Effect of Sevoflurane Anesthesia on Intraoperative Spikes, High-Frequency Oscillations and Phase-Amplitude Coupling in MRI-Normal Hippocampus

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Abstract:

Introduction: The purpose of this study was to determine the effect of sevoflurane anesthesia on spikes, high-frequency oscillations (HFO), and phase-amplitude coupling using a modulation index (MI) in MRI-normal hippocampus, with the aim of evaluating the utility of intraoperative electrocorticography (ioECOG) in identifying the epileptogenic hippocampus during sevoflurane administration.

Methods: Eleven patients with intractable temporal lobe epilepsy with a normal hippocampus on MRI underwent extra-operative electrocorticography (eoECoG) evaluation. Patients were assigned to the Ictal (+) or Ictal (−) group depending on whether the parahippocampal gyrus was included in the seizure onset zone. IoECoG was performed under 0.5 and 1.5 minimum alveolar concentration. The rates of spikes, ripples, fast ripples (FR), ripples on spikes (RonS), fast ripples on spikes (FRonS), and MI $_{\text{HFO (3-4 Hz)}}$ were evaluated.

Results: During the ioECoG procedure, sevoflurane administration was found to significantly increase the rate of spikes RonS, FRonS and MI $_{\text{HFO (3-4 Hz)}}$ in the Ictal (+) group ($P < 0.01$). In contrast, the Ictal (−) group exhibited a paradoxical increase in the rate of ripples and FR ($P < 0.05$).

Conclusions: Our findings indicate that the administration of sevoflurane during ioECOG in patients with MRI-normal hippocampus can lead to a dose-dependent enhancement of epileptic

biomarkers (spikes, RonS, FRonS, and MI (HFO 3-4)) in the epileptogenic hippocampus, while paradoxically increasing the rate of ripples and FR in the non-epileptogenic hippocampus. These results have significant implications for the identification of the MRI-normal hippocampus that requires surgical intervention and preservation of the non-epileptogenic hippocampus.

Keywords: Hippocampus, high-frequency oscillations, HFO on spike, phase-amplitude coupling, intraoperative electrocorticography, sevoflurane

1. Introduction

The surgical management of MRI-negative temporal lobe epilepsy (TLE) and lateral lesional TLE with an MRI-normal hippocampus requires a nuanced approach, as approximately 70% of MRI-negative TLE patients and 50% of patients with lateral lesional TLE have an epileptogenic hippocampus [1,2]. The resection of such a hippocampus has been shown to result in favorable post-operative outcomes, albeit with an increased risk of verbal and visual memory decline [3–5].

Extra-operative electrocorticography (eoECOG) and stereo electroencephalography (SEEG) are the most effective methods for determining the epileptogenicity of an MRI-normal hippocampus, though they are invasive in nature [1]. As an alternative, intra-operative electrocorticography (ioECOG) can be employed to less invasively assess the epileptogenic regions, though not all spikes necessarily require resection for good seizure control [6–8]. To enhance the results of ioECOG, other epileptogenic biomarkers such as high-frequency oscillations (HFO) can be utilized. Although HFOs are reported at higher rates in the epileptogenic zone, it can be challenging to differentiate between physiological and pathological HFOs [9]. A recent study indicated that the persistence of HFO during hippocampal ioECOG did not lead to poor outcomes [10]. The phase-amplitude coupling with a modulation index (MI) can aid in identifying pathological HFOs, as the preferential pairing of HFO amplitude with a slow wave of 3-4 Hz is more likely to be pathological [11,12]. Additionally, HFOs co-occurring with spikes can be used to differentiate between pathological and physiological activity, as HFOs superimposed on spikes are highly correlated with the seizure onset zone (SOZ) [13].

An important factor to consider in the assessment of intra-operative epileptic activity is the influence of anesthesia, which varies based on the dose and concentration of the administered agent [14]. Sevoflurane, a commonly utilized anesthetic, has been shown to have a pro-convulsant effect on epileptic biomarkers at increasing concentrations, potentially enabling the localization of epileptogenic regions [15–17].

This study aims to investigate the effect of increasing sevoflurane concentration on spikes, HFOs (ripples and fast ripples), HFOs co-occurring with spikes, and MI during ioECOG of an MRI-normal hippocampus, to determine if sevoflurane affects the epileptogenic and non-epileptogenic hippocampus differently and to verify the utility of ioECOG with sevoflurane in determining the

epileptogenic hippocampus. The hypothesis is that spikes, HFOs, HFOs co-occurring with spikes, and MI will increase in the epileptogenic hippocampus during ioECOG with increasing sevoflurane concentrations.

2. Materials and methods

2.1 Patients

The study was a retrospective review of 11 patients with refractory focal epilepsy who underwent eoECoG recording for pre-surgical evaluation between 2015 and 2020. None of the patients had hippocampal sclerosis or atrophy on MRI. All patients had interictal epileptiform discharges from the parahippocampal gyrus and showed involvement of medial temporal structures in the irritative zone. The patients had heterogeneous pathologies and underwent various pre-surgical evaluations, including scalp video EEG, MRI, and FDG-PET but the necessity for mesial temporal lobe resection could not be determined. The study was approved by the ethics committee of Nara Medical University (approval number: 2642).

