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Epileptogenic zone, electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy : a correlation study

THESE

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du Docteur Andrea O. Rossetti

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Par

Percy BONDALLAZ

Médecin diplômé de la Confédération Suisse
Originaire de Lausanne, Vaud

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Résumé :

Objectif : Etudier les résultats cliniques du traitement de patients atteints par une épilepsie mésiale du lobe temporal (MTLE) réfractaire, par stimulation cérébrale profonde (DBS) de l'hippocampe, en fonction de l'emplacement de l'électrode.

Méthodes : Huit patients atteints de MTLE implantés dans l'hippocampe et stimulés par DBS à haute fréquence ont été inclus dans cette étude. Cinq ont subi des enregistrements invasifs avec des électrodes profondes dans le but d'estimer la localisation du foyer ictal avant de procéder à une DBS chronique. La position des contacts actifs de l'électrode a été mesurée en utilisant une imagerie post-opératoire. Les distances par rapport au foyer ictal ont été calculées, et les structures hippocampiques influencées par la stimulation ont été identifiées au moyen d'un atlas neuro-anatomique. Ces deux paramètres ont été corrélés avec la réduction de la fréquence d'apparition des crises.

Résultats : Les distances entre la localisation estimée des contacts actifs de l'électrode et le foyer ictal étaient respectivement 11.0 ± 4.3 ou 9.1 ± 2.3 mm pour les patients présentant une réduction de $> 50\%$ ou $< 50\%$ de la fréquence des crises. Chez les patients ($N = 6$) montrant une réduction de $> 50\%$ de la fréquence des crises, 100% avaient des contacts actifs situés à < 3 mm du subiculum ($p < 0,05$). Les 2 patients ne répondant pas au traitement étaient stimulés par des contacts situés à > 3 mm du subiculum.

Conclusion : La diminution de l'activité épileptogène induite par DBS sur l'hippocampe dans les cas de MTLE réfractaires : 1) ne semble pas directement liée à la proximité des contacts actifs de l'électrode au foyer ictal déterminé par les enregistrements invasifs ; 2) pourrait être obtenue par une neuro-modulation du subiculum.

Rapport de synthèse

Enjeu et contexte de la recherche

L'épilepsie est une maladie neurologique fréquente qui affecte 0.5-1% de la population (Hauser *et al.*, 1993). Parmi ces patients, environ 30% souffriraient d'une forme réfractaire aux traitements médicamenteux (Kwan et Brodie, 2000), dont certains avec un foyer épileptique localisé dans la région du lobe temporal moyen (MTLE, « Mesial temporal lobe epilepsy ») (Engel, 2001) contenant notamment le complexe amygdalo-hippocampique. Bien que la résection chirurgicale de la partie antérieure du lobe temporal ait montré son efficacité dans le traitement de ce type d'épilepsie, elle n'est pas possible chez de nombreux patients pour qui la résection du complexe amygdalo-hippocampique aurait des conséquences délétères sévères sur le plan neurologique (Kwan et Brodie, 2000 ; Helmstaedter *et al.*, 2003), ou dans les cas impliquant des foyers épileptiques bitemporaux. Pour ces patients, la stimulation cérébrale profonde (DBS, « Deep brain stimulation ») a été proposée comme traitement alternatif consistant à moduler l'activité du tissu nerveux ciblé par la décharge d'impulsions électriques.

Cette technique a déjà démontré une efficacité dans la réduction de l'activité épileptiforme corticale (Iadarole et Gale, 1982; Ben-Menachem, 2002 ; Velasco *et al.*, 2005). Dans ces cas, les investigations faites avec des électrodes intracrânielles (Swanson, 1995 ; Spencer, 2002) suggèrent fortement que l'initiation et la propagation de la crise de MTLE impliquent l'amygdale et l'hippocampe.

Cliniquement, il a été montré que la stimulation hippocampique utilisant des électrodes profondes a significativement réduit la fréquence des crises chez une proportion variable de patients présentant une épilepsie réfractaire du lobe temporal (Velasco *et al.*, 2000 ; Velasco *et al.*, 2007 ; Vonck *et al.*, 2002 ; Vonck *et al.*, 2005 ; Tellez-Zenteno *et al.*, 2006 ; Boëx *et al.*, 2007 ; Boon *et al.*, 2007 ; Boëx *et al.*, 2011). Les mécanismes exacts par lesquels la DBS réduit la fréquence des crises restent inconnus. L'hypothèse que la réduction des crises serait liée à une lésion induite par l'insertion de l'électrode a pu être écartée par des études incluant une période initiale avec implantation d'électrodes sans stimulation (Osorio *et al.*, 2007).

