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Simultaneous scalp EEG improves seizure lateralization during unilateral intracranial EEG evaluation in temporal lobe epilepsy

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ABSTRACT

Purpose: To determine if simultaneous bilateral scalp EEG (scEEG) can accurately detect a contralateral seizure onset in patients with unilateral intracranial EEG (IEEG) implantation.
Methods: We evaluated 39 seizures from 9 patients with bitemporal epilepsy who underwent simultaneous scEEG and IEEG (SSIEEG). To simulate conditions of unilateral IEEG implantation with a missed contralateral seizure onset, we analyzed the IEEG recording contralateral to the seizure onset (CL- IEEG), in conjunction with simultaneous scEEG. The following criteria were evaluated between scEEG and CL- IEEG (1) latency: the time to onset of EEG seizure (2) location: concordance of ictal onset zones and (3) pattern: congruence of EEG morphology and frequency.
Results: SSIEEG correctly lateralized 36/39 (92.3%) seizures compared to 13/39 (33.3%) seizures using CL-IEEG alone (OR = 24.0, $p < 0.01$), 33 (84.6%) seizures using scEEG alone (OR = 2.2, $p = 0.29$) and 26 (66.9%) seizures using time of clinical onset alone (OR = 6.0, $p = 0.01$). For the three criteria evaluated, (1) 22/39 (56.4%) seizures had an earlier onset on the scEEG, compared to CL- IEEG; (2) lack of congruence of location of seizure onset was noted in 33/39 (84.6%) of the seizures; and (3) 22/39 (56.4%) seizures did not have a congruent ictal pattern.
Conclusions: The chronological, topographic and morphologic features of SSIEEG can accurately detect the hemisphere of seizure onset in most cases with unilateral IEEG implantation. SSIEEG is significantly better than, IEEG, scEEG or clinical onset alone in this scenario. We propose that SSIEEG should be considered in all cases of intractable focal epilepsy undergoing unilateral IEEG evaluation.

1. Introduction

Intracranial EEG (IEEG) studies are performed in patients with intractable focal epilepsy when noninvasive studies do not provide adequate information for resective epilepsy surgery. The complication risk with IEEG implantation, albeit small, increases proportional to the number of electrodes implanted, with a hemorrhage rate of 0.2% per electrode, which is one reason to limit the number of implanted electrodes [1].

IEEG can occasionally lead to false localization and even false lateralization of seizure onset zone [2,3]. In a study analyzing ictal onset in simultaneous depth and subdural electrodes in 21 patients, unclear localization was noted on subdural electrodes in 3 patients, while the onset of one seizure was falsely lateralized to the opposite temporal lobe in one patient [4]. Several reports also detail false lateralization of ictal onset by scalp EEG (scEEG) recordings [5,6]. In another study involving 105 patients with temporal lobe epilepsy, 4.7% of seizures were falsely noted in the scEEG to originate in the opposite hemisphere [7].

However, scEEG recorded simultaneously during IEEG evaluation

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can provide valuable additional data, including predicting surgical outcome, spike detection, measurement of brain impedance, and localization of seizure onset zone [8–15]. Even though electrical potentials decrease with distance and vary with conduction rates of different tissues as proposed by Gauss' law, we believe that the clinical analysis of the correlations between the scEEG and IEEG recorded simultaneously can provide additional critical information not provided by reviewing IEEG and scEEG recorded separately.

Recently, we studied 35 seizures in 13 patients with simultaneously recorded scEEG and IEEG and proposed three features based on latency, EEG pattern and location of seizure onset that are associated with detection of the seizure onset zone [16]. We found that concordance of the aforementioned three features in scEEG and intracranial EEG is associated with better outcome after epilepsy surgery. This information would also be useful in cases where the placement of contralateral IEEG electrodes is not desired to minimize complications and because of overwhelming evidence suggesting unilateral seizure onset [17–19]. Here, we attempt to analyze if simultaneously recorded bilateral scEEG and unilateral IEEG can accurately lateralize seizures from the hemisphere without IEEG electrodes in patients with bitemporal epilepsy.

2. Material and methods

2.1. Participants

We analyzed the records of all patients who underwent IEEG implantation with simultaneous scEEG monitoring at the University of Pittsburgh Medical Center from 2012 to 2015. A maximum of five seizures were selected for evaluation from each hemisphere in each of the included patients. Patients with IEEG coverage limited to only one electrode in each hippocampus were excluded.

scEEG- scalp EEG, IEEG- intracranial EEG, CL-IEEG- contralateral intracranial EEG, SSIEEG- simultaneous scalp and intracranial EEG

Seizures types were excluded from analysis that occurred: intraoperatively, prior to placing scalp electrodes, without changes on scEEG, or without clinical signs. Seizures that remained confined to one hemisphere but had scalp manifestations were not excluded. The implantation schema was determined during a multidisciplinary epilepsy patient management conference, after reviewing the results of an inpatient scalp video EEG evaluation, imaging with MRI/ CT and in some cases, MEG, PET and ictal SPECT. IEEG electrodes available commercially (Ad-Tech, Inc. Racine, WI) with 6–12 contacts (1.3 mm diameter; 8.88 mm2 surface area) were used. A 128-channel Xltech digital video-EEG system (Natus Medical Inc., Pleasanton, CA) was used to record EEG at a sampling rate of 1000–2000 Hz. This was not an invasive study according to the SEEG methodology but used bilateral depth electrodes placed stereotactically in most cases, in addition to subdural grid electrodes. We followed an institutional scheme with lower number of electrodes to evaluate the temporal lobes, but extra electrodes were placed in the temporal lobe of presumed seizure onset. Patients who had a non lesional MRI and complex cases where the imaging and scalp video EEG did not suggest a congruent seizure focus had denser coverage with intracranial EEG electrodes (See supplementary Fig. 1 for characteristic schemes). The scalp EEG coverage corresponded to the 10–20 system. We used 21 electrodes except in cases where a scalp electrode had to be moved or eliminated due to placement of intracranial electrodes.

