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RESEARCH ARTICLE

Implementing intraoperative high-density electrocorticography during epilepsy surgery

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Abstract

Objective: In intraoperative electrocorticography (ioECoG)–tailored epilepsy surgery, standard low-density (LD) electrode grids (16–20 electrodes, 10 mm inter-electrode distance) are used, covering ±20 cm^2 of cortex. High-density (HD) grids have shown advantages in basic research. We wanted to evaluate the clinical use of HD grids during epilepsy surgery. We assessed how often HD-ioECoG might have altered the presurgical hypothesis by recording highly localized epileptic spikes and high-frequency oscillations (HFOs) and by facilitating spike-onset localization.

Methods: Patients undergoing HD-ioECoG–tailored epilepsy surgery (64 electrodes, 5 mm inter-electrode distance; 2048 Hz sampling) were selected from our registry (2021–2023). We assessed clinical reports to evaluate the impact on surgical strategy. Intraoperative decision-making was guided mainly by interictal spikes. We visually marked spikes and HFOs (ripples 80–250 Hz and fast ripples [FRs] 250–500 Hz) in 1-min artifact-free epochs. We assessed number of events, and compared channels covering the resected and non-resected tissue and surgical outcome with logistic mixed models. We assessed focal events, which occurred in few channels and could be missed on LD grids. We analyzed spike-onset localization with Granger's causality.

Results: We included 36 HD grid positions from 20 patients. HD-ioECoG would have confirmed the original surgical plans in 11 patients and adapted it in 6. We found 41–5485 spikes, 0–2243 ripples (one patient none), and 0–1008 FR (three patients none) per patient. More FRs occurred in channels covering the resected areas than outside ($p < .001$), particularly in patients who became seizure-free ($p < .001$). Of the spikes, ripples, and FRs, 6.1%, 19.5%, and 46.7%, respectively,

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occurred on one or two channels; 58.3% of the HD spike-onset locations might be localized differently with standard LD grids.

Significance: HD-ioECoG can be used clinically for epilepsy surgery guidance. HD-ioECoG captured increased detail when identifying focal epileptic events, especially FRs, and pinpointing spike onsets, which may be missed with LD-ioECoG.

KEYWORDS

focal seizures, high-frequency oscillations, intraoperative tailoring, subdural EEG

1 | INTRODUCTION

Epilepsy surgery offers a potentially curative treatment for people with focal epilepsy. Precise delineation of epileptogenic tissue is crucial to achieve postsurgical seizure freedom.[1,2] Intraoperative electrocorticography (ioECoG) is employed to identify epileptogenic tissue by recording interictal epileptiform discharges directly from the cortex and guide surgical decision-making during the surgical procedure. This technique is known as surgical "tailoring."[3,4] The ioECoG electrode grids commonly used in clinical practice typically have a 4×4 or 4×5 electrode configuration with a 10 mm inter-electrode distance, which we classify here as low-density (LD). New high-density (HD) grids have been developed, with smaller inter-electrode distance, and thus higher resolution. Recent studies have shown advantages of HD grids in research, but not yet in clinical routine.[5]

ioECoG is based on the detection of interictal epileptiform transients. Due to the low resolution of LD grids, entire gyri, along with critical epileptiform transients over anatomic structures, can be completely missed, potentially leading to significant gaps in detection. Traditionally these epileptiform transients comprise spikes, the established electroencephalography (EEG) biomarkers of epileptogenic tissue. Interictal spikes are events that occur either in isolation or propagate from the spike-onset area to neighboring regions.[6] The ability to distinguish onset spikes from propagated spikes is crucial, since the removal of the spike-onset area is associated with favorable seizure outcome,[7] whereas propagated spikes do not need to be included in the resection plan.[8–10] Interictal high-frequency oscillations (HFOs) have emerged as EEG biomarkers with greater specificity for the epileptogenic tissue than spikes.[11,12] These fast oscillations, ranging between 80 and 500 Hz, are further subclassified into ripples (80–250 Hz) and fast ripples (FRs; 250–500 Hz).[11] The absence of HFOs after the resection has been associated with seizure freedom.[13,14]

HFOs are focal phenomena that could be missed when using LD electrodes.[15–17] With increased spatial resolution, HD grids may record HFOs more effectively. In addition, HD grids may better distinguish onset spikes and propagated spikes and facilitate reconstruction of propagation patterns. Recent studies have shown that HD grids provide advantages over LD grids in the detection of intraoperative microseizures[18] and HFOs,[17] and in connectivity analysis.[16] We aimed to evaluate the clinical use of HD grids during epilepsy surgery. We studied (1) the implementation of HD-ioECoG and evaluated if the HD-ioECoG recordings adapted the surgical plan, (2) the amount of detected events in the resected area in patients who became seizure-free, and (3) whether HD grids facilitated the detection of focal epileptic events and spike-onset localization.

Key points

- High-density (HD) grid recordings can be used and interpreted for surgical guidance.
- HD grid recordings can help to precisely localize spike onsets.
- HD grids record focal interictal events, which might be missed with low-density recordings.
- HD recordings identified ripples and fast ripples in most patients.
- More fast ripples were found inside than outside the eventually resected areas.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

Patients of all ages were considered eligible for clinical HD-ioECoG recordings when they were candidates for ioECoG-tailored epilepsy surgery, with a few exclusion criteria: (1) presumed epileptic focus in the occipital lobe, as this is associated with the presence of physiological HFOs[19]; (2) the presumed epileptic focus

was difficult to reach by the relatively rigid HD grid (e.g., interhemispheric, orbitofrontal); and (3) if the primary purpose of ioECoG was to decide on the necessity of a hippocampectomy.[20]

We retrospectively selected patients from this clinical HD-ioECoG cohort in the period from September 2021 to August 2023. Exclusion criteria for further analyses were (1) HD-ioECoG recording under awake conditions, since HFO occurrence under awake conditions differ from those under anesthesia,[21] and (2) HD-ioECoG recorded with the MicroMed LTM Express amplifier (MicroMed, Veneto, Italy) due to its low signal-to-noise (SNR) ratio for frequencies above 100 Hz.

2.2 | Ethical approval

All data were collected from the Registry for Epilepsy Surgery Patients in the UMC Utrecht and Stichting Epilepsie Instellingen Nederland (RESPect database). The collection of data in the RESPect database is approved by the institute's Medical Research Ethical Committee under protocol number 18-109. Participants included after 2018 gave consent in accordance with Declaration of Helsinki 2013 for collection and use of their data for research purposes.

