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Electrical Stimulation of Subiculum for the Treatment of Refractory Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis: A 2-Year Follow-Up Study

Daruni Vázquez-Barrón Manola Cuéllar-Herrera Francisco Velasco
Ana Luisa Velasco

Unit of Functional Neurosurgery, Stereotaxy and Radiosurgery, General Hospital of Mexico, Mexico City, Mexico

Keywords
Deep brain stimulation · Epilepsy surgery · Hippocampal sclerosis · Mesial temporal lobe epilepsy · Subiculum

Abstract
Introduction: Evidence has been provided that the subiculum may play an important role in the generation of seizures. Electrical stimulation at this target has been reported to have anticonvulsive effects in kindling and pilocarpine rat models, while in a clinical study of hippocampal deep brain stimulation (DBS), contacts closest to the subiculum were associated with a better anticonvulsive effect. ***Objectives:*** To evaluate the effect of electrical stimulation of the subiculum in patients with refractory mesial temporal lobe epilepsy (MTLE) who have hippocampal sclerosis (HS). ***Methods:*** Six patients with refractory MTLE and HS, who had focal impaired awareness seizures (FIAS) and focal to bilateral tonic-clonic seizures (FBTCS), had DBS electrodes implanted in the subiculum. During the first month after implantation, all patients were OFF stimulation, then they all completed an open-label follow-up of 24 months ON stimulation. DBS parameters were set at 3 V, 450 μs, 130 Hz, cycling stimulation 1 min ON, 4 min OFF. ***Results:*** There was a mean reduction of 49.16% (±SD 41.65) in total seizure number (FIAS + FBTCS) and a mean reduction of 67.93% (±SD 33.33) in FBTCS at 24 months. FBTCS decreased significantly with respect to baseline, starting from month 2 ON stimulation. ***Conclusions:*** Subiculum stimulation is effective for FBTCS reduction in patients with MTLE and HS, suggesting that the subiculum mediates the generalization rather than the genesis of mesial temporal lobe seizures. Better results are observed at longer follow-up times.

Introduction

Deep brain stimulation of the hippocampus (DBS-HC) is effective in the treatment of mesial temporal lobe epilepsy (MTLE) [1–4]. However, in patients with hippocampal sclerosis (HS), the antiepileptic effect is retarded and decreased in regard to patients with non-lesional MRI [3]. Conceivably, cell loss and scarring of the sclerotic hippocampus may be responsible for the decrease in the antiepileptic response. Although cell loss can be severe in the hippocampus of patients with MTLE, it is not common in the subiculum [5, 6].

karger@karger.com
www.karger.com/sfn

Ana Luisa Velasco
Functional Neurosurgery, Stereotaxy and Radiosurgery
General Hospital of Mexico, Cerrada Bosques de Moctezuma 55
Huixquilucan, Estado de Mexico, Mexico City 52784 (Mexico)
analuisav@yahoo.com

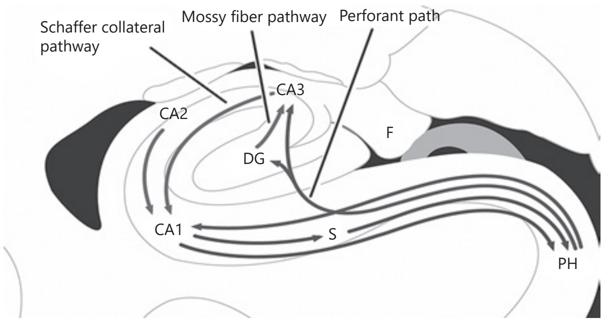

Fig. 1. Hippocampal formation pathways. PH, parahippocampus; S, subiculum; DG, dentate gyrus; F, fimbria.

For more than a decade, evidence has been provided that the subiculum may play an important role in the generation of seizures. Spontaneous rhythmical and synchronous EEG activity in the subiculum has been registered in epilepsy animal models and human epileptic tissue [7, 8]. This observation has led to the concept of a "pacemaker" that would be the result of neural plasticity after deafferentation, which would explain the persistence of seizures in spite of hippocampal cell loss [9].

