The nature, frequency and value of stimulation induced seizures during extraoperative cortical stimulation for functional mapping

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

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Abstract

Purpose: The aim of this retrospective service evaluation was to determine the nature, frequency and clinical value of seizure occurrence during extraoperative direct cortical stimulation for functional mapping in patients undergoing invasive recordings (icEEG) for epilepsy surgery workup.

Methods: We reviewed 145 sequential cases of patients with refractory focal epilepsy who underwent intracranial electrode implantation and extraoperative direct cortical stimulation (CS) for functional mapping. CS intended for mapping can elicit as a by-product electrical or electroclinical events, such as afterdischarges, subclinical EEG seizures, and stimulation-induced seizures (SIS) . SIS may have habitual or non-habitual semiology (as defined by comparison to the patient's spontaneous events).

Results: In our cohort, electrical (subclinical EEG seizures) or electroclinical events, (SIS) were recorded in 34.5% (50/145) patients during CS. SIS occurred in 23.4% (34/145) of all patients, of which over half were habitual SIS (SIS_{hab}). In most cases the location of contacts eliciting habitual SIS originated from the same location as the spontaneous ictal onset zone in icEEG. Of those with SIS_{hab} undergoing surgery (n=13), seizure freedom was achieved in 61.5%, and of those with SIS_{NH} undergoing surgery (n=10), 40% became seizure free (ns).

Conclusions: Electroclinical SIS occurs in about a quarter of CS for functional mapping; SIS are habitual in the majority of cases, and where elicited, SIS in icEEG could be an additional diagnostic tool to localize the seizure onset zone. However, a significant minority of stimulations leads to non-habitual SIS.

. **Keywords:**

Stimulation-induced seizures, Extraoperative direct cortical stimulation, Cortical mapping, Presurgical evaluation, Intracranial EEG.

Abbreviations:

CS, direct cortical stimulation; icEEG, intracranial EEG; SIS, stimulation-induced seizures;; SIS_{hab}, habitual SIS ; SIS_{NH} ,non-habitual SIS EZ, epileptogenic zone; SOZ, seizure onset zone;. SEEG, stereo electroencephalography.

Highlights:

- Electroclinical SIS were observed approximately in a quarter of patients who had extraoperative CS for functional cortical mapping.
- SIS were habitual just over half of the time (56%).
- In three-quarters of patients who had habitual SIS , the location of contacts eliciting habitual SIS originated from the same location as the spontaneous ictal onset zone in icEEG.

1. Introduction

Direct electrical cortical stimulation (CS) is used for mapping of eloquent cortex in patients with refractory focal epilepsy undergoing intracranial electroencephalography (icEEG) as part of their presurgical evaluation. CS can be performed with subdural grids, strips and depth electrodes (or combinations of these) after craniotomy or with stereotactically-inserted depth electrodes (stereo electroencephalography, SEEG)[1, 2]. CS remains the gold standard for functional mapping of language, motor and sensory areas in relation to the epileptogenic zone (EZ) prior to epilepsy surgery[1, 2]. Stimulation intended for mapping can elicit electrical or electroclinical events, such as afterdischarges, subclinical seizures, stimulation-induced seizures (SIS) . SIS may have habitual or non-habitual semiology compared to spontaneous events [3]. SIS with a non-habitual semiology can be considered a risk or unwanted side-effect of CS. In contrast, SIS with habitual semiology have been used to define the epileptogenic network [1, 4]. Indeed, SIS reproducing the patient's habitual seizure semiology has been promoted by Bancaud and Tailarach in defining the EZ and network [5] (see also refs[3, 6-8]) in this has been highlighted from some investigators performing SEEG investigations [4].

The purpose of this study was to determine the frequency and characterise the nature of SIS within our icEEG practice, in which we do not routinely attempt to stimulate seizures (instead performing CS purely for functional mapping). SIS were characterised as habitual or non-habitual in nature. Finally, we determined whether SIS were more likely to arise from or in proximity to the seizure onset zone. This may then indicate a diagnostic role for SIS in defining the seizure onset zone (SOZ).

