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Systematic 1 Hz direct electrical stimulation for seizure induction: A reliable method for localizing seizure onset zone and predicting seizure freedom

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A B S T R A C T

Objective: To prospectively investigate the utility of seizure induction using systematic 1 Hz stimulation by exploring its concordance with the spontaneous seizure onset zone (SOZ) and relation to surgical outcome; comparison with seizures induced by non-systematic 50 Hz stimulation was attempted as well.

Methods: Prospective cohort study from 2018 to 2021 with ≥ 1 y post-surgery follow up at Yale New Haven Hospital. With 1 Hz, all or most of the gray matter contacts were stimulated at 1, 5, and 10 mA for 30–60s. With 50 Hz, selected gray matter contacts outside of the medial temporal regions were stimulated at 1–5 mA for 0.5–3s. Stimulation was bipolar, biphasic with 0.3 ms pulse width. The Yale Brain Atlas was used for data visualization. Variables were analyzed using Fisher's exact, χ^2, or Mann–Whitney test.

Results: Forty-one consecutive patients with refractory epilepsy undergoing intracranial EEG for localization of SOZ were included. Fifty-six percent (23/41) of patients undergoing 1 Hz stimulation had seizures induced, 83% (19/23) habitual (clinically and electrographically). Eighty two percent (23/28) of patients undergoing 50 Hz stimulation had seizures, 65% (15/23) habitual. Stimulation of medial temporal or insular regions with 1 Hz was more likely to induce seizures compared to other regions [15/32 (47%) vs. 2/41 (5%), $p < 0.001$]. Sixteen patients underwent resection; 11/16 were seizure free at one year and all 11 had habitual seizures induced by 1 Hz; 5/16 were not seizure free at one year and none of those 5 had seizures with 1 Hz (11/11 vs 0/5, $p < 0.0001$). No patients had convulsions with 1 Hz stimulation, but four did with 50 Hz (0/41 vs. 4/28, $p = 0.02$).

Significance: Induction of habitual seizures with 1 Hz stimulation can reliably identify the SOZ, correlates with excellent surgical outcome if that area is resected, and may be superior (and safer) than 50 Hz for this purpose. However, seizure induction with 1 Hz was infrequent outside of the medial temporal and insular regions in this study.

1. Introduction

Approximately 30% of people with epilepsy have medically-refractory seizures, i.e. failed two or more appropriately chosen and dosed anti-seizure medications (ASM) [1]. When information from noninvasive studies is discordant or insufficient, intracranial EEG (ICEEG) recordings are required for additional localizing information and to perform awake extra-operative direct electrical stimulation (DES) mapping [2]. DES is primarily used for functional mapping to aid surgical planning with the main goal of reducing the occurrence of post operative neurological deficits. In addition, DES can elicit seizures. Such stimulation-induced seizures are primarily reported as a by-product of functional mapping using high-frequency stimulation [3].

The earliest report of using DES to induce habitual auras dates to 1909 [4]. Despite its widespread use over the past century, there have only been approximately 20 research studies published to date

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examining the utility of DES in identifying the SOZ. In several older studies, the induced seizures were considered a byproduct of functional mapping and were limited by selective stimulation of contacts (only stimulating the contacts in the SOZ), lack of comparison to spontaneous SOZ, and did not provide correlation with seizure outcome [3,5–7]. Traditionally, high frequency stimulation (typically 50 Hz) has been reported to have a higher chance of inducing seizures but also with high false positive rates (i.e., eliciting seizures outside of the seizure-onset zone) [6,8,9]. This was in contrast to low frequency stimulation which has a lower chance of causing seizures, even within the seizure-onset zone. However, when low frequency stimulation causes seizures, it is likely to be within the seizure-onset zone [10,11]. Two recent publications provided retrospectively analyzed data to support the utility of stimulation-induced seizures, particularly with low frequency, as a valuable tool to identify the SOZ and predict good outcome reliably [10,12].

The primary aim of this study was to systematically investigate the utility of identifying stimulation induced SOZ (SI-SOZ) using both surface (i.e. subdural strips and grid) and depth electrode contacts (i.e. stereo EEG). We utilized a standard stimulation protocol in a prospective cohort of patients to systematically stimulate all or most contacts not in white matter, and examined detailed electroclinical correlates, including concordance with the spontaneous SOZ (SP-SOZ). A secondary aim was to observe if the information obtained from stimulation induced seizures correlated with surgical outcome.