2.3 | Clinical data

We collected clinical characteristics, including sex, age at surgery, epilepsy duration, previous brain surgery, anatomic location of resection, magnetic resonance imaging (MRI) diagnoses, histopathological diagnoses, seizure outcome, and follow-up time from the RESPect database electronic data capturing system (Castor, Amsterdam, The Netherlands). One-year postsurgical seizure outcome was determined based on the International League Against Epilepsy (ILAE classification.[22]

2.4 | High-density (HD) intraoperative electrocorticography recordings

All patients underwent surgery under general anesthesia using propofol.[23] Propofol infusion was interrupted during HD-ioECoG recordings to achieve a continuous background pattern with minimal propofol effect.[24] HD-ioECoG was recorded with 8×8 silicone grids with 2 mm platinum electrodes (exposed surface 4.2 mm^2) with 5 mm inter-electrode distance (FG64C-SP05X-000, AdTech, Racine, WI, USA), placed directly on the cortex. HD-ioECoG has four times more electrodes than our standard LD-ioECoG, whereas the individual electrode contact surface area is the same (4.2 mm^2). Recordings were made with a 64-channel EEG-system (MicroMed LTM PLUS, MicroMed, Veneto, Italy) at a 2048 Hz sampling frequency. A unipolar electroencephalography (ECG) was included in the recordings, resulting in HD-ioECoG recordings of channel 1–63. HD-ioECoG was recorded from multiple positions on the cortex during different stages of surgery. Pre-resection recordings were performed to investigate the epileptic characteristics in the signal and to assist in defining the resection border. Recordings were performed at moments indicated by the surgeon to examine whether the resection of the epileptic area was completed or should be extended. The final recording, after the completion of the resection, was named the post-resection recording. Intraoperative tailoring is based on interictal spikes and ictal discharges. If an HFO expert (E.V.S./D.S.) was available, intraoperative HFO analysis was also incorporated in the tailoring of the resection plan. When analyzing HFOs intraoperatively, data were transferred to a separate computer to visualize HFOs. The settings used are described below in the section "visual marking of interictal events." Based on the epileptic events (either spikes alone or spikes in combination with ictal discharges and HFOs), advice was given by the clinical neurophysiologist to the neurosurgeon on the extent of the tissue to be resected in relation to the surgical plan. In the absence of any relevant events, the resection was performed based on the presurgical hypothesis of the epileptogenic zone, which is based on preoperative MRI, scalp EEG, and long-term intracranial EEG, if available. The added value of HD-ioECoG to the presurgical hypothesis, was determined post hoc based on the clinical reports and divided into three categories: (1) confirmation of surgical plan, defined by the presence of epileptic activity before resection and absence of epileptic activity after resection; (2) adaptation of surgical plan, defined by adaptation and/or extension of the resection; and (3) no added value, defined by the absence of epileptic activity before and after resection –.[15]

2.5 | Visual marking of interictal events

We included all pre-resection HD-ioECoG recordings (HD-ioECoG$_{pre}$) in our analyses. We used only visual analyses of interictal events without automated analysis methods during the clinical workup or the study, because of the short recording times and the great amount of intraoperatively recorded artifacts. We selected an artifact-free 1-min epoch of each HD-ioECoG$_{pre}$ recording that had minimal propofol effects (i.e., excluding burst suppression patterns). In these HD-ioECoG$_{pre}$ epochs, interictal spikes (by E.V.S.) and HFOs, ripples. and FRs (by D.S.) were visually marked

independently using BrainQuick (v1.01.0012, MicroMed, Veneto, Italy). In the case of uncertainty, expert reviewers (M.Z., M.A.K.) were consulted to reach consensus. Spikes were marked in an average montage with conventional EEG filter settings (0.16 Hz high-pass infinite impulse response (IRR) filter, 70 Hz low-pass IRR filter, gain of 800 μV/cm and timescale of 15 s/page). HFOs were defined as oscillatory events with at least four oscillations (to avoid marking solely the ringing effect of bandpass filtering sharp spikes) and were marked in a bipolar montage with the following settings: (a) ripples (80–250 Hz), high-pass finite impulse response (FIR) filter at 80 Hz, gain of 50 μV/cm and timescale of 1 s/page; and (b) FRs (250–500 Hz) high-pass FIR filter at 250 Hz, gain of 10 μV/cm and timescale of 1 s/page (Figure 1B). We reviewed the raw ioECoG signal next to marking HFOs to avoid marking false HFOs resulting from ringing effects due to the band pass filtering.

2.6 | Channel labels

We retrospectively matched intraoperative photos of the HD-ioECoG$_{pre}$ positions on the cortical surface with photos of the final resection cavity. For each HD-ioECoG$_{pre}$ recording, a researcher (E.V.S./S.H./Z.W.), who was blinded to the marked HD-ioECoG events, categorized all unipolar channels as follows: (1) resected, channels covering the complete post-surgical resection cavity and channels covering the cortex around the resection margin (5 mm); or (2) non-resected, channels covering the cortical tissue more