2.2. Study design

When unilateral IEEG recordings are done in patients on the side contralateral to seizure onset, false lateralization of seizures could occur. Previous studies have not examined whether simultaneous scEEG could help prevent false lateralization in this scenario. While ethical concerns would prevent such a study being ever performed, we recreated such a situation in patients undergoing bilateral IEEG evaluation by considering only the IEEG contralateral to true seizure onset. Data from IEEG electrodes contralateral to the seizure onset (CL-IEEG) and the time of onset clinical manifestations during seizures were analyzed and compared with data from bilateral scEEG alone and contralateral IEEG along with bilateral scEEG (CL- IEEG + scEEG) (Fig. 1). For example, a left temporal seizure was analyzed using IEEG recording in the right hemisphere and bilateral scEEG, to determine whether the left sided onset could be correctly determined. In this scenario (CL-IEEG + scEEG), the time of onset of clinical manifestations during seizures was also compared with the EEG onset in the CL-IEEG to see if the clinical onset was prior to, or after the intracranial EEG onset. Clinical onset of a seizure prior to, or at the same time as the intracranial onset in CL-IEEG with scEEG would mean that the seizures started in the hemisphere without intracranial electrodes, if adequate sampling in the hemisphere with IEEG electrodes is assumed, but clinical onset after intracranial onset would not have any lateralizing value.

The following three previously published criteria were determined for each seizure [16]. These three criteria, if satisfied, indicated that the seizure onset is not in the hemisphere with the intracranial electrodes.

2.3. Latency criterion

The latency criterion was deemed to be satisfied if the seizure onset in scEEG was earlier or at the same time as IEEG. The seizure onset time on the scEEG was subtracted from the seizure onset time on IEEG to calculate the latency. We hypothesized that in a patient with unilateral IEEG correctly placed in the seizure onset zone, the onset of seizure on the IEEG should be earlier than the onset recorded on scEEG. If the seizure onset in IEEG is at the same time of later than the scEEG, the IEEG electrode is possibly not in the seizure onset zone.

2.4. Location criterion

The location criterion was considered to be satisfied if the location of seizure onset or the first 3 s of spread on scEEG does not correlate with the location of seizure onset in the IEEG. The criterion was assessed in the first 3 s because surgical outcome seems to be most correlated with the activity in this time period [20].On the other hand, if the location of seizure onset on the scEEG could be explained by the onset noted in the IEEG electrode, the location was assumed to be congruent and the location criterion was not deemed to be satisfied. For example, if a seizure originated in the T7 scEEG electrode, an intracranial electrode onset in the left middle temporal gyrus or insula would be considered congruent. Absence of anatomical congruence between scEEG and IEEG indicated seizure onset in a location away from the IEEG electrode.

2.5. Pattern criterion

The pattern criterion was satisfied if EEG pattern at seizure onset or first 3 s of a seizure on scEEG is not congruent with the pattern in the CL- IEEG (supplementary table-1). The low voltage fast activity, repetitive spikes and other patterns analyzed were suggestive of ictal onset [21]. The lack of concordance of EEG patterns in scEEG and IEEG was deemed to indicate onset of seizure in a location outside the area covered by IEEG. A low amplitude fast activity or background suppression in the IEEG may not be seen on the scEEG or may present with similar scEEG patterns. Similarly, repetitive spikes or rhythmic slowing in IEEG during ictus may produce identical patterns in the scEEG or may not cause any change at all, especially if the seizures are limited to the hippocampus or other mesial/ basal regions.

As stated previously, we analyzed CL- IEEG + scEEG and compared it with CL- IEEG alone and scEEG alone. For example, in a patient with left temporal seizures, the three criteria would be evaluated assuming that there were no left hemispheric IEEG electrodes and that only right