2. Materials and methods

This is a single center prospective cohort study done at the Yale Comprehensive Epilepsy Center and Yale New Haven Hospital. The study cohort included consecutive patients with focal drug-resistant epilepsy who underwent intracranial electroencephalography (ICEEG) between October 1, 2018, and October 1, 2021. ICEEG was offered to patients requiring additional localizing information due to discordant information on non-invasive studies or requiring detailed extra-operative language mapping. ICEEG at our center includes either a combined study (combination of strips, depth electrodes±grid) or stereo EEG (SEEG, only depth electrodes, placed stereotactically with robotic assistance). The design of any ICEEG study was determined on an individual basis and tailored accordingly. 1 Hz stimulation protocol, solely for seizure induction was integrated into routine clinical care to complement the information gleaned from the analysis of spontaneous seizure onset zone (SP-SOZ). All patients underwent systematic 1 Hz stimulation for seizure induction but 50 Hz was only attempted in selected cases based on the clinical scenario. In many cases, 50 Hz was used for functional mapping. This cohort of patients were followed for one year through regular clinic visits to assess surgical outcomes.

The primary goal of our seizure induction protocol was to identify the seizure onset zone using data from stimulation induced seizures, and supplement information available from spontaneous seizures. Stimulation induced seizures were classified as habitual if they were semiologically and electrographically similar to spontaneous seizures. All contacts involved at onset were visually analyzed immediately following the stimulation burst (artifact) for 50 Hz and during stimulation for 1 Hz. Those contacts and the anatomical region involved at onset was identified as stimulation induced seizure onset zone (SI- SOZ). Classification of SP-SOZ was based on a recent publication of ictal onset patterns in a large cohort of patients by Lagarde et al. [13] We identified the following subregions for analyzing seizure onset: mesial temporal, temporal neocortical, orbitofrontal, mesial frontal, lateral frontal, other premotor frontal, Rolandic, operculum, insula, mesial parietal, lateral parietal, medial occipital, and lateral occipital. A clear focal onset was defined as involvement of only one subregion within the initial 2 s. On the other hand, diffuse onset encompassed cases where more than one subregion was involved within the first 2 s. Decisions regarding surgical procedure at the time of electrode explantation were formulated at the multidisciplinary epilepsy surgery conference. All patients had at least one year follow up. DES was performed as part of clinical care. Review of data for this study was approved by the Yale Institutional Review Board.

2.1. Charge density calculation

Charge per phase or pulse (Q), measured in micro coulombs (μC), is a product of pulse width (t), measured in milliseconds here (ms), and stimulation current (I, mA):

$$Q\ (\mu C) = I\ (mA)\ *t\ (ms)$$

Charge density (D), measured as $\mu C/cm^2$, is then calculated by dividing the charge per phase or pulse (Q) by the surface area of the electrode contact:

$$D\ (\mu C/cm^2) = Q\ (\mu C)\ /\ A\ (cm^2)$$

Charge density was calculated using AdTech Spencer depth electrode dimensions (diameter 1.1 mm and length 2.41 mm, giving a surface area of 0.081 cm^2), and surface electrode (exposed diameter 2.3 mm giving a surface area of 0.042 cm^2), which were used in our cases.

2.2. 1 Hz stimulation protocol

All patients underwent systematic 1 Hz stimulation for seizure induction. Contacts in the gray matter were identified using post implant CT with a CT-preimplant MRI reconstruction. All or most gray matter contacts were stimulated with 1 Hz, always starting with the 'silent' or non-epileptiform contacts and marching towards the 'active' or seizure-onset zone. One Hz stimulation was typically done after capturing some spontaneous seizures but not necessarily after restarting anti-seizure medications (ASM). Stimulation waveforms consisted of charge balanced biphasic square waves with pulse width of 0.3 ms. Stimulation was bipolar between adjacent contacts. Each pair of contacts was stimulated at a current of 1 mA, 5 mA, and 10 mA for a duration of 30 s to 1 min at each amperage. This translated to a charge density of 3.7 $\mu C/cm^2$, 18.5 $\mu C/cm^2$ and 36.7 $\mu C/cm^2$ at each amperage for depth electrodes, and 7.14 $\mu C/cm^2$, 35.71 $\mu C/cm^2$, and 71.4 $\mu C/cm^2$ for surface electrodes. If a seizure was induced at a lower current, for example at 1 mA, stimulation was terminated for that contact pair.

2.3. 50 Hz stimulation protocol

50 Hz stimulation purely for the purpose of seizure induction was only attempted in selected cases as dictated by clinical needs. In many cases, 50 Hz stimulation was performed for functional mapping to help delineate boundaries of language or sensorimotor cortex. Stimulation was always bipolar, biphasic and with a pulse width of 0.3 ms. Stimulation always started at 1 mA, and was increased in increments of 1 mA; when performed solely for seizure induction, a maximum of 5 mA was used, corresponding to charge density of 18.5 $\mu C/cm^2$ for depth electrode contacts and 36.7 $\mu C/cm^2$ for surface electrodes. Duration of stimulation ranged from 0.5 s to 3 s. 50 Hz stimulation was not performed for seizure induction purposes in patients who already had a habitual seizure induced with 1 Hz.

