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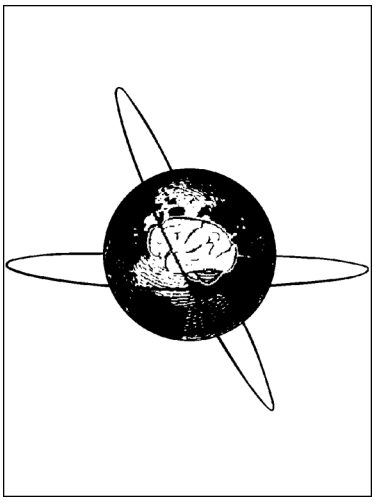

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Validation of direct cortical stimulation in presurgical evaluation of epilepsy

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Abstract

Objective: Direct cortical stimulation (DCS) is standard for intracranial presurgical evaluation in drug-resistant epilepsy (DRE). Few studies have reported levels of concordance between spontaneous seizure generators and triggered seizures during DCS. The present work reports validity measures of DCS for detecting the seizure onset zone (SOZ) during stereoelectroencephalography (SEEG).

Methods: We evaluated all patients who underwent SEEG evaluation at our epilepsy center between 2013 and 2019. Data were analyzed using contingency tables. Validity measures of the diagnostic test were computed for all patients evaluated with DCS and for seizure free patients.

Results: Fifty-eight consecutive patients were evaluated through DCS. One hundred seventy-three clinical seizures were elicited with DCS. Electroclinical identical to spontaneous seizures were considered true positive (TP) seizures. They showed a high specificity (96.9%) for detecting the SOZ in patients that remained seizure free one year after treatment. Sensitivity was low (23.0%), and a high percentage of false-negative stimulations was documented in the SOZ. The accuracy was 87.9%.

Conclusions: DCS is a technique with high specificity but a low sensitivity for the localization of the SOZ. The DCS validity measures need to be known when considered for surgical decisions. The interpretation of DCS-triggered seizures and the differentiation of true-positive vs false-positive seizures should be carefully evaluated.

Significance: DCS seizure triggering is highly specific for SOZ localization.

Keywords: epilepsy, direct cortical stimulation, surgery, drug-resistant, stereoelectroencephalography.

Highlights

- DCS is a technique with high specificity (96.9%) for defining the seizure-onset zone in the presurgical evaluation of drug-resistant epilepsy.
- DCS has low sensitivity (23.0%) due to a high percentage of false-negative stimulations obtained during SEEG monitoring.
- The resection of the contacts involved in eliciting true positive seizures is associated with a good surgical outcome.

Abbreviations: Direct cortical stimulation (DCS); drug-resistant epilepsy (DRE); seizure onset zone (SOZ); stereoelectroencephalography (SEEG); true positive (TP); epileptogenic zone (EZ); temporal lobe epilepsy (TLE); 18-fluorodexyglucose positron emission computerized tomography (18FDG-PET scan); ictal-interictal single photon emission computerized tomography (SPECT); digital subtraction co-registered over the anatomical image (SISCOM); voxel-based morphometry (VBM); and electrical source neuroimaging (ESI), Video-EEG (VEEG); robotic stereotactic surgical assistant ROSA; computerized tomography (CT-scan); radiofrequency thermocoagulation (RF-TC); anti-seizure medication (ASM); IQR interquartile range.

1. Introduction

The direct cortical stimulation (DCS) of the human brain is a widely used technique employed during intracranial explorations of patients with DRE (Bancaud et al., 1974; Bancaud and Chauvel, 1986; Kahane et al., 2006; Trébuchon and Chauvel, 2016; Wieser et al., 1979; Chauvel et al., 1993). It was first described by Cushing in 1909 (Cushing, 1909) and then applied by Penfield, Jasper and Foerster for intraoperative functional mapping (Foerster and Penfield, 1930; Penfield and Jasper; 1954). Whereas Bancaud and Talairach employed DCS to localize the epileptogenic zone (EZ), DCS has also been extensively used to map the human brain's eloquent cortex (Stephani and Lüders, 2011). The seizure onset zone (SOZ) is an electroclinical concept based on intracerebral electroencephalographic (iEEG) recordings and is defined as the exact anatomical point of electrical origin of seizures. The SOZ is interconnected with the initial configuration area, necessary to generate seizures (Bancaud et al. 1962, Bancaud and Chauvel 1986, Buser et al. 1973, Talairach and Bancaud 1973, Talairach et al., 1974). On the other hand, the American school defines the EZ as the minimal area of cortex that must be resected to produce seizure freedom, which includes the SOZ but also the irritative zone, the symptomatogenic zone, the epileptogenic lesion, and the functional deficit zone (Rosenow and Lüders, 2001). Therefore, this is a post-hoc definition, only verified after surgery. In contrast, the concept of EZ proposed by the French school is based primarily on the electrophysiological analysis of epileptic seizures, which is then translated into anatomical terms. This definition is mainly derived from an electroclinical working hypothesis that excludes interictal discharges or the epileptogenic lesion a priori (Kahane et al., 2006).