2.2 Intracranial electrodes and recording

Regions for the implantation of intracranial electrodes were selected based on the pre-surgical evaluation. For temporal lobe examination, three 1 x 6 subdural strip electrodes (Ad tech Inc.,

Wisconsin, USA) were placed sub-temporally directed at the mesial temporal structures; two 2 x 8 subdural grid electrodes were placed on the lateral temporal cortex; and additional electrodes including depth electrodes were placed on the other lobes, if necessary. Confirmation of electrode placement was done through MRI and CT scans. eoECoG was recorded for 7 or 14 days using EEG-1200 (Nihon Kohden, Tokyo, Japan) at a sampling rate of 2,000 Hz. For analysis, 10 artifact-free 3-minute epochs of intracranial eoECoG collected during slow-wave sleep were selected from each patient.

2.3 Determination of groups

In this study, the definition of ictal epileptiform discharges from the parahippocampal gyrus included three conditions: a) high-amplitude repetitive spikes, b) low-voltage fast activity, or c) spike-and-wave complex lasting more than several seconds with or without clinical symptoms [18]. The patients were allocated into two groups based on the presence of these discharges: the Ictal (+) group and the Ictal (−) group. The Ictal (+) group included patients who exhibited initial ictal epileptiform discharges only from the parahippocampal gyrus, or who had seizure onset zones in regions other than the mesial temporal lobe but also had independent initial ictal discharges from the parahippocampal gyrus, or who had initial discharges from both the lateral temporal lobe and the parahippocampal gyrus. These conditions were captured at least twice during eoECoG.

Patients who had no initial ictal epileptiform discharges from the parahippocampal gyrus during eoECoG were assigned to the Ictal (−) group. The decisions regarding patient grouping were made by two board-certified epileptologists (K.T. and R.S). in all cases

2.4 Seizure outcome

The decision to resect the mesial temporal structures was mainly based on the presence of initial ictal discharge from the parahippocampal gyrus during eoECoG, but other factors such as preoperative examination results and language laterality were also considered. The outcome of the surgery was evaluated 24 months after the procedure using the ILAE classification [19].

2.5 AED, anesthesia and ioECOG

Anti-epileptic medication was reduced during eoECoG and returned to normal dose after the epileptogenic region was identified, with a reduced dose maintained on surgery day to minimize effects on eoECoG and ioECoG results. Patients were anesthetized using a mixture of propofol (1-2 mg/kg body weight), fentanyl (2 μg/kg body weight, and rocuronium (0.5-0.6 mg/kg body weight). ioECoG was recorded using a Neurofax EEG-1200 machine before skin incision and after head fixation while under two different concentrations of sevoflurane, 0.5 minimal alveolar concentration (MAC) and 1.5 MAC, for 10 minutes each. Anesthesia was maintained using only sevoflurane during ioECoG recordings. Three 1-minute artifact-free epochs of ioECoG under 0.5 MAC and 1.5 MAC sevoflurane were selected for analysis. Only the parahippocampal contacts

were analyzed during both ioECoG and eoECoG for spikes, HFO, and MI HFO (3-4 Hz) by two authors (K.T. and R.D).

2.6 Spikes

The rates of spikes was assessed manually during slow-wave sleep and two levels of sevoflurane anesthesia (0.5 MAC and 1.5 MAC). The EEG was filtered at a range of 0.53-70 Hz with a 100 μV/mm amplitude and 3 cm/s time scale. A spike was defined as a sharp wave with double the baseline amplitude and a maximum duration of 80 ms [20].

2.7 HFOs

HFO rates were evaluated semi-automatically during slow-wave sleep and two levels of sevoflurane anesthesia (0.5 MAC and 1.5 MAC) using the RIPPLELAB toolbox in MATLAB (MathWorks, Natick, MA, USA). The EEG signals were filtered using finite impulse response filter at 80-250 Hz for ripples (R) and 250-500 Hz for fast ripples (FR) with a 95% threshold percentile. HFOs were detected using the MNI method. To avoid false oscillations or ringing artifacts, ripple on spike (RonS) and fast ripple on spike (FRonS) were marked manually in addition to the analysis in RIPPLELAB. The data was displayed at a 0.5 s/page resolution.

2.8 Modulation Index (MI)

MI was automatically calculated using The EEGLAB Toolbox PACTv.0.17 in the parahippocampal electrode based on the algorithm by Miyakoshi et al. [21] which utilizes mean resultant vector length as an output measure as reorted by Canolty et al. [22]. ECOG signal were

high-pass filtered (80 Hz for R, 250 Hz for FR), Hilbert transformed, and HFO amplitude percentile set at 5%. The significant threshold was 0.05, with 500 surrogations and 18 phase bins. The phase of slow wave of interest was set at 3-4 Hz.