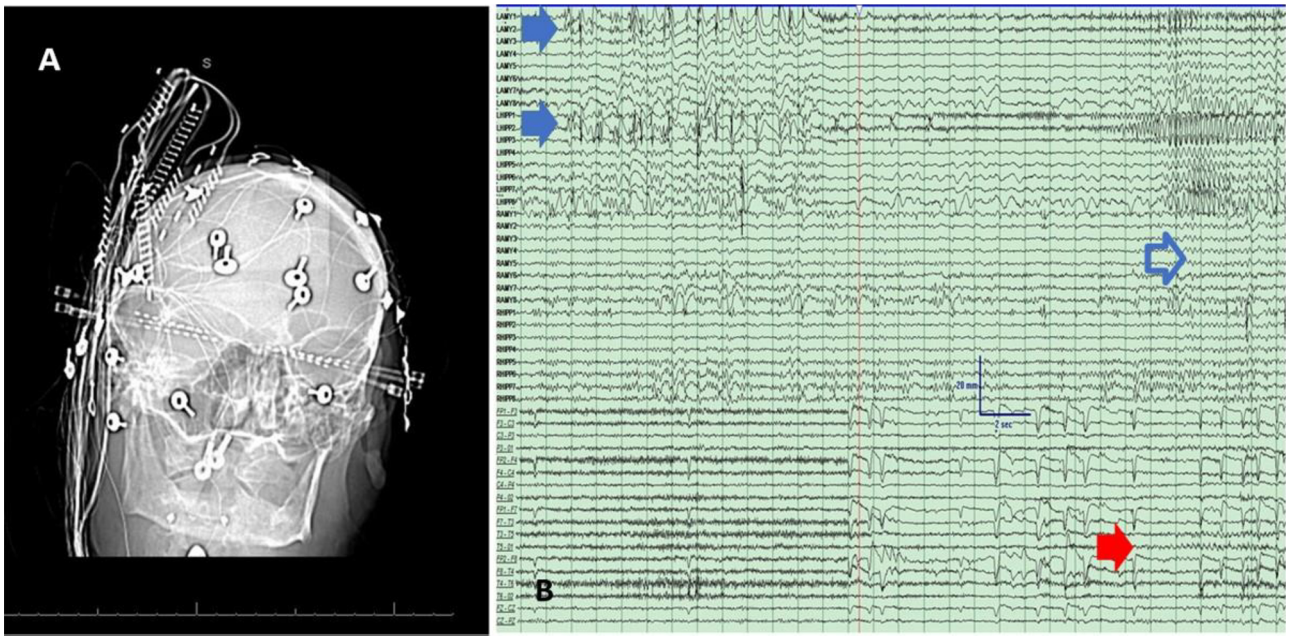

Fig. 1. (A) X-ray AP image showing bitemporal stereo EEG implantation (6 electrodes) and simultaneous scalp EEG electrodes. (B) Simultaneous scalp and stereo EEG recording showing a seizure with onset in the mesial contacts of the left hippocampus (LHIPP2) and left amygdala (LAMY 1, 2) (closed blue arrows) followed by scalp EEG changes 22 s later (T3/T5) (closed red arrow) before spreading to the right hemisphere (RAMY 1–4) (open blue arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

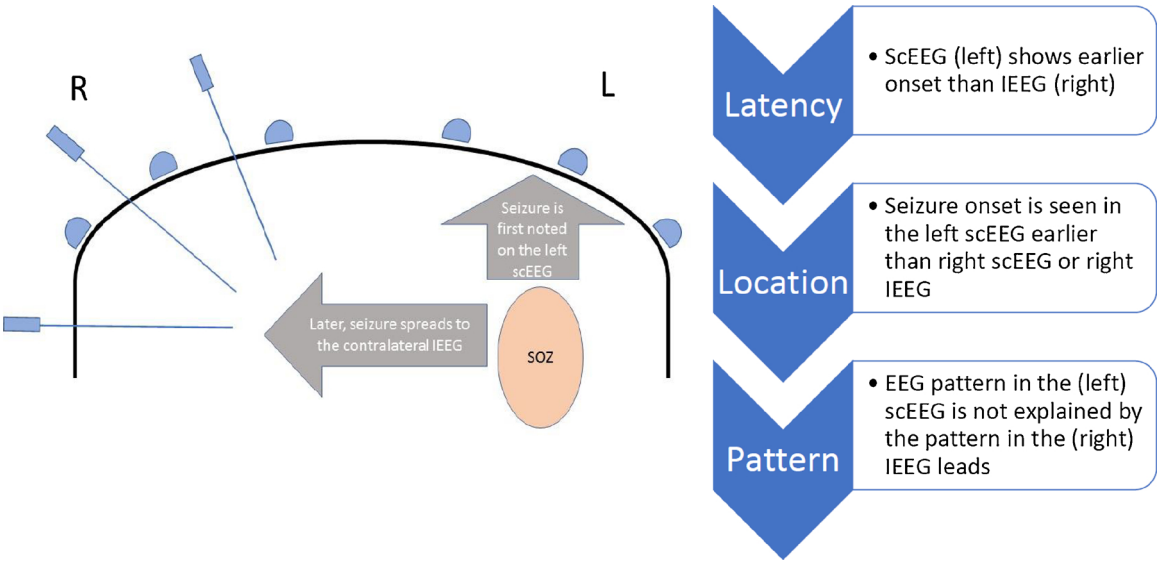

Fig. 2. Evaluation of the three criteria in a hypothetical patient with left temporal seizures who had right IEEG and bilateral scalp electrodes placed (see text for explanation). Sc EEG- scalp EEG, IEEG- intracranial EEG, SOZ-Seizure onset zone.

hemispheric IEEG electrodes (CL- IEEG in this case) and scEEG were present. We hypothesized that in this hypothetical patient with left temporal seizures, the location criterion comparing bilateral scEEG and right hemispheric IEEG, would indicate incongruous locations of seizure onset, since the earliest EEG changes suggesting seizures would be noted in the left hemispheric scEEG electrodes and later in the right hemispheric IEEG. We also hypothesized that in this scenario, the latency criteria would suggest seizure onset in the left hemisphere without IEEG electrodes, since the seizure would be noted earlier on scEEG and not on the IEEG electrodes. In the same patient, the pattern criterion would indicate absence of concordance, because in most cases the EEG pattern of the left temporal seizure recorded in the scEEG would not be explained by the EEG pattern in the right hemispheric IEEG leads at the same time (Fig. 2).

2.6. Statistical analysis

All statistical analyzes were conducted in SAS v9.4. Descriptive analyses included computing means, standard deviations, and percentages of seizure characteristics. To formally compare rates of correct lateralization among CL- IEEG alone, scEEG alone,CL- IEEG + scEEG, clinical onset, and combined CL- IEEG + scEEG and clinical onset while accounting for potential correlation from seizures within the same patient and the paired nature of the data where the localization of each seizure was evaluated in three ways, we used maximum pseudo-likelihood to fit a mixed-effects logistic regression model with a fixed effect for evaluation approach (CL- IEEG alone, bilateral scEEG alone, CL- IEEG + bilateral scEEG, clinical onset alone, CL- IEEG + bilateral scEEG + clinical onset), a random patient effect, and a random effect

Table 1
Demographics, clinical, imaging, electrophysiological features, stereo EEG implantation schema and surgical outcome of patients with bitemporal epilepsy and simultaneous scalp and intracranial EEG after detailed presurgical evaluation including scalp video EEG monitoring.