En résumé, peu de patients ont bénéficié de la DBS amygdalo-hippocampique comme traitement alternatif pour la MTLE. L'efficacité clinique, bien qu'évidente, reste cependant variable en terme de réduction de fréquence des crises. Ceci nécessite donc une meilleure

compréhension des mécanismes étant à la base de l'effet de l'application de courant électrique sur le tissu neural, aussi bien que l'identification de cibles et de paramètres de stimulation optimaux.

Les buts de cette étude sont d'évaluer la distance entre les électrodes profondes implantées et les foyers épileptiques supposés par le calcul de la distance euclidienne entre leurs coordonnées déterminées dans un référentiel stéréotaxique, puis de caractériser la relation entre cette distance et le résultat clinique. Les structures potentiellement influencées par la stimulation électrique seront également identifiées par mesure directe sur des projections fusionnées d'images post-opératoires avec un atlas neuro-anatomique, et les cibles potentielles permettant d'obtenir un effet clinique suffisant seront déterminées.

Conclusions et perspectives

Aucune relation claire n'a été observée entre les emplacements des contacts actifs des électrodes et les foyers ictaux présumés. Ces contacts ont tous été localisés à plus de 6 mm de la position estimée du foyer ictal, ne permettant plus une influence directe du courant électrique. Cependant, une réduction suffisante de la fréquence des crises a pu être observée, suggérant que des effets indirects puissent être obtenus par la stimulation d'une structure, ou d'une partie de cette structure, potentiellement impliquée dans l'initiation ou la propagation du courant épileptique.

Deuxièmement, l'analyse des structures amygdalo-hippocampiques situées dans la sphère d'influence des contacts actifs, réalisée sur la base d'un atlas neuro-anatomique, a montré que les contacts des électrodes qui étaient les plus proches du subiculum, ou qui pourraient avoir eu un effet microlésionnel sur le subiculum pendant l'insertion de l'électrode, sont associés à des réductions importantes de la fréquence des crises, tandis qu'aucune diminution significative n'a été observée quand les électrodes étaient placées à plus de 3 mm du subiculum, suggérant un rôle de cette structure dans l'efficacité de la DBS pour les cas de MTLE. Ces observations sont en accord avec la littérature récente (Huberfeld *et al.*, 2011), cependant notre étude est la première à fournir des données cliniques chez l'humain suggérant une telle implication potentielle du subiculum.

D'autres études prospectives multicentriques conduites sur un plus grand nombre de patients seront nécessaires afin de fournir un ensemble de données plus cohérent permettant d'augmenter la fiabilité de nos résultats afin de démontrer le rôle du subiculum dans la

stimulation électrique pour le traitement de la MTLE réfractaire, ainsi que pour confirmer l'effet neuro-modulateur de la DBS hippocampique sur le subiculum.

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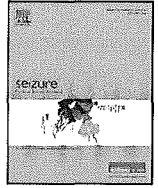
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Electrode location and clinical outcome in hippocampal electrical stimulation for mesial temporal lobe epilepsy

Percy Bondallaz^a, Colette Boëx^c, Andrea O. Rossetti^b, Giovanni Foletti^b, Laurent Spinelli^c, Serge Vuilliamoz^c, Margitta Seeck^c, Claudio Pollo^{a,*}

^a Department of Neurosurgery, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland

^b Department of Neurology, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland

^c Epilepsy Unit, Department of Neurology, University Hospital of Geneva, 1211 Geneva, Switzerland

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ABSTRACT

Purpose: To study the clinical outcome in hippocampal deep brain stimulation (DBS) for the treatment of patients with refractory mesial temporal lobe epilepsy (MTLE) according to the electrode location.

Methods: Eight MTLE patients implanted in the hippocampus and stimulated with high-frequency DBS were included in this study. Five underwent invasive recordings with depth electrodes to localize ictal onset zone prior to chronic DBS. Position of the active contacts of the electrode was calculated on postoperative imaging. The distances to the ictal onset zone were measured as well as atlas-based hippocampus structures impacted by stimulation were identified. Both were correlated with seizure frequency reduction.