2.4. Analyses

Electrode contacts were co-registered to the Yale Brain Atlas, which consists of 690 parcels, each 1 cm^2 built around conserved anatomical features to help communicate anatomically unambiguous localization (Fig. 2) [14]. The Yale Brain Atlas was used to generate composite maps to show contacts stimulated, contacts with induced seizures, and contacts with spontaneous seizures for comparison. Variables were analyzed using the Fisher's exact test, the χ^2 test, or the Mann–Whitney test, as appropriate. P values less than 0.05 were considered significant.

Multivariate analysis was not performed due to the relatively low number of events that limited the number of independent predictors that could be tested and to avoid overfitting the model. Statistical analyses were performed using SAS 9.4.

3. Results

Forty-one consecutive patients with drug resistant epilepsy who underwent ICEEG between October 1, 2018, to October 1, 2021 were included in the cohort. Twenty seven of 41 patients (66%) underwent a combined ICEEG study (depths and subdural electrodes) and the remaining 14/41 (34%) had SEEG study (only depths). The side of implant was as follows: 11/41 (27%) bilateral, 11/41 (27%) dominant hemispheric, and 19/41 (46%) non dominant hemispheric. All patients who had seizures induced with either 1 Hz or 50 Hz had seizure onset i.e. SI-SOZ in the region of stimulation. None of the patients' SI-SOZ was distant from the site of stimulation.

3.1. 1 Hz stimulation

All 41 patients underwent 1 Hz stimulation. 1 Hz stimulation of medial temporal regions was done in 32/41 (78%), insula in 29/41 (71%), temporal neocortical in 30/41 (73%), and extratemporal neocortical in 36/41 (88%). 23/41 (56%) patients had seizures induced with 1 Hz, and 19/23 (83%) were habitual (Fig. 1). Overall rate of atypical or non-habitual seizures was 10% (4/41), or 17% (4/23) of patients with stimulation-induced seizures. All but one patient (22/23, 96%) had an EEG correlate to the stimulation induced seizure, which was similar to the EEG pattern seen with their spontaneous seizures for habitual 1 Hz seizures. All four patients with non-habitual stimulation induced seizures resulted from stimulation of the medial temporal regions (hippocampus/amygdala/entorhinal cortex). Three of these four patients with non-habitual seizures had radiological evidence of mesial temporal sclerosis (MTS) in the region of stimulation induced seizures. 32/41 (78%) patients underwent 1 Hz stimulation of medial temporal regions with the following results: 17/32 (53%) with no seizures, 11/32 (34%) with habitual seizures, and 4/32 (13%) with non-habitual seizures. Of the 15 patients with seizures induced by 1 Hz stimulation of the medial temporal lobe, 27% (4/15) had an atypical seizure. All 41 patients had stimulation of neocortical electrode contacts and only 2/41 (5%) had stimulation induced habitual seizures, and 0/41 had atypical (non-habitual) induced seizures. 1-Hz stimulation of medial temporal (allocortex: hippocampus, amygdala or entorhinal cortex) or insular regions was more likely to induce seizures compared to other neocortical regions [15/32 (47%) vs. 2/41 (5%), $p < 0.001$, OR 17.21 (3.6–79.15)].

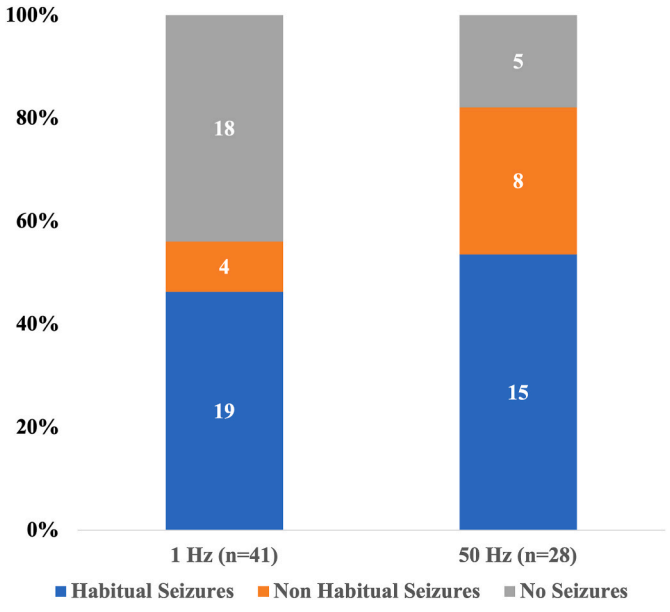

Fig. 1. Compares seizures induced, habitual and non-habitual across 1 Hz and 50 Hz stimulation.