The primary objectives of DCS are the definition of the EZ and cortical mapping (Bank et al., 2014, Kovac et al., 2016, Huang et al., 2019; Boido et al., 2014; Dionisio et al., 2019; Sarubbo et al., 2020; David et al., 2008, 2010 and 2013; Rahimpour et al., 2019; Boyer et al., 2020; Pizarro et al., 2018; Bartolomei et al., 2004; Kahane et al., 2003; Ojemann et al., 2008). For the evaluation of the EZ, most centers use high-frequency stimulations (50 Hz), while others also apply low-frequency pulses at 1 Hz for longer periods. The aim is to stimulate seizures in highly epileptogenic cortical areas (Voskuyl et al., 1989; Corley et al., 2017; Jacobs et al., 2010). In the early '90s, studies reported a high concordance of spontaneous and electrically triggered seizures (Bernier et al., 1990). Results were superior for patients with unilateral foci and temporal lobe epilepsy (TLE).

From the electrophysiological perspective, DCS can cause seizures or after-discharges (ADs), defined as epileptiform discharges evoked by and outlasting the stimulation. However, it was demonstrated that ADs were not a reliable predictor of the SOZ localization as they were documented in non-epileptic tissue (Wyler and Ward, 1981; Gollwitzer et al., 2018). Still, it was suggested that they could represent a marker of tissue epileptogenicity. In addition, ADs can lead to the erroneous localization of cortical functions if they disrupt regular brain activity (Blume et al., 2004). From a semiology perspective, DCS can elicit clinical seizures (typical or atypical for the patient) or auras without an associated electrical pattern (Ostroswsky et al., 2002; Halgren et al., 1978). The anatomical localization of the stimulus-induced clinical auras can aid localize the symptomatogenic zone and help locate the SOZ (Schulz et al., 1997; Chassoux et al., 2000). Finally, electrical stimulation can also be used for brain function mapping, but this topic is beyond the scope of this publication.

During the bedside evaluation, a careful double check should be performed. On the one hand, the electrical pattern of stimulated seizures should be the same as that of spontaneous seizures. On the other hand, the semiology recorded must also be identical. If these two requirements are met, they are defined as electroclinically identical to the patient's spontaneous seizures (Perrucca et al., 2014; Singh et al., 2015; Kämpfer et al., 2020).

Recent research has focused on the effectiveness and the clinical utility of DCS in delineating the EZ and the eloquent cortex. However, our study focuses on the validity measures of this technique for SOZ localization to be used during the presurgical decision-making process.

2. Materials and Methods

Study design and patient selection

We conducted a retrospective analysis of consecutive patients evaluated by SEEG between January 2013 and December 2019 who have undergone DCS. All patients were evaluated at the Epilepsy Monitoring Unit of Hospital del Mar, Barcelona, a national reference center for refractory epilepsy and member of the European Reference Network EPI-Care. After a non-invasive diagnosis, the decision to perform an SEEG for diagnostic purposes was taken at our multidisciplinary case discussion meeting.

Ethics committee

The Ethics Committee in Clinical Research (CEIC-Parc de Salut Mar) examined and approved the protocol. All patients signed informed consent to use their data in this protocol. The study complied with good clinical practices as required by the principles of the 2008 Declaration of Helsinki of the World Medical Association and current legislation on personal data protection (Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights).

Presurgical Diagnosis

The diagnostic protocol included a high-resolution magnetic resonance brain imaging (3T MRI) (3T Philips Achieva, Koninklijke Philips N.V., Netherlands) and extensive neuropsychological evaluation. Based on presurgical evaluation needs, we used brain 18-fluorodeoxyglucose positron emission computerized tomography [(18FDG]-PET scan), ictal-interictal single-photon emission computerized tomography (SPECT) with digital subtraction coregistered over the anatomical image (SISCOM), voxel-based morphometry (VBM), and electrical source neuroimaging (ESI). Video-EEG (VEEG) recordings were collected using a standard clinical EEG system (XLTEK®, Natus Medical), and the implantation strategies were decided based on the semiological, electrophysiological, and neuroradiological data. The patients were implanted with deep electrodes using the robotic stereotactic surgical assistant ROSA® (Medtech, France).

