

RESEARCH ARTICLE

Comparison of children and adults undergoing subdural grid electrode implantation or stereoelectroencephalography in a refractory epilepsy cohort from four European centers

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Abstract

Objective: Children with refractory focal epilepsy differ from adults, although many centers will offer invasive electroencephalography (iEEG) to both. Outcomes in terms of likelihood of resection and subsequent seizure outcome after either subdural grid electrode implantation (SDE) or stereoelectroencephalography (SEEG) have, however, not been directly compared between age groups. **Methods:** We retrospectively included adults and children undergoing iEEG monitoring at four European centers. We compared the two age groups and techniques regarding complication rate, chance of proceeding to resection, and seizure freedom.

Kees P. J. Braun and Pieter van Eijdsden contributed equally.

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Results: In total, 857 individuals were included (447 SEEG, 410 SDE; 572 adults, 285 children). Adults more often had a history of focal to bilateral tonic-clonic seizures (FBTCS) and prior epilepsy surgery and were more often magnetic resonance imaging-negative. Children had a higher seizure frequency and rate of pre-existing neurologic deficits. In SEEG, likelihood of resection was 64% in adults and 76% in children ($p < .05$), but chance of seizure freedom did not differ. Adults and children had similar chances of resection and seizure freedom rates after SDE. In children, postoperative seizure freedom was less likely after SDE than SEEG. In adults, history of FBTCS was associated with lower chance of seizure freedom. Overall complication rate was higher in children (22% vs. adults 15%) and in SDE (29% vs. SEEG 7%).

Significance: Either iEEG technique provides an equally valid but very different road to success, with no difference in seizure outcome between the two age groups, but with higher risk of complications in SDE. We found similar surgical results for dissimilar techniques and a higher threshold for children. In case of an assumed lower chance of focality of epilepsy or chance of seizure freedom after resection, adults were more often explored with iEEG, whereas children were more severely affected when considered for iEEG.

KEYWORDS

epilepsy surgery, invasive electroencephalography, SEEG

1 | INTRODUCTION

Successful surgical resection of the epileptogenic zone (EZ) depends on a firm hypothesis of its location and its relation to eloquent brain areas. When noninvasive pre-surgical diagnostic methods are inadequate to generate a robust hypothesis, invasive electroencephalography (iEEG) with subdural grid electrode implantation (SDE) or stereoelectroencephalography (SEEG) may be required.^{1,2,3} The two techniques have intrinsic differences. Their outcomes regarding the likelihood of proceeding to resection after iEEG and subsequent seizure freedom have recently been compared in a large multicenter cohort study of 1468 adults, using propensity score matching.⁴

Children with refractory epilepsy differ from adults in having different epilepsy etiology, potentially more challenging electroclinical correlates for focal seizures, and more difficulties in cooperating in (non-)invasive diagnostic procedures. Specific technical challenges, such as sufficient skull thickness and tolerability of invasive monitoring, also influence presurgical evaluation and surgical techniques.^{5,6} The potential treatment benefit in children extends beyond seizure freedom to include medication freedom and enhanced developmental capacities, highlighting the need to pursue a cure for pediatric refractory epilepsy.^{7–10,11} Neural plasticity is enhanced in young children,^{5,6} which enables them to undergo more extensive

Key points

- Children in both iEEG groups had higher seizure frequencies and a higher proportion of preexistent neurological deficits.
- A higher proportion of adults had a history of focal to bilateral tonic-clonic seizures, underwent prior epilepsy surgery, and were MRI-negative.
- This might reflect a more selective approach to iEEG in children, with a higher threshold for iEEG only in cases that were sufficiently severe but with a higher chance of success.
- Adults who underwent SDE had a higher likelihood of subsequent resection than those undergoing SEEG. In adults, type of iEEG did not predict seizure outcome.
- In children, type of iEEG did not influence the likelihood of resection, but children undergoing SDE did have a lower rate of seizure freedom after resection.

resections than adults. This increased plasticity allows for more complex cases to be considered for intracranial monitoring. These differences in advantages and disadvantages

in adults and children and differences in epilepsy etiology will most likely lead to different indications for iEEG and subsequent surgery and to differing results. In this light, we aimed to compare (1) inherent selection differences, (2) postoperative outcomes, and (3) determinants of outcomes between children and adults undergoing either SEEG or SDE in a large cohort from four European centers. We evaluated determinants of outcome for two main clinical questions: “What determines whether resection will follow after iEEG for either age group?” and “What determines whether there will be subsequent seizure freedom after resection following iEEG for either age group?”