2.9 Statistical analyses

The statistical analysis was done using SPSS Statistics 26 (IBM, Armonk, NY, USA) and involved comparing spikes, R, FRs, R, RonS and FRonS using ANOVA for within-group and t-tests for between-group... Friedman test was used to analyze the increase in $MI_{HFO\ (3\text{-}4\ Hz)}$ and posthoc comparisons were made with Dunn's test. Differences between groups were assessed using Mann-Whitney U, and Bonferroni correction was applied for multiple comparisons. The significance level was set at 0.05, and exact P values were reported unless $P < 0.001$

3. Results

3.1 Clinical profiles

Eleven patients were enrolled in the study with 6 (54%) in the Ictal (+) group and 5 (45%) in the Ictal (−) group. The average age at surgery was 34.16 years in the Ictal (+) group and 29 years in the Ictal (−) group. MRI-negative temporal lobe epilepsy was the most common diagnosis in both groups. All patients in the Ictal (+) group underwent hippocampal resection except one (#6), while all patients in the Ictal (−) group except one (#4) had their hippocampus spared. In the Ictal (+) group, 2 patients had mesial temporal sclerosis, 5 had good post-operative outcomes (ILAE 1a/1/2), and 1 had multifocal epilepsy with poor seizure outcomes (ILAE 4). In the Ictal

(−) group, 2 were seizure-free (ILAE 1a), and the rest had poor seizure outcomes (ILAE 4) (Table. 1)

3.2 Spikes

The data is summarized in Table 2.

The rate of spikes increased significantly with an increase in sevoflurane concentration in the Ictal (+) group during the ioECoG. The spikes were higher in the Ictal (+) group during SWS compared to the Ictal (−) group (P = 0.016). During ioECoG, spikes increased significantly from SWS to 0.5 MAC and from 0.5 MAC to 1.5 MAC (P = 0.014 and P = 0.008, respectively) (Figure. 1A).

3.3 R and RonS

The rate of R increased significantly with an increase in sevoflurane concentration from 0.5 MAC to 1.5 MAC during ioECoG in the Ictal (−) group. The rate of R was also higher in the Ictal (−) group compared to Ictal (+) group at 1.5 MAC (P = 0.005) (Figure. 1B). The rate of RonS in the Ictal (+) group was higher during SWS (P = 0.011) and at 0.5 MAC (P = 0.001) and 1.5 MAC (P = 0.001), and exhibited a significant increase from SWS to 0.5 MAC (P = 0.002) (Figure. 1D).

3.4 FR and FRonS

The results showed that the rate of FRs in the Ictal (+) group was higher compared to the Ictal (−) group during SWS (P = 0.008) and at 0.5 MAC (P = 0.035) during ioECoG, but there was no significant difference at 1.5 MAC. On the other hand, the Ictal (−) group showed an increase in the rate of FRs when the sevoflurane concentration was increased from 0.5 MAC to 1.5 MAC during ioECoG (P = 0.028) (Figure. 1C). The rate of FRonS in the Ictal (+) group was higher during SWS (P = 0.011) and at 0.5 MAC (P = 0.001) and 1.5 MAC (P = 0.001), and exhibited a significant increase from SWS to 0.5 MAC (P = 0.018) (Figure. 1E).

1

3.5 MI $_{HFO\ (3\text{-}4\ Hz)}$

The data is summarized in Table 3.

The results showed that both the Ictal (+) group and Ictal (−) group had significant increases in MI $_{R\ (3–4\ Hz)}$ and MI $_{FR\ (3–4\ Hz)}$ during ioECoG at 1.5 MAC

sevoflurane. However, the Ictal (+) group had higher values of $MI_{R\ (3–4\ Hz)}$ and $MI_{FR\ (3–4\ Hz)}$ compared to the Ictal (–) group (P = 0.009 and P = 0.017 respectively) (Figure. 2A and B)

4. Discussion

The current study is the first to evaluate the dose-dependent effect of sevoflurane on multiple biomarkers of epileptogenicity in an MRI-normal hippocampus. Our results indicate that the MRI-normal epileptogenic hippocampus shows an increase in spikes, RonS, FRonS, and $MI_{HFO\ (3\text{-}4\ Hz)}$ with increasing sevoflurane concentration, while the non-epileptogenic hippocampus exhibits a paradoxical increase in R and FR.

The results of the study are consistent with previous literature demonstrating that increased sevoflurane concentrations result in increased spikes and R/FRonS in the epileptogenic areas, but not in the non-epileptogenic regions [16,23]. The study further shows that while lower concentrations of sevoflurane lead to an increase in R/FR in the epileptogenic hippocampus, higher concentrations caused a peak in R/FR in the non-epileptogenic hippocampus. The novel