Implantation procedure and postprocessing imaging

The electrode targets and trajectories were established exclusively for clinical reasons using a stereo-electroencephalographic approach. The number of electrodes varied between patients with 5-18 contacts each (diameter: 0.8 mm; contacts 2 mm long, 1.5 mm apart) (DixiMédical, France). After implantation, electrodes' localization was determined by co-registering the high-definition head CT scan (General Electrics®, Boston, MA, USA) subtracted over the pre-implantation 3T MRI. Each contact was located and reviewed in three dimensional (3D) projections (3D Slicer, **http://www.slicer.org**, Surgical Planning Laboratory, Harvard University, Boston, MA, USA) to determine the exact anatomical localization. Additionally, a pre-resectional angio-3T MRI was co-registered with the post-implantation computerized tomography (CT-scan) for vessel avoidance during radiofrequency thermocoagulation (RF-TC). The SEEG recordings were visually inspected

by three epileptologists (ML, RR and AP) to determine the area involved in the SOZ. We analyzed the contacts involved in the first three seconds from the seizure onset. The seizure onset patterns were considered localizing if they were focal sub-lobar and non-localizing if they involved multiple sub-lobar areas or brain lobes.

DCS Methodology

After the electrophysiological plot test, only electrically compatible with gray matter contacts were chosen for DCS. High-frequency DCS (1-5 mA, 50 Hz, 5-10 seconds) of the selected cortical contacts was performed on all patients. We also delivered low-frequency pulses (1-5 mA, 1 Hz, 20-40 seconds) to patients with mesial temporal lobe epilepsy. Both types of DCS were performed after recording spontaneous seizures (except in one patient who showed no spontaneous seizures during three-week-long intracranial exploration). Patients received their regular anti-seizure medications (ASMs) regimen during DCS, which was re-started after recording spontaneous seizures. Additionally, clinical symptoms elicited by the stimulations were recorded, and particular emphasis was given to the elicited semiologically typical auras. ADs were defined as rhythmic transient epileptic activity caused by DCS, which does not produce clinical symptoms and shows no evolution but lasts for more than 2 seconds (Gollwitzer et al., 2018).

Statistical analysis

A descriptive analysis of all variables of interest was carried out. For this purpose, the mean, standard deviation, and range were calculated for numeric variables, and the absolute and relative frequencies were computed in the case of categorical variables.

Contingency tables were constructed by recording the spontaneous seizures and those caused by DCS. To build the contingency tables, all seizures and stimuli were classified. Triggered seizures electro-clinically identical to spontaneous seizures were considered as true positives (TP). A false positive (FP) seizure was considered when stimulation produced a seizure not electro-clinically concordant with the patient's spontaneous seizures (Fig. 1). A true negative (TN) was recorded when the stimuli outside the spontaneous recorded SOZ did not trigger a seizure. A false negative (FN) was considered when the stimulation of contacts within the SOZ did not cause seizures. In this analysis, we performed a two-fold analysis, first using the validation measures for the entire sample

of patients to compare the proportions of true positives between patients with good and poor postoperative outcomes. Subsequently, we performed the analysis considering patients who had become seizure free (SF) equivalent to Engel I, compared to those who were not seizure free (NSF), including Engel II to IV, to assess the proportion of DCS outcomes.

The true positive (sensitivity) and true negative (specificity) rates, as well as the positive (PPV) and negative (NPV) predictive values, have been estimated fitting mixed-effects logistic regression models. For the estimation of the TP and TN rates, the outcome variable of the model was a stimulated seizure, and the explicative variable was a spontaneous seizure. For the accuracy measure, a random-effects logistic regression model has been fitted to model seizures and stimuli concordance.

In addition, the associations of the classification in seizure free or non-seizure free with several variables of interest were studied using bivariate analyses. In the case of numeric variables, the t-test was used, and the chi-squared test was applied in the case of the categorical variables. Multivariate analyses were not carried out for two reasons: i) the small sample size; ii) the included variables were recorded at different time points.

After completing the evaluation, patients with localized epilepsy received treatment with RF-TC, LiTT or resective surgery as indicated. Unlike other groups, we perform RF-TC as a routine procedure in focal epilepsies even though the patient is a good candidate for surgical resection. If epilepsy relapsed after RF-TC, classic surgery was performed if indicated. Patients without localized epilepsy after SEEG diagnostic were ruled out of surgical procedures. However, in patients involving eloquent areas, RF-TC was performed after a case-by-case analysis if it was considered safe for the patient.