Results: The distances between active electrode location and estimated ictal onset zone were 11 ± 4.3 or 9.1 ± 2.3 mm for patients with a $>50\%$ or $<50\%$ reduction in seizure frequency. In patients ($N = 6$) showing a $>50\%$ seizure frequency reduction, 100% had the active contacts located <3 mm from the subiculum ($p < 0.05$). The 2 non-responders patients were stimulated on contacts located >3 mm to the subiculum.

Conclusion: Decrease of epileptogenic activity induced by hippocampal DBS in refractory MTLE; (1) seems not directly associated with the vicinity of active electrode to the ictal focus determined by invasive recordings; (2) might be obtained through the neuromodulation of the subiculum.

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1. Introduction

Epilepsy is a frequent neurological disease that affects 0.5–1% of the population.¹ About 30% of patients have a pharmacologically intractable form of epilepsy.² Mesial temporal lobe epilepsy (MTLE) is a particularly common form of pharmacoresistant epilepsy.³ Surgical resection of the amygdalo-hippocampal structures alone or together with the anterior portion of temporal lobe is an effective treatment of MTLE.^{4,5} However, ablative surgery is not possible in up to 30% of patients in whom resection of the amygdalo-hippocampal complex will result in severe neurological impairments such as memory deficits,^{2,6} or in cases involving bitemporal epileptic foci. In these patients electrical stimulation of the amygdala and hippocampus has been proposed as an alternative treatment.^{7–10}

Previous studies have highlighted the efficacy of high frequency deep brain stimulation (DBS) to reduce epileptic activity either by targeting intracerebral structures believed to have a triggering role in the epileptic network, such as the thalamus, the subthalamic nucleus, the caudate nucleus, and the cerebellum or the vagal nerve.^{11–13} Alternatively, the ictal onset zone may be targeted, with the hypothesis that stimulation may interfere with seizure initiation. The latter strategy has been described to be suitable to control seizures in patients with MTLE. In these cases investigations using intracranial electrodes^{14,15} have strongly suggested that seizure onset and propagation involve the amygdala and hippocampus.

Clinically, it has been shown that hippocampal stimulation using depth electrodes significantly reduces interictal EEG spikes^{16,17} and improves seizure outcome in patients with temporal lobe epilepsy.^{7–10,16,18,19} However, responses are variable in terms of seizure frequency reduction leading to the need for a better understanding of the mechanism by which DBS reduces seizure frequency, as well as identification of optimal targets and optimization of stimulation parameters. One hypothesis is that DBS may act through local inhibition of neurons adjacent to the

* Corresponding author at: Department of Neurosurgery, University Hospital Bern, CH-3010 Bern, Switzerland. Tel.: +41 031 632 08 10; fax: +41 031 382 24 14.
E-mail address: claudio.pollo@insel.ch (C. Pollo).

area of electrode implantation, thereby modulating the activity of cerebral structures triggering seizure onset. Alternatively, DBS may have an effect on the network of neuronal projections connecting several cerebral structures.²⁰ Since mesial temporal lobe structures are potentially involved in epileptic networks, the targeting of ictal foci in this region may also affect adjacent networks.

We previously published a study that focused on the efficiency of hippocampal stimulation on reducing seizure frequency and on the influence of stimulation parameters. One unresolved issue concerns the impact of electrode positioning on seizure treatment, which may in turn prove informative for targeting practices in general.

Therefore, in the present study, we retrospectively analyzed (1) the distance between the implanted DBS stimulating contact(s) relative to the ictal onset focus determined invasively, and (2) the anatomical structures possibly influenced by electrical stimulation. These two parameters were compared with the clinical outcome.

2. Methods

2.1. Patients and inclusion criteria

Eight patients with intractable MTLE epilepsy were selected for DBS treatment between June 2002 and April 2008 as previously described¹⁰ (5 women and 3 men, median age: 31.5 years, range: 25–47). The criteria for patient selection to proceed with DBS included pharmaco-resistance and proven MTLE seizure origin. Resective surgery is usually proposed as the treatment of choice in these patients. DBS was considered in patients with either concerns for possible post-operative significant worsening of memory, particularly verbal memory, or when bilateral epileptogenic zones were suspected. Details of inclusion criteria and of the presurgical protocol were published previously¹⁰ and include high-resolution brain MRI, video-EEG telemetry, interictal positron emission tomography (PET), ictal and interictal single photon emission computerized tomography (SPECT), as well as neuropathological and psychiatric examinations. High-resolution MRI showed a hippocampal sclerosis in 2 patients; the remaining 6 had non-lesional MTLE (Table 1).

