEEG-guided tailored treatments

	Engel Class I		Engel Class II - IV		
	n = 44		n = 48		*p*-value
Demographics					
Age (years, median [IQR])	11.5 [8-16]		10 [7.5-15]		.31
Center					.73
Semiology					
Predominant semiology type					
Motor	24	54.5%	26	54.2%	.97
Non-motor	20	45.5%	22	45.8%	
Indication for SEEG					
Lesion negative	15	34.1%	8	16.7%	**.01**
Lesion positive, define extent	15	34.1%	15	31.3%	
Lesion positive, discordant investigations	12	27.3%	5	10.4%	
Multiple lesions	1	2.3%	11	22.9%	
Recurrence following previous surgery/treatment	1	2.3%	9	18.8%	
SEEG factors					
Total electrodes (median [IQR])	14 [11-18]		14 [11-17.5]		.97
Number of lobes (median [IQR])	3 [2.5-4]		3.5 [3-4]		.44
Electrodes/lobes ratio (median [IQR])	4.5 [3.8-5.5]		4 [3.2-5]		.30
Laterality					
Unilateral	33	75.0%	33	68.8%	.51
Bilateral	11	25.0%	15	31.3%	
Number of seizures recorded					
<4	12	27.3%	6	12.5%	**.07**
4+	32	72.7%	42	87.5%	
Stimulation factors					
Seizure stimulated?	26	59.1%	25	52.1%	.32
Was it a habitual seizure?	24	54.5%	21	43.8%	**.20**
Surgical factors					
Lobe of resection					
Frontal	16	36.4%	23	47.9%	.74
Temporal	14	31.8%	10	20.8%	
Insula	3	6.8%	2	4.2%	
Parietal	3	6.8%	2	4.2%	
Occipital	1	2.3%	2	4.2%	
Multilobar	7	15.9%	9	18.8%	
Type of surgery					
Hemispherotomy	1	2.3%	1	2.1%	.30
Lesionectomy	26	59.1%	37	77.1%	
LITT	2	4.5%	0	0.0%	
Lobectomy	14	31.8%	9	18.8%	
TPO Disconnection	1	2.3%	1	2.1%	

(Continues)

TABLE 2 (Continued)

	Engel Class I		Engel Class II - IV		
	n = 44		**n = 48**		***p*-value**
Histology					
FCD type 1	3	6.8%	4	8.3%	**.006**
FCD type 2a	8	18.2%	4	8.3%	
FCD type 2b	10	22.7%	3	6.3%	
Hippocampal sclerosis	3	6.8%	0	0.0%	
Nondiagnostic/other	19	43.2%	28	58.3%	
TSC	1	2.3%	9	18.8%	
Duration of follow-up (years)	1.3 ± 0.6		1.2 ± 0.6		.48

Abbreviations: FCD, focal cortical dysplasia; LITT, laser interstitial thermal therapy; TPO, temporo-parieto-occipital; TSC, tuberous sclerosis complex.
Bold indicates factors that had a *p*-value of <= 0.25 that were included in the binary logistic regression model.

4 | DISCUSSION

We report a large multicenter retrospective series of 135 children with difficult-to-localize drug-resistant focal epilepsy undergoing 139 SEEG explorations. Overall, 86.7% of patients had a putative SOZ identified, 74.1% received subsequent surgical treatment, and 34.8% had an Engel class I outcome at median follow-up of 1.3 years (Figure 4a). Similar to other series, the Engel class I outcome in those undergoing surgical treatment was 47.0%.[4,9,17] Of interest, this figure is slightly lower than the large series from Milan showing 59.4% International League Against Epilepsy (ILAE) class I-II outcomes (comparable to Engel class I) in a largely adult population, perhaps a reflection of the complex developmental and genetic etiologies of the pediatric drug-resistant epilepsy population.[17] Our cohort from six of the seven UK pediatric SEEG centers adds a "real world" perspective to the existing data, as it represents the vast majority of UK pediatric SEEG cases to date and is representative of a national pediatric complex epilepsy population.