Seizure outcomes were calculated later on for all patients who received some form of surgical procedure. The data were compared between the seizure free and the non-seizure free groups. Validity measures of the diagnostic test were finally calculated in all groups.

All statistical analyses were carried out with the statistical software R, version 4.0.2. (Vienna, Austria; **https://www.r-project.org**) and the Python scientific library. Statistical significance was set at 0.05.

3. Results

3.1 Direct Cortical Stimulation

Of the 73 patients included in the study, six were implanted with subdural grids and thus excluded from the analysis. Sixty-seven patients were implanted with intracerebral electrodes (SEEG). Of these, nine were excluded from DCS due to medical complications, contraindications (hemorrhages, psychotic episodes, and status epilepticus), or incomplete information related to the DCS procedure. Among the remaining 58 patients, the average age was 35.9 years (SD 10.9 [15-59]). Twenty-two patients (37.9%) were women (Table 1). Thirty-three patients (56.9%) had temporal lobe epilepsy, seven (12.0%) frontal lobe epilepsy, six (10.3%) occipital lobe epilepsy, eight (13.8%) parietal lobe epilepsies, and four (6.9%) had insular involvement in the EZ. More than half of the patients had non-lesional epilepsy (55.2%). The mean age at epilepsy onset was 14.7 years (SD 8.7 [1-48]), and the mean length of disease duration was 21.1 years (SD 12.3 [3-50]). The mean duration of the intracranial studies was 10.2 days (SD 3.1 [5-19]). The average number of implanted electrodes per patient was 11.8 (SD 3.4 [5-19] total of 684) with a mean number of contacts of 130.4 (SD 44.7 [28-217] total of 7561). After the electrophysiological plot test and the 3D review of anatomical coordinates, we identified 4168 contacts in cortical positions (mean 73.1 SD 32.6 [11-171]). All contacts located in the white matter were excluded for visual analysis and as targets for DCS.

During intracranial recordings, a total of 4450 spontaneous seizures were registered. The median number of spontaneous seizures per patient was 13.5 (IQR: 8.0-51.0). Fifteen patients (25.9%) showed focal aware non-motor seizures, five (8.6%) focal aware motor seizures, six (10.3%) focal impaired awareness non-motor seizures, and 42 (72.4%) focal impaired awareness motor seizures. Thirteen patients (22.4%) showed spontaneous focal to bilateral tonic-clonic seizures. The most frequent seizure onset pattern in the SEEG was gamma activity (63.8% of patients), followed by beta (17.2%), alpha (12.1%) and delta (3.5%) rhythmic patterns. The average number of contacts involved in the first three seconds at seizure onset was 10.0 (SD 11.8 [1-68]).

During DCS, a total of 254 seizures were elicited. Among these seizures, 173 (mean 3.0 SD 3.0 [0-11]) (68.1%) were clinical seizures.

3.1.1 High-frequency stimulation

Stimulation at 50 Hz was performed on all 58 patients. Forty (69%) presented 166 clinical seizures (mean 2.9 SD 3.0 [0-11]). Nine patients presented a total of 30 focal aware non-motor seizures (18.1%), six had 20 focal impaired awareness non-motor seizures (12.0%), three 16 focal aware motor seizures (9.6%), 22 had 82 focal impaired awareness motor seizures (49.4%), and six, 18 focal to bilateral tonic-clonic seizures (10.3%). At the individual patient level, the most frequent pattern of seizure onset at 50 Hz was gamma activity (29.3% of patients), followed by beta (19.0%), alpha (12.1%) and theta (8.6%) patterns.

3.1.2 Low-frequency stimulation

Stimulation at 1 Hz was performed on 34 patients (58.6%), eliciting a total of seven clinical seizures. Seizures were elicited in only six patients (17.6%), all of them with TLE. Five out of six patients also presented seizures at 50Hz stimulation. One patient had one focal aware non-motor seizure (14.3%), two had two focal impaired awareness non-motor seizures (28.5%), three showed three focal impaired awareness motor seizures (42.8%), one had one focal to bilateral seizure (14.3%), and none showed focal aware motor seizures**.** On an individual basis, the most frequent seizure onset pattern at 1 Hz was gamma activity (11.8% of patients), followed by beta (2.9%) and alpha (2.9%) patterns.