finding reported herein could be attributed to semi-automated detection of HFO using the MNI detector. Among various automated detectors developed based on different energy functions, the MNI detector has demonstrated comparatively better performance than other automated detectors [24]. The MNI detector first identifies baseline segments and subsequently calculates the local energy threshold. Any segments with energy levels that exceed this threshold for more than 10 milliseconds are considered HFOs. However, channels with a substantial number of high-energy events, such as spikes and HFOs riding on spikes, exhibit significantly higher local energy thresholds and are prone to having lower HFO detection rates, since only segments that surpass the energy threshold are deemed to be HFOs [24]. As epileptic channels tend to have higher rates of spikes and HFO on spikes activity at 1.5 MAC, this consequently leads to lower rates of HFO detection in epileptic channels. In contrast, the non-epileptogenic channels exhibit lower rates of spikes and HFO on spikes, resulting in higher rate of HFOs. Automated detection of high-frequency oscillations is crucial to propel the clinical application of HFOs as visually marking HFOs is highly time-consuming [25]. Our findings not only provide a better understanding of the limitations and challenges associated with semi-automated HFO detection but also suggest a potential advantage of increasing sevoflurane concentration, as epileptic channels tend to show higher rate of spikes and HFOs on spike activity hence a lower rate of HFOs. It is also worth mentioning that the physiological FR generated by the hippocampus may impact the interpretation of pathological FR [9,26]. The use of FR as an indicator of hippocampal epileptogenicity has been subject to debate and may be less reliable than previously believed [26].

FR co-occurring with spikes is considered more pathological than either FR or spikes alone and exhibits similarities with spikes and HFOs with somatosensory potentials [27,28]. Previous research has established the usefulness of intraoperative FRonS under sevoflurane, but only in a sclerotic

hippocampus [16]. Our study reveals that augmentation of FRonS following the administration of sevoflurane in an MRI-normal hippocampus implies a heightened level of epileptogenicity. It is noteworthy that the same study also reported an increase in FRonS in non-epileptogenic areas in some patients under sevoflurane [16]; however, we did not observe such findings. This discrepancy may be due to the different concentrations of sevoflurane used in our study. Further, our study used ioECOG in the parahippocampal gyrus as an indicator of hippocampal epileptogenicity, as previously demonstrated in literature [29]. The electrophysiological changes in the parahippocampal gyrus are thus assumed to accurately reflect hippocampal activity.

Modulation Index

In the present study, the administration of sevoflurane resulted in augmentation of the MI $_{(HFO\ 3\text{-}4\ Hz)}$ in both the epileptogenic and non-epileptogenic hippocampus, with a greater increase observed in the former. MI quantifies the coupling between the phase of the 3-4 Hz slow wave and the amplitude of the HFO, which falls within the top 5% of the distribution site [21]. Previous research has established that the amplitude of HFO coincides with the 3-4 Hz slow wave in the epileptogenic regions [11,12,30]. However, when spikes are present, MI $_{(HFO\ 3\text{-}4\ Hz)}$ serves as an indirect measure of spike-and-wave discharges, given that each spike is accompanied by broad-spectrum high-frequency activity and a 3-4 Hz slow wave [31,32]. Therefore, the increase in MI $_{(HFO\ 3\text{-}4\ Hz)}$ in the epileptogenic hippocampus can be attributed to an increase in spike-and-wave discharges and FRonS. In the non-epileptogenic hippocampus, the increase in MI $_{(HFO\ 3\text{-}4\ Hz)}$ might have resulted from the spread of activity, including non-specific transients, at higher concentrations of sevoflurane [17]. Nonetheless, the augmentation of MI $_{(HFO\ 3\text{-}4\ Hz)}$ was more pronounced in the epileptogenic hippocampus.

The findings in our study align with previous research that found sevoflurane boosts MI $_{HFO\ (3\text{-}4\ Hz)}$ in epileptogenic areas, with each 0.2 increase in MI corresponding to a 2.44-fold increase in the likelihood of that region being classified as such [17]. However, the previous study's results were not limited to the hippocampus, and sevoflurane was dynamically increased from zero to 2.0 MAC. The same study also reported an increase in MI in non-epileptogenic regions at higher sevoflurane concentrations but did not compare the increase in MI between epileptogenic and non-epileptogenic sites [17].

Our results suggest that MI $_{(HFO\ (3\text{-}4\ Hz)}$ is likely to increase under sevoflurane at both sites where spikes propagate and sites where spikes are generated. However, the increase will be more significant at the sites where spikes are generated. This is supported by previous research, which shows that spike-generating sites have a higher amplitude of spike discharges compared to sites where spikes propagate [32,33], and regions with frequent and large spikes and slow waves have higher MI values compared to those with small and infrequent spikes [12,17]. Additionally, compared to spikes and HFO, the assessment of MI is more objective and less time-consuming [34] making it an ideal biomarker during ioECOG, as it has a better inter-rater agreement.

Our study suggests that the dose-dependent effects of sevoflurane on spikes, RonS, FRonS, and MI $_{HFO\ (3\text{-}4\ Hz)}$, during ioECOG may provide valuable information in identifying the MRI-normal hippocampus that requires resection and the hippocampus that can be preserved.

The findings in this study, along with prior studies [16,17], support the possibility of conducting a prospective study to explore if the augmentation of epileptogenic biomarkers under sevoflurane could predict postoperative seizure outcomes, potentially reducing the requirement for eoECOG assessment.

The limitations of our study include its retrospective design and small sample size due to the specific clinical factors (TLE/TPE with MRI normal hippocampus that underwent invasice EEG) which may limit the generalizability of our results. Some patients in the study did not achieve seizure freedom after surgery as they had TPE and multifocal epilepsy, making it difficult to determine the sole impact of hippocampal resection on seizure freedom. The effects of sevoflurane were only evaluated in the SOZ, not the entire EZ.. Additionally, our study highlights the need to determine an optimal sevoflurane concentration for intraoperative assessment due to observed inter-individual variability in epileptiform discharge activations during sevoflurane administration.