Fabó et al. [10] demonstrated spike generation and synchrony in the subiculum during intra-operative recordings and suggested that those spikes were strongly linked to seizures. Zhong et al. [11] found that electrical stimulation at the subiculum had anticonvulsant effects in kindling and pilocarpine rat models. In a publication on DBS-HC for the treatment of MTLE, Bondallaz et al. [12] reported that active contacts that were closest to the subiculum were associated with a better anticonvulsant effect, as compared to contacts located farther than 3 mm from the subiculum. Patients in this study had been previously described by Boëx et al. [13]: 2 of 9 patients had HS and one of them was the only to have focal to bilateral tonic-clonic seizures (FBTCS). It is reported that FBTCS disappeared right after implantation and first stimulation while focal impaired awareness seizures (FIAS) had a 67% reduction.

Aside from its intrinsic functions, the subiculum is considered to be an input and output gateway, or projection system, between the hippocampus and several cortical and subcortical structures (Fig. 1). In a way, this role can be considered similar to that of the centromedian nucleus, which has been widely studied by our group for the treatment of generalized epilepsy. This analogy and the fact that generalized seizures disappeared after electrode implantation near the subiculum in the study by Boëx et al. [13] made us think that the subiculum might also be involved in seizure propagation.

We herein present the experience of treating a group of patients with MTLE and HS through DBS electrodes targeted to the subiculum (DBS-SC), comparing the antiepileptic effect with that of our previous series with similar cases treated with DBS-HC.

Materials and Methods

Complying with the Declaration of Helsinki, this study was approved by the Institutional Review Board of the General Hospital of Mexico and by the Independent Ethics Committee and was given the reference No. DI/13/403/04/038. Patients received an explanation of alternatives for surgical treatment of epilepsy including the proposed study, and those who decided to participate signed an informed consent.

We designed a prospective observational study. Patients were implanted with DBS systems in the subiculum, and after 1 month OFF stimulation they completed a 24-month follow-up ON stimulation.

Selected patients were over 18 years of age, had drug-resistant MTLE corroborated by semiology and conventional EEG, had FBTCS among their seizure types, had complete neuropsychological tests, their MRIs showed HS on the same side of the epileptic focus for unilateral cases, and at least on one side for bilateral cases, had completed a seizure diary accurately and had attended to monthly consultations for at least 6 months. From May 2013 to May 2015, all patients from the Epilepsy Clinic of the General Hospital of Mexico who fulfilled the selection criteria were offered to participate in the study.

Seizure Count

Seizure count was obtained from the patients' seizure diary. All patients of our clinic are instructed on the filling of a diary where they keep a record of number and type of seizures on a monthly basis. The filling method is reinforced at every consultation.

Baseline

We considered a baseline (BL) period of 4 months before the implantation of intracranial electrodes to be compared with the postoperative outcome. The BL seizure count was determined by the median monthly seizure count during this period.

Seizure Onset Zone Localization

Seizure onset zone location was confirmed by video-EEG telemetry recorded with intracranial tubular octopolar recording electrodes (AD-TECH Medical, Racine, WI, USA) placed stereotactically at the subiculum, parallel to the major axis of the hippocampus, through occipital burr holes. On the day of implantation, a contrast CT scan with the stereotactic instrument (Leibinger, Freiburg, Germany) in place was performed. Pre-operative T1-weighted MRI axial views and CT scan were fused using the 3A Plus Praezis software (Inomed, Heidelberg, Germany) and coreg-

