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Epileptic Disorders

ORIGINAL ARTICLE

Lack of spontaneous typical seizures during intracranial monitoring with stereo-electroencephalography

Juan S. Bottan[1,2] | **Ashwaq Alshahrani**[2] | **Greydon Gilmore**[2] | **David A. Steven**[2,3] | **Jorge G. Burneo**[2,3,4] | **Jonathan C. Lau**[2] | **Richard S. McLachlan**[2] | **Andrew G. Parrent**[2] | **Keith W. MacDougall**[2] | **David C. Diosy**[2] | **Seyed M. Mirsattari**[2] | **Ana Suller Marti**[2,5]

[1]Section of Neurosurgery, Hospital General de Niños "Pedro De Elizalde", Ciudad Autónoma de Buenos Aires, Argentina

[2]Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[3]Department of Epidemiology & Biostatistics, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[4]Neuroepidemiology Unit, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

[5]Department of Paediatrics, Schulich School of Medicine and Dentistry, Western University, London, Ontario, Canada

Correspondence
Ana Suller Marti, Department of Clinical Neurological Sciences, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada.
Email: ana.sullermarti@lhsc.on.ca

Abstract

Objective: In the presurgical evaluation of patients with drug-resistant epilepsy (DRE), occasionally, patients do not experience spontaneous typical seizures (STS) during a stereo-electroencephalography (SEEG) study, which limits its effectiveness. We sought to identify risk factors for patients who did not have STS during SEEG and to analyze the clinical outcomes for this particular set of patients.

Methods: We conducted a retrospective analysis of all patients with DRE who underwent depth electrode implantation and SEEG recordings between January 2013 and December 2018.

Results: SEEG was performed in 155 cases during this period. 11 (7.2%) did not experience any clinical seizures (non-STS group), while 143 experienced at least one patient-typical seizure during admission (STS group). No significant differences were found between STS and non-STS groups in terms of patient demographics, lesional/non-lesional epilepsy ratio, pre-SEEG seizure frequency, number of ASMs used, electrographic seizures or postoperative seizure outcome in those who underwent resective surgery. Statistically significant differences were found in the average number of electrodes implanted (7.0 in the non-STS group vs. 10.2 in STS), days in Epilepsy Monitoring Unit (21.8 vs. 12.8 days) and the number of cases that underwent resective surgery following SEEG (27.3% vs. 60.8%), respectively. The three non-STS patients (30%) who underwent surgery, all had their typical seizures triggered during ECS studies. Three cases were found to have psychogenic non-epileptic seizures. None of the patients in the non-STS group were offered neurostimulation devices. Five of the non-STS patients experienced transient seizure improvement following SEEG.

Abbreviations: ASM, anti-seizure medication; DBS, deep brain stimulation; DRE, drug-resistant epilepsy; ECS, extra-operative cortical stimulation; EMU, epilepsy monitoring unit; EZ, epileptogenic zone; MRI, magnetic resonance imaging; PNES, psychogenic non-epileptic seizures; RNS, responsive neurostimulation; SD, standard deviation; SEEG, stereo-electroencephalography; SOZ, seizure onset zone; STS, spontaneous typical seizures; VNS, vagus nerve stimulation.

Part of the data was presented as a poster at the American Epilepsy Society (AES) Annual Scientific Meeting, Seattle, Washington, December 4–8, 2020.

Significance: We were unable to identify any factors that predicted lack of seizures during SEEG recordings. Resective surgery was only offered in cases where ECS studies replicated patient-typical seizures. Larger datasets are required to be able to identify factors that predict which patients will fail to develop seizures during SEEG.

KEYWORDS

absence of seizures, extra-operative cortical stimulation, implantation effect, insertional effect, lack of seizures, stereo-electroencephalography

1 | INTRODUCTION

Stereo-electroencephalography (SEEG) is becoming the preferred method for the identification of the seizure onset zone (SOZ) in preoperative evaluation of drug-resistant epilepsy (DRE).[1,2] SEEG consists of intracranial implantation of depth electrodes followed by continuous video-EEG recording of ictal and interictal phenomena.[3] Spontaneous typical seizures (STS) during SEEG provides crucial information to identify the SOZ and delineate the epileptogenic zone (EZ).[4,5]

Occasionally, some patients do not experience STS during an SEEG study, which limits recommendations for epilepsy surgery. This phenomenon is usually unpredictable and, although the interictal activity as well as the seizures captured during extra-operative cortical stimulation (ECS) provide useful information, a surgical recommendation based only on interictal information is not routinely done.[6] There is scarce literature describing this issue and management of these clinical scenarios in everyday epilepsy practice is based on each center's experience and preferences.