3.2 Surgical treatment

Following the DCS procedure, a total of 51 (87.9%) patients underwent a potentially curative surgical procedure.

Resective surgery was performed in 28 (54.9%) of these patients, 21 (41.1%) were treated with RF-TC only, two (3.9%) with LiTT. The remaining seven patients were offered different options of palliative surgeries or remained seizure free at the last follow-up: two had disconnections (hemispherotomy), one patient with vagal nerve stimulation (VNS), three were seizure free after SEEG alone, and one refused any form of treatment.

3.3 Validity measures of the diagnostic test

Among all patients irrespective of the treatment employed (n=58), 27 (46.5%) were seizure free after 12 months of follow up.

Considering the seizure free group (n=27), according to validity criteria, 59 seizures (50.8% of all triggered clinical seizures) were identified as TP (mean 2.2 SD 2.4 [0-9] TP/patient), while 57 (49.1%) seizures were classified as FP (2.1 SD 2.7 [0-10] FP/patient). On an individual basis, seventeen patients (63.0%) had TP seizures, while 13 (48.1%) had FP seizures. Specifically, eight patients (29.6%) presented TP seizures only, five had (18.5%) FP seizures only, 9 patients (33.3%) both types of seizures, and five (18.5%) neither (Table 2).

In the non-seizure free group (n=31), 23 seizures were identified as TP (0.7 SD 1.1 [0-5] TP/patient), whereas 34 seizures were classified as FP (1.1 SD 1.5 [0-6] FP/patient). On an individual basis, TP were observed in twelve patients (38.7%), while 15 patients (48.4%) presented FP seizures. Specifically, three patients (9.7%) had exclusively TP, seven (22.6%) patients presented FP only, nine (29.0%) patients presented both types, and 12 (38.7%) patients neither.

FN stimulations were obtained in 51 patients (87.9%). Subclinical seizures (SCS) were stimulated in 21 patients (36.2%) but not considered part of this validity analysis.

3.3 Favorable seizure outcome associated factors

Three main factors were associated with a favorable seizure outcome after intracranial exploration:

3.3.1. A localizing electrical pattern at the ictal onset: a localizing electrical pattern at the ictal onset during spontaneous seizures was associated with a positive surgical outcome (p=0.021). The seizure onset pattern was considered localized in 21 patients (77.8%) in the seizure free group vs 15 patients (48.4%) in the non-seizure free group. Even more so in the temporal lobe, where the proportion of seizure free patients (74.1%) was twice as high as in other focal epilepsies (p=0.014). A trend toward fewer contacts involved in the SOZ was documented in the favorable surgical outcome group (7.2 SD 6.5 [1-27] vs 12.5 SD 14.6 [2-68]; p=0.093).

3.3.2. Direct cortical stimulation results: factors associated with a favorable surgical outcome related to DCS involved three aspects: (1) typical auras, defined as the reproduction of the initial symptoms of a seizure but without an EEG correlate of ictal pattern, were twice as frequent in

the seizure free group of patients than in the non-seizure free group (p = 0.048); (2) total seizures triggered with DCS (p=0.001) and the stimulation of clinical seizures at 50Hz (p=0.003). Clinical seizures following 50 Hz stimulation were almost twice as frequent in the seizure free group than in the non-seizure free group, and (3) elicitation of TP seizures in the spontaneous SOZ. Seizure free patients have a higher number of TP compared to the non-seizure free group (2.2 vs 0.7, p=0.004); seventeen patients (63.0%) in the seizure free group presented electro-clinically typical seizures during DCS compared to 12 patients (38.7%) in the non-seizure free group (p = 0.065). Etiology and the number of ASMs during DCS were not predictors of seizure outcome. The presence or absence of a lesion and the type of lesion were not predictors of seizure triggering during DCS.

3.3.3. Agreement between RF-TC/resected contacts with the spontaneous SOZ or the DCS defined SOZ: the higher the agreement between the RF-TC contacts or the resected contacts with those involved in the spontaneous SOZ, the greater the probability of remaining seizure free one year after treatment (p = 0.005; p = 0.019). Similarly, our results show that the higher the agreement between the resected contacts with the contacts involved in the SOZ obtained by DCS (TP seizures only), the greater the probability of a positive surgical outcome (p<0.001). The agreement between RF-TC contacts and the contacts involved in the SOZ obtained by DCS was non-significant (p=0.587) (Fig. 2).