The study was approved by the local Ethics Committee of the University Hospitals of Geneva and Lausanne, and an informed consent was obtained from each patient.

2.2. Identification of ictal focus

In 5 of 8 patients (Pt4, 5, 7, 8, 9), the EEG ictal onset focus was estimated by invasive recordings using intracerebral depth

electrodes inserted perpendicular to the skull surface at amygdala, anterior and posterior hippocampal levels in both temporal lobes as previously described.¹⁰ Epileptogenic ictal focus was assigned to the contact (numbered 1 to 8) recording maximal ictal activity (pathological waveform). A high-resolution CT scan was then co-registered with a T1-weighted MRI acquired under stereotactic conditions (CRW, Radionics[®], Burlington, MA, USA) and processed using the Framelink 5.1 software on a Stealth workstation (Medtronic Inc, Minneapolis, MN, USA). The postoperative imaging was realigned to the anterior commissure–posterior commissure (AC–PC) coordinates system by identifying the anterior and posterior commissures and 3 midline landmarks. Origin was set at the midcommissural point. Three orthogonal planes of view were then used to localize the electrode contact. Its coordinates were calculated and expressed as (x) mm lateral to the midline, (y) mm antero-posterior and (z) mm supero-inferior to the mid-commissural plane.

2.3. Surgical procedure

Surgical planning and procedure were performed as previously described.¹⁰ The Pisces-Quad 3487A electrode and the Soletta 7426 stimulator (Medtronic Inc, Minneapolis, MN, USA) were implanted in the first 5 patients. The 4 cylinder-shaped contacts of the Pisces-Quad electrode are 3 mm in length and 1.27 mm in diameter. The intercontact distance is 6 mm, and the electrode is 30 mm in total length. The 3 remaining patients received the Sub Compact Octad 3876 electrode and the Restore stimulator (Medtronic Inc., Minneapolis, MN, USA). The Sub Compact Octad electrode is 34.5 mm in total length with 8 contacts (3 mm length, 1.27 mm diameter, 1.5 mm intercontact distance). The DBS electrodes were placed parasagittally in the amygdalo-hippocampal complex so that the distal contact (contact 0) could be implanted in the area of the amygdala. Internalization of the electrode and connection to the neurostimulator was performed 3–4 days after the implantation procedure to provide EEG recordings.

2.4. Stimulation parameters and follow-up

The setting of post-implantation stimulation parameters and neurological evaluations were performed as previously described.¹⁰ All patients were stimulated at high-frequency, i.e. 130 Hz, and with pulse width of 0.45 ms. The amplitude of stimulation (0.5–2 V) and the number of contacts stimulated (bi- or quadripolar) were, however, different across patients. In the quadripolar configuration, the 4 contacts were set as cathodes, and the case box of the neurostimulator was set as the anode. In the bipolar configuration, the cathode was set on the contact

Table 1
Clinical characteristics of patients.

Patient	Sex	Age/onset	Follow-up (months)	HS	Side	Ictal focus	Interictal focus	Stimulation contact	Amplitude (V)	Outcome (% reduction in seizure frequency)
Pt1	F	37/24	74	Yes	Left	–	C1	quad	1	67
Pt2	F	32/3	50	Yes	Right	–	C2	quad	1	88
Pt3	F	44/4	46	No	Right	–	C0	quad	0.5	72
Pt4	F	31/25	45	No	Left	LAH1-2	C1	C0–C1	0.5	84
Pt5	M	47/21	42	No	Right	RAH3	n.i.	C0–C1	1	100
Pt7	M	31/14	34	No	Left	LAH2	C2	C1–C2	1	0
								C2–C3	1	0
Pt8	M	25/13	11	No	Left	LA1 ^a	C2	C1–C2	1.5	22
Pt9	F	26/13	10	No	Left	LAH2	C0	off	0	100
							C4	off	0	100

HS: hippocampal sclerosis, quad: quadripolar stimulation, LAH: left anterior hippocampus, RAH: right anterior hippocampus, n.i.: not identified, LA: left amygdala, off: not stimulated, C: electrode contact.