The aim of this study was to determine potential risk factors for patients who did not have STS versus patients who did have STS during SEEG and to analyze the clinical outcomes for this set of patients.

Key points

- Capturing spontaneous seizures during stereo-electroencephalography (SEEG) is the single-most important clinical data needed to better identify the seizure onset zone (SOZ) in drug-resistant epilepsy (DRE).
- Although infrequent, the lack of experiencing these seizures during SEEG poses a significant challenge for clinicians and surgical planning is often difficult in this setting. Scarce literature is available on this matter.
- The underlying mechanism by which patients fail to develop spontaneous seizures when implanted with depth electrodes is unknown; the "insertional effect" is discussed as a possible mechanism.
- Extra-operative cortical stimulation (ECS) emerges as a suitable alternative for these patients to gather significant information and recommend surgery.
- We were unable to identify risk factors or predictors that would suggest which patients will not experience seizures during SEEG.

2 | METHODS

We conducted a retrospective analysis of all patients with DRE who underwent SEEG between January 2013 and December 2018. Demographic characteristics, seizure semiology, previous video-EEG, frequency of seizures, epilepsy risk factors, number of anti-seizure medications (ASMs) used, previous epilepsy surgery, neuroimaging, number, and location of depth electrodes implanted were collected. Interictal and ictal activity reports were reviewed in all cases. The number of clinical and electrographic seizures as well as the main electrographic patterns were reviewed. ECS studies were conducted toward the end of the SEEG study. ECS-induced patient-typical and non-patient-typical seizures were also recorded. The standardized stimulation parameters routinely used at our center are shown in Table 1. In those patients who went on to surgical resection, outcomes were defined using the Engel classification at 1-year post-surgery.

Statistical analysis was carried out using SPSS statistical software version 25.0 (IBM). The threshold for significance was $p < .05$. Patient consent was waived on the basis of being a retrospective chart review, and no identifiable data are shown. The study protocol was approved by the Human Research Ethics Office at our institution, following the Declaration of Helsinki code of ethics. The study was conducted following the STROBE Guidelines

TABLE 1 Extra-operative cortical stimulation parameters and technical characteristics of depth electrodes used.

Parameter	Value
High-frequency stimulation	50 Hz
Mode of stimulation	Bipolar
Pulse width	300 µs
Train of stimulation	5 s
Pulse duration	0.2 ms
Interval between stimulation	>10 s
Current	1–6 mA
Low-frequency stimulation	10 Hz
Mode of stimulation	Bipolar
Pulse width	250 µs
Train of stimulation	5 s
Pulse duration	0.2 ms
Interval between stimulation	> 10 s
Current	1–5 mA
Depth electrodes	
Manufacturer	Ad-Tech medical[a]
Model	Spencer® Probe
Diameter	1.1 mm
Number of contacts	10
Spacing between contacts	3, 4, 5 and 6 mm

Abbreviations: Hz, Hertz; mA, milliamps; mm, millimeters; ms, milliseconds; s, seconds; µs, microseconds.

[a]Ad-Tech Medical Instruments Corporation, Oak Creek, WI.

(https://www.strobe-statement.org). Data are available for revision if requested by the corresponding author.

3 | RESULTS

One hundred fifty-five cases underwent SEEG during this period. 11 cases (7.4%) did not experience any clinical seizures, while 145 experienced at least one patient-typical seizure during admission. Two cases in the latter group were excluded for insufficient information. The median age in non-STS group was 28 years (IQR = 23.15), and 45.4% (N = 5) were males (Table 2). The median ASM was three at the time of the SEEG implantation. Six patients (51%) had a lesion on MRI, and three (33%) had previous epilepsy surgery. Electrographic seizures were seen in four cases in the non-STS group (36.4%). No significant differences were found between STS and non-STS groups in terms of demographic distribution, lesional/non-lesional epilepsy ratio, pre-SEEG seizure frequency, number of ASMs used, localization of electrodes (Figures 1 and 2), presence of electrographic seizures, or the postoperative seizure outcome in those who underwent resective surgery (Table 3). Statistically significant differences were found in the average number of electrodes implanted (7.0 in the non-STS group vs. 10.2 in the STS group; p = .0001)

TABLE 2 Demographic data and epilepsy characteristics of patients included in the present study. "p" value calculated by Fisher's exact test unless otherwise specified.