4. Discussion

DCS is widely used during SEEG diagnosis for seizure-triggering to define the SOZ and map the eloquent cortex. The data analyzed in this study has assessed the validity measures of this technique. In our study, 70.6% of the patients presented DCS stimulated seizures, consistent with previous reports in which they occurred between 57.3% and 63% of patients (Cuello et al., 2019; Bernier et al., 1990). Indeed, stimulated seizures were associated with a better surgical outcome in the same direction as previously reported. Our results confirm that electroclinically typical DCS-triggered seizures (TP) are a good predictor of postsurgical seizure outcome as they occur more frequently in seizure free patients (p=0.004). Moreover, they have a specificity of 96.9% (CI (95%): [96.0-97.6]) in the localization of the epileptogenic zone, higher than that obtained with FDG-PET (71%; CI (95%): 0.63-0.78) (Niu et al., 2021). However, sensitivity (23%) was lower

when compared with PET (56%) or SPECT (87%) for localizing the EZ (Desai et al., 2013; von Oertzen, 2018).

Our analysis also showed that typical auras as a semiological phenomenon during stimulations are twice as frequent in the seizure free group than in the non-seizure free group. This finding is consistent with other reports in the literature. It suggests that the stimulated contacts are localized in the symptomatogenic zone, close to or in the SOZ (Cushing, 1909; Foerster and Penfield, 1930; Penfield and Jasper, 1954).

Stimulation studies have described that neither ADs nor SCSs are reliable biomarkers for SOZ localization (Bernier et al., 1990; Gollwitzer et al., 2018). Gollwitzer et al. (2018) studied the incidence of ADs and SCSs and the localization, duration, and probability of aborting them with brief pulse stimulation (BPS). They considered ADs to be an unwanted event that can interfere with the mapping of cortical functions and confound the localization of the SOZ. They observed ADs in the SOZ, the interictal zone and outside the epileptogenic zone. ADs were observed in 14% of our patient group, triggered by high and low-frequency stimulation patterns in various brain regions, with the hippocampus being the most prone area. We did not find any difference in ADs distribution or frequency comparing seizure free vs non-seizure free patients (96.3-83.9%, p=0.26). Induced SCS were present in 14.1% of patients with a good surgical outcome vs 54.8% of patients with a poor surgical outcome (p=0.004). Due to the lack of concordance between SCS and SOZ coupled with the absence of clinical correlation, we cannot conclude that electrically stimulated SCS has prognostic relevance. However, we cannot rule out that it reveals some potential epileptogenicity of uncertain significance during electrical stimulation.

DCS seizure stimulation has also resulted in good postsurgical outcomes in those patients who do not exhibit spontaneous seizures during SEEG (Cuello et al., 2019). In our registry, we identified a single case without spontaneous seizures but stimulated by DCS, who was seizure free after RF-TC. At present, however, there is little evidence to justify resective surgery in these conditions.

The diagnostic value of false-positive seizures is still debated. Our results suggest that the triggering of false-positive seizures may have some relevance, as they were more frequent in the seizure free group. When non-identical semiology occurs with a different SEEG pattern, this may reflect that the DCS is being administered in an epileptogenic tissue close to but not in the SOZ and

therefore not delineating the epileptogenic zone. Triggered seizures showing atypical semiology should therefore be given zero diagnostic value as they may be the consequence of direct stimulation of areas with a low seizure threshold or overstimulation of brain tissue unrelated to the epileptogenic network (Mariani et al., 2021; Blume et al. 2004).

The resection of the involved contacts apparently is associated with a good postsurgical outcome (Kämpfer et al., 2020). Our results corroborate that surgical resection of the contacts involved in the triggered TP seizures is associated with seizure freedom.

In terms of study limitations, our analysis only assessed the electrophysiological parameters used in the localization of the SOZ, but not in the delimitation of the EZ, which has a broader definition and includes the interictal area and early seizure propagation. In this work, we evaluated seizure freedom rates, which may introduce a hypothetical bias caused by the complete/incomplete resection of the EZ due to surgical limitations. In RF-TC, the proximity of vessels prevents the ablation of some contacts. In this regard, not all contacts involved in the SOZ can be targeted as desirable due to these circumstances. On the other hand, it is recognized that complete surgical resections cannot always be adequately performed due to patient safety concerns. In addition, the identification of eloquent areas during DCS limits the extent of some surgical resections.

Also, the number of contacts located in the EZ may have influenced the proportion of false-negative vs true-positive stimulations if the contacts were placed close to but not within the SOZ.