Of the 23 patients who had seizures with 1 Hz stimulation, the distribution of SI-SOZ was as follows: 15/23 (65%) medial temporal region, 6/23 (26%) insular, and 2/23 (9%) extra-temporal neocortical. Fig. 2 is a composite of all patients, and compares contacts stimulated with 1 Hz vs. contacts where habitual seizures were induced vs. electrode contacts involved in spontaneous seizure onset. Fig. 2a visually displays the degree of concordance between 1 Hz SI-SOZ and SP-SOZ. Fig. 2b displays the data of patients in whom seizures were not induced with 1 Hz. Table 1 shows the electroclinical characteristics of patients with at least one seizure induced with 1 Hz stimulation. There was no difference in the number of electrode contact pairs stimulated between the two groups: 41 contact pairs [interquartile range (IQR) 25–61] in the group with 1-Hz induced seizures and 46 contact pairs [IQR (29–58)] in the group without 1 Hz induced seizures. Patients with an aura [86% vs. 56%, $p = 0.03$, OR 5 (1.02–19.88)] and patients with a focal ICEEG onset pattern [78% vs 22%, $p < 0.001$, OR 12.6 (2.8–46)] were more likely to have a seizure with 1-Hz stimulation. The breakdown of MRI findings for the entire cohort was as follows: 15/41 (37%) non lesional, 11/41 (27%) showed cortical dysplasia, 7/41 (17%) had findings suggestive of mesial temporal sclerosis, and 8/41 (20%) exhibited other findings such as prior surgery, cystic lesions, or subtle signal abnormalities, among others. Overall, and upon subgroup analysis, there was no difference in the rate of 1 Hz seizure induction between lesional and non-lesional epilepsies. Patients with evidence of MTS on imaging were more likely [6/7 (86%) vs 17/34 (50%)] to have seizures with 1 Hz but this difference did not reach significance likely due to an underpowered sample size.

3.2. 50 Hz stimulation

50 Hz stimulation was performed in 28/41 (68%) patients. The primary indication for 50 Hz mapping was as follows: functional motor mapping in 8/28 (29%), functional language mapping in 6/28 (21%), and for the purpose of seizure induction in 14/28 (50%). Medial temporal region (hippocampus and amygdala) was stimulated in 7/28 (25%) patients, insula in 14/28 (50%), temporal neocortex in 18/28 (64%), and extra-temporal neocortex in 27/28 (96%). 50 Hz stimulation of the medial temporal region was generally avoided due to clinical concerns for inducing a convulsive seizure or higher likelihood of non-habitual seizures. Only five patients in this cohort had stimulation of the medial temporal region; 4/5 had stimulation-induced seizures and 2/4 were non habitual. Fig. 2c visually displays the degree of concordance between 50 Hz SI-SOZ and SP-SOZ. Fig. 2d displays the data of patients in whom seizures were not induced with 50 Hz.

Seizures were induced in 23/28 (82%) patients and 15/23 (65%) were habitual (Fig. 1). Overall rate of atypical or non-habitual seizures was 29% (8/28), or 35% (8/23) of patients with stimulation-induced seizures. Of the 23 patients who had seizures with 50 Hz stimulation, the distribution of SI-SOZ was as follows: 8/23 (35%) extra-temporal neocortical, 7/23 (30%) temporal neocortical, 4/23 (17%) insular, and 4/23 (17%) medial temporal (hippocampus and amygdala). Among the 15 patients with seizures induced in the neocortical region, five underwent resection, with only one becoming seizure free at one year. Seven had placement of RNS electrodes and three had DBS. Of those with atypical seizures (8/23), four had focal impaired aware (FIA), one focal aware (FA) and three focal to bilateral tonic clonic (FBTC) seizures. SI-SOZ for atypical seizures was as follows: 4/8 (50%) extra-temporal neocortical, 2/8 (25%) temporal neocortical, and 2/8 (25%) medial temporal.