	Non-STS group N = 11				STS group N = 143				
	N	%	Mean	SD	N	%	Mean	SD	p
Age			35.3	16.8			33.3	10.8	.553[a]
Genetic sex (M)	5	45.4			65	45.5			1.000
Hand dominance (R)	11	100			127	88.8			.606
BTC Sz	5	45.4			82	57.3			.534
N of ASMs									
1	3	27.3			15	10.5			.124
2	3	27.3			70	48.9			.215
3	4	36.4			44	30.8			.331
4 or more	0	0			15	10.5			.602
Sz frequency									
Daily	6	54.5			52	36.4			.334
Weekly	2	18.2			51	35.7			.331
Monthly	3	18.2			38	26.6			1.000
Yearly	0	0			1	0.7			1.000
Prev. epilepsy surgery	3	36.4			36	25.2			1.000
Lesion on MRI	6	54.5			88	61.5			.752

Abbreviations: %, percentage; ASMs, anti-seizure medications; BTC Sz, focal with progression to bilateral tonic–clonic seizures; M, male; N, number; Prev, previous; R, right; SD, standard deviation; STS, spontaneous typical seizure; Sz, seizures.

[a]Student's t-test.

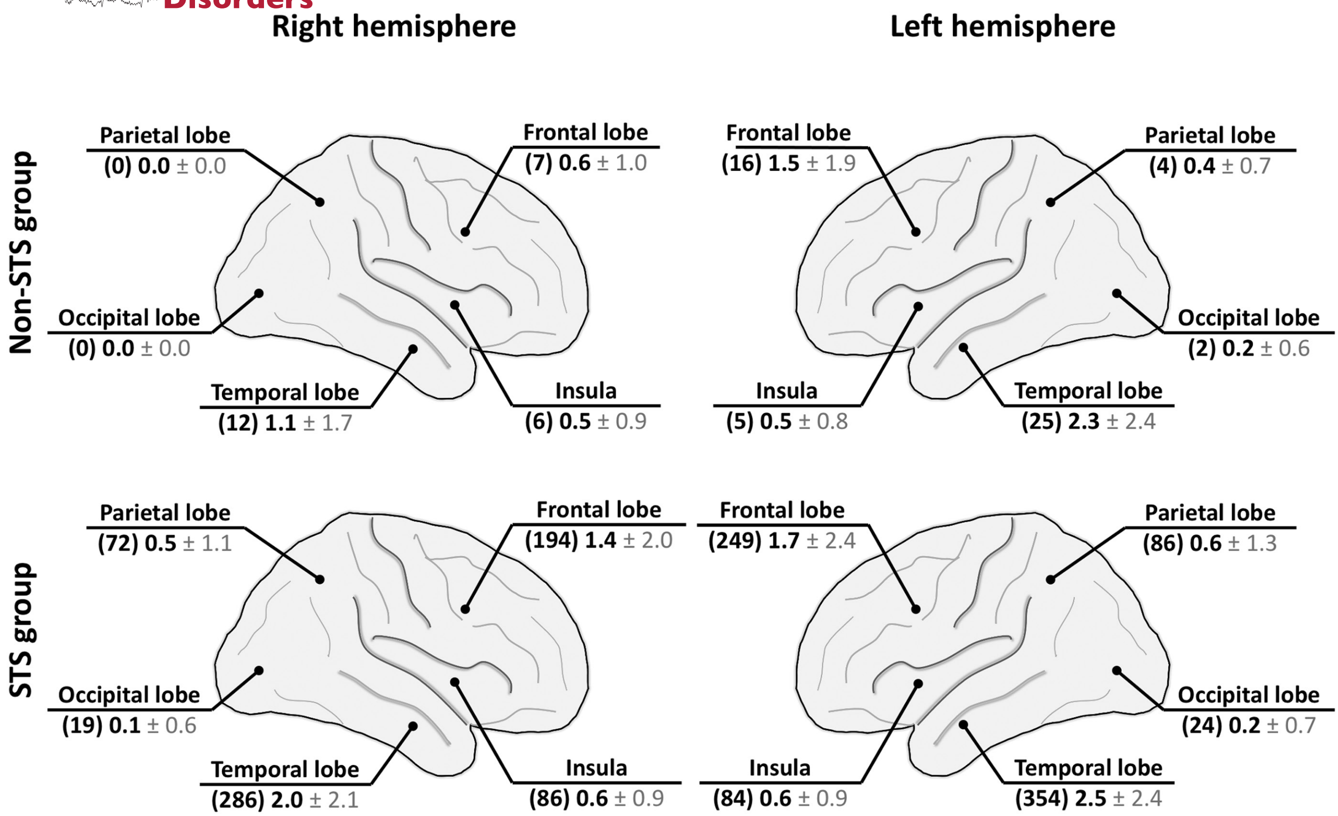

FIGURE 1 Localization of electrodes per hemisphere in Non-STS and STS groups. Between brackets, the total number of electrodes in that region. Mean number of electrodes per region is in bold, and in gray, the standard deviation.