Gender	Age	Age of onset (years)	Epilepsy Duration (years)	Risk factors* (number)	seizure frequency prior to surgery (qD)	Number of medications tried	MRI	Ictal SPECT	PET	MEG	Number of depth electrodes in each hemisphere	Duration of intracranial evaluation (days)	Number of seizures analyzed evaluated for the study	Final localization of seizure focus	Surgery Type
M	53	7	46	2	1	14	left HS	ND	ND	left temp	3 right, 3 left	8	5	left H	left temp lobectomy
F	22	4	18	0	28	5	normal	right parietal	normal	ND	5 right, 7 left**	14	2	left posterior STG and MTG	consider RNS/VNS
F	30	2	28	1	5	10	normal	left temp	right temp	ND	5 right, 5 left	7	2	left H	suggested RNS
F	39	11	28	2	1	9	bilateral HS	ND	ND	ND	2 right. 2 left	8	5	left H	patient refused surgery
F	29	24	5	2	1	5	right HS	left temp	right temp	ND	3 right, 2 left	15	5	right H	right ATL
F	44	33	11	2	2	10	normal	ND	ND	left temp	3 right, 3 left	8	5	left and right H	VNS
F	51	32	19	3	2	3	bilateral HS	left temp	left temp	bilateral temp	2 right, 2 left	8	6	left and right H	suggested RNS/VNS
F	46	12	34	2	2.5	7	bilateral heterotopia	ND	normal	right temp-parietal	4 right, 3 left	6	5	right PVH, left H, left posterior MTG	RNS
M	21	1	20	1	0.25	6	bilateral HS	right temp	ND	bilateral temp	4 right, 4 left	7	4	right amygdala	laser ablation

M-male, F-female, HS-hippocampal sclerosis, temp- temporal, ND-not done, NA-follow up not available, PVH- periventricular heterotopia, H- Hippocampus, STG- superior temporal gyrus, MTG- middle temporal gyrus, ATL- anterior temporal lobectomy.

* Risk factors analyzed include family history of seizures, perinatal complications, developmental delay, febrile seizures, illicit drug use, head trauma, meningitis/encephalitis, brain surgery.

** in addition to 3 right subdural strips and 2 left subdural strips.

for seizure within patient. We report estimated odds ratios and two-sized Wald p-values to compare and test the rates of correct lateralization among the three approaches.

2.7. Approval of protocol

The Institutional Review Board at the University of Pittsburgh approved the study.

3. Results

A total of 39 seizures in 9 patients with SSIEEG and IEEG recordings were analyzed. The demographic, clinical, imaging and electrophysiological features in addition to IEEG implantation schema and duration of intracranial evaluation are detailed in Table 1. Neuroimaging was positive in 7 (77.8%) patients. MRI lesions were noted in 6 (66.6%) patients and focal PET hypometabolism was observed in 3 out of 5 (60%) patients who underwent PET imaging.

Of the 39 seizures, 10 (25.6%) originated from the right temporal region and 29 (74.3%) from the left temporal region. Contralateral spread was seen in 1/10 (10%) right temporal seizures and 25/29 (86.2%) left temporal seizures. The mean latency for detection on contralateral IEEG was 11.4 s (SD = 18.7) for seizures with right temporal onset, and 7.0 s (SD = 7.7) for seizures with left temporal onset. The mean latency from intracranial detection to scEEG electrodes was 11.4 s (SD = 9.5).

At least one of the three criteria correctly identified the side of ictal onset in 36/39 (92.3%) of the seizures. Lateralization was aided by latency criteria in 22 seizures (56.4%), location criteria in 33 seizures (84.6%), and pattern criteria in 22 seizures (56.4%). Of the 36 seizures thus lateralized, seizures in which one, two or all three criteria indicated the hemisphere of seizure onset were 9,13 and 14 respectively.

Out of the 6 seizures where the location criteria did not correctly detect the side of seizure onset, two had earlier and prominent scEEG manifestations contralateral to the intracranial seizure onset and four seizures had diffuse scEEG manifestations without clear lateralizing features.

Out of the 39 seizures studied, 33 had mesial temporal onset and 6 originated in the neocortical temporal area. Using contralateral intracranial EEG and simultaneous scalp EEG, the hemisphere of seizure onset could not be accurately detected in 3/33 (9.1%) of the mesial temporal seizures, but none of the 6 seizures with a neocortical onset were falsely lateralized.

When the data from CL- IEEG alone was considered, 13/39 (33.3%) seizures could be lateralized, which was significantly lower compared to the 36/39 seizures (92.3%) lateralized when considering scEEG and CL- IEEG (OR = 24.0, $p < 0.01$). This is because CL- IEEG electrodes were not involved during 13 clinical seizures indicating that the seizure onset was not in the hemisphere with the recording electrodes. In comparison, 33/39 seizures (84.6%), could be lateralized using scEEG alone, which was significantly better than those that could be lateralized by CL- IEEG alone (OR = 11.0, $p < 0.01$), but not significantly different from scEEG and CL- IEEG (OR = 0.5, $p = 0.29$) (Table 2).

The mean time of clinical onset of seizures after intracranial onset was 12.7 s (SD = 16.5). Analyzing the three EEG criteria in combination with the time of onset of clinical manifestations during seizures correctly lateralized 37/39 (94.9%) seizures. This provided significantly better lateralization compared to analysis based on clinical onset alone which correctly lateralized 26/39 (66.7%) seizures (OR = 6.0, $p = 0.01$), but was not significantly different from analysis of EEG criteria alone which correctly lateralized 36/39 (92.3%) seizures (OR = 1.5, $p = 0.65$).

4. Discussion

In this study, chronological, topographic and morphological characteristics of ictal EEG in SSIEEG were reviewed in an attempt to validate the value of adding scEEG in patients with intractable bitemporal epilepsy undergoing unilateral invasive evaluation. We showed that adding simultaneous scEEG helped predict contralateral onset in 92.3% of the seizures in the hypothetical scenario when IEEG was placed only contralateral to the seizure onset zone, compared to 33.3% with IEEG alone. While the correlations of location, pattern and latency at seizure onset in simultaneously recorded scEEG and intracranial EEG has been studied previously, our study differs in that we took advantage of the bitemporal IEEG recording in addition to concurrently recorded scEEG to lateralize seizures.