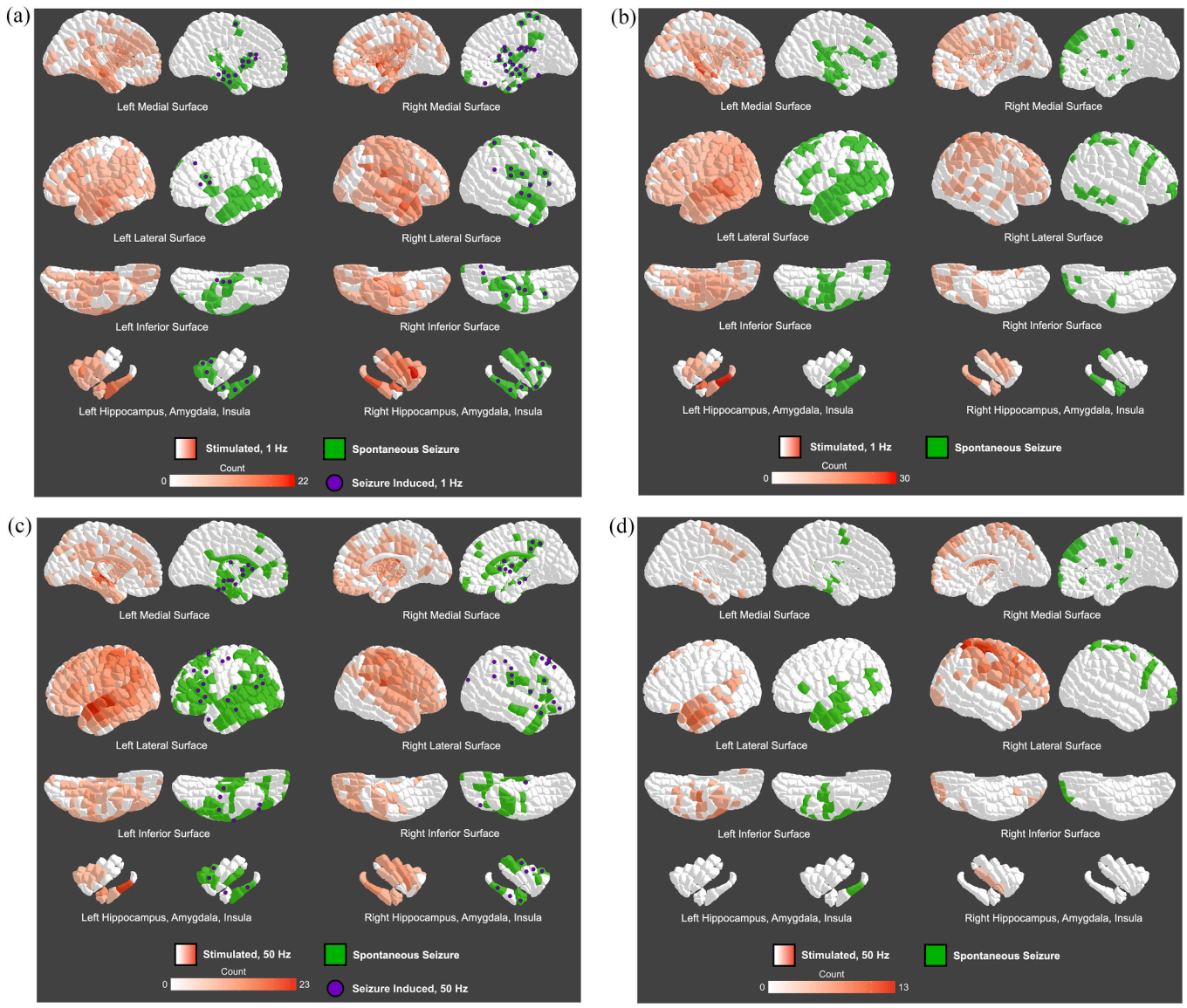

Fig. 2. This composite figure represents patients with electrode contacts co-registered to the Yale Brain Atlas, which comprises 690 one-square centimeter parcels. These parcels are color-coded as follows: red for all parcels stimulated with 1 or 50 Hz, green for parcels associated with spontaneous seizure onset, and purple dots for parcels where habitual seizures were induced. The overlap of purple dots with green-colored parcels indicates concordance between the stimulation-induced seizure onset zone and the spontaneous seizure onset zone. Fig. 2a presents the results for patients in whom seizures were induced with 1 Hz, while Fig. 2b depicts patients who did not experience seizures with 1 Hz. Fig. 2c presents the results for patients in whom seizures were induced with 50 Hz, while Fig. 2d depicts patients who did not experience seizures with 50 Hz. The scale indicates the number of times each parcel was stimulated across the cohort of patients.