A philosophical consideration that arises from these results surrounds the optimal target proportion of patients that should have a putative SOZ identified and have favorable outcomes following SEEG. This is dependent on patient selection thresholds, implantation strategy, and subsequent interpretation of the SEEG findings (Figure 1). The proportions in this study represent a fair balance, where the majority (but not all) of those that are explored have an SOZ identified (86.7%) and those that go on to have surgical treatment, due to the inherent complexity, are less likely to achieve an Engel class I outcome (47.0%) than the more straightforward cases that do not require invasive intracranial evaluation. Other factors that could affect these proportions include the delineation of extent of the SOZ and subsequent surgical success of resecting this intended SOZ.

In the first analysis, the odds of successfully finding a putative SOZ was 3.6-fold higher if ≥4 seizures were recorded compared to if <4 seizures were recorded during SEEG ($p = 0.03$). This may provide increased confidence in a stereotyped pattern of seizures with onset in the same area. However, ≥4 seizures were recorded more commonly in those who did not become seizure-free following surgery (Table 2, $p = 0.07$), indicating that factors that may improve the chances of SOZ identification may not necessarily be the same as those that improve chances of seizure freedom.

In the univariate analyses, the majority of significant factors included those directly related to the seizures, such as the number of seizures recorded, whether or not a seizure was stimulated, and whether this stimulated seizure was a habitual seizure (Table 1), all of which underscore the importance selecting patients that have frequent habitual seizures and stimulating these during intracranial recording.[18]

Another finding was that the odds of identifying a SOZ was 6.4-fold higher for non-motor seizures, compared to motor seizures ($p = 0.03$), a finding that has not been reported previously. Although there have been reports of high proportions of non-motor seizures in nonlesional epilepsy cohorts, this was not the case in our cohort.[19] This perhaps reflects the difficulty in children of ascertaining accurate non-motor semiology; many of the cases classified as motor semiology may in fact have preceding non-motor manifestations that were not able to be described accurately by the children. A more detailed analysis of the scalp EEG video-telemetry results might shed light as to whether there were electrographic changes prior to motor onset, suggesting that a non-motor onset may have been missed.

In the second analysis, the only significant factor associated with an Engel class I outcome was indication for SEEG ($p = 0.03$). When viewed as a function of all explorations, both the recurrence and multiple lesion cohorts have much poorer overall outcomes compared to the