^a Secondary focus.

corresponding to the maximal interictal epileptogenic activity, as determined from intracranial EEG recordings before the internalization of the neurostimulator, and the anode was set on the contact closest to the second major interictal epileptogenic site. After a 3 month off-period, patients were followed for a median duration of 43.5 months (range 10–74 months). Quantification of the clinical outcome and efficacy of stimulation was performed by the evaluation of the ratio between the improvement in seizure frequency after implantation compared to pre-implantation baselines determined prospectively as the mean number of seizures per month during the three months prior to implantation (according to patients' self-reports). Introduction of any new AED was not allowed after implantation in order to determine the effect of DBS, but minor changes in medication dosages were accepted as previously described.¹⁰ Characteristics of patients, stimulation parameters and clinical outcome are summarized in Table 1. For the following analysis, patients were then split into 2 groups according to their rate of seizure frequency reduction (i.e. > or =50% and <50%).

2.5. Determination of the distance between the active contact(s) of the DBS electrode and the estimated ictal focus

Postoperative imaging was processed using the Framelink 5.1 software on a Stealth workstation (Medtronic Inc, Minneapolis, MN, USA) and realigned to the AC–PC coordinates system with origin set at the midcommissural point. The electrode contact image artifact was localized in the 3 orthogonal planes of view. The center of the artifact was identified as the center of the electrode (Fig. 1A) according to a previous study of DBS in patients with Parkinson's disease.²¹ Its coordinates (x), (y) and (z) were calculated as explained above. In 5 patients, AC–PC coordinates were subtracted in each plane (dx , dy , dz) to determine the distance between the estimated ictal focus and the implanted electrode contacts. Euclidian distance in 3D space was then calculated (square root of ($dx^2 + dy^2 + dz^2$)). These 4 parameters, as well as clinical outcome, were used for further analysis. In each case, distances between the estimated ictal focus and all contacts of the

electrode were calculated in order to estimate the minimal distance to the electrode.

2.6. Determination of structures in the vicinity of the electrodes influenced by DBS

To identify structures in the vicinity of active electrode contacts, postoperative imaging was co-registered and adjusted with the corresponding template of a neuro-anatomical atlas²² prepared according to the Talairach standard transformation²³ (Fig. 1B). Structures overlapping a 3 mm-radius circle centered on the artifact of the electrode contact were considered as possibly influenced by electrical stimulation (Fig. 1C), according to the estimation of the volume of tissue activated taken from different existing finite element models of electrical propagation around the electrode.^{24,25} The nonparametric Spearman correlation test was used for the statistical analysis on small samples.

3. Results

3.1. Clinical outcome and stimulation parameters

Postoperative seizure frequencies were compared with a pre-implantation baseline period. Six of the 8 patients exhibited a reduction of seizure frequency of >50%, including 2 seizure-free patients (i.e. 100% reduction of seizure frequency). The 2 remaining patients were non-responders (i.e. no significant change in seizure frequency). Reasons that could explain such good results compared to other studies have been previously discussed.¹⁰ In the first group, Pt1 and Pt2 did not show any reduction when stimulated in a bipolar configuration with contacts C0 and C1. When stimulated in a quadripolar configuration, they experienced a significant reduction in seizure frequency (67% and 88%, respectively) as published previously.¹⁰ Pt3 and Pt4 also showed a major seizure reduction of 72% and 84% with the quadripolar and bipolar configuration, respectively. Pt5 and Pt9 became seizure free with a bipolar configuration; the latter remained seizure free after the electrode was implanted, and during the off-period without