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Figure 1.

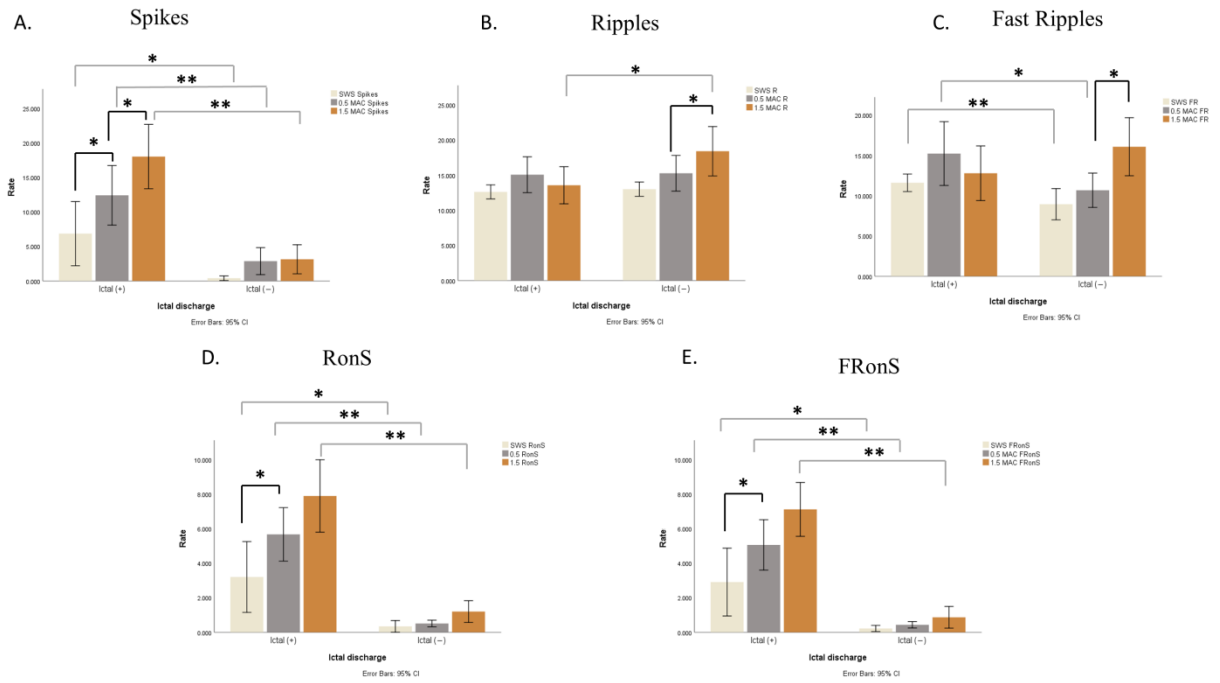
A.
Spikes
B.
Ripples
C.
Fast Ripples
D.
RonS
E.
FRonS
Rate
Ictal discharge
Ictal (+)
Ictal (−)
Error Bars: 95% CI
SWS Spikes
0.5 MAC Spikes
1.5 MAC Spikes
SWS R
0.5 MAC R
1.5 MAC R
SWS FR
0.5 MAC FR
1.5 MAC FR
SWS RonS
0.5 RonS
1.5 RonS
SWS FRonS
0.5 MAC FRonS
1.5 MAC FRonS

Figure 2.

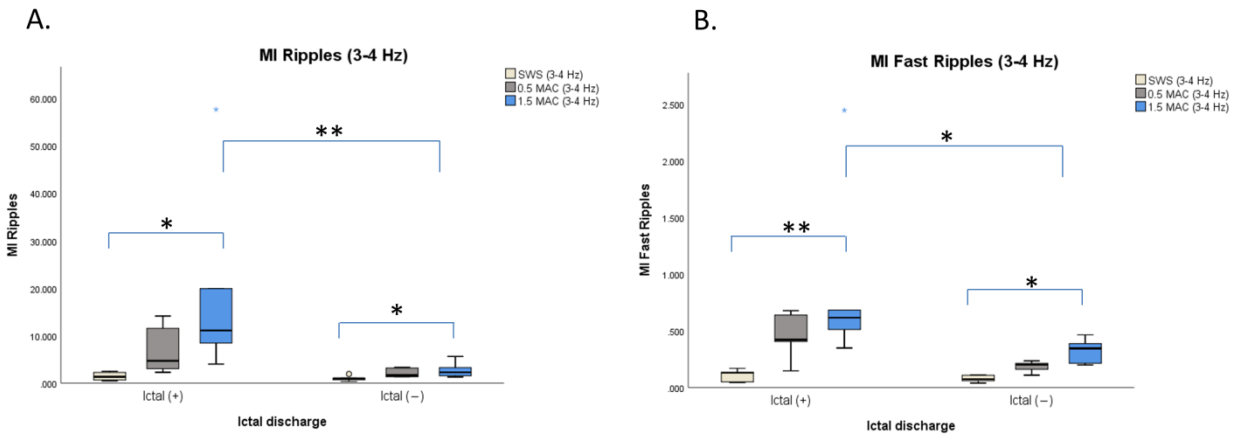
A.
MI Ripples (3-4 Hz)
SWS (3-4 Hz)
0.5 MAC (3-4 Hz)
1.5 MAC (3-4 Hz)
MI Ripples
60.000
50.000
40.000
30.000
20.000
10.000
.000
Ictal (+)
Ictal (−)
Ictal discharge
B.
MI Fast Ripples (3-4 Hz)
SWS (3-4 Hz)
0.5 MAC (3-4 Hz)
1.5 MAC (3-4 Hz)
MI Fast Ripples
2.500
2.000
1.500
1.000
.500
.000
Ictal (+)
Ictal (−)
Ictal discharge