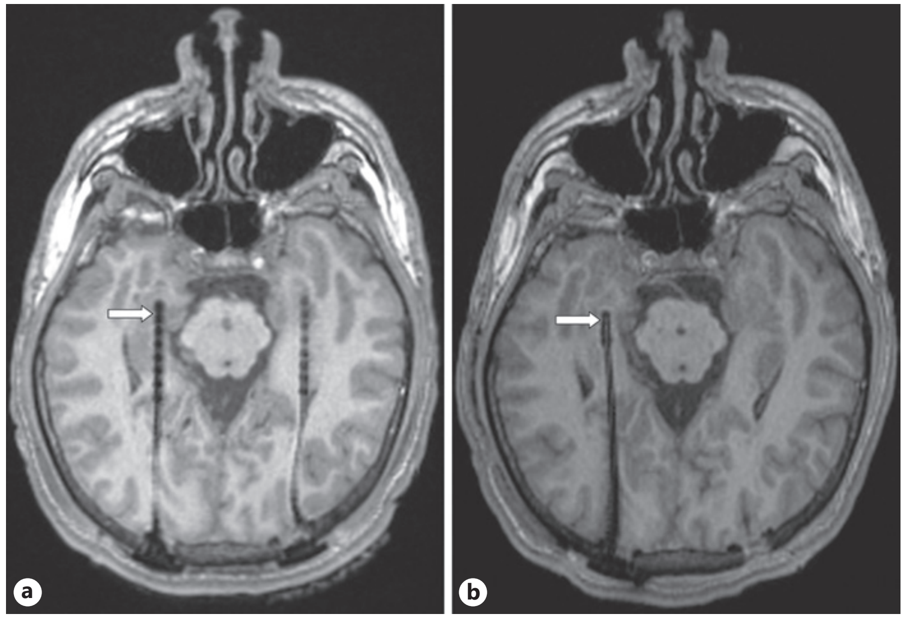

Fig. 2. Electrode position in patient 248. **a** Diagnostic electrode. **b** DBS electrode. The white arrow shows the site where the seizure onset zone was identified; note that active contacts are exactly at this same location.

istered with a stereotactic CT scan. The tip of the electrodes was located at the level of the amygdala, and the electrodes' contacts covered the entire length of the subiculum. The correct placement was confirmed with lateral and anteroposterior intra-operative fluoroscopy and with a postoperative MRI. Continuous video-stereo-EEG recordings through the implanted electrodes with patients OFF anticonvulsant medications were performed until at least 2 seizures were recorded, in order to define the contacts of seizure onset.

DBS Implantation

Activa-SC neurostimulators were implanted coupled to 3,387 DBS electrodes (Medtronic Inc., Minneapolis, MN, USA, tetrapolar electrodes with intercontact 1.5-mm distance). The target was set 2.0 mm distal to the contact where the seizure onset had been recorded in stereo-EEG studies to have the distal contact of the DBS electrode at the place where seizure onset had been recorded. Recording electrodes were removed and replaced by the DBS electrodes (Fig. 2). The correct location of the electrode contacts was verified in a postoperative MRI as described for recording electrodes.

Stimulation Parameters

The stimulation parameters were: bipolar with the cathode placed distally, 3 V amplitude, frequency of 130 Hz, pulse width 450 μs, cycling stimulation consisting of 1 min ON, 4 min OFF.

Follow-Up

The DBS system was left OFF in all patients for the first month (month 0) to rule out a possible antiepileptic effect induced by the microlesion at the electrode implantation site. Thereafter stimulators were turned ON, and all patients completed a 24-month follow-up (from months 1 to 24) ON stimulation. During this period, they continued to attend monthly consultations for seizure count and DBS system monitoring.

Life Quality Evaluation

The QOLIE-89 inventory was applied to all patients before surgery on month −4 of BL and after surgery by the end of the follow-up period. A scale of daily life activities was also performed taking into consideration independence, school and work activities.

Neuropsychological Evaluation

Evaluation was performed by a blinded examiner. It included the dichotic listening test for language dominance and the Edinburgh inventory for manual dominance, which were performed at month −4 of BL, and the Neuropsi test [14], a test validated for the Mexican population that evaluates memory, attention and combined memory-attention performance, which was applied on month −4 of BL and after surgery at the end of follow-up.

Statistical Analysis

Analyses were performed with SPSS 18.0 setting a $p < 0.05$ significance level. The Friedman test was used to compare seizure number.

Results

Patients

Table 1 shows the characteristics of each patient included. A total of 6 patients, aged 18–39 years (mean 28.83 ± SD 8.56), were enrolled.

The patients who underwent DBS in the subiculum had the following characteristics: one was not candidate for resection due to seizure onset recorded on both sides

Table 1. Patients' clinical characteristics

Patient	Gender	Age, years	Seizure type	MRI	Language dominance	Epileptic focus	BL total seizure count/month	BL FBTCS count/month	Implant	Active contacts
248	M	27	FBTCS	RHS	L	R	6	6	R	0–, 1+
258	M	39	FBTCS	RHS	U	B	4	4	B	both 1–, 2+
265	M	34	FIAS + BTCS	RHS	L	R	12	7	R	0–, 1+
266	F	18	FBTCS	LHS	R	L	24	24	L	0–, 1+
269	M	20	FIAS + BTCS	RHS	L	R	5	2	R	0–, 1+
275	F	35	FBTCS	LHS	L	L	5	5	L	1–, 2+

BL, baseline; FBTCS, focal to bilateral tonic-clonic seizures; FIAS, focal impaired awareness seizures; RHS, right hippocampal sclerosis; LHS, left hippocampal sclerosis; L, left; R, right; U, undetermined; B, bilateral.