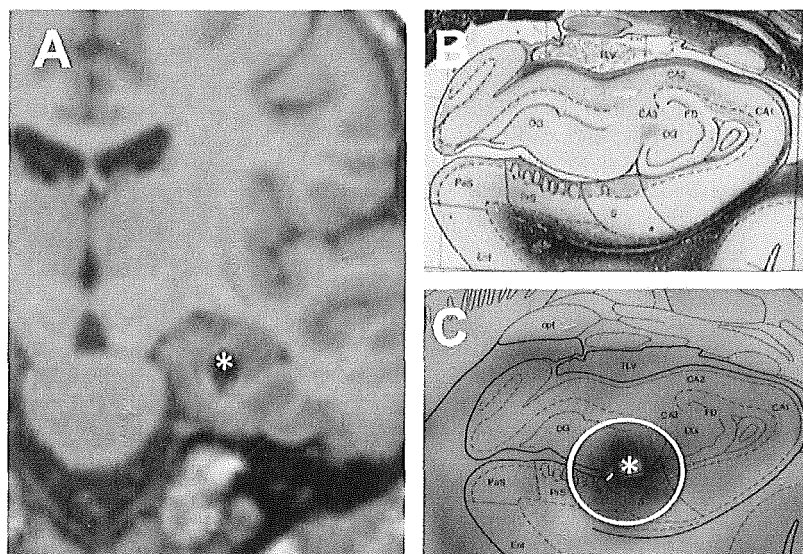


Fig. 1. MRI analysis using the surgical navigation system Stealth workstation (Medtronic Inc., Minneapolis, MN, USA). (A) Measurement of electrode contact (C1) position on post-operative brain T1-weighted MRI of Pt3 treated with DBS, enabling determination of stereotactic coordinates based upon the stereotactic surgical frame. Realignment of the scan to the AC–PC line is shown in the coronal plane. The white asterisk indicates the center of the DBS electrode contact. (B) Overview of the hippocampal and subicular regions with superimposed standard neuro-anatomical atlas (adapted from Mai JK, Assheuer J, Paxinos G. *Atlas of the human brain*. San Diego: Academic Press; 1998). (C) The white 3 mm-radius circle reflects the brain area supposed to be influenced by the electrode contact. CA, cornu ammonis; DG, dentate gyrus; Ent, entorhinal cortex; FD, fascia dentata; opt, optic tract; TLV, temporal horn of lateral ventricle; PaS, parasubiculum; PrS, presubiculum; S, subiculum.

stimulation. Pt7 and Pt8 did not show significant reductions in seizure frequencies during bipolar stimulation. Findings regarding Pt7 were previously reported and indicated a seizure reduction during the first 6 months, but unfortunately the electrode had to be reimplanted due to a fracture of the first Pisces Quad electrode. With the new Sub Compact Octad electrode, no seizure reduction was achieved during the months of bipolar stimulation at 1 V. The follow-up for each patient is indicated in Table 1. The outcome was not correlated to the follow-up (Spearman test, $\rho = -0.0599$, n.s.).

3.2. Distance of active contact to estimated ictal focus

The ictal focus was estimated in the 5 investigated patients with invasive recordings. Since Pt9 was seizure-free even without stimulation, distances of the estimated ictal focus to the contacts were not considered for the analysis. For the 4 remaining patients, the Euclidian distances between the location of electrode contacts used for stimulation and the contacts registering maximal ictal activity during pre-surgical invasive investigations were all greater than 6 mm (see Table 2). These values ranged from 1.6 to 7.8 mm in the latero-medial (*x*) axis, from 0.7 to 14.8 mm in the antero-posterior (*y*) axis, and from 0.8 to 7.0 mm in the supero-inferior (*z*) axis. The mean Euclidian distances are 11.0 ± 4.3 or 9.1 ± 2.3 mm for patients with a >50% or <50% reduction in seizure frequency, respectively. No relation could be observed between the distance of active electrode contacts to the estimated ictal focus and clinical outcome. Interestingly, the entire electrode of Pt9 is localized far from the estimated ictal focus (>10 mm).

3.3. Identification of cerebral structures impacted by electrode stimulation

In order to further characterize mechanisms underlying DBS effect on seizure frequency reduction, the amygdalo-hippocampal areas stimulated by the electrodes were identified on coronal MRI-slices. Most of the active electrode contacts are localized close to the CA1 field of the hippocampus and the subiculum (Table 3). In patients showing a >50% seizure frequency reduction, 100% had their subiculum localized at less than 3 mm from the active contacts. Pt7 and Pt8 presented no significant reductions in seizure frequency and were not stimulated in an area including the subiculum. The clinical outcome was significantly correlated with the proximity of the subiculum to the closest active contact

(Spearman test, $\rho = 0.677$, $p < 0.05$). On the other hand, all patients had their active contacts close to the CA1 field of the hippocampus, including the two non-responders, and no correlation was observed ($\rho = -0.5668$, n.s.). Furthermore, as described above, Pt1 and Pt2 showed better outcomes when stimulated in a quadripolar configuration including the contact C2, the nearest contact to the subiculum.