2 | MATERIALS AND METHODS

2.1 | Study population

We retrospectively assessed consecutive children (aged <18 years of age at implantation) and adults (aged 18 years and older) with focal drug-resistant epilepsies who underwent long-term iEEG between 2000 and 2016 at the University Medical Center Utrecht (UMCU) in Utrecht, the Netherlands; Great Ormond Street Hospital (GOSH) and National Hospital for Neurology and Neurosurgery (NHNN) in London, United Kingdom; and Niguarda Hospital in Milan, Italy.

The study was approved by the medical ethics committees of the UMCU and Niguarda. In the UK, it was deemed a service evaluation and approved as such. As data were retrospectively collected and fully anonymized, the need for individual informed consent was waived. Our adult population was included in the international multicenter cohort study that compared SEEG with SDE.⁴

2.2 | Data collection

Individual data were obtained from the medical records at participating centers by one investigator (M.R.) under the supervision of the local medical teams. Demographics included sex, age at seizure onset, duration of epilepsy and age at iEEG, handedness, deficit at neurological exam before iEEG, first-degree family history of epilepsy, and prior epilepsy surgery (including prior iEEG). We extracted details on seizure frequency and history of febrile seizures and focal to bilateral tonic-clonic seizures. Seizure frequency was arbitrarily categorized as (1) high: daily seizures; (2) intermediate: more than two seizures per month, but not daily; and (3) low: up to two per month.

Based on clinical reports, we noted whether scalp EEG findings (ictal or interictal) were lateralizing and whether

magnetic resonance imaging (MRI) showed a probable causative lesion (in the latter case, this was deemed MRI-negative). In some individuals, positron emission tomography (PET), single photon emission computed tomography (SPECT), magnetoencephalography (MEG), and functional MRI (fMRI) were performed. For PET, SPECT, and MEG, the proportion of tests with a localizing abnormality was based on the conclusion of the reports. We noted whether fMRI was performed (independent of the type of function tested).

Based on all available preimplantation information, a hypothesis and implantation strategy were formulated during multidisciplinary epilepsy surgery meetings and collected as noted in the meetings' reports or from medical records.

2.3 | iEEG methods

iEEG was categorized as either SEEG or SDE. SEEG was defined as the stereotactic implantation of multiple intracerebral electrodes; SDE was the implantation of subdural grid electrodes. When individuals underwent more than one iEEG implantation during the inclusion period, only the first was included for analysis. iEEG implantation details included side, number of electrodes and electrode contacts, duration of implantation, and EZ hypothesis formulated based on iEEG findings.

2.4 | Change of hypothesis

The preimplantation hypothesis on EZ location was compared to iEEG findings. A change of hypothesis was categorized as “(sub)lobar,” “extent,” or “multifocality” discordance. (Sub)lobar discordance was assigned when the iEEG-defined EZ was not part of the preimplantation hypothesis on a (sub)lobar level. Extent discordance refers to a more extensive EZ than suspected, and multifocality discordance indicates that a single EZ was suspected initially, but iEEG revealed multiple sources. When iEEG gave inconclusive results, and no hypothesis could be formulated, this was also noted.

2.5 | Proceeding to resection (first primary outcome measure)

If iEEG led to resection, the size and type of resection (temporal, extratemporal, both) and histology results were noted. The reason for individuals not proceeding to resection was determined. Those who underwent thermocoagulation

only or palliative surgery (multiple subpial transections or corpus callosotomy or palliative hemispherectomy) were not included in the resection group.

2.6 | Seizure outcome after resective surgery (second primary outcome measure)

Postoperative seizure outcome was determined at the last follow-up, which was at least 12 months after resection. Engel I was considered being free from disabling seizures, including freedom from all seizures (Engel Ia) or only experiencing auras since surgery, seizure freedom for at least 2 years, or only experiencing seizures after antiseizure medication withdrawal.¹²

2.7 | Complications

Any unexpected adverse event directly related to iEEG and symptomatic or requiring treatment was considered a complication. Major complications were defined as those requiring surgery or early unplanned removal of electrodes, or leading to status epilepticus treated with therapeutic sedation, or resulting in permanent neurologic deficits or death. The individual was classified according to the most serious in the case of multiple complications.

2.8 | Statistics

Statistical analyses were performed using IBM SPSS Statistics (v29.0).

Differences in baseline characteristics and outcomes between adults and children, and associations between relevant variables and the two primary outcomes, “proceeding to resective surgery after iEEG” and “seizure outcome after resection,” were explored with univariable analyses (with statistical significance at $p < .05$). Categorical data were analyzed using Pearson chi-squared (χ^2) or Fisher exact tests based on sample size. Continuous data were analyzed using independent samples t -tests and analysis of variance for parametric data or Mann–Whitney U or Kruskal–Wallis tests (with Bonferroni correction for multiple comparisons) for nonparametric data. A multivariable binary logistic regression was performed for children and adults separately for each of the two primary outcomes. A false discovery rate correction for multiple comparisons was performed on the probability values.¹³ For seizure

outcome, only individuals who underwent resection and had available seizure outcomes with at least 12 months of follow-up were included.