3.3. 1 Hz vs. 50 Hz stimulation

As shown in Table 2, compared to 1 Hz, 50 Hz stimulation was more likely to induce seizures overall [82% vs. 56%, p = 0.03, 3.6 (1.1–9.9)], with subdural electrode contacts [59% vs. 21%, p = 0.01, 5.48 (1.38–19.6)], and on the neocortical surface [54% [15/28] vs. 5% [2/41], p < 0.001, 22.5 (4.46–103.9)]. Fig. 2 displays composite results for both 1 Hz and 50 Hz. No patients had convulsions with 1 Hz stimulation, even with stimulating the medial temporal regions (0/32), but four patients had convulsions with 50 Hz stimulation (0% [0/14] vs. 14% [4/21], p = 0.02), with three of those four occurring with stimulation outside of the medial temporal region and 3/4 using surface electrodes. Medial temporal regions were more frequently stimulated with 1 Hz compared to 50 Hz (78% [32/41] vs. 25% [7/28], p < 0.001, 10.67 (3.29–33.41)]. However, there was no difference between the number of contacts per patient, whether the stimulation targeted insular, temporal neocortical or extra-temporal regions, type of contacts stimulated (subdural vs. depth), charge densities or rate of seizure induction with depth electrodes between the two groups (Table 2).

3.4. Outcome

Surgical procedures after electrode explantation for this cohort were as follows: 13/41 (32%) resection alone, 3/41 (7%) resection + responsive neurostimulation (RNS), 14/41 (34%) RNS alone, 9/41 (22%) deep brain stimulation (DBS), and two patients did not have any surgical intervention. Of the 16 patients who underwent resection±RNS, 11/16 had habitual seizures induced with 1 Hz stimulation, all of whom had that area resected. All 11 patients had a good outcome (ILAE class I or II) at one year follow up (P < 0.0001), while the remaining five patients (no seizures induced with 1 Hz) had a poor outcome (ILAE class III or IV). This yielded a sensitivity of 100% (95% CI, 74–100%) and specificity of 100% (95% CI, 57–100%) for predicting seizure freedom with resection of the 1 Hz SI-SOZ, assuming it was a habitual seizure.

Table 1
Electroclinical characteristics of patients who underwent 1 Hz direct electrical stimulation.

Variables	Seizures with 1 Hz DES (n = 23)	No Seizures with 1 Hz DES (n = 18)	P Value, OR (95% CI)
Female, n (%)	11 (48)	14 (78)	ns
Age at onset, y	17 (7–23)	14 (3–21)	ns
History of bilateral tonic clonic seizures, n (%)	19 (83)	14 (78)	ns
Baseline Aura, n (%)	19 (86)	10 (56)	**0.03, 5 (1.02–19.88)**
Epilepsy duration, y	17 (10–32)	19 (14–27)	ns
Duration of icEEG, d	8 (5–9)	8 (7–11)	ns
Electrode contacts, n (%)	160 (136–184)	180 (135–208)	ns
Lesional MRI, n (%)	17 (74)	9 (50)	ns
Focal icEEG onset pattern, n (%)	18 (78)	4 (22)	< **0.001, 12.6 (2.8–46)**
Electrode contact pairs stimulated	41 (25–61)	46 (29–58)	ns
Depth electrode contact pairs stimulated	18 (13–33)	23 (9–32)	ns
Surface electrode contact pairs stimulated	42 (34–47)	30 (17–50)	ns
Seizure free at 1 y post resection, n (%); n = 16*	11/11 (100)	0/5	< **0.0001**

Data is presented as median (interquartile range) or N (%).
* 16 patients in this cohort underwent resection±responsive neurostimulation.

Table 2
Electroclinical characteristics of 1 Hz vs. 50 Hz DES.

Variables	1 Hz DES (n = 41)	50 Hz DES (n = 28)	P Value, OR (95% CI)
Electrode contact pairs stimulated	41 (24–61)	52 (34–64)	ns
Depth electrode contact pairs stimulated	18 (13–33)	17 (6–25)	ns
Surface electrode contact pairs stimulated	42 (34–47)	50 (38–71)	ns
Regional stimulation per patient			
Medial temporal, n (%)	32/41 (78)	7/28 (25)	< **0.0001, 10.67 (3.29–33.41)**
Insula, n (%)	29/41 (71)	14/28 (50)	ns
Temporal neocortical, n (%)	30/41 (73)	18/28 (64)	ns
Extra-temporal neocortical, n (%)	36/41 (88)	27/28 (96)	ns
Sz induced, n (%)	23/41 (56)	23/28 (82)	**0.03, 3.6 (1.1–9.9)**
Habitual seizures, n (%)	19/23 (83)	15/23 (65)	ns
Sz induced with true neocortical (temporal and extra-temporal, excluding insula) contacts, n (%)	2/41 (5)	15/28 (54)	< **0.001, 22.5 (4.46–103.9)**
Sz induced with depth electrode contacts, n (%)	18/38 (47)	10/15 (67)	ns
Sz induced with surface electrode contacts, n (%)	5/24 (21)	13/22 (59)	**0.01, 5.48 (1.38–19.6)**
Sz charge density, μC/cm^2	15 (4–37)	24 (15–36)	ns
Lesional MRI, n (%)	17/23 (74)	15/23 (65)	ns
Focal ICEEG onset pattern, n (%)	18/23 (78)	13/23 (57)	ns
Convulsions, n (%)	0/41	4/28 (14)	**0.02**

Abbreviations: ICEEG = intracranial EEG, Sz = Seizure.
Data is presented as median (interquartile range) or N (%).