4.1. Location criterion

We found that the location criterion was most sensitive in determining the hemisphere of seizure onset. Initial spread to the ipsilateral surface EEG from IEEG prior to contralateral spread was also noted in most seizures by Lieb et al [9]. Similarly, Hashiguchi et al reported that the scEEG corresponded with intracranial location in a small study on eight patients who underwent EEG evaluation using scEEG and subdural strips [22]. Two seizures in our study, both in a patient with bilateral periventricular heterotopia, showed initial prominent surface EEG accompaniments on the contralateral hemisphere. This pathology is occasionally marked by non-localizing EEG findings with significantly large amplitude and widespread field interictal discharges, that often appear bilateral and synchronous, and thus representing a disadvantage and more of a challenge for the scEEG criteria [23,24].

Diffuse or bilateral EEG changes in the scEEG were noted at seizure onset in 4 seizures (10.2%) in our study, which is similar to a study which showed that seizure onset was characterized by generalized rhythmic waves in 11 out of 97 seizures (11.3%) on scEEG recorded simultaneously with IEEG [25]. Diffuse scEEG changes at ictal onset were noted in 63% of patients with poor surgical outcome in cohort of 44 patients who were studied with depth electrodes and limited scEEG montage with orthopedic scEEG nails [8]. In another study involving 236 seizures from 34 patients who underwent simultaneous scEEG and intracranial EEG, 16.9% of the seizures showed concurrent, bilateral, scEEG reflections [9]. Several studies have detailed cases of false lateralization of seizure onset by scEEG, and even subdural electrodes, but we found that it is rare when it is recorded and reviewed simultaneously with IEEG in at least one cerebral hemisphere [5,6,26–28]. In a study by Pacia et al, 8.3% of the patients with temporal lobe epilepsy were found to have seizures with contralateral spread, simultaneously or earlier than the involvement of ipsilateral temporal neocortex, with attenuation or diffuse slowing noted on simultaneous scEEG [11].

4.2. Pattern and latency criteria

Both the pattern and latency criteria lateralized seizure onset in 56.4% of seizures. The pattern criteria was partially based on the detailed description of scEEG correlate of intracranial activity by Pacia et al [11]. We also utilized assorted findings from several studies to assess congruence of EEG patterns recorded simultaneously in scEEG and intracranial EEG [21,22,25,29]. In formulating the analysis criteria, we took into consideration the fact that seizures limited to hippocampus or deeper regions of the brain may not have a correlate on scEEG. ScEEG may not reflect perturbations in the intracranial rhythm at seizure onset well, and rather characterize the evolution, propagation and synchrony, especially in temporal lobe seizures; so, we included the first few seconds of onset of the seizures in the analysis [11]. We specifically chose to analyze the first 3 s of a seizure because better surgical outcome has been reported with resection of the area involved in this short epoch in neocortical temporal seizures [20]. We decided to use the same duration of 3 s of in our mixed cohort of mesial and neocortical temporal cases since no other criterion was available specifically

Table 2
Number of seizures selected and evaluation of criteria.

Seizure	Patient	Hemisphere of seizure onset (BL SEEG)	Hemisphere of seizure onset (CL-IEEG)	Hemisphere of seizure onset (scEEG)	scEEG + CL-IEEG						
					Latency 1* (seconds) SOZ to CL-IEEG	Latency 2** (seconds) SOZ to scEEG	Latency 3*** (seconds) CL-IEEG to scEEG	Latency criteria	Location criteria	Pattern criteria	Hemisphere of seizure onset (scEEG + CL-IEEG)
1	1	left	right	left	22	24	2		x		left
2		left	right	left	24	23	−1	x	x	x	left
3		left	right	left	18	21	3		x	x	left
4		left	right	left	16	19	3		x	x	left
5		left	right	left	15	17	2		x	x	left
6	2	Left^^	right	left	3	−15****	−18	x	x	x	left
7		Left^^	right	left	8	1	−7	x	x	x	left
8	3	left	right	left	2	7	5		x	x	left
9		left	right	left	19	20	1		x	x	left
10	4	left	right	left	1	4	3		x	x	left
11		left	right	right^	2	6	4				right^
12		left	right	left	1	1	0	x	x		left
13		left	right	left	9	7	−2	x	x		left
14		left	right	right ^	6	16	10				right ^
15	5	right	N/A	right	N/A	17	17	x	x	x	right
16		right	N/A	right	N/A	16	16	x	x	x	right
17		right	N/A	right	N/A	12	12	x	x	x	right
18		right	N/A	right	N/A	5	5	x	x	x	right
19		right	N/A	right	N/A	4	4	x	x	x	right
20	6	left	right	left	1	6	5		x		left
21		left	right	left	1	8	7		x		left
22		left	right	left	8	2	−6	x	x	x	left
23		left	right	left	6	14	8		x	x	left
24		left	right	left	4	10	6		x	x	left
25	7	left	N/A	left	N/A	19	19	x	x	x	left
26		left	N/A	left	N/A	4	4	x	x	x	left
27		left	NA	left	NA	1	1	x	x	x	left
28		left	N/A	left	N/A	16	16	x	x	x	left
29		left	right	left	38	15	−13	x	x		left
30		right	left	right	90	40	−50	x	x	x	right
31	8	left	right	bilateral ^	0	10	10				unknown ^
32		Left^^	right	left	1	11	10		x		left
33		Left^^	right	bilateral^	0	0	0	x			unknown
34		Left^^	right	left	1	9	8		x		left
35		Left^^	right	left	1	9	8		x		left
36	9	right	N/A	right	N/A	5	5	x	x		right
37		right	N/A	right	N/A	16	16	x	x		right
38		right	N/A	bilateral ^	N/A	24	24	x			unknown
39		right	N/A	bilateral^	N/A	21	21	x			unknown