3 | RESULTS

Included were 857 individuals; 447 underwent SEEG and 410 SDE, 572 were adults at the time of iEEG, and 285 were children (Table S1). In 211 SDE cases, additional depth electrodes were implanted. At the UMCU, all but one case underwent SDE. At Niguarda, all underwent SEEG. The two UK centers offered both techniques (SEEG: GOSH from 2014, NHNN from 2011 onward). Children underwent SDE more frequently than adults (62% compared to 41%, $p < .001$).

3.1 | Age group differences in baseline variables

Within the SEEG and SDE group, age at seizure onset and duration of epilepsy at implantation were lower in children. In the SEEG group, adults were more likely to have a history of focal to bilateral tonic-clonic seizures than children (61% compared to 39%). In the SDE group, adults had undergone prior epilepsy surgery more frequently than children (17% compared to 10%). Children in both groups were more likely to have had a high seizure frequency (72% compared to 39% in adults) and a higher rate of preexisting neurological deficits (34% compared to 12% in adults). Children who underwent SDE were more often left-handed than adults (Table S1).

3.2 | Age group differences in preimplantation diagnostics

The percentage of MRI-negative individuals was higher in adults than in children in both iEEG groups (overall 37% compared to 17%; Table S2). Individuals who underwent SEEG more often had a negative MRI than those who underwent SDE (38% compared to 22%, $p < .001$). Interictal PET was performed in 403 (48%) individuals, more often in adults than children (56% compared to 32%). Interictal PET showed a localizing abnormality in 78%, with no age group difference. Before SDE, ictal SPECT was performed more often in children, and interictal MEG and fMRI were performed more often in adults (Table S2). Ictal SPECT showed a localizing abnormality in 89% and ictal MEG in 79% of patients, with no age group difference.

3.3 | Age group differences in preimplantation hypothesis

A left-sided preimplantation hypothesis was more frequent in SDE than in SEEG (58% vs. 36%, $p < .001$); a non-lateralizing hypothesis was more frequent for SEEG (9% vs. 3%, $p < .001$), as was a multilobar hypothesis (42% vs. 19%, $p < .001$). A temporal hypothesis was less frequent in children, but an extratemporal hypothesis was more frequent than in adults. There was no difference in multilobar hypotheses between age groups (Table S2).

3.4 | Implantation details

Left-sided implantation was more common for SDE (52%) than for SEEG (34%, $p < .001$). In the SEEG group, children underwent a left-sided implantation more often than adults (43% compared to 31%). Bilateral implantations were more frequent in adults in both the SEEG and SDE groups (17% compared to 7%).

Overall, 47 (12%) individuals in the SDE group underwent bilateral implantation, consisting of contralateral strips or contralateral depth electrodes, compared to 15% in SEEG ($p = .20$). A median of 76 electrode contacts were implanted in the SDE group and 164 in the SEEG group, with a median number of intracerebral electrodes of 13 (range = 3–21) in SEEG. Children in the SEEG group had a higher number of electrode contacts than adults; in SDE, the adult group had more extensive implantations with a higher number of electrode contacts and a higher frequency of additional intracerebral electrodes (Table S3). The duration of implantation was shorter in SDE compared to SEEG, with a median of 7 (range = 1–45) days for SDE and 8 (range = 0–56) for SEEG ($p < .001$). Children had a shorter duration of monitoring than adults (Table S3).

3.5 | Implantation results

iEEG was inconclusive in 7%, with no difference between iEEG groups ($p = .14$). Within the SDE group, children had an inconclusive iEEG more often than adults (11% compared to 7%). In 168 individuals (20%), the proposed EZ changed after iEEG, with no difference between iEEG groups ($p = .25$). In the SDE group, a change in the EZ hypothesis after iEEG occurred more often in adults than in children (23% compared to 12%). Sublobar discordance was most frequent in SEEG (38%, SDE: 24%), whereas for SDE, extent and multifocality discordance were most frequent (both 38%). There was no difference in type of discordance between age groups within the SDE and SEEG groups.

3.6 | Resection details

Individuals from the SDE group more often proceeded to resective surgery than those who underwent SEEG (79% vs. 67%, $p < .001$). In the SEEG group, children proceeded to surgery more often than adults (76% compared to 64%); in the SDE group, there was no age group difference (Table 1). In the SEEG group, 58 (40%) of those not proceeding to resection underwent thermocoagulation (all at Niguarda).