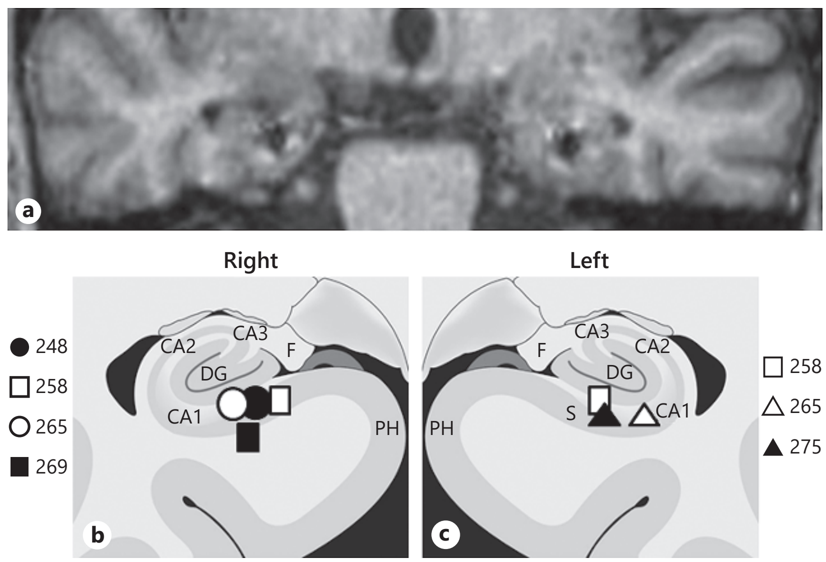

Fig. 3. Electrode position. PH, parahippocampus; S, subiculum; DG, dentate gyrus; F, fimbria. **a** MRI of patient 258 with bilateral DBS electrodes. **b**, **c** Plotting of the electrodes on a coronal section of the right (**b**) and left (**c**) hippocampal formation diagram. Different figures identify different patients, the white square in both diagrams corresponds to the patient with bilateral DBS electrodes shown in **a**.

and had bilateral DBS systems implanted; another refused temporal lobectomy due to religious reasons; one was not considered candidate for a resective procedure due to language dominance at the same side as seizure onset; the other 3 patients preferred a less invasive procedure.

DBS Implantation

Four patients were implanted unilaterally and 1 patient bilaterally. In all cases the active contacts were in the subiculum or <3 mm from it (Fig. 3). In patient 269 the electrode tip was slightly below the ideal site, but still 3 mm adjacent to the subiculum, therefore it was not considered necessary to re-implant it. Patient 258 was implanted with 2 generators.

Insertional Effect

During the first month after implantation (month 0), total number of seizures, and predominantly FBTCS, dramatically decreased in all patients when compared to BL. By the second month after implantation, the number of seizures went almost back to BL.

Seizure Count

There was a mean reduction of 49.16% (±SD 41.65) in total seizure number and a mean reduction of 67.93% (±SD 33.33) in FBTCS at 24 months (Table 2). Due to the small sample size we performed the non-parametric Friedman test and found a significant difference with respect to BL, starting from month 2 ON stimulation ($p < 0.05$; Fig. 4).

Table 2. Patients' condition at 24-month follow-up

Patient	Total seizure reduction, %	FBTCS reduction, %	BL condition	Present condition
248	50	100	Partially employed, family dependent	Fully employed, economically independent
258	100	100	Partially employed, family dependent	Fully employed, economically independent
265	41.67	14.29	Fully employed, economically independent	No changes in lifestyle
266	83.3	83.3	Had dropped school	Back in school
269	–20	50	Partially employed, family dependent	Fully employed, economically independent
275	40	60	Housewife	No changes in lifestyle

FBTCS, focal to bilateral tonic-clonic seizures; BL, baseline.