^: Hemisphere of seizure onset not detected accurately.
^^: neocortical temporal seizure onset.
N/A: not applicable because the seizure did not spread to CL-IEEG.
SOZ: seizure onset zone.
CL-IEEG: contralateral SEEG (contralateral to the hemisphere of seizure onset).
BLSEEG: bilateral SEEG.
scEEG: scalp EEG.
* Latency 1: Time to spread from the SOZ to the CL-IEEG.
** Latency 2: Time to spread from the SOZ to scEEG.
*** Latency 3: Time delay between detection of seizure in the CL-IEEG until seizure detection in the SCALP.
**** Seizure appeared on scEEG prior to BLSEEG, possibly due to seizure onset in a location away from the area of intracranial electrode implantation.

for mesial temporal seizures. Lieb et al noted worse post-surgical outcome in patents with an interhemispheric propagation time of less than 5 seconds [30]. Similarly better surgical outcomes have been reported in patients with longer interhemispheric propagation time in several studies [31,32].

4.3. Superiority of SSIEEG

Unilateral IEEG electrodes without simultaneous scEEG recording could lateralize seizure onset only in 33.3% (13/39) seizures. IEEG data alone could suggest the hemisphere of seizure onset in these 13 seizures in our study because they did not spread to involve these electrodes during clinical seizures. The absence of EEG changes in unilateral IEEG electrodes during clinical seizures would mean that the EEG seizures occurred in the opposite hemisphere, provided all possible seizure onset zones in the hemisphere with IEEG were adequately sampled. However, scEEG alone could lateralize 84.6% of the seizures, missing the hemisphere of onset in 6 seizures due to bilateral or diffuse EEG activity at seizure onset. The latency criterion was satisfied in three of these six seizures, increasing the ability of simultaneous scEEG with unilateral EEG to lateralize seizure onset to 92.3%. This slight improvement, though not statistically significant, suggested that analysis of simultaneous scEEG with unilateral IEEG can provide more information than scEEG or unilateral IEEG alone.

4.4. Safety of SSIEEG

Many epilepsy centers avoid placing scalp electrodes simultaneous with intracranial EEG citing increased risk of infection. In our study we did not have any case of infections with placement of 21 electrodes and found it to be generally safe. Studies by Yamazaki et al utilizing 256 channel array scalp EEG with intracranial EEG, reported improved localization of interictal epileptiform discharges compared to regular EEG and MEG without escalation in complication rates [33,34]. The additional resources needed to place, safely maintain, record and store dense array EEG prevented us from using it.

4.5. Limitations

Our study had several shortcomings. The effect of seizure medications and slight variation in the positions of scEEG electrodes were not taken into consideration. The examined criteria did not differentiate contralateral seizures in 3 out of 39 seizures. In addition, specificity and predictive values could not be analyzed because we exclusively studied if the hemisphere of seizure onset could be determined without considering intracranial electrodes in the hemisphere of seizure onset and did not analyze any cases where the IEEG data contralateral to the seizure onset zone was disregarded. Short electrographic seizures without a correlate on scEEG that remain confined to the hemisphere of onset may be missed, but these seizures were not common in our study. One reason may be that patients undergoing IEEG implantation are screened by a scalp video EEG evaluation first and seizures without behavioral manifestations are less likely to spread to the surface [9]. Also, electrographic seizures and patients with exclusive seizures without surface accompaniments were excluded.Thirteen seizures in our study remained confined to one hemisphere, but had changes on scalp EEG in the same hemisphere. The exact reason for contralateral spread in more seizures with left temporal onset compared to the right temporal seizures is unclear, but there is evidence of left temporal epilepsy causing more connectivity changes than right temporal epilepsy [35,36]. It could be proposed that because of intact right temporal lobe in left temporal epilepsy (compared to vice versa), there is a higher chance of left temporal spreading to right. These criteria can falsely suggest seizure onset contralateral to the IEEG implantation even if the ictal onset zone is ipsilateral, but away from the IEEG implantation sites. Seizures with onset in areas not adequately sampled by the IEEG electrodes could produce changes in the scalp EEG leading to false conclusions. Therefore, it is important to make sure that IEEG electrodes cover the most plausible epileptogenic zones when these criteria are utilized. If the initial intracranial implant suggests false lateralization and localization, a second intracranial study is recommended in most centers. Our study does not provide evidence that simultaneous scalp EEG would provide any additional localization value or contribute to the hypothesis for the second IEEG implantation, but it is possible that the lateralization provided by simultaneous scalp EEG in such cases might help plan the second implant in the correct hemisphere. We found that none of the seizures of neocortical onset were falsely lateralized compared to 9.1% of mesial temporal seizures, but it is unclear if this is due to the low number (n = 6) of neocortical seizures sampled in our study or if the rate of false lateralization is genuinely higher in mesial temporal seizures.

Our study creates a hypothetical scenario where IEEG was done only on the wrong side. By and large, implantations are accurately placed in the ipsilateral side, and when in doubt placed bilaterally. However, sometimes a contralateral seizure may be recorded in patients with unilateral IEEG implantation, for example in bitemporal epilepsy. In a retrospective analysis of data in 82 patients implanted with RNS in the bilateral mesial temporal regions and followed for an average of 4.7 years, King-Stephens et al found that 63.6% of the 11 patients who were presumed to have unilateral seizure onset, later were found to have independent bitemporal seizures [37]. In our series, we found that 15.4% and 66.7% of seizures were falsely lateralized by surface EEG alone and contralateral IEEG alone respectively while simultaneous scEEG and IEEG decreased the false lateralization rate to 7.7%.