A left-sided resection was more frequent after SDE than SEEG (60% vs. 38%, $p < .001$), with no difference between children and adults. Most children in both groups underwent extratemporal resections (71%). After SDE, a resection involving both temporal and extratemporal structures was rare (4%) but involved 27% of all resections after SEEG ($p < .001$) and occurred more often in children than in adults (31% compared to 25%). Adults underwent temporal resections more often than children (37% compared to 16%). Focal cortical dysplasia (FCD) was children's most common histopathological finding, involving half of all cases in both groups. Hippocampal sclerosis was rare in children (2% vs. 16% in adults, $p < .001$). In the SEEG group, 46% of cases had no clear pathology or abnormalities (e.g., gliosis or scar) compared to 25% in the SDE group ($p < .001$). This was more frequent in adults than in children (41% vs. 24%, $p < .001$). Low-grade epilepsy-associated tumors (LEATs) were found more often in individuals who underwent SDE than in those who underwent SEEG (15% compared to 3%, $p < .001$) and within the SDE group in children more often than in adults (21% compared to 11%).

3.7 | Complications

The overall complication rate was higher in children than adults (22% compared to 15%) and in SDE compared to SEEG patients (29% compared to 7%, $p < .001$). The rate of major complications was also higher in SDE than in SEEG (12% vs. 3%, $p < .001$). In the SDE group, major complications were found more frequently in adults than in children (15% vs. 9%, $p = .047$).

3.8 | Seizure outcome following resection

After a median follow-up of 52 months, more individuals in the SEEG group had an Engel I outcome after resection than in the SDE group (61% and 48%, $p = .003$). There was no significant difference between SEEG and SDE when considering only Engel Ia outcomes

TABLE 1 Resection details and seizure outcome.

	Total group			SEEG			SDE					
	Overall total	Total adults	Total children	<i>p</i>	Total SEEG	Adults	Children	<i>p</i>	Total SDE	Adults	Children	<i>p</i>
Proceeding to resection, <i>n</i> (%) ^a	618 (72.5)	396 (69.6)	222 (78.4)	.006	296 (67.0)*	216 (64.3)	80 (75.5)	.033	322 (78.5)*	180 (77.3)	142 (80.2)	.468
Left-sided resection, <i>n</i> (%) ^b	304 (49.4)	189 (48.0)	115 (51.8)	.361	113 (38.3)*	78 (36.3)	35 (43.8)	.241	191 (59.5)*	111 (62.0)	80 (56.3)	.304
Location of resection, <i>n</i> (%) ^c												
Temporal	185 (30.1)	149 (37.9)	36 (16.2)	<.001	77 (26.2)*	69 (32.2)	8 (10.0)	<.001	108 (33.6)*	80 (44.7)	28 (19.7)	<.001
Extratemporal	339 (55.1)	182 (46.3)	157 (70.7)		138 (46.9)*	91 (42.5)	47 (58.8)		201 (62.6)*	91 (50.8)	110 (77.5)	
Involving both temporal and extratemporal	91 (14.8)	62 (15.8)	29 (13.1)		79 (26.9)*	54 (25.2)	25 (31.3)		12 (3.7)*	8 (4.5)	4 (2.8)	
Histology, <i>n</i> (%) ^d												
Hippocampal sclerosis	65 (11.1)	61 (15.7)	4 (2.0)	<.001	28 (9.8)	25 (12.0)	3 (3.8)	.015	37 (12.3)	36 (20.1)	1 (.8)	<.001
FCD or mild MCD, including TSC	220 (37.4)	119 (30.7)	101 (50.5)		101 (35.2)	62 (29.7)	39 (50.0)		119 (39.5)	57 (31.8)	62 (50.8)	
Low-grade epilepsy-associated tumor	52 (8.8)	25 (6.4)	27 (13.5)		8 (2.8)*	6 (2.9)	2 (2.6)		44 (14.6)*	19 (10.6)	25 (20.5)	
Gliosis/scar/no abnormality/unclear	208 (35.4)	160 (41.2)	48 (24.0)		132 (46.0)*	102 (48.8)	30 (38.5)		76 (25.2)*	58 (32.4)	18 (14.8)	
Other, including dual	43 (7.3)	23 (5.9)	20 (10.0)		18 (6.3)	14 (6.7)	4 (5.1)		25 (8.3)	9 (5.0)	16 (13.1)	
Complications, <i>n</i> (%) ^e												
Overall	145 (17.1)	84 (14.9)	61 (21.5)	.016	30 (6.7)*	21 (6.2)	9 (8.3)	.444	115 (28.6)*	63 (27.9)	52 (29.5)	.713
Major	60 (7.0)	42 (7.4)	18 (6.3)	.552	11 (2.5)*	8 (2.4)	3 (2.8)	.811	49 (12.2)*	34 (15.0)	15 (8.5)	.047
Seizure outcome after resection	304 (54.5)	211 (58.3)	93 (47.4)	.014	164 (61.0)*	125 (63.8)	39 (53.4)	.122	140 (48.4)*	86 (51.8)	54 (43.9)	.184
Engel I, <i>n</i> (%) ^f												
Seizure outcome after resection	218 (39.1)	147 (40.6)	71 (36.2)	.311	114 (42.4)	81 (41.3)	33 (45.2)	.567	104 (36.0)	66 (39.8)	38 (30.9)	.121
Engel Ia, <i>n</i> (%) ^f												
Follow-up duration, months, median (IQR) ^g	52 (26–85)	56 (29–89)	42 (24–79)	.011	60 (29–96)*	55 (28–90)	76 (39–109)	.023	44 (24–72)*	57 (30–87)	36 (20–55)	<.001