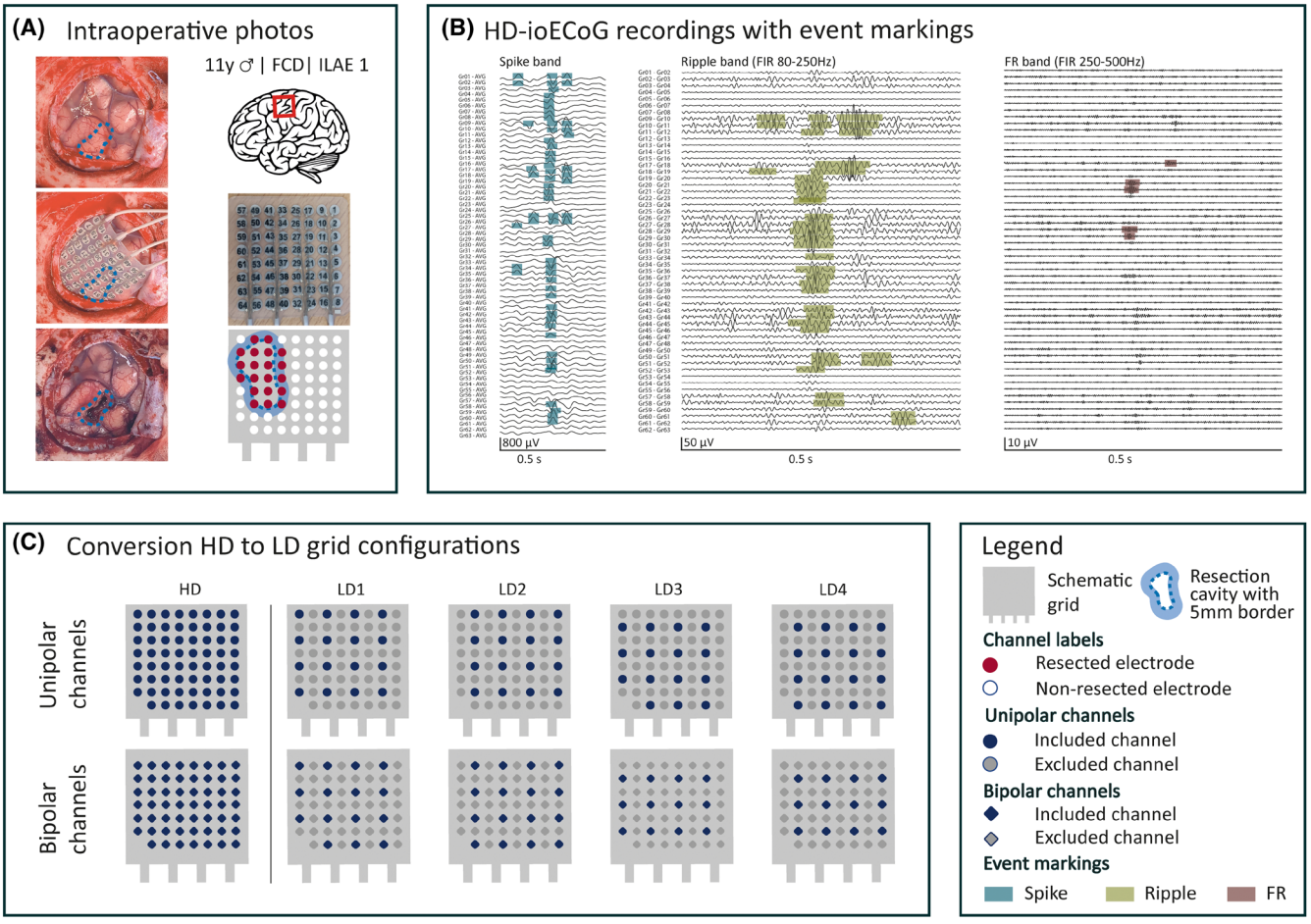


FIGURE 1 Schematic representation of methodological aspects of channel labeling, event detection, and HD vs LD grid configurations. (A) A patient example (Patient 4) of the intraoperative photos that were used to determine channel positions and resected and non-resected channels. (B) The patient's corresponding HD-ioECoG signals including marked events; 0.5 s of raw data with marked spikes in common average montage (0–70 Hz, IRR filtered) (left panel), ripples in bipolar montage (80–250 Hz FIR filtered) (middle panel), and FRs in bipolar montage (250–500 Hz FIR filtered) (right panel). (C) Schematic illustration of conversion method form HD to LD grid configuration. HD grids have four times more electrodes than LD grids, so four different simulated LD grid configurations could be constructed to compare the HD grid findings to the corresponding hypothetical LD grid findings. FCD, focal cortical dysplasia; FIR, finite impulse response; FR, fast ripple; HD, high density; ioECoG, intraoperative electrocorticography; IRR, infinite impulse response; LD, low density; μV, microvolt.

than 5 mm distance away from the border of the resection cavity. In cases where a channel partially covered the resection cavity and its 5 mm edge, this channel was considered "resected" if >50% of the channel covered the resection cavity including the 5 mm edge (Figure 1A). Bipolar channels, required for HFOs analysis, were categorized using the unipolar channel categorization as follows: (1) *resected*, if both unipolar channels were labeled resected, or if one was labeled as resected and the other as non-resected; or (2) *non-resected*, if both unipolar channels were labeled as non-resected.

We quantified in how many cases the resected channels of HD-ioECoG recorded interictal epileptic events. We repeated this measure for the four simulated LD-ioECoG by calculating the mean frequency that LD-ioECoG would record interictal epileptic events in the resected channels and compared this to the HD-ioECoG.

2.7 | Focality of interictal epileptic events

To assess the focality of interictal epileptic events, we retrospectively counted the number of channels with simultaneously occurring events over time for each event type. We classified events into three groups: focal, semi-focal, or scattered. A focal event was defined as occurring in one channel only, a semi-focal event as one occurring in two channels, and a scattered event if more than two channels were involved. We counted the number of focal and semi-focal events, as we assume that these are the type of highly localized events that might have been missed if recording with an LD grid.

2.8 | Spatial clustering of interictal epileptic events

In order to further evaluate which events might have been missed with LD grids, we retrospectively studied events on adjacent electrodes. We defined spatial clusters as one or more event(s) on adjacent channels. We counted the number of clusters consisting of 1, 2, or 3 channels, as we assume that these are the highly localized clusters that might have been missed if recorded with an LD grid. Spatial cluster analyses were repeated for four different simulated LD configurations (i.e., subsampled from HD grids to create LD configurations with 1 cm inter-electrode distance) to create spatial clusters as they would have been with LD recordings (Figure 1C). We examined if the same spatial clusters occurred in the simulated LD configurations in comparison to those on the HD grid. This analysis is performed only on HD-ioECoG recordings with events.

2.9 | Interictal spike onset localization

We retrospectively used the Granger's causality to analyze the propagation of interictal propagating spikes. Granger's causality is a bivariate measure, resulting in a $N \times N$ matrix, where N is the number of channels. This $N \times N$ matrix shows the causality of each channel to all other channels. We calculated outflow by applying the sum over one direction of the $N \times N$ matrix. This outflow represents propagation, since it shows the causalities of one channel to all other channels. The $1 \times N$ matrix was transformed back to the 8×8 grid configuration to display spike propagation. The spike-onset channel was defined as the channel with the highest outflow. We included HD-ioECoG recordings in this analysis if spike propagation was present, defined by spikes co-occurring on at least one third of the grid (i.e., ≥21 channels). These spike-onset localization analyses were repeated for four different simulated LD configurations, to create spike propagation patterns as they would have been with LD recordings (Figure 1C). We assumed that spike-onset location with LD grid might have been located differently if HD spike onset differed >.5 cm—the interelectrode distance between twos electrodes—from LD spike onset.

2.10 | Statistical analysis

Based on intraoperatively performed analysis, we counted the numbers of patients per category of clinical added value by HD-ioECoG. We calculated medians and interquartile ranges (IQRs) for continuous clinical variables. All further analyses described were performed post hoc and were not taken into account in the clinical decision-making. We calculated the total number of events per interictal event type (spikes, ripples, FRs) on channels covering resected and non-resected tissue, and the mean and standard deviation (SD) of the number of events per channel. We compared numbers of events between channels covering resected and non-resected tissue using a logistic mixed model:

$$\log\left(\text{resection}_{\text{patient}}\right) = \alpha + \beta x_{\text{event type}} + \alpha_{\text{patient}} + \gamma_{\text{patient}} x_{\text{event type}} + \varepsilon_{\text{patient}}$$

where $\text{resection}_{\text{patient}}$ was the binary dependent variable (resected/non-resected), $x_{\text{event type}}$ the type of interictal event, α the fixed intercept, β the average relation between the dependent variable and the $x_{\text{event type}}$. The effects α_{patient} and $\gamma_{\text{patient}} x_{\text{event type}}$ represented the random intercept and slope for each patient. $\varepsilon_{\text{patient}}$ represented the residuals. $\beta > 0$ indicates a positive association between number of events and resected tissue, whereas $\beta < 0$ indicates a positive association between number

of events and non-resected tissue. These analyses were performed for the total population, irrespective of the follow-up length, good outcome (ILAE 1), and poor outcome (ILAE ≥2) subgroups. To assess the focality of epileptic events, we calculated the numbers of focal, semi-focal and scattered events; the number of clusters per event type; and the number, median, and IQR of channels within each cluster. We calculated the percentage of focal and semi-focal events with respect to the total number of events as well as the percentages of clusters with 1, 2, or 3 channels with respect to the total number of clusters. To assess spike onset in HD-ioECoG, a spike propagation pattern was calculated for each patient showing spike propagation. The spike onset found in HD was compared with respect to resected and non-resected tissue. All data were processed and analyzed in Matlab 2023b (The MathWorks, Inc., Natick, Massachusetts, USA). All statistics were performed in RStudio 2023.12.1 (R Core Team, 2023). We considered a two-sided tested p-value ≤ .05 significant.

3 | RESULTS

3.1 | Clinical data

Between September 2021 and August 2023, a total of 27 patients underwent HD-ioECoG recordings. Seven patients were excluded for this study: five had LTM Express recordings and two had recordings under awake conditions. We included 20 patients (7 female). The median age at epilepsy onset was 6 years (IQR 11 years) and the median age at surgery was 24 years (IQR 23.5 years). One patient had prior brain surgery, two patients underwent stereo-EEG at 4 and 6 months preceding resection. The anatomic location of the resection was temporal in 10 patients, frontal in 7 patients, and parietal in 3 patients. Focal cortical dysplasia (MRI: $n = 8$; histopathology: $n = 8$) and central nervous system tumors (MRI: $n = 4$; histopathology: $n = 6$) were the most common MRI and histopathological diagnoses. One-year seizure outcome was good (ILAE 1) in 13 patients and poor (ILAE ≥2) in 7 patients (Table 1).