4. Discussion

DBS has been shown to be successful in the treatment of refractory epilepsy, despite the wide spectrum of results produced in clinical experiences in the literature. Pioneering studies concerning hippocampal stimulation for MTLE are based on small patient populations.^{8,9,18,19} Its mechanisms of action remain largely unknown. In the present study we first examined the relationship between electrode contacts and estimated ictal onset zone locations to further investigate its impact on clinical outcome in MTLE. We did not observe any clear relationship between the location of active contacts and the presumed ictal onset focus. DBS active electrode contacts were all found to be positioned more than 6 mm from the estimated ictal onset focus. The accuracy of ictal onset focus localization by invasive recordings may be questioned, especially in the antero-posterior direction where the sampling with depth electrodes was performed in the range of 1 cm, and as the recorded EEG (local field potentials) is supposed to reflect the synchronous activity of numerous neurons.²⁶ However, it is reasonable to think that the error in the antero-posterior direction should not exceed the range of 5 mm (i.e. half the distance between two electrodes). Moreover, as the mean Euclidian distance between the ictal focus and the stimulated contacts for patients with a >50% or <50% reduction in seizure frequency are comparable, and calculated with the same probability of error, we suggest that the seizure outcome is not directly related to the vicinity of the ictal focus determined with invasive electrodes. As an illustrative example, Pt9 showed a good outcome without stimulation (probably due to a micro-lesional effect). Since the entire electrode of Pt9 is localized >10.6 mm from the estimated ictal focus, it seems difficult to associate this outcome through a direct effect on the ictal focus.

Due to the small number of patients it was difficult to perform statistical analyses, but no trend seems to separate one group from the other in any axis, or according to patients' characteristics (presurgical seizure frequency, type of seizure, hippocampal sclerosis). However, considering that the current spread from the electrode is presumed to be smaller than 4 mm in radius according to DBS models, we observed that sufficient reduction in seizure frequency was obtained even when the contacts were localized at higher distances. This suggests that indirect effects could be produced by stimulation of a particular structure, or part of it, potentially involved in the onset or propagation of the epileptic current of mesio-temporal seizure. In our experience, patients with hippocampal sclerosis generally needed a more extended area of stimulation and had more electrode contacts stimulated, compared to the non-lesional cases. Although we do not have a definitive explanation, one speculation is that morphological changes induced by sclerosis may result in less functional tissue that can be stimulated and/or in an increase in tissue impedance.

Interestingly, the contacts presenting maximal ictal activity during presurgical invasive recordings were the contacts closest to the subiculum in 3 of 5 patients. Due to the spatial resolution,²⁶ it is not possible to exclude that ictal activity of other structures could be nonetheless recorded at these sites. Therefore, caution should be taken before drawing conclusions regarding the possible role of the subiculum in generation or in propagation of epileptic currents.

Table 2
Distances from electrode contacts to estimated ictal focus.

Patient	Stimulated contact	Distance (mm)			
		<i>dx</i>	<i>dy</i>	<i>dz</i>	3D
Pt4	C0*	7.7	6.9	3.9	11.1
	C1 ⁻	7.2	1.8	0.8	7.5
Pt5	C0 ⁻	4.6	14.8	7.0	17.0
	C1*	1.6	6.7	5.0	8.5
Pt7	C1*	4.2	8.2	6.2	11.1
	C2 ⁻	4.8	2.7	4.2	7.0
	C3*	5.0	0.8	3.5	6.1
Pt8	C1*	7.6	0.7	6.7	10.1
	C2 ⁻	7.8	3.6	6.9	11.0
Pt9	C0	6.7	13.0	0.5	14.6
	C1	8.2	7.9	1.3	11.4
	C2	9.4	4.5	2.4	10.7
	C3	11.2	0.1	3.8	11.8
	C4	12.6	4.7	5.4	14.5
	C5	13.3	8.2	6.0	16.7
	C6	14.8	12.0	7.0	20.3
C7	15.9	16.7	8.5	24.6	

*: Polarity of the stimulated contacts.

3D: Euclidian distance.

Table 3
Structures localized near the stimulated contacts.

