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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 Vulliemoz [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.

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).

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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 described[10] (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 previously[10] 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 neuropsychological 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 amygdalar, 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 Soletra 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 parasagittaly 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.