3.2 | High-density (HD) intraoperative electrocorticography recordings

Pre-resection HD-ioECoGs were recorded in one position in eight patients, two different positions in nine patients, and in three different positions in four patients. The median duration of each HD recording in each position is 4 min 29 s [IQR 2 min 32 s to 8 min 7 s]. The HD-ioECoG findings confirmed the surgical plan in 11 patients, adapted the surgical plan in 6 patients, and did not have additional value in 3 patients (Table 1). A total of 36 HD-ioECoG$_{pre}$ recordings were included for further analyses, consisting of 2188 unipolar channels (1006 resected and 1182 non-resected) vs 1888 bipolar channels (981 resected and 907 non-resected). Intraoperative HFO analysis was performed in 11 of 20 patients (7 with good outcome).

3.3 | Visual marking of interictal events

No electrographical seizure were captured. A total of 21358 spikes were found in all HD-ioECoG$_{pre}$ recordings in all patients. Mean (±SD) number of spikes per channel per minute was 9.95 (±13.83) in resected and 8.31 (±13.61) in non-resected tissue. Channels in the resected area captured spikes in 35 HD-ioECoGs (97%). In the simulated LD-ioECoG, channels in the resected area in 30 LD-ioECoGs (83%) captured spikes. This is 14% lower compared to HD-ioECoG.

A total of 8288 ripples were found in 34 HD-ioECoG$_{pre}$ recordings in 19 patients. Mean (±SD) number of ripples per channel per minute was 4.02 (±5.68) in resected and 3.80 (±5.56) in non-resected tissue. Channels in the resected area captured ripples in 30 HD-ioECoGs. In the simulated LD-ioECoG, channels in the resected area in 27 LD-ioECoGs captured ripples. This is 8% lower compared to HD-ioECoG.

A total of 2610 FRs were found in 29 HD-ioECoG$_{pre}$ recordings in 17 patients. Mean (±SD) number of FRs per channel per minute was 1.24 (±2.47) in resected and 0.99 (±1.78) in non-resected tissue. Channels in the resected area captured FRs in 26 HD-ioECoGs. In the simulated LD-ioECoG, channels in the resected area in 19 LD-ioECoGs captured FRs. This is 20% lower compared to HD-ioECoG.

Over the whole patient population, a significant positive association was found between resected tissue and numbers of events per channel for FR ($\beta = .021$, $p < .001$). In the good outcome group, a significant positive association was found between resected tissue and number of events per channel for FR ($\beta = .024$, $p < .001$), whereas this association was absent in the poor outcome group ($\beta = .018$, $p = .69$) (Table 2).

3.4 | Focality of interictal epileptic events

We found 669 focal spikes (3.1%), 630 semi-focal spikes (3.0%), and 20 059 scattered spikes (93.9%). We

TABLE 1 Clinical patient characteristics.

Pat. nr.	Sex	Epilepsy duration (in years)	Age at surgery (in years)	Pre-operative MRI lesion	Hemi-sphere	Anatomic location	Included number of grid positions	HD-ioECoG contribution to surgical plan	Intraoperative HFO analysis	Histopathology	Postsurgical outcome (ILAE class)
1	M	5	25	+	L	Parietal	1	Confirmation	No	Gangioglioma (WHO 1)	ILAE 4
2	M	41	52	+	L	Temporal	1	Confirmation	No	Gangioglioma (WHO 1)	ILAE 1
3	M	36	39	+	L	Temporal	2	Confirmation	No	Others	ILAE 3
4	M	4	11	+	L	Frontal	2	Adaptation	Yes	FCD 2A	ILAE 1
5	F	8	14	+	L	Parietal	1	Adaptation	No	Glioma (WHO 2)	ILAE 1
6	M	6	11	+	R	Temporal	3	Adaptation	No	TSC	ILAE 1
7	M	11	53	−	R	Temporal	3	Adaptation	Yes	FCD 2A	ILAE 5
8	M	12	28	+	R	Temporal	2	Adaptation	Yes	Gliosis	ILAE 3
9	M	4	12	+	L	Parietal	3	Confirmation	Yes	TSC	ILAE 1
10	F	31	31	+	R	Frontal	2	Confirmation	Yes	FCD 2A	ILAE 3
11	M	34	39	+	R	Frontal	1	Limitation	Yes	FCD 2A	ILAE 1
12	M	5	18	+	R	Temporal	3	Confirmation	Yes	DNET (WHO 1)	ILAE 1
13	F	19	23	+	L	Frontal	1	Confirmation	Yes	FCD 2A	ILAE 1
14	F	32	34	+	L	Frontal	2	Confirmation	No	FCD 2B	ILAE 1
15	M	4	6	+	R	Temporal	2	Confirmation	Yes	FCD 2A	ILAE 1
16	M	5	29	+	L	Temporal	2	Confirmation	No	DNET (WHO 1)	ILAE 1
17	M	5	7	+	L	Frontal	1	Adaptation	No	FCD 2A	ILAE 1
18	F	1	1	+	L	Frontal	2	Limitation	Yes	Others	ILAE 3
19	F	1	18	+	R	Temporal	1	Confirmation	Yes	Gangioglioma (WHO 1)	ILAE 1
20	F	31	39	+	R	Temporal	1	Limitation	No	TSC	ILAE 4

Abbreviations: F, female; FCD, focal cortical dysplasia; HD-ioECoG, high-density intraoperative electrocorticography; HFO, high frequency oscillation; ILAE, International League Against Epilepsy; L, left; M, male; MRI, Magnetic Resonance Imaging; Pat. nr., patient number; R, right; TSC, tuberous sclerosis complex; WHO, World Health Organization; +, positive MRI; -, negative MRI.

TABLE 2 Event numbers for interictal epileptic events inside and outside the resection and in relation to post-surgical outcome.

	Total population ($n=20$)			ILAE 1($n=13$)
	Resected channels	Non-resected channels	Resected vs non-resected$^{\xi}$	Resected channels
Spikes ($n=20$)				
Total events, mean (±SD)	10 452 522.6 (±726.2)	10 906 545.3 (±950.0)		6213 443.8 (±459.1)
No. vents per channel, mean (±SD)	10.0 (±13.8)	8.3 (±13.6)	$\beta=.016$ $p=.69$	10.4 (±15.8)
No. events per channel with events, mean (±SD)	13.18 (±13.83)	11.03 (±13.81)	$\beta=.0324$ **$p=.003$**	12.60 (±14.82)
Ripples ($n=19$)				
Total events, mean (±SD)	4529 226.5 (±373.4)	3759 188.0 (±270.0)		2790 199.3 (±338.4)
No. events per channel, mean (±SD)	4.0 (±5.7)	3.8 (±5.6)	$\beta=-.015$ $p=.74$	4.0 (±5.7)
No. events per channel with events, mean (±SD)	6.81 (±6.42)	6.90 (±6.69)	$\beta=-.0272$ $p=.19$	5.99 (±5.63)
Fast ripples ($n=17$)				
Total events, mean (±SD)	1370 68.5 (±140.1)	1240 62.0 (±132.2)		1085 77.5 (±161.4)
No. events per channel, mean (±SD)	1.2 (±2.5)	1.0 (±1.8)	$\beta=.021$ **$p<.001$**	1.6 (±3.0)
No. events per channel with events, mean (±SD)	3.42 (±3.39)	4.00 (±3.47)	$\beta=-.0022$ $p=.66$	3.70 (±3.83)

Note: ILAE 1 = good outcome, ILAE ≥2 = poor outcome, ξ = logistic mixed model, $\beta>0$ = positive association, $\beta<0$ = negative association. $p<.05$ is considered as a statistically significant result (bold values).