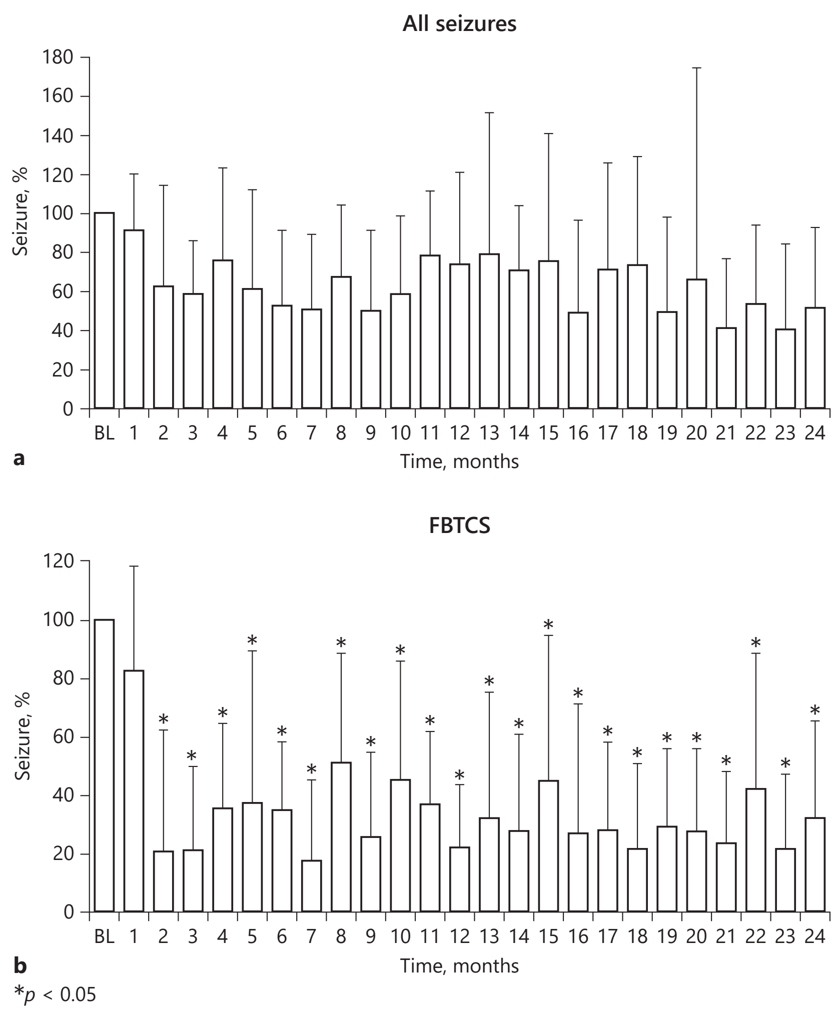

Fig. 4. Monthly seizure average during follow-up. **a** When counting all seizures (FIAS + FBTCS), there was no significant difference from BL at any time during this phase. **b** On the other hand, FBTCS were significantly reduced from month 2.

Patients were considered responders if they had a reduction of FBTCS ≥50%. Five patients were responders. Patient 258 has been FBTCS free from month 15 and seizure free from month 16. Patient 248 had an increase in total seizure count during most of the follow-up, and this was related to FIAS increase. Yet, FBTCS were decreased during all of the study; by the end, he had been FBTCS free since month 21, so he was still considered a responder. Patient 265 was considered a non-responder, with only 41.67% reduction of the total number of seizures and 14.29% reduction of FBTCS. By month 24, patient 269 had an increase in total seizure number and a reduction of only 50% of FBTCS, but along the study total seizure increase was observed only in 3 months, which were not continuous, and he was FBTCS free for 17 months; his remaining seizures were exclusively nocturnal.

Neuropsychological Evaluation

No significant differences were found between BL and postsurgical neuropsychological evaluation for the group.

Adverse Events

Patient 265 had 2 adverse events during the study: (1) in the immediate postsurgical period after DBS implantation, he underwent a 5-h period of perseverating ideas after which he completely recovered; (2) in the first month after implantation, a DBS electrode fractured during a seizure; he was re-implanted successfully and continued the study.

Life Quality Evaluation

Even though the QOLIE-89 inventory did not show a significant difference between presurgical and postsurgical life quality overall score at 24 months, in 4 patients there was a positive difference on daily life activities (Table 2). In the particular case of patient 248, in spite of a total seizure count increase, the reduction of FBTCS allowed him to keep a regular job. Patient 269 could also keep a regular job since his remaining seizures are nocturnal.

Discussion

Patients with HS and unilateral seizure onset zone, particularly in the language non-dominant hemisphere, are the best indication for anterior temporal lobectomy, so a large sample size for DBS treatment in this population is uncommon and directed to patients with a high risk for major surgical procedures or those patients who prefer a less invasive procedure. Therefore, the main limitation of this study is that it is restricted to a small number of patients.