Note: Missing number of cases: ^a1 (1%) and not yet decided at the time of data collection for 4 (.5%); ^b2 (.3%); ^c3 (.5%); ^d30 (4.9%); ^e9 (1.1%), ^f9 (1.5%), follow-up of at least 1 year not reached by an additional 51 (8.3%); ^g1 (.2%). Bold indicates statistical significance.

Abbreviations: FCD, focal cortical dysplasia; IQR, interquartile range; MCD, malformation of cortical development; SDE, subdural grid electrode implantation; SEEG, stereoelectroencephalography; TSC, tuberous sclerosis complex.

*Indicates a statistically significant difference between the overall SEEG and SDE group.

(42% and 36%, $p = .12$), nor was there a difference in seizure outcome between the age groups within the SEEG and SDE groups (Table 1).

3.9 | Determinants of “proceeding to resective surgery”

Adults undergoing SDE were more likely to proceed to resective surgery compared to those undergoing SEEG (odds ratio [OR] = 3.5). A longer duration of iEEG monitoring led to lower odds of proceeding to resective surgery in adults (OR = .2) as did a change in hypothesis in both adults and children (OR = .2 and .06) or indeterminate outcome of iEEG monitoring (OR = .06 and .06; Table 2).

3.10 | Determinants of “postoperative seizure freedom”

iEEG modality was related to seizure freedom (Engel I) after resection only in children, not adults. The odds of seizure freedom were lower in children after SDE (OR = .2).

In adults, history of focal to bilateral tonic-clonic seizures was associated with a lower chance of seizure freedom (OR = .3). In children, a histopathologic finding of either FCD or mild malformation of cortical development or LEAT was associated with higher odds of seizure freedom (Table 3).

4 | DISCUSSION

Requirements for the presurgical evaluation and surgery in the pediatric age group have recently been established by the International League Against Epilepsy Pediatric Epilepsy Surgery Task Force.¹⁴ Many dedicated epilepsy surgery centers offer epilepsy surgery to children and adults; in a survey of 24 European epilepsy surgery centers, 88% performed epilepsy surgery in both age groups.¹⁵ Analyzing both groups in one large cohort and comparing them in terms of baseline characteristics and outcomes is relevant for clinical practice. The two age groups differ in multiple domains, including underlying etiology, seizure semiology, cooperation levels in the preoperative diagnostics and in the intracranial monitoring itself, and technical aspects of the implantation.^{5,6} The potential benefit of pediatric epilepsy surgery extends beyond seizure freedom to improvement in long-term neurodevelopmental outcome, highlighting the need to pursue a cure for pediatric refractory epilepsy even in more challenging cases.^{7-10,11-17}

Ideal strategies to select iEEG candidates and determine the subtype—SEEG or SDE—will lead to a high proportion of individuals proceeding to resective surgery after monitoring and high rates of seizure freedom after resection. However, to avoid a trade-off that excludes people with a lower chance of success following iEEG monitoring, these ideal strategies will most likely use a mixture of both techniques, selectively applied in suitable individuals. What this mixture is, what the selection criteria should be, and how this differs between children and adults is unknown.

Multiple inherent selection differences could be identified between iEEG groups and between age groups. A higher proportion of children underwent SDE than adults. Children in both iEEG groups had higher seizure frequencies and a higher proportion of preexistent neurological deficits. Conversely, a higher proportion of adults seemed to have an a priori lower chance of success.^{18,19,20} A higher proportion of adults had a history of focal to bilateral tonic-clonic seizures (in SEEG). More underwent prior epilepsy surgery (in SDE), although this might also be due to their longer life span and disease duration. A higher proportion of adults were MRI-negative (in SEEG and SDE), in line with previous studies that have shown a low incidence of MRI-negative cases in pediatric epilepsy surgery.^{21,22}