5. Conclusion

Simultaneous scEEG in patients with unilateral IEEG implantation can reliably detect contralateral seizure onset in most cases. Absence of congruence of ictal onset location in simultaneous scEEG was a more sensitive feature in detecting the hemisphere of seizure onset than pattern or latency-based criteria. Simultaneous scEEG, when added to unilateral IEEG, provided better lateralization than the time of onset of clinical manifestations during seizures. Adding scEEG is a low cost and effective way of increasing the sensitivity and reducing error while performing unilateral IEEG recordings. We anticipate that the findings in this case series would be confirmed by larger studies assessing the utility of simultaneous scEEG in all patients with intractable epilepsy undergoing unilateral IEEG evaluation, avoiding false lateralization in most cases, alleviating the need for extra IEEG electrodes, and thus mitigating complications.

Conflicts of interest

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

Ethical publication statement

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.

Declarations of interest

None

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2018.11.015.

References

[1] Gonzalez-Martinez J, Bulacio J, Alexopoulos A, Jehi L, Bingaman W, Najm I. Stereoelectroencephalography in the "difficult to localize" refractory focal epilepsy: early experience from a North American epilepsy center. Epilepsia 2013;54:323–30. https://doi.org/10.1111/j.1528-1167.2012.03672.x.

[2] Schiller Y, Cascino GD, Sharbrough FW. Chronic intracranial EEG monitoring for localizing the epileptogenic zone: an electroclinical correlation. Epilepsia 1998;39:1302–8. https://doi.org/10.1111/j.1528-1157.1998.tb01328.x.

[3] Brna P, Duchowny M, Resnick T, Dunoyer C, Bhatia S, Jayakar P. The diagnostic utility of intracranial EEG monitoring for epilepsy surgery in children. Epilepsia 2015;56:1065–70. https://doi.org/10.1111/epi.12983.

[4] Sperling MR, O'Connor MJ. Comparison of depth and subdural electrodes in recording temporal lobe seizures. Neurology 1989;39:1497–504. https://doi.org/10.1212/WNL.39.11.1497.

[5] Sammaritano M, Frcp C, De Lotbinisre A, Andermann F, Olivier A, Frcs C, et al. False Lateralization by Surface EEG of Seizure Onset in Patients with Temporal Lobe Epilepsy and Gross Focal Cerebral Lesions. Ann Neurol 1987;21(4):361–9. https://doi.org/10.1002/ana.410210408.

[6] Adamolekun B, Afra P, Boop FA. False lateralization of seizure onset by scalp EEG in neocortical temporal lobe epilepsy. Seizure 2011;20:494–9. https://doi.org/10.1016/j.seizure.2011.01.019.

[7] Mintzer S, Cendes F, Soss J, Andermann F, Engel J, Dubeau F, et al. Unilateral hippocampal sclerosis with contralateral temporal scalp ictal onset. Epilepsia