Figure 3.

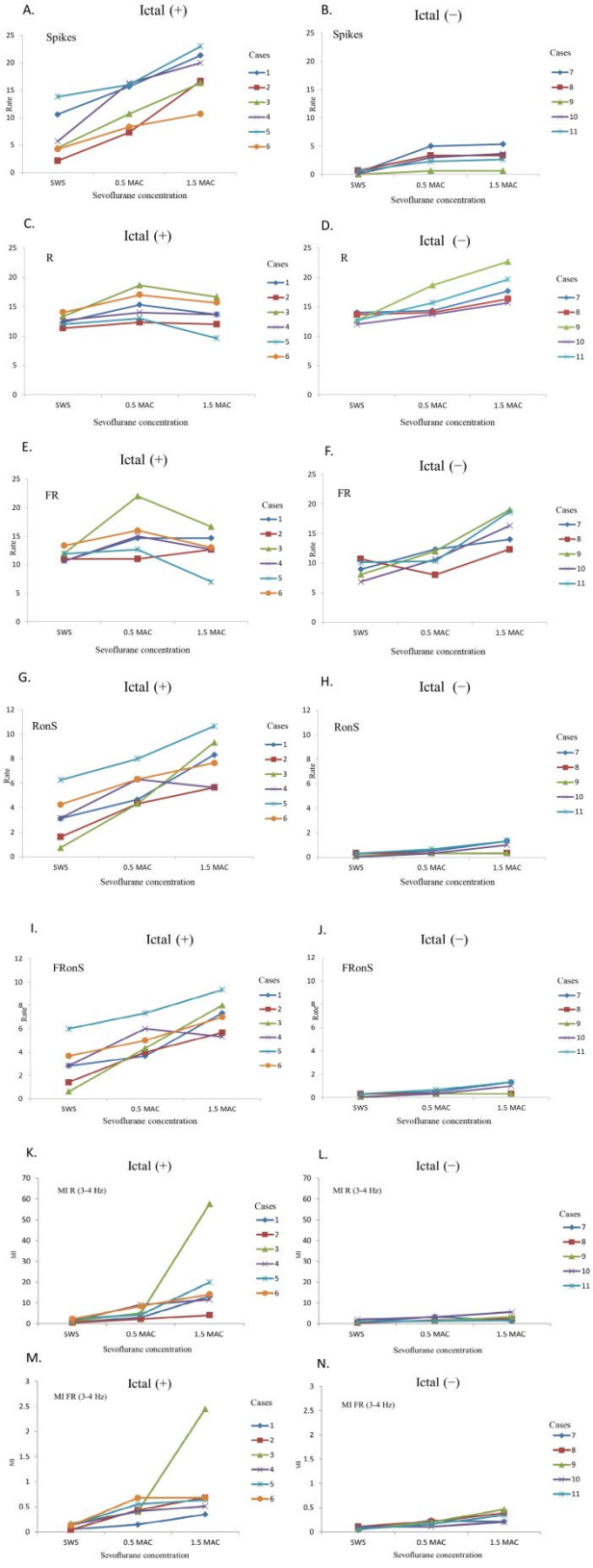
A.
Ictal (+)
Spikes
B.
Ictal (−)
Spikes
C.
Ictal (+)
R
D.
Ictal (−)
R
E.
Ictal (+)
FR
F.
Ictal (−)
FR
G.
Ictal (+)
RonS
H.
Ictal (−)
RonS
I.
Ictal (+)
FRonS
J.
Ictal (−)
FRonS
K.
Ictal (+)
MI R (3-4 Hz)
L.
Ictal (−)
MI R (3-4 Hz)
M.
Ictal (+)
MI FR (3-4 Hz)
N.
Ictal (−)
MI FR (3-4 Hz)
Rate
MI
Cases
SWS
0.5 MAC
1.5 MAC
Sevoflurane concentration

Figure legends:

Fig 1: (A) shows significant increases in the rate of spikes in the Ictal (+) group as compared to the Ictal (−) group, as demonstrated by the results of one-way repeated measures ANOVA and an independent t-test. (B) The rate of R was found to be higher in the Ictal (−) group at 1.5 MAC with a significant increased noted in the Ictal (−) group from 0.5 MAC to 1.5 MAC. (C) The rate of FRs was found to be higher in the Ictal (+) group during slow-wave sleep and at 0.5 MAC of sevoflurane with a significant increase from 0.5 MAC to 1.5 MAC observed in the Ictal (−) group. (D) and (E) The rate of RonS and FRonS were higher in the Ictal (+) group both during slow-wave sleep and at 0.5 and 1.5 MAC of sevoflurane.