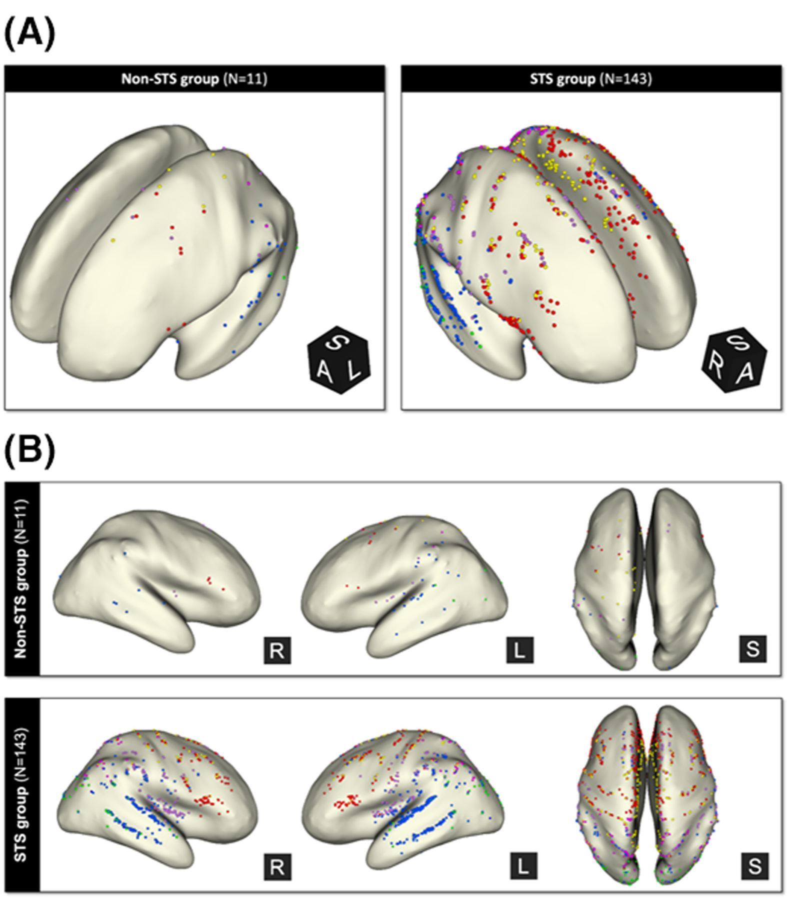

FIGURE 2 Localization of electrodes in Non-STS and STS groups in a brain template. Electrodes trajectories have been grouped by colors according to the region of the target: cingulate (yellow), frontal (red), temporal (blue), parietal and occipital (light green), insular (purple). A depicts all trajectories in oblique view. B shows trajectories per hemisphere on lateral view and combined from a superior view.

and in the number of days admitted in the epilepsy monitoring unit (EMU) (21.8 in the non-STS group vs. 12.8 days, $p=.0001$). During ECS, three patients had their typical seizures reproduced and subsequently underwent resective surgery.

Following SEEG, three patients in the non-STS group underwent resective surgery versus 87 in the STS group (27.3% vs. 60.8%, $p=.052$). All three patients who underwent epilepsy surgery in the non-STS group became seizure free at 1 year, whereas 48 (55.2%) in the STS group were seizure free after surgery ($p=.255$). None of the patients in the non-STS group were offered neurostimulation procedures (VNS, DBS, or RNS). Five patients in the non-STS group experienced a period of seizure freedom following SEEG which ranged between 3 months and 3 years. Clinical characteristics, procedures, and outcomes of the non-STS group are summarized in Table 4. The most relevant information on the ECS procedure is further shown in Table 5. Three patients who did not have surgery were found to have psychogenic non-epileptic seizures (PNES) after the SEEG analysis and further psychological evaluations (Table 6). One patient (Case 1) complained of stereotypic auditory phenomena and had a left temporal lesion (DNET). The second case (Case 2) had a parieto-occipital meningioma with a hypothetical SOZ around the lesion and further frontal spread. The final case (Case

TABLE 3 Summary of the SEEG results. "*p*" value calculated by Chi-Square unless otherwise specified.