In conclusion, our data indicate that DCS is a highly specific technique for defining the SOZ, although with low sensitivity. As a biomarker of SOZ, TP seizure triggering represents a factor associated with favorable seizure outcomes. The contacts involved in triggering seizures should be considered when planning surgical procedures in patients with focal epilepsy refractory to ASMs.

Ethical considerations

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.

The authors declare that the journal policies in the authors' guide have been reviewed.

Data accessibility statement

Data exposed in this paper are accessible to be shared with other researchers interested in accessing the databases.

Conflict of interest

None of the authors has potential conflicts of interest to be disclosed. The authors declare that all authors in this paper have reviewed its content and agree with its final version.

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Author contributions

Miguel Ley Nácher was responsible for data collecting, statistical analysis, medical writing, and methodology design.

Nazaret Peláez contributed to data collection and manuscript reviewing.

Alessandro Principe contributed with medical writing, neurophysiological and graphical contents.

Klaus Langhor was responsible for the statistical analysis and methodology.

Riccardo Zucca reviewed the article, corrected the edition, and analysed the methodology.

Rodrigo Rocamora was responsible for the study concept, methodology design and medical writing.

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Legends

Table 1: Demographics and seizure outcome-related factors. n: sample size available for each variable. In parenthesis, the number of seizure free and non-seizure free patients is reported. p: p-value obtained from either t-test or chi-squared test. NSF: non-seizure free + non-surgical/radiofrequency thermo-coagulation/laser interstitial thermo-ablation candidates' group. SD: standard deviation. TLE: temporal lobe epilepsy; FLE: frontal lobe epilepsy; IE: insular epilepsy; PLE: parietal lobe epilepsy; OLE: occipital lobe epilepsy; MRI: magnetic resonance imaging; Sz: seizures. SOZ: seizure onset zone; DCS: direct cortical stimulation; Hz: Hertz; s: seconds; RF-TC: radiofrequency thermo-coagulation; LiTT: laser interstitial thermotherapy.

Table 2: Contingency table of elicited seizures and stimulations, validity measures of the diagnostic test and distribution of seizure type/stimulations in seizure free group. n: number of patients; CI: confidence interval; SD: standard deviation. PPV: positive predictive value; NPV: negative predictive value; TPS: true positive seizures; FPS: false positive seizures; TNS: true negative stimulations; FNS: false-negative stimulations.

Figure 1. Example of a patient in which RF-TC targeted only the contacts involved in true positive seizures elicitation during DCS rendering a seizure free state one year after treatment. A: iEEG recording of a spontaneous seizure. Electrical pattern showing SOZ on the left amygdala. Ictal time-frequency plot of the SOZ (contact A'1-2). B: iEEG recording of a true positive seizure generated after electrical stimulation of the left amygdala (50Hz). Ictal time-frequency plot of the SOZ (contact A'1-2). C: a false positive elicited seizure. D & E: implantation strategy. F: anatomical seizure onset zone (left amygdala, targeted with electrode A'). RF-TC: radiofrequency thermocoagulation; DCS: direct cortical stimulation; iEEG: intracranial electroencephalography; SOZ: seizure onset zone; s: seconds; Hz: Hertz; dB/Hz: decibels vs Hertz. A'-C': contact position in the brain.

Figure 2. Comparison between the seizure free (SF) and non-seizure free candidates (NSF/NC) groups in relation to the targets obtained with the radiofrequency thermocoagulation (RF-TC) and the resection on the spontaneous seizure onset zone (SOZ) and that obtained by direct cortical stimulation (DCS). (RF-TC vs Spontaneous SOZ: percentage of contacts involved in the

spontaneous SOZ that were targeted with RF-TC; RF-TC vs DCS-SOZ: percentage of contacts involved in TP seizures obtained during DCS that were targeted with RF-TC; Resection vs Spontaneous SOZ: percentage of contacts of the spontaneous SOZ that were resected with surgery; Resection vs DCS-SOZ: percentage of contacts involved in TP seizures obtained during DCS that were resected with surgery). % percentage; p = p-value; TP: true positive seizures.