Eleven patients who achieved seizure freedom underwent the following resective procedures upon explant: standard anterior medial temporal lobectomy in four cases, insulectomy in four cases, a combination of anterior medial temporal lobectomy and insulectomy in one case, and focal resection of frontal neocortex in one case. All five patients who did not experience 1 Hz induced seizures underwent neocortical resection, with two being supplemented by RNS, yet none achieved seizure freedom at one year. Ten patients in the 50 Hz stimulation cohort proceeded to resection; eight had habitual seizures induced by 50 Hz and had that region resected, and 6/8 had a good outcome. However, all six patients also had habitual seizures induced with 1 Hz stimulation in the resected area. Two patients had habitual seizures induced with 50 Hz but not with 1 Hz; both neocortical (temporal pole and frontal) and underwent resection of that region; however, neither achieved seizure freedom. Supplemental Table 1 presents patient level data comparing SP-SOZ, SI-SOZ, and outcomes.

4. Discussion

In this prospective cohort study of 41 consecutive patients who underwent systematic DES for seizure induction, we found that low frequency stimulation with 1 Hz has a greater than 50% chance of inducing a seizure, a low rate of inducing atypical seizures (4/41, 10%), and no convulsive seizures occurred. Patients with auras and a focal spontaneous SOZ were more likely to have seizures with 1 Hz. If the region where 1 Hz stimulation induced a habitual seizure was resected, this was highly predictive (100% sensitive and specific) of seizure freedom at one year (11/11 patients), consistent with prior reports [10,12] However, among these 11 patients, only one underwent a true neocortical (excluding insula) resection supplemented by RNS and achieved seizure freedom, suggesting that seizure freedom might have been primarily attributable to the region of the brain resected. 50 Hz stimulation was more likely to induce a seizure (82% vs. 56% with 1 Hz), but had a higher likelihood of inducing an atypical seizure (8/28, 29% vs 4/41, 10% with 1 Hz) along with a significantly higher possibility of inducing a convulsive seizure (4/28, 14% vs. 0/41, 0%, p = 0.02). In addition, in the two patients who had a 50-Hz induced habitual seizure but did not have a 1-Hz induced habitual seizure, resection of that region did not result in seizure freedom. Overall, these findings imply that regions where habitual seizures are induced by 1 Hz are more likely to be in the seizure-onset zone compared to those induced by 50 Hz.

Additionally, resection of these regions more closely correlates with achieving seizure freedom. However, it is worth noting that in his cohort, 1 Hz induced SOZ primarily involved the medial temporal (15/23, 65%) or insular regions (6/23, 26%). Despite the higher likelihood of inducing seizures in the neocortical region, 50 Hz SI-SOZ does not reliably predict seizure freedom. This is evidenced by the fact that only 1/15 patients overall having seizures induced by 50 Hz stimulation of the neocortical regions, and 1/5 who underwent neocortical resection of the 50 Hz SI-SOZ were seizure-free at one year. Prior studies found a low likelihood for seizure induction overall but a very low rate of non-habitual seizures, specifically with 1 Hz, and we report similar findings [10,12]. The percentage of seizures induced with 1 Hz stimulation was higher in our cohort (56%) compared to a recent publication (18.2%) that provided this detail [10]. The reasons for this observation are unclear; it is possible this may be a reflection of stimulating more electrode contacts overall, or perhaps indicating the proximity of stimulated electrodes to the true seizure onset zone. Although our stimulation amperage appears high (up to 10 mA), the calculated charge density (the more important measure) is actually lower than that used in prior publications due to our smaller pulse width of 0.3 ms as opposed to 1–3 ms [10,12]. This raises an important issue: charge density (uC/cm^2) should always be reported, as amperage alone can be misleading [15]. Moreover, prior studies, predominantly based on animal data, have reported an inhibitory effect with 1 Hz stimulation, leading to seizure suppression [16–18]. This effect is likely attributed to the longer

duration of stimulation (several hours in animal studies) and lower reported charge density. Such factors may contribute to a subacute or chronic inhibitory effect, as opposed to the acute, presumably excitatory effect observed with shorter duration and higher charge densities, as seen in our data and in previous studies examining low frequency stimulation induced seizures [10,12].