	Non-STS group				STS group				
	N = 11				*N* = 143				
	N	**%**	**Mean**	**SD**	***N***	**%**	**Mean**	**SD**	***p***
N of electrodes	77		7.0	2.5	1454		10.2	3.2	.0001 [a]
Right-sided	25		2.3	3.2	657		4.6	4.1	.006 [a]
Left-sided	52		3.6	3.6	797		5.6	4.4	.001 [a]
Right hemisphere									
Frontal lobe	7		0.6	1.0	194		1.4	2.0	.294
Temporal lobe	12		1.1	1.7	286		2.0	2.1	.144
Parietal lobe	0		0	0	72		0.5	1.1	
Occipital lobe	0		0	0	19		0.1	0.6	
Insula	6		0.5	0.9	86		0.6	0.9	.793
Left hemisphere									
Frontal lobe	16		1.5	1.9	249		1.7	2.4	.743
Temporal lobe	25		2.3	2.4	354		2.5	2.4	.687
Parietal lobe	4		0.4	0.7	86		0.6	1.3	.762
Occipital lobe	2		0.2	0.6	24		0.2	0.7	1.000
Insula	5		0.5	0.8	84		0.6	0.9	.809
Patients with bilateral implantation	3	27.3			70	48.9			.217
Days in EMU			21.8	11.0			12.8	7.3	.0001 [a]
N of electrographic Sz	16		1.45	2.42	2209		16.0	53.2	.274 [a]
Patients with electrographic Sz	4	36.4			72	50.3			.534
N clinical Sz	0				1481		10.4	0.5	
Stimulation	5	45.5			64	44.8			
Patient-typical Sz during stimulation	3/5	60			22/64	34.4			.337
Patients who underwent surgery after SEEG	3	27.3			87	60.8			.052 [b]
Engel I at 1 year	3/3	100			48/87	55.2			.255

Abbreviations: %, percentage; EMU, epilepsy monitoring unit; *N*, number; Prev, previous; SD, standard deviation; SEEG, stereo-electroencephalography; STS, spontaneous typical seizure; Sz, seizures.

[a]Student's *t*-test.

[b]Determined to be not quite statistically significant.

TABLE 4 Clinical data on the non-STS subgroup.

Case	Genetic sex	Prev. epilepsy surgery	Age (Y)	MRI lesion	Type of seizure onset	Semiology	Longest seizure freedom period
1	Male	No	70	Lt temporal DNET	Sensory (Auditory)	*Aura continua* and auditory hallucinations	None
2	Male	No	43	Parieto–occipital meningioma	Motor	I. Asymmetric R posturing. II. Gelastic seizures	4M
3	Female	No	21	–	Cognitive (Déjà vu)	Déjà vú, hot sensation, anxiety/fear. LOA, oral automatisms. L head deviation. L dystonic posturing. Occasional BTC.	N/A
4	Female	Yes	30	HH RF-TC.	Emotional (Gelastic)	I. Gelastic. II. Aura: epigastric rising. Palpitations. Hand jerking. III. BTC	N/A
5	Male	No	28	Lt frontal DNET	Sensory (Visual)	Tunnel vision, speech arrest	N/A
6	Male	No	48	–	Generalized?	I. Nocturnal BTC. II Behavioral arrest	N/A
7[a]	Female	No	22	–	Cognitive (Déjà vu)	Déjà vú, dizziness, headache. Confusion. L tonic contraction and jerking. BTC	9W
8[a]	Female	No	23	–	Cognitive (Déjà vu)	Déjà vú, dizziness, headache. Confusion. L tonic contraction and jerking. BTC	3M (after SEEG)
9	Female	Yes	27	Lt temporal LGG	I. Autonomic (Epigastric). II. Sensory (Auditory)	I epigastric discomfort. Behavioral arrest. Bimanual automatisms. II. auditory hallucinations	1 Y
10	Male	No	20	–	Sensory (Auditory)	Sound both ears. Sensation R side body. Mioclonic jerks during sleep	2M
11	Male	Yes	57	Lt temporal lobectomy		Brief behavioral arrest episodes.	N/A

Abbreviations: ATL, anterior temporal lobectomy; DNET, dysembrioplastic neuroepithelial tumor; ECS, extra-operative cortical stimulation; HH, hypothalamic hamartoma; LGG, low-grade glioma; Lt, left; M, months; N/A, not available; NES, non-epileptic spells; Prev, previous; RF-TC, radiofrequency thermocoagulation; Rt, right; SEEG, stereo-electroencephalography; STS, spontaneous typical seizure; W, week/s; Y, year/s.