Abbreviations: ILAE, International League Against Epilepsy; SD, standard deviation.

found 924 focal ripples (11.1%), 1522 semi-focal ripples (18.4%), and 5842 scattered ripples (70.5%). We found 683 focal FRs (26.2%), 534 semi-focal FRs (20.5%), and 1393 scattered FR (53.3%). The number of highly localized events (i.e., focal and semi-focal events) was thus 6.1% of the spikes, 19.5% of the ripples, and 46.7% of the FRs (Figure 2A).

3.5 | Spatial clustering of interictal epileptic events

We identified 88 spike clusters, ranging from 1 to 8 spike clusters per HD-ioECoG$_{pre}$ recording. The number of channels with spikes per cluster ranged from 1 to 63 channels, with a median of 4 (IQR 17.75) channels in average montage. Twenty-nine clusters (33.0%) consisted of one channel, five clusters (5.7%)consisted of two channels, nine clusters (10.2%) consisted of three channels, and 45 clusters (51.1%)consisted of more than three channels. We found a total of 43 of 88 (48.9%) highly localized clusters with spikes. Comparing simulated LD clusters to HD clusters with events, similar cluster locations were found in 103 of 144 LD configurations. Thus, 28.4% of the spike clusters might be missed with standard LD grids.

We identified 68 ripple clusters in 19 patients, ranging from 1 to 5 ripple clusters per HD-ioECoG$_{pre}$ recording. We found 0 to 10 clusters per patient (median 3). Each patient had 0 to 116 bipolar channels with ripples, with a median of 35. Each cluster had 1 to 49 bipolar channels with ripples, with a median of 6 (IQR 20.25). Seven clusters (10.3%) consisted of one channel, 10 clusters (14.7%) consisted of two channels, four clusters (5.9%) consisted of three channels, and 47 clusters (69.1%) consisted of more than three channels. We found a total of 21 of 68 (30.9%) highly localized clusters with ripples. Comparing simulated LD clusters to HD clusters with events, similar cluster locations were found in 77 of 136 LD configurations. Thus, 43.4% of the ripple clusters might be missed with standard LD grids.

We identified 74 FR clusters in 17 patients, ranging from 1 to 4 FR clusters per HD-ioECoG$_{pre}$ recording. This is 1 to 9 clusters per patient (median 4) and each patient had 0 to 89 bipolar channels with FRs (median 12). Each cluster has 1 to 32 bipolar channels with FRs (median 3, IQR 3.75). Nineteen clusters (25.7%) consisted of one channel, 17 clusters (22.9%) consisted of two channels, 10 clusters (13.5%) consisted of three channels, and 28 clusters (37.9%) consisted of more than three channels. We found a total of 46 of 74 (62.1%) highly localized clusters with FRs (Figure 2B). Comparing simulated LD clusters to HD clusters with events, similar cluster locations were found in 51 of 116 LD configurations. Thus, 56.0% of the FR clusters might be missed with standard LD grids.

		ILAE≥2($n=7$)		
Non-resected channels	Resected vs non-resected[ξ]	Resected channels	Non-resected channels	Resected vs non-resected[ξ]
6428 459.1 (±905.0)		4239 706.5 (±737.6)	4478 746.3 (±1019.6)	
6.4 (±10.9)	$\beta=.056$ $p=.31$	9.1 (±8.9)	11.9 (±17.0)	$\beta=-.034$ $p=.60$
8.87 (±10.49)	$\beta=.0408$ $\mathbf{p=.012}$	14.42 (±11.29)	16.07 (±18.51)	$\beta=.0352$ $p=.34$
2343 167.4 (±223.7)		1739 289.8 (±438.0)	1416 236.0 (±359.5)	
2.9 (±3.1)	$\beta=-.017$ $p=.81$	4.1 (±5.7)	5.5 (±8.2)	$\beta=-.009$ $p=.54$
5.93 (±4.55)	$\beta=-.0363$ $p=.27$	9.65 (±8.00)	9.64 (±10.11)	$\beta=-.0181$ $p=.80$
1064 76.0 (±154.0)		285 47.5 (±63.3)	176 29.3 (±37.0)	
1.1 (±2.1)	$\beta=.024$ $\mathbf{p<.001}$	.7 (±.8)	.7 (±.9)	$\beta=.018$ $p=.69$
4.34 (±3.92)	$\beta=-.0034$ $p=.52$	2.73 (±1.77)	3.24 (±1.95)	$\beta=.0395$ $p=.48$

3.6 | Interictal spike onset localization

We analyzed spike propagation patterns in 18 HD grid positions of nine patients with Granger's causality (Figure 3). The onset spike was located in the resected area in six patients (four were seizure-free and two had recurrent seizures). The onset spike was located outside the resected area in three patients (two were seizure-free and one had recurrent seizures). Comparing HD onset spike to simulated LD onset spike, the location differed >0.5 cm in 42 of 72 LD configurations. Thus, 58.3% of the spike-onset locations might be located differently with standard LD grids.

4 | DISCUSSION

We investigated the potential added value of HD-ioECoG within the clinical context of epilepsy surgery. We assessed the ability of HD-ioECoG to record highly localized epileptic events and to contribute to the surgical plan. Our findings indicated that HD-ioECoG provided confirmation or adaption of the resection plan in 17 of 20 patients (85%). Epileptic events, including FRs, were detected in the majority of patients. FRs were more present over the resected area, especially in patients who were seizure-free after surgery. Post hoc analyses on the focality and spatial clustering of epileptic events revealed that a substantial number of highly localized events could potentially be missed with standard LD grids recordings. HD grid recordings can differentiate between onset spikes and propagated spikes, whereas our simulated LD grids would mislocate the onset spike in more than 50% of the cases.

We conducted HD-ioECoG recordings in 20 patients, with 17 patients (85%) showing FRs. We did not record with LD grids in the same 20 patients. Based on our simulations, we argue that 46.7% of focal and semi-focal FRs and 56.0%–62.1% of localized FR clusters may go undetected by LD grids. We compared our findings with the previous studies from our group using LD grids. In those studies, the electrode contact surface of LD and HD grids is the same (4.2 mm^2). Straumann et al.,[25] who excluded mesiotemporal recordings in accordance with our exclusion criteria, found FRs in 13 of 33 patients (39.4%). Van 't Klooster et al.,[26] who included 54 patients of whom 8 underwent mesiotemporal recordings, identified FRs in 38 patients (70.7%). After excluding 8patients with mesiotemporal recordings from that study, 31 of 46 patients (67.4%) showed FRs. This suggests that HD-ioECoG recordings facilitate FR detection in a larger proportion of patients than LD recordings (increase of 17.5%–45.6%). Our finding is in agreement with those of Boran et al.,[17] which showed that increasing the electrode density of HD-ioECoG brings the electrodes closer to the FR generator and improves the probability of measuring the maximal intensity of FRs. HFO generators, particularly those responsible for FRs, are characterized by their small size