	n	Seizure free	Non-seizure free	p-value
Age (years)	58 (27/31)	35.3 (SD 11.5 [19-59])	36.3 (SD 10.5 [15-53])	0.733
Gender (Female)	58 (27/31)	10 (37.0%)	12 (38.7%)	0.896
Type of epilepsy	58 (27/31)			0.090
TLE		20 (74.1%)	13 (41.9%)	
FLE		3 (11.1%)	4 (12.9%)	
IE		0	4 (12.9%)	
PLE		2 (7.4%)	6 (19.4%)	
OLE		2 (7.4%)	4 (12.9%)	
MRI Lesion	58 (27/31)	9 (33.3%)	17 (54.8%)	0.100
Epilepsy onset (years)	58 (27/31)	15.1 (SD 10.1 [1-48])	14.4 (SD 7.4 [1-30])	0.777
Epilepsy duration (years)	58 (27/31)	20.3 (SD 11.9 [5-44])	21.9(SD 12.9 [3-50])	0.617
Localizing spontaneous Sz Pattern	58 (27/31)	21 (77.8%)	15 (48.4%)	**0.021**
DCS typical Sz onset pattern	39 (21/18)	14 (66.7%)	12 (66.7%)	0.459
Number of spontaneous Sz	58 (27/31)	15.0 (SD 21.3 [0-94])	130.5 (SD 423.2 [2-2386)	0.162
Number of 1Hz DCS Sz	34 (17/17)	0.35 (SD 0.6 [0-2])	0.06 (SD 0.2 [0-1])	0.073
Number of 50Hz DCS Sz	58 (27/31)	4.1 (SD 3.5 [0-11])	1.8 (SD 1.9 [0-6])	**0.003**
Number of DCS contacts	57 (27/30)	73.3 (SD 29.0 [21-129])	73.0 (SD 35.9 [11-171])	0.976
Number of implanted electrodes	58 (27/31)	11.2 (SD 3.1 [5-15])	12.3 (SD 3.7 [6-19])	0.242
Total seizures triggered	58 (27/31)	4.3 (SD 3.5 [0-11])	1.8 (SD 1.9 [0-6])	**0.001**
Patients with after-discharges	58 (27/31)	26 (96.3%)	26 (83.9%)	0.264
Patients with interictal rhythmic spikes	58 (27/31)	7 (25.9%)	12 (38.7%)	0.301
Number of contacts involved in 3 s	57 (26/31)	7.2 (SD 6.5 [1-27])	12.5 (SD 14.6 [2-68])	0.093
DCS elicited Sz -spontaneous SOZ agreement (in %)	57 (26/31)	26.0 (SD 28.8 [0-100])	7.6 (SD 16.8 [0-66])	**0.004**
Number of typical auras elicited	58 (27/31)	3.6 (SD 4.8 [0-18])	1.6 (SD 2.7 [0-10])	**0.048**
Patients with subclinical DCS Sz concordant with SOZ	58 (27/31)	3 (11.1%)	6 (19.4%)	0.387
Number of DCS elicited Sz non-concordant with spontaneous SOZ	58 (27/31)	2.0 (SD 2.6 [0-10])	1.2 (SD 1.7 [0-6])	0.139
Patients treated with RF-TC	58 (27/31)	16 (59.3%)	21 (67.7%)	0.503
Patients treated with resection	58 (27/31)	15 (55.6%)	13 (41.9%)	0.300
Patients treated with RF-TC + resection	58 (27/31)	7 (25.9%)	7 (22.6%)	0.766
RF-TC & Spontaneous SOZ agreement (in %)	39 (15/24)	55.0 (SD 27.9 [10-100])	28.6 (SD 25.7 [0-100])	**0.005**
RF-TC & DCS-SOZ agreement	25 (12/13)	55.6 (SD 37.2 [0-100])	46.8 (SD 42.4 [0-100])	0.587
Resection & Spontaneous SOZ agreement (in %)	24 (15/9)	89.1 (SD 20.0 [43-100])	56.8 (SD 42.6 [0-100])	**0.019**

Resection & DCS SOZ agreement (in %)	23 (13/10)	89.4 (SD 26.9 [12.5-100])	23.3 (SD 41.7 [0-100])	**<0.001**
LiTT	58 (27/31)	0	2 (6.5%)	0.534

Seizure elicited	**Electro-clinically identical seizure** Yes	No		
Yes	True positive (59)	False-positive (57)		
No	False-negative (198)	True negative (1784)		
Seizure free				
n	27			
Sensitivity	23.0%; CI (95%): [18.2-28.5]			
Specificity	96.9%; CI (95%): [96.0-97.6]			
PPV	50.9%; CI (95%): [41.9-59.8]			
NPV	90.0%; CI (95%): [88.6-91.3]			
Accuracy	87.9%; CI (95%): [86.4-89.2]			
	n	Mean	SD	Rank
TPS	27	2.2	2.4	0-9
FPS	27	2.1	2.7	0-10
TNS	27	66.1	30.7	18-134
FNS	27	7.3	10.7	0-51