2004;45:792–802. https://doi.org/10.1111/j.0013-9580.2004.35703.x.
[8] Lieb JP, Engel J, Gevins A, Crandall PH. Surface and deep EEG correlates of surgical outcome in temporal lobe epilepsy. Epilepsia 1981;22:515–38. https://doi.org/10.1111/j.1528-1157.1981.tb04124.x.
[9] Lieb JP, Walsh GO, Babb TL, Walter RD, Crandall PH, Tassinari CA, et al. A comparison of EEG seizure patterns recorded with surface and depth electrodes in patients with temporal lobe epilepsy. Epilepsia 1976;17:137–60. https://doi.org/10.1111/j.1528-1157.1976.tb03392.x.
[10] Ray A, Tao JX, Hawes-Ebersole SM, Ebersole JS. Localizing value of scalp EEG spikes: a simultaneous scalp and intracranial study. Clin Neurophysiol 2007;118:69–79. https://doi.org/10.1016/j.clinph.2006.09.010.
[11] Pacia SV, Ebersole JS. Intracranial EEG Substrates of Scalp Ictal Patterns from Temporal Lobe Foci 38. 1997. p. 642–54. https://doi.org/10.1111/j.1528-1157.1997.tb01233.x.
[12] Ramantani G, Maillard L, Koessler L. Correlation of invasive EEG and scalp EEG. Seizure 2016;41(10):196–200. https://doi.org/10.1016/j.seizure.2016.05.018.
[13] Ramantani G, Dümpelmann M, Koessler L, Brandt A, Cosandier-Rimélé D, Zentner J, et al. Simultaneous subdural and scalp EEG correlates of frontal lobe epileptic sources. Epilepsia 2014;55:278–88. https://doi.org/10.1111/epi.12512.
[14] Koessler L, Cecchin T, Colnat-Coulbois S, Vignal JP, Jonas J, Vespignani H, et al. Catching the invisible: mesial temporal source contribution to simultaneous EEG and SEEG recordings. Brain Topogr 2014;28:5–20. https://doi.org/10.1007/s10548-014-0417-z.
[15] Abraham K, Ajmone Marsan C. Patterns of cortical discharges and their relation to routine scalp electroencephalography. Electroencephalogr Clin Neurophysiol 1958;10:447–61. https://doi.org/10.1016/0013-4694(58)90006-3.
[16] Abramovici S, Antony A, Baldwin ME, Urban A, Ghearing G, Pan J, et al. Features of simultaneous scalp and intracranial EEG that predict localization of Ictal Onset Zone. Clin EEG Neurosci 2018;49(May (3)):206–12. https://doi.org/10.1177/1550059417738688.
[17] Wasade V, Gaddam S, Burdette D. Intracranial electrographic analysis of preictal spiking and ictal onset in uni-and bitemporal epilepsy. Epileptic Disord 2015;17(2). https://doi.org/10.1684/epd.2015.0748. 156-6.
[18] Spanedda F, Cendes F, Gotman J. Relations between EEG seizure morphology, interhemispheric spread, and mesial temporal atrophy in bitemporal epilepsy. Epilepsia 1997;38:1300–14. https://doi.org/10.1111/j.1528-1157.1997.tb00068.x.
[19] Steinhoff BJ, So NK, Lim S, Lüders HO. Ictal scalp EEG in temporal lobe epilepsy with unitemporal versus bitemporal interictal epileptiform discharges. Neurology 1995;45:889–96. https://doi.org/10.1212/WNL.45.5.889.
[20] Kim DW, Kim HK, Lee SK, Chu K, Chung CK. Extent of neocortical resection and surgical outcome of epilepsy: intracranial EEG analysis. Epilepsia 2010;51:1010–7. https://doi.org/10.1111/j.1528-1167.2010.02567.x.
[21] Perucca P, Dubeau F, Gotman J. Intracranial electroencephalographic seizure-onset patterns: effect of underlying pathology. Brain 2014;137:183–96. https://doi.org/10.1093/brain/awt299.
[22] Hashiguchi K, Morioka T, Yoshida F, Miyagi Y, Nagata S, Sakata A, et al. Correlation between scalp-recorded electroencephalographic and electrocorticographic activities during ictal period. Seizure 2007;16:238–47. https://doi.org/10.1016/j.seizure.2006.12.010.
[23] Wyllie E, Lachhwani D, Gupta A, Chirla A, Cosmo G. Successful surgery for epilepsy due to early brain lesions despite generalized EEG findings. Neurology 2007;69(4):389–97. https://doi.org/10.1212/01.wnl.0000266386.55715.3f. 24.
[24] Dubeau F, Tampieri D, Lee N. Periventricular and subcortical nodular heterotopia A study of 33 patients. Brain 1995;118(5):1273–87. https://doi.org/10.1093/brain/118.5.1273.
[25] Sakai Y, Nagano H, Sakata A, Kinoshita S, Hamasaki N, Shima F, et al. Localization of epileptogenic zone in temporal lobe epilepsy by ictal scalp EEG. Seizure 2002;11(3):163–8. https://doi.org/10.1053/seiz.2001.0603.
[26] Alarcon G, Guy CN, Binnie CD, Walker SR, Elwes RD, Polkey CE. Intracerebral propagation of interictal activity in partial epilepsy: implications for source localisation. J Neurol Neurosurg Psychiatry 1994;57:435–49. https://doi.org/10.1136/jnnp.57.4.435.
[27] Binnie CD, Elwes RD, Polkey CE, Volans A. Utility of stereoelectroencephalography in preoperative assessment of temporal lobe epilepsy. J Neurol Neurosurg Psychiatry 1994;57:58–65. https://doi.org/10.1136/jnnp.57.1.58.
[28] Brekelmans GJF, Emde Boas W, Velis DN, Lopes da Silva FH, Rijen PC, Veelen CWM. Comparison of combined versus subdural or intracerebral electrodes alone in presurgical focus localization. Epilepsia 1998;39:1290–301. https://doi.org/10.1111/j.1528-1157.1998.tb01327.x.
[29] Tanaka H, Khoo HM, Dubeau F, Gotman J. Association between scalp and intracerebral electroencephalographic seizure-onset patterns: a study in different lesional pathological substrates. Epilepsia 2018;59:420–30. https://doi.org/10.1111/epi.13979.
[30] Lieb JP, Engel J, Babb TL. Interhemispheric propagation time of human hippocampal seizures: I. Relationship to surgical outcome. Epilepsia 1986;27:286–93. https://doi.org/10.1111/j.1528-1157.1986.tb03541.x.
[31] Weinand ME, Wyler AR, Richey ET, Phillips BB, Somes GW. Long-term ictal monitoring with subdural strip electrodes: prognostic factors for selecting temporal lobectomy candidates. J Neurosurg 1992;77:20–8. https://doi.org/10.3171/jns.1992.77.1.0020.
[32] Cascino GD, Trenerry MR, Sharbrough FW, So EL, Marsh WR, Strelow DC. Depth electrode studies in temporal lobe epilepsy: relation to quantitative magnetic resonance imaging and operative outcome. Epilepsia 1995;36:230–5. https://doi.org/10.1111/j.1528-1157.1995.tb00989.x.
[33] Yamazaki M, Tucker DMD, Fujimoto A, Yamazoe T, Okanishi T, Yokota T, et al. Comparison of dense array EEG with simultaneous intracranial EEG for interictal spike detection and localization. Epilepsy Res 2012;98(February (2-3)):166–73. https://doi.org/10.1016/j.eplepsyres.2011.09.007.
[34] Yamazaki M, Tucker DM, Terrill M, Fujimoto A, Yamamoto T. Dense array EEG source estimation in neocortical epilepsy. Front Neurol 2013;4:42. https://doi.org/10.3389/fneur.2013.00042.
[35] Haneef Z, Lenartowicz A, Yeh HJ, Levin HS, Engel J, Stern JM. Functional connectivity of hippocampal networks in temporal lobe epilepsy. Epilepsia 2014;55(January (1)):137–45. https://doi.org/10.1111/epi.12476.
[36] Ahmadi ME, Hagler DJ, McDonald CR, Tecoma ES, Iragui VJ, Dale AM, et al. Side matters: diffusion tensor imaging tractography in left and right temporal lobe epilepsy. Am J Neuroradiol 2009;30(October (9)):1740–7. https://doi.org/10.3174/ajnr.A1650.
[37] King-Stephens D, Mirro E, Weber PB, Laxer KD, Van Ness PC, Salanova V, et al. Lateralization of mesial temporal lobe epilepsy with chronic ambulatory electrocorticography. Epilepsia 2015;56:959–67. https://doi.org/10.1111/epi.13010.