2. Methods

We performed a retrospective review of 193 patients with refractory focal epilepsy admitted for icEEG and identified those who underwent CS as a part of their presurgical evaluation at the National Hospital for Neurology and Neurosurgery from January 2008-December 2017. The review was approved by the local ethics committee as part of a retrospective audit of safety and effectiveness of CS. Patients consented to CS after having been informed of the benefits for cortical mapping and risks including SIS. CS was performed in 145 patients using bipolar or monopolar stimulation techniques to identify motor, sensory and in the dominant hemisphere as defined by fMRI also to map language areas underlying the implanted stimulated electrode contacts. Bipolar and monopolar CS are equally effective in identifying cortical areas as eloquent[9]. Monopolar or bipolar CS was adopted in studies with implanted grids whereas bipolar stimulation was used in all SEEG cases.

CS was performed on full doses of anti-seizure medication[9, 10]; for patients who had undergone drug reduction, medications were resumed at full dose with a loading dose administered the day prior to CS. For both bipolar or monopolar CS the standard stimulation setting was 500μs pulse duration at 50Hz pulse rate, initial current intensity 0.5-1mA and train duration up to 5s[9]. Depending upon electroclinical response, further trains was delivered with gradual intensity increases (increments of 0.5-1mA) up to 7mA. Mesial temporal structures (hippocampus and amygdala) were not routinely stimulated for mapping purposes, and therefore only CS outside the medial temporal lobe are included.

Electronic medical records of CS and video-EEG segments were reviewed, SIS identified and classified as habitual or non-habitual.

2.1 Definitions of CS-induced electro-clinical events

Habitual seizures were seizures with semiology resembling spontaneous seizures, as recorded during previous scalp video-EEG telemetry and icEEG. Habitual or non-habitual nature of seizures was confirmed with the patient and family during icEEG recording [11].

Stimulation-induced clinical seizures (SIS) are subjective symptoms and objective clinical signs time-locked to an EEG seizure wherein EEG discharges outlast the electrical stimulus. In habitual SIS (SIS_{hab}), clinical semiology is comparable to spontaneous seizures and the intracranial EEG pattern evolves in frequency and distribution as observed in spontaneous seizures [3]. Non-habitual SIS are referred to as "SIS_{NH}".

We only analysed subjective sensations similar to the habitual spontaneous focal aware seizures when associated with EEG changes because otherwise these symptoms may reflect functional activation in this area and may not represent an ictal phenomenon [4]. *Subclinical EEG seizures* were defined as EEG discharges fulfilling criteria for stimulation-induced EEG seizures (CS-elicited afterdischarges which spread) without clinical change[3].

2.2 Electrode localization in SIS and relation to surgical resection

For the subset of patients with SIS who eventually underwent surgical resection (n=23), the relationship of relevant stimulated contacts to resection cavities was assessed by identification of these contacts on CT-imaging during icEEG coregistered (using SPM12; http://www.fil.ion.ucl.ac.uk/spm) with post-operative imaging.

2.3 Clinical follow-up post-resection

Postoperative outcomes were classified on Engel/ILAE outcome scales. Patients were followed up prospectively at three months after surgery and at 6-12 months. Statistical analyses used SPSS (IBM SPSS 25.0, Chicago, IL, USA) for Chi-Square tests (significance level $p<0.05$) and Cramer's V measure when necessary.

3. Results

In total, 145 patients with refractory focal epilepsy underwent icEEG (68 [46.9%] with SEEG) and CS for mapping of eloquent cortex during the period reviewed. Patient selection flow chart is presented in **Figure 1**.