[a]Same patient. Two different SEEG admissions.

11) had a prior temporal lobectomy and was presumed to have a posterior resection and/or insular focus. These MRI-positive cases did not show clear manifestations on video-EEG.

4 | DISCUSSION

Although infrequent, it has been our observation that a group of patients with DRE do not develop seizures during SEEG studies, these accounted for over 7% of our cases. The lack of STS had a negative effect on the recommendation for surgery: Only one out of three patients were subsequently operated on, compared with the group that presented with STS, where over 60% of the patients underwent resective surgery. The reproduction of patient-typical seizures with ECS in the non-STS group had a positive effect on the recommendation of resective surgery. We were unable to find any factors that would suggest an increased risk of not developing seizures during SEEG. Interestingly, more than half of the patients in the non-STS group reported having daily seizures prior to the SEEG study. Additionally, none of the patients included had any post-implantation complications that could alter seizure frequency after explanation.

One patient with a hypothesis of right temporal lobe epilepsy failed to develop STS during the SEEG. After the

Interval between Video-EEG and SEEG (Y)	Admission (days)	ECS	STS induced	Implantation effect	Surgery	Type of surgery	Pathology	Outcome (Engel)
0.5	13	No	–	No	No	–	–	NES
0.4	25	Yes	No	No	No	–	–	NES
–	25	Yes	Yes	No	Yes	Rt ATL	Gliosis	Ia
1.3	18	No	–	No	No	–	–	
0.4	30	Yes	Yes	5M	Yes	Lt frontal lesionectomy	DNET (1p19q negative)	Ib
1.7	15	No	–	6M	No	–	–	
0.6	45	No	–	3M	No	–	–	
–	33	Yes	Yes	No	Yes	Rt ATL	Non-specific changes	Ia
2.4	10	No	–	3 Y	No	–	–	
0.9	16	Yes	No	14M	No	–	–	
1.1	10	No	–	No	No	–	–	NES

first investigation, there was insufficient interictal information to confidently recommend surgery. She underwent a subsequent SEEG study 1 year later and failed to develop seizures again. However, the ECS of electrodes within the right hippocampus was able to reproduce her typical seizures and was subsequently offered surgery (right ATL) and became seizure free.

Besides the negative impact on a surgical recommendation, there could be other potential setbacks with these patients: A longer admission can negatively impact a patient's mood and compliance with further testing and cooperation, including not being motivated to do sleep deprivation as efficiently or frequently as the epileptologist may recommend. In addition, a longer period of implantation might pose a higher risk of infection rate (although no infections where registered in our SEEG series[7]). As a general rule, longer admissions may have a direct negative impact in institutional profitability, however, some authors have questioned this in the particular setting of SEEG.[8] Despite this, the need to reschedule other patients for delays in beds' turnover can affect workflows and ultimately have a negative economic impact in the institution.

An interesting finding in our study was the fact that three patients were found to have PNES (Table 6). The decision to proceed with SEEG investigations was thoroughly

TABLE 5 Summary of most relevant findings from extra-operative cortical stimulation (ECS) results in the non-STS group. Only patient-typical electroclinical findings were included.

Case	High frequency	Electrode location	Intensity (mA)	ADs	EEG	Seizure description
3	Yes	Rt Ant Hc	3	No	Sz extending to posterior hippocampus and amygdala for 40 s	Déjà vu and epigastric sensation with feeling hot and sweating, with retained awareness and ability to speak
5	Yes	Rolandic	8	Yes	Sz in lesion electrode, extending to left frontal lobe	Confusion, speech impairment
8	Yes	Rt Ant insula	2–4	Yes	No	Throat sensation, déjà vu, sensory sensations in Lt side of head and hemibody
	Yes	Lt Ant Hc	3	Yes	No	Aura
	Yes	Rt Post Hc	2	–	Polyspikes in Rt Hc extending to mesial structures, temporal pole and later, orbitofrontal, and anterior insula electrodes. 2 min	Déjà vu, confusion, no loss of awareness, speech preserved
	Yes	Rt OrFr	4	Yes	No	Strange taste in mouth, epigastric and sensation and throat constriction
10	Yes	Lt Post Hc	2–3	Yes	Multiple electrographic Sz from 15 to 35 s	Auditory phenomena in Sz elicited from neocortical contacts

Abbreviations: ADs, after discharges; Am, amygdala; Ant, anterior; Hc, hippocampus; LPDs, lateralized periodic discharges; Lt, left; mV, millivolts; Op, operculum; OrFr, orbitofrontal; Par, parietal; Post, posterior; Rt, right; Sz, seizure.