The effectiveness of hippocampal formation as a DBS target for treating MTLE with HS has already been reported with results ranging from 66% seizure reduction to seizure freedom [3, 13, 15, 16]. The purpose of this study was to optimize DBS in the treatment of patients with MTLE and HS using a different target within the hippocampal formation that escaped the sclerotic process, such as the subiculum.

Although there is information regarding EEG activity in the subiculum in animal models and human tissue, the exact effect of subiculum stimulation on MTLE could not be accurately predicted since it may depend on factors like the model used and the type of activation (electric, optogenetic, chemical-genetic). In a hippocampal kindling model, Wang et al. [17] found that subicular optogenetic activation did not change the BL epileptogenic sensitivity, but it mainly inhibited the seizure spread. Similarly, we found good control of generalized seizures with electric stimulation, which has proved to modulate γ-aminobutyric acid levels locally and to have a long-term effect [18].

In the present study, during the first month after electrode implantation in the subiculum, there was a decrease in the number of seizures. This effect due to electrode insertion has been previously described [19]. At the end of the study, DBS-SC did not significantly decrease the total number of seizures along the 24-month follow-up; however, FBTCS were significantly decreased from month 2 ON stimulation ($p < 0.05$), and this effect was maintained along all of the follow-up. It also seems that seizure control and life quality have a greater improvement in the longer term.

Regarding hippocampal electric stimulation, in a study of DBS-HC Velasco et al. [3] reported a 50–70% reduction in total number of seizures (FIAS + FBTCS) at 18 months in patients with HS. In a 6-month double-blind trial of DBS-HC in patients with FIAS and focal aware seizures, Cukiert et al. [19] reported an average reduction of 78.33% in FIAS in patients with HS in the active group. A long-term responsive neurostimulation study reported a 53% reduction of seizures (focal aware seizures, FIAS and FBTCS) at 2 years in patients with mesial temporal lobe onset, neocortical onset or both [20]. Among these studies, only the one by Velasco et al. [3] can be compared to our series since both share seizure type, onset zone and the presence of HS. We can see that although DBS-SC is effective in reducing disabling seizures, it is not superior to DBS-HC in reducing overall seizure frequency. We think that the decrease in FBTCS but not in FIAS indicates that DBS-SC interferes more with generalization than with seizure genesis. This observation contributes to a better understanding of the role of the subiculum in MTLE.

Further studies are required to optimize the treatment of MTLE in patients with HS who cannot undergo resective options. Future designs should include randomization, double-blind periods of at least 6 months and larger sample sizes. Aspects like other targets and stimulation parameters can still be addressed. In our study, we found that in patients with the best results, electrode location in the subiculum was closer to the entorhinal cortex; on the other hand, in patients with modest seizure control the electrode was closer to CA1. This is an interesting finding which might be worth considering. For stimulation parameters, the main debate seems to be which mode to use. We think that there is still not enough information to prefer continuous, cycling or responsive stimulation, since good results have been reported in all modes [3, 13, 19, 20] and there have been no studies up to now that have made a comparison among them.

Conclusion

Subicular cycling stimulation is effective in decreasing FBTCS in patients with MTLE and HS, and it does not affect neuropsychological performance, but it is not superior to hippocampal stimulation for total seizure reduction; so, the latter should still be preferred. Thus, the subiculum could be considered as a suitable target in patients in whom FBTCS are a constant and who have severe sclerosis where the tissue consistency and atrophy make it difficult to insert the DBS electrodes in the hippocampus.

Statement of Ethics

Complying with the Declaration of Helsinki, this study was approved by the Institutional Review Board of the General Hospital of Mexico and by the Independent Ethics Committee; it was given the reference No. DI/13/403/04/038. Patients received an explanation of alternatives for surgical treatment of epilepsy including the proposed study, and those who decided to participate signed an informed consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

D.V.-B.: conception and design of the work; data acquisition, analysis and interpretation; work drafting, revision for intellectual content; final approval of the version to be published; ensuring that the work was appropriately investigated and resolved. M.C.-H.: data acquisition; revision for intellectual content; final approval of the version to be published; ensuring that the work was appropriately investigated and resolved. F.V.C. and A.L.V.: conception of the work; data interpretation; revision for intellectual content; final approval of the version to be published; ensuring that the work was appropriately investigated and resolved.