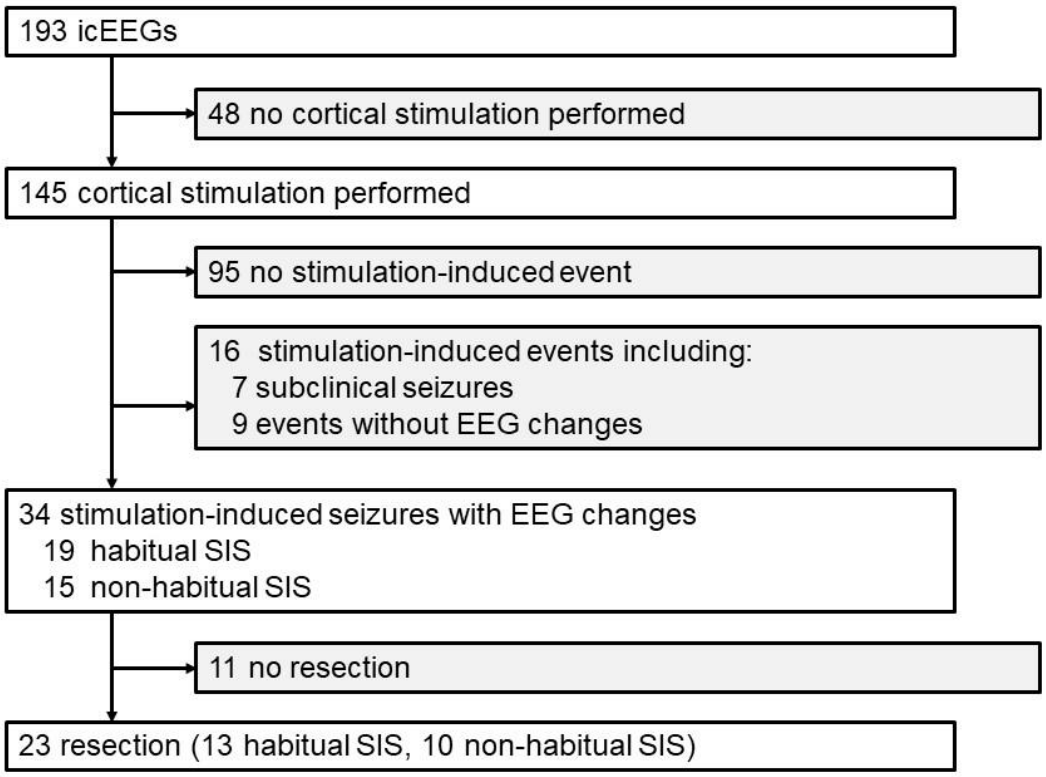

Figure 1: *Patient flowchart*

50 patients (34.5%) had SIS (habitual/non-habitual) or a subclinical EEG seizure elicited during extraoperative CS. Of these, 34 patients (23.4%) experienced CS-induced electro-clinical events as SIS with EEG changes. Here, we report these electro-clinical SIS and not subclinical EEG seizures. The details of the characteristics of these 50 patients are summarized in **Table 1.**

Table 1: *Characteristics of patients with electrical and electroclinical events during cortical stimulation*

Number of patients	50
Age in years (mean ± SD)	32.6 ± 8.8
Duration of epilepsy, years, mean ± SD	20.5 ± 10.8
Female /Male, N (%)	22 (44%) / 28 (56%)
Type of epilepsy N (%)	
Frontal lobe epilepsy (FLE)	17 (34%)
Temporal lobe epilepsy (TLE)	10 (20%)
Parietal lobe epilepsy (PLE)	6 (12%)
Other types of epilepsy*	17 (34%)
MRI pathology N (%)	
Lesional	33 (66%)
Non lesional	17 (34%)
Type of implantation N (%)	
SEEG	18 (36%)
Subdural grid(s) with or without depth electrodes and additional strips	32 (64%)
Number of electrodes implanted, median (range)	85 (42–132)
Number of electrodes stimulated, median (range)	39 (5-117)
Resection/no resection/N (%)	23 (67,6%) /11(32,3%)
Engel/ILAE outcome scale in operated 23 pts N (%)	
Class IA/1: Completely seizure-free since surgery	12 (52%)
Class II/2: Rare disabling seizure	-
Class III/3: Worthwhile improvement	3 (13%)
Class IVA/4: No worthwhile improvement	6 (26%)
Class IV/5 :No improvement	2 (8,6%)

*Other types of epilepsy: Insula, multilobar (parietooccipital, hemispheric, frontotemporal, temporooccipital, bitemporal, pericentral.