Multiple differences in outcomes were also found. Adults undergoing SDE proceeded to resection at a higher rate than those undergoing SEEG. Intrinsic differences in diagnostic strategy and technique between SEEG and SDE may explain this result. SEEG offers the possibility of thermocoagulation, whereas for SDE there is a lower technical threshold for resection, as grid removal requires general anesthesia and craniotomy.¹ A change in the hypothesis after iEEG occurred more often in adults undergoing SDE than in children, possibly reflecting a more robust preimplantation hypothesis in the pediatric population. However, this did not lead to differences in success in terms of seizure outcomes after resection between adults and children in univariable analysis. We found higher seizure freedom rates after resection in the SEEG group compared to the SDE group when looking at Engel I outcomes, comparable to previous reports.^{4,23} However, when comparing Engel Ia seizure outcome scores, there was no difference between iEEG or age groups. An explanation for this finding might lie in the fundamental difference in the concept of electroclinical sampling between SEEG and SDE. SEEG was developed to sample and identify a possible focal EZ and its propagation along a broader epileptogenic network.²⁴ Resective surgery following SEEG could also involve interruption of this network, possibly not leading to complete seizure freedom in terms of Engel Ia outcome but sufficient success in terms of Engel I outcome.

TABLE 2 Multivariable analysis for the outcome “proceeding to resective surgery”.

Variables in the equation	Proceeding to resection, <i>n</i> = 657			
	Adults, <i>n</i> = 436		Children, <i>n</i> = 221	
	Odds ratio (95% CI)	Corrected <i>p</i>	Odds ratio (95% CI)	Corrected <i>p</i>
iEEG				
SEEG	Reference		Reference	
SDE	3.467 (1.775–6.770)	<.001	.904 (.320–2.548)	.999
Sex				
Male	.625 (.370–1.056)	.229	1.145 (.481–2.727)	.999
Female	Reference		Reference	
Age at implantation, years	.987 (.954–1.022)	.713	1.001 (.871–1.149)	.999
Duration of epilepsy at implantation, years	1.015 (.984–1.047)	.604	.924 (.796–1.071)	.864
Febrile seizures in history	1.180 (.547–2.543)	.849	.941 (.244–3.629)	.999
Focal to bilateral tonic-clonic seizures in history	.648 (.371–1.131)	.319	2.252 (.873–5.810)	.539
Seizure frequency				
High	.442 (.153–1.279)	.319	3.653 (.515–25.915)	.707
Intermediate	.406 (.150–1.099)	.229	2.374 (.299–18.834)	.864
Low	Reference		Reference	
Preoperative neurologic deficit	1.106 (.514–2.382)	.942	1.203 (.444–3.258)	.999
Handedness				
Right	Reference		Reference	
Left	.974 (.455–2.084)	.946	.719 (.238–2.171)	.959
Both	1.088 (.239–4.952)	.946	.417 (.022–8.043)	.959
Family history positive for epilepsy	.909 (.294–2.809)	.942	5.230 (.787–34.739)	.539
Prior epilepsy surgery	1.574 (.706–3.512)	.518	.868 (.208–3.628)	.999
Lateralizing scalp (video) EEG	1.262 (.567–2.809)	.750	1.744 (.505–6.028)	.864
MRI-negative	1.885 (1.052–3.379)	.156	.618 (.174–2.190)	.882
Localizing abnormality on interictal PET				
Performed, but no localizing abnormality	Reference		Reference	
Localizing abnormality	2.393 (1.022–5.605)	.186	.802 (.107–6.039)	.999
No PET performed	2.822 (1.165–6.835)	.123	.400 (.057–2.806)	.864
Localizing abnormality on ictal SPECT				
Performed, but no localizing abnormality	Reference		Reference	
Localizing abnormality	.495 (.048–5.088)	.750	–	.999
No SPECT performed	1.193 (.128–11.097)	.942	–	.999
Localizing abnormality suggesting an epileptogenic source on interictal MEG				
No MEG performed	Reference		Reference	
Performed but no localizing abnormality	.512 (.111–2.368)	.632	.211 (.008–5.562)	.864
Localizing abnormality	.433 (.104–1.810)	.518	1.240 (.050–3.479)	.999
Side preimplantation hypothesis				
Uncertain lateralization	Reference		Reference	
Left	1.386 (.522–3.676)	.742	3.359 (.559–21.199)	.707
Right	2.448 (.944–6.346)	.229	3.767 (.656–21.633)	.662
Location preimplantation hypothesis				
Temporal	Reference		Reference	
Extratemporal	.691 (.338–1.411)	.562	.498 (.093–2.679)	.864
Both temporal and extratemporal	1.064 (.514–2.201)	.942	1.325 (.224–7.844)	.999

TABLE 2 (Continued)

Variables in the equation	Proceeding to resection, <i>n</i> = 657			
	Adults, <i>n</i> = 436		Children, <i>n</i> = 221	
	Odds ratio (95% CI)	Corrected <i>p</i>	Odds ratio (95% CI)	Corrected <i>p</i>
Duration of monitoring in days	.190 (.861–.961)	<.001	.884 (.782–1.000)	.474
Change in hypothesis				
No change	Reference		Reference	
Yes, change	.194 (.112–.335)	<.001	.064 (.021–.198)	<.001
No clear seizure onset zone found	.063 (.019–.207)	<.001	.056 (.015–.209)	<.001
Major complication after iEEG	.522 (.174–1.561)	.518	.814 (.093–7.156)	.999

Note: An odds ratio > 1.0 indicates a higher likelihood of proceeding to resective surgery. Bold indicates statistical significance.