References

1 Velasco M, Velasco F, Velasco AL, Boleaga B, Jimenez F, Brito F, et al. Subacute electrical stimulation of the hippocampus blocks intractable temporal lobe seizures and paroxysmal EEG activities. Epilepsia. 2000 Feb;41(2):158–69.
2 Vonck K, Boon P, Achten E, De Reuck J, Caemaert J. Long-term amygdalohippocampal stimulation for refractory temporal lobe epilepsy. Ann Neurol. 2002 Nov;52(5):556–65.
3 Velasco AL, Velasco F, Velasco M, Trejo D, Castro G, Carrillo-Ruiz JD. Electrical stimulation of the hippocampal epileptic foci for seizure control: a double-blind, long-term follow-up study. Epilepsia. 2007 Oct;48(10):1895–903.
4 Boëx C, Vulliémoz S, Spinelli L, Pollo C, Seeck M. High and low frequency electrical stimulation in non-lesional temporal lobe epilepsy. Seizure. 2007 Dec;16(8):664–9.
5 Fisher PD, Sperber EF, Moshé SL. Hippocampal sclerosis revisited. Brain Dev. 1998 Dec;20(8):563–73.
6 Dawodu S, Thom M. Quantitative neuropathology of the entorhinal cortex region in patients with hippocampal sclerosis and temporal lobe epilepsy. Epilepsia. 2005 Jan;46(1):23–30.
7 Cohen I, Navarro V, Clemenceau S, Baulac M, Miles R. On the origin of interictal activity in human temporal lobe epilepsy in vitro. Science. 2002 Nov;298(5597):1418–21.
8 Wozny C, Kivi A, Lehmann TN, Dehnicke C, Heinemann U, Behr J. Comment on "On the origin of interictal activity in human temporal lobe epilepsy in vitro". Science. 2003 Jul;301(5632):463.
9 Fritschy JM. Le role de la neurotransmission GABAergique dans l'epilepsie mésiale du lobe temporal. Epileptologie. 2003;20:2–7.
10 Fabó D, Maglóczky Z, Wittner L, Pék A, Eröss L, Czirják S, et al. Properties of in vivo interictal spike generation in the human subiculum. Brain. 2008 Feb;131(Pt 2):485–99.

11 Zhong K, Wu DC, Jin MM, Xu ZH, Wang Y, Hou WW, et al. Wide therapeutic time-window of low-frequency stimulation at the subiculum for temporal lobe epilepsy treatment in rats. Neurobiol Dis. 2012 Oct;48(1): 20–6.
12 Bondallaz P, Boëx C, Rossetti AO, Foletti G, Spinelli L, Vulliemoz S, et al. Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy. Seizure. 2013 Jun;22(5):390–5.
13 Boëx C, Seeck M, Vulliémoz S, Rossetti AO, Staedler C, Spinelli L, et al. Chronic deep brain stimulation in mesial temporal lobe epilepsy. Seizure. 2011 Jul;20(6):485–90.
14 Ostrosky-Solis F, Esther Gomez-Perez M, Matute E, Rosselli M, Ardila A, Pineda D. NEUROPSI ATTENTION AND MEMORY: a neuropsychological test battery in Spanish with norms by age and educational level. Appl Neuropsychol. 2007;14(3):156–70.
15 Boon P, Vonck K, De Herdt V, Van Dycke A, Goethals M, Goossens L, et al. Deep brain stimulation in patients with refractory temporal lobe epilepsy. Epilepsia. 2007 Aug; 48(8):1551–60.
16 Cukiert A, Cukiert CM, Burattini JA, Lima AM. Seizure outcome after hippocampal deep brain stimulation in a prospective cohort of patients with refractory temporal lobe epilepsy. Seizure. 2014 Jan;23(1):6–9.
17 Wang Y, Xu C, Xu Z, Ji C, Liang J, Wang Y, et al. Depolarizad GABAergic signaling in subicular microcircuits mediates generalizad seizure in temporal lobe epilepsy. Neuron. 2017 Aug;95(5):1221.
18 Cuéllar-Herrera M, Velasco M, Velasco F, Velasco AL, Jiménez F, Orozco S, et al. Evaluation of GABA system and cell damage in parahippocampus of patients with temporal lobe epilepsy showing antiepileptic effects after subacute electrical stimulation. Epilepsia. 2004 May;45(5):459–66.
19 Cukiert A, Cukiert CM, Burattini JA, Mariani PP, Bezerra DF. Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. Epilepsia. 2017 Oct;58(10):1728–33.
20 Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Longterm treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015 Feb;84(8):810–7.