Patient	Stimulated contact	LaV	Lal	LaDA	BM	BL	BLVM	BLI	HiH	DG	CA3	CA2	CA1	S	PrS	Ent	PHG	TLV
Pt1	C0	+++	++					++	+									
	C1										+++	++	+					
	C2										+++		+	++				
	C3										+++	+++	+++					
Pt2	C0			++		++	+		+									
	C1										+++		+	+				
	C2										++		+	+++				+
	C3												++	+				++
Pt3	C0								++				++			++		
	C1									+++				+++	++			
	C2										+		+	+++				
	C3									++	+	+	+++	+				+
Pt4	C0		++	++												++		
	C1									+++			++	+				
Pt5	C0		+++	+	++													
	C1									+			+++	++				
Pt9	C0				+++	++												
	C1				+++			+										
	C2				++	+++							++					++
	C3									+								++
	C4									+++	+++		+	++				
	C5										+++		+	++				
	C6										+++	+++	++	++				
	C7										+++		++	+++				
Pt7	C1									++								+++
	C2									++			+++			+		+
	C3												++			++		+
Pt8	C1		+			+	+		+++									
	C2												+++					

Patients with a >50% reduction in seizure frequency are grouped in the upper part of the table and indicated in bold type. The proximity of the subiculum to the stimulated contacts is also indicated in bold type. + to +++: proportion of the structure localized in a 3 mm-radius area around the electrode contact. BL: basolateral amygdaloid nucleus, BLI: basolateral amygdaloid nucleus intermediate part, BLVM: basolateral amygdaloid nucleus ventromedial part, BM: basomedial amygdaloid nucleus, CA1: CA1 field of the hippocampus, CA2: CA2 field of the hippocampus, CA3: CA3 field of the hippocampus, DG: dentate gyrus, Ent: entorhinal cortex, HiH: hippocampal head, LaDA: lateral amygd. nucl. dorsal anterior part, Lal: lat. amygdaloid nucl. intermed. part, LaV: lateral amygdaloid nucl. ventral part, PHG: parahippocampal gyrus, PrS: presubiculum, S: subiculum, TLV: temporal horn of lateral ventricle.

Second, atlas-based analysis of amygdalo-hippocampal structures located within a 3 mm-radius sphere around the active contacts of stimulation showed that all patients were well-stimulated in the CA region of the hippocampus. Interestingly, the electrode contacts that were closer to the subiculum, or may have had a lesional effect on the subiculum during the electrode insertion, were associated with important reductions in seizure frequency, whereas no significant effect was observed when the electrode was located farther than 3 mm from the subiculum. This observation suggests that the efficacy of DBS might be associated with the involvement of the subiculum, which also carries axons of the perforant pathway, and that the beneficial effects may be obtained through neuromodulation of this structure.

Several studies have highlighted the role of the dentate gyrus and CA1 region in hippocampal sclerosis models.^{27,28} More recently, several studies^{29–33} have demonstrated that the subiculum and parahippocampal structures, but not the hippocampus itself, play an active role in the generation and propagation of temporal lobe seizures, even in non-sclerotic hippocampal tissues.³⁴ Our study is the first to provide clinical data in humans supporting a potential involvement of the subiculum in the generation and/or propagation of seizures in MTLE.

There are no data underlying the direct neuromodulatory effect of electrical stimulation on the subiculum in refractory MTLE. Studies have suggested that changes in GABAergic signaling causing (1) hyperexcitability in the subiculum, that recalls the GABAergic excitation^{29,35} of early development, as well as (2) the

vulnerability of GABAergic interneurons, that may give rise to an input-specific impairment of inhibition,³² are the mechanisms underlying development of MTLE at a cellular level. According to these observations, neuromodulatory effects of high-frequency DBS may decrease the excitability of the subiculum and then improve the inhibitory effect of GABAergic pathways on generation and/or propagation of MTLE.

The reliability of our results could be improved by increasing the series size, especially when subgroups are considered. Further prospective multicentric studies involving a greater number of patients are necessary to provide more consistent data confirming the role of the subiculum in electrical stimulation in refractory MTLE.

In conclusion, our results suggest that decreases of epileptogenic activity induced by hippocampal high frequency DBS in refractory MTLE seem not to be associated with the vicinity of the active electrode to the ictal focus determined by invasive recordings. Instead, they might be associated with the vicinity of the active electrode to the subiculum and obtained through the neuromodulation of this structure. Further prospective studies conducted on a larger group of patients are necessary to confirm the neuromodulatory effect of hippocampal DBS on the subiculum.

Conflict of interest statement

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

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