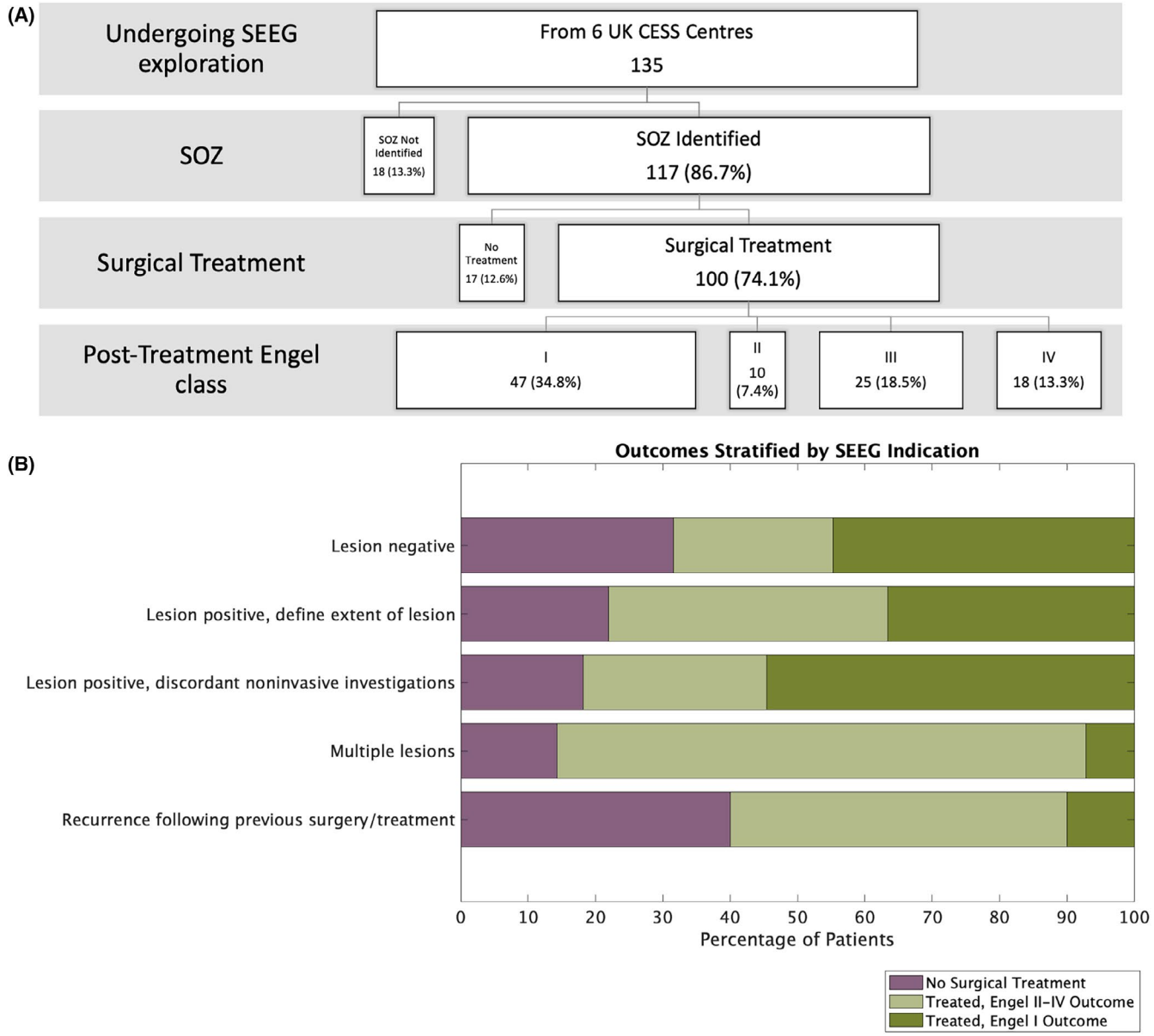

FIGURE 4 (A) Summary flowchart of outcomes in the 135 patients undergoing SEEG in this multicenter retrospective UK cohort study. (B) Outcome of treatment stratified by indication for SEEG

other indications (Figure 4b). As a result of this finding, we explored the recurrence and TSC (most of the multiple lesions) cohorts further. In the recurrence cohort, only 10.0% went on to become seizure-free. None of the repeat lesionectomy patients (including five with FCD IIa or IIb histology) became seizure-free, although we were not aware of whether these were focal resections adjacent to (ie, residual lesion) or distant from the original resections.[20] Irrespective of this, the finding reinforces the concept of "surgical refractoriness" that has been purported recently in the literature.[21] It suggests that those with ongoing seizures or recrudescence following surgery probably warrant consideration of more aggressive approaches (such as larger lobar resections, TPO disconnection, or hemispherotomy), although the risks and benefits need to be assessed on an individual basis. Quantitative analyses in these patients may also be a helpful adjunct to assess how the network architecture changes to support ongoing seizures following initial surgery.[22]

Although not significant ($p = 0.10$) on the final regression analysis, the histology had an important bearing on the outcome following SEEG-guided surgical treatment. Consistent with the established literature, those with a diagnosis of FCD type IIa or IIb had a 8.9× and 10.4× higher odds of seizure freedom ($p = 0.02$ and $p = 0.01$, respectively) compared to a nondiagnostic/other histology.[23] However, histology and indication for SEEG covaried in a way that histology lost significance in the final analysis.

Despite complex resections involving multiple tubers and mesial temporal structures, outcomes were poor in the cohort with TSC that was explored with SEEG, with only 7.7% achieving seizure freedom. However, a total of 69.2% achieved Engel class I-III outcomes, indicating at least a worthwhile improvement following epilepsy surgery; in some of these cases, patients would have had multiple seizure types with the explicit understanding that only one would be targeted (eg, the most disabling) during SEEG and subsequent resective surgery. This highlights the complexity of the epileptogenic networks in TSC. A recent national series from China, where they performed a combination of tuber-only, tuber and surrounding cortex, and larger lobar resections has demonstrated that good outcomes are possible in tuberous sclerosis, with >70% achieving seizure freedom at 1 year and 60% at 4 years.[24] Going forward, comparisons need to be made to outcomes in children undergoing resection in TSC without SEEG to assess whether these poor outcomes are restricted to a small number of more complex patients. This will allow a critical view on whether certain factors (eg, tuber burden, presence of single large/outstanding tuber, presence of multiple semiologies, EEG characteristics) predict for poor outcome in TSC, which will help refine the choice of candidates for SEEG exploration.