3.1 CS-induced seizures and implantation/epilepsy type

Thirty-four of 145 patients undergoing functional mapping experienced electroclinical SIS (23.4%), seven (4.8 %) experienced subclinical seizures only, nine (6.2%) other subjective events without EEG change.

Of the 34 patients with SIS, 25 had SIS with objective clinical signs only, four had more than one SIS, with both objective clinical signs and also SIS associated with subjective symptoms only (focal aware seizures with EEG change); five had SIS with subjective symptoms only. In

19 patients SIS were of habitual semiology (SIS_{hab}) and in 15 patients SIS were not habitual (SIS_{NH}).

Of 19 SIS_{hab} patients, five underwent SEEG implantation and 14 subdural grids; of 15 SIS_{NH} patients, five underwent SEEG and 10 subdural grids. The frequency of SIS_{hab} and SIS_{NH} did not differ depending on implantation type ($p>0.6$). SIS_{NH} patients overwhelmingly had FLE or multilobar epilepsy (14/15) whereas SIS_{hab} patients had more variable lobar classification. Details of the patients with SIS_{hab}/SIS_{NH} are summarized in **Table 2.**

Table 2 (Part 1): *Stimulation-induced habitual seizures*

ID	Age (sex)	Type of epilepsy/ EZ	MRI lesion	Type of implantation	Type of surgery	Histology	Concordance SIS_{hab} SOZ vs SOZ in icEEG	Outcome Engel / (ILAE 1→5)	All SIS contacts resected
1	40(F)	FLE/ OF (right)	encephalomalacia	SEEG	OF (right)	Normal	N	IV/5	N
2	28(F)	FLE/ SFG SMA (right)	N	SD grids +STR	FL (right)	FCD type II	Y	IA/1	Y
3	28(F)	Multilobar /POL (right)	TS	SD grids +STR+D	OL (right)	TS	Y	IA/1	Y
4	44(M)	LTLE/ STG (right)	DNET or FCD	SD grids +D	TL (right)	Glioneuronal tumour (Grade I)	Y	IA/1	Y
5	32(F)	PLE /Plob (right)	FCD	SD grids +D	PL (right)	FCD type IIb	Y	IA/1	N
6	39(M)	PLE-/PL (left)	cavernoma	SD grids +D	PL (left)	Cavernous haemangioma / Severe chronic gliosis	N	IVA/4	Y
7	24(F)	LTLE/ latTL(right)	N	SD grids +STR+D	TL (right)	FCD type IIB	Y	IA/1	Y
8	41(M)	PLE/PL (left)	FCD	SD grids +STR+D	PL (left)	FCD type IIB	Y	IA/1	Y
9	23(F)	Multilobar/ PL (right)	encephalomalacia	SEEG	N/A	-	N	-	-
10	24(M)	LTLE/ latTL(right)	N	SD grids +D	antTL (right)	No specific pathology.	Y	IVA/4	Y
11	30(F)	Multilobar/ biTL	glioneuronal lesion	SEEG	N/A	-	N	-	-
12	48(F)	FLE /SFG (right)	Non-specific lesions	SD grids +D	FL (right)	FCD type IIB	Y	III/3	Y
13	28(M)	LTLE /STG (left)	N/A	SD grids +D	TL (left)	Normal	Y	IA/1	Y
14	43(F)	Multilobar /pericentral (left)	N	SD grids +STR	FL (left)	No specific pathology	Y	IVA/4	Y
15	23(M)	PLE /PL (right)	N	SD grids +STR+D	N/A	-	Y	-	-
16	41(F)	FLE/ SFG-SMA (left)	Non-specific lesions	SD grids +STR	FL (left)	FCD type IIB	Y	IA/1	Y
17	34(F)	MTLE (left)	HS	SEEG	N/A	-	N	-	-
18	33(M)	MTLE (right)	N	SEEG	N/A	-	Y	-	-
19	26(M)	PLE /PL (left)	FCD	SD grids +STR+D	N/A	-	Y	-	-