Abbreviations: CI, confidence interval; EEG, electroencephalography; iEEG, invasive EEG; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; SDE, subdural grid electrode implantation; SEEG, stereo-EEG; SPECT, single photon emission computed tomography.

TABLE 3 Multivariable analysis for the outcome “seizure freedom after resection” (if resection performed).

Variables in the equation	Seizure freedom, <i>n</i> = 431			
	Adults, <i>n</i> = 281		Children, <i>n</i> = 150	
	Odds ratio (95% CI)	Corrected <i>p</i>	Odds ratio (95% CI)	Corrected <i>p</i>
iEEG				
SEEG	Reference		Reference	
SDE	.883 (.417–1.870)	.845	.157 (.046–.540)	.034
Sex				
Male	1.922 (1.051–3.514)	.231	.601 (.250–1.443)	.963
Female	Reference		Reference	
Age at implantation, years	1.010 (.969–1.052)	.845	1.020 (.874–1.190)	1.000
Duration of epilepsy at implantation, years	.989 (.953–1.027)	.845	1.025 (.861–1.220)	1.000
Febrile seizures in history	1.859 (.738–4.679)	.639	.952 (.233–3.889)	1.000
Focal to bilateral tonic-clonic seizures in history	.310 (.156–.615)	<.001	1.175 (.441–3.130)	1.000
Seizure frequency				
High	.595 (.194–1.822)	.785	4.020 (.171–94.485)	1.000
Intermediate	.695 (.243–1.987)	.785	2.825 (.107–74–814)	1.000
Low	Reference		Reference	
Preoperative neurologic deficit	.895 (.373–2.151)	.882	.524 (.194–1.410)	.854
Handedness				
Right	Reference		Reference	
Left	1.226 (.504–2.982)	.846	.845 (.283–2.520)	1.000
Both	2.658 (.407–17.374)	.746	–	1.000
Family history positive for epilepsy	.923 (.274–3.112)	.925	.920 (.137–6.172)	1.000
Prior epilepsy surgery	.628 (.266–1.484)	.746	.612 (.092–4.086)	1.000
Lateralizing scalp (video) EEG	1.272 (.446–3.626)	.845	1.211 (.249–5.884)	1.000
MRI-negative	.439 (.220–.874)	.215	.789 (.194–3.218)	1.000
Localizing abnormality on interictal PET				
Performed, but no localizing abnormality	Reference		Reference	
Localizing abnormality	1.643 (.536–5.036)	.785	.058 (.004–.748)	.197
No PET performed	.681 (.218–2.128)	.785	.065 (.005–.859)	.215

(Continues)

TABLE 3 (Continued)

Variables in the equation	Seizure freedom, <i>n</i> = 431			
	Adults, <i>n</i> = 281		Children, <i>n</i> = 150	
	Odds ratio (95% CI)	Corrected <i>p</i>	Odds ratio (95% CI)	Corrected <i>p</i>
Localizing abnormality on ictal SPECT				
Performed, but no localizing abnormality	Reference		Reference	
Localizing abnormality	4.614 (.265–80.407)	.746	–	1.000
No SPECT performed	2.555 (.169–38.578)	.785	–	1.000
Localizing abnormality suggesting an epileptogenic source on interictal MEG				
No MEG performed	Reference		Reference	
Performed but no localizing abnormality	.597 (.136–2.627)	.785	.528 (.029–9.668)	1.000
Localizing abnormality	2.321 (.607–8.884)	.677	.729 (.044–12.222)	1.000
Side preimplantation hypothesis				
Uncertain lateralization	Reference		Reference	
Left	.273 (.056–1.329)	.412	.509 (.039–6.630)	1.000
Right	.278 (.058–1.328)	.412	.339 (.026–4.494)	1.000
Location preimplantation hypothesis				
Temporal	Reference		Reference	
Extratemporal	.857 (.363–2.021)	.845	1.261 (.126–12.637)	1.000
Both temporal and extratemporal	1.074 (.473–2.439)	.919	1.586 (.155–16.188)	1.000
Duration of monitoring in days	1.015 (.937–1.099)	.845	1.005 (.867–1.164)	1.000
Change in hypothesis				
No change	Reference		Reference	
Yes, change	.359 (.163–.787)	.187	.710 (.126–3.997)	1.000
No clear seizure onset zone found	.173 (.023–1.279)	.412	.973 (.121–7.817)	1.000
Major complication after iEEG	3.315 (.808–13.596)	.412	.879 (.121–6.401)	1.000
Type of procedure				
Resective surgery alone	Reference		Reference	
Resective surgery after thermocoagulation	1.442 (.521–3.988)	.785	.209 (.025–1.782)	.738
Histology				
No abnormality or unclear [i.e., gliosis or scar]	Reference		Reference	
Hippocampal sclerosis	1.219 (.451–3.290)	.845	–	1.000
FCD or mild MCD, including TSC	2.364 (1.106–5.053)	.221	11.258 (2.974–42.613)	<.001
Low-grade epilepsy-associated tumor	1.609 (.473–5.471)	.785	39.789 (5.453–290.319)	<.001
Other, including dual	.988 (.270–3.618)	.985	8.506 (1.290–56.065)	.197