Except for two patients who had a 1-Hz stimulation induced seizure when stimulating extra-temporal neocortical (frontal and parietal) regions, the remainder were from the medial temporal region or insula. These findings are similar to prior studies showing a higher likelihood for 1 Hz to induce seizures from medial temporal regions [10]. Our investigation yielded similar results with insular stimulation as well. We think this may be more due to the restrictive nature of the seizure onset seen in these anatomical regions, which is often not the case with other true neocortical (excluding insula) epilepsies. In that regard, 1 Hz stimulation induced seizures may serve as a surrogate marker for a focal SOZ. Interestingly, stimulation of subdural electrode contacts with 1 Hz was less likely to induce seizures compared to depth electrode contacts. We believe this is likely due to the depth electrode contacts more often being closer (or within) the seizure onset zone and potentially be attributed to the restrictive nature of the SOZ in the medial temporal and insular regions. However, systematic 50 Hz stimulation was not performed in all patients, specifically in those who had a habitual seizure already induced with 1 Hz or concern for inducing non-habitual seizures or convulsions. The increased likelihood of inducing seizures along with a higher rate for non-habitual seizures with 50 Hz stimulation in our study is also similar to recent reports [10].

5. Strengths and limitations

The strengths of our study include the prospective design, standardized stimulation protocol, systematic stimulation of all or most cortical contacts with 1 Hz, comparing seizures induced across surface and depth electrode contacts, which has not been described before, precise anatomical correlation, detailed electroclinical analysis including the reporting of concordance with spontaneous SOZ, and correlation with seizure outcomes. Our detailed analysis and systematic stimulation protocol provides useful insights into the actual utility of low frequency stimulation as an aid to primarily identifying the SOZ and possibly predicting surgical outcome.

Our study has several limitations. First is the moderate sample size, which may exaggerate effect size and limit generalizability. The number of patients undergoing resection was low, further accentuating the limitation of a small sample size when predicting outcome. Moreover, only 1/11 patients who experienced seizures induced by 1 Hz stimulation underwent a true neocortical (excluding insula) resection supplemented by RNS and achieved seizure freedom. This limitation hampers the generalizability of this finding when considering neocortical resections. Additionally, the lack of systematic 50 Hz stimulation was due to clinical concerns regarding the potential induction of non-habitual seizures or convulsions, especially in the medial temporal regions. This limitation restricts our ability to adequately compare 50 Hz stimulation with 1 Hz. This limitation is difficult to overcome as patient safety is of the highest priority during ICEEG monitoring, and a convulsive seizure could compromise patient safety.

6. Conclusions

1 Hz stimulation induced seizures in 56% of patients in our cohort with a high percentage of habitual seizures. 1 Hz induced seizures were more common in patients with a focal ICEEG onset, in patients with an aura, and when stimulating medial temporal or insular regions. Resection of the region of 1 Hz induced habitual seizures predicts seizure freedom reliably, with all 11 such patients becoming seizure free but this was primarily confined to the temporal or insular regions in our cohort. 1 Hz stimulation is significantly less likely to cause convulsions than 50 Hz stimulation. Inability to induce an habitual seizure with 1 Hz was associated with a lower chance of seizure freedom (0 out of 5 patients); thus, the inability to induce an habitual seizure with 1 Hz suggests that electrodes are not in the seizure onset zone or that the patient's epilepsy is not amenable to surgical cure by focal resection, though these findings should be replicated. Our findings add to the growing body of evidence to suggest a role for the routine use of stimulation-induced seizures to supplement the information available for identifying the seizure onset zone and predicting outcome. Inducing a habitual seizure, especially with 1 Hz, may yet be the most reliable surrogate marker confirming adequate sampling of the seizure onset zone and a high chance of a good surgical outcome, especially if confirmed by additional studies.

Data availability

Anonymized data not published within this article will be made available by a reasonable request from any qualified investigator.

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.

CRediT authorship contribution statement

Adithya Sivaraju: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft, Writing – review & editing. **Imran Quraishi:** Data curation, Methodology, Writing – review & editing. **Evan Collins:** Data curation, Visualization, Writing – review & editing. **Hari McGrath:** Data curation, Visualization, Writing – review & editing. **Alexander Ramos:** Data curation, Formal analysis, Writing – review & editing. **Nicholas B. Turk-Browne:** Resources, Writing – review & editing. **Hitten Zaveri:** Methodology, Resources, Software, Supervision, Writing – review & editing. **Eyiyemisi Damisah:** Conceptualization, Data curation, Investigation, Methodology, Resources, Writing – review & editing. **Dennis D. Spencer:** Conceptualization, Supervision, Writing – review & editing. **Lawrence J. Hirsch:** Conceptualization, Investigation, Methodology, Project administration, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2024.03.011.

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