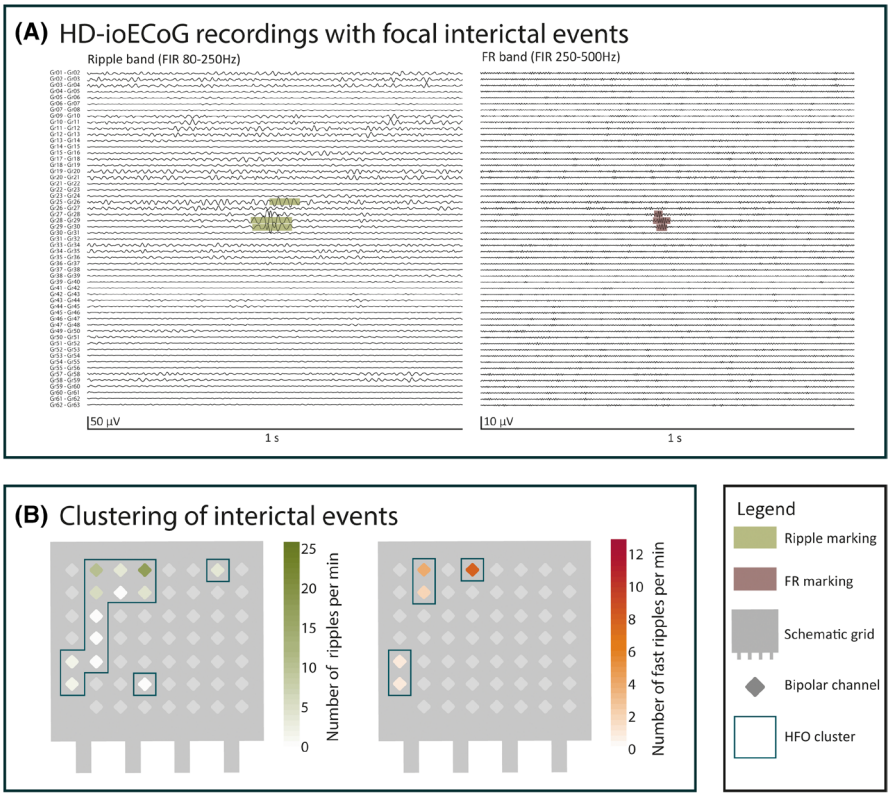


FIGURE 2 Two patient examples demonstrating highly localized events. (A) Focality of interictal events. A patient example (Patient 6) showing 1 s HD-ioECoG data in the ripple band (FIR 80–250 Hz) and the FR band (FIR 250–500 Hz). Note the simultaneous ripples on two neighboring bipolar channels and the FRs on three bipolar channels. These HFOs might have been missed without HD recordings, since HD recordings have four times more electrodes (Figure 1C). (B) Clustering of interictal events. HD grid configuration (Patient 9), showing bipolar channels. Clusters are outlined with a dark blue line. In this patient, there are three ripple clusters: One cluster contained 10 channels with ripples and two clusters contained one channel with ripples; and three FR clusters: Two clusters contained two channels with FRs and one cluster contained one channel with FRs. These HFOs might have been missed without HD recordings, since HD recordings have four times more electrodes (Figure 1C). FIR, finite impulse response; FR, fast ripple; HFO, high-frequency oscillation; µV, microvolt.

and high spatial signal attenuation.[27,28] Studies in rats have shown that FR-generating areas do not exceed 1 mm^2.[29] In addition, in humans, recording techniques with high spatial density are crucial for capturing FRs. This may suggest that optimal detection of FRs may require even higher-resolution grids. However, increasing grid resolution has associated limitations. To achieve similar cortical coverage with higher resolution, a larger number of electrodes is necessary, which complicates real-time interpretation of ioECoG during surgery. Reducing grid size to limit channels would increase recording time, as different grid positions are needed to record whole area of interest. Our results showed that HD-ioECoG with a 5 mm interelectrode distance effectively records highly localized HFOs in most patients, while maintaining readablity in real-time.

FRs were recorded more frequently in the resected area compared to the non-resected area in people who were seizure-free after surgery, suggesting that the presence of FRs is indicative of seizure-generating tissue. This association was not found in people with seizure recurrence. Even though we found a difference between FRs in the resected and non-resected tissue, the effect size was limited. This limits the potential clinical impact. IoECoG recordings may not always measure HFOs, even if with an HD configuration. This may be due to types of pathologies or epileptic tissue in the depth. Recording with flexible electrode grids or adding depth electrodes to the surface recordings may improve the clinical value and needs further investigation.

The specificity of spikes for the epileptic tissue and therefore the use of ioECoG has been debated.[4,30,31] Interictal spikes often extend beyond the epileptogenic tissue and are seen in multiple contacts due to rapid propagation, which limits its sensitivity for delineating epileptogenic tissue. Onset spikes are suggested to be more accurate predictors for epileptogenic tissue compared to interictal spikes alone but their specificity is not 100%.[8] Onset spikes in the non-resected areas of seizure-free patients in our study suggest low specificity, but the numbers are too small to draw conclusions. Literature highlights the importance of intracranial recording of HFOs and spikes for seizure outcome. The resection of FR-generating areas