*P < 0.05 **P < 0.01. OR (S), occurrence rate of spikes; OR (R), occurrence rate of ripples; OR (FR), occurrence rate of fast ripples; OR (R/FRonS), occurrence rate of ripples on spikes/fast ripples on spikes.

Fig 2: Each box shows the 25^{th} to 75^{th} percentiles with the whiskers showing the highest and lowest values. The thick line is at the median and the dots indicate outliers. A) MI $_{\text{Ripples (3–4 Hz)}}$ increased significantly at 1.5 MAC of sevoflurane in the Ictal (+) group. The Ictal (−) group also exhibits a significant increase in MI $_{\text{Ripples (3–4 Hz)}}$ at 1.5 MAC, but MI was higher in the Ictal (+) group. B) MI $_{\text{Fast Ripples (3–4 Hz)}}$ increased in both the Ictal (+) and Ictal (−) groups at 1.5 MAC of sevoflurane, but the value of MI was higher in the Ictal (+) group. (Friedman's test and Mann–Whitney U test). *P < 0.05 **P < 0.01. MI, modulation index.

Fig 3: : A, G, I, K and M) Each patient in the Ictal (+) group exhibits increase in the rate of spikes, RonS, FRonS and MI HFO (3-4 Hz). D and F) Each patient in the Ictal (−) group exhibits

an increase in rate of R and FR. The increase was statistically significant at a group level for spikes, RonS, FRonS and MI HFO (3-4 Hz) in the Ictal (+) group and for R and FR in the Ictal (-) group.

S, spikes; R, ripples; FR, fast ripples; FRonS, fast ripples on spikes; MI, modulation index; MAC, minimal alveolar concentration

Table 1: Patient characteristics

S.N	Age	Sex	MRI	Side	Past history	Diagnosis after eoECoG findings	IID pattern from the hippocampus	Hippocampal resection	Lateral temporal lobe pathology	Hippocampal pathology	Seizure freedom (ILAE)
1.	39	M	Lateral temporal contusion	R	Contusion	Lateral TLE	N/A	Not resected	Gliosis	N/A	4
2.	51	M	Negative	L	-	TPE (parietal + lateral temporal)	N/A	Not resected	FCD type IIa	N/A	4
3.	19	M	Negative	R	-	TPE (frontal + lateral temporal)	N/A	Not resected	Normal	N/A	1a
4.	13	F	Negative	R	Mental retardation	TPE (frontal + lateral and mesial temporal)	N/A	Resected	Normal	Normal	4
5.	23	F	Negative	L	-	TPE (frontal + lateral temporal)	N/A	Not resected	Normal	N/A	1a
6.	21	F	Negative	L	-	Lateral TLE+ Mesial TLE	SWC	Not resected	Normal	N/A	2
7.	44	M	Negative	R	Viral encephalitis	Multifocal including (lateral temporal+ mesial temporal)	SWC	Resected	Normal	Normal	4
8.	45	F	After removal of lateral temporal AVM	R	Unruptured AVM	TPE (parietal + lateral temporal + mesial temporal)	LVF	Resected	Gliosis	Normal	2
9.	40	F	Amygdala enlargement	R	-	Mesial TLE	SWC	Resected	Normal (amygdala:	MTS	1a

									normal)		
10.	27	M	Temporal pole encephalocele	L	-	Lateral TLE + Mesial TLE	LVF	Hippocampal transection	N/A	N/A	1
11.	28	F	Negative	R	-	Lateral TLE + Mesial TLE	LVF	Resected	Normal	MTS	1a

IID, initial ictal discharge; SWC, spike and wave complex; LVF, low voltage fast; FCD, focal cortical dysplasia; AVM, arteriovenous malformation; TPE, temporal plus epilepsy; TLE, temporal lobe epilepsy; eoECoG, extra-operative electrocorticography; MTS, mesial temporal sclerosis; MRI, magnetic resonance imaging; M, male; F, female; N/A, not available; R, right; L, left.