Note: An odds ratio > 1.0 indicates a higher likelihood of seizure freedom. Bold indicates statistical significance.

Abbreviations: CI, confidence interval; EEG, electroencephalography; FCD, focal cortical dysplasia; iEEG, invasive EEG; MCD, malformation of cortical development; MEG, magnetoencephalography; MRI, magnetic resonance imaging; PET, positron emission tomography; SDE, subdural grid electrode implantation; SEEG, stereo-EEG; SPECT, single photon emission computed tomography; TSC, tuberous sclerosis complex.

A resection involving both temporal and extratemporal structures was rare after SDE, but involved one quarter of all resections after SEEG, more often in children than in adults. Although we did not analyze exact resection volumes, this might suggest more extensive resections after SEEG. Again, this might be a reflection of the inherent technical differences between SDE and SEEG, where SEEG might be applied more to sample broader

epileptic networks and SDE to delineate a focal EZ from eloquent cortex.²⁴

We were able to identify multiple determinants for the two primary outcomes. In both age groups, individuals were less likely to proceed to resection when iEEG results were indeterminate or when iEEG led to a change in EZ hypothesis. Adults who underwent SDE had a higher likelihood of subsequent resection than

those undergoing SEEG. Still, the type of iEEG did not predict seizure outcome in this group after multivariable analysis. In children, we found the opposite; the type of iEEG did not influence the chance of proceeding to resection in univariable or multivariable analysis, but children undergoing SDE did have a lower likelihood of seizure freedom after resection, as was found in a previous meta-analysis.²³ In adults, history of focal to bilateral tonic-clonic seizures was a negative predictor of seizure freedom, as previously reported.^{18,19,20} A histopathological result showing an LEAT had the strongest association with seizure freedom in children, similar to earlier findings.^{18,20}

Our overall complication rate was higher in the SDE group and higher in children. This higher complication rate in children must be weighed against the benefits of epilepsy surgery in this population. Our rates are comparable to previous reports.^{4,23,25}

A strength of our study is the large and diverse population, comprising individuals who underwent both techniques of iEEG and both adults and children. This was only possible by performing a multicenter study with a long inclusion period. The four centers serve similar roles in their countries as large tertiary expertise centers for epilepsy surgery. However, the multicenter design might have introduced bias, as the centers might differ in referral and selection for surgery and iEEG, applied presurgical diagnostics and strategies, and surgical techniques. The choice of candidates will be influenced by the technique available and preferred. Selection bias might have occurred at centers offering only one iEEG modality, as might bias in referral for iEEG and surgery rejection policies. At centers where both techniques were available, selection for either technique might have introduced bias. SEEG was introduced during our inclusion period for the two UK centers, possibly influencing the SEEG results, as surgeons' and epilepsy teams' experience was developing and inclusion for SEEG was broadening. Another limitation of our study is that we only looked at seizure outcome of those patients undergoing resection. SEEG also offers the possibility of thermocoagulation. As seizure outcome analysis after thermocoagulation was not an outcome variable in our study, we might have underestimated seizure freedom after SEEG.

5 | CONCLUSIONS

SDE and SEEG provide equally valid but distinct pathways to successful epilepsy surgery in children and adults. Although there is no difference in seizure outcomes between age groups, the threshold to perform iEEG might

have been higher for children. In case of an assumed lower chance of focality of epilepsy or chance of seizure freedom after resection, adults were more often explored with iEEG, whereas children were more severely affected when considered for iEEG. Considering the potential benefits of epilepsy surgery in children, reaching beyond seizure freedom to medication reduction and developmental improvement due to neural plasticity, a less stringent selection might be considered.

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study was approved by the medical ethics committees of the UMCU and Niguarda. In the UK, it was deemed a service evaluation and approved as such. As data were retrospectively collected and fully anonymized, the need for individual informed consent was waived. 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 can be found online in the Supporting Information section at the end of this article.

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