The utility of PET in MRI lesion-negative patients remains an area of interest and has been found to be useful in patients with malformations of cortical development undergoing SEEG.[25,26] We found that PET hypometabolism was not concordant with the SEEG-defined SOZ in 60.0% of cases. When those in whom an SOZ was not identified are removed, the proportion of patients with a class I outcome was similar irrespective of PET findings (Figure 3b). In this study, the PET analysis was limited to text fields and the imaging was not formally reviewed; therefore, the findings must be interpreted with caution. The impact of PET information on the hypothesis generation and planning of SEEG electrode locations is difficult to assess retrospectively and requires careful prospective study designs to ascertain the true impact.

In the final exploratory analysis, we examined the concordance between MRI lesions and the SEEG-defined putative SOZ in those who underwent SEEG for discordant noninvasive investigations. The results emphasize the importance of thorough presurgical evaluation and only resecting MRI lesions if there is concordance with semiology and EEG video-telemetry. All patients with discordance who underwent focal resection had a nondiagnostic histology but three-fourths still achieved seizure freedom.

4.1 | Limitations

Surgical failures are presumed due to either inaccurate localization or incomplete resection of the epileptogenic zone.[4] Although many localization factors have been considered in this study, we did not analyze specific features of the SEEG recordings at seizure onset. Previous studies have shown that certain pathologies may be associated with specific patterns of EEG change at seizure onset, some of which may be associated with better postsurgical outcomes.[27-29] Instead, we used expert neurophysiologist-reported assessment as a measure of seizure onset. Another limitation of our study is that we did not assess the completeness of resection of the SOZ.[17] In these difficult-to-localize cases, this is often challenging to assess, as it is not limited to just the MRI-visible lesion and requires additional postoperative image post-processing to specifically identify which contacts have been resected. Despite these limitations, we have considered a comprehensive list of factors from the noninvasive evaluation and the SEEG procedure that shed light on this complex population of children. We envisage that the results will be useful to multidisciplinary teams planning SEEG in children and in the counseling of children and families prior to undertaking SEEG.

In addition, the study is susceptible to all the traditional biases of a multicenter retrospective cohort study. The rarity and complexity of SEEG ensures that cases were not missed in this cohort, although there remains recall bias associated with gathering data retrospectively from clinical records.

4.2 | Future directions

In addition to refining the selection of patients, implantation strategy, and subsequent surgical planning in SEEG patients using clinical data, we are likely to see increasing incorporation of quantitative methods in SEEG planning, including automated analysis of MRI[30] and computational analysis of SEEG recordings.[22,31,32] Although seizures (both spontaneously recorded and stimulated) have been shown to be crucial to outcomes in this present series, concepts such as identification of the SOZ from interictal recordings,[33] using additional methods such as microelectrode recordings,[34] or network-based analyses[22,35] may improve the interpretation of SEEG recordings as we move from a location-focused to network-based interventions.

5 | CONCLUSION

In this large multicenter series of 135 children undergoing 139 SEEG explorations in the UK, we demonstrate that 86.7% of patients had a putative SOZ identified, 74.1% received subsequent surgical treatment, and 34.8% had an Engel class I at a median follow-up of 1.3 years. Of those undergoing SEEG-guided surgical treatment, 47.0% achieved an Engel class I outcome. Seizure semiology and number

of seizures recorded were important factors associated with the identification of a putative SOZ, whereas indication for SEEG was the most important factor associated with postsurgical outcome.

Epilepsy in children that requires intracranial evaluation prior to surgical intervention is a complex entity, and this study highlights the positive impact that can be had as a result of SEEG exploration in this cohort, as 82.0% of those undergoing SEEG-guided surgical treatments experience at least a worthwhile improvement with 47.0% achieving seizure freedom.

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CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATIONS

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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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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