Table 2: The rate of spikes, ripples, fast ripples, ripples on spike, and fast ripples on spike during slow-wave sleep, 0.5 MAC and 1.5 MAC of sevoflurane in the Ictal (+) and Ictal (−) groups

Mean (standard deviation)	SWS	0.5 MAC	1.5 MAC	*P*
Ictal(+) n = 6				
Spikes	6.844 (4.424)	12.388 (4.106)	17.999 (4.437)	SWS–0.5 MAC: 0.014* 0.5 MAC–1.5 MAC: 0.008* SWS–1.5 MAC: 0.001*
Ripples	12.610 (0.952)	15.055 (2.435)	13.554 (2.518)	N/A
Fast Ripples	11.594 (1.035)	15.222 (3.777)	12.777 (3.229)	N/A
RonS	3.199 (1.953)	5.666 (1.475)	7.888 (1.996)	SWS–0.5 MAC: 0.002* 0.5 MAC–1.5 MAC: 0.124 SWS–1.5 MAC: 0.009*
FRonS	2.905 (1.870)	5.055 (1.389)	7.110 (1.485)	SWS–0.5 MAC: 0.018* 0.5 MAC–1.5 MAC: 0.076 SWS–1.5 MAC: 0.005*
Ictal(−) n = 5				
Spikes	0.366 (0.304)	2.866 (1.574)	3.132 (1.693)	N/A
Ripples	12.999 (0.816)	15.266 (2.046)	18.399 (2.832)	SWS–0.5 MAC: 0.295 0.5 MAC–1.5 MAC: 0.005* SWS–1.5 MAC: 0.050
Fast Ripples	8.936 (1.559)	10.666 (1.715)	16.066 (2.900)	SWS–0.5 MAC: 0.765 0.5 MAC–1.5 MAC: 0.028* SWS–1.5 MAC: 0.040*
RonS	0.339 (0.270)	0.506 (0.153)	1.199 (0.505)	N/A
FRonS	0.219 (0.142)	0.432 (0.148)	0.866 (0,505)	N/A

Mean (standard deviation)	Slow-wave sleep			0.5 MAC			1.5 MAC		
	Ictal(+)	Ictal(−)	*P*	Ictal(+)	Ictal(−)	*P*	Ictal(+)	Ictal(−)	*P*
Spikes	6.844	0.366	0.016*	12.388	2.866	0.001*	17.999	3.132 (1.193)	0.001*

	(4.424)	(0.034)		(4.106)	(1.574)		(4.437)		
R	12.610 (0.952)	12.999 (0.816)	0.491	15.055 (2.435)	15.266 (2.046)	0.881	13.554 (2.518)	18.339 (2.832)	0.015*
FR	11.594 (1.035)	8.936 (1.559)	0.008*	15.222 (3.775)	10.666 (1.715)	0.035*	12.777 (3.229)	16.066 (2.900)	0.112
RonS	3.199 (1.953)	0.339 (0.270)	0.011*	5.666 (1.475)	0.506 (0.153)	0.001*	7.888 (1.996)	1.199 (0.505)	0.001*
FRonS	2.905 (1.870)	0.219 (0.142)	0.011*	5.055 (1.389)	0.432 (0.148)	0.001 *	7.110 (1.485)	0.866 (0.505)	0.001*

MAC, minimal alveolar concentration; SWS, slow-wave sleep; RonS, ripples on spike; FRonS, fast ripples on spike; N/A, not applicable; *P < 0.05

Table 3: Modulation Index between the Ictal (+) and Ictal (−) groups during slow-wave, 0.5 MAC and 1.5 MAC of sevoflurane.

Median (IQR)	Slow-wave sleep			0.5 MAC			1.5 MAC		
	Ictal(+)	Ictal(−)	*P*	Ictal(+)	Ictal(−)	*P*	Ictal(+)	Ictal(−)	*P*
$MI_{R(3–4\ Hz)}$	1.322 (0.608–2.317)	0.983 (0.530–1.486)	0.429	4.686 (2.849–12.200	1.662 (1.331–3.256)	0.052	11.101 (7.329–29.353)	2.276 (1.431–4.444)	0.009*
$MI_{FR(3–4\ Hz)}$	0.130 (0.048–0.144)	0.074 (0.050–0.109)	0.247	0.422 (0.341–0.649)	0.202 (0.134–0.224)	0.052	0.617 (0.471–1.125)	0.345 (0.206–0.426)	0.017*

Median (IQR)	Slow-wave sleep	0.5 MAC	1.5 MAC	*P*
Ictal(+)				
$MI_{R\ (3–4\ Hz)}$	1.322 (0.608 –2.317)	4.686 (2.849–12.200)	11.101 (7.329–29.353)	SWS–0.5 MAC: 0.063 0.5 MAC–1.5 MAC: 1.000 SWS–1.5 MAC: 0.012*
$MI_{FR\ (3–4\ Hz)}$	0.130 (0.048–0.144)	0.422 (0.341–0.649)	0.617 (0.471–1.125)	SWS–0.5 MAC: 0.130

				0.5 MAC–1.5 MAC: 0.745 SWS–1.5 MAC: 0.004*
Ictal(−)				
$MI_{R\ (3–4\ Hz)}$	0.983 (0.530–1.486)	1.662 (1.331–3.256)	2.276 (1.431–4.444)	SWS–0.5 MAC: 0.063 0.5 MAC–1.5 MAC: 0.012* SWS–1.5 MAC: 1.000
$MI_{FR\ (3–4\ Hz)}$	0.074 (0.050–0.109)	0.202 (0.134–0.224)	0.345 (0.206–0.426)	SWS–0.5 MAC: 0.173 0.5 MAC–1.5 MAC: 1.000 SWS–1.5 MAC: 0.013*

MI, modulation index; R, ripple; FR, fast ripple; MAC, minimal alveolar concentration; *$P < 0.05$