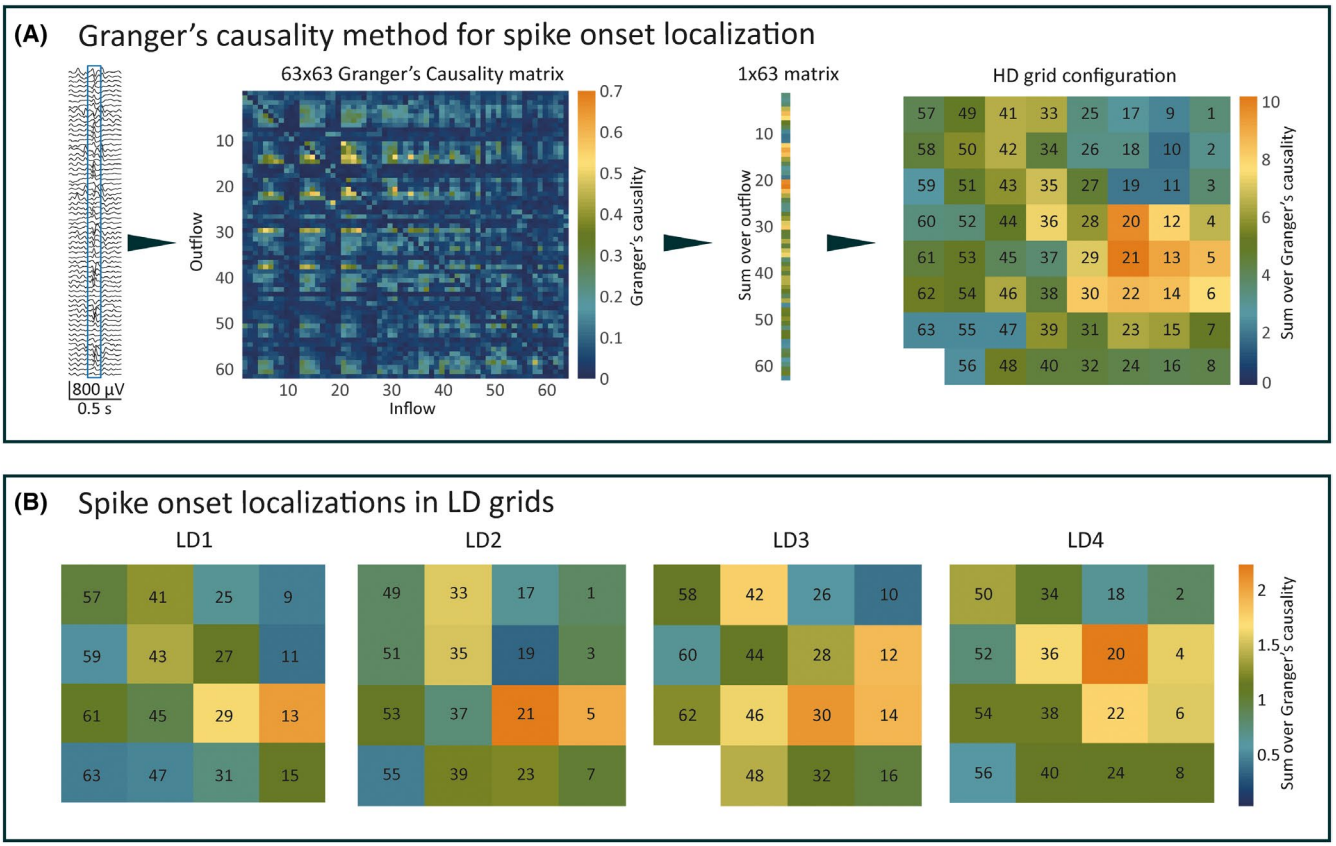
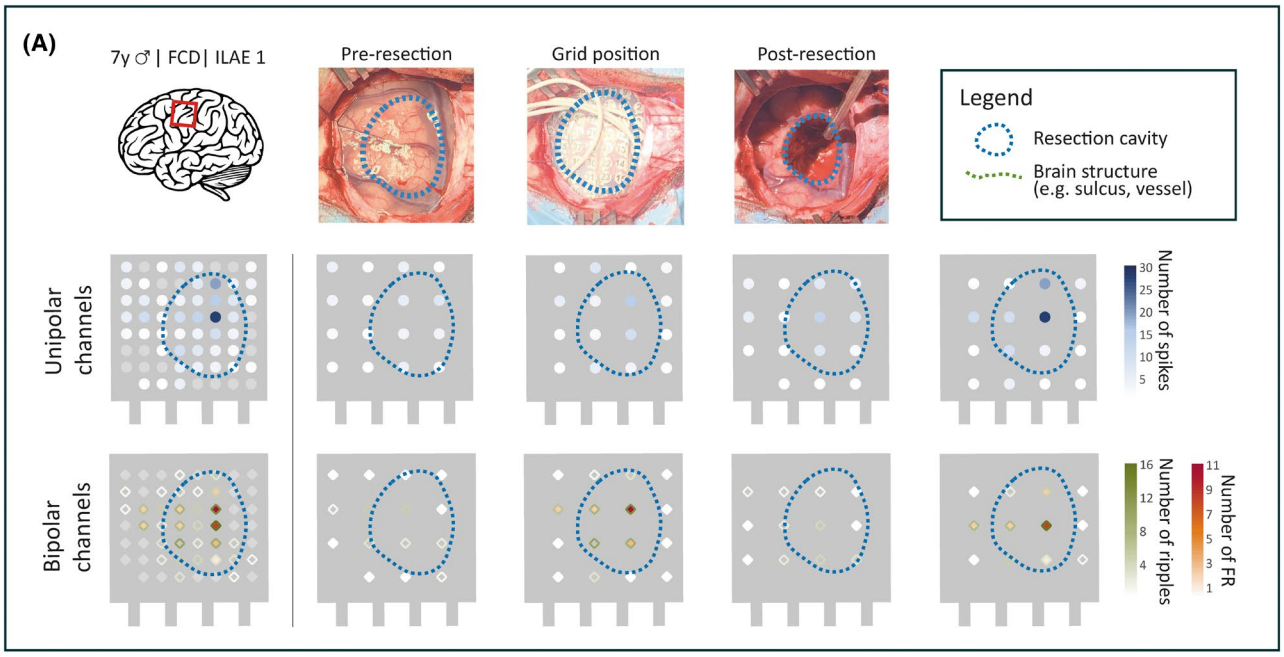


FIGURE 3 Spike-onset localization with Granger's causality. (A) Spike-onset localization with Granger's causality is based on a three-step approach. Based on 63 HD-ioECoG channels with signal—channel 64 was used as a reference—(L-R Panel 1), as a first step a 63×63 matrix was calculated (L-R Panel 2). In the second step, the sum over the outflow of the Granger's causality matrix was taken. This outflow represents propagation, since it shows the causalities of one channel to all other channels. This resulted in a 1×63 matrix (L-R Panel 3). In the final step, this 1×63 matrix was transformed back into the 8×8 HD grid configuration to display spike propagation. The spike-onset channel was defined as the channel with highest outflow (L-R Panel 4). In this patient (Patient 4; see intraoperative photos in Figure 1A) the spike onset is located on grid 21. (B) Spike-onset localization calculated for the four LD grid configurations (Figure 1C). Note that due to the reduced resolution, the spike-onset location differs for the LD grid configurations, albeit they are all located within 0.5 cm of the spike onset in the HD grid configuration. HD, high density; LD, low density; L-R, left-to-right; µV, microvolt.

and overlapping spikes and ripple-onset areas have been shown to be associated with favorable seizure outcome.[7,32] IoECoG-assisted surgery based on interictal spikes may be associated with extended resection beyond the true epileptogenic zone. That is why in clinical practice the ioECoG spikes should always be reviewed with the actual extension of the lesion, MRI, tissue appearance, and the expected pathology taken into consideration.

This study evaluated the clinical implementation of HD-ioECoG to tailor epilepsy surgery. Implementing HD-ioECoG in a clinical setting presents some challenges. First, epileptologists in our center are accustomed to performing real-time visual ioECoG analysis on 16–20 electrodes, whereas HD grids incorporate 64 electrodes. To assist epileptologists in the adjustment, we created different LD configurations (Figure 1C) that could be used in real time. We observed that after a learning curve of ~1 year, after ~15 HD-ioECoG recordings, our epileptologists began to prefer HD-ioECoG over standard LD recordings. Second, a neurosurgical challenge is the stiffness of the HD grid. The HD-grid's electrode characteristics were similar to those of standard LD-grids (both manufactured by ADtech), with comparable diameter and contact surface. Therefore, we expect the SNR in the fast ripple band to be in line with the previous literature.[33] However, these HD grids are made with a thicker silicon layer than that of LD grids, which might result in reduced pliability over the cortex, potentially introducing more noise. Recent studies have shown that flexible strips, such as the WISE Cortical Strip WCS using novel thin-film technology, significantly improve SNR. These flexible strips, incorporating platinum nanoparticles in a polymer base, enhance the detection of small amplitude FR events.[33–35] The gains used in this HD study are similar to those used in our previous LD studies.[15,25,26] We observed no visually perceivable differences in the amplitudes of spikes, ripples,


(A)
7y ♂ | FCD| ILAE 1
Pre-resection
Grid position
Post-resection
Legend
Resection cavity
Brain structure (e.g. sulcus, vessel)
Unipolar channels
Bipolar channels
Number of spikes
Number of ripples
Number of FR