TABLE 6 Summary of the patients with non-epileptic events.

Case	Symptoms	Prior video-EEG		MRI findings	PET
		Interictal	Ictal		
1	Auditory phenomena (*aura continua*)	No clear IEDs	Presumed obscured by muscle artifacts	Lt temporal DNET	Negative
2	1. Asymmetric Rt tonic posturing. 2. Gelastic sz	No clear IEDs	No changes	Lt parieto-occipital meningioma	Subtle Lt parieto-occipital hypometabolism
11	Brief BA episodes	Occasional sequential spikes and theta waves T3. 1 electrographic Sz	Sequential spikes and semi-rhythmic theta waves T3-F7	Lt ATL	–

Abbreviations: Ant, anterior; ATL, anterior temporal lobectomy; BA, behavioral arrest; BTC, bilateral tonic–clonic seizures; DNET, dysembrioplastic neuroepithelial tumor; IEDs, interictal epileptiform discharges; LOA, loss of awareness; Lt, left; Mid, middle; PET, positron emission tomography; PNES, psychogenic non-epileptic seizures; Post, posterior; RF-TC, radiofrequency thermocoagulation; Rt, right; SEEG, stereo-electroencephalography; SMA, Supplementary motor area; SPECT, single-photon emission computed tomography; STS, spontaneous typical seizure; Sup, superior; Sz, seizures.

discussed in each case. All of these patients experienced the typical clinical events during invasive recording and were found not to have EEG alterations. The presence of PNES in this particular scenario should be considered and semiology, as well as an appropriate SEEG implantation plan, should be taken into consideration.

In our series, we found five patients in the non-STS group who sustained a transient period of seizure freedom. This improvement has been associated with the "implantation effect" or "insertional effect," terms used to describe a transient and rare phenomenon of seizure improvement following intracranial electroencephalography.[9–11] This effect has been reported by others, even resulting in seizure freedom for prolonged periods of time.[12–16] A transient period of electro-corticographical post-implantation changes recorded through responsive neurostimulation (RNS) devices has been reported as well.[17] These alterations could be explained in local neuroinflammatory changes that may alter epileptogenic networks as some experimental models have suggested.[18] Lane et al. found that there was a longer period of latency from implantation to first seizure when comparing non-invasive EEG to invasive EEG.[15] This fact suggests that local post-implantation changes can alter seizure frequency transiently. Furthermore, they identified that larger arrays of electrodes (depth or subdural electrodes) correlated positively with longer seizure latency. Other potential mechanisms could include cortical manipulation, use of steroids or anesthetic medications.[13]

As expected, we found that patients in the non-STS group had significantly longer admissions when compared to the other group (21.8 vs. 12.8, respectively $p = .0001$), ranging from 10 to 45 days. At our center, patients admitted to the EMU for either invasive and non-invasive video-EEG that sustain a prolonged latency period are routinely given sessions of photic stimulation and hyperventilation to induce seizures.[19] These patients are also sleep-deprived routinely 24 h after all ASMs have been fully discontinued, with variable patient collaboration. Despite these actions, no seizures were triggered in these group of patients. 6 weeks is the maximum time of admission in the EMU for non-invasive and invasive video-EEG. Patients are encouraged to stay as long as possible to allow for spontaneous seizures to resume, but occasionally decide to discontinue the study and are discharged against medical advice.

Long-term RNS data have brought increasing attention to the multi-day variation in seizure activity for each patient.[20] Baud et al. found that interictal epileptiform activity fluctuates with slower multidien rhythms that vary across subjects but are relatively stable within subjects over the years. Seizure risk may be affected by these changes. This factor may also play a role in the decrease or absence of seizures during SEEG. It poses the question of whether treating physicians should attempt to better correlate intracranial studies with the moment of highest seizure frequency to better capture ictal information.

The number of electrodes implanted did show a statistical significance between both groups (seven electrodes per patient in the non-STS group vs. 10.2 in the control, $p = .0001$), but we have no explanation to this observation other than a selection bias. Interestingly, the lower number of electrodes in this group does not support the findings commented by Lane et al.[15] in relation to the number of electrodes as a potential cause for seizure latency or, furthermore, to explain the absence of spontaneous

				SEEG	
SPECT	**Other investigations**	**SEEG coverage**	**Clinical events**	**Interictal**	**Ictal**
Negative	Autoimmune panel (negative)	Lt temporal lesion, Lt post hippocampus, Lt ant hippocampus, Lt parietal, Lt parietal, Lt amygdala, Lt post temporal lobe	Yes	No clear IEDs	No changes
Negative	Movement disorders evaluation (Negative)	Lt Rolandic cortex, Lt SMA, Lt mid and anterior frontal region, Lt post cingulate and lesion periphery	Yes	No clear IEDs	No changes
–	–	Post sup temporal gyrus, Lt post hippocampus, Lt Heschl gyrus, Lt insula, Lt orbitofrontal cortex	Yes	1 electrographic Sz	No changes

seizures during SEEG. We looked further at the localization of electrodes to determine whether the density of coverage in certain regions of the brain could be at a higher risk of generating an implantation effect, but we found no correlation (Table 3 and Figures 1 and 2A,B).