Table 2 (Part 2): *Stimulation-induced non habitual seizures*

ID	Age (sex)	Type of epilepsy/EZ	MRI lesion	Type of implantation	Type of surgery	Histology	Concordance SIS_{NH} SOZ vs SOZ in icEEG	Outcome Engel / (ILAE 1→5)	All SIS contacts resected
1	40 (M)	FLE/ SFG (right)	N	SD grids+STR+D	FL (right)	FCD type IIB	N	IA/1	N
2	34 (F)	FLE / IFG/MFG (left)	FCD	SD grids	FL (left)	FCD type IIB	Y	IA/1	Y
3	28 (M)	FLE/ posterior IFG/peri-central (left)	Post-operative changes	SD grids+STR	FL (left)	Recurrent pilocytic astrocytoma	N	IVA/4	N
4	27 (F)	Multilobar / anterior quadrant (left)	N/A	SD grids+STR	FL (left)	FCD type IIA	N	IA/1	N
5	18 (M)	FLE/ SFG (right)	N	SEEG	FL (right)	FCD type IIB	N	III/3	Y
6	19 (M)	Multilobar/ posterior quadrant (left)	Non-specific lesions	SD grids+STR+D	N/A	-	N	-	-
7	45 (M)	FLE/ SFG (left)	Non-specific lesions	SD grids+STR+D	N/A	-	N	-	-
8	41 (M)	FLE/ MFG/SFG (left)	N	SD+depth	FL (left)	Normal	Y	IVA/4	Y
9	48 (M)	FLE/ SMA(left)	N	SD grids+STR+D	N/A	-	N	-	-
10	30 (M)	FLE/ prefrontal/anterior cingulum (left)	N	SEEG	FL (left)	No specific pathology	N	IVA/4	N
11	17 (F)	FLE/ IFG (left)	DNET	SD grids+STR+D	FL (left)	DNET	Y	III/3	Y
12	46 (F)	MTLE / (Right medial temporal lobe)	Non-specific lesions	SEEG	TL (right)	Hippocampal sclerosis (ILEA type 2)	Y	IA/1	Y
13	19 (M)	Multilobar / (R. STG and R. IFG)	Cortical lesions	SD grids+STR	TL (right)	Normal	N	IV/5	N
14	34 (M)	Multilobar/ (multilobar)	N	SEEG	N/A	-	N	-	-
15	43 (M)	Multilobar / (Left anterior quadrant)	N	SEEG	N/A	-	N	-	-

Abbreviations: EZ: Epileptogenic zone; me: mesial, lat: lateral sup: superior, ant: anterior, post: posterior; OF: orbitofrontal; FG: frontal gyrus; SMA: supplementary motor area; POL: parietal-occipital lobe; Plob: parietal lobule; PL: parietal lobe; TL: temporal lobe, FLE: frontal lobe epilepsy TLE: temporal lobe epilepsy MTLE: Mesial temporal lobe epilepsy, LTLE: Lateral temporal lobe epilepsy, PLE: parietal lobe epilepsy AM: amygdala, HP: hippocampus, N: No, Y: Yes, N/A: Not available, FCD: focal cortical dysplasia, DNET: dysembryoplastic neuroepithelial tumour, SD: subdural, STR: strips, D: depth electrodes, SEEG: Stereo-electroencephalography,
SFG: Superior frontal gyrus, MFG: middle frontal gyrus, IFG: Inferior frontal gyrus.

3.2 Concordance of SIS sites vs SOZ of spontaneous seizures

We evaluated whether contacts involved in SIS_{hab} were concordant with the SOZ of spontaneous seizures captured during icEEG. 14/19 SIS_{hab} patients (73.7%) had full concordance between contacts involved in SIS_{hab} and contacts implicated in the SOZ of spontaneous seizures. The remaining five patients all had SIS with EEG changes (all focal aware seizures) and stimulation sites were not fully concordant with the spontaneous SOZ established by icEEG. Concordance between SIS and spontaneous SOZ did not differ by epilepsy type (FLE, PLE, TLE, others; $p>0.8$).