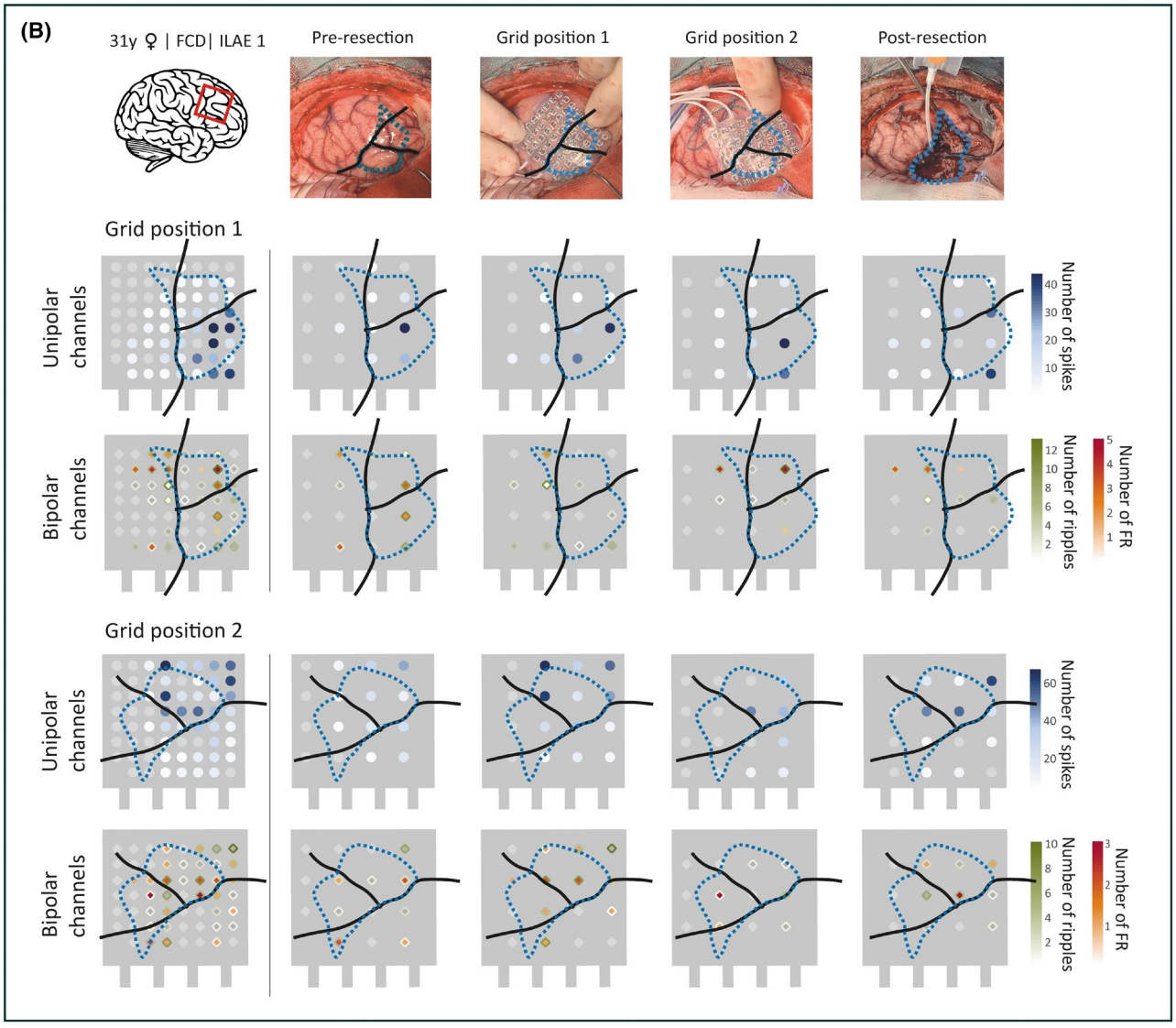

(B)
31y ♀ | FCD| ILAE 1
Pre-resection
Grid position 1
Grid position 2
Post-resection
Grid position 1
Grid position 2
Unipolar channels
Bipolar channels
Number of spikes
Number of ripples
Number of FR

FIGURE 4 Two patient examples demonstrating the clinical benefits of performing HD-ioECoG to tailor epilepsy surgery. (A) This patient example (Patient 17) demonstrates the ability of HD-ioECoG to record highly localized events. In contrast, if an LD grid had been used, there would have been a high chance of missing these highly localized events, in particular ripples and FRs. (B) This patient example (Patient 10) demonstrates that the presence of anatomic brain structures (e.g., deep sulci, large blood vessels) impacts the amount of events that can be captured in the recorded signal. If these recordings would have been made with an LD grid, there is a high chance of putting only a few electrodes on top of these brain structures and thereby missing out on capturing interictal events of clinical importance. This emphasizes the importance of high-resolution recordings for tailoring purposes in epilepsy surgery. FCD, focal cortical dysplasia; FR, fast ripple; y, year.

and FRs between the HD and earlier LD recordings. A direct comparison is difficult, as different amplifiers were used. We hypothesize that the choice of montage used for marking epileptic activity—different for spikes and HFOs in current study—may have a greater impact on observed amplitude differences than the grid itself. This will be the subject of a future study. Third, these HD grids have limited transparency, which can impede the recognition of the cortical surface.

An unexpected advantage of using HD grids in clinical practice is the ability to rapidly recognize both epileptic and normal patterns, such as ictiform spike patterns and burst-suppression, because of the increased number of channels provided by HD grids compared to LD grids. We hypothesized that HD grids enhance the recording of focal phenomena, including highly localized interictal events and electrographic seizures detected on a limited number of electrodes. We did not record electrographic seizures, but we found highly localized interictal spikes and HFOs, especially FRs, that could otherwise be missed. Another interesting finding is that, in some cases, the pattern of event clusters aligns with the distribution of the anatomic gyrus–sulcus pattern, with events recorded only on the gyrus but not on the sulcus of the brain (Figure 4B).

A limitation of our study is the absence of LD-ioECoG recordings in the same patients, which prevents a direct comparison between HD and LD recordings. We attempted to design our data analysis to draw conclusions as if LD recordings were available for the same patients. We reconstructed four simulated LD grid configurations of the electrode positions of the HD grid (Figure 1C). Our reconstruction closely resembles "real" LD grid recordings, since it maintains the same characteristics of the LD grid in terms of electrode size and inter-electrode distance. We analyzed epochs of 1 min, while it is known from long-term invasive EEG that recordings of at least 5 min are needed to recognize a somewhat stable pattern[36] and that sleep and diurnal rhythms affect HFO occurrence.[37] Another limitation is the lack of long-term follow-up, which may restrict the conclusions we can draw regarding patient outcomes. In addition, the patient population in our study is small and heterogeneous, with varying underlying pathologies. Despite that, this diverse sample demonstrates the potential applicability of HD-ioECoG across different cases.

5 | FUTURE RECOMMENDATIONS AND CONCLUSION

Future work should investigate using HFOs for clinical decision-making and elaborate on pathology-specific signal characteristics. The development of flexible HD grids is currently ongoing.[5] Clinical implementation of these new grids should be evaluated, but these flexible grids are able to overcome some of the current clinical challenges. Grid designs should focus on enabling recording on different brain structures (gyri and sulci anatomy), and the possibility to record (partially) under the skull. Such a grid may improve the SNR ratio, especially when the recording is facilitated by low-noise amplifier. Less noise facilitates fully automated HFO detection.[38] In addition, EEG software needs adaptation toward facilitating the review of large numbers of channels, regardless of the montage of choice.

In conclusion, we provide strong indications that HD recordings can provide added value in clinical settings. Specifically, HD-ioECoG is able to (1) record highly localized interictal events; (2) identify FRs in a larger number of patients compared to LD-ioECoG while ensuring they remain specific to the resected area in those who achieve seizure freedom; (3) record FR specifically over the resected area in people who are seizure-free; and (4) characterize spike propagation and spike-onset area.

AUTHOR CONTRIBUTIONS

E.V.S., D.S., M.A.K., and M.Z. conceptualized the study. E.V.S., D.S., S.H., Z.W., F.S.S.L., and P.E. helped with data acquisition and post-processing. E.V.S., D.S., N.F.R., P.R., M.A.K., and M.Z. designed the data analyses. E.V.S. and D.S. performed the data and statistical analysis. E.V.S., D.S., N.F.R., P.R., M.A.K., and M.Z. helped with the interpretation of the data. E.V.S. prepared the tables and figures. E.V.S. and D.S. drafted the manuscript. M.A.K. and M.Z. critically reviewed the manuscript. All authors reviewed the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

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

DATA AVAILABILITY STATEMENT

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

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