Although ECS during SEEG studies is a procedure that has been performed since the early stages in stereo-electroencephalography history,[21–23] it is more recently emerging as a validated method of study.[24] This could result in an alternative to favoring surgery in this particular group of patients. In this group, stimulation was useful in three of the patients following our ECS protocol.[25] This included only high-frequency stimulation of interictally active contacts and the ones with potential implications in their seizures, as well as mapping of eloquent cortex. The study provided relevant information that helped with the localization of the SOZ and subsequently seizure freedom after surgery.

Stimulation studies are considered an important method to delineate the EZ and the electroclinical correlate from STS, which helps to map and determine the EZ in patients who undergo SEEG.[6] Although stimulation is performed routinely now in our center, 6 of the 11 cases in this series did not undergo stimulation during their SEEG study either because it was not offered at the time or they declined. Other groups have mentioned the relevance of stimulation in their particular clinical settings.[6,24,26] The seizures triggered during ECS always need to be the typical seizures that the patient experiences. If different seizures are elicited, this may suggest a different EZ and could be associated with diagnostic errors. ECS findings in this context need to be interpreted cautiously.

Other interictal information may be useful to further categorize epileptic networks in the absence of STS. High-frequency oscillations (HFOs) are used as diagnostic tools for the EZ. The interest of the scientific community regarding the implications and potential value for EZ localization using HFOs has increased.[27–29] Moreover, there is current debate in the literature suggesting that analysis of intracranially recorded interictal spikes networks can accurately predict the seizure onset zone.[30,31] More recently, other interictal biomarkers such as infra-slow activity have shown some promise in identifying the EZ.[32,33] Further developments in this line of research may mitigate the current relevance of recording STS for confidently determining the EZ.

Our study has limitations, the most evident one is the retrospective nature of the design and the relatively low number of cases in the non-STS group. Yet, lack of STS is a rare phenomenon, so series of these cases will most likely be low. Additionally, ECS is now a commonly used method in our clinical practice, but it was not common or routinely used at the time some of these patients were investigated. Further studies on larger sets of patients would be relevant to more correctly assess the nature and implications of this phenomenon in clinical practice. Despite this, we believe this study arises for consideration this specific scenario.

5 | CONCLUSION

The absence of seizures during SEEG is a problem that can prolong EMU admission and ultimately obviate resective surgery. We were unable to identify any factors associated with the lack of seizures during SEEG. Resective surgery was only offered in cases where the ECS replicated seizures. More data are required to identify factors that predict which patients will fail to develop seizures during their SEEG study.

AUTHOR CONTRIBUTIONS

Juan S. Bottan: Study design; data collection; statistical analysis; manuscript drafting. Ashwaq Alshahrani: data collection. Greydon Gilmore: Neuroimaging processing and figures preparation. David A. Steven: Critical manuscript revision; statistical analysis. Jorge G. Burneo, Jonathan C. Lau, Richard S. McLachlan, Andrew G. Parrent, Keith W. MacDougall, David C. Diosy, and Seyed M. Mirsattari: Critical manuscript revision. Ana Suller Marti: Study conceptualization and design; study supervision; critical manuscript revision.

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CONFLICT OF INTEREST STATEMENT

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ORCID

Juan S. Bottan https://orcid.org/0000-0002-7126-4682
Jorge G. Burneo https://orcid.org/0000-0002-3644-2826
Jonathan C. Lau https://orcid.org/0000-0002-8452-8915
Ana Suller Marti https://orcid.org/0000-0002-8421-1125

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. What are the potential implications for a patient that fails to develop spontaneous patient-typical seizures during stereo-electroencephalography (SEEG)?
2. What is the potential mechanism underlying the lack of spontaneous typical seizures in patients implanted with depth electrodes for (SEEG)?
3. What alternatives are available if a patient fails to develop seizures during a SEEG study to localize the epileptogenic zone?

Answers may be found in the *supporting information*.