3.3 Surgical outcome

The proportion of seizure-freedom (Engel class IA/ILAE class 1 outcomes) after epilepsy surgery in our cohort was 52% (12/23).

Of SIS_{hab} patients, 13/19 proceeded to resective surgery. Of those, eight had seizure-free outcome (Engel/ILAE class IA/1, 8/13, 61.5%). In two cases contacts at which SIS_{hab} were elicited were incompletely resected (for one, none of these contacts fell within the resection; for the other, 1/2 contact positions were resected); for the other 11 patients all contacts were included within resection margins. The resulting numbers of SIS_{hab}-resected and SIS_{hab}-not resected are too small for statistically meaningful comparison (7/11 patients for whom resection included all contacts where SIS_{hab} were elicited had Engel class I outcomes and 1/2 in whom the resection margins spared at least some of those contacts). Of $SIS_{NH,}$ 10 proceeded to resection and 4/10 (40%) became seizure free.

4. Discussion

We investigated the frequency of stimulation-induced seizures resembling spontaneous seizures (SIS_{hab}) and non-habitual seizures (SIS_{NH}) in a large cohort of patients with refractory focal epilepsy who underwent icEEG. During the time-period reviewed, extraoperative CS was performed for cortical mapping without the intention of stimulating seizures. In our cohort, CS-induced electro-clinical events (defined as above) occurred in a quarter of all stimulations, and the seizures induced were habitual in over half of the cases.

Previous studies have shown similar rates of SIS during extra-operative CS (33%-35.2%)[12, 13]. The frequency of SIS in this study is lower than a recent study which evaluated the association of SIS with outcome (56/102, 55%)[4]. In that study, however, stimulation was performed with an intent to induce seizures, potentially leading to more trials at higher intensities. Furthermore, in our centre we do not systematically perform stimulation mapping in medial temporal structures, a location which seizures are frequently elicited using CS.

Strikingly, SIS_{NH} were almost exclusively seen in patients with FLE or multi-lobar epilepsy, whereas SIS_{hab} were seen in all subcategories examined. There was no difference between groups in the types of implantation (SEEG/grids).

We also investigated concordance of SIS_{hab} with the SOZ of spontaneous seizures (ictal onset zone in icEEG) and found a high concordance rate, as have other studies, between 75-100%[3]. Groups of patients with or without concordance between habitual SIS and spontaneous seizures in icEEG did not differ by type of epilepsy ($p>0.8$) in contrast to the study by Chauvel and colleagues[14]. They found high spatial overlap of SIS and spontaneous seizures in mesial TLE whereas this overlap was less pronounced in neocortical TLE and FLE.

Groups of patients with or without concordance between spontaneous and CS-induced seizures did not differ by type of implantation (only 1/3 of the patients with CS-induced electro-clinical events underwent SEEG rather than grid implantation).

SIS may aid prediction of post-operative seizure-freedom as part of presurgical workup[15]; we addressed this by examining postsurgical outcomes in patients with SIS. The proportion of seizure-freedom (Engel class IA/ILAE class 1 outcomes) after epilepsy surgery was 52% (12/23) in patients with SIS_{hab} or SIS_{NH}, with numerical tendency to better outcomes after SIS_{hab} (seizure-freedom in 8/13; 61.5%) than after SIS_{NH} (4/10; 40%). In previous studies favourable seizure outcomes (Engel class I) were observed in 58-64% of icEEG cases[11, 16].

5. Conclusion

Electrical cortical stimulation for functional mapping is safe, with electroclinical seizures occurring in in about a quarter of the cases. They were habitual just over half of the time (56%), leaving a sizable minority of non-habitual seizures.

In the majority of patients who had habitual SIS (14/19; 73.7%), the electrodes eliciting SIS_{hab} were in the same location as the spontaneous SOZ. Patients with SIS who progressed to resective surgery had good outcomes on average.

SIS may support SOZ localisation.

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